2nd Global Conference on Myositis

William F. Bolger Center
Potomac, MD, USA

May 5-8, 2017

Program and Abstract Book

GCOM 2017

May 5-8, 2017 • Potomac, Maryland • U.S.A.

Welcome to the Second Global Conference on Myositis!

Idiopathic inflammatory myopathies, or myositis syndromes, are systemic disorders with diffuse organ involvement requiring care by an interdisciplinary team. Yet, often the many specialists caring for myositis patients, and those performing basic, clinical and translational research in this area, do not interact directly. To facilitate such multidisciplinary collaboration in research and to develop new clinical care and therapeutic modalities, Dr. Ingrid Lundberg recognized that a new approach was needed and organized the First International Conference on Myositis in May 2015 in Stockholm, Sweden. This Second Global Conference on Myositis (GCOM 2017) continues this innovative series of meetings in different locations throughout the world. We hope to stimulate additional collaborative research and clinical trials in myositis globally and across the many disciplines involved in these complex diseases.

The target audience for this meeting includes clinicians and scientists with interest in all forms of adult or juvenile myositis, who are involved in caring for myositis patients and/or in clinical, epidemiological, translational, or basic science, as well as patient support groups whose important perspectives bring new dimensions to the priorities of the work. We hope that this will be an important networking event, that new insights into pathogenesis and treatment will be discussed during the meeting, and that many new collaborations and friendships will be formed. Poster and oral abstract presentations by young scientists, with an emphasis on trainees, will be an important part of the conference, and world-renowned experts in the field will provide broad perspectives.

May in the Washington, D.C. area is still spring-like with mild weather, and the venue at the Bolger Center is located on a wooded campus not far from the city center by Metro or other transportation. We hope that the Second Global Conference on Myositis will be an interesting and stimulating meeting for you and that you will enjoy your stay.

We thank the members of the Steering, Scientific, and Organizing Committees who have labored selflessly for over a year to bring about this important event that we strongly believe will have a long-lasting impact on the future of myositis clinical care and research. We also thank Jeanne Torbett, the Executive Director of GCOM 2017, and her team for their outstanding efforts in coordinating this complex event, as well as all those who have generously sponsored this conference.

On behalf of the GCOM 2017 Committees,

Frederick Miller, MD, PhD, Chair, Steering and Scientific Committees

Lisa Christopher-Stine, MD, MPH, Chair, Organizing Committee

Lisa Rider, MD, Vice-Chair, Scientific Committee

Kanneboyina Nagaraju, DVM, PhD, Vice-Chair, Organizing Committee

2nd Global Conference on Myositis

May 5 - 8, 2017

Bolger Center, Potomac, MD, USA

All Times Listed are US Eastern Standard Time

Friday May 5

6:00 - 8:00 am	**Breakfast at Osgood's Dining Room in Osgood Building** *(meal ticket required)*
7:00 - 8:00 am	**Pre-Conference Registration**

Pathology Pre-Conference Workshop

(Pre-registration required)

Muscle, Skin and Lung Pathology Pre-Conference Workshop – A review of the major pathologic features in muscle, skin and lung relevant to the inflammatory myopathies and including illustrative case histories.

8:00 – 8:05 am	Welcome and Goals – *Frederick W. Miller, MD, PhD*
8:05 – 8:30 am	Classic & Atypical Findings of Muscle – *Werner Stenzel, MD*
8:30 – 8:55 am	Classic & Atypical Findings of Skin – *Inbal Sander, MD*
8:55 – 9:20 am	Classic & Atypical Findings of Lung – *Frank Schneider, MD*
9:20 – 9:45 am	**Break in Nourishment Hub**
9:45 –10:10 am	Review of Informative Cases with Medical Histories - Muscle – *Werner Stenzel, MD*
10:10–10:35 am	Review of Informative Cases with Medical Histories - Skin – *Inbal Sander, MD*
10:35–11:00 am	Review of Informative Cases with Medical Histories - Lung – *Frank Schneider, MD*

Juvenile Myositis Pre-Conference Workshop

Juvenile Myositis Pre-Conference Workshop - A session of research presentations and selected abstracts for juvenile and adult myositis investigators, trainees, and patient support group leaders to learn about important new developments in areas of research pertaining to juvenile myositis, not covered in the main meeting. Sponsored by Cure JM Foundation.

Moderators: Susan Kim, MD, MMSc and Annett van Royen-Kerkhof, MD, PhD

8:00 - 8:05 am	Welcome and Goals - *James Minow, Executive Director, Cure JM*
8:05 - 8:30 am	Update on Pathogenesis of Juvenile Dermatomyositis - *Ann M. Reed, MD*
8:30 - 8:55 am	Muscle Biopsies and Biomarkers and What They Tell Us About Juvenile Myositis Prognosis - *Lucy R. Wedderburn, MD, PhD, FRCP*
8:55 - 9:20 am	The Interferonopathies and Their Relationship to JDM - *Scott Canna, MD*
9:20 - 9:45 am	**Break in Nourishment Hub**
9:45 -10:10 am	Insights From the Genetic Muscular Dystrophies of Childhood - *Carsten G. Bonnemann, MD*
10:10 - 10:35 am	Environmental Factors for Juvenile Dermatomyositis and a National Registry in Brazil - *Adriana Sallum, MD, PhD*
10:35 - 10:55 am	Galectin-9, CXCL 10 and TNFR2, Biomarkers for Disease Activity in Juvenile Dermatomyositis Are Myositis Specific and May Reflect Highly Activated and Dysfunctional Endothelium - *Judith Wienke, MD (248)*

11:00 - 12:30 pm **Lunch at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

11:00 - 12:30 pm **Conference Registration at Franklin Ballroom in Franklin Building**

Scientific Session

12:30 - 12:40 pm Welcome and Acknowledgments - *Frederick W. Miller, MD, PhD*

12:40 - 1:30 pm Global Opportunities and Challenges for Future Neuromuscular Clinical Trials - *Robert Griggs, MD*

Risk Factors and Prevention

Moderators: Simon Rothwell, PhD and Hector Chinoy, MBBS, PhD, MRCP

1:30 - 1:50 pm Using Genetic and Genomics to Understanding Autoimmune Diseases - *Soumya Raychaudhuri, MD, PhD*

1:50 - 2:10 pm Genetics of Idiopathic Inflammatory Myopathies - *Janine Lamb, DPhil*

2:10 - 2:30 pm New Developments in the Genetics of Inclusion Body Myositis - *Thomas Lloyd, MD, PhD*

2:30 - 3:00 pm **Break and Exhibits**

3:00 - 3:20 pm Environmental Risk Factors for Adult and Juvenile Myositis from United States Registries - *Frederick W. Miller, MD, PhD*

3:20 - 3:35 pm Infectious and Respiratory Risk Factors for Idiopathic Inflammatory Myopathies - *John Svensson, PhD (100)*

Immunology and Autoantibodies

Moderators: David Fiorentino, MD, PhD and Olivier Benveniste, MD, PhD

3:35 - 3:50 pm DNA-Damaging Autoantibodies and Disease - *James E. Hansen, MD*

3:50 - 4:10 pm Autoantibody Detection and Standardization - *Masataka Kuwana, MD, PhD*

4:10 - 4:40 pm **Break and Exhibits**

4:40 - 5:00 pm Autoantibody Phenotypes in Children vs. Adults - *Sarah Tansley, MBChB*

5:00 - 5:20 pm Clinical Epidemiology and Multidimensional Analysis of Idiopathic Inflammatory Myopathies – Kuberaka *Mariampillai*

5:20 - 5:40 pm Autoantibody Lessons Learned in Asia - *Manabu Fujimoto, MD*

5:40 - 5:55 pm Validation of Commercial Myositis Line Blots - *Zoe Betteridge, PhD (101)*

5:55 - 6:10 pm Anit-NT5C1A Autoantibodies Are Frequent in Juvenile Myositis and Associated with Increased Illness Severity - *Richard Yeker, BS (102)*

6:30 - 8:30 pm **Dinner at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Saturday May 6

6:00 - 8:00 am	**Breakfast at Osgood's Dining Room in Osgood Building** *(meal ticket required)*
7:00 - 8:00 am	**Registration & Poster Set-up at Franklin Ballroom in Franklin Building**
8:00 - 8:10 am	Logistics and Announcements - *Frederick Miller, MD, PhD*

Pathology and Biomarkers

Moderators: Anthony Amato, MD and Tahseen Mozaffar, MD

8:10 - 8:30 am	Up-to-date Myopathology in Myositis, IMNM/IBM vs. Anti-Synthetase Pathology - *Werner Stenzel, MD*
8:30 - 8:50 am	Pathology and Biomarkers of Skin Disease in Dermatomyositis - *David Fiorentino, MD, PhD*
8:50 - 9:10 am	Magnetic Resonance Imaging in Inclusion Body Myositis - *Pedro Machado, MD, PhD*
9:10 - 9:30 am	Biomarkers of Interstitial Lung Disease and Extramuscular Complications - *Guochun Wang, MD, PhD*
9:30 - 9:45 am	Novel Serum Broad-Based Proteomic Discovery Analysis Identifies Proteins and Pathways Dysregulated in Juvenile Dermatomyositis (JDM) and Myositis Autoantibody Groups - *Hanna Kim, MD, MHSc (103)*
9:45 - 10:00 am	The Vasculopathy of Juvenile Dermatomyositis - *Charalampia Papadopoulou, MD (104)*
10:00 - 12:00 pm	**Break, Exhibits and Poster Session 1**
11:30 - 1:00 pm	**Lunch at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

New Developments in Defining Phenotypes

Moderators: Guochun Wang, MD, PhD and Cheilonda Johnson, MD, MHS

1:00 - 1:20 pm	New Approaches to Phenotyping Autoimmune Diseases - *Rae Yeung, MD, PhD*
1:20 - 1:40 pm	Phenotyping Muscle Dominant Disease - *Andrew Mammen, MD, PhD*
1:40 - 2:00 pm	Phenotyping Skin Dominant Disease - *Victoria Werth, MD*
2:00 - 2:20 pm	Phenotyping Lung Dominant Disease - *Dana P. Ascherman, MD*
2:20 - 2:35 pm	The EuroMyositis Registry: An International Characterisation of Myositis - *James B. Lilleker, MBChB (105)*
2:35 - 2:50 pm	Subclinical Left Ventricular Dysfunction in Juvenile Dermatomyositis Patients: A Two-Dimensional Speckle-Tracking Echocardiographic Study - *Maria de Fatima Rodrigues Diniz, MD (106)*
2:50 - 3:15 pm	**Break and Exhibits**
3:15 - 6:30 pm	Concurrent Optional Breakout Activities - *(Exhibits and Posters will be open for viewing)*
	(See optional breakout schedules below for complete details)
6:30 - 8:30 pm	**Dinner at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Saturday Optional Breakout Activities

Breakout Session #1

Questions and Answers Regarding Contemporary Myositis Concerns
Sponsored by The Myositis Association

3:15 - 4:00 pm	Myositis-specific Antibodies and What They Tell Us About the Different Forms of Myositis - *Olivier Benveniste, MD, PhD*
4:00 - 4:45 pm	Genetic and Enviromental Risk Factors in Inflammatory Muscle Disease - *Janine Lamb, PhD*
4:45 - 5:30 pm	Interstitial Lung Disease - *Sonye Danoff, MD, PhD*
5:30 - 6:15 pm	Heart Disease and Myositis - *Hector Chinoy, MBBS, PhD, MRCP*

Breakout Session #2

Visions for the Current State and Future Priorities for Research in Juvenile Myositis
Sponsored by Cure JM Foundation

Moderators: Lisa Rider,MD; Adam Huber, MD, MSc; and Cure JM Executive Director James Minow

3:15 - 3:20 pm	Brief Statement of the Objectives and Organization of the Session by the Chairs Visions for the Current State and Future Priorities for Research in Juvenile Myositis
3:20 - 3:40 pm	Priorities for the Future of Juvenile Myositis Basic Research - *Ann Reed, MD*
3:40 - 4:00 pm	Priorities for the Future of Juvenile Myositis Clinical Research - *Lauren Pachman, MD*
4:00 - 4:20 pm	Priorities for the Future of Juvenile Myositis Translational Research - *Lucy Wedderburn, MD, PhD*
4:20 - 4:40 pm	Priorities for Methodologic and Resource Needs for the Future of Juvenile Myositis Research – *Brian Feldman, MD, MSc*
4:40 - 5:00 pm	Patient Perspectives on Research Priorities for Juvenile Myositis - *Cure JM Representative Ms. Mitali Dave*
5:00 - 5:15 pm	**Restroom Break**
5:15 - 6:05 pm	Discussion of Current State and Future Priorities for Research in Juvenile Myositis **Basic Research** - *Andrew Mammen, MD, PhD and Dana P. Ascherman, MD* **Translational Research** - *Lisa Rider, MD and Annet van Royen, MD, PhD* **Clinical Research** - *Helga Sanner, MD, PhD and Angelo Ravelli, MD* **Methodologic & Resource Needs** - *Rohit Aggarwal, MD, MS; Adam Huber, MD, MSc; and James Minow*
6:05 - 6:25 pm	Summary and Conclusions

Breakout Session #3

Myositis Mentoring - A session for trainees and young investigators to learn about career options and best practices in the path to a successful research career

3:15 - 3:45 pm	Career Options for Clinical Scientists - *Paul Plotz, MD & Ingrid Lundberg, MD, PhD*
3:45 - 4:00 pm	NIH Funding Opportunities - *Marie Mancini, PhD*
4:00 - 4:15 pm	Private Funding Opportunities - *James Minow, Executive Director, Cure JM; Bob Goldberg, Executive Director, TMA*
4:15 - 5:15 pm	Grant Writing Tips - *Kanneboyina Nagaraju, PhD, DVM & Ingrid Lundberg, MD, PhD*
5:15 - 6:00 pm	Panel Discussion and Q&A - *Drs. Plotz; Lundberg; Nagaraju and Mancini*
6:30 - 8:30 pm	**Dinner at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Sunday May 7

6:00 - 8:00 am	**Breakfast at Osgood's Dining Room in Osgood Building** *(meal ticket required)*
7:00 - 8:00 am	**Registration & Poster Set-up at Franklin Ballroom in Franklin Building**
8:00 - 8:10 am	Logistics and Announcements - *Frederick W. Miller, MD, PhD*

Pathogenesis 1

Moderators: Hitoshi Kohsaka, MD, PhD and Kanneboyina Nagaraju, PhD, DVM

8:10 - 8:30 am	Neutrophil-Interferon Cross-Talk in the Pathogenesis of Systemic Autoimmune Diseases - *Mariana J. Kaplan, MD*
8:30 - 9:00 am	Autoimmune Reactions Targeting Muscle - *Ingrid Lundberg, MD, PhD*
9:00 - 9:15 am	Pathogenic Role of Anti-SRP and Anti-HMGCR Antibodies in Necrotizing Myopathies: Antibodies Induce Myofiber Atrophy and Impair Muscle Regeneration - *Yves Allenbach, MD, PhD (107)*
9:15 - 9:45 am	**Break and Exhibits**

Pathogenesis 2

Moderators: Paul Plotz, MD and Britta Maurer, MD

9:45 - 10:05 am	Muscle Regeneration and Repair - *Terry Partridge, PhD, FMedSci*
10:05 - 10:20 am	Calcium Dysregulation, Functional Calpainopathy, and Endoplasmic Reticulum Stress in Sporadic Inclusion Body Myositis - *David Amici (108)*
10:20 - 10:35 am	Distinctive Interferon-y Signature in Anti-Synthetase Myositis and Inclusion Body Myositis - *Jerome Authier, MD, PhD (109)*
10:35 - 1:30 pm	**Exhibits and Poster session 2**
11:00 - 1:30 pm	**Lunch at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Prognosis

Moderators: Adam M. Huber, MD, MSc and Lisa Christopher-Stine, MD, MPH

1:30 - 1:50 pm	Juvenile Myositis - *Helga Sanner, MD, PhD*
1:50 - 2:10 pm	Prognosis in Adult Myositis - *Olivier Benveniste, MD, PhD*
2:10 - 2:30 pm	Lung Disease as a Driver of Prognosis - *Sonye Danoff, MD, PhD*
2:30 - 2:45 pm	Mortality in Idiopathic Inflammatory Myopathy: Results from a Swedish Nationwide Population-based Cohort Study - *Marie Holmqvist, MD, PhD (110)*
2:45 - 3:00 pm	The Impact of Myositis-specific Autoantibodies on the Survival of Patients with Polymyositis and Dermatomyositis - *Jingli Shi, PhD (111)*
3:00 - 3:15 pm	**Restroom Break**

Outcome assessment

Moderators: Helene Alexanderson, PhD, RPT and Rohit Aggarwal, MD, MS

3:15 - 3:35 pm	Patient Reported Outcomes in Polymyositis, Dermatomyositis and Inclusion Body Myositis - *Lisa Christopher-Stine, MD, MPH*
3:35 - 3:55 pm	Muscle Outcome Measures - *Jean Yves Hogrel, MD*
3:55 - 4:15 pm	Juvenile Dermatomyositis Outcome Measures - *Angelo Ravelli, MD*

4:15 - 4:30 pm	Development of an Internationally Agreed-upon Optimal Dataset for Juvenile Dermatomyositis (JDM) for Clinical and Research Use - *Liza J. McCann, MBBS, MMedSc (112)*
4:30 - 4:45 pm	Manual Muscle Testing and Hand-Held Dynamometry in Patients with Inflammatory Myositis: A Reliablility and Validity Study - *Pierrette Baschung Pfister, PT, MPH (113)*
4:45 - 6:00 pm	**Exhibits and Poster Session 2**
6:30 - 8:30 pm	**Dinner at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Monday May 8

6:00 - 8:00 am	**Breakfast at Osgood's Dining Room in Osgood Building** *(meal ticket required)*
7:00 - 8:00 am	**Registration at Franklin Ballroom in Franklin Building**
8:00 - 8:10 am	Logistics and Announcements - *Frederick W. Miller, MD, PhD*

Novel therapies

Moderators: Chester V. Oddis, MD and Marianne de Visser, MD, PhD

8:10 - 8:30 am	Innovative Research Designs to Meet the Challenges of Clinical Trials for Myositis - *Brian M. Feldman, MD, MSc*
8:30 - 8:50 am	Exercise as Treatment in Juvenile Dermatomyositis - *Marco van Brussel, PhD*
8:50 - 9:05 am	Vamorolone - Clinical Studies of a New Dissociative Steroid, and Integration of Pharmacodynamic Biomarkers in the Clinical Program - *Eric Hoffman, PhD (114)*
9:05 - 9:20 am	Cannabinoid Reduces Inflammatory Cytokines in Dermatomyositis in Vitro - *Majid Zeidi, MD (115)*
9:20 - 9:40 am	New Myositis Treatments on the Horizon - *Ingrid Lundberg, MD, PhD*
9:40 - 10:10 am	**Break at Nourishment Hub**

The Way Forward

Moderators: Andrew Mammen, MD, PhD and Hector Chinoy, MBBS, PhD, MRCP

Patient research priorities

10:10 - 10:20 am	Juvenile Myositis Priorities - *James Minow, Executive Director, Cure JM*
10:20 - 10:30 am	Adult Myositis Priorities - *Bob Goldberg, Executive Director, TMA*
10:30 - 10:45 am	Discussion

Research priorities for Phenotypes

10:45 - 10:51 am	Adult Polymyositis and Dermatomyositis - *Robert Cooper, MD, FRCP*
10:51 - 10:57 am	Juvenile Myositis - *Adam M. Huber, MD, MSc*
10:57 - 11:03 am	Inclusion Body Myositis - *Mazen Dimachkie, MD*
11:03 - 11:09 am	Skin Disease - *Victoria P. Werth, MD*
11:09 - 11:15 am	Research Priorities for Lung Disease in Myositis - *Sonye Danoff, MD, PhD*
11:15 - 11:35 am	Discussion

Repositories, collaborations and beyond

11:35 - 12:00 pm	Current Adult and Juvenile Myositis Registries and Repositories - *Ingrid Lundberg, MD, PhD & Lisa Rider, MD*
12:00 - 12:20 pm	The Vasculitis Clinical Research Consortium: Lessons for Studying Rare Diseases - *Peter Merkel, MD, MPH*
12:20 - 12:40 pm	Discussion
12:40 - 12:55 pm	Brief meeting summary - *Frederick W. Miller, MD, PhD*
12:55 - 2:00 pm	**Lunch at Osgood's Dining Room in Osgood Building** *(meal ticket required)*

Oral Presentations

248 - Galectin-9, CXCL10 and TNFR2, Biomarkers for Disease Activity in Juvenile Dermatomyositis, Are Myositis Specific and May Reflect Highly Activated and Dysfunctional Endothelium

Juvenile Myositis Pre-Conference Workshop – Friday, May 5 (10:35 - 10:55 am)

Judith Wienke*[1], Felicitas Bellutti Enders[2], Luuk van den Hoogen[1], Jorre Mertens[1], Henny Otten[1], Ruth Fritsch[1], Clarissa Pilkington[3], Kiran Nistala[3], Timothy Radstake[1], Wilco de Jager[1], Lucy Wedderburn[3], Femke van Wijk[1] and Annet van Royen-Kerkhof[1]

[1]UMC Utrecht, [2]Centre Hospitalier Universitaire Vaudois, [3]Great Ormond Street Hospital

Background: Juvenile dermatomyositis (JDM) is a chronic systemic autoimmune disease in children, affecting the microvasculature in muscle and skin, causing muscle weakness and a typical skin rash. Clinical evaluation of disease activity remains challenging, as reliable and objective markers for disease activity are lacking. We identified three proteins that highly correlate with disease activity in two independent JDM cohorts: Galectin-9 (Gal-9), CXCL10 and TNF receptor 2 (TNFR2). Here, we aimed to validate their biomarker potential and assess their disease specificity. As endothelial cells are important producers of these proteins, we further explored the endothelial function and activation in patients with JDM compared to other pediatric and adult systemic autoimmune diseases.

Methods: A panel of 22 analytes, comprising previously identified disease biomarkers and proteins reflecting endothelial function and activation, was measured in serum of pediatric and adult patients with dermatomyositis, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and morphea by multiplex immunoassay. Data were analyzed using principal component analysis (PCA) and non-parametric ANOVA.

Results: Gal-9, CXCL10 and TNFR2 again potently discriminated between active disease and remission in JDM. This biomarker potential proved to be specific for (J)DM. PCA of all measured analytes, including endothelial markers, separated the patient cohort into three main disease clusters: myositis, SLE and morphea. Notably, all patients with clinical myositis clustered together, regardless of their primary diagnosis (SLE, MCTD, JDM). The proteins responsible for this separation were Gal-9, CXCL10, TNFR2, CCL2, soluble VCAM-1 and ICAM-1. This protein combination may thus be specific for myositis. Additionally, we found evidence for a highly activated endothelium in JDM during active disease. Furthermore, JDM patients had a disturbed balance between angiogenic and angiostatic proteins, including low levels of VEGF and angiopoietin-1 and high levels of soluble Tie-2, during both the active and chronic phase of the disease.

Conclusion: We confirmed the biomarker potential of Galectin-9, CXCL10 and TNFR2, which highly correlate with disease activity in JDM. Introduction of these biomarkers into clinical practice can facilitate tailor-made personalized treatment. In combination with ICAM-1, VCAM-1 and CCL2 these proteins seem specific for myositis, independent of the 'background disease'. Their high levels combined with the profile of endothelial activation and dysfunction in JDM patients points toward the involvement of endothelium in the pathogenesis of JDM.

100 - Infectious and Respiratory Risk Factors for Idiopathic Inflammatory Myopathies

Risk Factors and Prevention – Friday, May 5 (3:20 – 3:35 pm)

John Svensson[*1], Marie Holmqvist[1,2], Ingrid Lundberg[1,2] and Elizabeth Arkema[1]
[1]Karolinska Institutet (Stockholm), [2]Karolinska University Hospital (Solna)

Background: Both infections and respiratory diseases have been suggested as risk factors for Idiopathic inflammatory myopathies but the epidemiologic evidence of this association is limited.

Methods: A case-control study was performed using Swedish nationwide registers. Adults with newly diagnosed IIM were identified between 2002 and 2011 from the national patient register (NPR) by ICD-codes and from the Swedish rheumatology register (N=957). Controls were identified from the total population register and matched by age, sex and place of residence (N=9476).

Outpatient visits and hospitalizations preceding IIM diagnosis indicating infection or respiratory disease were identified from NPR. Conditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI). Sensitivity analyses were performed varying the definition of exposure, adjusting for previous health care consumption and excluding individuals with IIM related conditions (cancer, lung phenotype and connective tissue diseases).

Results: Preceding infection were more common in IIM-cases compared to controls (13% vs. 9%) and were associated with an increased risk of IIM (OR 1.5, 95% CI 1.2-1.9). Gastro-intestinal and respiratory infections were associated with an increased risk of IIM while cutaneous infections were not (Figure 1).

Preceding respiratory disease was present in 10% of IIM-cases and in 4% of the controls (OR 2.3, 95%CI 1.8-3.0). Both upper and lower respiratory diseases were associated with an increased risk of IIM (Figure 1). Variations in exposure and outcome definitions did not greatly affect the results.

Conclusion: Infections and respiratory diseases are associated with an increased risk of IIM. Whether or not this is due to casual mechanisms or other shared factors is unclear.

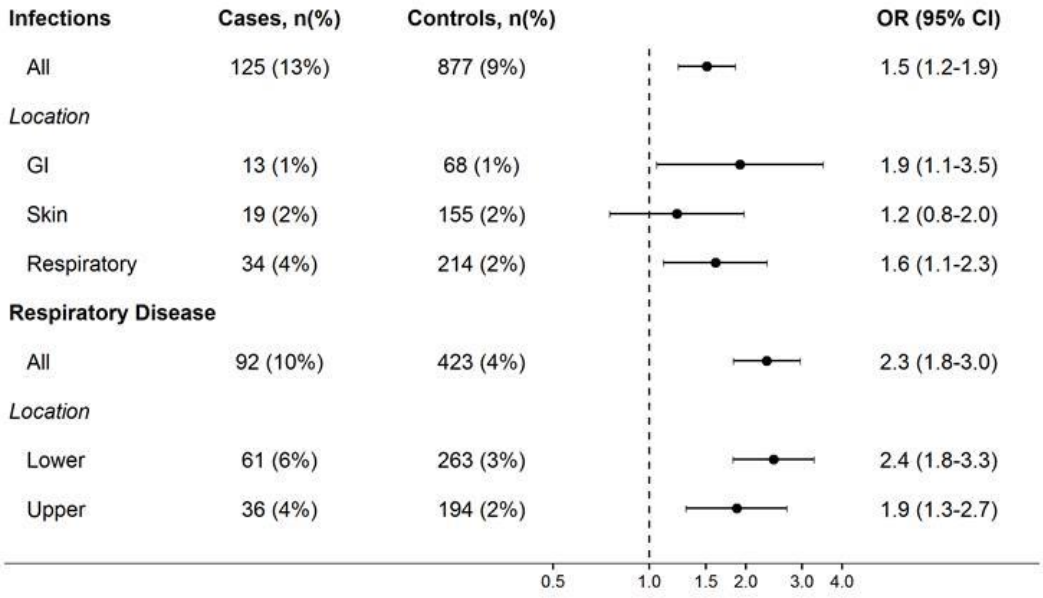

Figure 1. Odds ratios of developing Idiopathic inflammatory myopathies when having a history of hospitalization and/or outpatient visit for infections or respiratory disease (Overall and by location). Groups are not mutually exclusive. Exposures occurring within one year of IIM diagnosis were not considered. Odds ratios were estimated with the use of conditional logistic regression conditioned on the matching set.
OR = Odds ratio, CI = Confidence interval, GI = Gastro intestinal

101 - Validation of Commercial Myositis Line Blots

Immunology and Autoantibodies – Friday, May 5 (5:40 - 5:55 pm)

Zoe Betteridge*[1], Hector Chinoy[2], Paul New[3], Robert Cooper[3], Neil McHugh[1] and UKMyoNet
[1]*University of Bath,* [2]*The University of Manchester,* [3]*University of Liverpool*

Background: Myositis specific autoantibodies (MSAs) are important biomarkers in the diagnosis of myositis, helping to sub-categorize patients and predict disease complications. The current 'gold standard' method for testing MSAs is radio-immunoprecipitation (IPP), however whilst this method is highly sensitive and can concurrently screen for multiple specificities, it requires specialist facilities and training and is unsuitable for use in most routine diagnostic laboratories. Recently companies have developed commercial assays testing of a range of MSAs, with a small number of studies completed investigating their clinical utility and validity. However, due to rarity of myositis and some of autoantibody specificities, these studies have been underpowered to fully evaluate all of the MSA specificities. The aim of this study was to utilise the UKMyoNet serum-bank to validate the EuroImmun myositis line blot in comparison to IPP.

Methods: 1561 serum or plasma samples from adult myositis patients recruited to the UKMyoNet study were screened for MSAs by IPP using S^{35} labelled K562 cell extracts. Using the data from the IPP screen, 207 samples were selected for testing using the EuroImmun Myositis 4 line blots (LB). The selected samples were chosen to ensure adequate positive coverage of all the MSAs on the LBs, along with sufficient negative controls. Statistical analysis (Sensitivity, Specificity and Cohen's Kappa coefficient) were completed using 'R' software on 2 x 2 tables using IPP as the gold standard.

Results: Of the 207 samples tested by IPP and LB, there was complete agreement on 150 samples (72.5%). 57 samples had discrepancies, including 40 samples with false positives, 20 samples with false negatives on LB. Whilst the majority of discrepant samples only disagreed on one MSA, 8 samples (3.9%) had 2-5 discrepant readings between the two assays. When the specificities were analysed individually, almost high-level agreement (kappa 0.81-1.00) was found with EJ, PL12, PL7, Jo-1, PMScl (75 and/or 100), SAE and TIF. Substantial agreement (kappa 0.61-0.80) was seen with SRP, Ku, NXP2, MDA5 and Mi-2 (alpha and/or beta), whilst poor agreement (0.00) was found with OJ.

MSA	Prevalence in myositis cohort	IPP+ LB+	IPP- LB+	IPP+ LB-	IPP- LB-	Agreement	Cohen's Kappa	Sensitivity	Specificity
Anti-SAE	3.1%	10	0	0	197	100.0%	1.00	100.0%	100.0%
Anti-PL7	1.5%	11	2	0	194	99.0%	0.91	100.0%	99.0%
Anti-EJ	0.4%	7	0	2	198	99.0%	0.87	77.8%	100.0%
Anti-TIF1	7.3%	17	3	0	187	98.6%	0.91	100.0%	98.4%
Anti-PL12	1.6%	10	3	1	193	98.1%	0.82	90.9%	98.5%
Anti-Jo-1	16.1%	16	4	0	187	98.1%	0.88	100.0%	97.9%
Anti-PMScl	8.1%	14	5	0	188	97.6%	0.84	100.0%	97.4%
Anti-MDA5	2.4%	9	4	1	193	97.6%	0.77	90.0%	98.0%
Anti-Mi-2	5.9%	9	5	1	192	97.1%	0.74	90.0%	97.5%
Anti-NXP2	2.3%	9	1	6	191	96.6%	0.70	60.0%	99.5%
Anti-Ku	1.6%	15	10	0	182	95.2%	0.73	100.0%	94.8%
Anti-SRP	2.2%	11	10	0	186	95.2%	0.66	100.0%	94.9%
Anti-OJ	0.9%	0	1	9	197	95.2%	-0.01	0.0%	99.5%

Conclusion: Overall, we found good agreement between LB and IPP demonstrating the LB to be a useful tool in diagnostic laboratories with limited access to IPP. In terms of individual MSAs, the LB appears to be an adequate assay for the screening of most MSAs, especially EJ, PL12, Jo-1, SAE and TIF1. The LB however, failed to detect any of the OJ positive patients, and is therefore not recommend for the detection of this MSA. Furthermore, whilst the LB managed to detect all of the SRP and Ku positive samples, these MSAs had a reasonably high number of false positives, so a secondary confirmatory assay would be recommended for these specificities. Further validation should be undertaken on a less selected sample, ideally in a prospective study.

102 - Anti-NT5C1A Autoantibodies are Frequent in Juvenile Myositis and Associated with Increased Illness Severity

Immunology and Autoantibodies – Friday, May 5 (5:55 - 6:10 pm)

Richard Yeker*[1], Iago Pinal-Fernandez[1], Takayuki Kishi[2], Ira Targoff[3], Frederick W Miller[2], Lisa G Rider[2] and Andrew Mammen[1]

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Background: Autoantibodies (Abs) against 5Õ-Nucleotidase, Cytosolic 1A (NT5C1A) have been portrayed as a potential diagnostic aide in distinguishing inclusion body myositis (IBM) and polymyositis (PM) in adults. However, 4-21% of dermatomyositis (DM) patients also have Abs to NT5C1A. The prevalence and clinical features of anti-NT5C1A Abs in juvenile-onset myositis (IIM) patients is unknown, so we sought to examine this in a large cohort.

Methods: We screened 381 juvenile IIM patients meeting probable or definite Bohan and Peter criteria for anti-NT5C1A Abs by immunoblotting for the full length NT5C1A protein in transfected and non-transfected lysates. Clinical characteristics and HLA typing were compared between juvenile IIM patients who were anti-NT5C1A positive (Ab+) and those who were anti-NT5C1A negative (Ab-).

Results: In this cohort, 27% (103) of juvenile DM, 12% (3) of juvenile PM, and 33% (15) of juvenile overlap myositis patients tested positive for anti-NT5C1A Abs. Compared with anti-NT5C1A Ab- patients, anti-NT5C1A Ab+ juvenile IIM patients showed a similar distribution of race, gender, and association with myositis-specific Abs (Table 1). However, NT5C1A Ab was associated with anti-TIF1 Abs ($p=0.04$). The only observed clinical difference was an increased frequency of V- or shawl-sign rashes ever present (43% vs. 26%, $p=0.003$). Disease severity was increased in anti-NT5C1A Ab+ patients, based on more frequent hospitalizations ($p=0.02$), more medications used ($p<0.001$), and more treatment trials per year ($p<0.001$). Additionally, pulse steroids ($p<0.001$) and intravenous immunoglobulin therapy ($p<0.001$) were prescribed more frequently in anti-NT5C1A Ab+ than Ab- patients. The HLA alleles DRB1*07 (20% vs. 9%, $p<0.05$) and DQA1*0201 (21% vs. 7%, $p<0.01$) were present more frequently in anti-NT5C1A Ab- compared to Ab+ patients.

Conclusion: Anti-NT5C1A Abs are commonly present in juvenile DM and juvenile overlap myositis patients, and are present more frequently in patients with anti-TIF-1 Abs, but are also seen in association with other myositis specific Abs. Consistent with data in adult IIM patients, anti-NT5C1A Abs have few distinguishing clinical features in juvenile myositis, but are associated with increased illness severity marked by increased hospitalizations and receipt of additional therapy.

Table 1: Comparison of NT5C1A autoantibody positive and negative juvenile myositis patients

	NT5C1A + (n=103)	NT5C1A - (n=278)	univariate	multivariate
Age at diagnosis	9.3 (4.4)	8.8 (4.3)	0.3	0.3
Delay to diagnosis (y)	0.7 (1.0)	0.7 (1.2)	0.8	0.8
Race				
White	67% (69)	65% (182)	0.8	0.8
Black	11% (11)	17% (47)	0.1	0.1
Hispanic	7% (7)	6% (17)	0.8	0.8
Other races	16% (16)	12% (32)	0.3	0.3
Myositis autoantibodies (MSA)				
Anti-TIF1	44% (44)	31% (83)	0.02	0.04
Anti-NXP2	22% (22)	21% (58)	0.9	0.9
Anti-MDA5	22% (9)	21% (23)	0.9	0.9
Antisynthetase autoantibodies	4% (4)	4% (10)	0.8	0.9
Anti-SRP	0% (0)	3% (7)	.	.
Anti-Mi2	4% (4)	3% (9)	0.7	0.8
Anti-HMGCR	1% (1)	1% (4)	0.7	0.4
MSA negative	18% (19)	29% (78)	0.04	0.1
Clinical features at diagnosis				
Proximal weakness	96% (98)	97% (269)	0.5	0.7
Distal weakness	45% (46)	35% (91)	0.07	0.08
Dysphagia	29% (29)	23% (60)	0.2	0.4
Interstitial lung disease	6% (6)	4% (12)	0.6	0.7
Dyspnea on exertion	23% (23)	14% (36)	0.03	0.08
Arthritis	37% (37)	31% (82)	0.2	0.5
Heliotrope	81% (80)	72% (197)	0.08	0.1
Gottron's papules	83% (82)	79% (213)	0.4	0.5
Calcinosis	2% (2)	4% (12)	0.3	0.6
V- or shawl-sign rash	22% (21)	14% (37)	0.06	0.1
Early total symptom score	0.3 (0.1)	0.2 (0.1)	0.007	0.1
Muscle enzymes				
Peak creatine kinase	1229 (312-3971)	655 (252-5427)	0.9	1
Peak aldolase	10 (6-21)	10 (5-18)	0.4	0.4
Hospitalized	65% (63)	55% (147)	0.09	0.1
Number of hospitalizations	**1.6 (2.4)**	**1.1 (1.7)**	**0.02**	**0.02**
History of wheelchair use	20% (20)	18% (47)	0.6	0.5
Disease course				
Monocyclic course	15% (12)	23% (53)	0.1	0.1
Polycyclic course	18% (14)	24% (55)	0.3	0.5
Chronic continous course	67% (52)	53% (120)	0.03	0.09
Response to treatment				
Complete clinical response	22% (18)	35% (75)	0.05	0.5
Remission	15% (12)	28% (62)	0.02	0.4
Total number of medications use	**5 (3- 6)**	**3 (2- 5)**	**< 0.001**	**< 0.001**
Treatment trials per year	**2.4 (1.6)**	**1.6 (1.3)**	**< 0.001**	**0.02**
Medications received				
Oral steroids	99% (80)	100% (223)	0.5	0.3
Pulse steroids	**80% (65)**	**48% (108)**	**< 0.001**	**< 0.001**
Methotrexate	84% (68)	74% (165)	0.06	0.6
Intravenous immunoglobulin	**70% (57)**	**27% (60)**	**< 0.001**	**< 0.001**
Other DMARDs	33% (27)	21% (48)	0.03	0.1

** <0.05; ** <0.01; *** <0.001*

Dichotomous variables were represented as percentage (count) and continuous variables as mean (SD) if normally distributed or as median (Q1-Q3) if not. Logistic regression was used to compare dichotomous variables, while continuous variables were compared using linear regression. Non-normally distributed variables were log-transformed prior to regression analysis. For the multivariate analysis, variables were adjusted for age at diagnosis. Clinical features and medications were also adjusted for time of follow-up.

103 - Novel Serum Broad-Based Proteomic Discovery Analysis Identifies Proteins and Pathways Dysregulated in Juvenile Dermatomyositis (JDM) and Myositis Autoantibody Groups

Pathology and Biomarkers – Saturday, May 6 (9:30 - 9:45 am)

Hanna Kim[*1], Angélique Biancotto[2], Foo Cheung[2], Terrance O'Hanlon[3], Ira Targoff[4], Yan Huang[5], Frederick Miller[6], Raphaela Goldbach-Mansky[5] and Lisa G Rider[3]

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Background: Juvenile dermatomyositis (JDM) is a complex heterogeneous autoimmune disease. Myositis-specific autoantibodies (MSAs), present in up to 80% of JDM patients, help define distinct phenotypes within JDM and may indicate distinct pathogeneses. To define biomarkers and better understand JDM pathogenesis, aptamer-based proteomic technology was used to mine the serum proteome in a well-characterized JDM cohort.

Methods: Sera from 41 JDM patients (prevalent cases on variable treatment) were selected for relatively high disease activity (physician global activity or PGA median 4.0 (IQR 3.0-5.0)) with anti-TIF1 (n=21), NXP-2 (n=10), and MDA5 MSAs (n=10), and compared with 28 age- and gender-matched healthy controls (HC). Broad proteomic analysis of 1306 targets using SOMAscan assay of slow off-rate modified aptamers (SomaLogic, CO) generated simultaneous quantitative serum levels. Internally-controlled discovery was done by dividing into 2 independently-analyzed groups each with JDM and HC sera, stratified to evenly distribute PGA, MSA, gender, and age. Proteins with Mann Whitney U FDR corrected p values of <0.15 (JDM vs. HC) common to both groups with expression ratio of >1.3 were analyzed using Ingenuity Pathway Analysis or IPA (Qiagen, CA). Exploratory analysis of JDM sera was done by linear regression modeling of protein target levels versus PGA, also divided by MSA groups.

Results: 162 proteins met criteria and overlapped between the 2 groups of JDM and HC sera, with 69 proteins upregulated in JDM vs. HC and 93 downregulated (top dysregulated proteins in Table 1). IPA of the 53 with expression ratio of >1.3 revealed granulocyte and agranulocyte adhesion and diapedesis, IL-17 signaling, and interferon (IFN) signaling as the top dysregulated pathways in JDM. Linear regression of serum protein levels with PGA identified positive correlations with 6 proteins for JDM overall (R^2 0.10-0.20, p value 0.003-0.047), 7 proteins in MDA5 Ab group (R^2 0.46-0.72, p 0.004-0.044), 19 proteins in NXP-2 Ab group (R^2 0.40-0.76, p 0.001-0.049) and none in TIF1 MSA group. Individual somamers account for more of the variability in PGA and MSA groups compared to JDM overall, and some proteins are only identified after MSA-specific analysis (e.g. IFNB, CXCL10, and ISG15 in NXP-2 Ab group).

Conclusion: Broad quantitative proteomic analysis identified granulocyte and agranulocyte adhesion and diapedesis, as well as IL-17 and IFN signaling as the most dysregulated pathways in JDM sera. Several protein levels correlated with PGA, with more IFN-related proteins noted in the NXP-2 MSA group. While in need of confirmation in other cohorts, these proteins identified through a high-throughput screen bring to light new pathways that may be important in JDM and potentially MSA-group specific pathogenesis.

This research was supported by the Cure JM Foundation and the Intramural Research Program of the NIH, NIEHS, NHLBI, NIAID, NIAMS and the CC.

Table 1: Top Dysregulated Proteins in JDM vs. HC

A. Top Upregulated Proteins by Expression Ratio in JDM versus HC

TargetFullName	Target	UniProt	JDM/HC expression ratio	Wilcoxon FDR p value Gp 1	Wilcoxon FDR p value Gp 2
Leukotriene A-4 hydrolase	LKHA4	P09960	5.979	0.002	0.011
Stromelysin-1	MMP-3	P08254	5.773	0.001	0.003
Ubiquitin-like protein ISG15	UCRP	P05161	5.385	<0.001	<0.001
C-X-C motif chemokine 10	IP-10	P02778	5.164	0.005	0.003
Complement C3b	C3b	P01024	4.203	0.006	0.106

B. Top Downregulated Proteins by Expression Ratio in JDM versus HC

TargetFullName	Target	UniProt	JDM/HC expression ratio	Wilcoxon FDR p value Gp 1	Wilcoxon FDR p value Gp 2
6-phosphogluconate dehydrogenase, decarboxylating	6-Phosphogluconate dehydrogenase	P52209	0.422	0.012	0.059
Angiotensin-converting enzyme 2	ACE2	Q9BYF1	0.462	0.079	0.080
Creatine kinase M-type:Creatine kinase B-type heterodimer	CK-MB	P12277 P06732	0.464	0.009	0.010
Mast/stem cell growth factor receptor Kit	SCF sR	P10721	0.468	<0.001	<0.001
Growth/differentiation factor 11/8	GDF-11/8	O95390 O14793	0.478	0.006	0.075

104 - The Vasculopathy of Juvenile Dermatomyositis

Pathology and Biomarkers – Saturday, May 6 (9:45 - 10:00 am)

Charalampia Papadopoulou*[1], Ying Hong[1], Petra Krol[1], John Ioannou[2], Clarissa Pilkington[3], Hema Chaplin[2], Marietta Charakida[4], Lucy Wedderburn[3], Paul Brogan[1] and Despina Eleftheriou[1]

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Background: Vasculopathy is considered central to the pathogenesis of Juvenile Dermatomyositis (JDM). The interplay between persistent JDM-vasculopathy, traditional cardiovascular risk factors, exposure to corticosteroids, and chronic inflammation could create a perfect storm for early atherogenesis. One major hurdle to the study and detection of the vasculopathy of JDM, monitoring of its trajectory over time and contribution to excess cardiovascular disease has been a lack of non-invasive biomarkers. Recently, we described a number of methods for detecting endothelial cell components in blood which allow non-invasive assessment of vascular injury: circulating endothelial cells (CEC), and endothelial microparticles (EMP).

Methods: 74 patients recruited to the UK JDM Cohort & Biomarker Study were included; median age 10.51 (range 6.94 – 14.02) years with median disease duration of 1.5 (0.3-4.6) years. 46 (62.2%) were females. Inactive disease was defined as per modified PRINTO criteria: no skin rashes, CK≤150, CMAS≥ 48, MMT8≥78, Physician 's global assessment ≤0.2 on a visual analogue scale. CECs and MPs were identified with immunomagnetic bead extraction and flow cytometry, respectively. MP function as assessed by thrombin generation was determined using a fluorogenic assay. Cytokines and chemokines were measured by electrochemiluminiscence. Arterial stiffness was assessed using pulse wave velocity (PWV). Results are expressed as median and range.

Results: CECs were higher in JDM patients at 68 (32-128) cell/ml compared to 12 (8-21) cells/ml in 66 healthy controls, p<0.0001. Patients with active JDM had higher CEC than those with inactive JDM, p=0.02. Patients with calcinosis had higher CEC compared to patients without calcinosis, p=0.03. Newly diagnosed patients with a score ≥ 1 in the muscle biopsy vascular domain and patients with present nailfold capillary changes had also higher number of CECs. CEC counts significantly correlated with levels of inflammatory cytokines/chemokines implicated previously in JDM disease pathogenesis: interferon regulated Monocyte Chemoattractant Protein-1 (MCP-1; r=0.63, p=0.02) and interleukin-8 (IL-8; r=0.65 and p=0.01). Total circulating MP counts were also significantly higher in active JDM, 1781 (981-2616) x103/ml compared to inactive JDM, 1116 (263-1393) x103/ml, p=0.02; and healthy controls 89 (25-236) x103/ml, p=0.0001. These circulating MPs were predominantly of platelet and endothelial origin. Enhanced MP mediated thrombin generation was demonstrated in active compared to inactive JDM (p=0.03) and controls (p=0.001). Lastly, children with JDM had increased carotid-radial PWV adjusted for age compared to healthy controls (p=0.005).

Conclusion: Our data demonstrate: 1. Increased endothelial injury in children with active JDM, possibly driven by proinflammatory cytokines; 2. High levels of circulating MP with propensity to drive thrombin generation and hence occlusive vasculopathy; and 3. Increased arterial stiffness, suggestive of accelerated atherosclerosis in paediatric patients with JDM. Validation of these biomarkers in multicentre prospective studies will provide data regarding their prognostic relevance.

105 - The EuroMyositis Registry: An International Characterisation of Myositis

New Developments in Defining Phenotypes – Saturday, May 6 (2:20 - 2:35 pm)

James B Lilleker[*1,2], Jiri Vencovsky[3], Guochun Wang[4], Lucy R Wedderburn[5], Louise P Diederichsen[6], Jens Schmidt[7], Paula Jordan[8], Olivier Benveniste[9], Maria Giovanna Danieli[10], Katalin Dankó[11], Nguyen Thi Phuong Thuy[12], Monica Vazquez-Del Mercado[13], Øyvind Molberg[14], Boel De Paepe[15], Jan De Bleecker[15], Britta Maurer[16], Nicolo Pipitone[17], Neil McHugh[18,19], Zoe Betteridge[19], Paul New[20], Robert G Cooper[1,20], William E Ollier[1], Janine A Lamb[21], Niels Steen Krogh[22], Ingrid E Lundberg[23], Hector Chinoy[1,24] and On behalf of UKMYONET and all contributors to the EuroMyositis Registry

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Background: The idiopathic inflammatory myopathies (myositis) are a rare and heterogeneous group of multisystem autoimmune diseases affecting at least 250,000 patients worldwide. The rarity of myositis has hampered research efforts resulting in remarkably limited therapeutic evidence. The EuroMyositis registry was created to pool resources and expertise between myositis researchers internationally. This study examines pooled data from the registry with comparisons made between countries and diagnostic categories.

Methods: A full download of data from centres agreeing to participate (Belgium, China, Czech Republic, Hungary, Italy (two centres), Mexico, Norway, Sweden, Switzerland, United Kingdom and Vietnam) was obtained and a descriptive analysis performed. Data included demographics, clinical details and serological findings. Associations between myositis specific antibody status and clinical features (including the occurrence of malignancy, cardiac involvement and respiratory involvement) were assessed using multivariable logistic regression.

Results: Data regarding 3,196 patients from 12 centres in 11 countries were obtained, pooled and analysed. The largest contributor was the UK with 1,307 patients enrolled. Cross sectional data was held for 2,544 patients and longitudinal data (with up to 37 individual visits recorded) for the remainder. The most common diagnoses were dermatomyositis (34%), polymyositis (32%) and connective tissue disease-overlap myositis (15%). Of those with anti-synthetase syndrome (7%), 85% had myopathic muscle weakness, 86% interstitial lung disease and 58% arthritis. Corticosteroid usage was recorded in 94% overall and the most common disease modifying agents used were methotrexate (49%) and azathioprine (30%).

Overall, 43% of patients were positive for a myositis specific antibody, the most common being anti-Jo-1 antibodies (20%). Malignancy was more common in those with dermatomyositis (OR 2.21, 95% CI 1.59-3.06, $p<0.001$) and in those with anti-TIF1-gamma antibodies (OR 4.66, 95%CI 2.39-9.07, $p<0.001$). The presence of antisynthetase antibodies and anti-MDA5 antibodies were associated with interstitial lung disease (OR 8.65, 95% CI 6.74-11.10, $p<0.001$ for anti-Jo-1 antibodies; OR 6.37, 95%CI 3.71-10.94, $p<0.001$ for non-Jo-1 anti-synthetase antibodies; OR 2.71, 95% CI 1.31-5.62, $p=0.007$ for anti-MDA5 antibodies). Cardiac involvement was recorded in 9% of cases overall and was associated with the presence of anti-SRP antibodies (OR 5.08, 95% CI 2.36-10.95, $p<0.001$). A number of important research outputs produced using data from the EuroMyositis registry were identified.

Conclusion: Analysis of this large international cohort demonstrates that within the heterogeneity of myositis, clinical and serological features of the disease interact. The EuroMyositis registry has facilitated international collaborative research outputs, highlighting the benefits of harmonised data collection methodology between centres.

106 - Subclinical Left Ventricular Dysfunction in Juvenile Dermatomyositis Patients: A Two-Dimensional Speckle-Tracking Echocardiographic Study

New Developments in Defining Phenotypes – Saturday, May 6 (2:35 - 2:50 pm)

Maria de Fatima Rodrigues Diniz*[1], Adriana Maluf Elias Sallum[2], Gabriela Nunes Leal[1], Clovis A Silva[2], Katia Tomie Kozu[2], Maristela T Cunha[3], Alessandro C Lianza[1], Nadia E Aikawa[2] and Juliana C Ferreira[4]

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Background: Cardiac involvement in adult onset dermatomyositis ranges from 6% to 75%, representing one of the major causes of death. Myocardial compromise is attributed to myocarditis, fibrosis, atherosclerosis and vasculitis, mostly with a long subclinical course. Nevertheless, little is known about left ventricular (LV) function in pediatric patients with juvenile dermatomyositis (JDM), especially regarding early detection of myocardial impairment in asymptomatic individuals with preserved ejection fraction (EF). The present study aimed to identify subclinical LV systolic and diastolic dysfunction in JDM using two-dimensional speckle-tracking echocardiography (2DST), a sensitive diagnostic tool for myocardial deformation analysis.

Methods: 20 consecutive JDM patients without cardiac symptoms were enrolled during their outpatient visits, between July to December 2016. Clinical data were collected from medical records and all the echocardiograms were performed by the same experienced pediatric cardiologist, unaware of patients' conditions. A control group included 20 healthy community volunteers and informed consent was obtained from all participants.

Results: Patients and controls had similar sex (7F:13M x 10F:10M; p=0.52) and age (12.1 ± 4.7 x 12.9 ± 3.6; p = 0.54). Median of JDM duration was 7 (0-16) years and only 5/20 (25%) had active disease, as defined by PRINTO criteria (2012). The median Myositis Damage Index (MDI) severity score was 0 (0-0.142) and the median MDI extent score was 0 (0-0.209). Conventional echo revealed preserved LV EF (≥ 55%) in all individuals, although values were lower in JDM (65±5.28% x 75±5.43%; p=0.005). Classic LV diastolic function parameters were similar comparing patients and controls: mitral E/A (1.77 ± 0.28 x 1.8 ± 0.35; p = 0.6), mitral lateral e' (0.20 ± 0.035 m/s x 0.22 ± 0.041 m/s; p = 0.12), E/e' (4.73 ± 0.8 x 4.79 ± 0.77; p = 0.8). In the JDM group, 2DST identified significant reduction of LV peak systolic longitudinal strain (-18.2 ± 3.35% x -23.2 ± 3.45%; p < 0.0001) and strain rate (-1.1 ± 0.32 s^{-1} x -1.35 ± 0.27 s^{-1}; p = 0.039), as well as lower longitudinal strain rate in early diastole (1.63±0.37s^{-1}x1.97 ± 0.62 s^{-1}; p = 0.047). LV peak systolic circumferential strain (-23.6 ± 3% x -24 ± 2.97%; p = 0.63) and strain rate (-1.74 ± 0.23 s^{-1} x -1.6 ± 0.29 s^{-1}; p=0.20), as well as circumferential strain rate in early diastole (2.11 ± 0.6 s^{-1}x 1.99 ± 0.47 s^{-1}; p = 0.51) were not different comparing JDM and controls. There was a negative correlation between creatine-phosphokinase (CPK) serum levels and LV peak systolic longitudinal strain (r = - 0.5; p = 0.023). Patients with a MDI severity score > 0.027 showed lower LV peak systolic longitudinal strain than those with MDI severity score ≤ 0.027 (-15.34 ± 3.3% x -19.14 ± 2.87%; p= 0.024).

Conclusion: LV longitudinal 2DST derived strain was able to detect early systolic and diastolic dysfunction in pediatric JDM patients, even though conventional echo had failed to do so. Besides, LV peak systolic longitudinal strain impairment seems to correlate with muscular damage, as reflected by CPK serum levels. 2DST is a valuable tool for LV function evaluation in JDM, in spite of a scenario of low disease activity and damage.

107 - Pathogenic Role of Anti-SRP and Anti-HMGCR Antibodies in Necrotizing Myopathies: Antibodies Induce Myofiber Atrophy and Impair Muscle Regeneration

Pathogenesis 1 – Sunday, May 7 (9:00 - 9:15 am)

Louiza Arouche-Delaperche[1], Yves Allenbach[*2], Damien Amelin[1], Corinna Preusse[3], Vincent Mouly[4], Wladimir Mauhin[5], Gaelle Dzangue_Tchoupou[1], Laurent Drouot[6], Olivier Boyer[6], Werner Stenzel[7], Gillian Butler-Browne[4] and Olivier Benveniste[2]

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Background: Immune mediated necrotizing myopathies (IMNM) may be associated with either anti-SRP or anti-HMGCR antibodies (Abs) and the titer of these Abs is correlated with the disease activity. Patients may develop clinical muscle atrophy. Pathomechanisms involved in those damages remain to clarify.

Methods: Patient's muscle biopsies were analyzed for atrophy and regeneration by measuring the fibers size and by performing immunostaining of neonatal myosin heavy chain. To understand the role of the Abs in the physiopathology, we performed muscle cell co-culture with the Abs. Atrophy and regeneration were evaluated based on the myotube surface area as well as gene and cytokine profiles.

Results: Biopsies of muscle patients with anti-SRP$^+$ and anti-HMGCR$^+$ Abs showed a large number of small fibers. Proportion of small muscle fibers was measured using atrophy factors which was increased in anti-SRP$^+$ (533±95.9) and anti-HMGCR$^+$ Abs patients (447.8±86.8) compared to normal muscle (6.83±1.7; p=0.0005). Small fibers represented not only regenerating fibers (positive MHCneo staining), but also atrophic fibers (negative MHCneo staining).

In vitro, mature muscle cells cultured with either anti-SRP or anti-HMGCR Abs led to a significant decrease of cells surface compare to the control (116.8 ± 2 µm^2; 117.8 ± 2 µm^2 and 172.9 ±3.4 µm^2, respectively; p=0.05). This atrophy was associated with an increased the transcription of *MAFbx* and *Trim63* genes, two key regulators genes for atrophy. In addition, high levels of pro-inflammatory cytokines such TNF, IL-6 and reactive oxygen species was measured in the culture.

The presence of anti-SRP or anti-HMGCR Abs with myoblasts induced an impairment of muscle regeneration attested by low fusion index 35.3±1.5% and 34.2±2.1% respectively, compared to controls 59.5±0.8% (p=0.05). Along that line, a decrease of cell surface was observed in both conditions compare to IMNM. The impairment of regeneration was due to a defect of myoblast fusion associated with a decreased production of IL-4 and IL-13. The fusion was completely rescued by the addition of IL-4 and/or IL-13.

Conclusion: *In vitro* anti-SRP and anti-HMGCR Abs induce pro-inflammatory cytokines and muscle fibers atrophy with an up-regulation of atrogenes. The Abs also impair muscle regeneration by decreasing IL-4 and IL-13 myokynes necessary for myoblasts fusion. Together those data suggests the potential role of Abs in muscle damages occurring in IMNM

108 - Calcium Dysregulation, Functional Calpainopathy, and Endoplasmic Reticulum Stress in Sporadic Inclusion Body Myositis

Pathogenesis 2 – Sunday, May 7 (10:05 - 10:20 am)

David Amici[*1,2], Iago Pinal-Fernandez[2], Davi Mázala[1], Thomas Lloyd[3], Andrea Corse[3], Lisa Christopher-Stine[3], Andrew Mammen[2] and Eva Chin[1]

[1]University of Maryland, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), [3]Johns Hopkins University

Background: Sporadic inclusion body myositis (IBM) is the most common primary myopathy in the elderly, but its pathogenesis is still unclear. Perturbed myocellular calcium homeostasis can exacerbate many of the factors proposed to mediate muscle degeneration in IBM, such as mitochondrial dysfunction, protein aggregation, and endoplasmic reticulum stress. Calcium dysregulation in IBM may plausibly be initiated by immune-mediated membrane damage and/or abnormally accumulating proteins, but no studies to date have investigated calcium regulation in IBM patients.

Methods: Immunoblotting quantified protein expression, comparing muscle biopsies from IBM patients (n=7), dermatomyositis patients (DM; n=4), and non-myositis controls (n=5). RNA-sequencing quantified muscle biopsy transcript expression between IBM (n=9) and non-myositis control (n=7) patients, and subsequent pathway and network analysis was performed using Ingenuity Pathway Analysis™ software.

Results: Immunoblots revealed altered expression of multiple calcium-regulatory proteins in IBM compared with controls and DM, including reduction of both sarco/endoplasmic reticulum calcium ATPase (SERCA) isoforms critical for maintaining calcium homeostasis (Figure 1a). The canonical calcium signaling pathway was significantly altered compared with all stored pathways, with 54 of 183 (29.5%) of genes differentially expressed in IBM vs. controls. Using an established statistical approach to relate genes with causal transcription networks, calcium overabundance was considered a significant upstream regulator of the observed transcriptome changes. Post-hoc analyses of calcium-regulatory mRNA and protein data indicated less protein relative to transcript in IBM samples vs. controls, which we hypothesized may reflect increased protein degradation and decreased translation. Supporting this hypothesis, we observed robust increases in autolytic activation of a calcium-dependent protease, calpain-1, which is known to cleave certain calcium-regulatory proteins (Figure 2a), decreased expression of calpain-3, which is thought to prevent degradation of SERCA proteins (Figure 2b), and increased signaling for translational attenuation (eIF2_ phosphorylation) downstream of unfolded protein response activation (Figure 2c, d).

Conclusion: The data in this study provide novel insight into mechanisms by which intracellular calcium regulation is perturbed in IBM and offer evidence of pathological downstream effects.

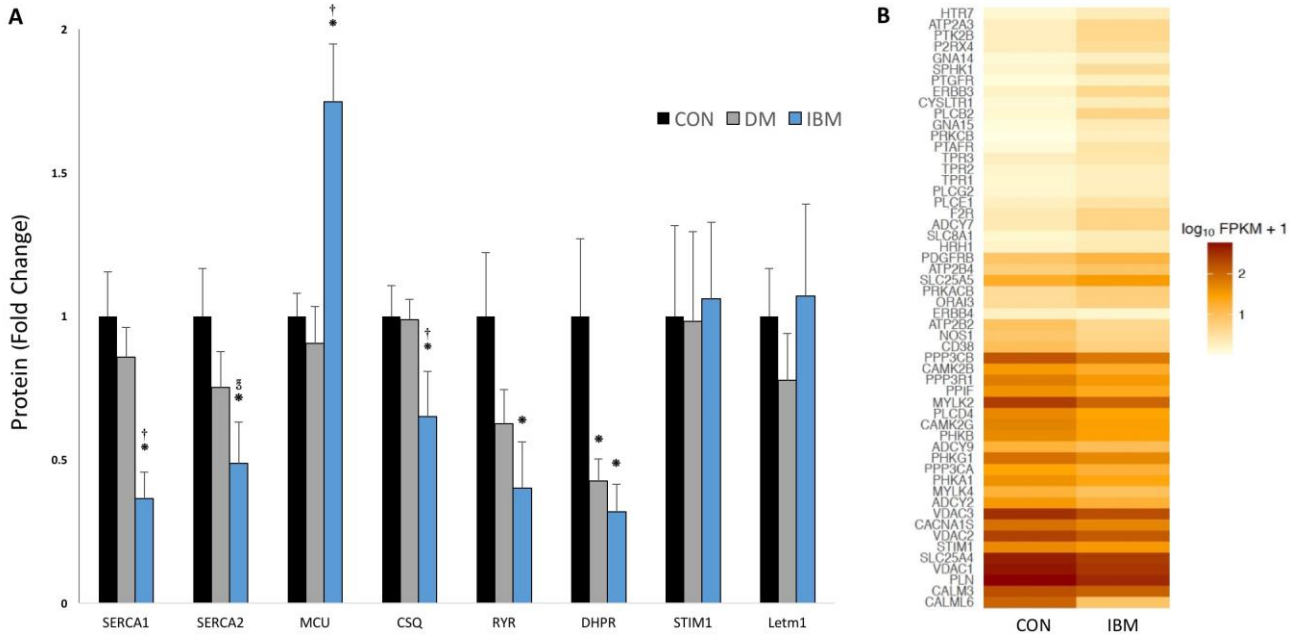


Figure 1: Altered expression of calcium-regulatory proteins and calcium signaling genes in IBM. **A.** Expression of a pre-specified panel of calcium-regulatory proteins which have been implicated in myopathy. Mean + SEM; *P<0.05 vs CON; †P<0.05 vs DM; §P=0.07 vs DM. **B.** Heat map of the 54 (of 183; 29.5%) differentially expressed genes from the KEGG calcium signaling pathway.

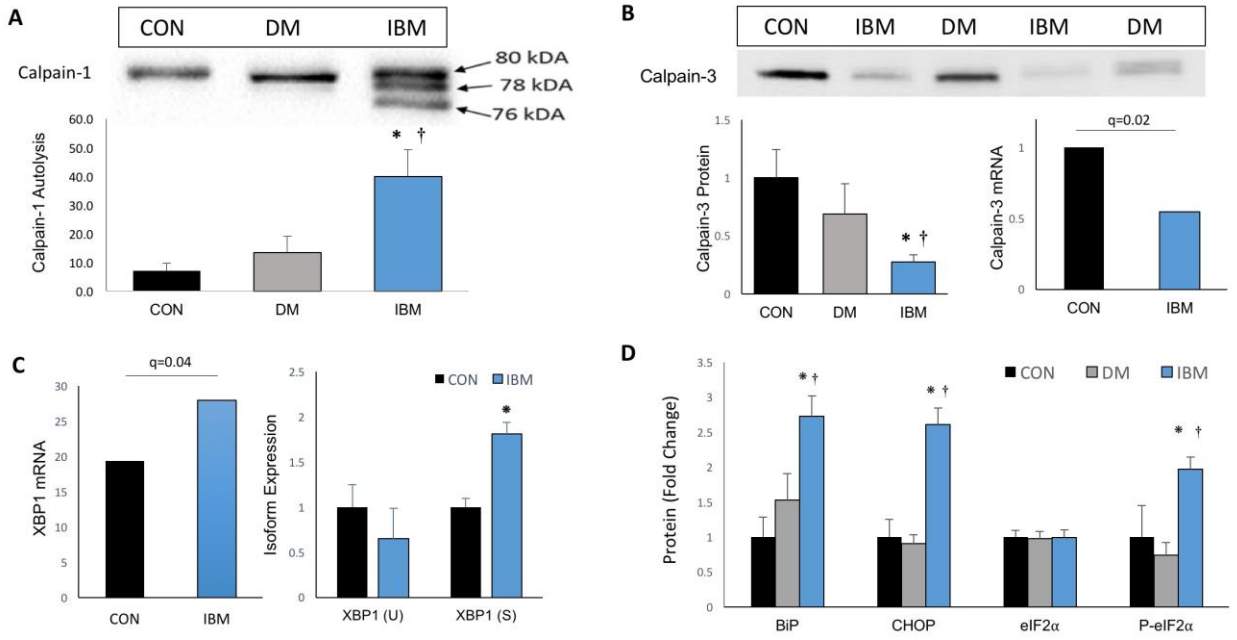


Figure 2: Functional calpainopathy and endoplasmic reticulum stress in IBM. **A.** Increased autolytic activation of calpain-1. **B.** Reduced calpain-3 mRNA and protein. **C.** XBP1 induction and preferential splicing to the XBP1s isoform, which initiates the unfolded protein response. **D.** Up-regulation of unfolded protein response effectors in IBM. Mean + SEM; *P<0.05 vs CON; †P<0.05 vs DM

109 - Distinctive Interferon-γ Signature in Anti-synthetase Myositis and Inclusion Body Myositis

Pathogenesis 2 – Sunday, May 7 (10:20 - 10:35 am)

Jerome Authier*, Muriel Rigolet, Cyrielle Hou, Jessie Aouizerate, Yasmine Baba Amer, Baptiste Periou and Romain Gherardi

Paris Est-Creteil University

Background: Primary inflammatory/dysimmune myopathies (PIDM) include (i) polymyositis (PM)/inclusion body myositis (IBM), (ii) dermatomyositis (DM), (iii) necrotizing autoimmune myopathy, and (iv) overlap myositis (OM). Since OM and IBM differ from other PIDM by the presence of major histocompatibility complex (MHC)-2 expression by myofibers, we hypothesized that they are characterized by interferon (IFN)γ-mediated inflammation.

Methods: To test this hypothesis, we evaluated by qPCR the expression of IFNg, six IFNγ–induced genes (HLA-DM, -DO, -DP, -DR, CIITA, GBP2), and IFNα-induced gene ISG15 in muscle biopsy samples from patients with IBM (n=10), DM (n=10), NAM (n=10), antisynthetase myositis (ASM, n=10), and normal muscle (n=10).

Results: Muscle IFNγ expression was found increased x50 in ASM and x80 in IBM compared to control, that of CIITA x4 and x3 (respectively) as well of HLA-DR (x5 and x8) and HLA-DM (x16 and x15). None of these genes were overexpressed in DM and NAM. ISG15 was increased x300 in DM, but not in other conditions.

Conclusion: Our results confirmed that ASM and IBM are characterized by interferong signature in contrast to DM associated with interferona/b signature.

110 - Mortality in Idiopathic Inflammatory Myopathy: Results from a Swedish Nationwide Population-based Cohort Study

Prognosis – Sunday, May 7 (2:30 - 2:45 pm)

Gerd Cecilie Dobloug[1], Ingrid E Lundberg[2,3] and Marie Holmqvist[*2,3]

[1]Oslo University Hospital, [2]Karolinska Institutet, [3]Karolinska University Hospital

Background: Previously presented studies on mortality in idiopathic inflammatory myopathy (IIM) have been small, lacked general population comparator, or were based on non-contemporary cohorts of IIM. We therefore set out to assess the risk of death following a diagnosis of IIM in a nationwide population-based cohort of IIM patients diagnosed 2002-2011.

Methods: We used nationwide fully covering health care registers to identify all individuals who were treated by a rheumatologist, neurologist, or dermatologist for IIM and who had a listing of IIM at ≥two visits within 1-12 months between 2002 and 2011. Each identified patient was matched to 10 general population comparators randomly sampled from the census register. They were then linked to the cause of death register to identify all who died during followup and from what they died.

Results: 733 individuals were included in the NPR IIM cohort; 56% were women, mean (SD) age at start of follow up was 61 (14) years. In the general population (n=7,340), the proportion women and the mean age at start of follow up was the same. The educational level was similar to the educational level in the general population; 25% spent >12 years in school. The total follow up in the study was 48,055 person years (3,726 in IIM patients, 44,329 in the general population comparators). Median (IQR) follow up in the NPR IIM cohort was 4 (6) years, and in the comparator cohort 6 (6). 228 (31%) of the NPR IIM cohort and 888 (12%) of the comparators died during follow-up. This corresponded to a crude incidence rate (95% CI) of 61.2 (43.3-79.1) deaths/1,000 person-years in IIM, and 20.0 (16-8-23.3) deaths/1,000 person-years in the comparators. The cumulative mortality at 1 year after diagnosis was 10% in IIM and 1% in the general population. At 5 years it was 24% in IIM and 7% in general population, and at ten years the proportion was 31% and 12% (figure 1). The overall incidence rate ratio (IRR) (95% CI) of death comparing the NPR cohort and its comparator, was 3.5 (3.0-4.0). When restricting the outcome to cardiovascular disease-, cancer-, infection-, and pulmonary disease- specific death we noted increased risks in all outcomes in IIM compared to the risk in the general population. When we stratified on time since diagnosis we noted an increased absolute and relative risk of death in the first year of diagnosis (table1).

Conclusion: IIM patients are still today at increased risk of death. The highest risk increase was noted within a year of diagnosis which calls for extra vigilance with respect to comorbidities during the first year of IIM diagnosis.

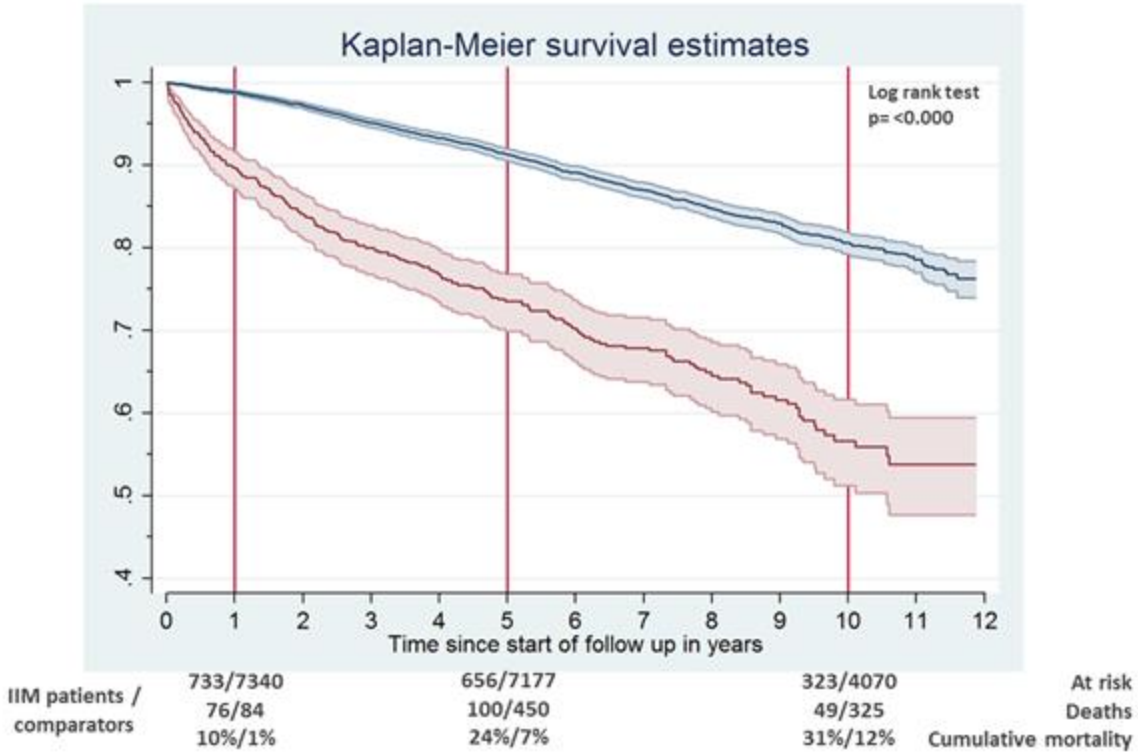


Figure 1. Kaplan-Meier curves of death in idiopathic inflammatory myopathy (IIM) (red line) and comparators (blue line).

Table 1. Hazard ratio (HR) and 95% confidence intervals (CI) comparing the risk of death in idiopathic inflammatory myopathy (IIM) patients identified in the National Patient register between 2002 and 2011 and in an individually matched general population comparator. Adjusted for matching factors (sex, residential area, year of diagnosis), age and educational level. Overall and stratified by underlying cause of death and time since IIM diagnosis.

	IIM duration categories HR (95% CI) Incidence rate/1,000 person years for death in IIM patients / comparators			
	<1 year	**1-<5 years**	**5-10 years**	**>10 years**
Overall death	10.29 (7.46-14.19) 110.8 (86.7-134.9)/ 11.6 (9.1-14.1)	3.17 (2.53-3.99) 51.2 (33.9-68.5)/19.6 (16.4-22.9)	2.56 (1.84-3.57) 48.2 (24.3-72.2)/24.7 (19.9-29.6)	2.41 (0.63-9.22) 42.1 (-3.7-87.9)/27.7 (17.9-37.5)
Cardiovascular disease	5.26 (2.80-9.87) 21.9 (11.2-32.6)/4.4 (2.9-6.0)	2.34 (1.55-3.53) 14.9 (5.5-24.2)/8.0 (5.9-10.1)	2.41 (1.38-4.19) 16.7 (2.6-30.8)/ 10.0 (7.0-13.1)	6.49 (1.05-40.02) 28.1 (-9.4-65.5)/13.4 (6.6-20.2)
Cancer	12.37 (7.38-20.75) 46.7 (31.0-62.3)/4.2 (2.7-5.6)	3.19 (2.11-4.83) 15.4 (5.9-24.9)/5.5 (3.8-7.2)	3.10 (1.60-6.01) 12.8 (0.5-25.1)/5.6 (3.3-7.9)	1.46 (0.14-14.95) 14.0 (-12.4-40.5)/ 6.7 (1.9-11.5)
Pulmonary disease	22.49 (4.23-119.68) 7.3 (1.1-13.5)/0.1 (-0.1-0.4)	5.17 (2.47-10.84) 6.1 (0.1-12.1)/0.3 (-0.1-0.8)	2.37 (0.66-8.51) 3.0 (-3.0-8.9)/1.0 (0.0-2.0)	0.00 (0.00-.) 0.0 (0.0-0.0)/0.0 (0.0-0.0)
Infections	0.00 (0.00-.) 0.0 (0.0-0.0)/ 0.1 (-0.1-0.4)	5.04 (1.16-22.00) 1.5 (-1.5-4.5)/0.3 (-0.1-0.8)	1.72 (0.32-9.37) 2.0 (-2.9-6.8)/1.0 (0.0-2.0)	0.00 (0.00-.) 0.0 (0.0-0.0)/0.0 (0.0-0.0)

111 - The Impact of Myositis-specific Autoantibodies on the Survival of Patients with Polymyositis and Dermatomyositis

Prognosis – Sunday, May 7 (2:45 - 3:00 pm)

Jingli Shi*, Shanshan Li, Hanbo Yang, Xiaolan Tian, Fang Chen, Qinglin Peng, Guochun Wang and Xin Lu
Department of Rheumatology, China-Japan Friendship Hospital

Background: In idiopathic inflammatory myopathy (IIM), a variety of myositis-specific antibodies (MSAs) have been identified. Distinct MSAs exhibit different clinical phenotypes and are associated with prognosis. The aim of study was to investigate the association of MSAs with long-term survival of patients with polymyositis (PM) and dermatomyositis (DM).

Methods: We analyzed the clinical data and outcome of patients with PM and DM who were hospitalized in the department of rheumatology of China-Japan Friendship hospital from 1994 to 2015, and evaluated the impact of MSAs on the prognosis of patients.

Results: A total of 383 PM/DM patients were followed up for 1～333 months. Cumulative survival and 10-year survival rate in all patients were 68.6% and 76.2%, respectively. The survival rate of 80.4% and 77.1% at 3 and 5 years in patients with MSAs were lower than that in patients without MSAs who had survival rate of 90.1% and 87.4% at 3 and 5 years, respectively. There was significant difference for long-term survival in all MSAs positive groups (P< 0.0001). Anti-MDA5 positive patients with 10-year survival rate of 28.7% had the worst prognosis, while, anti-HMGCR positive patients with 10-year survival rate of 100% had the best outcome within all groups. Furthermore, multivariate cox regression analysis showed that independent risk factors associated with the long-term survival of patients were age of onset, complicated with malignancies, dysphagia, rapidly progress interstitial lung disease, anti-MDA5 antibody positive, increased serum aspartate transferase and C reaction protein.

Conclusion: MSAs are strongly associated with the prognosis of patients with PM/DM. Patients with MSAs has worse 5-year overall survival than those without MSAs, which indicated that screening MSAs and aggressive treatment for PM/DM patients in very early stage of disease may improve the outcome of them.

112 - Development of an Internationally Agreed-upon Optimal Dataset for Juvenile Dermatomyositis (JDM) for Clinical and Research Use

Outcome Assessment – Sunday, May 7 (4:15 - 4:30 pm)

Liza J McCann[*1], Clarissa Pilkington[2], Adam M Huber[3], Angelo Ravelli[4], Duncan Appelbe[5], Jamie Kirkham[5], Paula Williamson[5], Amita Aggarwal[6], Lisa Christopher-Stine[7], Tamas Constantine[8], Brian Feldman[9], Ingrid E Lundberg[10], Susan Maillard[11], Pernille Mathiesen[12], Ruth Murphy[13], Lauren M Pachman[14], Ann Reed[15], Lisa G Rider[16], Annet van Royen[17], Ricardo Russo[18], Stefan Spinty[1], Lucy R Wedderburn[19] and Michael W Beresford[20]

[1]Alder Hey Children's NHS Foundation Trust, [2]Great Ormond Street Hospital, [3]IWK Health Centre and Dalhousie University, [4]Università degli Studi di Genova and Istituto Giannina Gaslini, [5]MRC North West Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool, [6]Sanjay Gandhi Postgraduate Institute of Medical Sciences, [7]Johns Hopkins University, [8]Semmelweis University, [9]The hospital for Sick Children and University of Toronto, [10]Karolinska Institutet, [11]Great Ormond Street Hospital NHS Foundation Trust, [12]Naestved Hospital, Region Zeeland, [13]Queens Medical Centre, Nottingham University Teaching Hospitals, [14]Ann & Robert H. Lurie Children's Hospital of Chicago, [15]Duke Children's Hospital, [16]NIEHS, NIH, [17]UMC Utrecht, [18]Paediatric Hospital Dr. Juan P. Garrahan, [19]UCL GOS Institute of Child Health, [20]Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool and Alder Hey Children's NHS Foundation Trust

Background: JDM is a rare inflammatory myopathy of childhood. To aid international collaboration it is essential to have a core set of data that all clinicians and researchers collect in a standardised way. The aim of this study was to reach consensus on an internationally agreed dataset for JDM for clinical use to enhance collaborative efforts.

Methods: A template developed from background work [1] was used to aid a structured multi-stage consensus process, described in detail in the published study protocol [2]. Through a Delphi process, two web-based questionnaires were distributed to members of IMACS, CARRA, PReS JDM working group, UK JDRG, and PRINTO, engaging the opinion of a large number of clinicians with JDM interests. Participants were asked to rank importance of each variable for clinical use and research on a scale of 1-9. A parallel process engaged the opinion of patients with JDM and their parents via a questionnaire ranking the same variables as 'not that important', 'important' and 'very important'; distributed via Cure JM and Myositis UK patient groups and via UK JDCBS and Netherlands clinicians. Results informed a nominal group consensus meeting of 18 internationally representative experts in juvenile and adult-onset myositis. The resulting dataset is currently being tested for feasibility in clinical practice and will be reviewed by the steering committee and partner organizations.

Results: 181 professionals completed round 1 Delphi; 146 completed round 2 (19% attrition). A simplified patient / parent questionnaire was formulated with 23 outcomes; increased to 30 outcomes after parent / patient focus groups. 301 responses were received (198 parents, 103 patients. All items were discussed at the consensus meeting, with finalization of damage items by Survey Monkey®. The resulting dataset (121 outcomes) including validated outcome measures, demographic data, clinical, laboratory and patient / parent reported outcomes, is currently being tested for feasibility in clinical practice.

Conclusion: An optimal dataset for JDM has been produced that can be incorporated into national and international efforts, including existing clinical research databases.

References:

1. McCann LJ, et al. Pediatric Rheumatology Online Journal. 2014;12:31. doi:10.1186/1546-0096-12-31.
2. McCann LJ et al. Trials. 2015;16:268. doi:10.1186/s13063-015-0784-0.

Acknowledgements: Arthritis Research UK [grant number 20417]. Members of IMACS, CARRA, PReS JDM working group, UK JDCBS, PRINTO Directors, Euromyositis Steering Committee, Cure JM, Myositis UK, JDM YP group, NIHR YP Advisory Group, COMET, OMERACT, BSPAR parent group, UK Trainee Group, CSG Consumers, administrators / note takers & advisors.

113 - Manual Muscle Testing and Hand-Held Dynamometry in Patients with Inflammatory Myositis: A Reliability and Validity Study

Outcome Assessment – Sunday, May 7 (4:30 - 4:45 pm)

Pierrette Baschung Pfister*[1], Eling D de Bruin[2], Iris Sterkele[3], Britta Maurer[4] and Ruud H Knols[5]

[1]Functioning and Rehabilitation CAPHRI Care and Public Health Research Institute, Maastricht University, [2]Institute of Human Movement Sciences and Sport, ETH, [3]Physiotherapy and Occupational Therapy, University Hospital Zurich, [4]Department of Rheumatology, University Hospital Zurich, [5]Directory of Research & Education, University Hospital Zurich

Background: Although muscle strength is one of the core measures for assessing myositis disease activity and damage, there is no consensus about the most accurate way to assess muscle strength in patients with inflammatory myopathy. MMT8 and Hand-Held Dynamometry (HHD) are both commonly used, but their psychometric properties have not yet been sufficiently studied. Thus, the aim of this study is to evaluate reliability and validity of MMT8 and HHD.

Methods: The maximum isometric strength of eight muscle groups was evaluated with MMT8 using the 10 point Kendall scale and with HHD indicating strength in Newton. To evaluate reliability of HHD, intra-class correlation coefficients (ICC), the standard error of measurements (SEM) and smallest detectable changes (SDC) were calculated. To measure reliability of MMT8 linear Cohen`s Kappa was computed for single muscle groups and ICC for total score. Additionally, correlations between MMT8 and HHD were evaluated with Spearman Correlation Coefficients.

Results: Fifty patients with established diagnosis of IM (polymyositis: 22, dermatomyositis: 17, associated myositis: 11) were included. Participants were 56±14 years old and 76% of them were female. Intra- and-inter tester reliability of HHD yielded excellent ICCs (0.75-0.97) for all muscle groups, except for inter-tester reliability of ankle extension (0.61). The corresponding SEMs% of the single muscle groups ranged from 8 to 28% and the SDCs% from 23 to 65%. MMT8 total score revealed excellent intra- and inter-tester reliability (ICC>0.9). Intra-tester reliability of single muscle groups was substantial for shoulder and hip abduction, elbow and neck flexion, and hip extension (0.64-0.69); moderate for wrist (0.53) and knee extension (0.49) and fair for ankle extension (0.35). Inter-tester reliability was moderate for neck flexion (0.54) and hip abduction (0.44); fair for shoulder abduction, elbow flexion, wrist and ankle extension (0.20-0.33); and slight for knee extension (0.08). Correlations between the two tests were low for four muscle groups (wrist, knee, ankle, and, hip extension), moderate for three muscle groups (elbow and neck flexion, hip abduction) and good for shoulder abduction.

Conclusion: The MMT8 total score is a reliable assessment to consider general muscle weakness in patients with IM but not for single muscle groups. On the contrary, our results confirm that HHD could be recommended to evaluate strength of single muscle groups. Previous studies showed that HHD has good validity compared with the gold standard isokinetic testing. The fact that the correlation between HHD and MMT8 is not satisfactory raises some doubts whether the MMT8 measures the same construct (isometric strength) as HHD.

114 - Vamorolone - Clinical Studies of a New Dissociative Steroid, and Integration of Pharmacodynamic Biomarkers in the Clinical Program

Novel Therapies – Monday, May 8 (8:50 - 9:05 am)

Eric Hoffman*[1], Kanneboyina Nagarajui[2], John McCall[1], Jesse Damsker[1], Paula Clemens[3], Michela Guglieri[4], Yetrib Hathout[5] and Kate Bushby[4]

[1]ReveraGen BioPharma, [2]Binghamton University SUNY, [3]University of Pittsburgh School of Medicine, [4]Newcastle University, [5]Children's National Medical Center

Background: Corticosteroids remain standard of care in many chronic inflammatory states, including myositis. Chronic use leads to an array of side effects that can seriously negatively impact patient quality of life, inclusive of bone fragility, mood disturbances, and sarcopenia. A new steroidal drug that was able to retain the anti-inflammatory efficacy, but lose some or all of the safety concerns of corticosteroids could be important in treatment of myositis.

Methods: A steroidal backbone was developed (delta 9,11 modification), and a lead compound selected, vamorolone (VBP15) that showed desirable dissociative activities. The drug was developed in partnership with the NIH TRND program, and has completed Phase 1 studies through foundation and government support. Phase 2 trials are underway in Duchenne muscular dystrophy, continuing under a venture philanthropy model. Innovations in clinical outcomes, biomarker outcomes, and clinical trial design have been discussed with both FDA and EMA.

Results: Phase 1 single ascending dose and multiple ascending dose studies of an oral suspension formulation in 86 adult volunteers showed excellent dose proportionality, ~3 hr half life (similar to corticosteroids), and a 'no observed adverse effect level' (NOAEL) of 20 mg/kg/day (the highest dose tested). Pharmacodynamic biomarkers of safety showed loss of side effects of corticosteroids: no changes in bone turnover markers, insulin resistance markers, immune suppression markers, and a 100-fold improvement of adrenal suppression compared to traditional corticosteroids. A 48 subject first-in-patient Phase 2a and extension studies are underway in 4-7-year-old steroid-naive DMD boys, with children showing similar pharmacokinetics as adult volunteers.

Conclusion: Vamorolone is a novel dissociative steroidal drug that has shown retention of NFkappaB inhibitory activity (transrepression), loss of receptor-mediate gene transcriptional activity (transactivation), change of mineralocorticoid receptor agonist activity of corticosteroids to an antagonist activity similar to epleronone, and loss of bone turnover and metabolic side effects of corticosteroids. The venture philanthropy model has proven to be risk tolerant, enabling innovations in clinical trial design and conduct.

115 - Cannabinoid Reduces Inflammatory Cytokines in Dermatomyositis *In Vitro*

Novel Therapies – Monday, May 8 (9:05 - 9:20 am)

Majid Zeidi[*1,2], Elizabeth S. Robinson[1,2], Paul Alves[1,2], Muhammad M. Bashir[1,2], Hee Joo Kim[1,2,3], Rui Feng[4] and Victoria P. Werth[1,2]

[1]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, [2]Corporal Michael J. Crescenz VAMC, [3]Department of Dermatology, Severance Hospital, Yonsei University College of Medicine, [4]Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania

***Background*:** Dermatomyositis is a multisystem autoimmune disease that severely decreases quality of life. Available treatments for cutaneous dermatomyositis are frequently ineffective and/or have toxic side effects. We hypothesized that ajulemic acid, an experimental therapy, could suppress production of inflammatory cytokines from immune cells of dermatomyositis patients *in vitro* and thus potentially provide a new therapeutic option for dermatomyositis. Ajulemic acid is a nonpsychoactive analog of tetrahydrocannabinol that selectively binds pro-resolving receptor on immune cells.

***Methods*:** Peripheral blood mononuclear cells were isolated from 18 dermatomyositis patients and treated with increasing concentrations of ajulemic acid: 0, 3, 10 and 15 μM. The cells were incubated with lipopolysaccharide and CpG oligonucleotides to quantify the effect of ajulemic acid on the cellular production of TNFα, interferon alpha (IFN-α), and interferon beta (IFN-b), key pathogenic cytokines in dermatomyositis. Cytokine production was measured by enzyme-linked immunosorbent assay. The mean ln(TNFα) and ln(IFN-α) values at each AJA dose were compared using a linear mixed model adjusted for within subject-correlations.

***Results*:** The lipopolysaccharide stimulated cells secreted mean (standard error) ln(TNFα) levels of 7.37 (0.38), 7.69 (0.39), 5.56 (0.39) and 4.16 (0.40) pg/ml at 0, 3, 10 and 15 μM concentrations of ajulemic acid, respectively. CpG stimulated cells treated with 0, 3, 10 and 15 μM ajulemic acid secreted mean (standard error) of ln(IFN-α) of 5.33 (0.53), 1.38 (0.57), 1.06 (0.75) and -0.03 (0.86) pg/ml. Compared to untreated cells, ajulemic acid suppressed cellular secretion of TNFα at 10 μM ($p=0.0002$) and 15 μM ($p<0.0001$) (Figure 1). Ajulemic acid also decreased IFN-α ($p\leq0.0007$) (Figure 2) and IFN-b secretion from CpG stimulated cells at all studied ajulemic acid concentrations.

***Conclusion*:** Ajulemic acid, an investigational, nonpsychoactive cannabinoid suppressed secretion of TNFα, IFN-α, and IFN-b from immune cells of dermatomyositis patients *in vitro*. These cytokines are thought to be key immunostimulatory cytokines causing cutaneous dermatomyositis. Based on the results of this study combined with data from prior animal studies and phase I clinical trials, a phase II study of ajulemic acid in 20 patients with significant dermatomyositis skin disease is currently underway. Ajulemic acid may offer patients with cutaneous dermatomyositis a new therapeutic option that is potentially more effective and less toxic than the currently available treatments.

Figure 1

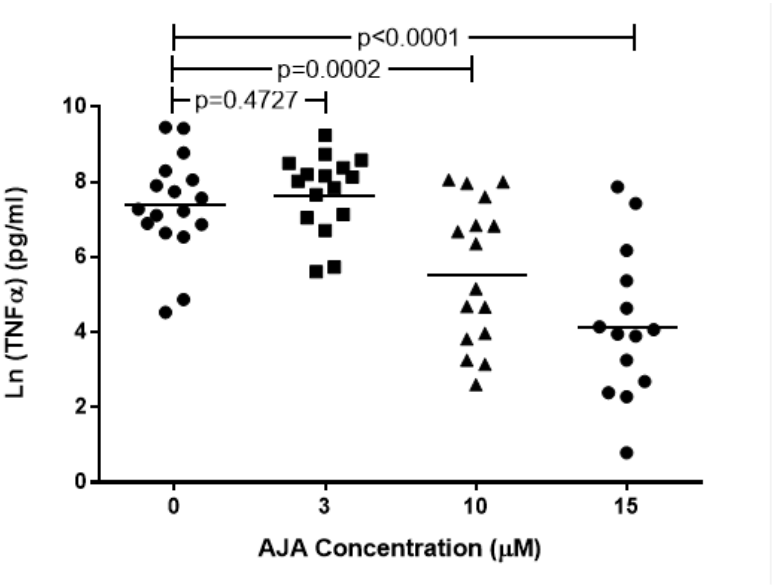
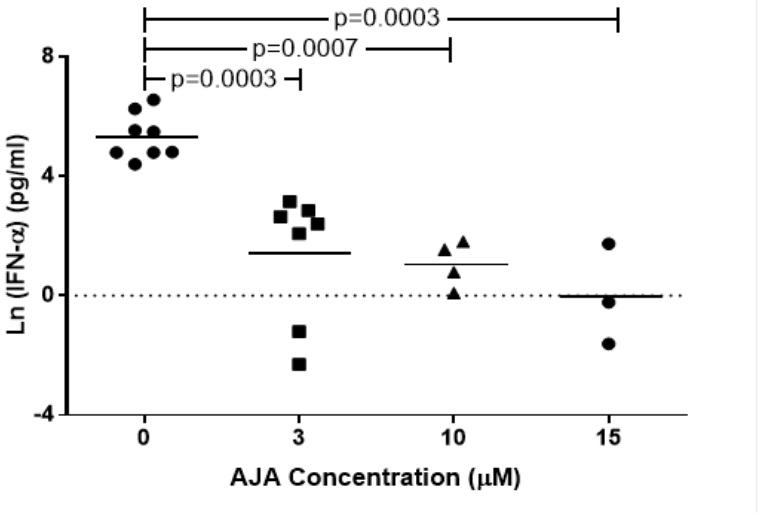


Figure 2



Poster Session 1

Saturday, May 06, 2017

10:00 AM – 12:00 PM

200 - Specific HLA II Genotypes Confer Susceptibility to Dermatomyositis in Chinese

Lin Jinming*
Capital Medical School

Background: Genetic variability in human leukocyte antigen (HLA) genes plays an important role in the pathogenesis of dermatomyositis (DM). Epidemiological studies have implicated both environmental and genetic factors in class II major histocompatibility complex (MHC) and the causes of etiology and pathogenesis for DM were unknown. The aim of this study was to investigate HLA class II associations with DM in Chinese.

Methods: 224 DM and 300 Health controls were examined for high resolution HLA-DRB1, DQA1, DQB1 genotype. 180 patients were clinical follow-up study to associate with HLA genotype. All match serological testing are needed to exam by commercial kit.

Results: This is fist using high resolution genotype analyzing definition of *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1* in Chinese population. We found *HLA-DRB1*0901* (P< 0.0001, OR = 0.31, 95% CI = 0.25-0.40); *HLA-DRB1*1201*(P< 0.0001, OR = 0.30, 95% CI = 0.24-0.39) were genetic risk for DM compared to controls. In addition, *HLA-DRB1*1201* (P=0.0006, OR =2.52, 95% CI =1.2-5.2) was highly associate with anti-MDA5 antibody. Furthermore, *HLA-DRB1*0901* (p= 0.0048, 18.26(2.42-137.5) patients had a harmful survival with Anti–Melanoma Differentiation–Associated Gene 5 Antibody–Positive DM in the Chinese population.

Conclusion: This study demonstrate that HLA alleles may be involved in susceptibility to adult DM in Chinese populations.

201 - Focused HLA Analysis in Idiopathic Inflammatory Myopathy Identifies Significant Associations of Classical HLA Alleles and Amino Acids with Autoantibody Subgroups

Simon Rothwell[*1], Hector Chinoy[2], Janine A Lamb[3], Frederick W Miller[4], Peter Gregersen[5], John Bowes[1], Lucy R Wedderburn[6], Neil McHugh[7], Zoe Betteridge[8], Jiri Vencovsky[9], Katalin Dankó[10], Vidya Limaye[11], Albert Selva-O'Callaghan[12], Lauren M Pachman[13], Ann Reed[14], Lisa G Rider[4], Øyvind Molberg[15], Olivier Benveniste[16], Pernille Mathiesen[17], Timothy Radstake[18], Andrea Doria[19], Jan De Bleecker[20], Boel De Paepe[20], Michael G. Hanna[21], Pedro Machado[22], William E Ollier[23], Leonid Padyukov[24], Terrance O'Hanlon[4], Annette Lee[5], Christopher Amos[25], Mike Seldin[26], Ingrid E Lundberg[27], Robert G Cooper[28] and The Myositis Genetics Consortium (MYOGEN)

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Background: The strongest genetic risk for the idiopathic inflammatory myopathies (IIM) lies within the major histocompatibility complex, and previous studies have confirmed a number of strong human leukocyte antigen (HLA) associations that correlate with serological subgroups of IIM. This study aimed to identify novel genetic biomarkers in this region to better understand disease pathogenesis.

Methods: We used SNP2HLA to impute classical HLA alleles and amino acids from Immunochip genotyping data. HLA imputation was undertaken in 2,566 Caucasian adult and juvenile IIM cases available through the MYOGEN consortium. Analysis was conducted on 12 serological subgroups, with autoantibodies (Abs) detected using immunoprecipitation, lineblot and/or ELISA. Results are reported for both the strongest HLA associations and amino-acid associations.

Results: We used existing HLA typing data to show high accuracy for SNP2HLA imputation. Associations with alleles of the 8.1 AH were observed for patients with anti-Jo1, anti-PMScl, anti-cN1A, and for the first time, anti-TIF1 and anti-SAE Abs. However, the most associated HLA allele on this haplotype differs between Abs. Interestingly, 79.0% of patients with anti-Jo-1 antibodies had at least one copy of HLA-DRB1*03:01, while only 27.3% of patients with anti-PL7 Abs had this allele. Anti-HMGCR and anti-Mi-2 were the only Abs tested that showed associations with HLA alleles outside of the 8.1 AH. Notably, we found no differences at the HLA-DPB1 locus between anti-PMScl and anti-Jo1 Abs, in contrast to previous studies.

The strongest association in this study was with anti-Jo-1 Abs and position 74 of HLA-DRB1 ($p=1.09x10^{-67}$), with an independent effect of position 9 of HLA-B ($p=1.58x10^{-11}$). This was markedly more significant that the strongest classical HLA association (HLA-B*08:01, $p=1.28x10^{-55}$). Position 74 of HLA-DRB1 was also significantly associated with anti-PMScl Abs, suggesting this may be a functionally important residue. An arginine at position 74 of HLA-DRB1 confers the strongest risk for both anti-Jo-1 (odds ratio, 95% confidence interval (OR), = 2.90, 2.02-4.19) and anti-PMScl Abs (OR = 16.22, 9.82-28.37).

Conclusion: The strongest associations demonstrated were with alleles of the 8.1 AH. Myositis Abs subgroups may have unique HLA associations and there is evidence that specific amino acids within the HLA region may be functionally important. Associations of clinical subgroups with the HLA locus may be explained by the strong associations with prevalent Abs. This analysis confirms that stratifying patients by serology is vital to expand our knowledge of IIM immunogenetics.

202 - HLA Class I and II Associations with Myositis Autoantibody Profiles in Caucasians with Polymyositis and Dermatomyositis: A Literature Review

Rita Volochayev*, Sara Faghihi-Kashani, Adam Schiffenbauer, Terrance O'Hanlon, Lisa Rider, Anna Jansen and Frederick Miller

NIEHS, NIH

Background: Although studies have suggested HLA associations with certain myositis-specific autoantibodies (MSAs), an overview and summary of all the current associations is lacking. Therefore, we performed a literature review to assess the data available in this area.

Methods: A PubMed search of the English language literature was performed using search terms "HLA" and "autoantibody" and "myositis" and references within discovered papers were also reviewed. Reported are significant HLA Class I (HLA-A, B and Cw) and Class II (DRB1 and DQA1) risk and protective factors associated with MSAs (anti-Jo-1, -PL-7, -PL-12, -OJ, -EJ, -KS, -Mi-2, -MJ, -SRP, -p155/140, and -HMGCR) in Caucasian polymyositis and dermatomyositis (PM/DM) patients as defined by comparisons to race-matched controls.

Results: The most described PM/DM MSA associations with HLA alleles were anti-Jo-1 (14), -PL-7 (9), -Mi-2 (8), and -SRP (6) (Table). HLA allele associations with anti-p155/140 (2), -PL-12 (2) and -HMGCR (1) were infrequent. HLA associations with other autoantibodies (including anti-OJ, -EJ, -KS and -MJ) were not described in Caucasians, although they were mentioned in other ethnic populations (including Japanese, African-Americans, and Latinos). Of interest, DRB1*07 was a risk factor for anti-PL-7, -Mi-2 and -SRP, but was protective for anti-Jo-1 autoantibodies, and DQA1*02 was a risk factor for anti-Mi-2 and anti-p155/140, but was protective for anti-Jo-1 autoantibodies.

Conclusion: This literature review revealed incomplete assessments of HLA associations with all MSAs, in particular with the rarer autoantibodies. These findings suggest that the same HLA allele(s) may serve as risk factors for one MSA while being protective for other MSAs, suggesting a possible explanation for the observed mutual exclusion and long-term stability of these autoantibody groups. Additional studies of the genetic associations with MSAs and other myositis phenotypes in different ethnic groups, and understanding mechanisms for their associations, could enhance diagnostic, prognostic and pathogenic efforts in the future.

Table. Summary of the literature review of HLA associations with myositis-specific autoantibodies in Caucasians with PM/DM

HLA-allele	Anti-Jo-1	Anti-PL-7	Anti-PL-12	Anti-Mi-2	Anti-SRP	Anti-P155/140	Anti-HMGCR
HLA-A*01	↑ (1,3)						
HLA-A1*0104		↑ (1)		↑ (1)	↑ (3)		
HLA-A1*0501	↑ (1)						
HLA-B*08	↑ (1)						
HLA-B*0801	↑ (2)						
HLA-B*5001		↑ (1)		↑ (1)	↑ (1,3)		
HLA-Cw*0304		↑ (1)		↑ (1)	↑ (1)		
HLA-Cw*04	↓ (1)						
HLA-Cw*07	↑ (3)						
HLA-Cw*0701	↑ (1)						
HLA-DQA1*0101	↓ (1)						
HLA-DQA1*0104		↑ (1)		↑ (1)	↑ (1)		
HLA-DQA1*02	↓ (3)			↑ (3,6)		↑ (3)	
HLA-DQA1*0201	↓ (1)			↑ (1)			
HLA-DQA1*0301						↑ (3,7)	
HLA-DQA1*0501	↑ (1)						
HLA-DQB1*02				↑ (6)			
HLA-DQB1*0201	↑ (3,9)						
HLA-DRB1*01	↓ (1)						
HLA-DRB1*03	↑ (1,3,4)		↑ (1)				
HLA-DRB1*0301	↑ (3,9)		↑ (1)				
HLA-DRB1*07	↓ (3)			↑ (5,6)			
HLA-DRB1*0701	↓ (1)	↑ (1)		↑ (1)	↑ (1)		
HLA-DRB1*1101							↑ (10)
HLA-DRB1*1104		↑ (1)		↑ (1)	↑ (1)		

↑: increased risk (risk factor); ↓: decreased risk (protective factor); numbers in parentheses represent the reference and only significant associations reported are listed. References for Table: 1) O'Hanlon TP et al. 2006; 2) Miller et al., 2015; 3) O'Hanlon TP et al., 2009; 4) Chinoy H et al., 2012; 5) Shamim EA et al., 2002; 6) Chinoy H et al., 2006; 7) Targoff IN et al., 2006; 8) Chinoy H et al., 2009; 9) Arnett FC et al., 1996; 10) Mammen et al., 2012

203 - Low Gene Copy Number of Total C4 and Complement C4A Deficiency Are Strong Genetic Risk Factors for Idiopathic Inflammatory Myopathies of European Ancestry

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Background: Inflammation and complement-mediated destruction of perivascular endothelium, which lead to perifascicular ischemia and degeneration of muscle fibers, are marked features in muscle biopsies of dermatomyositis. Whether complement is engaged in the breakdown of immune tolerance in idiopathic inflammatory myopathies (IIM) is being investigated. Among Caucasians, HLA-DRB1*03:01 is a risk factor for IIM and this allele tends to link to a genetic deficiency of complement C4A. There are multiple layers of diversity for complement C4, including multi-allelic copy number variation (CNV) with 2 to 10 copies of C4 genes in a diploid genome among different individuals. Each C4 genes either codes for an acidic C4A or a basic C4B protein. The objective of this study was to investigate the CNVs of total C4 and C4A deficiency as risk factors of IIM.

Patients and Methods: Our study population included 727 IIM patients of European ancestry and 945 race-matched healthy controls. CNV of complement C4 and its variants were determined by genomic Southern blot analyses and/or TaqMan-based, quantitative real-time PCR. The CNV data were validated rigorously by which the gene copy numbers (GCNs) of total C4=C4A+C4B=long C4+short C4. The differences between cases and controls were compared by t-test for mean GCNs, and by χ^2analyses for frequencies of low GCN for total C4 (2 or 3 copies), and of C4A-deficiency (C4A=0 for homozygous and C4A=1 for heterozygous deficiency).

Results: The mean GCN (±SD) of total C4 was 3.40±0.73 for IIM and 3.84±0.71 for controls, with a p-value of $9.5x10^{-35}$. The mean GCN of C4A was 1.68±0.86 for IIM and 2.10±0.77 for controls, with a p-value of $3.9x10^{-25}$. IIM patients had a consistent decrease for >0.4 copies in mean copy number of total C4 or C4A genes. By contrast, the mean GCNs of C4B were remarkably constant in both IIM and controls at 1.7±0.6 (p=0.7). Low copy numbers of total C4 were present in 57.6% of IIM and 28.3% of controls [odds ratio 3.45 (95% confidence interval 2.81-4.24), $p=5.4x10^{-34}$]. C4A deficiency occurred in 45.1% of IIM patients and 18.7% of controls ($p=2.0x10^{-31}$). Notably, the odds ratio for homozygous C4A deficiency [OR=6.64 (3.08-14.3), $p=1.5x10^{-8}$] was twice as much as heterozygous C4A deficiency [OR=3.35 (2.17-5.16), $p=1.3x10^{-7}$].

Conclusion: Differences in CNVs of total C4 and C4A but not C4B were observed between IIM patients and controls of European ancestry. C4A deficiency is one of the strongest genetic risk factors for IIM, which also manifests a dosage effect between homozygous and heterozygous deficiency. This project is being extended to larger sample size to allow IIM patient sub-group analyses, and to include subjects of other ethnicities.

204 - HLA-DQA1*05 is Associated with Interstitial Lung Disease in Caucasian Patients with Polymyositis and Dermatomyositis Independent of Autoantibody Status

Sara Faghihi-Kashani[*1], Frederick Miller[1], Terrance O'Hanlon[1], Willy Flegel[2], Sharon Adams[2], Ira Targoff[3], Chester Oddis[4], Rohit Aggarwal[4], Lisa Rider[1], Steven Ytterberg[5], Lisa Christopher-Stine[6], Sonye Danoff[7], Paul Dellaripa[8], Ejaz Shamim[9], Andrew Mammen[10] and Adam Schiffenbauer[1]

[1]NIEHS, NIH, [2]NIH, [3]University of Oklahoma Health Sciences Center, [4]University of Pittsburgh, [5]Mayo Clinic, [6]Johns Hopkins University, [7]Johns Hopkins University School of Medicine, [8]Brigham and Women's Hospital, [9]Mid-Atlantic Permanente Research Institute, [10]National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

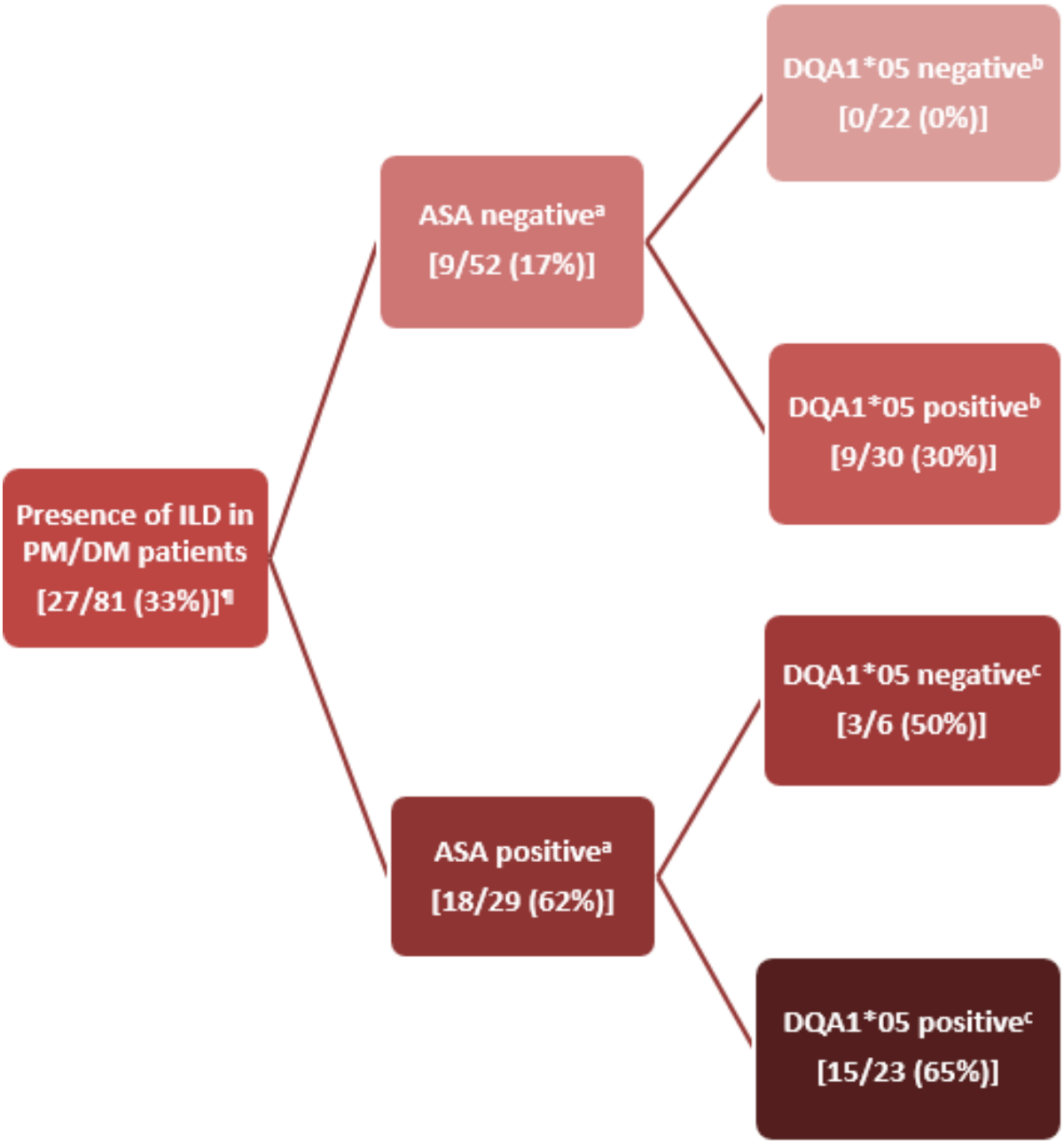
Background: Interstitial lung disease (ILD) is a frequent complication and a major contributor to mortality and morbidity in polymyositis and dermatomyositis (PM/DM). Previous studies have linked the presence of anti-aminoacyl tRNA synthetase autoantibodies (ASA) and part of the HLA 8.1 ancestral haplotype (AH8.1 = HLA-A*01, B*08, Cw*07, DRB1*0301, DQA1*05) to ILD in PM/DM patients. The aim of this study was to evaluate the contribution of HLA-DQA1*05 to the presence of ILD in Caucasian PM/DM independent of ASA.

Methods: Caucasian patients with adult-onset PM/DM per Bohan and Peter criteria and with HLA class I (A, B and Cw) and class II (DRB1 and DQA1) evaluated by sequence-specific oligonucleotide probe hybridization and priming techniques or sequencing methods were included. ILD status was determined by retrospective chart review based on imaging results and/or treating specialist's diagnosis. ASA were determined by standard immunoprecipitation methods. Pearson chi-square (Fischer exact when appropriate), multiple logistic regression tests and forward stepwise logistic methods were applied. $P < 0.05$ was considered statistically significant.

Results: Overall, 27 (33%) had ILD, 29 (36%) were positive for the presence of ASAs and 29 (36%) carried the AH8.1. ILD was associated with ASA (OR=7.82, 95%CI: 2.77 – 22.09, P<0.001) and with the AH8.1 (OR=3.57, 95%CI: 1.35 – 9.45, P=0.010) as expected. Of the five AH8.1 alleles, HLA-DQA1*05 was the only locus significantly associated with ILD after adjusting for the presence of ASA (OR=5.81, 95%CI: 1.43 – 23.57, P=0.014). This association remained significant after adjusting for the presence of the other alleles of the AH8.1 and ASA status (OR=11.94, 95% CI: 1.75-81.54, P=0.011). Chi squared tables, categorizing the cohort based on the presence or absence of each AH 8.1 allele, were used to assess the independent effect of HLA-DQA1*05 on risk of ILD conditioned on ASA status and the frequency of ILD was higher in DQA1*05 carriers, however, due to limited power, not all comparisons met statistical significance. Additionally, forward stepwise logistic analysis was performed while keeping ASA in the model regardless of step, DQA1*05 was the only HLA allele that remained in the best fit model for risk of ILD (OR=5.81, 95% CI: 1.43 – 23.57, P=0.014). Figure 1 shows the risk of ILD in Caucasian PM and DM patients based on the ASA and DQA1*05 status.

Conclusion: Our results show that HLA-DQA1*05 is associated with an increased risk of ILD in Caucasian PM and DM patients, independent of ASA and other AH8.1 alleles, implying that HLA-DQA1*05 impacts the risk of ILD independently from ASA in Caucasian PM/DM. HLA-DQA1*05 seems to be a useful test for evaluating the risk of ILD in ASA negative PM/DM patients. This suggests HLA-DQA1*05 has diagnostic, prognostic and pathogenic implications for myositis-associated ILD, that should be further assessed in additional cohorts.

Figure 1. ILD risk in Caucasian PM/DM patients based on anti-synthetase autoantibody (ASA) and HLA DQA1*05 allele status



¶ Numbers in the brackets represent those positive for the presence of ILD over the total number in that study group. Percentages are shown in parenthesis.

[a] comparison between these groups has yielded OR=7.82, P<0.001.

[b] comparison between these groups has yielded OR=19.88, P=0.007 (OR is calculated using Woolf-Haldane Correction method).

[c] comparison between these groups has yielded OR=1.87 P=0.50.

205 - Tobacco Smoking Associations with Serologic and Clinical Profiles in Patients with Polymyositis and Dermatomyositis

Sara Faghihi-Kashani*[1], Frederick Miller[1], Terrance O'Hanlon[1], Ira Targoff[2], Chester Oddis[3], Rohit Aggarwal[3], Lisa Rider[1], Steven Ytterberg[4], Lisa Christopher-Stine[5], Sonye Danoff[6], Paul Dellaripa[7], Ejaz Shamim[8], Andrew Mammen[9] and Adam Schiffenbauer[1]

[1]NIEHS, NIH, [2]University of Oklahoma Health Sciences Center, [3]University of Pittsburgh, [4]Mayo Clinic, [5]Johns Hopkins University, [6]Johns Hopkins University School of Medicine, [7]Brigham and Women's Hospital, [8]Mid-Atlantic Permanente Research Institute, [9]National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Background: Polymyositis (PM) and dermatomyositis (DM) are complex, acquired, immune-mediated diseases characterized by muscle inflammation and weakness. Recent findings suggest that environmental exposures in certain genetic backgrounds contribute to these disorders. Tobacco smoking is an important environmental factor linked to development and progression of many autoimmune diseases and is poorly understood in inflammatory myopathies. Here we explore the association between tobacco smoking and clinical and serologic phenotypes of patients with PM and DM.

Methods: Individuals with adult-onset PM or DM who fulfilled Bohan and Peter criteria for definite or probable disease with available smoking data were included. Demographic and clinical data were assessed retrospectively. Smokers were defined as smoking 1 cigarette a day for 3 or more months. Serum samples were evaluated for the presence of myositis-specific and myositis-associated autoantibodies by immunoprecipitation. Smoking frequency was adjusted for age, gender and race as appropriate. Multiple logistic regression tests were applied.

Results: The cohort included 462 patients (329 Caucasians, 97 African Americans (AA) and 36 patients with other or mixed race). There was a greater proportion of females (71%) and PM diagnosis (58%). There were 176 (38%) with a smoking history and 158 (36%) patients had interstitial lung disease (ILD). The frequency of ILD was greater in AAs than Caucasians (45% vs. 32%, P=0.030, respectively). In Caucasians, smoking history was more prevalent among PM than DM patients (adjusted OR=2.36, 95% CI: 1.48 – 3.77). The same trend was observed in AAs, but did not reach statistical significance. In Caucasians, ILD was more frequent in smokers (37%) than those who never smoked (28%), while in AAs, nonsmokers (47%) had a greater frequency of ILD than those with a smoking history (40%), but none of these associations reached significance in the adjusted models (P>0.05).

Tobacco smoking was associated with an increased risk of anti-synthetase (ASA) and anti-Jo1 autoantibodies in Caucasian patients (adjusted OR=1.96, 95%CI: 1.13 – 3.38 and adjusted OR=1.96, 95%CI: 1.10 – 3.50, respectively), whereas AAs showed an opposite trend, as ASA and anti-Jo1 frequencies were greater in nonsmokers, albeit not statistically significantly so (adjusted OR=0.45, 95%CI: 0.12 – 1.63 and adjusted OR=0.81, 95%CI: 0.19 – 3.36, respectively). In Caucasians, anti-p155/140 autoantibodies were less frequent in ever smokers (adjusted OR=0.30, 95%CI: 0.11 – 0.81). In AAs, the frequency of anti-p155/140 autoantibodies did not differ significantly between ever and nonsmokers (0% vs. 7%, P=0.23, respectively).

Conclusion: In Caucasian PM and DM patients, tobacco smoking was associated with an increased risk of PM, ILD, ASA and anti-Jo1 autoantibodies, and a decreased risk of anti-p155/140 autoantibodies. African American patients showed trends opposite to Caucasians in regard to associations of smoking with ILD, ASA and anti-Jo1 autoantibodies. Our findings suggest possible racial disparity regarding the impact of tobacco smoking on clinical and serologic phenotypes in PM and DM.

206 - Influence of Season and Residential Environment on Development of Anti-Melanoma Differentiation-associated Gene 5 Antibody-positive Polymyositis/Dermatomyositis with Interstitial Lung Disease

Naoshi Nishina[*1], Shinji Sato[2], Yasushi Kawaguchi[3], Atsushi Kawakami[4], Maasa Tamura[5], Kei Ikeda[6], Takahiro Nunokawa[7], Yoshinori Tanino[8], Katsuaki Asakawa[9], Yuko Kaneko[1], Takahisa Gono[10], Kenichi Masui[11], Masataka Kuwana[10] and JAMI investigators

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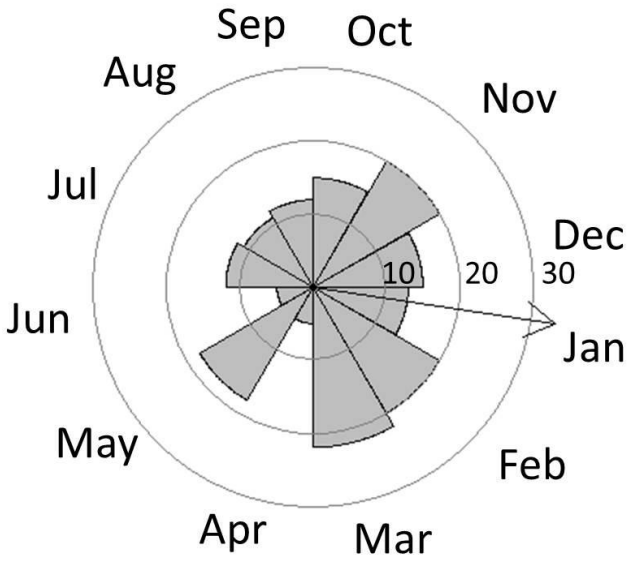
Background: Environmental triggers such as infection are considered to be involved in pathogenesis of polymyositis (PM) and dermatomyositis (DM). This study was aimed to investigate influence of season and residential environment on development of PM/DM-associated interstitial lung disease (ILD), in association with myositis-specific autoantibodies.

Methods: This study used data recorded in a multicenter retrospective cohort of Japanese patients with PM/DM-associated ILD (JAMI cohort), which involved 44 institutions across Japan. Inclusion criteria of the JAMI cohort were adult-onset, definite or probable PM/DM including clinically amyopathic DM (CADM), ILD confirmed by imaging, and availability of serum samples at diagnosis. Demographic and clinical information was retrospectively collected by chart review, and sera were subjected to autoantibody assays; ELISA for anti-melanoma differentiation-associated gene 5 (MDA5) and RNA immunoprecipitation for anti-aminoacyl-tRNA synthetase (ARS), including Jo-1, PL-7, PL-12, EJ, OJ, and KS. Seasonality was assessed by Rayleigh test for uniformity in patients who developed the disease in the past 5 years. As for residential environment, we evaluated if patients□f residence at disease onset was close to waterfront. The waterfront was defined as area within 1.75 km from sea, large river, lake, or pond calculated on the Google map.

Results: Of 498 patients enrolled, anti-MDA5 and anti-ARS antibodies were detected in 212 (42%) and 165 (33%), respectively. Since one had both antibodies, 122 (24%) were regarded as the anti-MDA5/ARS-negative group. Anti-MDA5-positive patients represented a higher frequency of CADM (76% versus 24% or 30%; P <0.01 for both comparisons), and a lower cumulative survival rate at 6 months (67% versus 97% or 96%; P <0.01 for both comparisons), compared to anti-ARS-positive or anti-MDA5/ARS-negative group. Interestingly, seasonality of the disease onset was found in anti-MDA5-positive patients (P = 0.04); onset peaked at December and January (Figure). In contrast, seasonality was not apparent in anti-ARS-positive or anti-MDA5/ARS-negative group (P = 0.73 and 0.59, respectively). The proportion of patients who resided in waterfront at disease onset was significantly higher in anti-MDA5-positive group than in anti-ARS-positive or anti-MDA5/ARS-negative group (70% versus 55% or 55%; P <0.01 for both comparisons). When freshwater and saltwater sites were assessed separately, the association of residing in the waterfront at disease onset with anti-MDA5 antibody was detected only for the freshwater site (P <0.01).

Conclusion: Anti-MDA5 antibody-positive PM/DM-associated ILD developed predominantly in autumn/winter and clustered around freshwater, suggesting roles of environmental triggers in development of the disease.

Seasonality of anti-MDA5 antibody-positive patients



Arrow: representing mean angle
p=0.04 (Rayleigh test)

207 - Infections and Medications Associated with Onset of Myositis in MYOVISION, A National Myositis Patient Registry

Nastaran Bayat[1], Payam Noroozi Farhadi[2], Jesse Wilkerson[3], Abdullah Faiq[2], John McGrath[3], Kathryn Rose[3], Lukasz Itert[4], Hermine Brunner[4], Bob Goldberg[5], Frederick Miller[2] and Lisa Rider[*1]

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Background: Myositis is a rare systemic autoimmune disease with suspected environmental and genetic risk factors, but little is known about specific infections and medications that might be triggers.

Methods: Myositis patients (362 dermatomyositis [DM], 250 polymyositis [PM], 256 inclusion body myositis [IBM], and 60 juvenile dermatomyositis [JDM]) enrolled in MYOVISION, diagnosed after 2001, and who met Bohan and Peter or Griggs criteria were included. Infections and medications received within the 12 months prior to diagnosis were queried. Significant univariable results were examined in multivariable logistic regression. Odds ratio point estimates with 95% confidence intervals and p-values were reported for each subtype pairwise comparison, after adjusting for age, gender, race, and year of diagnosis.

Results: Overall, infections in the 12 months prior to diagnosis were reported most frequently in JDM (OR 3.55: 95% CI 1.29-9.77, p≤0.05) and more frequently in DM (OR 1.86: 95% CI 1.19-2.92, p ≤0.01) and PM (OR 1.61: 95% CI 1.01-2.55, p ≤0.05) than in IBM. The same trends were seen for gastroenteritis (OR 6.80: 95% CI 1.58-29.2 JDM vs. IBM, OR 3.45:1.44-8.25 DM vs. IBM, OR 3.39:1.40-8.20 PM vs. IBM, p ≤0.01) and respiratory infections, including upper respiratory infections, influenza, pneumonia and Strep pharyngitis (OR 3.31: 95% CI 1.18-9.28 JDM vs. IBM, OR 1.76:1.07-2.89 DM vs. IBM, OR 1.82: 1.10-3.02 PM vs. IBM, p ≤0.05). Febrile illnesses were reported most frequently in JDM (OR 11.0: 95% CI 2.37-50.6, p ≤0.005), and more frequently in DM (OR 3.18: 95% CI 1.26-8.05, p ≤0.05) and PM (OR 3.49: 95% CI 1.37-8.90, p ≤0.01) than in IBM. Hepatitis, urinary tract and skin infections were reported in ≤10% of patients in each subgroup and did not differ among subgroups. Pneumonia (OR 5.31: 95% CI 2.67-10.6, p≤.0001) and antibiotic usage (OR 1.76: 95% CI 1.18-2.63, p ≤0.01) was increased only in patients with an anti-synthetase phenotype. NSAIDs were used less frequently in JDM than IBM (OR 0.25: 95% CI 0.09-0.72, p ≤0.05), and more frequently in DM and PM than JDM (OR 2.71: 95% CI 1.12-6.54 DM vs. JDM, OR 2.99:1.21-7.41 PM vs. JDM, p ≤0.05) in the 12 months prior to diagnosis. Statins were used more frequently in DM and PM than IBM (OR2.22: 95%CI 1.33-3.70 DM vs. IBM, OR 2.13: 1.26-3.58 PM vs. IBM, p ≤0.005) in the year prior to diagnosis. Diabetes medications (OR 3.35: 95%CI 1.36-8.23, p =0.005) and levothyroxine (OR 2.20: 95%CI 1.03-4.71, p =0.042) were also reported to be used more frequently in PM than IBM in the year prior to diagnosis. Use of antibiotics, blood pressure medicines and other lipid lowering agents did not differ by subgroup.

Conclusion: Variations among myositis subgroups in infections and medications received within the 12 months prior to diagnosis suggest possible risk factors for myositis. Certain infections, particularly gastrointestinal and respiratory infections within the 12 months prior to diagnosis, are increased in JDM, DM and PM patients relative to IBM. A history of pneumonia and antibiotic usage are particularly increased in patients with lung disease. Controlled studies examining these factors may be helpful in elucidating their role in disease development.

208 - Analysis of the Characteristics of Lung Involvement in 240 Children with Rheumatic Diseases

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Background: Analysis of the clinical characteristics of children with common rheumatic diseases combined with pulmonary involvement, especially in patients with interstitial lung disease (ILD)To achieve the objective of early diagnosis and treatment of the disease and improve the prognosis of the patients with pulmonary imaging and functional studies of the patients.

Methods: Retrospective analysis of 2011.1.1-2015.12.31 the first diagnosis and treatment of pediatric patients with rheumatic pulmonary involvement in 240 cases, statistical analysis of their clinical characteristics, and summarizes the pulmonary imaging. The children of common rheumatic disease is the main disease of SLE, JDM or MCTD, SS, JIA. To analyze the characteristics of various kinds of diseases combined with pulmonary diseases, and to compare the outcome of pulmonary lesions in different treatment periods. Statistical methods used SPSS20.0

Results: Among the 240 children with connective tissue disease, JDM patients had the highest proportion of ILD (57.8%), followed by systemic sclerosis (40.2%), systemic lupus erythematosus (33.1%), juvenile idiopathic arthritis (11.2%). The proportion of arthritis in ILD group was higher than those in other groups ($P < 0.05$). The positive rate of ANA, anti-Jo-l antibody, RF (all $P < 0.05$) were also higher than those in other groups. Pulmonary lesions and clinical symptoms of 170 cases with ILD improved after regular treatment. The condition of 68 patients improved after treatment, but the examination did not improve.2 patients died of respiratory failure.

Conclusion: The most common type of pulmonary involvement in CTD is chronic interstitial infiltration of the disease. Pleural and lung disease can be the initial manifestation of patients who did not make a diagnosis of CTD. Early diagnosis and treatment of these diseases is very important to improve the prognosis of the patients.

209 - Inclusion Body Myositis and Human Immunodeficiency Virus Type 1: A New Case Report and Literature Review

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Background: Prevalence of muscle disease in human immunodeficiency virus (HIV) infection is present in less than 1% of patients with AIDS. Sporadic inclusion body myositis (sIBM) is observed in few cases of patients infected by retroviruses as HIV-1 or human T-cell leukaemia virus type 1 (HTLV-1). Thus we report a new case of co-occurrence of HIV and sIBM, and make a literature review in order to determine clinical and histopathological specific features of this association.

Methods: We reported a new case of a men suffering from HIV and sIBM. Then we investigated through the National Library of Medicine's MEDLINE database for relevant literature using the key words: “IBM and HIV” or “IBM and retrovirus”. Twenty eight references were found in the English and French literature. We extracted 22 patients from 6 articles published between 1980 and 2016. The demographic and clinical characteristics, biological and histological results, treatments received and outcomes were collected.

Results: **Case description:** A Caucasian man was diagnosed HIV when he was 30 years old. He was treated with Zidovudine and Didanosine during three years and then with different antiretroviral combinations so the viral load was undetectable and CD4 cells count was 600/mm3 when the diagnosis of inclusion body myositis was confirmed. Histological finding were typical of sIBM. The treatment consisted in subcutaneous immunoglobulins during one year without any efficacy. **Literature review:** The combination of HIV and sIBM is not fortuitous since 22 patients were found in the English and French literature. They were younger than those who suffer from sIBM without HIV (median age = 47 [30 to 59]). They are mostly men with a severe rhabdomyolysis (median CPK = 1330 [465 – 10270]) and most of them were treated by Zidovudine.

Conclusion: The origin of sIBM remains controversial and the implication of viruses is unclear. First hypothesis to explain the co-occurrence of HIV and sIBM is a potential implication of immune deregulation mediated by regulatory T cell (Treg). Another hypothesis may be premature aging (evocated hypothesis in primary sIBM) and muscular degeneration due to HIV itself.

210 - Sarcoidosis in Patients with Anti-Synthetase Syndrome: Prevalence, Presentation and Outcome

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Background: Combination of anti-synthetase syndrome (aSS) with sarcoidosis is uncommon: reported only in two cases in literature. We conducted a retrospective multicentric study to investigate the prevalence, presentation and outcome of this co-occurrence.

Methods: This study received institutional review board approval and the requirement for signed informed consent was waived according to French legislation (CLEA-2016-028). It was conducted from January 2000 to November 2015 among a cohort of 352 patients with aSS from 10 French university hospitals (women/men ratio = 2.8; median age at diagnosis = 50). Fourteen patients with noncaseous granulomas on biopsy were selected from the whole cohort. Four patients did not fulfil sarcoidosis diagnosis according to ATS/ERS statement. Thus, 10 patients with sarcoidosis associated with aSS were included. Demographic, clinical and paraclinical data and outcome were collected. All computed tomography (CT) scans were reviewed by a radiologist with a 15 years' experience in diagnosis of ILD.

Results: 2.8% of patients with aSS had also sarcoidosis. The onset of diseases occurred at the median age of 50 years. Median follow-up was 49 months. Most of the time, sarcoidosis and aSS occurred simultaneously (n=7). Antibody testing revealed anti-Jo1 (n=5), anti-PL7 (n=4), or anti-PL12 (n=1). Lung CT patterns were: NSIP (n= 6), NSIP-OP (n = 2) and unclassified interstitial lung disease (n=2). Most patients had bilateral mediastino-hilar lymphadenopathies (n=7). Noncaseating granulomas were observed on bronchial (n=5), mediastinal (n=1), pleural (n=1), skin (n=2) or salivary glands biopsy (n=1). Inflammatory myopathy was confirmed on muscular biopsies (n=4/6) but muscle histology never revealed granuloma. All patients were treated with steroids. Nine patients needed immunosuppressive therapy. At the end of follow-up, no patient suffered from a worsening of muscular condition. Deterioration in respiratory status occurred in 5 patients, while 3 remained stable and only 2 improved. Pulmonary hypertension was diagnosed by right heart catheterization in two patients. One patient underwent lung transplantation and one died.

Conclusion: Sarcoidosis appears unexpectedly frequent in patients with aSS. Intrathoracic lymphadenopathies were often typical of sarcoidosis but pulmonary presentation and evolution resulted rather from aSS. Atypical clinical, imaging and biology features may lead to think such association. Both diagnoses are important to make since they involve particular monitoring and managements.

211 - Myositis-specific (MSA) and Myositis-associated Antibodies (MAA) in Patients with Idiopathic Inflammatory Myopathies (IIM) from the PANLAR Myositis Study Group

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Background: Dermatomyositis (DM) and polymyositis (PM) are forms of IIM that involve skeletal muscle as well as many other organs. As in other systemic rheumatic diseases the IIM are characterized by the production of various autoantibodies that are of diagnostic and prognostic help because they are frequently associated with specific clinical subgroups. The objective of the study was to determine the frequency of anti-nuclear (ANAs), myositis specific (MSA) and myositis associated autoantibodies (MAA) in Latin-American patients with IIM from the PANLAR Myositis Study Group.

Methods: Serum samples from 210 unselected patients with IIM were included in the study: 112 from México, 46 from Colombia, 20 from Peru, 16 from Dominican Republic, 10 from Argentina and 6 from Guatemala. DM and PM were diagnosed according to the Bohan and Peter criteria**.** ANAs were detected by IIF on HEp-2 cells (Antibodies Inc., Davis, CA, USA), MSA and MAA were tested by a line immunoassay method in serum samples from Mexico, Dominican Republic, Peru, Argentina and Guatemala (Euroline Myositis Antigens Profile 3) (Euroimmun, Luebeck, Germany); in serum samples from Colombia MSA and MAA were tested by another immunoassay method "DIA Spot Polymiositis/ Scleroderma IgG" (DIASource-Belgium). In addition, anti-HMGCR was detected with an addressable laser bead immunoassay (ALBIA Luminex).

Results: Of the 210 IIM patients, 139 (66%) had DM, 59(28%) PM and 12 (5.7%) JDM. Mean age 43.5 (6-79 years), 157 (74.8%) were female and 53 (25.2%) were male. The frequency of ANAs was 59%, being more frequent in Colombia (86%) and Mexico (55%) than in Argentina (50%), Dominican Republic (43.8%), Peru (45%) and Guatemala (33.3%). The most frequent patterns were speckled (78.3%) and cytoplasmic (7.3%).

The general frequency of MSA was Mi-2 (28%), Jo-1 (11.9%), HMGCR (6.3%), SRP (5.7%), PL-12 (3.3%), PL-7 (1.9%), EJ (1.2%), and OJ (0.8%). The most frequent MSA was Mi-2 being more frequent in serum samples of Colombia (37%), Mexico (31%), Argentina (30%), Peru (15%) and Dominican Republic (12%). Anti-Jo-1 was present in 17% of serum samples from Mexico and in 10% of serum samples from Argentinian and Colombian patients. Furthermore, in the sera from Peru, Dominican Republic and Guatemala anti-Jo1 was absent.

The general frequency of MAA was Ro-52/TRIM21 (17.6%), PM-Scl75 (6.6%) and Ku (3%). The most frequent MAA was Ro-52/TRIM21: in Argentinian patients, it was 30%; in Mexican patients, 24%; in Dominican Republic patients, 18.8%; and in Peruvian patients, 5%. However, anti-Ro52/TRIM21 was not detected in sera from Guatemala.

Conclusion: This is the first study of ANAs, MSA and MAA from five countries from the PANLAR myositis study group. We observed a general prevalence of 59% of ANAs by IIF, more frequently in Colombia (86%) and Mexico (55%). In relation to MSA and MAA, anti-Mi-2 was the more frequent (28%), a finding that is in contrast to studies in other geographic areas in which anti-synthetase antibodies tend to be more common. In general, we found some differences in the presence of these two groups of antibodies in the Latin-American countries included in this study.

212 - The Spectrum and Clinical Significance of Myositis-specific Autoantibodies in Chinese Patients with Idiopathic Inflammatory Myopathy

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Background: Myositis-specific autoantibodies (MSAs) are crucial in identifying unique clinical subtypes, treatment outcomes and prognosis of idiopathic inflammatory myopathy (IIM). The aim of this study is to analyze the prevalence of MSAs and to elucidate their associations with clinical features in Chinese polymyositis (PM) and dermatomyositis (DM) patients.

Methods: Twelve subsets MSAs including anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1 , anti-SRP, anti-Jo-1, anti-PL-7 , anti-PL-12 , anti-EJ , anti-OJ and anti-HMGCR antibodies were detected. Six hundreds and four PM/DM patients were enrolled in the retrospective study. Clinical features and laboratory data were collected by a systemic review in detail for 497 patients. The frequency of MSAs and the correlations between MSAs and clinical phenotypes in PM/DM patients were calculated by SPSS 21.0.

Results: The positivity of MSAs was 64.6% in PM/DM patients. Anti-aminoacyl-transfer RNA synthetases (Anti-ARS), anti-TIF1-γ and anti-MDA5 were the three highest MSAs in IIM patients. DM patients had higher frequency of MSAs in comparison with those in PM patients (68.5% vs 52.9%, p=0.001). Anti-TIF1-γ (19.3%) was the most frequently detected in DM, and the frequency of anti-ARS (20.3%) was the highest in PM. Anti-MDA5 (OR 3.544, 95%CI 1.636-7.679, p=0.001) was proved to be a risk factor for Gottron's sign and there was no MSA subtype associating with cutaneous ulcer. Patients with anti-NXP2 or anti-SRP seemed had more frequency of muscle weakness but they were not independent factors. Patients with anti-NXP2 were more likely to develop calcinosis (OR 11.922, 95%CI 3.006-47.289). Anti-TIF1-γ (OR 2.993, 95%CI 1.729-5.180), anti-SRP (OR 2.723, 95%CI 1.196-6.201) and anti-NXP2 (OR 2.596, 95%CI 1.116-6.041) could increase the tendency of dysphagia in IIM patients. In contrast, anti-MDA5 (OR 0.285, 95%CI 0.120-0.676) might decrease the prevalence of this manifestation. Interstitial lung disease (ILD) was observed more frequently in patients with anti-EJ (OR 13.042, 95%CI 1.565-108.697), anti-Jo-1 (OR 8.870, 95%CI 3.032-25.947), anti-MDA5 (OR 3.326, 95%CI 1.633-6.777). On the contrary, anti-Mi-2 (OR 0.325, 95%CI 0.134-0.793), anti-TIF1-γ (OR 0.175, 95%CI 0.089-0.346) and anti-HMGCR (OR 0.071, 95%CI0.009-0.556) were revealed as protective factors of ILD. Anti-TIF1-γ was an independent risk factor in cancer-associated myositis (OR 5.251, 95%CI 2.308-11.947).No MSAs were correlated with cardiac manifestation.

Conclusion: Patients with PM/DM had a high frequency of MSAs. They were independent factors of different rash and clinical phenotypes, which were crucial complications in IIM development. These indicated MSAs could be useful biomarkers in monitoring the extramuscular features in IIM patients.

213 – Myositis-specific Antibodies Associated with Cancer in Patients with Polymyositis and Dermatomyositis: A Longitudinal Study in a Large Cohort of Chinese Patients

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Background: Dermatomyositis (DM) and polymyositis(PM) have been extensively reported to be associated with increased risk of cancer. However, the association between variant myositis specific antibodies (MSAs) and cancer-associated myositis (CAM) has not been systematically clarified.

Methods: Sera from 436 polymyositis/dermatomyositis (PM/DM) patients were tested for MSAs. The cancer risk with different MSAs was estimated by standardized incidence ratio (SIR). The temporal relationship between PM/DM and cancer diagnoses, as well as the correlation between the clinical course of myositis and cancer in patients with different MSAs were also evaluated.

Results: Compared with the general Chinese population, PM/DM patients with anti-TIF1-γ antibodies (SIR=17.82, 95% CI: 12.26 to 25.00); anti-NXP2 antibodies (SIR=8.84, 95% CI: 1.77 to 25.92); or anti-SAE1 antibodies (SIR=12.46, 95% CI: 2.49 to 36.54), or who were MSA-negative (SIR=3.46, 95% CI: 1.39 to 7.13) faced an increased risk for cancer. There was no association between specific MSA subtypes and certain types of cancer. A close temporal relationship between PM/DM and cancer diagnoses was identified in the patients carrying anti-TIF1-γ, as well as other MSAs. In addition, a parallel between clinical course of PM/DM and cancer was observed in patients from various MSA subgroups. There were no prognostic differences among the CAM patients from different MSA subgroups. However, patients with cancer developing within 1 year of myositis diagnosis had a shorter survival time than those suffered from cancer beyond 1 year of myositis (11.5 vs. 40.5 months, p=0.02).

Conclusion: Our large cohort study indicates that, besides anti-TIF1-γ, other MSAs including anti-NXP2 and anti-SAE1 are also associated with cancer in PM/DM patients. Moreover, these CAM-associated MSAs can be used as clues that offer insight into the pathogenesis of paraneoplastic myositis.

214 - Comparison of Clinical Characteristics and Laboratory Parameters of Patients with Dermatomyositis-specific Autoantibodies and Autoantibody-negative Patients

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Background: Myositis is a systemic autoimmune connective tissue disease in which autoantibodies are of great importance. Aim of the authors was to determine the frequency of dermatomyositis-specific autoantibodies (anti-Mi-2, anti-transcriptional intermediary factor 1 gamma, anti-nuclear matrix protein 2, anti-small ubiquitin-like modifier activating enzyme, anti-melanoma differentiation-associated gene) in a Hungarian myositis-population. Another aim was to compare the clinical features of these patients with the characteristics of patients without any myositis-specific antibodies serving as control group.

Methods: Peripheral blood samples were taken from 330 myositis patients treated at the Department of Clinical Immunology, Institute of Internal Medicine, University of Debrecen. Sera of patients were stored at -20°C. Anti-Mi-2 was detected by membrane-fixed immuno-blot. The other four antibodies were detected by radiolabelled protein immunoprecipitation. Retrospective analysis of clinical findings of the patients has been introduced by revision of the medical history.

Results: 121 patients had myositis-specific antibody positivity, 48 of them were dermatomyositis-specific antibody positive. With the exception of anti-Mi-2 and anti-SAE the frequency of these autoantibodies was lower in the investigated Hungarian population than in other international studies. 209 patients had no antibody, 48 patients of these patients served as control group in the comparison. The initial manual muscle testing score of the patients with dermatomyositis-specific autoantibody positivity was significantly lower than the manual muscle testing score of negative patients (41.54±13.87 vs. 53.19±12.54, retrospectively; $p<0.001$). The comparison of the initial creatine kinase muscle enzyme levels also supported this result (5402.92±10213.48 vs. 2086.06±4415.47, retrospectively; $p<0.001$). Interestingly muscle pain during disease was significantly more frequent in patients without any antibody. The frequency of most of the classical skin lesions (face erythema: $p=0.041$, heliotrope rash: $p=0.038$, Gottron's papule: $p=0.04$, periorbital edema: $p=0.049$, scarf sign: $p=0.018$) was significantly higher in patients with dermatomyositis-specific autoantibodies. As extramuscular manifestation, definitive pulmonary fibrosis was significantly more frequent ($p=0.031$) in patients with dermatomyositis-specific autoantibodies.

Conclusion: It has to be underlined, as it was confirmed in other studies, that the frequency of these antibodies is not always the same because of the various populations investigated worldwide. Authors draw attention to the acute and severe onset of the patients presented with dermatomyositis-specific autoantibodies in contrast to the patients without any myositis-specific antibodies. Antibodies are useful markers for distinct clinical subsets and for predicting the prognosis of myositis.

215 - The Sensitivity and Specificity of Enzyme-linked Immunosorbent assays (ELISA) Compared to Immunoprecipitation for Myositis Autoantibodies

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Background: Anti-Jo-1, anti-SSA (Ro), and anti-SSB (La) autoantibodies (Abs) are frequently present in the serum of myositis patients. For both diagnostic and prognostic reasons, developing sensitive and specific autoantibody tests is important. The current gold standard for myositis Abs is immunoprecipitation (IP), which is labor intensive, slow and expensive. Enzyme-linked immunosorbent assays (ELISA) overcome these barriers, however, concerns about their sensitivity and specificity have been raised. We sought to determine how ELISA tests compared to IP for selected Abs in sensitivity and specificity in patients with idiopathic inflammatory myopathies.

Methods: Autoantibody results were obtained on 308 adult and juvenile patients meeting probable or definite Bohan and Peter criteria for polymyositis or dermatomyositis (PM/DM). For each patient, samples were tested by both ELISA at the NIH clinical lab and IP at Oklahoma Medical Research Foundation. For patients for whom multiple ELISA tests were performed, results were used from only the test which occurred closest in date to the IP test.

In September of 2001, the ELISA kit was changed from the legacy Bio-Rad ELISA kit to the Bio-Rad 96EP ELISA kit. In August of 2011, the legacy instrument used to administer the ELISA test was replaced by a Magellan Biosciences Dynex instrument. Separate analyses were run for each of these combinations of machinery and reagents. ELISA results from September 2001 and August 2011 were excluded from analysis because the exact days on which the kit and instrument changes took place are not available. Sensitivity and specificity were calculated for the ELISA test using IP as the gold standard.

Results: For all patients, the ELISA sensitivity and specificity for anti Jo-1 were 78.3% and 98.2% (n=291) respectively. The change in ELISA kit increased sensitivity from 72% to 90% and specificity from 97% to 100% (n=246). The change in instrumentation further improved sensitivity from 90% to 100% (n=127) and maintained the specificity of 100%.

The overall ELISA sensitivity and specificity for anti-SSA were 50.0% and 95.3% (n=225), respectively. The kit change decreased sensitivity from 58% to 38% and increased specificity from 92% to 100% (n=179). The instrument change increased sensitivity from 38% to 67% and maintained specificity at 100% (n=109).

The overall sensitivity and specificity for anti-SSB were 46.2% and 91.1% (n=234), respectively. The combination of kit and instrument changes increased sensitivity from 42% to 100 % and specificity from 99% to 100%. The effect of the two factors alone could not be calculated due to insufficient sample size.

Conclusion: The ELISA kit used and the machine it is run on both contribute to the sensitivity and specificity of autoantibody tests. Machine and kit changes have resulted in improvements in these parameters for selected Abs in patients with myositis. For the systems and Abs studied, ELISAs have a high specificity compared to IP, but the sensitivity of ELISA lags behind IP. Given the increasing roles played by myositis Abs in diagnosis and prognosis and research more evaluation of the comparability of myositis Abs assays is needed.

216 - Analysis of Patients with Different Anti-Synthetase Antibodies

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Background: The antisynthetase syndrome (ASS) is a systemic inflammatory disease, affecting multiple organs, including the lung, joints, heart, gastrointestinal organs, skin and skeletal muscle. However, interstitial lung disease (ILD) and myositis are by far the most prevalent manifestations of ASS. A diagnosis of the disease is possible through presence of one of eight aminoacyl-transferase RNA synthetases (AARS) autoantibodies (ASA), while these antibodies also give the specific name to sub forms of the disease e.g. histidyl-tRNA synthetase (HRS) in Jo-1 syndrome or anti-threonyl-tRNA synthetase in PL-7 syndrome.

Methods: All patients are diagnosed as ASS by presence of one of the AARS. Analyses will be performed on histological level with standard histology and immune fluorescence. In addition, electron microscopy visualizes nuclear inclusions. On the molecular level we performed qPCR and isolation of RNA from cytoplasmic and nuclear fractions.

Results: In our previous work, we could demonstrate that morphological alterations predominantly localized in the perimysial area arise in Jo-1$^+$ patients. These alterations especially comprise macrophage infiltration, as well as perifascicular necrosis. With electron microscopy, we could further demonstrate the development of filamentous inclusions inside the nuclei on an ultrastructural level. These inclusions consist of nuclear G-actin. In addition, we have analyzed molecular levels of genes involved in actin shuttling and could demonstrate an altered expression. The current study now expands the investigation to patients with other AARS autoantibodies and will demonstrate the similarities and differences between patients with anti-PL-7-/PL-12 - ASA in comparison to Jo-1$^+$patients. On histological, as well as molecular level clear pattern were identified.

Conclusion: First results hint to interesting differences in the degree of the immune reaction in the different groups. The expression of some genes that are involved in the immune reaction seem to be stronger expressed in Jo-1$^+$ patients, while there is only a minor difference between PL-7$^+$ and PL-12$^+$ patients. The affection of the patient therefore seems to be affected by the specific ASA.

217 - Identification of a Novel Pro-Inflammatory T Cell Epitope from His-tRNA-Synthetase Associated with Interstitial Lung Disease in Anti-Jo-1–positive Patients

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Background: Previous studies have demonstrated that CD4+ T cells from peripheral blood of anti-histidyl-tRNA synthetase (anti-His-tRNA) also known as anti-Jo-1 positive patients proliferate in response to stimulation with full-length His-tRNA and a N-terminal fragment comprising residues 1-60. Our group has already characterized a specific CD4+T cell response towards the full length His-tRNA-synthetase and a peptide in the N-terminal fragment in blood and broncho-alveolar lavage of myositis patients. In this study we are presenting a novel epitope that identifies patients with moderate-severe interstitial lung disease (ILD).

Methods: Sixteen anti-Jo-1 positive patients with antisynthetase syndrome followed at the Karolinska University Hospital were enrolled. As controls we included HLA-DRB1*03-positive healthy individual (HCs, n=8). Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque density centrifugation and *in vitro*stimulated with: a) full length His-tRNA protein; b) a novel HLA-DR*03:01 binding peptide from native His-tRNA; c) an altered peptide ligand (APL) variant of His-tRNA, designed to prevent recognition by HLA-DR3/His-tRNA-specific TCRs. T cell activation was assessed by CD40L up-regulation and expression of pro-inflammatory cytokines (IFN-g, IL-2 and IL-17A) by flow cytometry. Clinical and laboratory data were documented: myositis-specific and associated autoantibodies, manual muscle test (MMT-8), health assessment questionnaire (HAQ) and interstitial lung disease (ILD). Descriptive statistics are shown with mean and standard deviation or median and IQR. Student's T test or Mann-Withney U-test were used to analyze differences between groups.

Results: At the time of blood sampling the patients had a mean age of 58 years (48-83 years), with a median disease duration of 50 months (11-70 months), MMT8 score 80 (79-80), HAQ 0.25 (0-13-0.75). Eighty-four percent were female, 13/16 patients had ILD and 13/16 had muscle weakness. T cell activation towards the novel His-tRNA peptide was observed in two of the 16 anti-Jo-1 positive patients. When stimulating with the APL version of His-tRNA, no T cell activation was observed in one of the patients that was reactive for the peptide. For evaluation of pro-inflammatory features, the His-tRNA-specific T cells displayed significant up-regulated levels of IFN-g ($p<0.05$) compared to HC ($p<0.05$). Additionally one out of eight healthy donors displayed a modest response to both the novel His-tRNA peptide and the full length His-tRNA protein. In this context only IL-2, and no other pro-inflammatory cytokine production was observed. The patients that showed an upregulation of CD40L in CD4+T cells to the novel His-tRNA peptide had a moderate-severe clinical progression of ILD that required aggressive immunosuppressive treatment.

Conclusion: In this study, we demonstrate the presence of His-tRNA-reactive CD4+ T cells in peripheral blood from anti-Jo-1 positive patients and a novel His-tRNA peptide, characterized by the expression of IFN-g. This phenotype seemed to correlate to a moderate-severe clinical progression of ILD.

218 - Extracellular Histidyl-tRNA Synthetase in Myositis

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Background: Histidyl-transfer RNA synthetase (HisRS) is a major autoantigen in myositis with lung involvement. We investigated the presence of HisRS in the extracellular compartments sera and bronchoalveolar lavage fluid (BAL). In addition, the occurrence of anti-HisRS antibody isotypes was evaluated in BAL and sera from myositis patients.

Methods: HisRS antigen expression was evaluated by dot-blot in: 1) sera from 38 myositis (18 anti-HisRS positive (+); 20 anti-HisRS negative (-)), 15 rheumatoid arthritis (RA) and 7 sarcoidosis patients, and 22 healthy controls (HC); 2) BAL from 8 myositis (5 anti-HisRS+; 3 anti-HisRS-) and 8 sarcoidosis patients, and 8 HC. In order to confirm dot-blot results, western-blot (WB) was performed on a representative number of individuals from myositis (n=8), sarcoidosis (n=3), and HC (n=3) groups. The presence of anti-HisRS antibody isotypes was evaluated in myositis and healthy BAL and sera by ELISA and addressable laser bead immunoassay.

Results: Extracellular HisRS antigen was detected by dot-blot in sera from myositis, RA, and HC groups. However, HisRS antigen was found in a higher number of myositis patients (24 of 38 myositis sera, specifically 12 of 18 anti-HisRS+ and 12 of 20 anti-HisRS- sera) in comparison to RA (3/15), sarcoidosis (0/7) and HC (5/22). In BAL analysed by dot-blot, HisRS antigen was detected in 4 of 8 myositis (2 anti-HisRS+ and 2 anti-HisRS-), 6 of 8 HC and 5 of 8 sarcoidosis individuals. WB confirmed the presence of HisRS antigen in BAL from myositis, sarcoidosis and HC. Blocking experiments (the commercial antibody used to detect extracellular HisRS was pre-incubated with recombinant HisRS antigen) were performed by dot-blot to confirm the presence of extracellular HisRS antigen in BAL. A strong black signal was observed in the myositis BAL whereas no signal could be detected in sarcoidosis and HC BAL. The presence of this unknown factor with high binding capacity for HisRS and HisRS complexed with anti-HisRS-N-terminal antibody was not identified as C1q-immune complexes. Surprisingly, anti-HisRS antibody isotypes were detected in myositis BAL: 1) Anti-HisRS IgG were found in 5 of 8 myositis BAL; and 2) Anti-HisRS IgA and anti-HisRS IgM were identified in 3 of 8 myositis BAL. All patients with anti-HisRS isotypes in BAL were anti-HisRS IgG seropositive and diagnosed with interstitial lung disease.

Conclusion: The HisRS antigen was detected in extracellular compartments, namely sera and BAL, of myositis, sarcoidosis, RA and HC. An unknown binding factor was identified exclusively in myositis BAL, and may be attributed to the presence of local selective autoantibody reactivities. The identification of extracellular HisRS and anti-HisRS antibody isotypes in myositis BAL may suggest local production of autoantibodies and may provide additional clues for the development of autoimmunity in the myositis lung.

219 - Activity of Autoantibody Titers Against SRP Subunits and SRP RNA in Anti-SRP–associated Myopathy

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Background: Anti-SRP associated myopathy is the most debilitating form of immune-mediated necrotizing myopathy (IMNM). Treatment efficacies and clinical courses are highly variable, so study of prognostic markers and disease mechanisms is warranted. Anti-SRP myopathy patients develop autoantibodies against one or more of the six protein subunits of the SRP complex as well as the associated 7SRNA. Thus, we sought to understand the prevalence and activity of various SRP-reactive autoantibodies, and determine whether reactivity to different components of SRP defines disparate disease progressions.

Methods: All patients from a single-center longitudinal cohort study confirmed as anti-SRP positive using two validated methods were included. Proximal muscle strength (recorded using the MRC scale and transformed to Kendall's 0-10 scale) and the logarithm of serum creatine kinase (CK) levels were used for analysis. Patient sera drawn at the first (38/38 patients) and most recent visits (25/38 patients) were tested for reactivity to the 19kDa (SRP19), 54kDa (SRP54), and 72kDa (SRP72) subunits of SRP by immunoprecipitation (IP) of ^{35}S-methionine-labeled proteins generated by *in vitro* transcription and translation. Titers were quantitated by densitometry. Titer contraction was defined as a titer decrease of ≥10%, while elevations of ≥10% were considered as titer increase. IPs for 7SRNA were performed on HeLa cell lysate and purified HeLa cell RNA. Univariate analyses were used to compare strength and CK among SRP subunit autoantibody groups.

Results: 38 patients with 381 visits were included. At the first visit, 32 patients (84%) had anti-SRP19 autoantibodies (aSRP19+), 28 (74%) had SRP54 autoantibodies (aSRP54+), and 14 (37%) had SRP72 autoantibodies (aSRP72+). All sera tested (29) were positive for 7SRNA when HeLa cell lysate was used as the IP substrate, but all were negative when purified HeLa cell RNA was used. Of the patients tested for subunit autoantibodies at two time points, 16 (73%) aSRP19+ patients, 12 (60%) aSRP54+ patients, and 8 (100%) aSRP72+ patients had autoantibody titer contraction, while less than 20% of the patients experienced increase in any of the subunits over time. Treatment with Rituximab was significantly associated with the aSRP titer decrease ($p=0.03$). However, autoantibody levels did not correlate with strength or CK at any time point (all $p > 0.05$).

Conclusion: In this cohort of patients with anti-SRP myopathy, autoantibodies against SRP19 and SRP54 were more common than those against SRP72, though all combinations were present. No patient in this cohort had autoantibodies directly reactive to the 7SRNA component of the SRP complex. Most patients' SRP subunit autoantibody titers decreased over time and Rituximab treatment was associated with that decrease. However, autoantibody titers were unrelated to strength or CK levels in these patients.

220 - Immune-mediated Necrotizing Myopathies with Anti-Signal Recognition Particle Antibodies: Case Series of 147 Patients in a Cross-Sectional Study

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Background: Anti-Signal Recognition Particle (SRP) autoantibodies are one of serological hallmarks of immune mediated necrotizing myopathies. The main objective of our study was the analysis of clinical and laboratory features associated with the presence of anti-SRP antibodies and the response to treatment with the constitution of a multicenter retrospective cohort of patients.

Methods: This was an observational cross-sectional study of retrospective multicenter with comparative analyzing into subgroups. Clinical and laboratory data were retrospectively obtained from calls to observations through scientific societies involving adult patients with anti-SRP antibodies positive (on D-tek™ or EUROIMMUN™ line blot assays) and combination of compatible clinical features.

Results: We analyzed the characteristics of 147 patients with anti-SRP antibodies. The sex-ratio female/male was 1.41 with a mean age at onset of symptoms of 46.6 ± 1.5 years. Myopathy was present in 85.7% of the cases. In the majority of the cases, the disease had a rapid onset and caused major disability. Actually, 54.3% of patients presented at their first medical visit a Modified Rankin Scale ≥ 3 (moderate disability; requiring some help, but able to walk without assistance) and 27.5% were ≥ 4 (unable to walk without assistance or bedbridden). Furthermore, 39% also presented general signs marked by weight loss. It was frequently noted dysphagia (38.8%) and myalgia (67.3%). The motor deficit (72.1%), myalgia and muscle atrophy usually predominated in the lower limbs with a symmetrical (86.3%) and proximal (96%) weakness. Average levels of CPK were 6754 ± 640 IU/L. Muscle biopsies showed necrosis of muscle fibers (84.8%) with moderate inflammatory infiltrates (42.4%) and deposit of membrane attack complex C5b9 (59.7%). A cardiac involvement was defined as a disorder of the rhythm or conduction, myocarditis, pericarditis or cardiac insufficiency leading to acute pulmonary oedema. If cardiac involvement was frequent (49.7%), cardiac insufficiency was observed in 8.4% of cases. The prevalence of lung infiltrative disease was estimated in 37% of the cases. In this situation TLCO was <70% in 55.7% of cases, but patients remained generally asymptomatic. Associated autoimmune diseases were found in 32.7% of the cases with especially dysimmune thyroid dysfunction (9.5%), Sjögren's syndrome (5.4%), lupus erythematosus systemic (4.8%), or scleroderma (4.8%). The disease was frequently dependent on steroids (70.8%) with frequent relapses (1,8 ± 0,2 events) in 45.1% of cases during the follow-up (31.2 ± 3.6 months). Methotrexate (57.1%) and azathioprine (29.3%) were the main immunosuppressive therapies while intravenous immunoglobulins (IVIG) or rituximab were useful and led frequently to remission.

Conclusion: The anti-SRP antibodies may be useful to define a distinct subset of inflammatory myopathy. Anti-SRP myopathies appeared severe and difficult to treat. Dedicated clinical trials are now needed to define the best immunosuppressive drug combination.

221 - Analysis of the Phenotypal Role of Anti-Ro52 Antibodies (TRIM21) in Anti-tRNA Synthetase Syndrome: Predictive Marker of Severity?

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Background: The antisynthetase syndrome (ASS) is highly variable leading to heterogenous outcomes. Specific anti-aminoacyl-tRNA synthetase antibodies (ARS) determine different subsets but there is a need of biomarkers that better refine phenotype and prognosis within the syndrome. Myositis-associated autoantibodies such as anti-Ro52 (TRIM21), could be an interesting marker. Their clinical significant is controversial. The objective of this study was to analyze the phenotypic role of isolated anti-Ro52/TRIM21 in ASS patients.

Methods: This retrospective multicentric study (10 different centers) analyzed patient characteristics with anti-Ro52/TRIM21 antibodies (Ro52+) compared to patients without anti-Ro52/TRIM21 antibodies (Ro52-) in ASS. Patients with i) clinical involvement in accordance with ASS, including pulmonary, muscle, dermatological or rheumatic involvements ii) with two successive positive tests for anti-ARS iii) and available status for anti-Ro52 confirmed by two consecutive tests, were included. Clinical data were reviewed using a standardized form.

Results: We included 146 patients, 78 (53.4%) with and 68 (46.58%) without anti-Ro52 antibodies. Age (47.4 ± 1.9 vs. 48.6 ± 2 y/o), sex-ratio (3.33 vs. 2.24; p=0.35) and distribution of anti-ARS specificities were not different between the two groups (e.g. anti-Jo1 : 64.5% vs. 58.2%; p=0.79). There was no difference in muscle involvement but dyspnea (68.4% vs. 53.7%; p=0.041) with higher severity (NYHA III or IV, p=0.002) was found in the Ro52+ group, without difference in interstitial lung disease (84.6% vs. 76.5%; p=0.713). Thus, we noted a higher frequency of pulmonary hypertension estimated by echocardiography or right heart catheterization (25.9% vs. 3.6%; p<0.001). Presentation with "mechanic's hands" was also more frequent in the Ro52+ group (41.7% vs. 22.4%; p=0.021). The incidence of other skin features does not differ, especially sclerodactyly (p=0.2). There was no difference in muscle and joint involvement. Subjective dry mouth syndrome was more common in the Ro52+ group (without anti-SSA or anti-SSB) (p=0.027), unconfirmed by objective analysis (such as histology of salivary glands or functional tests). Cancer was not more frequent. Finally, Ro52- patients received more frequently initial low-dose of corticosteroids (defined by dose <0.5 mg/kg/day) (p=0.005) and Ro52+ patients required more frequently immunosuppressive drugs (1.7 ± 0.1 vs. 1.3 ± 0.2 drugs; p=0.021). A higher relapse rate was more common in the Ro52+ group when decreasing or discontinuing corticosteroid therapy was achieved (p=0.041), but survival was not different (p=0.88).

Conclusion: These data tend to position anti-Ro52/TRIM21 antibodies as predictive marker of severity in ASS. The anti-Ro52/TRIM21 antibodies should lead to regular screening of pulmonary involvement, particularly detection of pulmonary arterial hypertension (OR=7.04 [1.5-66.8]). These patients should benefit from corticosteroid therapy at initial high doses with early immunosuppressive relays considering the more severe prognosis of patients with ASS associated with anti-Ro52/TRIM21 antibodies. It mays help to better personalize the care of ASS patients.

222 - Anti-Mi2 Dermatomyositis Revisited: Pure DM Phenotype with Muscle Fiber Necrosis and High Risk of Malignancy

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Background: Anti-Mi2 autoantibodies (Aabs) have been proposed to be highly specific for dermatomyositis (DM) and to be associated with a DM classical phenotype consisting of typical skin rashes and low extra-muscular features. Cancer has been estimated in about 30% of all DM patients. Patients with anti-Mi2 DM are considered having a good prognosis, possibly related to a markedly lower risk of malignancy reported in this subset. Nonetheless, there has been only a few and small cohort descriptions of this DM subgroup. Our objective was therefore to describe the phenotype of anti-Mi-2 DM in a large French cohort.

Methods: A national multicenter retrospective cohort study was performed (15 medical centers) including all patients with a clinical phenotype suggestive of DM (cutaneous manifestations and/or muscle involvement) and a positive anti-Mi2 Aabs. Medical records were retrospectively reviewed. Muscle strength was assessed using the Medical Research Council (MRC) scale and cancer-associated myositis (CAM) was defined as a cancer occurring ± 3 years of diagnosing myositis.

Results: A total of 65 patients were identified, 62% were female and mean age at diagnosis was 54 years old (yo) (±17 yo). DM skin rash was reported in 88% of patients, most frequently Gottron papules and/or sign (68%), periungueal erythema (51%) and heliotrope rash (40%). Peripheral muscle weakness was reported in 92% of patients and dysphagia was reported in 34% of patients. At diagnosis, patients displayed severe muscle weakness (MRC 3/5, ±1/5*)* with mean CK level of 5085 UI/L (±5535 UI/L). Systematic review of muscle biopsies (n=11) showed marked and diffuse inflammatory infiltrates. Strikingly, necrosis and regeneration were identified in all patients (n=11/11). C5b-9 deposition was found in all patients mainly on non-necrotic fibers but only sparsely on capillaries and without prominent capillary loss. Arthritis, Raynaud phenomenon and interstitial lung disease were reported in less than 20 % of patients**.** CAM was identified in 18.5% of patients and detected within one year and a half of DM diagnosis in most patients (n=11/12). All CAM patients, but one (37 yo), were diagnosed over 50 yo. There was no predominant histological subtype of malignancy (gastro-intestinal, urological, gynecological and pulmonary) and cancer was metastatic in a third of patients. Survival rate was 83% after a mean follow-up of 4.9 years from cancer diagnosis. A standardized incidence ratio (SIR) of 4.34 ($p < 0.001$) compared to general population of the same age and gender was found. Ninety-seven percent of patients were initially treated with corticosteroids (CS), in combination with an immunosuppressant (IS) and/or intravenous immunoglobulin (IVIg) in 76% of cases. Patients treated initially with CS monotherapy (n=14), needed second-line agents upon follow-up in 69% of cases. In all, 52% of patients relapsed upon CS and/or IS tapering.

Conclusion: In this large French cohort, patients with anti-Mi2 DM displayed a clinical phenotype with 3 main characteristics (i) pure DM phenotype (low overlap features) (ii) necrotizing myositis (severe weakness, high CK level and muscle fiber necrosis) and (iii) high risk of malignancy.

223 - Clinical Heterogeneity of Idiopathic Inflammatory Myopathies with Anti-Mi-2 Subtypes

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Background: To investigate the clinical characteristics of different subtypes of anti-Mi-2 antibodies in patients with idiopathic inflammatory myopathies (IIMs).

Methods: The serum from 672 patients with IIMs was detected for anti-Mi-2 antibodies using immunoblotting tests. The clinical characteristics of the anti-Mi-2 antibodies positive subtypes were analyzed.

Results: Among the 672 patients with IIMs, 37 were positive for anti-Mi-2 antibodies, with a positive rate of 5.5%, mainly seen in patients with dermatomyositis(DM) (31/37). In the 37 patients, anti-Mi-2α+anti-Mi-2β- accounted for 29.7% (11 cases), anti-Mi-2α-anti-Mi-2β+ accounted for 37.8% (14 cases), and anti-Mi-2α+anti-Mi-2β+ accounted for 32.4% (12 cases). 29.7% (11/37) of the anti-Mi-2 antibodies positive patients could be combined with other myositis specific antibodies (MSAs), but the combination of DM or anti-synthetase syndrome related MSAs were found in anti-Mi-2α-anti-Mi-2β+ group. And anti-SRP antibody and anti-HMGCR antibody associated with immune-mediated necrotic myopathy were found in anti-Mi-2α+anti-Mi-2β- patients. In Mi-2α-anti-Mi-2β+ patients, the incidence of interstitial lung disease(ILD) was significantly higher than that in the other two groups ($P = 0.026$), and 3 patients with cancer were also found in this group. The overall response to treatment is optimistic.

Conclusion: The positive rate of anti-Mi-2 antibodies in IIMs is 5.5%. The positive rate and clinical manifestation of the anti-Mi-2α and anti-Mi-2β antibodies are similar. However, the incidence of ILD in patients with anti-Mi-2α-anti-Mi-2β+ is high and the incidence of cancer can be complicated.

224 - Characteristics of Anti-MDA5 Autoantibodies Associated with Juvenile Dermatomyositis (JDM) in North America

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Background /Purpose: Anti-MDA5 Abs have been reported to associate with clinically amyopathic and classic adult and juvenile dermatomyositis (JDM), and in particular with severe progressive interstitial lung disease (ILD) and poor prognosis in Japanese pts. The aim of this study was to examine the frequency and characteristics of anti-MDA5 Abs associated JDM in North America.

Methods: Demographic, clinical, laboratory and outcome features of anti-MDA5 Ab+ JDM and JCTM/DM patients meeting probable or definite Bohan and Peter criteria were assessed and compared to 60 MSA/MAA negative (Ab-) JDM patients from a US registry of juvenile myositis. Myositis Abs were tested by standard immunoprecipitation (IP) and MDA-5 tested by reverse IP-immunoblot. Differences were evaluated by Fisher's exact and Mann-Whitney tests. Significant univariable results were examined in multivariable logistic regression.

Results: Anti-MDA5 Abs were identified in 37 (7.9%) patients out of cohort of 467 JDM and JCTM/DM patients. MDA5 Ab+ patients had lower serum CK (median 182 vs. 746 U/L, p <0.0001) and aldolase levels (median 8.5 vs. 12.1 U/L, p=0.019) compared to Ab- patients. MDA5 Ab+ patients more frequently had arthralgia (86% vs. 47%, p=0.0001), arthritis (86% vs. 42%, p<0.0001), periungual capillary changes (84% vs. 63%, p=0.021), abnormal PFTs (32% vs. 11%, p=0.038), dyspnea at exertion (43% vs. 15%, p=0.004), ILD (24% vs. 1.7%, p=0.0007), weight loss (81% vs. 29%, p<0.0001), and adenopathy (40% vs. 15%, p=0.008) compared to Ab- patients. MDA5 Ab+ patients tended to have more frequent fatigue (95% vs. 80%, p=0.07) and fever (65% vs. 43%, p=0.06). MDA5 Ab+ patients less frequently had myalgia (43% vs. 55%, p=0.048). The median skeletal (0.5 vs. 0.0, p < 0.0001), pulmonary (0.0 vs. 0.0, p=0.018) and constitutional (0.5 vs. 0.25, p<0.0001) symptom scores at diagnosis were higher in MDA5 Ab+ patients, but the median overall clinical symptom score at diagnosis was lower in MDA5 Ab+ patients compare to Ab- patients (0.27 vs. 1.2, p<0.0001). Race, age, and gender distributions, delay to diagnosis and family history of autoimmune disease did not differ between anti-MDA5+ and Ab- patients. Anti-MDA5 Ab+ patients did not differ in total number or types of medications received, or in time to discontinuation of steroids or other major therapies. Frequencies of complete clinical response and remission were also similar between MDA5 Ab+ vs. Ab- patients.

Multivariate analysis revealed weight loss (p<0.0001), arthritis (p=0.007) and lower serum CK level (p=0.005) were significantly associated with anti-MDA5 Abs vs. Ab- patients. At median follow-up of 2.7 yrs, MDA5 Ab+ patients tended to more often have active disease (70% vs. 51%, p=0.08) and skin rashes (58.3% vs. 33.9%, p=0.032). There were no differences in other outcomes, including disease course, and mortality.

Conclusion: JDM patients with anti-MDA5 Abs in a large US myositis registry have frequent arthritis, arthralgia, weight loss, adenopathy, and ILD, but lower serum muscle enzyme levels (CK and aldolase). These patients have comparable outcomes and treatment responses to Ab- patients.

225 - Anti-Mitochondrial Antibodies in Inflammatory Myopathies

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Background: Anti-mitochondrial antibodies type 2 (AMA2) are classical hallmarks of primary biliary cholangitis. They have also been involved in 11.3% of inflammatory myopathies in a Japanese cohort, then associated with frequent cardiac involvement, muscle atrophy and granuloma on muscle biopsy. Therefore they have been considered as marker of severity. In order to confirm these findings we conducted an analysis of clinical and biological data, imagery and muscle biopsies of AMA2-positive patients identified in our prospective cohort of patients.

Methods: In November 2015 we screened the Myositis database that includes patients referred for inflammatory myopathies. Inflammatory myopathies were classified according to ENMCcriteria. AMA2 were assessed with line immunoassays for multiparametric detection (Euroimmun®, Luebeck, Germany). Missing data were excluded from analysis. Non-parametric Fisher exact test was used.

Results: Among 1098 patients in the database, AMA2 status was available for 141 patients who were included. Eleven patients among these 141 had positive AMA2 (7.8%). Nevertheless, no specific histological or clinical feature emerged except a trend towards higher proportion of polymyositis (n=5; 45.5% of AMA2 positive vs n=25; 19.0% of AMA2 negative; p=0.06). Nine AMA2-positive patients exhibited muscle weakness (proximal n=9; axial n=2; distal n=1). Swallowing difficulties were observed in 3. Muscle atrophy assessed with MRI was not different among groups. Median (IQ) CK level at diagnosis was 1500U/L (481-8100) in AMA2 positive patients versus 3843U/L (1050-9000) in AMA2-negative (p=0.20). No granuloma was observed in AMA2-positive patients but in 2 AMA-negative. Cardiac involvement was equally frequent (36.4% in AMA2-positive vs 29.5% in AMA-negative, p=0.73). Cutaneous manifestations were less frequent in AMA2 positive patients compared to AMA2 negative patients (respectively 27.3% vs 64.8%, p=0.02). The presence of other associated autoantibodies was not different between groups. AMA2 were associated with myositis specific autoantibodies in 4: anti-SRP (n=1), anti-HMGCoA-reductase (n=1), anti-Jo1 (n=1), anti-PL-7 (n=1). AMA2 were the only autoantibodies found in 2 patients. Five AMA2-positive patients had definite associated auto-immune diseases: lupus (n=1), anti-phospholipids syndrome (n=1), rheumatoid arthritis (n=1), anti-synthetase syndrome (n=2), Sjögren syndrome (n=3). Three AMA2-positive patients had previously diagnosed primary biliary cholangitis, no new diagnosis was made from muscular symptoms. Except one patient who died from HCV-associated cirrhosis, all patients benefited from immunosuppressive therapy (muscle weakness stabilization n=4, clinical improvement n=6). All patients received corticosteroids, 7 methotrexate, 2 azathioprine, 2 rituximab, 2 mycophenolate mofetil, 3 cyclophosphamide, 5 plasmatic exchanges and 6 intravenous immunoglobulin.

Conclusion: AMA2 appear not to be associated with a specific pattern of inflammatory myopathy, granuloma or cardiac involvement in this second and independent series of patients.

226 - Multiple Faces of Acquired Myopathies During HIV Infection: From Myofibers Mitochondrial Dysfunction to Muscular Inflammatory Damages

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Background: Myopathies occurring during HIV infection remain rare and poorly described. The aim of this work is to define the main characteristics of acquired myopathies observed in HIV patients.

Methods: Through a systematic review of the department of pathology computerised database, HIV-positive subjects who underwent a muscle biopsy between 2005-2012 were selected. Medical charts were retrieved and analyzed for clinic-pathological contents, and compared to the usual myositis data.

Results: Fifty-five muscle biopsies were performed on 47 HIV-positive patients during this period of time, from which 40 were pathological. For patients who underwent several muscular biopsies, only the ones which led to a diagnosis were retained. Histological abnormalities (n=40) encountered various pattern, apportioned as follows: polymyositis (PM) pattern 50 % (n=20), isolated mitochondrial abnormalities (MA) 30 % (n=12), sporadic inclusion body myositis (sIBM) pattern 12.5 % (n=5), and others 7.5% (n=3 one necrotizing myopathy, one corticosteroid induced myopathy and one myofasciitis) (Figure 1). For the purpose of comparing HIV-PM with non-HIV-associated myositis, we have considered an Anti Synthetase cohort (n=50). It is noteworthy that HIV-PM had significantly less severe weakness (MRC manual testing ≥ 4/5 83% in HIV+ *vs*. 54%; $p<0.05$) and lower Creatine Kinase levels (mean 917 vs. 4975 IU/L, $p<0.05$). Interestingly, viral load was significantly different between HIV-PM, HIV-isolated MA subsets, and HIV-sIBM: undetectable in respectively 35%, 100% and 100% cases ($p<0.05$). Patients with HIV-isolated MA were systematically undergoing highly active anti-viral therapy, particularly nucleosidic analogues reverse transcriptase inhibitory (NRTI). Regarding the HIV-PM subset, favourable evolution of the myopathy occurred in 60% (n=12), whereas HIV-isolated MA rarely improved (8%) and all HIV-sIBM worsened ($p<0.05$). A particular subset of HIV-PM departed from the global subset, since in addition to the myositis pathological features, mild mitochondrial abnormalities was observed and slow clinical worsening occurred (n=8). This raise the unresolved questions the continuum between some PM with mitochondrial abnormalities and IBM.

Conclusion: Acquired myopathy during HIV infection can take various forms. Often associated with uncontrolled HIV replication, HIV-PM seems to be most frequent and having a good prognosis. Conversely HIV-isolated MA occurred in undetectable viral load patient, often treated with NRTI. Lastly, HIV-IBM was the more serious HIV associated myopathy with a constant poor prognosis.

227 - Clinical Significance of Anti-PUF60 Autoantibody in Chinese Patients with Idiopathic Inflammatory Myositis and Other Rheumatic Diseases

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Background: Autoantibodies against PUF60 have been reported in Caucasian dermatomyositis (DM) and Sjogren's syndrome (SS) patients. Interestingly, no anti-PUF60 autoantibodies were found in Asian DM patients previously. The aim of this study was to detect the existence and analyze the clinical significance of anti-PUF60 antibody in Chinese patients with idiopathic inflammatory myopathy (IIM) and other rheumatic diseases.

Methods: This study involved 357 IIM patients [including 245 patients with DM, 76 patients with polymyositis (PM) and 36 patients with CTD (connective tissue disease)-associated myositis], 211 disease controls [including 28 patients with neuromuscular disease (NMD), 104 patients with systemic lupus erythematosus (SLE) and 79 patients with SS] and 167 healthy controls (HCs). An enzyme-linked immunosorbent assay (ELISA) was developed to detect anti-PUF60 antibody titers. Further immunoblotting analyses were performed to validate the ELISA results.

Results: Anti-PUF60 antibodies could be detected in 39/357 (10.9%) patients with IIM, 18/104 (17.3%) patients with SLE and 8/79 (10.1%) patients with SS, 1/28 (3.6%) patients with NMD, and 4/167 (2.4%) healthy controls (IIM vs HCs, P=0.001; SLE vs HCs, P<0.001; SS vs HCs, P=0.009; NMD vs HCs, P=0.716). Meanwhile, the prevalence of antibodies against PUF60 for IIM subgroups were significantly higher than HCs. The antibody presented in 10.2% (25/245, P=0.002) DM patients, 9.2% (7/76, P=0.018) PM patients and 19.4% (7/36, P<0.001) CTD-associated myositis patients. Anti-PUF60 antibodies implied different clinical significances in different immune disease groups. For DM patients, the antibody was particularly associated with higher prevalence of mechanic's hands and abnormal peripheral blood lymphocytes subsets (including elevated and reduced percentages of B2 and NK lymphocytes respectively). For patients with other rheumatic diseases, the antibody was significantly associated with higher prevalence of cutaneous manifestation, rheumatoid factor and antibodies against SSB, RNP in SS patients, and related to higher incidence of younger onset, alopecia, hypocomplementemia, elevated B1-cell subpopulations and antibodies against dsDNA, Sm, SSB in SLE patients.

Conclusion: Anti-PUF60 antibody can be detected in Chinese patients with IIM, SLE and SS, and it is associated with distinct clinical features in different rheumatic diseases. This finding indicates that anti-PUF60 antibody is associated with different pathogenesis processes in different systemic rheumatic diseases.

228 - The Serum Levels of CXCL10 in Patients with Dermatomyositis are Correlated with Disease Activity

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Background Dermatomyositis (DM) is a complement-mediated endotheliopathy, accompanied by abnormal production and function of cytokines and chemokines, particularly associated with Th1-mediated immune response. CXCL10, belonging toα-chemokines, may contribute to the pathogensis of DM through Th1 response. The present study aimed to investigate the serum levels of CXCL10 in patients with DM, and illuminate its clinical significance.

Methods Serum CXCL10 levels of 61 DM patients and 32 matched healthy controls were measured by ELISA. The score of disease activity was measured by the same doctor under the direction of MDAAT. And further analyzed its correlation with serum levels of CXCL10. The results of two groups were compared using unpaired Mann-Whitney U test and the relevance was analyzed using Spearman correlation analysis.

Results Serum levels of CXCL10 in DM patients were significantly higher than healthy controls [1002.65 (446.80，1679.42) pg/ml & 85.85 (65.88，111.05) pg/ml; Z=-6.886, P=0.000]. Patients with ILD had higher serum CXCL10 levels than the patients without ILD (Z=-2.975, P=0.003). A cross-sectional assessment revealed that serum CXCL10 levels were positively correlated with global disease activity (r=0.614，P=0.000), muscle activity (r=0.45，P=0.000), skin activity (r=0.439，P=0.000) and lung activity (r=0.373，P=0.004).

Conclusion Serum CXCL10 levels were increased in DM and positively correlated with disease activity. Meanwhile, the levels of serum CXCL10 can reflect the disease activity and therapeutic efficacy of DM. Further studies are urgently needed to clarify the pathogenic roles of CXCL10 in DM.

229 - Peripheral Lymphocyte Subset Repertoires Reflect Clinical Features of Polymyositis and Dermatomyositis

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Background: Polymyositis (PM) and dermatomyositis (DM) are major forms of idiopathic inflammatory myopathies, which often affect various extra-muscular organs such as the skin and lungs. For PM/DM treatment, high dose corticosteroids, immunosuppressive cytotoxic drugs, and calcineurin inhibitors, which suppress T-cell activation, are used as the first line therapies. Additionally, some clinical trials reported the effectiveness of B-cell targeted therapy. While the effectiveness of treatment targeting T- and B-cells indicates their involvement in the pathogenesis, the alteration of peripheral lymphocyte subset repertoires remains unclear. Analyzing the alteration will allow us to understand the immune status of the patients and provide new insights into the pathogenesis. The aim of the present study was to study the peripheral lymphocyte subset repertoires in PM/DM patients.

Methods: Peripheral blood lymphocytes from 17 (4 PM and 13 DM) patients who satisfied the Bohan and Peter criteria or the proposed Sontheimer's criteria, including 8 patients with interstitial lung diseases (ILDs), and from 18 healthy donors (HDs) were examined for lymphocyte subsets with flow cytometry based on the standardized immunophenotyping (Nat Rev Immunol 2012). In 6 DM patients, the lymphocyte subsets before and after the successful treatment were examined.

Results: The proportions of naïve CD4 T- and naïve B-cell subsets were higher while those of naïve CD8 T-, central memory CD8 T-, effector memory CD4 T-, Th1-, and memory B-cell subsets were lower in the patients than HDs. When these subsets were compared among the patients with ILDs, those without ILDs, and HDs, their proportions, except for those of Th1- and naïve B-cell subsets, were different only between the patients with ILDs and HDs. In contrast, the proportions of lymphocyte subsets were not different between PM and DM patients. After treatment of DM, the transitional B-cell subset vanished with increase of the memory B-cell subset.

Conclusion: The differences in proportions of lymphocyte subsets between the patients and HDs should represent defects in lymphocyte homeostasis such as differentiation, survival, and death in PM/DM patients. On the other hand, the decrease in CD8 T_{CM}-, CD4 T_{EM}-, and memory B-cell subsets might be attributable to shift of those subsets from peripheral blood into the inflamed tissues in PM/DM patients. The presence of ILD associates with larger deviation in the proportions of lymphocyte subsets among PM/DM patients. The association between disease activity of DM and B-cell subset repertoires indicates the B-cell involvement in the pathogenesis. Altogether, peripheral lymphocyte subset repertoires reflect clinical features of PM/DM.

230 - Multidimensional Analysis of Patients with Anti-Ku Antibodies Identifies Two Phenotypical Subgroups with Distinct Prognosis Recognized by Anti-DNA Status

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Background: The presence of anti-Ku antibody is associated with a wide variety of clinical manifestations and various outcomes. We attended to refine anti-Ku associated disease by identifying subgroups of Ku-positive patients with similar clinico-biological features and prognosis.

Methods: We reviewed clinical, biological characteristics, diagnosis and management of 24 patients with anti-Ku antibody. A multidimensional analyze was performed to highlight homogeneous groups of patients. We search for features that most strongly match with each group.

Results: Anti-Ku positive patients had joint (n = 19), muscle (n = 10), lung (n = 9), skin (n = 9), renal (n = 9), hematological (n = 8), thrombotic (n = 6), serous (n = 6) and gastrointestinal (n = 4) involvements. Associated antibodies were anti-DNA (n = 7), -SSA (n = 6), -RNP (n = 4), -SSB (n = 1), -Sm (n = 1), rheumatoid factor (n = 9) and ACPA (n = 4). Diagnosis were overlap myositis (n = 9), lupus erythematosus (n = 8), Sjögren's syndrome (n = 7), rheumatoid arthritis (n = 3), undifferentiated connective (n = 2), and systemic sclerosis (n = 2). Many patients had criteria for several connectivite tissue diseases. Managements were heterogeneous.

Multidimensional analysis identified two groups that were mutually exclusive:

i) Patients characterized by scleroderma-like skin disease, myositis and ILD, frequently treated with high dose of corticosteroids,

ii) Patients with lupus like skin disease, haematological and renal involvements frequently receiving cyclophosphamide and mycophenolate mofetil.

Anti-DNA antibody, absent in the first group and present in the second was the most powerful criteria to distinguish these two subsets of the anti-ku associated disease (sensibility 93% and a sensitivity of 86%).

Conclusion: Anti-DNA status distinguishes patients at risk of muscle and lung involvement (anti-DNA negative) from patients at risk of renal involvement (anti-DNA positive). These data significantly refine anti-Ku associated disease and help to personalize monitoring and care of the patients.

231 - Idiopathic Inflammatory Myopathies: Evaluation of Skeletal Muscle Glucose Metabolism by PET-CT ^{18}FDG

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Background: There is a need for tools to measure muscle disease activity in inflammatory myopathies (IM). We assessed the contribution of metabolic imaging with positron emission tomography combined with computed tomography (PET-CT) ^{18}F fluorodeoxyglucose-(^{18}FDG) for muscle disease activity assessment in patients with IM.

Methods: Thirty-eight adults with IM who performed a PET-CT with ^{18}FDG for oncologic purpose were retrospectively included. Twenty patients who performed a ^{18}FDG PET-CT for the characterization of a pulmonary nodule with no history of IM were included as controls. In both groups, the skeletal muscle glucose metabolism (SMGM) was assessed by two methods: 1) a visual analysis of the muscle uptake compared with the mediastinum and the liver and 2) a quantitative analysis by measuring the maximal standardized uptake value (SUVmax) in 9 proximal muscle groups. The SMGM was confronted to muscle histological data, serum creatine kinase levels (CK) and the myositis intention to treat activity index (MITAX).

Results: The SMGM was higher in IM than in the control group in visual analysis ($p < 0.001$) and quantitative analysis ($p < 0.001$). In addition, the quantitative measurement of SMGM was significantly correlated with serum CK levels (Spearman $\rho = 0.47$, $p < 0.01$) and with the MITAX (Spearman $\rho = 0.72$; $p=0.001$). No significant correlation was found between the SMGM and the muscle histological findings. Finally, in 9 patients who underwent two consecutive ^{18}FDG PET-CT, the evolution of the SMGM was concordant with the clinical course according to the MITAX in 8.

Conclusion: These data suggested that ^{18}FDG PET-CT, which is useful for the screening of cancer associated IM, is also helpful for the measurement of IM muscle disease activity.

232 - Inflammatory Myopathies Associated with Sjogren's Syndrome Do Not Differ from Those Without Sjogren's Syndrome Aside from Older Age at Diagnosis and Less Frequent Normal Muscle Biopsy

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Background: Prevalence of secondary Sjogren's syndrome (SS) in inflammatory myopathies (IM) and whether IM patients with SS represent a distinct disease subset are currently unknown. We attended to assess the signification of SS in IM with regard to phenotype and prognosis.

Methods: IM patients with SS (IM-SS group) were identified among a cohort of 270 patients with IM using European-American Consensus Group (EACG) classification criteria. Clinical, serological, muscle pathological features, management and outcomes of IM-SS patients were retrospectively studied and compared to the IM patients who had been assessed for SS but did not fulfill these criteria (IM-noSS group).

Results: EACG criteria were available in 63 IM patients of the total cohort among which 29 (46%) were diagnosed as having SS. These IM-SS patients were older at IM diagnosis than the 34 IM-noSS patients (56±3.1 vs 47.7±2.8 years, p=0.05), sex ratio wasn't different. SS was mostly diagnosed at the time of IM diagnosis (n=23, 79%) and less frequently preceded (n=3: 1, 3 and 4 years) or followed (n=3, 3, 6 and 30 years) IM diagnosis. IM-SS patients had subjective sicca syndrome (29/29, 100%) with objective dryness (10/12, 92%), anti-SSA/SSB antibodies (14/29, 48%) and/or focus score ≥3 in minor salivary glands biopsy (n=21/24, 88%). Creatine kinase level was not different between IM-SS and IM-noSS (1400±320 vs 2538±214 UI/L, p=0.5). A normal muscle biopsy was less frequently found in IM-SS than in IM-noSS patient (7/28 vs 1/24 p=0.05). According to the ENMC criteria, DM was the more frequent muscle histological finding in IM-SS patients (n=10, 42%) but all histological patterns were represented (including nonspecific IM: 6 (25%), inclusion body myositis: 4 (17%), polymyositis: 2 (8%), necrotizing myopathy: 1 (4%). This distribution was not different from the IM-noSS group. IM-SS patients also suffered from interstitial lung disease (n=10, 34%), arthralgia and/or arthrithis (n=17, 59%), skin involvement (n=14 48%) and Raynaud syndrome (n=14, 48%) which occurrence characteristics were not different from IM-noSS group. Anti-SSA (n=13, 45% vs n=1, 3%, p=0.0001) and anti-SSB (n=6, 21% vs n=0, 0% p<0.01) were more frequent in IM-SS groups. Other auto-antibodies were found in 14 IM-SS patients (48%) and in 19 IM-noSS patients (56%, p=0.62) which specificities were not significantly different between the two groups. Cryoglobulin was also found with a similar frequency in both groups (n=3, 10% vs n=3, 9%; p=1.0). Six IM-SS patients (21%) were diagnosed with cancer versus 4 IM-noSS patients (12%) (p=0.49). Mean number of immunomodulatory drugs was not different between the two groups (1.9±0.2951 vs 1.6±0.2616; p=0.41) and after a follow-up >7 years, 6 patients died in both groups, without any significant difference in survival (p=0.23).

Conclusion: SS is frequently observed in IM. No difference was found between IM-SS and IM-noSS with regards to phenotype, serotype and survival aside from older age at diagnosis and less frequent normal muscle biopsy.

233 - Autoantibody Profile of Children with Juvenile Dermatomyositis from a Single Centre in North India

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Post Graduate Institute of Medical Education and Research

Background: Juvenile dermatomyositis (JDM) is a rare childhood autoimmune inflammatory muscle disorder that can result in severe disability or death. Children with JDM can have autoantibodies in their sera like other autoimmune diseases. Over the last few years, few novel Myositis Specific Antibodies (MSA) have been identified, like anti-p155/140 (Anti-TIF1γ), anti-p140 (anti NXP2), CADM-140 (anti MDA5), anti-SAE and anti 200/100 (anti HMG-CoA reductase). Some phenotypical associations have been described with these autoantibodies. Few of these autoantibodies have not been studied in children. We undertook this study to look for autoantibodies including anti p200/100 (anti HMG CoA reductase) which has not been evaluated in children and anti p-140 (anti NXP2) which has been shown to have correlation with calcinosis in children with JDM.

Methods: Cross-sectional study. All children diagnosed to have JDM for more than 2 years and registered in Pediatric Rheumatology Clinic at Post Graduate Institute of Medical Education and Research, Chandigarh, India, were deemed eligible for recruitment. Study period: January 1, 2015 to June 30, 2016. Autoantibody testing for MSA and myositis associated autoantibodies (MAA) was done for enrolled children. Immunodot was done to detect Immunoglobulin G (IgG) antibodies against Jo1, threonyl-tRNA synthetase (PL7), alanyl-tRNA synthetase (PL12), glycyl-tRNA synthetase (EJ), Signal Recognition Particle (SRP), Mi-2, MDA-5, Transcriptional intermediary factor 1-γ (TIF-1γ), Ku, PMScl 100, Scl 70 and SSA/Ro 52. Evaluation for anti p-140 or Nuclear Matrix Protein (NXP2) and anti 200/100 or 3-Hydroxy-3-Methyglutaryl-Coenzyme (HMG CoA reductase) was done using ELISA.

Results: Antinuclear antibody (ANA) testing was done in 34 patients. Fourteen (40%) tested positive. In addition, MSA and MAA were assessed. Anti-SRP antibodies were present in 4 (11.4%) children, anti-MDA5 in 3 (8.6%), anti-Mi2 in 1 (2.9%) and 1 patient tested positive for anti-SSA/Ro52 antibodies. All 4 children with anti-SRP were girls, had polycyclic course and 2 of them had calcinosis and signs of disease activity at the time of evaluation. Patients with anti-MDA5 had predominant skin involvement, less severe muscle disease and followed a monocyclic course. Two of them had arthritis/arthralgia at the time of presentation. The only patient in our study with anti-Mi2 had normal muscle strength/endurance at the time of cross-sectional assessment. None of the patients had anti synthetase antibodies (anti-Jo1, anti-PL-7, anti-PL-12, anti-EJ), anti-ku or anti-Scl-70. None of the subjects tested positive for anti-NXP2 or anti- HMG CoA.

Conclusion: Prevalence of autoantibodies in children with JDM in our study is similar to what has been described previously. Type of autoantibodies, though, is not similar. This may be due to ethnic differences of the population. Autoantibodies were tested in children while they were on treatment. This may have resulted in lower positivity. Evaluation of autoantibody profile at the time of diagnosis may assist in predicting the course of disease and response to treatment.

234 - Calcinosis in Children with Juvenile Dermatomyositis from a Single Centre in North India

Avinash Sharma*, Anju Gupta, Ankur Jindal, Amit Rawat, Deepti Suri and Surjit Singh
Post Graduate Institute of Medical Education and Research

Background: Juvenile dermatomyositis (JDM) is a rare childhood autoimmune inflammatory muscle disorder that can result in severe disability or death. Calcinosis is a unique and a poorly understood long-term complication of JDM. Calcinosis can present in various forms like nodular calcinosis, tumoral deposits, calcinosis universalis. We present here the images of calcinosis in children with JDM.

Methods: All children diagnosed to have JDM and registered in Pediatric Rheumatology Clinic at Post Graduate Institute of Medical Education and Research, Chandigarh, India, were evaluated for presence of calcinosis. Consent was taken from patients or caregivers.

Results: A total of 36 patients were evaluated. Twelve (33.33%) patients had calcinosis (Fig 1 and Fig 2). Interestingly, 4 children had calcinosis at the time of diagnosis.

Conclusion: Calcinosis is a distinct complication of JDM which is uncommon in inflammatory myopathies in adults. Calcinosis can be disabling and disfiguring. It may not be obviously visible in all patients and radiographs help reveal the extent of involvement.

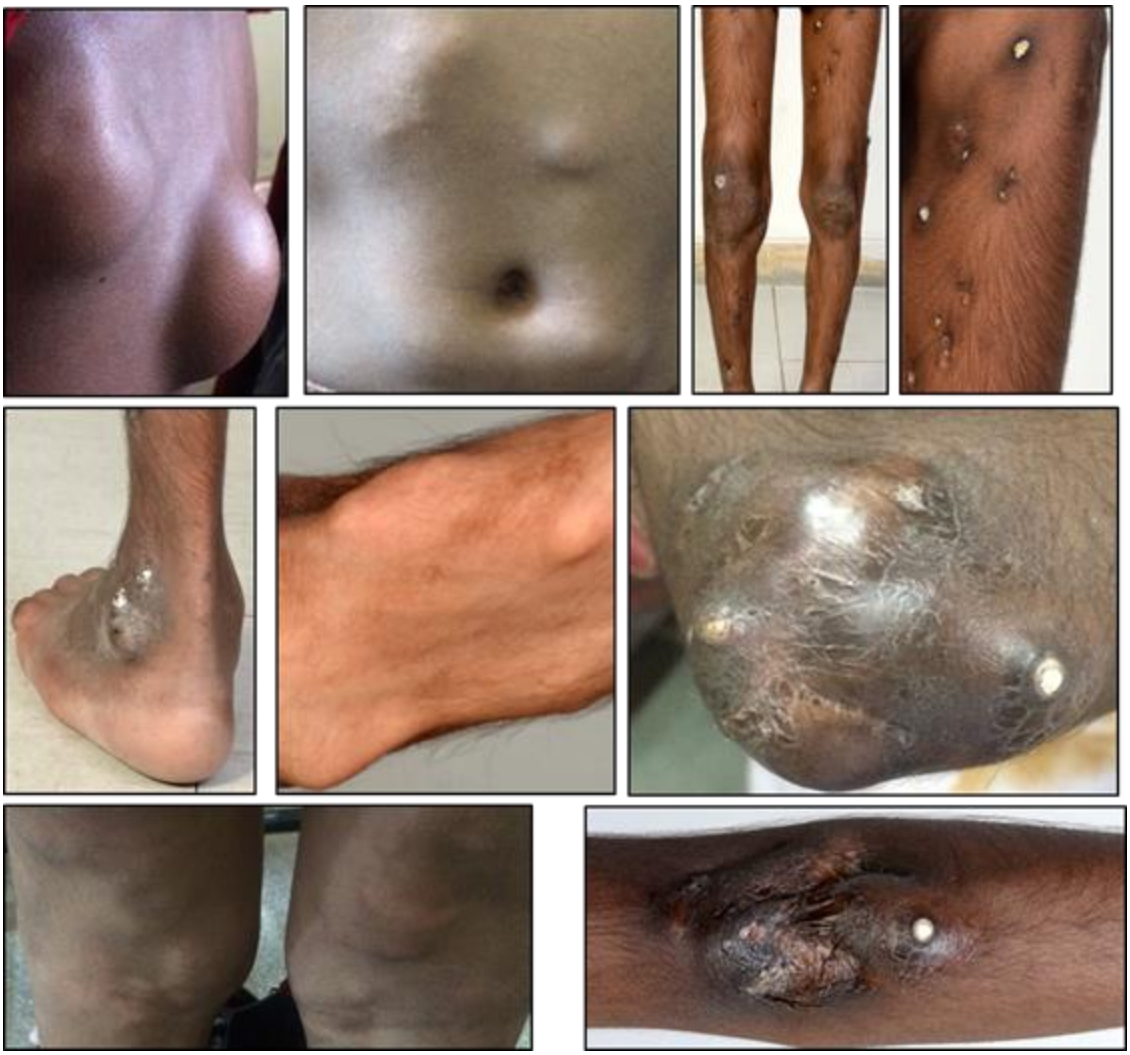

Figure 1: Calcinosis in children with JDM

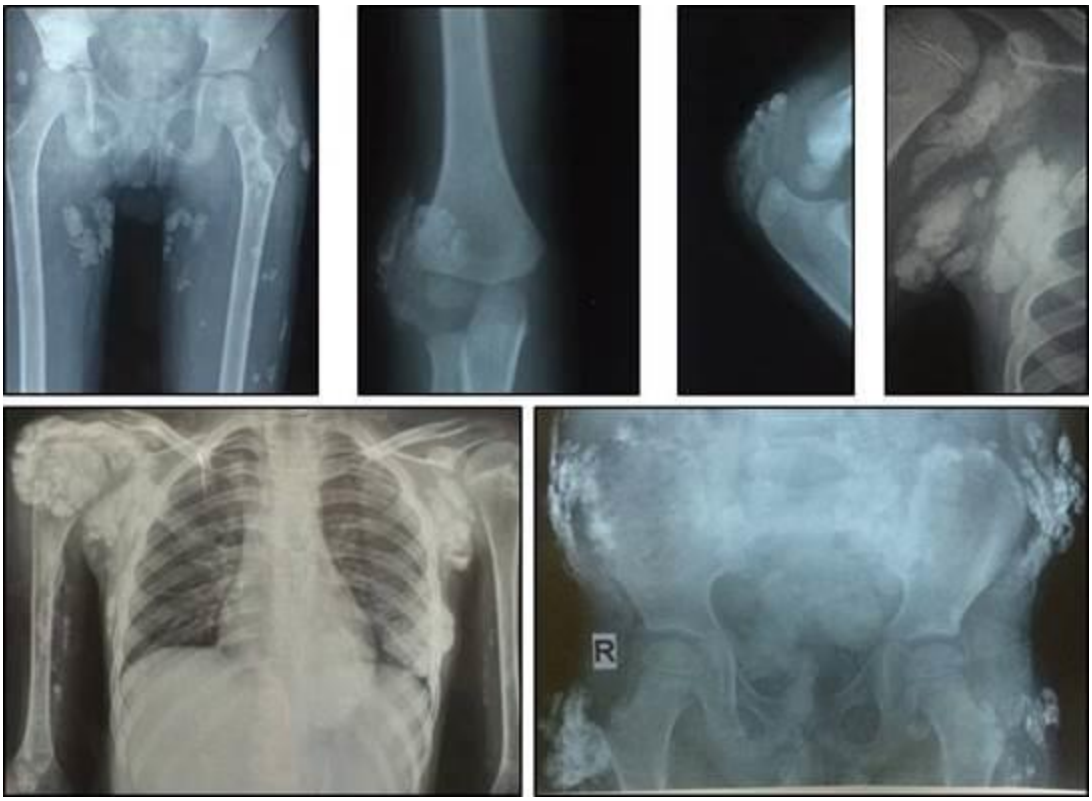

Figure 2: Radiographs showing Calcinosis in children with JDM

235 - Small Fiber Neuropathy in a Patient with Amyopathic Dermatomyositis, and Positive P155/ 140 Autoantibody

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Background: P155/140 autoantibody is associated with Dermatomyositis (DM). It has been shown that anti-p155/140- positive cases have more severe cutaneous involvement and an increased risk of malignancy.

Methods: A 59-year-old Caucasian female with Amyopathic Dermatomyositis (ADM) was referred to our clinic for bilateral upper extremity burning sensation and pain worsening over 3 months prior to visit. Patient was diagnosed with ADM based on cutaneous macular rash with no weakness. EMG/ NCS and muscle biopsy were unremarkable. Myositis panel was negative except positive anti- P155/ 140 antibody.

On neuroexamination, patient had patchy decreased sensation to soft touch and pinprick in bilateral upper and lower extremities, decreased vibration and position sensation in bilateral toes, and positive Romberg test.

Results: Neuropathy work- up including Hb A1c, serum vitamin B1, B6, B12, Methylmalonic acid, Folic acid, and Copper levels as well as serum and urine protein electrophoresis were normal. Skin biopsy was consistent with Small Fiber Neuropathy (SFN).

Conclusion: Our patient with ADM, positive P155/140 antibody and sensory symptoms was found to have SFN. We propose that P155/140 antibody might have played a role in development of SFN and that this antibody might be associated with different diseases. Further case- reports and studies are required to delineate the possible association between other autoimmune pathologies and P155/140 antibody.

236 - Subgroups of Low-Score Muscle Biopsies in Juvenile Idiopathic Inflammatory Myopathies

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Background: Juvenile idiopathic inflammatory myopathies encompass several new clinico-serological subtypes. We hypothesised that myopathological findings may align with these, potentially indicating differences in pathogenesis.

Methods: We studied a cohort of 101 muscle biopsies from patients with clinically and serologically defined juvenile idiopathic inflammatory myopathy. Biopsies were analysed using the international JDM score tool and by blinded histological review. Autoantibody data were correlated with histological findings.

Results: Autoantibody analysis was available for 90 cases. Major autoantibody groups in the cohort were positive for anti-TIF1γ (18/90), -NXP2 (15/90), -MDA5 (11/90), -Mi2 (5/90), and -PmScl (6/90). JDM severity scores had a wide interquartile range with consistently low scores in the MDA5 positive group, high scores in the Mi2 positive group, and wide score distribution in the other groups. Based on histological review, low score biopsies without significant fibre pathology across all groups were subdivided into a group with diffuse endomysial macrophage infiltrates combined with MHC class I expression (40/101) and a minimal change group meeting only one or none of these criteria (24/101). Minimal change pathology segregated predominantly in the MDA5 group, while diffuse endomysial macrophage pathology constituted a large proportion of cases in the NXP2 and TIF1g groups, suggesting pathobiological significance. High score biopsies were grouped under 6 descriptive labels indicating dominant fibre pathology: Perifascicular atrophy (22/101), macrophage rich necrosis (6/101), scattered necrosis (2/101), clustered necrosis (2/101), inflammatory fibre invasion (2/101), and chronic myopathic change (1/101). High-score biopsies from most serological groups fell into more than one descriptive category but systematic differences were difficult to ascertain given small numbers.

Conclusion: These data suggest that low-score biopsies in TIF1g and NXP2 serological subgroups differ from MDA5 associated biopsies in their degree of macrophage infiltration and MHC I expression. Evidence is accruing that MDA5 inflammatory myopathy is pathobiologically distinct.

237 - Muscle Ischemia is Associated with AntiNXP2 Autoantibodies in Juvenile Dermatomyositis

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Background: Myositis-associated autoantibodies are useful biomarkers to divide juvenile dermatomysitis (JDM) into different subgroups. Anti-NXP2 antibodies are present in 20% of JDM (Tansley et al, 2014) and reported to be associated with increased risk of calcinosis and less primary inflammation on the histological study (Pinal-Fernandez et al., 2015). However, clinical outcome and histological features of NXP2 patients remain not well known yet. The aim of this study was to define the frequency and associated clinical and histological phenotype of anti-NXP2 autoantibodies in patients with JDM.

Methods: We retrospectively assessed clinical, biological and histological findings from 12 consecutive JDM patients diagnosed from June 2013 to January 2015. Systematic auto-antibodies screening (Mi2, MDA5, TIF1-gamma, NXP2, SAE, Ro52, Jo1, PL7, PL12, EJ, SRP, Ku, PM-Scl, Scl70,) and myopathological study of deltoid muscle biopsy (including immunohistochemistry for endothelial cells (CD31/PECAM), regenerating myofibers (CD56/NCAM) macrophages (CD68), T cells (CD3), B cells (CD20), anti-human major histocompatibility complex (MHC) class I (HLA-ABC), class II (HLA-DR), and C5b-9/MAC) were performed in all patients. All biopsies were reviewed using the recently validated score tool for muscle biopsy evaluation in patients with JDM (Varsani et al, 2015).

Results: Anti-NXP2 antibodies were identified in 5/12 of JDM patients. Patients with NXP2 auto-antibodies (NXP2+ group) as compared to those without NXP2 auto-antibodies (NXP2- group) exhibited more severe clinical presentation including vasculopathy-related features (limb subcutaneous edema, gastrointestinal involvement) leading to more aggressive treatment (plamapheresis and immunoadsorption). Regarding the histological features, NXP2+ group compared to NXP2- group displayed more frequent myofibers with ischaemic punch-out vacuoles, microinfarcts and capillary dropout (p=0,07 for vascular lesions, Varsani score).

Conclusion: Positive detection of anti-NXP2 abs in JDM may contribute to indentify patients with more severe ischemic involvement and adapt therapeutic strategy.

238 - Major Histocompatibility Complex (MHC) Class II Immunostaining for Diagnosing Inflammatory and Dysimmune Myopathies

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Background: Idiopathic immune myopathies (IIM) are commonly divided in four main groups: dermatomyositis (DM), polymyositis (PM)/inclusion body myositis (IBM), necrotizing autoimmune myopathy (NAM), and overlap myositis (OM). Current diagnostic approaches of IIM require immunohistochemical evaluation of lymphocyte subsets, myofiber MHC-1 expression and complement activation (C5b9). Recently, we demonstrated that OM with antisynthetase antibodies was characterized by myofiber MHC-II/HLA-DR expression with unique perifascicular pattern.

Methods: We retrospectively evaluated myopathological findings from 505 patients who had muscle biopsy for diagnostic purposes. Immunohistochemistry was performed for MHC-I/HLA-ABC, MHC-II/HLA-DR, membrane attack complex (C5b-9), NCAM/CD56 expression, and inflammatory cell subsets. The pattern of MHC-II myofiber expression was classified as (i) perifascicular, (ii) patchy, or (iii) absent, and was blindly compared to the clinicopathological diagnosis.

Results: IIM was diagnosed in 137/505 (27.1%). Myofiber MHC-II expression was observed in 55 cases (10.9%), and was perifascicular in 20 (OM in 13/20) and patchy in 35 (IBM or PM 20/35). Perifascicular and patchy MHC-II patterns correlated with the diagnosis of OM and IBM, respectively ($p<0.0001$). Among the 450 MHC-II-negative cases, 82 (18.2%) patients had IIM, including all patients with NAM (n=17). In the 20 patients with DM, 19 (95%) were negative for MHC-II.

Conclusion: Myofiber MHC-II immunostaining is useful for the differentiation of IIM subsets with three distinctive situations: perifascicular positivity in OM, patchy positivity in IBM, and negativity in DM and NAM.

239 - Expression of Type I and Type II Interferons is Increased in Muscle Biopsies of Juvenile Dermatomyositis Patient and Related to Clinical and Histological Features

Gian Marco Moneta[*1], Denise Pires Marafon[1], Margherita Verardo[1], Adele D'Amico[1], Luisa Bracci-Laudiero[1,2], Fabrizio De Benedetti[1] and Rebecca Nicolai[1]

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Background: Juvenile dermatomyositis (JDM) is the most common autoimmune inflammatory myopathy of childhood, with a still not fully clarified immunopathogenesis. There is substantial evidence for an involvement of interferons (IFNs) in the chronic inflammation that characterizes JDM. A better characterization of their role may provide promising targets for new therapies. The aim of this study was to investigate the expression of type I (IFNα/β) and type II (IFNγ) IFN inducible genes in muscle biopsies of JDM patients and their correlations with clinical and histological aspects in these patients.

Methods: In a retrospective cohort of patients diagnosed with JDM (n=22), mRNA expression levels of specific genes induced by IFNα/β (IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1), by IFNγ (CXCL9, CXCL10, CXCL11, CIITA), and IFNγ itself, were analyzed from muscle biopsies and compared with samples from Duchenne muscular dystrophy (DMD) patients (n=24). We also analyzed mRNA expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. For each patient charts were reviewed to record clinical features at diagnosis, physician's global assessment of the patient's overall disease activity, serum levels of muscle enzymes (CK, ALT, AST, LDH), ESR, CRP level, antinuclear antibodies status, time to inactive disease, number of immunosuppressants used over disease course and relapses. We also evaluated typical histological aspects of JDM (inflammatory infiltrate, necrosis, perifascicular atrophy, fibrosis) on tissue sections of the muscle biopsies.

Results: Since steroid therapy strongly reduced expression levels of cytokines, JDM patients treated before biopsy were excluded from final statistics. The mRNA expression of type I IFN signature genes ("I-IFN score") was higher in untreated JDM patients (n=16) compared with DMD patients ($p<0.0001$). Expression levels of IFNγ, CIITA, CXCL9, CXCL10, and CXCL11 ($p<0.01$, $p<0.01$, $p<0.01$, $p<0.0001$, $p<0.0001$) were significantly higher in biopsies of untreated JDM patients compared with those of DMD patients. Expression levels of TNF-α, but not IL-6 and IL-1β, were higher in untreated JDM samples compared with those of DMD patients ($p<0.01$). I-IFN score correlated with ERS, time to inactive disease and number of immunosuppressants of untreated JDM patients ($p<0.05$, $p<0.05$, $p<0.01$). IFNγ mRNA levels correlated with time to inactive disease and polycyclic disease course ($p<0.05$, $p<0.01$). Moreover, we performed histological analysis of JDM patient biopsies to evaluate quantity of muscle inflammatory infiltrate, necrosis, perifascicular atrophy and fibrosis. We also found that type I-IFN score correlated with inflammatory infiltrate and necrosis ($p<0.01$), while IFNγ correlated with inflammatory infiltrate, perifascicular atrophy and fibrosis ($p<0.05$, $p<0.05$, $p<0.01$).

Conclusion: The increased expression of IFN related genes in muscle biopsies of JDM patients and their association with clinical and histological features suggest a pathogenic role of IFNs in muscle damage and inflammation in JDM. Thus, both type I and type II IFNs pathways may represent therapeutic targets in JDM.

240 - Increased IL-9 Levels in Sera, Muscle, and Skin of Patients with Dermatomyositis

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Background: Dermatomyositis (DM) is an autoimmune connective tissue disorders characterized by the inflammation of striated muscle. The aim of this study is to investigate serum interleukin 9 (IL-9) levels and the expression of IL-9 in the muscle and skin tissues of patients with DM.
Methods: Serum IL-9 levels in 40 patients with DM were measured using an enzyme-linked immunosorbent assay (ELISA). IL-9 expression in affected skin and muscle tissues was examined by immunohistochemical staining.
Results: In ELISA assay, serum IL-9 levels were significantly higher in patients with DM than in healthy controls (6.4 ± 17.8 pg/ml vs 1.7 ± 4.4 pg/ml, respectively, $p < 0.05$). All 4 patients with elevated serum IL-9 levels were positive for the anti-Mi-2 antibody (Ab), and IL-9 levels were significantly higher in patients with than in those without anti-Mi-2 Ab (29.9 ± 36.1 pg/ml vs 1.6 ± 1.9 pg/ml, respectively, $p < 0.001$). CD4+IL-9+ T cells were observed in both the skin and muscle tissues of DM patients with elevated serum IL-9 levels.
Conclusion: These results suggest that IL-9 may be involved in the development of DM and serve as a biological marker for the severity of myositis.

241 - Itch in Dermatomyositis and the Role of Increased Skin Interleukin-31

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Background: Interleukin-31 (IL-31) has been implicated in pruritus associated with various itchy skin diseases, including atopic dermatitis and cutaneous T cell lymphoma. While pruritus is a prominent feature in dermatomyositis (DM), there are few studies to evaluate clinical characteristics and pathogenesis of itch in DM. We examined the prevalence and severity of pruritus in patients with DM, and hypothesized that IL-31 and IL-31 receptor contributed to the pathophysiology itch in DM patients.

Methods: Pruritus and disease activity of DM were evaluated by a visual analog scale (VAS) and the Cutaneous Disease and Activity Severity Index (CDASI), respectively. Gene expression of IL-31 and IL-31 receptor alpha (IL-31RA) in lesional DM skin was evaluated by qRT-PCR, and was compared with that of non-lesional DM and healthy control (HC) skin. Immunohistochemical analysis assessed IL-31 expression in skin tissue. To identify cellular sources of IL-31 in DM, flow cytometry was performed on skin cells isolated from lesional DM skin, using CD4, CD8, CD11b, CD11c, CD68 as cell population markers.

Results: Half of 164 patients with DM (25 male, 139 female; 61 classic DM and 103 clinically amyopathic DM; mean age ± SD 52.5 ± 14 years) had moderate to severe itch (28.66% moderate, 20.73% severe itch). Pruritus in DM was positively correlated with disease activity, with a correlation coefficient of 0.337 between VAS itch score and CDASI activity score ($p<0.01$). IL-31 gene expression was significantly higher in lesional DM skin than either non-lesional DM ($p<0.05$) or HC skin ($p<0.01$). IL-31RA gene expression was upregulated only in lesional DM skin compared to HC skin ($p<0.05$). IL-31 mRNA expression was positively correlated with VAS itch score ($r= 0.6748$, $p=0.039$). Immunoreactivity for IL-31 was also stronger in lesional skin of DM ($p=0.0001$). Flow cytometry showed that CD4+ cells are the most common cell types to produce IL-31 in DM, while other cell types that express CD8, CD68, CD11b, or CD11c also secrete IL-31 in DM.

Conclusion: We confirmed that itch is a prevalent symptom in many patients with DM involving the skin, and that skin IL-31 is significantly higher in DM than in HC. This is the first study to suggest IL-31's crucial role in the skin for pruritus in DM.

242 - Finger Eruptions Histologically Characterized by Psoriasiform Dermatitis and Eczematous Reaction in Dermatomyosits with Anti-aminoacyl-tRNA Synthetase Antibodies

Naoko Okiyama*[1], Rei Watanabe[1], Yukie Yamaguchi[2], Masanari Kodera[3], Yasuhito Hamaguchi[4], Hiroo Yokozeki[5], Naoko Ishiguro[6] and Manabu Fujimoto[1]

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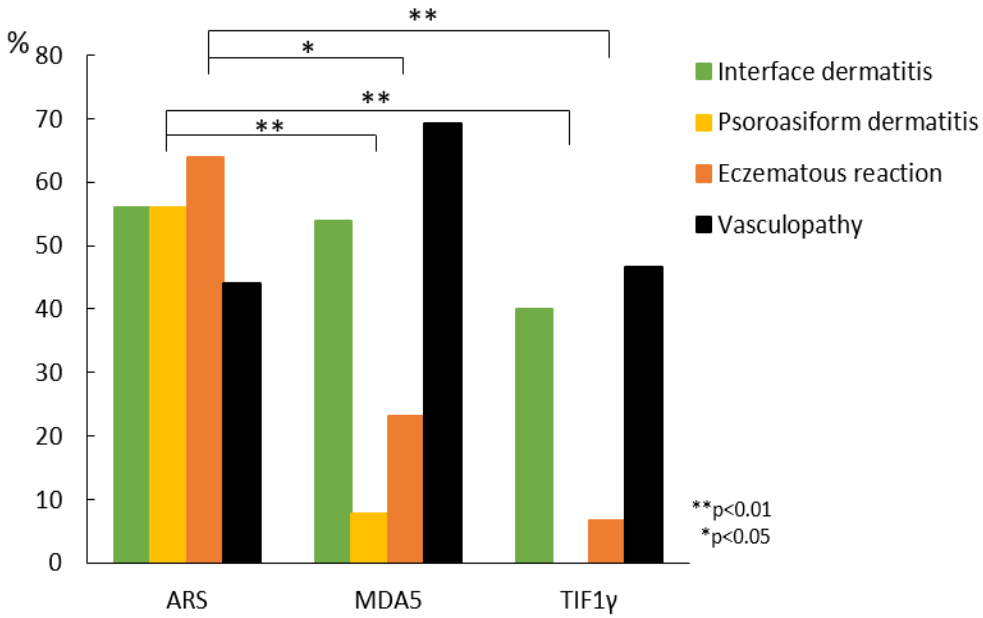
Background: Characteristic eruptions on the fingers of patients with dermatomyositis (DM) include Gottron's papules, palmer erythema and mechanic's hand, which develop on the dorsal, palmar and lateral fingers, respectively. There are few reports that show histological analyses of the features.

Methods: Skin biopsy specimens stained with H & E from the fingers of DM patients with anti-aminoacyl-tRNA synthetase (ARS) antibodies (25 cases), anti-melanoma differentiation-associated protein 5 (MDA5) antibodies (13 cases), and anti-transcriptional intermediary factor 1 (TIF1)-γ antibodies (15 cases) were analyzed histologically. We classified the histological findings to (i) interface dermatitis with liquefaction degeneration and dyskeratotic keratinocytes, (ii) psoriasiform dermatitis with psoriasiform acanthosis and parakeratosis, (iii) eczematous reaction with epidermal spongiosis, and (iv) vasculopathy with infiltration of inflammatory cells into vessel walls and hemorrhagia.

Results: Interface dermatitis was observed in half of the specimens from each group of ARS, MDA5 or TIF1-γ. Fourteen patients in ARS group (56 %) developed psoriasiform dermatitis, while only one patient did in MDA5 and TIF1-γ groups (7.7 % and 0 %, respectively). Moreover, eczematous reaction was observed more frequently in ARS group (16 cases, 64.0 %) than in MDA5 group (3 cases, 23.1 %) and in TIF1-γ group (one case, 6.7 %). In contrast, vasculopathy was found often in MDA5 group (9 cases, 69.2 %).

Conclusion: These results argue that eruptions on the fingers of DM patients with anti-ARS antibodies, which include Gottron's papules and mechanic's hand, are characterized by not only interface dermatitis but also psoriasiform dermatitis and eczematous reactions. In addition, vasculopathy might be a distinctive feature for cases with anti-MDA5 antibodies.



243 - Combined Evaluation of Myositis-specific Autoantibodies and Serum Conventional Biomarkers is Useful for Stratification of Prognosis in Polymyositis/Dermatomyositis with Interstitial Lung Disease

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Background: Interstitial lung disease (ILD) is one of the poor prognosis factors in polymyositis (PM)/dermatomyositis (DM). Clinical course and prognosis of ILD depend on the subtypes of ILD in PM/DM. Detection of myositis-specific autoantibodies (MSAs) is extremely useful for prediction of clinical characteristics, including clinical course, response to treatment and prognosis in PM/DM. Anti-amynoacyl-transfer RNA synthetase (ARS) and anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies are strongly related to the complication of ILD in PM/DM. ILD with anti-MDA5 is more rapidly progressive and poorer prognosis than ILD with anti-ARS. In addition, serum inflammatory markers such as C-reactive protein (CRP) and ferritin, and serological marker of ILD such as KL-6 and surfactant protein-D (SP-D), are relatively simply measured and useful for evaluation of disease activity/severity of ILD in daily clinical practice.

The aim of this study is to investigate stratification of prognosis in PM/DM with ILD, using data of MSAs and conventional serum biomarkers mentioned above.

Methods: From a multicenter cohort of PM/DM-ILD including 44 institutions, 497 patients with PM/DM-ILD who satisfied Bohan and Peter criteria were enrolled. Anti-MDA-5 antibody and anti-ARS antibody was detected by enzyme linked immunosorbent assay and immunoprecipitation, respectively. We investigated risk factors for prognosis using MSAs and serum biomarkers including CRP, ferritin, KL-6 and SP-D.

Results: The overall survival rate was 83% at 1 year, 81% at 2 years in the entire cohort. The mortality rate was significantly higher in the subset with CRP≥1 mg/dl or ferritin≥500 ng/ml in patients with anti-MDA-5 (n=206) or those with anti-ARS (n=159). On the other hand, in patients without anti-MDA-5 or anti-ARS, the mortality rate was significantly higher in the subset with KL-6≥1000 mg/dl or SP-D≥100 ng/ml. The multivariate analysis revealed that a presence of anti-MDA-5 (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.0-5.9), CRP≥1 mg/dl (HR 2.7, 95%CI 1.6-4.7) and KL-6≥1000 mg/dl (HR 2.2, 95%CI 1.3-3.7) were risk factors for poor prognosis in PM/DM with ILD. The mortality rate was less than 5%, 10%, 35% and 60% in patients without any risk factors, with any one, with any two and with all of the three, respectively.

Conclusion: The combined evaluation of autoantibodies and serum biomarkers is a significant clinical tool to stratify prognosis of PM/DM-ILD.

244 - Expression of Circulating MicroRNAs in Patients with Idiopathic Inflammatory Myopathies

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Background: MicroRNAs (miRNAs) are small noncoding RNAs that modulate protein translation and regulate numerous immunologic and inflammatory pathways involved in autoimmune reactions. Idiopathic inflammatory myopathies (IIM) are a group of connective tissue diseases of unknown etiology characterized by chronic inflammation and the production of autoantibodies. Our objective was to investigate the expression of cell-free circulating miRNAs in patients with IIM compared to controls to assess biomarker and disease subgrouping and disease activity potential.

Methods: Eighty-two well-characterized patients diagnosed with IIM (poly- or dermatomyositis) and 104 age and sex matched controls from the general Danish population were included in the study. Total RNA was purified from plasma and 46 different specific, mature miRNAs were determined using qRT-PCR on a microfluidic platform. To investigate the expression of circulating miRNAs between IIM patients and controls univariate non-parametric analysis was applied.

Results: Forty-two miRNAs were consistently detected. Of those, 13 circulating miRNAs were identified to be differentially distributed in IIM patients compared to controls. There were no obvious correlations with autoantibody status, disease activity or other recorded parameters.

Conclusion: The study shows, for the first time that patients with IIM have a differential expression of circulating miRNAs compared to controls. Even though the results need to be validated in independent cohorts they do suggest diagnostic uses of miRNA profiling in this group of patients as well as clues to possible dysregulated pathways associated with IIM.

245 - Microarray Analysis of MicroRNA Expression in Peripheral Blood Cells of Polymyositis and Dermatomyositis

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Background: MicroRNAs (miRNAs) have emerged as a new class of biomarker in connective tissue diseases, but the expression of miRNAs in peripheral blood mononuclear cells (PBMCs) of patients with polymyositis (PM) and dermatomyositis (DM) has not been fully studied. In this study, we investigated miRNAs expression profile in PBMCs from PM /DM patients.

Methods: Microarray technology was used to investigate differentially expressed miRNAs obtained from 6 untreated PM/DM patients and 3 healthy controls (HCs). TaqMan-based stem-loop real-time polymerase chain reaction was used for validation in 34 PM/DM patients and 20 HCs.

Results: Microarray analysis of the PM/DM patients and HCs revealed 38 differentially expressed miRNAs, 24 up-regulated and 14 down-regulated. Four miRNAs (miR-320a, miR-335-3p miR-34a-5p and miR-454-3p) were chosen for real-time PCR validation in PM/DM patients and HCs. The expression of miR-34a-5p was significantly up-regulated in PM/DM group($P < 0.05$). In subgroup analysis, miR-34a-5p was significantly up-regulated in interstitial lung disease (ILD) group and DM group ($P < 0.001$). The level of SIRT1, a validated target of miR-34a, was significantly lower in PBMCs of PM/DM patients compared to HCs.

Conclusion: There is a possibility that miR-34a-5p participates in the pathogenesis of PM/DM through SIRT1 and miR-34a-5p may be used as a new biomarker for PM/DM.

246 - Increased Levels of Soluble Programmed Death Ligand 1 (sPD-L1) in Patients with Dermatomyositis /Polymyositis and the Association with Malignancy

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Background: The programmed death 1 /programmed death ligand 1 (PD-1/PD-L1) pathway is one of the immune checkpoint signaling functioning by regulating immune responses. However, the impact of soluble form of programmed death ligand 1 (sPD-L1) in idiopathic inflammatory myopathies (IIMs) remains unknown. Here we aimed to investigate the expression of sPD-L1 in dermatomyositis /polymyositis patients and evaluate its association with malignancy.

Methods: sPD-L1 levels were measured in serum from 152 patients with DM/PM (30 patients with malignancies), 78 disease controls (48 other autoimmune diseases and 30 solid cancers) and 30 healthy individuals by ELISA. We use Myositis Disease Activity Assessment (MYOACT) scores to evaluate disease activity of IIM patients.

Results: Serum concentrations of sPD-L1 were significantly increased in DM/PM patients [13.60ng/ml(2.45-46.88ng/ml)] compared to healthy individuals[1.39ng/ml(0-6.26ng/ml), $p<0.001$]. Serum sPD-L1 in IIM patients positively correlated with disease activity ($r=0.391$, $P=0.0399$) and patients received corticosteroids or immunosuppressive agents before admission had lower sPD-L1 levels than those not [13.36ng/ml(5.253-43.01ng/ml) VS. 16.07ng/ml(5.379-35.11ng/ml),$P=0.032$]. In our cohort, there are 30 IIM patients with malignancies and 12 patients among them were newly diagnosed with cancers. Notably, the mean sPD-L1 level in IIM patients with newly diagnosed cancers is 22.03ng/ml, which was much higher than in IIM with stable cancers (10.66ng/ml, $P<0.0001$). ROC curve analysis revealed that the sPD-L1 cutoff value that best discriminated IIM patients with newly diagnosed cancers from others was 17.76ng/ml and the diagnostic sensitivity and specificity was 83.3% and 71.2% respectively. The area under the curve was 0.746 and the 95% Confidence interval (CI) was 0.606-0.807, $P=0.005$.

Conclusion: Increased serum concentrations of sPD-L1 may play an important immune regulatory role in disease progression of IIM and high sPD-L1 level is a possible indicator for newly diagnosed with malignancies.

247 - Serum Muscle Damage Markers in the Idiopathic Inflammatory Myopathies: Quantifying Disease Activity and Identifying Cardiac Involvement

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Background: Limitations in methods of quantifying and monitoring disease activity in the idiopathic inflammatory myopathies (IIM) may contribute to poor outcomes. Cardiac involvement occurs in up to 75% of IIM but is under-recognised and often subclinical.

We investigated the role of a panel of serum muscle damage markers (creatine kinase [CK], cardiac troponin T [cTnT], cardiac troponin I [cTnI] and creatine kinase-MB [CK-MB]) in quantifying disease activity and identifying cardiac involvement in IIM. Each marker is thought to be differentially indicative of damage to different muscle types, with cTnI felt to be most specific for cardiac disease.

Methods: Adults with confirmed IIM (n=43) were evaluated using the International Myositis Assessment and Clinical Studies Group disease activity Core Set Measures (CSMs), and by measurement of serum CK, cTnT, cTnI and CK-MB. Cardiac involvement was assessed using the cardiac domain of the Myositis Disease Activity Assessment Visual Analogue Scales (cardiac-MYOACT).

Spearman's ranked correlation was used and differences between those with 'active' and 'inactive' disease (using the Rituximab in Myositis study definitions) were examined using logistic regression.

Results: Disease subgroups included dermatomyositis (47%), polymyositis (37%), anti-synthetase syndrome (12%) and connective tissue disease-overlap (5%). The mean age was 53 years (SD 16). 74% were female.

The different markers correlated strongly with each other, except cTnI which did not correlate significantly with CK. cTnT levels correlated significantly with manual muscle test (rho -0.403, p=0.005) and Health Assessment Questionnaire (HAQ) (rho 0.330, p=0.025) results. CK-MB levels correlated significantly only with the HAQ (rho 0.306, p=0.041). CK and cTnI levels did not correlate significantly with any other CSM.

cTnT levels were significantly higher in active compared to inactive disease (median 220 versus 22 ng/L, p=0.009). There were also non-significant trends towards increased CK and CK-MB, but no difference in cTnI levels between these groups. In those with a normal CK (n=26), cTnT was increased in 39%, cTnI in 12%, and CK-MB in 19%. None of these cases had a cardiac-MYOACT score >0. However, using cTnT, cTnI or CK-MB instead of CK within the active disease definition failed to identify any additional cases.

No marker reliably predicted a cardiac-MYOACT score >0. Where this was >0 (n=6), raised CK and cTnT levels were found in all whereas cTnI and CK-MB levels were raised in 33%. During follow-up 67% of those with a raised cTnI (n=6) were felt to have cardiac involvement. In such cases, there was a trend towards higher cTnT levels compared to those with a normal cTnI (median 121 versus 22 ng/L, p=0.134).

Conclusion: Using cTnT and CK-MB may improve accuracy when quantifying IIM disease activity. We did not identify a marker that was reliably predictive of cardiac involvement, although a raised cTnI in combination with very high cTnT levels may be indicative.

248 - Galectin-9, CXCL10 and TNFR2, Biomarkers for Disease Activity in Juvenile Dermatomyositis, Are Myositis Specific and May Reflect Highly Activated and Dysfunctional Endothelium

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Background: Juvenile dermatomyositis (JDM) is a chronic systemic autoimmune disease in children, affecting the microvasculature in muscle and skin, causing muscle weakness and a typical skin rash. Clinical evaluation of disease activity remains challenging, as reliable and objective markers for disease activity are lacking. We identified three proteins that highly correlate with disease activity in two independent JDM cohorts: Galectin-9 (Gal-9), CXCL10 and TNF receptor 2 (TNFR2). Here, we aimed to validate their biomarker potential and assess their disease specificity. As endothelial cells are important producers of these proteins, we further explored the endothelial function and activation in patients with JDM compared to other pediatric and adult systemic autoimmune diseases.

Methods: A panel of 22 analytes, comprising previously identified disease biomarkers and proteins reflecting endothelial function and activation, was measured in serum of pediatric and adult patients with dermatomyositis, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and morphea by multiplex immunoassay. Data were analyzed using principal component analysis (PCA) and non-parametric ANOVA.

Results: Gal-9, CXCL10 and TNFR2 again potently discriminated between active disease and remission in JDM. This biomarker potential proved to be specific for (J)DM. PCA of all measured analytes, including endothelial markers, separated the patient cohort into three main disease clusters: myositis, SLE and morphea. Notably, all patients with clinical myositis clustered together, regardless of their primary diagnosis (SLE, MCTD, JDM). The proteins responsible for this separation were Gal-9, CXCL10, TNFR2, CCL2, soluble VCAM-1 and ICAM-1. This protein combination may thus be specific for myositis. Additionally, we found evidence for a highly activated endothelium in JDM during active disease. Furthermore, JDM patients had a disturbed balance between angiogenic and angiostatic proteins, including low levels of VEGF and angiopoietin-1 and high levels of soluble Tie-2, during both the active and chronic phase of the disease.

Conclusion: We confirmed the biomarker potential of Galectin-9, CXCL10 and TNFR2, which highly correlate with disease activity in JDM. Introduction of these biomarkers into clinical practice can facilitate tailor-made personalized treatment. In combination with ICAM-1, VCAM-1 and CCL2 these proteins seem specific for myositis, independent of the 'background disease'. Their high levels combined with the profile of endothelial activation and dysfunction in JDM patients points toward the involvement of endothelium in the pathogenesis of JDM.

249 - Molecular Targeted Imaging Biomarkers for Personalized Medicine Strategies in Interstitial Lung Disease

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Background: Interstitial lung disease (ILD) is a life-threatening complication in myositis and systemic sclerosis (SSc). Substantial research progress has identified distinct genomic and molecular subtypes and brought targeted therapies within reach. However, personalized medicine approaches are lacking since clinically applicable tools for individualized patient stratification are not yet available. Thus, we evaluated molecular targeted imaging as potential biomarker for the stage-dependent assessment of ILD in the mouse model of bleomycin-induced lung fibrosis.

Methods: Expression of integrin αvβ3 and FR-β was analyzed in lung sections from patients with idiopathic pulmonary fibrosis (IPF), SSc-ILD (n=5-6), and healthy controls (n=4-5) as well as from bleomycin treated mice and saline treated controls (n=6) using immunohistochemistry. In vivo imaging was performed at days 3, 7, and 14 using the integrin $\alpha_v\beta_3$-specific ^{177}Lu-c(RGDfK)-ligand, ^{177}Lu-folate, and ^{18}F-FDG. The specific pulmonary accumulation of the radiotracers over time was confirmed by ex vivo SPECT or PET/CT and biodistribution studies.

Results: In IPF and SSc-ILD, the expression of integrin αvβ3 was increased compared with healthy controls ($p<0.05$). In contrast, FR-β expression on activated macrophages was only upregulated in SSc-ILD ($p<0.05$). Notably, in vivo SPECT/CT targeting integrin αvβ3 and FR-β (Fig.1A) successfully visualized ILD in the bleomycin lung model thereby discriminating pulmonary inflammation and/or incipient fibrosis in a time-dependent manner in correspondence with the expression on tissue level (Fig.1C), The pulmonary accumulation of ^{177}Lu-c(RGDfK)-ligand, ^{177}Lu-folate, and ^{18}F-FDG in diseased lungs was about 2-fold, 1.9-fold and 6-fold enhanced compared to controls. The biodistribution data were confirmed by ex vivo SPECT/CT and PET/CT scans (Fig.1B).

Conclusion: Our preclinical data suggest that the stage-dependent in vivo visualization of ILD with radiotracers, that specifically target key molecular players of inflammation and fibrosis, has great potential for clinical application. As opposed to the unselective imaging of metabolic activity by ^{18}F-FDG, the introduction of non-invasive and specific imaging biomarkers for the individualized management of patients with ILD in the context of myositis or SSc could represent the first step towards precision medicine.

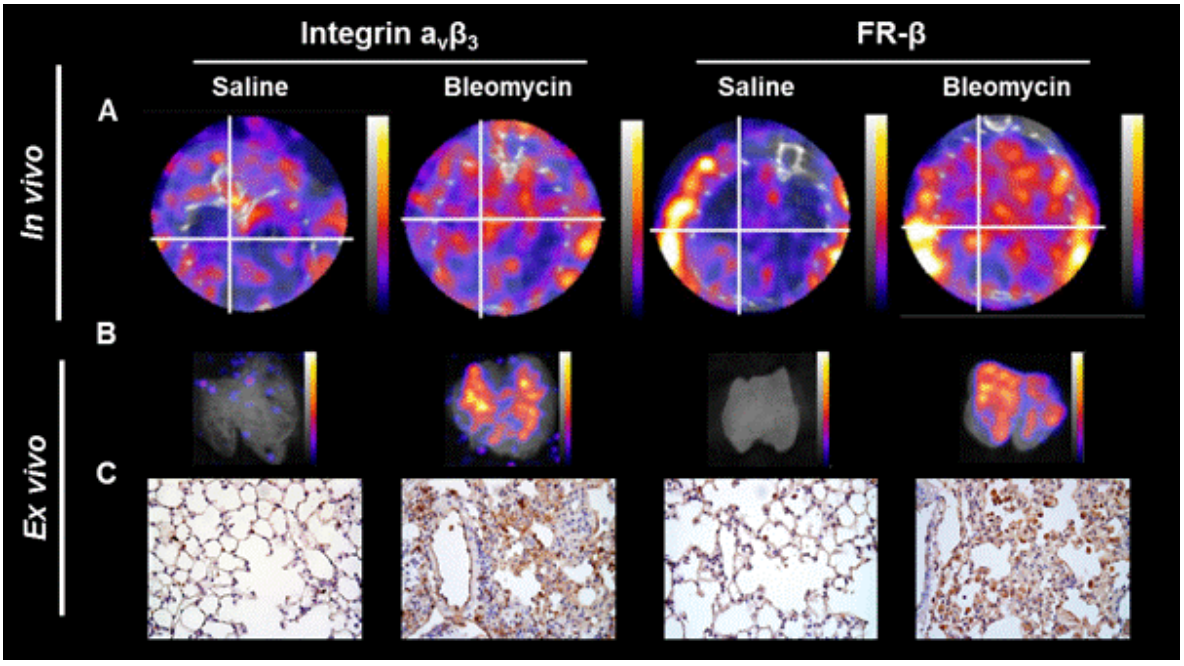

Figure 1

250 - Early Detection of Soft Tissue Calcification Using Electrical Impedance Spectroscopy

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Background: Calcinosis is a debilitating challenge as it occurs in about 40% of patients with Juvenile Dermatomyositis. The knowledge on pathogenesis and stages of calcinosis is sparse. It is crucial to identify the process of calcinosis, as early as possible as it becomes increasingly difficult to resolve as calcinosis progresses in size, density and numbers throughout the soft tissues. Currently, there is no effective or practical (office-based) method to allow early detection of calcinosis. Our long-term objective is to utilize Electrical Impedance Spectroscopy (EIS) to measure the electrical impedance across tissue, and use the information to screen early stages of calcinosis.

Methods: We developed a device prototype using the Arduino Technology Platform with clinical grade electrodes. Electrodes can be placed on the surface of the tissue to deliver current into the tissue and also, to collect voltage readings across the tissue simultaneously. The device was interfaced with a Matlab based graphical user interface (GUI) for intuitive data collection and signal processing while providing a user-friendly interface. The impedance was determined based on the applied known current and collected voltage readings. The device was tested on synthetic skin tissues (SynDaverTM) presoaked with calcium phosphate at varying concentrations ranging from healthy levels to high levels found in metastatic calcification. Testing was performed by placing electrodes on synthetic tissue surface at varying distances for current delivery at various frequencies. The results were displayed graphically for impedance versus frequency.

Results: The impedance increased as the distance between electrodes increased within a tested frequency. This was a common trend for all tested frequencies within a tested concentration level of calcium phosphate present in the synthetic tissue. Furthermore, for a given concentration of calcium phosphate in the sample tissue, as the tested frequency value was increased, the impedance dropped sharply and then leveled off at a characteristic impedance value. The rate of impedance drop and the saturation limit of the impedance provided the signature values.

Conclusion: A low impedance spectroscopy device was developed to operate in a frequency range between 300 Hz and 10 kHz with a user-friendly GUI. Our preliminary findings indicate that the concentrations of physiologically relevant tissue bound calcium phosphate could be distinguished based on impedance measurements.

Future: We envision that our results may lead to the development of a portable, battery operated, low-cost electrical impedance measurement device and software as a platform to generate electrical impedance spectroscopy. If successful, this new device will allow early detection and intervention of calcinosis to improve quality of life and to reduce long term health-care cost.

251 - Hospitalization Mortality and Associated Risk Factors in Patients with Polymyositis/Dermatomyositis: A Retrospective Case-Control Study from China

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Background: Polymyositis and dermatomyositis (PM/DM) are systemic autoimmune diseases with multiple organ involvement. In addition to muscle and skin disorders, intestinal lung disease (ILD) and malignance are the most common visceral complications of PM/DM that were reported to be the most common causes of death. However, the condition in China is unclear. We reviewed the medical charts of PM/DM patients admitted to Peking Union Medical College Hospital (PUMCH) during 2008 to 2014 in order to identify the possible related risk factors for death among these patients.

Methods: The deceased group included 45 patients who were with "deceased discharge" status or were confirmed death in two weeks after discharged from hospital. The demographic data, clinical manifestations, and the direct causes of death were analyzed retrospectively. Medical records of 180 PM/DM patients were selected as controls by age and sex matching method from 982 successively admitted in-patients of the same center during the same period. In addition to the comparison of clinical manifestations between the two groups, binary logistic regression was conducted to explore the related risk factors of mortality of PM/DM.

Results: Over the last 6 years at PUMCH, the in-hospital mortality rate in patients with PM/DM was 4.58%. The three most frequent death causes of PM/DM were pulmonary infection (44.4%), ILD deterioration (17.8%), or both of above (20%). Pulmonary infection (P<0.001, OR 187.2, CI 25.8-1356.4), myocardial involvement (P=0.041, OR 35.0, CI 1.2-1054.9), Gottron's sign (P=0.002, OR 13.2, CI 2.6-67.0), and elevated ESR (P=0.005, OR 9.9, CI 2.0-49.0) were independent risk factors for in-hospital mortality in PM/DM patients.

Conclusion: PM/DM is still a kind of disease with high in-hospital mortality. Pulmonary infection is the strongest predictor of poor prognosis in PM/DM patients. PM/DM patients with myocardial involvement, Gottron's sign, and elevated ESR are often associated with poor outcomes.

252 - Ultrasonographic Assessment of Arthritis in Patients with Idiopathic Inflammatory Myopathies

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Background: Arthritis is commonly seen in patients with IIM. Ultrasonography is a sensitive tool to detect arthritis and allows for quantification of the inflammation severity. The objective of this study was to determine the prevalence and severity of ultrasonographic manifestations in joints of patients with idiopathic inflammatory myopathies (IIM).

Methods: Fifty-four random patients with IIM treated in a single centre were included in this cross-sectional study. A positive control group consisted of 60 patients with RA. Seventeen healthy controls were used for standardisation. Ultrasonographic joint assessment was performed using US-7 score which evaluates unilateral synovitis, tenosynovitis and bone erosions in wrist, MCP 2, 3, hand PIP 2, 3, and MTP 2, 5 joints. The side with clinically more severe involvement, or the dominant side, if involved equally, was scored. Both Grey-Scale (GS) and PowerDoppler (PD) were used in grading of synovitis and tenosynovitis. The maximum score for the total US-7 is 112, maximum partial scores of GS and PD synovitis are 39 each, maximal GS and PD tenosynovitis are 5 and 15 respectively, and maximum for erosion score is 14.

Results: Total US7 score was significantly lower in IIM patients than in RA controls (7.39±9.10 vs. 15.27±75, $p<0.0001$). Similarly, GS and PD synovitis, GS and PD tenosynovitis, as well as erosion partial scores were also lower in IIM (4.48±5.50 vs. 8.67±7.33, $p<0.0001$; 2.54±3.43 vs. 3.88±4.05, $p=0.0079$; 0.01±0.55 vs. 0.53±0.77, $p<0.0001$; 0.20±0.94 vs. 0.58±1.08, $p=0.0023$; 0.07±0.43 vs. 1.60±2.53, $p<0.0001$, respectively). Ultrasonographic findings were significantly less often seen in IIM than in RA: GS and PD synovitis (70% in IIM patients vs. 95% in RA controls; $p<0.0001$, and 61% vs. 90%; $p<0.0004$, respectively), GS and PD tenosynovitis (3.7% vs. 38%; $p<0.0001$, and 5.6% vs. 28%; $p=0.0013$, respectively), and erosions (3.7% vs. 42%; $p<0.0001$). When individuals with negative findings were excluded from the analysis and only those patients who had quantifiable synovitis were taken into account, no difference was found in the total US-7 PD synovitis score (4.15±3.55 vs. 4.32±4.05, NS), and with the exception of wrists (IIM 4.54±3.39 vs. RA 5.93±3.87, $p=0.0495$), no difference was also found between IIM and RA in MCP, PIP and MTP joints with quantifiable synovitis.

Conclusion: Our data suggest that ultrasonographic joint involvement is a common feature of myositis and US-7 score is a sensitive tool for its detection. In IIM, active synovitis is the most common finding; tenosynovitis and bone erosions are rare. In comparison with RA, the arthritis is, as expected, less frequent in IIM, but if present, the activity of synovitis is comparable with RA.

253 - Cardiovascular Abnormalities in Adult and Juvenile Dermatomyositis

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Background: To assess the prevalence of cardiovascular involvement in adult and juvenile dermatomyositis(DM).

Methods: Inpatients records between January 2006 and October 2016 fulfilling Peter and Bohan criteria for DM admitted in our rheumatology department were included for the study. Demographic, clinical and laboratory data were noted. Clinical parameters included cutaneous, musculoskeletal, Vasculitic manifestations (ulcers and rash), cardiovascular, respiratory, gastrointestinal involvement. All patients admitted with inflammatory myositis undergo ECG and 2D echocardiography as per department protocol, and investigated further after cardiologist advice if required. Data was compiled in Microsoft excel sheet and basic statistics performed. Multiple logistic regression analysis and Chi square test were used to assess phenotypic associations with cardiac abnormalities.

Results: Total 140 patients were identified with a diagnosis of DM (Juvenile DM, 29). Twenty-two (16.4%) patients had cardiovascular involvement (Definite DM 13, Probable DM 7 and Possible DM 2). Three had juvenile DM. Female patients were 15, mean age is 36.6±14.2 years, median disease duration is 12±11.7 months. The cardiovascular abnormalities and the frequencies are represented in Table 1. Excluding Aortic Stenosis presence of vasculitis (P=0.03) manifestations, calcinosis (p=0.0001), Gottron's papules, heliotrope rash (P=0.0001), ILD (P=0.04) was significantly associated with cardiac involvement. There is no significant association with age at presentation, disease duration (P=0.89), pharyngeal weakness (P=0.16), or creatinine phosphokinase levels (P=0.18).

Table 1. Patterns of cardiovascular abnormalities in adult and juvenile dermatomyositis patients.

Cardiovascular abnormality (n=23)	Number(%)	CTD Overlap	Comorbidities
Pulmonary arterial hypertension(PAH)	10(7.2)	2 SLE ,1 SSc,1 SSc with ILD	3 DM related ILD
Myocarditis	6(4.2)	-	1 Diabetes+HTN
Myocarditis and PAH	2(1.4)	-	-
Aortic stenosis	2(1.4)	-	1 HTN, 1 Diabetes+ HTN
Supraventricular tachycardia	1(0.7)	-	-
Diastolic dysfunction	1(0.7)	SLE	-
Interatrial septal aneurysm	1(0.7)	-	-

CTD- Connective tissue disease, ILD- Interstitial Lung disease, HTN- Hypertension, SSc- Systemic sclerosis

Conclusion: Pulmonary arterial hypertension with or without myocarditis is the common cardiac abnormality observed. Dermatomyositis specific rash, vasculitic rash, subcutaneous calcinosis and ILD are predictors of cardiac involvement.

254 - Lupus Myopathy: An Uncommon Manifestation of a Multisystemic Autoimmune Disease

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Background: In patients with systemic lupus erythematosus (SLE), the incidence of myopathy is reported to be 4-16%. However, little is known about the clinical or muscle biopsy features of SLE patients with muscle involvement.

Objectives: The purpose of this study is to describe the clinical characteristics and muscle biopsy features of SLE patients with concomitant myopathy.

Methods: This is a retrospective study of all subjects enrolled in the Hopkins Lupus Cohort database from May 1987 to June 2016 to select those with suspected muscle disease. This database included 2,437 subjects who met the 1982 American College of Rheumatology criteria for Lupus or the SLICC criteria for the classification of SLE. Patients were selected based on the presence of elevated creatine kinase in association with muscle edema on MRI, abnormal electromyography or positive muscle biopsy. Clinical data analyzed included demographic, SLE manifestations, serological markers, and SLE-associated damage. All available muscle biopsies were reviewed and assessed for myofiber necrosis, perifascicular atrophy, primary inflammation, perivascular, endomysial or perimysial inflammation. Based on their individual features, there were categorized as polymyositis, dermatomyositis, necrotizing myopathy or nonspecific.

Results: Amongst the patients reviewed, 179 (7.3%) had a history of myositis. These patients were more likely to have malar rash (OR 1.67, 1.22-2.29), photosensitivity (OR 1.43, 1.04-1.96), arthritis (OR 1.81, 1.21-2.69), pleurisy (OR 1.77, 1.3-2.42), pericarditis (OR 1.49, 1.06-2.08) or acute confusional state (OR 2.07, 1.09-3.94). Associated serological markers included lymphopenia (OR 1.64, 1.2-2.24), anti-dsDNA antibodies (OR 1.52, 1.09-2.13) or lupus anticoagulant (OR 1.42, 1-2). Furthermore, myositis was correlated with the presence of cataract (OR 1.5, 1.04-2.18), cognitive impairment (OR 1.87, 1.12-3.13), pulmonary hypertension (OR 1.98, 1.13-3.47), pleural fibrosis (OR 2.01, 1.27-3.18), premature gonadal failure (OR 1.9, 1.05-3.43), diabetes (OR 1.92, 1.22-3.02) or hypertension (OR 1.45, 1.06-2). 16 muscle biopsies were available for review; half were consistent with necrotizing myositis and 38% had perifascicular atrophy, the hallmark histopathologic feature of dermatomyositis (38%).

Conclusion: Seven percent of the Hopkins Lupus Cohort had myopathy. These patients had distinctive clinical and serological characteristics. Necrotizing myopathy and dermatomyositis were the most prevalent histopathologic categories in weak lupus patients who underwent muscle biopsy.

Table 1 Association between myositis and SLE manifestation.

SLE manifestation		Myositis N(%)	Not Myositis N(%)	Odds Ratio	P value	Adj. Odds Ratio	Adj. P value
Malar rash		103 (57.5%)	1095 (48.6%)	1.44 (1.06,1.95)	0.0212	**1.67 (1.22,2.29)**	**0.0014**
Discoid rash		41 (23.2%)	432 (19.2%)	1.27 (0.88,1.83)	0.1977	0.99 (0.68,1.45)	0.9784
Photosensitivity		100 (55.9%)	1172 (52%)	1.17 (0.86,1.59)	0.3217	**1.43 (1.04,1.96)**	**0.0273**
Oral/Nasal Ulcers		96 (53.6%)	1164 (51.6%)	1.08 (0.8,1.47)	0.6041	1.26 (0.92,1.72)	0.1524
Arthritis		147 (82.1%)	1594 (70.8%)	1.9 (1.28,2.81)	0.0014	**1.81 (1.21,2.69)**	**0.0035**
Serositis	Pleurisy	102 (57%)	951 (42.2%)	1.82 (1.34,2.47)	0.0001	**1.77 (1.3,2.42)**	**0.0003**
	Pericarditis	56 (31.3%)	479 (21.3%)	1.68 (1.21,2.35)	0.0021	**1.49 (1.06,2.08)**	**0.0214**
Renal disorder		11 (6.1%)	182 (8.1%)	0.74 (0.4,1.39)	0.3556	0.62 (0.33,1.18)	0.1474
Neurologic	Seizures	21 (11.7%)	210 (9.3%)	1.3 (0.8,2.09)	0.2872	1.3 (0.8,2.1)	0.2898
	Acute confusional state	12 (6.7%)	69 (3.1%)	2.28 (1.21,4.29)	0.0107	**2.07 (1.09,3.94)**	**0.0269**
Hematologic	Hemolytic anemia	23 (13.9%)	213 (9.7%)	1.5 (0.94,2.38)	0.0863	1.39 (0.87,2.22)	0.1699
	Leukopenia	99 (55.3%)	1019 (45.2%)	1.5 (1.1,2.04)	0.0096	1.31 (0.96,1.78)	0.0925
	Lymphopenia	94 (52.8%)	900 (40.2%)	1.66 (1.22,2.26)	0.0011	**1.64 (1.2,2.24)**	**0.0017**
	Thrombocytopenia	39 (21.9%)	454 (20.2%)	1.11 (0.77,1.61)	0.5783	1.09 (0.75,1.58)	0.6589
Immunologic	Anti-dsDNA	127 (70.9%)	1376 (61.1%)	1.55 (1.11,2.17)	0.0095	**1.52 (1.09,2.13)**	**0.0149**
	Anti Sm	41 (23.3%)	443 (20.2%)	1.2 (0.83,1.73)	0.3308	0.95 (0.65,1.38)	0.7791
Anti-phospholipid	Anti-cardiolipin	90 (52.3%)	1047 (47.8%)	1.2 (0.88,1.63)	0.2541	1.24 (0.91,1.7)	0.1730
	Anti- B2 Glycoprotein	33 (30.3%)	398 (29%)	1.06 (0.69,1.62)	0.7830	1.13 (0.73,1.73)	0.5854
	False positive RPR	28 (17.4%)	277 (13.9%)	1.31 (0.85,2)	0.2196	1.39 (0.9,2.14)	0.1401
	LAC	53 (30.8%)	569 (26%)	1.27 (0.91,1.78)	0.1645	**1.42 (1,2)**	**0.0478**
ANA		174 (97.8%)	2165 (96.5%)	1.59 (0.57,4.39)	0.3729	1.38 (0.5,3.85)	0.5361

Table 2 the association between myositis and Damage.

DAMAGE COMPONENT	Myositis N(%)	Not Myositis N(%)	Odds Ratio	P value	Adj. Odds Ratio	Adj. P value
Cataract	41 (23.2%)	374 (16.8%)	1.5 (1.04,2.16)	0.0307	**1.5 (1.04,2.18)**	**0.0318**
Retinal changes	11 (6.2%)	96 (4.3%)	1.48 (0.78,2.83)	0.2288	1.47 (0.76,2.82)	0.2498
Cognitive impairment	19 (10.8%)	150 (6.7%)	1.69 (1.02,2.79)	0.0422	**1.87 (1.12,3.13)**	**0.0166**
Seizure	9 (5.1%)	102 (4.6%)	1.13 (0.56,2.27)	0.7337	1.23 (0.61,2.5)	0.5674
Cranial or Peripheral neuropathy	21 (11.9%)	199 (8.9%)	1.39 (0.86,2.24)	0.1784	1.42 (0.88,2.31)	0.1527
Transverse myelitis	1 (0.6%)	17 (0.8%)	0.75 (0.1,5.64)	0.7773	0.6 (0.08,4.59)	0.6234
GFR <50	10 (5.7%)	142 (6.3%)	0.89 (0.46,1.72)	0.7274	0.75 (0.38,1.46)	0.3962
Proteinuria	16 (9.1%)	184 (8.2%)	1.11 (0.65,1.9)	0.6912	0.93 (0.54,1.6)	0.7860
Pulmonary hypertension	16 (9.1%)	97 (4.3%)	2.21 (1.27,3.84)	0.0050	**1.98 (1.13,3.47)**	**0.0171**
Pulmonary fibrosis	25 (14.2%)	154 (6.9%)	2.24 (1.42,3.53)	0.0005	**2.01 (1.27,3.18)**	**0.0030**
Pleural fibrosis	8 (4.6%)	58 (2.6%)	1.8 (0.84,3.82)	0.1290	1.74 (0.81,3.75)	0.1567
Pulmonary infarction	1 (0.6%)	12 (0.5%)	1.06 (0.14,8.2)	0.9558	1.45 (0.18,11.49)	0.7244
Angina/ CABG	5 (2.8%)	82 (3.7%)	0.77 (0.31,1.92)	0.5724	0.86 (0.34,2.17)	0.7475
Cardiomyopathy	9 (5.1%)	79 (3.5%)	1.47 (0.73,2.99)	0.2827	1.24 (0.6,2.54)	0.5613
Valvular heart disease	8 (4.6%)	61 (2.7%)	1.71 (0.8,3.63)	0.1631	1.66 (0.77,3.56)	0.1963
Pericarditis/ pericardiectomy	6 (3.4%)	38 (1.7%)	2.04 (0.85,4.9)	0.1092	1.71 (0.7,4.15)	0.2371
Claudication	3 (1.7%)	32 (1.4%)	1.2 (0.36,3.95)	0.7683	1.17 (0.35,3.92)	0.7989
Minor Tissue Loss	2 (1.1%)	15 (0.7%)	1.7 (0.39,7.51)	0.4816	1.44 (0.32,6.48)	0.6325
DVT	6 (3.4%)	82 (3.7%)	0.93 (0.4,2.16)	0.8638	1.02 (0.43,2.4)	0.9634
Mesenteric Insufficiency	1 (0.6%)	8 (0.4%)	1.6 (0.2,12.83)	0.6604	1.34 (0.16,11.03)	0.7861
Peritonitis	1 (0.6%)	7 (0.3%)	1.82 (0.22,14.91)	0.5751	1.62 (0.19,13.67)	0.6561
Upper GI surgery	2 (1.1%)	22 (1%)	1.16 (0.27,4.97)	0.8417	1.1 (0.25,4.78)	0.9025
Muscular atrophy/ weakness	19 (10.7%)	45 (2%)	5.89 (3.37,10.32)	<.0001	**5.43 (3.05,9.66)**	**<.0001**
Arthritis	19 (10.7%)	130 (5.9%)	1.93 (1.16,3.2)	0.0112	1.66 (0.99,2.78)	0.0546
Osteoporosis	23 (13.1%)	277 (12.3%)	1.08 (0.68,1.7)	0.7443	1.26 (0.79,2)	0.3355
Osteomyelitis	2 (1.1%)	18 (0.8%)	1.42 (0.33,6.16)	0.6414	1.56 (0.35,6.95)	0.5580
Alopecia	9 (5.1%)	97 (4.3%)	1.19 (0.59,2.4)	0.6293	0.77 (0.38,1.57)	0.4745
Scarring of panniculum	4 (2.3%)	53 (2.4%)	0.96 (0.34,2.68)	0.9360	0.71 (0.25,2.01)	0.5247
Skin ulceration	2 (1.1%)	30 (1.3%)	0.84 (0.2,3.56)	0.8160	0.8 (0.19,3.41)	0.7622
Premature gonadal failure	14 (8%)	100 (4.5%)	1.85 (1.03,3.3)	0.0390	**1.9 (1.05,3.43)**	**0.0346**
Diabetes	26 (14.8%)	168 (7.5%)	2.13 (1.37,3.33)	0.0009	**1.92 (1.22,3.02)**	**0.0048**
HTN	79 (44.9%)	720 (32.4%)	1.7 (1.24,2.31)	0.0008	**1.45 (1.06,2)**	**0.0212**

255 - Inflammatory Myopathies with Granuloma in the Muscle Have an Inclusion Body Myositis-like Muscle Phenotype while Inflammatory Myopathies with Extramuscular Granuloma Do Not Differ from Inflammatory Myopathies Without Granulomatous History

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Background: The significance of granulomatosis in inflammatory myopathies (IM) is unknown.

Methods: Patients with non-caseating granuloma (muscle or other tissue=IM granuloma) were identified among a monocentric cohort of 291 patients diagnosed with IM (ENMC criteria). Rheumatology and internal medicine practitioners in French and Belgian centers were also asked to report their observations.

Clinical, biological, histological features and outcome were retrospectively studied and compared with a control group of 30 randomly selected patients suffering from IM without identified granuloma.

Results: 31 IM-granuloma patients, with a median follow-up of 72 months were included. Granuloma was identified with a delay of 44 months before myopathy, in muscle (n=22), lymph node (n=14), skin (n=3), liver (n=2) tissues. Angiotensin converting enzyme amount was 109U/l [range 49-244], and calcemia was 2.32 mmol/l [2, 1-3.9].

We identified 2 groups of IM-granuloma patients: 7 patients (4 women, 62 [28-68] years at IM diagnosis) were categorizable as a defined IM subset because of histological and/or immunological features: antisynthetase syndromes (n=3), inclusion body myositis (IBM, n=2), scleromyositis (n=1), dermatomyositis (n=1). Granuloma were systematically identified in extra muscular tissues : lymph nodes (n=4), skin (n=2), liver (n=2). 3 patients were considered to have sarcoidosis. These patients mostly presented with proximal weakness (n=6). Mean CK level was 780 U/l [63-3900]. Patients received corticosteroids and meanly one another immunological drug (n=1±0,8) that improve muscle disease (according to IMACS) except for one patient. None of these features was significantly different from the control group.

24 patients (11 women, 54 [25-81] years) did not meet definitive clinical, serological or histological criteria of a specific IM. Most of these patients had granuloma in the muscle (n=22). Serological test for myositis specific or associated antibodies were negative. As compared with the control group, time between first symptoms and diagnosis was longer (12 [1-96] vs 5 [1-204] months, p=0,01), they presented more often with distal weakness (n=16/24, OR 6,66, p=0.03) and lower CK level (264 [29-2500] vs. 1122 [147-7204] U/l, p<0.0001). Besides granuloma, muscle biopsy revealed more often rimmed vacuoles (n=5, 20% vs 2%) and endomyosial inflammatory cell infiltration (n=15, 63 vs 35%). The patients experienced interstitial pneumonia (n=13), polyarthralgia, nodes (n=10). Despite a higher number of immunomodulatory drugs (1.8 VS 1,2, p=0,12) absence of muscle improvement was more frequent (n=16/24, 67% vs. 11/30, 36%, p<0.01) as compared with the control group.

Conclusion: Some IM patients with granulomatosis in extra muscular tissues match diagnostic criteria for a well-defined IM subtypes without clinical particularity aside from the granuloma. The others patients, which cannot be definitively classified, present mostly granuloma in muscle, are characterized by an IBM-like phenotype with progressive onset, distal weakness, low CK level, rimmed vacuoles and frequent unfavorable muscular response to treatment despite not meeting criteria for definite sIBM.

256 - Inflammatory Myopathy Following Allogenic Hematopoietic Stem Cell Transplantation: Report of 12 Cases

Jean Herlé Raphalen[1], Regis Peffault de la tour[2], Jean David Bouaziz[2], Stephanie Nguyen[1], Brigitte Bader-Meunier[3], Gerard Socié[2], Olivier Benveniste[4] and Baptiste Hervier[*4]

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Background: Acute and chronic graft *vs*. host disease (GVHD) is the main complication of allogenic haematologic transplantation (aHSCT). If some GVHD manifestations are frequent and well-described, other chronic GVHD -such as muscle GVHD- are particularly rare and detailed descriptions are lacking.

Methods: From 2005 to 2016, all the patients referred to our university center for a muscular disease following aHSCT were included (n=10). Two similar pediatric patients from the national center for immunodeficiencies were added to this cohort.

Results: Twelve patients (5/7 women/men, median age 39, 0.5-58) were included. Hematologic diseases leading to aHSCT were acute/chronic myeloid leukemia (n=3), B cell (n=5) or T cell (n=2) malignancies, as well as severe combined immunodeficiency (n=2). aHSCT followed different chemotherapies as induction and/or maintenance and conditioning regimens, which included alkylants, purine analogs, intercalating agents as well as total body irradiation (n=3). Bone marrow (n=3), peripheral HSCT (n=8) and umbilical cord-blood (n=1) transplantations were either haploidentical (n=9) or mismatched (n= 3).

Muscle disease appeared concomitantly to chronic lung (n=6) and skin (n= 8) GVHD, after a median of 109 weeks (15-261) and despite the use of immunosuppressive drugs or low dose of steroids (<10 mg/d) in 9 and 6 patients, respectively. Clinical features included myalgia (n=9), proximal (n=8) and/or axial (n=7) weakness. Median creatine kinase was 600 IU/L (22-5303). Electromyogram (n=9) always confirmed myogenic features and muscle MRI (n=7) often disclosed myositis (n=4) and fasciitis (n= 3). Myositis-specific autoantibodies were positive only once (HMGCR$^+$) in a patient diagnosed as non-statin-induced-HMGCR$^+$ immune mediated necrotizing myopathy. In the remaining 11 cases, muscular histology was heterogeneous showing irregular myofiber diameters (n=7), necrotic/regenerating processes (n=4) and perifascicular atrophy (n=1). Fasciitis was seen in two cases. Lymphocytic infiltrates were inconstant (n=6) and both perimysial and/or endomysial. Capillary C5b9 deposits were rare and weak, whereas myofiber MHC-I expression was always abnormal but warrying in intensity and localization. Finally, diagnoses were unspecific myositis (n=6) including myofasciitis in two cases, necrotizing myopathy (n=3), polymyositis (n=1) and dermatomyositis (n=1).

First line treatments consisted in at least 1 mg/kg/d of steroids in all cases, associated to IV-Ig (n=5) and/or conventional immunosuppressive drugs (n=11), such as cyclosporine (n=5) or methotrexate (n=2) etc. With a median follow-up of 62 (1-252 months), these treatments led to complete (n=5) or partial remissions (n= 3) but 4 patients didn't improve. Moreover, relapses occurred four times. These relapses responded at least partially to steroid increase (n=2) or to imatinib or ruxolitinib.

Conclusion: Muscle disease following aHSCT is most of the time a chronic GVHD, which has no specific histological pattern. Muscular GVHD is a severe and difficult to treat condition. More descriptions from international registries are needed to better define prognostic factors.

257 - Oedematous Myositis: An Original Subtype of Autoimmune Myopathy Characterized by Intense C5-b9 Deposits on Capillaries and a High Risk of Malignancy

Mathilde Duchesne*[1], Sarah Léonard-louis[2], Thierry Maisonobe[2], Werner Stenzel[3], Nicolas Schleinitz[4], Aurélie Grados[4], Odile Dubourg[5], André Maues De Paula[6], Baptiste Hervier[7], Olivier Benveniste[7] and Yves Allenbach[7]

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Background: Skin changes are frequent in autoimmune myopathies (AIM). Erythema is frequently observed, especially in dermatomyositis (DM), but oedema is unusual. The rare case reports and series (n = 4) of myositis associated with limb oedema described so far suggest that this association is not fortuitous and is mainly observed in severe DM, sometimes associated with malignancy. Aim: To determine if 'oedematous myositis' is a homogeneous subtype of AIM based on clinical and histological characteristics.

Methods: Patients with inflammation on muscle biopsy performed from 2008 to 2015 suffering from upper limbs oedema were enrolled (three European centers). In addition to clinical data, for each muscle biopsy a qualitative analysis of muscle fibres damages, muscle inflammation and vascularisation were performed.

Results: Sixteen patients were included (mean age 53.8±13.9 years). Most (75%) of the patients had severe proximal and symmetrical muscle weakness (mean MRC score 2.9±1.1), with loss of autonomy (93.7%) and dysphagia (68.7%). The mean CK level was 5373±4177 I.U/L.

In addition to oedema, only 43.7% patients harboured typical DM skin rash. Four patients (25%) had a malignancy occurring ±3 years the diagnosis of the myositis. Only one patient had an interstitial lung disease. Associated DM specific antibodies were anti-TIF1γ (n= 3), anti-Mi2 (n=1) and anti-NXP2 (n=3).

Pathological analysis showed that perifascicular atrophy was rare (13.3%) and multifocal micro-infarcts were seen in a quarter of the cases. A diffuse and intense positivity of HLA I was frequently observed (69.2%). However, the striking observation was presence of oedema in the perimysium with positive alkaline phosphatase staining (81.8%). In addition, C5-b9 (membrane attack complex) deposits on endothelial cells were intense and diffuse in 76.9% of cases. Inflammatory infiltrates were mainly composed by CD8+ cells and macrophages (66.7%) with a perimysial repartition. Finally, only 2 cases (13.3%) met the definite criteria for DM.

The mean duration of the follow-up was 28.3±25.2 months. The mortality was very high (18.7%) during the year following the diagnosis (all due to malignancy). All patients, but one (corticosteroids alone), received corticosteroids in association with immunosuppressive treatment (the mean number was 1.6 per patient). The mean treatment duration was 26.1±24.4 months. Among the patients followed over than 18 months, the treatment was stopped in most of the cases (62.5%) without any relapse.

Conclusion: Oedematous myositis seems to represent an original subtype of autoimmune myopathy characterized by a specific skin phenotype associated with distinctive pathological muscle features (intense and diffuse deposits of C5-b9 on capillaries). Oedematous myositis is associated with a high risk of malignancy and mortality.

258 - HTLV-1: A Less-Known Cause of Myopathy

Simona Treidler*[1], Roberta Seidman[2], Yaacov Anziska[1], Paul Maccabee[1], Brian Anziska[1], George Vas[1] and Adrian Marchidann[1]

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Background: More than 20 million people worldwide are infected with Human T-lymphotropic virus type 1 (HTLV-1). About 2-5% will develop a chronic encephalopathy or HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 is a less known cause of myopathy.

Methods: We present a series of 7 patients with HTLV-1 HAM/TSP from an endemic population of Caribbean Islanders (Jamaica, Haiti, Trinidad Tobago, Saint Vincent) living in Brooklyn NY, who developed a new proximal weakness, myalgia and elevated creatine kinase (CK).

Results: Clinical examination revealed spastic paraparesis and significant proximal muscle weakness. All 7 patients had positive HTLV-1 serology and elevated CK; one was anti-SSA positive, one was anti-RNP Abs positive, one was hepatitis C positive and another had low vitamin B12. EMG showed myopathic pattern. Nerve conduction studies identified axonal neuropathy in 3 cases. MRI spine was normal in one patient and showed a thin thoracic spinal cord in 4 other patients. Muscle biopsy variously revealed focal endomysial inflammation, fibrosis, muscle fiber regeneration and upregulated MHC class I. In one case, rimmed vacuoles were seen. Six patients received various combinations of prednisone with IVIG, azathioprine, mycophenolate mofetil, and cyclosporine. One patient was not treated. All patients had a poor outcome; 5 are wheelchair bound, one uses a walker and another a cane.

HTLV-1 myositis is reported in endemic areas including Japan, Caribbean Islands and South America. Histopathological HTLV-1 infection can be associated with muscular inflammation characterized by direct invasion of the muscles by the HTLV-1 infected mononuclear cells, variation in fiber size and regeneration. HTLV-1 gp46 has been identified by immunochemistry in many of the invading cells and polymerase chain reaction demonstrated the presence of HTLV-1 Tax gene.

However, there is no evidence of viral infection of the muscle fibers by HTLV-1 either in HTLV-1 polymyositis or in HTLV-1 inclusion body myositis. This suggests that the HTLV-1 myositis is not caused by direct viral infection but rather reflects release of cytokine and or viral Tax transactivator from the mononuclear cells which induces cytopathic changes when taken up by the muscle fibers.

Conclusion: Inflammatory myopathy should be considered in patients with HAM/TSP with progressive proximal muscle weakness and elevated CK. HTLV -1 serology in patients with myopathy is recommended in the population at risk. These patients have a more protracted course than patients with idiopathic polymyositis and typically respond poorly to immunosuppressants.

259 - Focal Myositis: New Insights on Diagnosis and Pathology

Laure Gallay[*1,2], Arnaud Hot[3], Philippe Petiot[4], Delphine Maucort-Boulch[5] and Nathalie Streichenberger[6]
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Background: Due to the rarity of the entity, the literature on focal myositis (FM) fails to address important questions on its nosology, associated disorders, clinical presentation and therapeutic management. We sought to shed light on clinical, pathological, and therapeutic features of FM through the analysis of data from a large patient cohort.

Methods: We searched for confirmed cases of FM in the Lyon University Hospital's pathological database of patients diagnosed with myositis since year 2000. FM was diagnosed as per the usual clinicopathological definition. Clinical, serological, imaging, pathological and therapeutic data were collected. When missing from the original pathological analysis, complementary immunohistochemistry was redone when possible.

Results: Of the 924 patients included in the myopathological database, 37 (4%) had confirmed FM (23 males, 14 females, mean age=44). The main clinical signs were focal muscular pain (81%), local erythema (32%), both in relation with the muscle mass, and fever (24%). Serum creatine kinase was usually normal (78%); conversely, immune abnormalities were found in the sera of 52% of the patients. Beyond confirming previously-reported findings, the pathological analyses also illustrated significant rates of vascularitis (68%) and fasciitis (73%). FM was frequently associated with immune-mediated inflammatory disease (IMID) (32%), neoplasia (24%), radiculopathy (11%) and trauma (5%). Two-thirds of the cohort received immunosuppressive therapy. The recurrence rate was 41%.

Conclusion: In contrast to the classic view of a seldom painful and spontaneously resolving disorder, this study suggests that FM can be clinically and pathologically serious and require particular attention. Moreover, these results suggest that FM patients should receive IMID and neoplasia screening.

260 - Corticosteroid-associated Pneumatosis Intestinalis in Juvenile Dermatomyositis: A Case Report

Bita Arabshahi*[1], John Lee[2] and Ian Leibowitz[1]
[1]Pediatric Specialists of Virginia, [2]Fairfax Radiologic Consultants

Background: Reports of pneumatosis intestinalis (PI) in juvenile dermatomyositis (JDM) are limited and often attribute the process to intestinal ischemia secondary to vasculitis. In patients with asymptomatic PI, however, the role for intestinal ischemia is not clear. Corticosteroids have been shown to cause submucosal lymphoid tissue atrophy with subsequent air-dissection of the bowel wall. We aimed to examine the role of corticosteroids in PI, notwithstanding clinical resolution of vasculitis.

Methods: We report the case of a three-year-old Asian girl with anti-MDA-5 positive JDM and severe cutaneous vasculitis who demonstrated persistent asymptomatic PI upon resolution of cutaneous vasculitic lesions on cyclophosphamide and corticosteroids.

The child developed worsening deep cutaneous ulcers while on standard treatment with weekly subcutaneous MTX 1mg/kg, daily oral prednisone 2mg/kg, monthly IVIG 2g/kg and daily hydroxychloroquine 6.5 mg/kg. Incidental note was made at this time of PI on a chest CT to screen for interstitial lung disease. MTX was replaced with a 6-month course of cyclophosphamide, resulting in complete resolution of her cutaneous lesions. No change, however, was noted in PI. A year later, resolution of PI was noted upon a slow wean off corticosteroids.

Results: Although the presence of anti MDA-5 antibodies is correlated with a higher risk of vasculitis, in our patient, there was no observed correlation between the activity of cutaneous vasculitis and PI. There did, however, appear to be a correlation between corticosteroid wean and resolution of PI.

Conclusion: Our observation suggests that PI in JDM may be multifactorial, and the role of corticosteroids should be considered in this process.

261 - A Case of Eosinophilic Myositis

Shazdeh Butt* and Alfred Denio
Geisinger Medical Center

Background: Limb Girdle Muscle Dystrophy type 2A presents as symmetrical proximal muscle weakness and atrophy. It is associated with elevated CPK levels and sometimes eosinophilic myositis. It has an indolent course that ultimately leads to extensive weakness and patients are wheel chair bound at 30-40 years of age. Physical therapy and rehabilitation are the mainstays of therapy to prevent contractures and maximize strength.

Methods: 21yo college student who presented to adult rheumatology as a referral for evaluation of eosinophilic myositis. At age 14, he was seen at pediatric rheumatology with nausea, generalized fatigue, occasional muscle aches and loss of power noted particularly going up and down steps. Physical examination at that time, including muscle strength, was normal. Laboratory study demonstrated eosinophilia as high as 1,704, CPK 6,286 (upper limit of normal 225 U/L) and elevated transaminases. Extensive GI workup was negative. He had a quadriceps muscle biopsy that showed eosinophilic infiltration in the endomysium consistent with eosinophilic myositis. (Fig. 1)

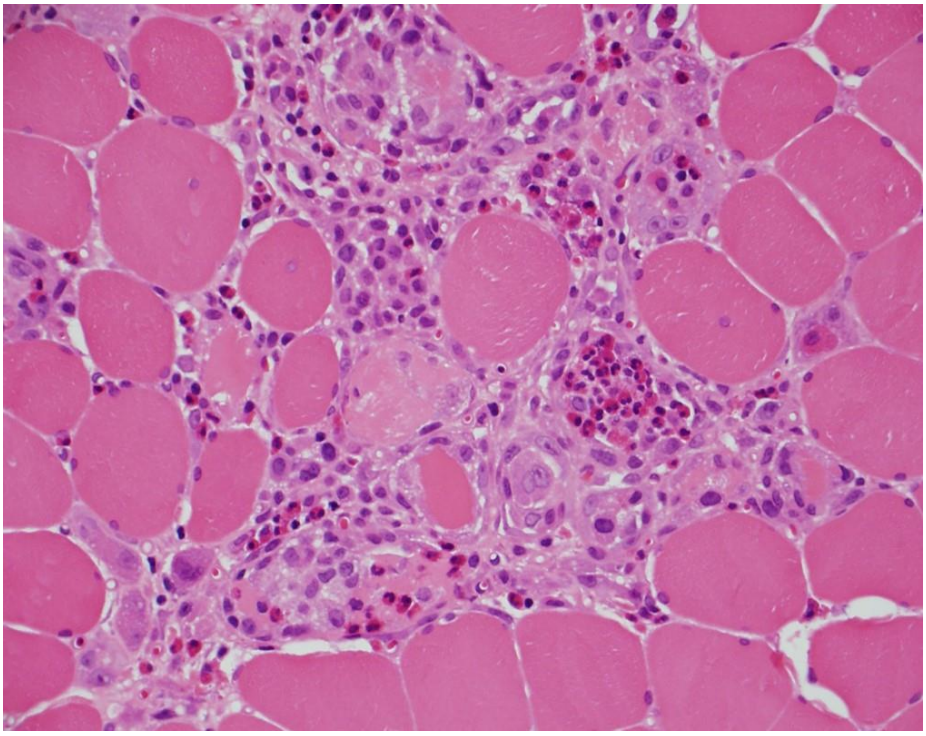
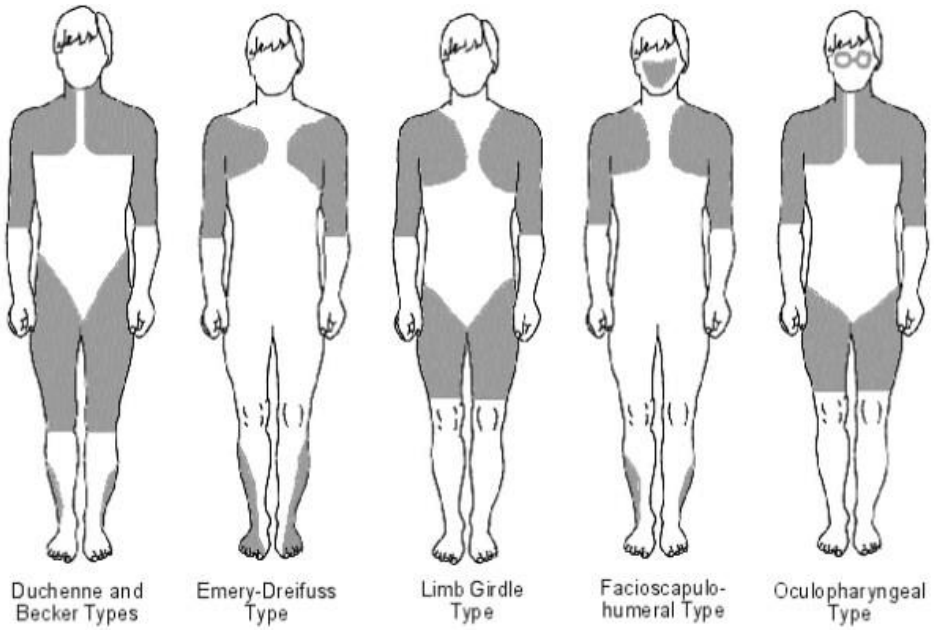


Fig 1: Muscle biopsy H&E high power

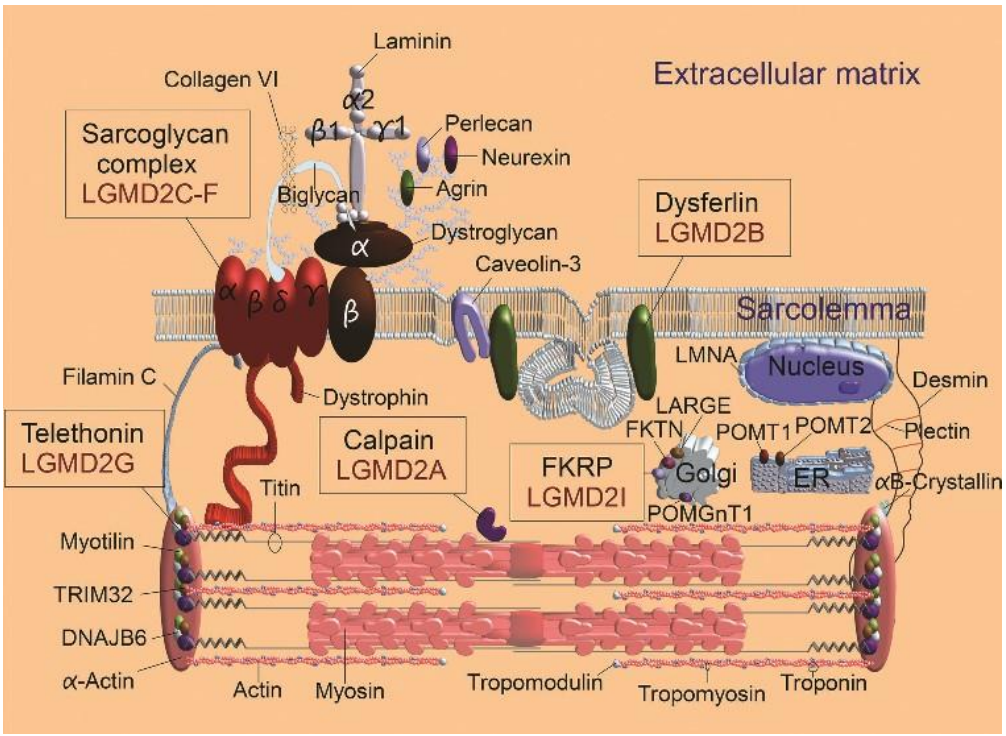
He was treated with high doses of glucocorticoids, methotrexate and IVIG. However, none of these treatments helped and he stopped taking all of his medications and was lost to follow up 3 years previously. He and his mother now had noticed gradual worsening of symptoms, easy fatigability (dropped out of sports, difficulty getting from one college class to another on time). Sister had also noted that he had to crawl going upstairs. Physical examination now demonstrated stiff gait, exaggerated lordosis, scapular winging, marked proximal muscle weakness. There was a high suspicion for Limb Girdle Dystrophy and genetic testing revealed mutation in CAPN3 indicating autosomal recessive limb girdle muscular dystrophy type 2A.



Main areas of muscle weakness in different types of dystrophy

Mercuri, Eugenio, and Francesco Muntoni. "Muscular dystrophies." *The Lancet* 381.9869 (2013): 845-860.

Results: Patient and family are now aware of the genetic etiology of his disorder and no further need for immunosuppression. He was followed up in the muscular dystrophy clinic.



Cotta, Ana, et al. "Limb girdle muscular dystrophy type 2G with myopathic-neurogenic motor unit potentials and a novel muscle image pattern." *BMC clinical pathology* 14.1 (2014): 41.

Conclusion: Limb Girdle muscular dystrophy can initially present with only fatigue symptoms and mimic idiopathic inflammatory autoimmune myopathies. Consider CAPN3 genetic testing in patients with idiopathic eosinophilic myositis.

Poster Session 2

Sunday, May 07, 2017

10:35 AM – 1:30 PM

300 - Cell Bound Levels of Complement Activation Products on Erythrocytes E-C4d and E-C3d May Reflect Disease Complications of Juvenile Dermatomyositis

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Background: Complement-mediated vasculopathy leading to degeneration of muscle fibers is probably engaged in the pathogenesis of juvenile dermatomyositis (JDM). Cell-bound levels of complement C4 activation products on erythrocytes, E-C4d, and sometimes activation products of C3, E-C3d, reflect past complement activation on self-cellular membranes, which may culminate in tissue damage. We have recently shown that complement C4 gene copy number variations (CNVs) and C4A gene deficiency are important genetic risk factors for JDM. The objective of this study is to investigate whether genotypic and phenotypic diversities of complement modulate the disease presentations such as calcinosis, lipodystrophy and recent severe infections in JDM.

Methods: Upon IRB approval, 53 JDM patients and 206 healthy subjects were enrolled for this cross-sectional study. C4 CNVs were determined by genomic Southern blot analyses using *Taq*I and *Psh*AI/*Pvu*II digested genomic DNA. C4A and C4B protein polymorphisms were elucidated by immunofixation of EDTA-plasma. Cell-bound levels of E-C4d and E-C3d were measured by flow cytometry using specific monoclonal antibodies. Intra-group comparisons of E-C4d and E-C3d for patients with and without a disease complication were performed by one-way analysis of variance for normally distributed data, and Mann-Whitney's U test for non-normally distributed data.

Results: When compared with healthy subjects, significant elevation of E-C4d levels (p=0.004) but not E-C3d levels was observed in JDM. JDM patients were stratified into subgroups according to the status of C4A or C4B gene copy numbers. The C4A-deficiency group (GCN≤1, n=15) had a median mean fluorescence intensity (MFI) of 1426 (IQR: 601-1744) for E-C4d, which was significantly higher than that of the C4A-proficient group (GCN≥2, n=25; median MFI=454 (234-718); p=0.0003). The C4B-deficiency group (GCN≤1; n=11) had a median E-C4d MFI of 308 (226-505), which was significantly lower than that of the C4B-proficient group (GCN≥2, n=29; median MFI=775 (495-1458); p=0.003). As for intra-group analyses between patients with and without complications, significantly higher E-C4d levels were found in patients with calcinosis (p=0.013), ulcerations (p=0.03), osteonecrosis (p=0.0013) and severe infections (p=0.004). Moreover, significantly higher E-C3d levels were found in patients with lipodystrophy (p=0.029) and osteonecrosis (p=0.0003).

Conclusion: Our data suggested a protective role of C4A and a potentially deleterious role of C4B on complement-mediated pathogenesis of JDM. Complement activation products E-C4d and E-C3d could serve as biomarkers for disease complications and disease activity of JDM.

301 - The Lymphocyte Repertoire in Juvenile Dermatomyositis

Kacie Hoyt*[1], Edwin Anderson[1], Megan Curran[2], Robert Fuhlbrigge[3], Luigi Notarangelo[4], Lauren Pachman[2], Susan Kim[5] and Lauren Henderson[1]

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Background: In adult dermatomyositis (DM), clonal populations of T and B cells with shared variable (V) gene usage have been identified in affected muscle, suggesting aberrant lymphocyte responses to a common antigen. Using highly sensitive next generation sequencing (NGS), we aimed to determine if these previously identified repertoire abnormalities in the muscle of adult DM patients could be detected in the peripheral blood (PB) of children with juvenile DM (JDM).

Methods: PB was obtained from JDM patients with skin and muscle disease (classic JDM) at diagnosis, during active disease, and at remission when patients were off medication. Amyopathic patients and healthy controls were also studied. $CD8^+$ T cells and $CD19^+$ B cells were isolated from PB mononuclear cells (PBMC) by magnetic beads. The remaining lymphocyte populations were isolated from PBMCs by fluorescence activated cell sorting: CD4/CD8 naïve (N) T cells ($C3^+CD4^+/CD8^+CD45RA^+CCR7^+$), CD4/CD8 memory (M) T cells ($CD3^+CD4^+/CD8^+CD45RA^-$), Treg cells ($CD3^+CD4^+CD25^+CD127^{lo}$), Teff cells ($CD3^+CD4^+CD25^-$), Naïve B cells ($CD19^+IgD^+CD27^-$), and $CD21^{lo}$ B cells ($CD19^+CD21^{lo}CD38^{lo}$). The TCR β (*TRB*) and BCR heavy (*IgH*) chains were amplified by multiplex PCR with a standard quantity of genomic DNA serving as the template (ImmunoSEQ™). Illumina HiSeq platform was used for sequencing. Productive sequences were analyzed using the ImmunoSEQ set of online tools. Mann Whitney and 1-way ANOVA tests were used to compare the clonality index, Shannon entropy, and clone sharing in study groups. 2-way ANOVA with Bonferroni correction was used to compare TCRVβ family usage.

Results: Clinical characteristics of the patients are in Table 1. $CD21^{lo}$ B cells, a population of B cells associated with autoimmunity, were more clonal in classic JDM patients with active disease compared to those in remission ($p=0.03$). Similarly, the Treg repertoire was significantly more clonal in classic JDM patients with active disease than JDM patients in remission ($p<0.0001$) and amyopathic patients ($p=0.002$). CD19, CD19N, CD8, CD4/8 N/M, and Teff cells were polyclonal and diverse across all JDM patient groups. In Treg and Teff subsets, TCRVβ families 7, 10, and 28 were used more and Vβ families 3, 5, and 19 were used less in classic JDM patients with active disease compared to controls ($p<0.0001$for Treg and Teffs). Inter-individual sharing of Teff clonotypes was observed in JDM patients with active disease compared to controls ($p<0.001$).

Conclusion: Clonal expansions in $CD21^{lo}$ B and Treg cells noted in JDM patients with active disease resolved upon remission. Skewed TCRVβ family usage was observed in active JDM patients with increased usage of Vβ7, a Vβ family that has been linked with other autoimmune conditions. Inter-individual sharing of Teff clonotypes was also observed. Our pilot results suggest that lymphocyte repertoire abnormalities may contribute to disease pathogenesis in JDM and can be detected in PB by NGS.

Table 1. Characteristics of Study Subjects

Sample Name	Clinical Status	Age (years)	Sex	Auto-antibodies	Disease Duration (mo)	MMT8 Score	DAS (total/muscle/skin)	Medications
Classic JDM1	Diagnosis	4.7	M	MJ	6.0	N/A	N/A	None
Classic JDM2	Diagnosis	9.2	F	p155/140	7.0	76	N/A	None
Classic JDM3	Diagnosis	9.4	M	Neg	2.0	58	N/A	Pred, MTX
Classic JDM4	Diagnosis	2.1	F	N/A	5.0	N/A	N/A	None
Classic JDM5	Diagnosis	3.3	M	N/A	2.0	58	N/A	None
Classic JDM6	Diagnosis	7.4	M	N/A	0.8	60	N/A	None
Classic JDM7	Diagnosis	7.9	F	Anti-Jo	24.0	78	N/A	None
Classic JDM8	Active	6.6	M	MJ	7.5	N/A	4/3/1	MTX
Classic JDM9	Active	5.9	M	Neg	38.4	N/A	7.5/5.0/2.5	MTX, HCQ
Classic JDM10	Active	6.2	F	p155/140	4.0	N/A	12/14/8	MTX
Amyo JDM1	Amyopathic	11.9	F	Neg	108.0	N/A	4	HCQ
Amyo JDM2	Amyopathic	4.5	F	MDA	23.0	N/A	6	IVIG, CellCept
Amyo JDM3	Amyopathic	9	F	MDA	5.0	N/A	6	MTX Cellcept
Amyo JDM4	Amyopathic	10.4	M	MDA	57.0	N/A	7	CellCept
Classic JDM 11	Remission	11.2	F	p155/140	72.4	N/A	0/0/0	None
Classic JDM12	Remission	11.8	F	p155/140	75.8	N/A	0/0/0	None
Classic JDM13	Remission	11.2	M	MJ	63.6	N/A	0/0/0	None
Classic JDM14	Remission	13.1	F	p155/140	86.9	N/A	0/0/0	None
Classic JDM15	Remission	5.9	M	Neg	47.0	80	0/0/0	None
Adult HC1	Control	35	M					
Adult HC2	Control	32	M					
Adult HC3	Control	35	F					
Adult HC4	Control	32	F					
Pedi HC1	Control	13.1	F					
Pedi HC2	Control	16.1	M					
Ped HC3	Control	9.2	M					

MMT8, manual muscle testing 8; DAS, disease activity score; pred, prednisone; MTX, methotrexate; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin

302 - Juvenile Dermatomyositis Patient-Derived, Induced Pluripotent Stem Cells Do Not Exhibit Residual Disease-Related miRNA or Coding Gene Disease Expression Signatures

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Background: Monozygotic twins discordant for JDM are rare, composing only 1% of our entire registry of 569 JM patients. These individuals represent a unique opportunity identify persistent gene expression differences in JDM children by allowing for a control with an identical genome, as well as environmental control with respect to early development.

Methods: We recruited a pair of monozygotic, white, male twins discordant for Juvenile Dermatomyositis (JDM), age 9.5 years, and a race, sex matched 7.2-year-old control for this IRB approved study. The JDM+ twin (MJ+ MSA) held his medications (oral prednisone 7 mg, Sub Q MTX 12.5 mg) at blood draw. We isolated PBMCs within two hours of blood draw and expanded erythroblasts in culture for 9-12 days. We induced pluripotency by transduction with Sendai virus carrying *Oct3/4*, *Sox2*, *Klf4*, and *cMyc*. We profiled the transcriptomes of 3 separate clones from each of the three individuals to detect persistent JDM gene expression differences using RNA-Seq and microRNA (miRNA) microarrays.

Results: We confirmed a normal karyotype for each clone, and then confirmed pluripotency by Pluritest. RNA-Seq comparison of the JDM iPSC clones to the unrelated control identified 56 potentially differentially expressed (DE) genes, 11 of which were concordant between at least 2 algorithms. All three tests were concordant for increased expression of *HLA-DQB1* (FC 7.6-7.8) and decreased expression for *ZNF718* (FC -2.6). 2 of 3 algorithms agreed that the JDM-derived clones also had increased expression of *HLA-DRB1*(FC 4.8).

However, the same genes were DE in comparison of the unaffected twin iPSCs to unrelated control iPSCs. Comparing the JDM affected twin and the unaffected twin clones revealed two potentially DE genes (*ZDBF2* and *NNAT*). Neither of these genes were different in the JDM Twin compared to the unrelated control. Clustering of consistently DE genes demonstrated that the twins cluster with each other, rather than the unaffected twin clustering with the unrelated control. Using RT-qPCR we confirmed that the *HLA-DQB1* was not detectable in the unrelated control iPSCs, and its expression was no different between twins. We also confirmed increase expression of *LAPTM4B* in the twins compared to the unrelated control and decreased expression of *ZNF718*. However, we were not able to confirm *ZNF880*differences with our primer set.

miRNA array profiling demonstrated only 16 DE miRNAs when comparing the unaffected twin to the unrelated control; no other comparisons were significant.

Conclusion: 1) iPSC generation reprograms any baseline JDM disease signatures from the original PBMCs. 2) There are inter-individual genetic differences that affect baseline gene expression for coding RNA and miRNAs, as evidenced by the shared expression patterns between discordant twins.

Speculation: Genetic factors increase risk for developing JDM, but the initiation of the disease process requires a trigger. Similarly, JDM iPSCs and tissue-relevant differentiated cells may only demonstrate variable gene expression when exposed to the correct stimulus, such as treatment with interferon or with patient serum.

303 - The Role of Harakiri, a Mitochondrial Apoptosis Mediator, in Maintaining Membrane Stability of Myositis Muscle

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Background: Currently, the cause of myositis is unknown, but disease onset has been associated with viral infections. Although attempts to identify viruses in myositis skeletal muscle have failed, several studies have shown that a viral signature is present. Therefore, we postulated that viruses affect the epigenome in individuals with a susceptible genetic background. To investigate this, we hypothesized that a virus alters DNA methylation in the promoter regions of genes, leading to their aberrant expression and disease phenotype in skeletal muscle.

Methods: Gene expression and methylation profiling were performed on myositis (PM and DM) skeletal muscle biopsies and human myotubes infected with Coxsackie B (8 MOI for 120 h) virus. A comparison analysis was performed to identify common changes in methylation and gene expression from myositis muscle and infected myotubes when compared to controls. Validation studies to investigate potential mechanisms were performed *in vitro* using skeletal muscle cells.

Results: Comparison between data sets identified genes involved in membrane stability (*TRIL*, *COL5A1*, *MFAP4*, *MBP*) and cell death (*HRK*). We find that harakiri (*HRK*) is up-regulated in myositis skeletal muscle cells and show that these cells repair poorly after injury when compared to controls. Interestingly, *HRK* is activated by innate immune pathways and localizes to mitochondria, which are recruited to the site of injury during membrane repair and are located around the periphery of muscle fibers in myositis patients.

Conclusion: Here, we demonstrate that *HRK*-induced mitochondrial deficiency could contribute to membrane instability and weakness of the muscle.

304 - The Effect of Rituximab on Skeletal Muscle Signaling in Myositis

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Background: Rituximab has been shown to improve disease phenotype in myositis patients. The molecular mechanisms by which Rituximab provides benefit are unclear. It is postulated that it binds to CD20 on B cells and depletes them; however, recent reports indicate that CD20 is also expressed on skeletal muscle cells and potentially serves as a store operated calcium channel. Here, we hypothesize that Rituximab benefits are both due to its effects on immune cells and skeletal muscle.

Methods: CD20 expression, viability, and cytokine profiles using MSD pro-inflammatory panels were measured on Rituximab-treated B cells (Raji), macrophages (THP-1) and skeletal muscle cells (immortalized). To investigate potential disease modifying pathways, methylation status, microRNA and gene expression profiling were performed on Rituximab-treated myositis skeletal muscle. Significant findings were assessed by using a paired t-test ($p<0.05$, FC > 1.3) and data integration was preformed through Partek, miTarVis, and USCS Genome Browser.

Results: *In vitro* studies show that treatment with Rituximab causes B cell death and alters the cytokine profile of both B cells and macrophages. In myositis skeletal muscle, we determine that 46 genes are significantly changed after Rituximab. Additionally, these genes had opposite expression of methylation in their promoter regions (59 total changed loci identified), as well as opposite expression of predicted microRNA targets (6 total). Through bioinformatic analysis, we reveal that Rituximab may have an effect on myogenic differentiation as it was shown to alter gene expression of two MyoD inhibitors (*CCND1* and *NR2F2*).

Conclusion: Rituximab could provide therapeutic benefit through modulating myogenic signaling in skeletal muscle, while also inducing B cell death and modifying cytokine profiles in B cells and macrophages.

305 - Membrane Repair Defects in the Pathogenesis of Myositis

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Background: Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous disorders with distinct clinical and pathologic features that allow their classifications into subtypes: polymyositis, dermatomyositis, inclusion-body myositis, and necrotizing autoimmune myositis. Two animal models have recently provided insight into the pathogenic mechanisms of myositis. Synaptotagmin VII null (SytVII$^{-/-}$) mice display impaired sarcolemmal repair capacity and develop mild myositis. In order to investigate the role of abnormal release of muscle antigens, we developed a more robust model of myositis that combines the Syt VII$^{-/-}$ model with a FoxP3 mutation (FoxP3$^{-/Y}$/Syt VII$^{-/-}$). This mouse strain combines impaired membrane repair with regulatory T-cell deficiency. Adoptive transfer of lymph node cells from FoxP3$^{-/Y}$/Syt VII$^{-/-}$ mice to immunodeficient RAG-1$^{-/-}$ recipients results in even more pronounced muscle inflammation.

Methods: Serum samples from myositis patients were obtained from OSU and UPMC, following IRB approval at both institutions. To screen for the presence of autoantibodies against TRIM proteins, human embryonic kidney cells were transfected to express recombinant TRIM proteins of interest, tagged with eGFP. Whole cell lysates were enriched for TRIM protein using immune pull down of eGFP and separated by SDS-Page. Autoantibodies against TRIM proteins were detected by immunoblot. To examine the kinetics of membrane resealing in the adoptive transfer murine model of myositis, individual muscle fibers were injured with an infrared laser and the kinetics of membrane resealing were quantified by measuring FM4-64 dye entry into the injured fibers. Similar methods were used to test the ability of TRIM polyclonal antibodies to compromise membrane resealing of isolated flexor digitorum brevis muscle fibers isolated from a C57BL/6 mouse.

Results: Earlier studies established the cellular framework of the membrane repair process utilizes exocytotic and endocytotic vesicle trafficking to restore membrane integrity. Previous work by our lab and others identified TRIM72 as a critical component of the membrane repair process in skeletal muscle and other tissues. Patients with myositis have also been shown to have autoantibodies against TRIM28, 24, 33 and 21. Our studies here identified additional autoantibodies against TRIM proteins in IIM patient sera: TRIM72, 27, and 2. Using an adoptive transfer model to induce myositis in mice, we show that membrane repair is broadly compromised in skeletal muscle of these mice, even in areas where no significant inflammation is observed. We also demonstrate that exogenous delivery of antibodies against TRIM proteins can compromise membrane repair in healthy skeletal muscle in an *in vitro* model system.

Conclusion: Taken together our data suggest that autoantibodies to certain TRIM family proteins predicate a defect in membrane resealing that permits the aberrant exodus of intracellular proteins. Thus, creating conditions that are permissive to the development of functionally significant muscle injury. Ongoing studies are examining the role of these antibodies both *in vitro* and *in vivo*.

306 - IL-23 as a Therapeutic Target of Inflammatory Myopathy

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Background Polymyositis and dermatomyositis (PM/DM) have been treated with non-specific immunosuppressants. Inflammatory cytokines suppressed in preclinical and clinical trials are produced by macrophages or muscle fibers even in the non-inflamed muscles. Optimal treatment should suppress cytokines specifically expressed in the inflamed muscles. IL-23 is produced from activated macrophages and dendritic cells to activate themselves and to expand Th17 cells. It is reportedly high in the serum from the PM/DM patients. To discern if it could be a specific therapeutic target, we studied its expression in the inflamed muscles and investigated its role in C protein-induced myositis (CIM), a murine model of PM.

Methods Muscle specimens were examined immunohistochemically for IL-23 and CD68 expression. Serum IL-23 were quantified with specific ELISA. Mice were injured with bupivacaine hydrochloride (BPVC) at their muscles or immunized with C-protein fragments/ Freund's complete adjuvant (CFA) for CIM induction alone or together with injection of anti-IL-23R monoclonal antibody (mAbs). Draining lymph node cells from CIM mice were transferred adoptively into naïve mice with their hind footpads treated with CFA for activation of local innate immunity. The severity of myositis was evaluated histologically.

Results IL-23 was significantly higher in the sera from CIM mice than that from control mice immunized with CFA alone. Immunohistochemical analyses disclosed that IL-23 was expressed by CD68+ cells infiltrating in the inflamed muscles from patients as well as from CIM mice. It was also expressed by CD68+ cells accumulated in the murine muscles after chemical injury with BPVC injection. In contrast, it was not expressed by CD68+ cells in the non-inflamed muscles that were recruited by CFA injection at the ipsilateral footpads. When IL-23-null mice were immunized with the C-protein fragments, they were resistant to CIM. When anti-IL-23R mAbs were administered to the CIM mice after the onset of myositis, it suppressed the myositis. Myositis was transferred from CIM donor mice comparably to wild type and to IL-23p19-null recipient mice.

Conclusion IL-23 was produced by macrophages specifically in the inflamed muscles in humans and mice. Its induction should be triggered by muscle damage. While IL-23 blockade ameliorated CIM, the adoptive transfer experiments demonstrated that it is essential for induction of autoaggressive T cells. Since the past studies disclosed that IL-17A was dispensable for CIM, IL-23 should be acting on antigen presenting cells involved in myositis. It has been a therapeutic target in psoriasis clinics, and could be in the future myositis clinics.

307 - The Host Defense Peptide LL-37 a Possible Inducer of the Type I Interferon System in Patients with Polymyositis and Dermatomyositis

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Background: Polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune diseases whose pathogenesis remain unclear. Although PM is classically thought to be driven by adaptive immunity and DM is associated with dysregulated innate immune pathways, emerging data suggest that the contribution of anti-microbial peptides may contribute to both conditions. LL-37, the sole member of the human cathelicidin family, has numerous immune system-modulating properties in addition to its anti-microbial activity and is implicated in the pathogenesis of several autoimmune diseases. The aim of this study was to explore a potential role of LL-37 in the pathophysiology of PM and DM.

Methods: Muscle biopsies (6 PM, 6 DM, and 5 controls) and skin biopsies (3 PM, 5 DM, and 6 controls) were immunohistochemically stained for LL-37, CD66b(mark for neutrophil), MxA, BDCA-2(mark for pDC), CD68 and CD163(both macrophage markers). Double staining for LL-37 and CD66b was performed by immunoflurence. The expression of LL-37 in muscle was confirmed with western blot. Serum levels of vitamin D were investigated.

Results: LL-37 expression was increased in muscle tissue and symptomatic skin of patients. LL-37 was mainly expressed by neutrophils, as confirmed with double stainings and strong correlation. BDCA-2 positive pDCs was increased in muscle tissue and symptomatic skin and MxA was increased in muscle tissue of patients. Low levels of vitamin D was also fund in patients. Moreover, the muscular expression of LL-37 and CD66b correlated with increased serum creatine kinase level.

Conclusion: The data presented here identify a novel pathogenetic expression of neutrophil-derived LL-37 in muscle and skin specimens of PM and DM patients.

308 - *In Vitro* Activation of Type I Interferon Pathway Reproduces the Characteristic Damages Observed in Dermatomyositis Patients

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Background: The type I interferons (IFN-I) including IFN-a, and IFN-b are key cytokines involved in innate immune response to viral infection. Almost all cells can produce IFN-I, express IFN-I receptor (IFNAR) and induce the transcription of IFN stimulated genes (ISGs), which have anti-viral effects and immunomodulatory activities. Idiopathic inflammatory myopathies (IIMs) are acquired auto-immune diseases. Among IIMs, Dermatomyositis (DM) is characterized by skin lesions, muscle specific pathologic features combining perifascicular muscle fibers atrophy with HLA-I over-expression and vasculopathy. It is known that ISGs are up-regulated in DM patients, however the cell injury induced by IFN-I activation remain unknown. Our aim is to determine the effect of the IFN-I pathway activation on myoblasts (MB), myotubes (MT) and endothelial (EC).

Methods: MB, MT and EC were stimulated with recombinant IFN-I pathway activators (either IFN-I, or IFN-a, or IFN-β or Poly (I:C) (PIC, an agonist of TLR3 receptor).

Results: Myoblasts stimulated with PIC, IFN-a and IFN-β abolished myotube formation in association with decreased myogenin (MyoG) expression. In differentiated MT, all stimuli induced *MxA* and *OAS1* expression. Moreover, IFN-a, IFN-β and PIC dramatically reduced myotube surface (A-B). In accordance we observed an upregulation of genes involved in muscle atrophy such as *Murf1* and *Atrogin* (C-D). Atrophy genes expression was confirmed at the protein level in muscle biopsies from DM patients. The expression was observed in perifascicular for both proteins. All stimuli induced HLA-I expression in differentiated MT. We also observed the presence of IFN-a in the supernatants in MB and MT, indicating that muscle cells can produce IFN-I. Next, IFN-a and IFN-b neutralization and IFNAR blocking experiments confirmed the specificity of the results. Neutralization and blocking experiments in differentiating MB treated with IFN-I, IFN-a and PIC, reverted the myotube surface. Ruxolitinib is an inhibitor of the JAK 1 and 2 tyrosine kinases and approved for the treatment of myeloproliferative disorders. Myoblasts treated with ruxolitinib prevent IFN-b inhibition of differentiation (E-F). In EC, the activation of IFN-I pathway, led to a decrease in cell proliferation and ISG up-regulation (*MxA, RIG-I and ISG15*). Tube formation assay with EC stimulated with IFN-I showed a disruption of vascular network formation, indicating that IFN-I impairs angiogenesis *in vitro*.

Conclusion: Treatment, *in vitro*, with IFN-I pathway activation recapitulates the characteristic pathological features (muscular and vascular damage) defined in DM. The treatment with Ruxolitinib, an ongoing clinic drug, revert the effects observed during differentiation and IFN-I pathway activation. Together our results show the key role of the IFN-I pathway in cell injury in DM, and emphasize the interest of specific treatment targeting IFN-I pathway.

309 - The Role of MDA5 Autoantibodies in the Pathogenesis of Dermatomyositis

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Background: Dermatomyositis (DM) is a heterogeneous disease which pathogenesis is not fully understood but it has been considered that vascular injury and type I interferons (IFN-I) play an important role in the muscle pathology. A particular form of DM is defined by the presence of autoantibodies (Abs) against the melanoma differentiation-associated gene 5 (MDA5) protein and it is strongly associated to a characteristic phenotype including mild or absent muscle weakness and severe extra muscular manifestations including rapidly progressive interstitial lung disease and skin lesions. Although clinically they have absent or mild muscle involvement, we previously reported that the muscle of these patients also display IFN-I signature but in a less degree compared with classical DM. In addition, skin biopsies in MDA5 patients showed evidences of vascular damage suggesting that both IFN-I and vasculopathy may have a role in this disease.

Methods: The aim of this study is to analyze *in vitro* the effect of anti-MDA5 Abs in muscle and in angiogenesis and their effect *in vivo* with intraperitoneal injection of plasma from 3 MDA5 patients to mice (n=5). We cultured human muscle cells with plasma or total IgGs from 3 MDA5 patients or controls and we analyzed myotube surface and fusion index in differentiating myoblasts and in myotubes. To analyze their effect on angiogenesis we performed a time-lapse tube-formation assay in endothelial cells (HMEC) in the presence of total IgGs from 3 MDA5 patients or controls to follow the formation of capillary-like structures.

Results: *In vitro* experiments in myoblasts showed that plasma and MDA5 total IgGs reduce the fusion index compared to controls (45±4.6% vs 65±4.1%, p=0.007; 44±3.3% vs 52±0.5%, p=0.009 respectively). We observed a reduction in the surface in the presence of MDA5 plasma compared to controls in differentiating myoblasts (31±3.7% vs 52±8.0%, p=0.007) and in mature myotubes (33±3.6% vs 48±2.5%, p=0.004). These results showed that MDA5 Abs disrupt muscle regeneration indicating a possible negative effect on myogenesis. Angiogenesis studies showed a decrease in the total segment length in the presence of total IgGs from the 3 different MDA5 patients (1794±440, 1668±453 and 2227±343) compared to control IgGs (3709±218, p<0.01). Along the same lines, we observed a reduction in the number of nodes in the presence of MDA5 total IgGs (78.7±13.8, 87.7±14 and 106.2±13.5) compared to control IgGs (147±11.5, p<0.01). These results showed that MDA5 Abs disrupt the vascular network organization indicating a possible negative effect on angiogenesis. *In vivo* experiments showed that passive transfer of MDA5 plasma up regulate significantly in the lung molecules involved in fibrosis (*Tgfb*, *Pdgfb*, *Col1a*) and involved in IFN-I (*Stat1*, *Ifih1* (MDA5)) compared to mice injected with control plasma.

Conclusion: We conclude that the effects observed in muscle cells are more related to circulating molecules, such as IFN-I, rather than the MDA5 Abs itself. Importantly, MDA5 Abs induce vascular damage *in vitro* and could explain the previous findings observed in the skin biopsies of MDA5 patients. *In vivo* experiments indicate that circulating molecules may induce lung damage promoting fibrosis and IFN-I.

310 - The Inflammasome in an *In Vitro* Model of Inclusion Body Myositis

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Background: Inclusion body myositis (IBM) is the most common acquired myopathy in patients over 50 years. The pathogenesis involves degenerative and inflammatory processes. Proinflammatory cytokines lead to increased cell stress in muscle fibers and a dysregulated protein homeostasis. In muscle cells stimulated with proinflammatory cytokines, an increased secretion of IL-1b occurs. It is known that the inflammasome cleaves and activates the precursor of Il-1b in macrophages. b-amyloid, a misfolded protein found in muscles fibres of patients with inclusion body myositis was described as an activator of the inflammasome. An activation of the inflammasome might play a role in the pathogenesis of IBM (Menu and Vince 2011; Rawat et al., 2010).

Methods: The regulation of the inflammamasome was investigated in a well-established proinflammatory cell culture model using a myoblast cell line and primary muscle cell cultures. We performed quantitative PCR, Western Blot and immunocytochemistry in muscle cell stimulated with the proinflammatory cytokines IL-1b and IFN-g. Furthermore, we investigated NLRP3 n muscle biospies of patients with inclusion body myostis, dermatomyositis, polymyositis and non-inflammatory myopathies.

Results: There was a significant upregulation of NLRP3, a protein of the inflammasome, in the pro-inflammatory environment compared to the untreated control sample in Western blot, qPCR and immunocytochemistry.

Conclusion: Taken together, our data shows an upregulation of the inflammasome as a proinflammatory muscle cell response to stimulation with IL1b + IFN-g. This could lead to an ongoing chronic muscle inflammation as seen in inclusion body myositis. We hope to determine the role of the inflammasome in the disease development of inclusion body myositis and to develop new therapy strategies to stop chronic inflammation in myositis (Ozaki, Campbell and Doyle 2015).

311 - Nitric Oxide (NO) Stress in a Mouse Model of Inclusion Body Myositis (IBM)

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Background: IBM is characterized by a mononuclear cell inflammation and an accumulation of degeneration associated proteins such as beta-amyloid. Recently, inducible NO synthase (iNOS) has been identified as an essential mediator of inflammatory cell stress in skeletal muscle of IBM patients. In a double transgenic mouse model for IBM with a muscle-specific overexpression of amyloid-precursor-protein (APP) and presenilin (PS)- 1 under the CK-promotor, an increased accumulation of beta-amyloid has been demonstrated in skeletal muscle. This was accompanied by progressive weakness after 12 months of age. By assessing clinical as well as pathological parameters, we here studied the role of iNOS in the APP/PS-1 transgenic mouse model.

Methods: APP/PS-1 ("IBM"), iNOS deficient IBM (IBM/iNOS-/-) and age-matched iNOS deficient and C57/Bl6-wildtyp mice were placed in separate cages equipped with a running wheel. Running parameters like velocity, distance, time and number of runs were recorded continuously from the age of 3 months until end of study at 24 months. Every week, grip strength and bodyweight were measured. At 6, 12, 18 and 24 month, 10 animals of each group were sacrificed and blood and limb muscle were sampled for quantitative PCR and histological analysis.

Results: IBM mice showed a progressive, age-dependent decrease in all voluntary wheel running parameters as well as grip strength and an increase of myopathic changes as well as beta-amyloid deposits. iNOS deficiency significantly improved the running behaviour, the central nuclei index (CNI) as an indicator of myopathic changes and beta-amyloid deposits in leg muscles as evidenced by Thio-S staining.

Conclusion: By using sensitive, investigator-independent computerized readout parameters, we demonstrate that IBM mice have an impaired running wheel performance. Deficiency of iNOS ameliorates the clinical and pathological phenotype. The data support the relationship between chronic inflammatory and beta-amyloid associated cell stress in skeletal muscle and how this is modulated by NO. The study may further our efforts to identify new therapeutic strategies for IBM.

312 - MicroRNA and mRNA Profiling in Polymyositis, Dermatomyositis and Inclusion Body Myositis Using Next-Generation RNA Sequencing

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Background: MicroRNA (miRNA) are short, non-coding RNA which bind to specific mRNA and suppress translation or induce degradation of the transcript. In this manner miRNA regulate a wide variety of biological processes and dysregulation of microRNA is known to play a role in cancer and autoimmunity. The aim of this study is to use RNA sequencing to profile the microRNA and mRNA present in blood samples from polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) patients compared to non-myositis controls.

Methods: Blood in tempus tubes was collected from patients with definite IIM as part of the myositis research tissue bank (MRTB). The MRTB uses Bohan and Peter classification criteria for PM or DM and Griggs or European Neuromuscular Centre or Medical Research Council criteria for IBM. Total RNA was extracted from 9 PM, 8 DM, 5 IBM and 5 non-myositis controls. Extraction efficiency of miRNA across batches was assessed by spiking a mirVana™ miRNA mimic of *arabidopsis thaliana* miRNA, ath-miR159a, into blood tubes and then measuring the amount of spike present after extraction using a Taqman® Advanced MicroRNA assay. RNA integrity was measured using an Agilent 2100 Bioanalyzer®. cDNA library preparation was performed for both mRNA and small RNA. Both sets of libraries were then sequenced on the Illumina HiSeq 2500. Nine samples were run per lane with a read depth of approximately 11 million per sample.

Sequencing results will be analysed using a Galaxy bioinformatics workflow to identify differential expression of miRNA between myositis and control groups and between myositis subtypes. TargetScan will be used to predict the mRNA targets of dysregulated miRNA. The mRNA sequencing results will then be analysed to assess how well mRNA differential expression correlates with the predicted dysregulation by miRNA.

The possible downstream effects of miRNA and mRNA dysregulation will be investigated using analysis tools such as GOseq (an R package) and Ingenuity Pathway Analysis (QIAGEN). A panel of dysregulated miRNA and/or mRNA from PM, DM, IBM or all subtypes vs controls will be selected depending on the RNAseq analysis results. These will then be validated by RTqPCR in further blood samples from PM, DM, IBM and controls, and investigated in other tissue types such as plasma and muscle.

Results: Extraction efficiency of miRNA was consistent across batches of total RNA extraction, a one way ANOVA showed no significant differences ($F(6,16)=2.059$, $P=0.116$) between the amounts extracted from each batch (analysis performed using IBM SPSS Statistics version 22 using mean Ct values for each sample). The yield of total RNA extracted varied between samples with a range of 2.8-26.9µg. RNA integrity numbers (RIN) measured by the Agilent 2100 Bioanalyzer® had a mean of 7.2 and standard deviation 1.3 (RIN is on a scale from 1 to 10, with 1 being totally degraded RNA and 10 being perfectly intact RNA).

Conclusion: A greater understanding of the mechanisms involved in myositis revealed by the profiling of microRNA and mRNA in blood samples may lead to novel and more specific treatments. It may also add to our understanding of the differences between the three major subtypes of myositis.

313 - Predictors of Corticosteroid Discontinuation, Complete Clinical Response and Remission in Patients with Juvenile Dermatomyositis

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Background: Factors affecting treatment (Rx) responses in juvenile dermatomyositis (JDM) are not well understood. We examined a large JDM registry for the frequency, and predictors of excellent Rx responses, including final discontinuation of corticosteroid therapy (CS-DC), complete clinical response (CCR, clinically inactive disease for ≥6 continuous months on Rx), and remission (inactive disease for ≥6 continuous months off all Rx).

Methods: A retrospective review of Rx responses in 318 pts with probable or definite JDM diagnosed from November 1968 to September 2014 (median August 1994) was conducted. The median follow-up duration was 44 months [IQR 23-80] and Rx duration was 31 months [IQR 19-61]. Three pts who died and 13 whose Rx outcome was unknown were excluded; 185 pts (58%) were lost to follow-up before achieving CCR or remission. We evaluated the probability of achieving CCR, and remission by Weibull time-to-event models with the date of last follow-up used with censored observations. We also evaluated the frequency and median time to achieve each outcome. Univariable predictors of the time to achieve each outcome were evaluated by Cox proportional hazards. Significant predictors (hazard ratio $P<0.05$) were then examined in multivariable time-to-event analysis using Markov chain Monte Carlo (MCMC) Weibull extension models, reporting variables where the parameter credible intervals did not overlap zero.

Results: Fifty-two percent (167 pts) experienced final CS-DC a median of 28 months after initial Rx [IQR 16- 53]. Thirty-two percent (104 pts) achieved CCR a median of 24 months from Rx start [IQR 16-46]. From Weibull modeling, the probability of achieving CCR was 22% at 36 months, 50% at 94 months and 75% at 182 months. After first CCR, 50% (52 pts) achieved remission and 22% (23 patients) had a disease flare a median of 11 months after CCR. Twenty-eight percent (84 patients) achieved remission a median of 36 months after initial Rx [IQR 26-54], including 32 patients who achieved remission without CCR first. From Weibull modeling, the probability of remission was 16% at 36 months, 50% at 113 months, and 75% at 196 months. Thirty percent (25 patients) who achieved remission experienced a flare a median of 22 months after remission, and 48% (12 patients) achieved CCR and/or remission again.

From MCMC Weibull modeling (Table), disease flare, anti-p155/140 Abs, calcinosis, and lipodystrophy were associated with longer time to achieve these 3 outcomes. Three additional variables were associated with 2 outcomes, and 5 variables were associated with 1 Rx outcome each.

Conclusion: A large proportion of JDM patients achieve positive Rx responses, including CS-DC, CCR, and remission, although timelines for these important outcomes are relatively long. Factors associated with longer time to achieve these Rx outcomes include selected clinical features, TIF1 Abs, delay to treatment initiation, environmental factors, and year of diagnosis.

Table. Multivariable time-to-event analysis using Markov chain Monte Carlo Weibull extension models to examine predictors of corticosteroid discontinuation, complete clinical response and remission in 318 juvenile dermatomyositis patients.

	DS-CS		CCR		Remission	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Intercept	-4.98	0.29	-4.72	0.39	-5.84	0.63
Disease flare	-1.49	0.19	-0.60	0.21	-0.92	0.26
Lipodystrophy	-0.72	0.34	-1.35	0.38	-1.99	0.53
Calcinosis	-0.64	0.19	-0.42	0.22	-1.28	0.31
Anti p155/140 autoantibody	-0.24	0.17	-0.17	0.20	-0.55	0.27
History of hospitalization	-0.35	0.17			-0.50	0.25
Infection within 6month of diagnosis	-0.31	0.19			-0.85	0.33
Diagnosis after 1997			-1.15	0.35	-0.83	0.37
Wheelchair use	-0.33	0.27				
Treatment delay from diagnosis >4 months	-0.33	0.16				
Vaccination in 12 month before diagnosis			-0.56	0.41		
Age at 1st treatment >7years old					-0.68	0.25
Cardio-pulmonary-GI symptoms					-0.35	0.23

314 - Juvenile Dermatomyositis: Is Periodontal Disease Associated with Dyslipidemia?

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Background: Recently the association between periodontal disease and dyslipidemia was reported in healthy adults. However, to our knowledge, a systematic evaluation of concomitant periodontal diseases and lipid profile assessment was not carried out in juvenile dermatomyositis (JDM) population.

Methods: A cross-section study was performed in 25 JDM patients and 25 healthy controls. They were assessed according to demographic data, complete periodontal evaluation, fasting lipoproteins and anti-lipoprotein lipase antibodies. Disease parameters, laboratorial tests and treatment were also evaluated in JDM patients.

Results: The mean of current age was similar in JDM patients and healthy controls (11.5±3.75 vs. 11.2±2.58 years, p=0.703). A trend of a high frequency of dyslipidemia was observed in JDM patients compared to controls [68% vs. 40%, p=0.087]. The median of VLDL [16(6-68) vs. 13(4-36) mg/dL, p=0.020] and triglycerides [80(31-340) vs. 61(19-182)mg/dL, p=0.011] were significantly higher in JDM patients *versus* controls. The frequency of gingival vasculopathy pattern was significantly higher in the former group (60% vs. 0%, p=0.0001), as well as the median of GBI [24.1(4.2-69.4) vs. 11.1(0-66.6)%, p=0.001] and PPD [1.7(0.6-2.4) vs.1.4(0-2.12)mm, p=0.006]. Further analysis between JDM patients with and without dyslipidemia revealed that the median of PI [100(26.7-100) vs. 59(25-100)%, p=0.022], PPD [1.9(0.6-2.4) vs. 1.4(1.2-1.8)mm, p=0.024] and CAL [1.31(0.7-1.7) vs. 0.8(0.6-1.7) mm, p=0.005] were significantly higher in JDM patients with dyslipidemia compared to those without this complication. Positive Spearman's correlations were found between total cholesterol and PI (r_s=+0.498, p=0.0114) and LDL and PI (r_s=+0.421, p=0.0357).

Conclusion: Our study showed that gingival inflammation seems to be related to dyslipidemia in JDM patients, suggesting underlying mechanisms for both complications.

315 - Patient-Reported Outcomes in Childhood Idiopathic Inflammatory Myopathies

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Background: Few studies describe the natural course and long term outcomes of myositis in childhood in large, prospectively-followed patient cohorts, treated in the modern era.We aimed to describe long term patient-reported outcomes in adolescents and young adults (≥ 16 y) who had myositis in childhood and to find outcome predictors from data in the Juvenile Dermatomyositis Cohort and Biomarker Study, UK and Ireland (JDCBS).

Methods: Participants in the JDCBS, previously diagnosed with idiopathic inflammatory myopathy, currently 16 years or over, completed the SF36 v2, HAQ and a newly developed questionnaire to collect information on current disease features and damage, medication use and side effects, and education and employment opportunities.

Results: 84 (41%) sets of questionnaires were returned. Average age of respondents was 21.5 years (maximum 30.8y). Average disease duration 11.8 y (SD 5.1), age at onset 9.2y (SD 4.3) and female to male ratio 4.25:1. Most patients were white (82.1%) and had a diagnosis of Definite Juvenile Dermatomyositis (69%). Of the 68 who had Myositis-specific autoantibody testing, eight (11.8%) had TIF1γ and eight had NXP2. Six (8.8%) were positive for Mi2. Nine (13.2%) had unknown bands and 14 (20.6%) were negative. Of note, 49 (59%) reported persistently active disease and 54 (65%) were still taking immunosuppressive medication for myositis. Among respondents at school or in higher education, 13 out of 29 (44.8%) reported that their academic results were adversely affected by myositis, and that time missed, muscle weakness and fatigue were all significant contributors. Around two-thirds of respondents found that myositis had made it difficult to study. Fourteen of 50 (28%) reported career compromise caused by myositis; of these, 10/37 (27%) were employed and 4/13 (30.8%) were unemployed. Among 47 patients aged 18 to 24 there were 21 (44.7%) who were employed; patients in this study were twice as likely to be unemployed compared to the corresponding age group in the UK population (p=0.001, OR 0.456, 95% CI 0.24, 0.84). SF36 Physical Composite Scores (PCS) were significantly better in those who did not report current myositis (p=0.0003) arthritis (p=0.002) or muscle weakness (p=0.0001). Mental Composite Scores (MCS) were also better in those who did not report current arthritis (p=0.03) or muscle weakness (p=0.013). Smoking (M,F) and alcohol use (F) were lower than in the general UK population. However, there was a trend towards higher rates of living with a parent/guardian.

Conclusion: We found high patient-reported rates of persistently active disease and medication use in long term follow-up of juvenile myositis, although response bias exists. The young people had reduced rates of employment compared to the UK general population. Persistent muscle disease affected quality of life outcomes in this cohort.

316 - Trajectories of Cardiorespiratory Fitness in Patients with Juvenile Dermatomyositis

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Background: Juvenile dermatomyositis (JDM) is a rare systemic autoimmune vasculopathy characterized by capillary inflammation that affects predominantly the musculoskeletal and cutaneous systems. The disease course is heterogenic, varying from mild muscle symptoms that quickly respond to therapy, to a very protracted therapy resistant chronic course. Prominent clinical features are significant muscle weakness, reduced anaerobic and aerobic capacity and fatigue, even in clinical remission with and without medication. Longitudinal data are vital in order to provide relevant clinical information regarding the need for additional physical activity or exercise training in the follow-up of this population. In addition, possible factors influencing cardiorespiratory fitness (CRF), such as medication and duration of the disease, should be studied as well. Therefore, the aim of this study was to determine trajectories CRF in patients with both monocyclic and chronic type JDM, and the possible effects on these trajectories.

Methods: Twenty-six children with JDM (mean ± SD age 9.3 ± 3.2 years at diagnosis), treated in the pediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands, were included. All patients performed a cardiopulmonary exercise test (CPET) more than two times between 2003 and 2016 as part of usual care and research. Patients performed a CPET using an electronically braked cycle ergometer and respiratory gas analysis system. Exercise parameters were analyzed, including peak oxygen uptake (VO_{2peak}), peak work rate (W_{peak}), ventilatory anaerobic threshold (VAT) and oxygen uptake to work rate relation ($\Delta VO_2/\Delta WR$). Multilevel analyses, in which repeated measures are nested within the children were applied to analyze trajectories over time (both absolute values as well as Z-scores). In addition, multilevel analyses were used to determine confounding factors influencing the outcome parameters (e.g. prednisone use, disease duration, and diagnosis delay).

Results: Results indicate a developmental increase of absolute values of CRF over time in concurrence with growth and development. However, compared to age and gender matched reference values no increase or even a decrease over time was observed in CRF, in both monocyclic and chronic subtypes of JDM. Multilevel analyses indicated a negative effect of prednisone on different exercise parameters, indicating lower exercise performance with higher Prednisone doses.

Conclusion: In both monocyclic and chronic type of JDM long-term CRF is decreased in which treatment with prednisone affects the outcome levels of CRF. This indicates long-term follow-up should include regular evaluation of physical activity and cardiopulmonary levels even in monocyclic patients. Exercise interventions to improve these levels are also warranted and should be tailored made in order to prevent further physical dysfunction and work-related problems.

317 - Longitudinal Predictors of Physical Function in Juvenile Myositis

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Background: Juvenile myositis (JM) is marked by skin rashes, proximal muscle weakness, and deconditioning causing potentially severe disability. Studies examining long-term physical function in JM remain scant. This study aims to define longitudinal predictors of physical function in JM.

Methods: JM patient data collected prospectively at routine clinic visits from January 2000 to June 2014 at Ann & Robert H. Lurie Children's Hospital of Chicago was used in this study. Only patient visits with documented Childhood Health Assessment Questionnaire (CHAQ) summary scores were included for analysis. Demographic/clinical variables were extracted, including: gender, race, duration of untreated disease, Disease Activity Score (DAS) - muscle/skin domains, Childhood Myositis Assessment Scale (CMAS), muscle enzymes (i.e. CPK, AST, LDH, aldolase), nailfold capillary end row loops (NFC-ERL), von Willebrand factor antigen (vWFAg), calcinosis, lipodystrophy, possible markers of disease severity (i.e. NK cell absolute counts, TNFalpha-308A allele), and treatments.

Descriptive statistics were calculated. CHAQ was dichotomized (0 vs. >0) as most scores equaled zero. Generalized estimating equations for binary data specifying logit link function were used to evaluate effects for each covariate with a main effect for time. Covariates were univariably analyzed at $p < 0.10$, with all univariably significant covariates entered into a multivariable model for CHAQ > 0 using a manual backward selection method.

Results: Table 1 describes the study sample (i.e. n = 187 patients with 2293 study visits and median follow-up 3.58 years). The following univariably significant covariates (at $p < 0.10$) were included in the multivariable model: time (years from visit 0) (p <0.0001), black race (p = 0.035), DAS-skin (p = 0.006), DAS-muscle (p <0.0001), CMAS (p <0.0001), LDH (p = 0.005), aldolase (p = 0.013), NFC-ERL (p = 0.002), abnormal vWFAg (p = 0.0001), lipodystrophy (p <0.0001), cyclosporine (p = 0.0725), and IV solumedrol (p = 0.0002). Complete data for the multivariable model was available for 892 study visits from all 187 unique patients. Significant adjusted associations persisted in the multivariable model for CMAS (OR: 0.91, p <0.0001), aldolase (OR: 1.1, p = 0.0024), and lipodystrophy (OR: 2.2, p = 0.0126), with a trend towards significance for NFC-ERL (OR: 0.84, p = 0.0502).

Conclusion: To our knowledge, this is the largest longitudinal study of prospectively collected physical function data yet reported in JM. Measures of muscle weakness/inflammation (i.e. CMAS, aldolase) predict long-term physical function. The relationships between lipodystrophy, vasculopathy (i.e. NFC-ERL), and physical function warrant closer attention and replication.

Table 1: Patient and Visit Level Descriptives		
	n = # with available data	n (%) / median (IQR)
Patient Level (n = 187):		
Race	187	
White		131 (70.1%)
Hispanic		37 (19.8%)
Black		11 (5.9%)
Other*		8 (4.3%)
Female Gender	187	139 (74.3%)
Age of Onset (years)	187	5.39 (2.9-7.9)
Duration of Untreated Disease (months)	185	4.5 (2.1-10.1)
Calcinosis (ever experienced)	186	37 (19.8%)
Lipodystrophy (ever experienced)	186	60 (32.26%)
TNFalpha-308A Allele	178	
AA		2 (1.12%)
GA		50 (28.1%)
GG		126 (70.8%)
Visit Level (n = 2293)		
CHAQ summary score value	2252	0 (0-0.38)
CHAQ summary score > 0	2252	1072 (47.6%)
DAS-Skin	2293	4 (1-5)
DAS-Muscle	2293	1 (0-2.5)
CMAS	1795	47 (43-52)
AST	2043	27 (22-32)
CPK	2105	88 (60-124)
LDH	2072	224 (187-281)
Aldolase	1989	6.4 (5.3-8)
NFC-ERL	1279	5.42 (4.6-6.2)
vWF Ag (abnormal value)	2018	184 (9.1%)
NK cell absolute count	2080	185 (120-274)
Calcinosis present at visit	2259	229 (10.1%)
Lipodystrophy present at visit	2257	210 (9.3%)
Medications:**		
On any medication at study visit	2254	1919 (85.1%)
Oral Steroids	2266	1369 (60.4%)
IV Steroids	2265	626 (27.6%)
Methotrexate	2266	1472 (65%)
Intravenous immune globulin	2106	176 (8.4%)
Cyclosporine	2125	354 (16.7%)
Hydroxychloroquine	2268	688 (30.3%)
Mycophenolate Mofetil***	1344	684 (50.9%)

*Other race comprised of: Asian (n =4), "Indian" (n = 2), American Indian/Alaskan Native (n =1), "Other" (n = 1)

**11 treatment courses of Rituximab, 7 study visits on Etanercept, 1 study visit on Infliximab, and 1 study visit on Azathioprine were documented

***n = 1344 study visits with data on Mycophenolate available because use of this medication began in the middle of the study period

318 - Cardiovascular and Cerebrovascular Comorbidities of Juvenile Dermatomyositis in United States Children

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Background: Juvenile dermatomyositis (JDM) is an autoimmune disease that causes vasculopathy and inflammation of skin and muscles. Previous studies in adult dermatomyositis suggest increased risks of cardiovascular disease, but such assessments in JDM remain underexplored. This study evaluates cardiovascular risk factors and outcomes in children with versus without JDM.

Methods: Data were analyzed from the 2002-2012 Nationwide Inpatient Sample, containing a representative 20% stratified sample of all hospitalizations in the United States. Primary (i.e. condition chiefly responsible for inpatient admission) vs secondary diagnoses of JDM (age <18 years) were identified using the previously validated *ICD-9-CM* code 710.3. Comorbidities were identified using *ICD-9-CM* codes in NIS for each patient discharge. Survey weighted logistic regression models were used to determine associations of JDM with comorbidities. Multivariate models included age, sex and race/ethnicity (model-1), as well as obesity, hypertension and diabetes (model-2) as binary covariates. A 2-sided p-value <0.05 was considered statistically significant.

Results: From 2002-2012, 909 primary and 498 secondary diagnoses of JDM were identified (from 14,535,620 pediatric hospital discharges). JDM inpatients were 34.6% male, 49.0% white, 18.5% black and 24.1% Hispanic. Twelve of 13 cardiovascular comorbidities were significantly associated with JDM (Table 1). Hypertension was the most common comorbidity in children with JDM (8.78% JDM patients vs 0.43% those without JDM, OR [95% CI]: 22.25 [15.51-31.92]). JDM was also associated with higher rates of obesity, uncomplicated diabetes, and lipid abnormalities. JDM inpatients had higher odds of cardio/cerebrovascular disorders, i.e. peripheral/visceral atherosclerosis, late effects of cerebrovascular disease, personal history transient ischemic attack/cerebral infarction, pulmonary circulatory disorder, arrhythmia, bradycardia, and hypotension. In multivariate regression models adjusting for age, gender and race/ethnicity, associations with JDM remained significant in 10 of 13 comorbidities.

Conclusion: JDM is associated with higher odds of cardiovascular and cerebrovascular risk factors and disease. The possible interaction of chronic inflammation, vasculopathy, and treatment side effects with sociodemographic and cardiovascular risk factors requires further study.

Table 1. Association between juvenile dermatomyositis and cardiovascular comorbidities in US children.

Comorbidity	Dermatomyositis							
	No (n=14,485,143)	Yes (n=1,407)						
					Model-1		Model-2	
	Freq (%)	Freq (%)	Crude OR (95% CI)	P	Adj OR (95% CI)	P	Adj OR (95% CI)	P
Obesity	68662 (0.48%)	38 (2.75%)	**5.87 (3.44-10.02)**	**<0.0001**	**2.27 (1.30-3.98)**	**0.004**		
Hypertension	61715 (0.43%)	119 (8.78%)	**22.25 (15.51-31.92)**	**<0.0001**	**11.64 (7.63-17.76)**	**<0.0001**		
Diabetes, uncomplicated	24811 (0.17%)	18 (1.35%)	**7.95 (4.21-15.00)**	**<0.0001**	**2.72 (1.25-5.89)**	**0.01**		
Any lipid abnormalities	11008 (0.08%)	6 (0.44%)	**5.84 (2.77-12.31)**	**<0.0001**	1.74 (0.58-5.20)	0.32	0.76 (0.21-2.76)	0.68
Lipodystrophy	137 (0.0009%)	2 (0.14%)	**151.08 (38.24-596.86)**	**<0.0001**	**43.32 (5.93-316.46)**	**0.0002**	**30.77 (3.67-257.75)**	**0.002**
Peripheral and visceral atherosclerosis	5857 (0.04%)	6 (0.41%)	**10.09 (3.70-27.56)**	**<0.0001**	**5.82 (1.86-18.19)**	**0.003**	**4.07 (1.27-13.07)**	**0.019**
Late effects of cerebrovascular disease	5234 (0.04%)	9 (0.56%)	**15.49 (2.37-101.43)**	**0.004**	**8.74 (1.38-55.37)**	**0.02**	**6.47 (1.01-41.53)**	**0.049**
Personal history of TIA and cerebral infarction w/o residual deficits	4001 (0.03%)	4 (0.30%)	**10.82 (2.46-47.65)**	**0.002**	**6.00 (1.43-25.19)**	**0.01**	4.08 (0.93-17.97)	0.06
Pulmonary circulatory disorder	12971 (0.09%)	15 (1.10%)	**12.23 (2.59-57.73)**	**0.002**	**11.76 (2.52-54.82)**	**0.002**	**7.69 (1.67-35.36)**	**0.009**
Arrhythmia	129723 (0.90%)	47 (3.41%)	**3.93 (2.80-5.52)**	**<0.0001**	**1.89 (1.27-2.82)**	**0.002**	1.42 (0.92-2.19)	0.11
Valvular heart disease	154358 (1.06%)	17 (1.19%)	1.13 (0.71-1.78)	0.61	1.54 (0.93-2.55)	0.09		
Bradycardia	52631 (0.36%)	21 (1.52%)	**4.22 (2.65-6.74)**	**<0.0001**	**2.17 (1.27-3.70)**	**0.005**	1.65 (0.94-2.90)	0.08
Hypotension*	41033 (0.31%)	9 (0.81%)	**2.62 (1.27-5.39)**	**0.009**	1.82 (0.84-3.93)	0.13		

* Since hypotension can be related to both cardiovascular and infectious etiologies, all cases with comorbid infections were excluded from the analyses, including any skin infection (*CCS* code 197), cellulitis (*ICD-9-CM* 681.00, 681.10, 681.9, 682.0, 682.1-682.9), any fungal infection (*CCS* code 4), septicemia (*CCS* code 2), any bacterial infection (*CCS* code 3), herpes simplex virus infection (054, 054.0, 054.10-054.13, 054.19, 054.2, 054.3, 054.40-054.44, 054.49, 054.5, 054.6, 054.71-054.74, 054.79, 054.8-054.9), streptococcal infection (*ICD-9-CM* 034.0, 038.0, 041.00-041.05, 041.09), any viral infection (*CCS* code 7), osteomyelitis (*ICD-9-CM* 730.00-730.29, 730.80-730.99), urinary tract infection (*CCS* code 159), infectious arthritis (*ICD-9-CM* 711.0, 711.00-711.09, 711.40-711.59, 711.80-711.99, 730.88), pneumonia (*CCS* code 122), tuberculosis (*CCS* code 1), and HIV/AIDS (*AHRQ* pre-coded).

319 - Predictors of Hospitalization, Length of Stay and Costs of Care Among Adults with Dermatomyositis in the United States

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Background: Dermatomyositis (DM) is a rare autoimmune disease that causes significant morbidity and quality of life impairment. However, little is known about the inpatient burden of DM in the United States. This study analyzes the prevalence and predictors of hospitalization, cost of care, and length of stay in US patients with DM.

Methods: Data on 72,651,487 hospitalizations from the 2002-2012 Nationwide Inpatient Sample (NIS), a 20% stratified sample of all acute-care hospitalizations in the United States, was analyzed. Previously validated ICD-9-CM code 710.3 was used to identify hospitalizations with a primary (i.e. condition chiefly responsible for inpatient admission) vs secondary diagnosis of DM. The control group included all hospitalizations without any diagnosis of DM. Hospitalizations with diagnoses of scleroderma, lupus, polymyositis, mixed connective tissue disease, and undifferentiated connective tissue disease were excluded to minimize misclassification. Survey logistic regression models were used to determine predictors of hospitalization for DM. Adjusted ORs were obtained via multivariate regression including age, sex, race/ethnicity, health insurance, number of chronic conditions, and hospital location. Linear regression models with log transformed cost of care or length of stay were used to determine predictors of cost of hospitalization and length of stay using the aforementioned covariates.

Results: There were 9,687 and 43,188 weighted admissions with a primary or secondary diagnosis of DM, respectively. Prevalence of hospitalization for patients with a primary or secondary diagnosis of dermatomyositis significantly increased for all years after 2003 compared with years 2002-2003 (generalized linear models, $P<0.05$). In multivariable logistic regression models with stepwise selection, female sex (logistic regression; adjusted odds ratio [95% confidence interval]) (2.05 [1.80-2.34]), non-white race (black: 1.68[1.57-1.79]; Hispanic: 2.38[2.22-2.55]; Asian: 1.54[1.32-1.81]; multiracial/other: 1.65[1.45-1.88]), and multiple chronic conditions (2-5: 2.39[2.20-2.60]; 6+: 2.80[2.56-3.07]) were all associated with higher rates of hospitalization for DM. The weighted total length of stay (LOS) and inflation-adjusted cost of care for patients with a primary inpatient diagnosis of DM was 80,686 days and $168,076,970, with geometric means [95% CI] of 5.38 days [5.08-5.71] and $11,682 [$11,013-$12,392], respectively. LOS and costs of hospitalization were significantly higher in hospitalizations with DM compared to those without DM. Notably, race/ethnicity was associated with increased LOS (log-linear regression; adjusted beta [95% confidence interval] for black: 0.14 [0.04-0.25]; Asian: 0.38 [0.22-0.55]) and cost of care (Asian: 0.51 [0.36-0.67]).

Conclusion: There is a significant and increasing inpatient burden for DM in the US. There appear to be racial differences as non-whites have higher prevalence of admission, increased LOS and cost of care.

320 - Long-Term Outcome of Children with Juvenile Dermatomyositis: A Single-Centre Study from North India

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Background: Juvenile dermatomyositis (JDM) is a rare inflammatory myopathy seen in children. There have been few studies on long-term outcome in children with JDM using validated outcome measures. Against this background, we undertook this study to assess the long-term outcome of JDM using validated measures of outcome.

Methods: Cross-sectional observational study. All children diagnosed to have JDM for more than 2 years and registered in Pediatric Rheumatology Clinic at Post Graduate Institute of Medical Education and Research, Chandigarh, India, were deemed eligible for recruitment. Study was conducted from January 1, 2015 to June 30, 2016. Those who were not on regular follow-up were called for assessment. Assessment was done by a single observer using Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing 8 (MMT8), Myositis Disease Activity Assessment Tool (MDAAT), abbreviated cutaneous assessment tool (aCAT), Myositis Damage Index (MDI) and Childhood Health Assessment Questionnaire (CHAQ).

Results: Thirty-five children were enrolled in this study. Twenty-two (62.9%) children were on regular follow-up. Mean age of patients was 13.9 years (range 4-29 years). Mean age at diagnosis was 7.51 ± 3.56 years with median time-interval between onset of symptoms and diagnosis being 5 months. Mean duration of disease at the time of enrolment was 7.18 years.

Disease course was monocyclic in 24 (68.6 %). Muscle strength was normal in 71.4% with MMT8 score of 80 and normal CMAS. Severe involvement defined as MMT8 score below 64 was seen in 8.6%. Cutaneous activity was determined by aCAT with 14 (40%) children having a score of ≥ 1 suggesting some form of cutaneous activity. Based on MYOACT, 31.4% children in our study had evidence of disease activity at the time of cross-sectional assessment with skin being the commonest organ system involved in 28.6% followed by muscles in 22.9% subjects. Twenty-one (60%) children had some form of cutaneous damage. Calcinosis was seen in 12 (34.3%) children and lipodystrophy in 8 (22.9%). Twenty-four (68.6%) subjects had an MDI score of ≥ 1 at the time of evaluation suggesting damage in at least one organ system. Most commonly affected organs were cutaneous, endocrine and muscles in 20 (57.1%), 12 (34.3%) and 9 (25.7%) subjects respectively. Nine (25.7%) subjects in our study had some form of a physical dysfunction suggested by a CHAQ score above 0 at the time of cross-sectional assessment.

Conclusion: The highlight of this study is the use of validated outcome measures for evaluation of long-term outcomes. After mean disease duration of 7.18 years, one-third subjects had evidence of disease activity with almost one-tenth having moderate to severe activity. About 2/3rd had damage in at least one organ system. Skin was the most common organ affected by activity as well as damage. About 1/4th had reduced physical functioning. Therefore, JDM is not a disease where one time treatment would suffice and regular long-term follow-up is required. Counselling of the caregivers is also critical for them to adhere to follow-up. Larger long-term studies using validated outcome measures are required to confirm these findings.

321 - Polymyositis in a Child: Difficult Course with a Favourable Outcome

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Background: Polymyositis in children is a rare childhood inflammatory muscle disorder. Its treatment is uncertain and consists of immunosuppressive therapy. We present here a case of childhood polymyositis with a challenging course who responded to therapy.

Methods: A 12-year-old boy presented with a history of progressive weakness in lower and upper limbs. Weakness was involving proximal muscles to begin with and later involved distal muscles as well. There was a history of nasal regurgitation of feeds and change of voice. Examination revealed diffuse muscle tenderness, markedly weak gag reflex, nasal speech, diffuse limb edema and reduced muscle power. Proximal muscle power being less than distal. There was no rash (Figure 1). Investigations revealed normal hemoglobin and platelets, polymorphonuclear leukocytosis. Lactate dehydrogenase 1693 IU/L (N= 240-480), Creatine phosphokinase 1137 IU/L (N= 26-308), AST 199 IU/L (N < 45), ALT 213 IU/L (N < 45). Electromyography revealed increased spontaneous activity and small amplitude, polyphasic muscle unit action potentials, features suggestive of inflammatory myopathy. Magnetic Resonance Imaging thighs showed diffuse hyperintensities involving all groups of thigh muscles and subcutaneous fat planes in T2 & STIR sequences. Similar hyperintense signal was seen in muscles of bilateral glutei and pelvis (Figure 1). Muscle biopsy was performed which showed rarefied muscle fibers, myocyte necrosis, CD8+ T-cell inflammatory infiltrate and absence of perifascicular atrophy (Figure 2). Diagnosis of polymyositis was made and pulse intravenous methyl prednisolone 30 mg/kg/dose was given for 5 days. Child did not show any improvement. Injection methotrexate was started and Rituximab was given 2 weekly for two doses. Muscle weakness, however, deteriorated. It was decided to give cyclophosphamide which was given as intravenous pulses at 500mg/m^2 every 2 weeks for 6 doses followed by every 4 weeks for 3 additional doses.

Results: Child showed a gradual recovery and 14 months later had power of 4/5 in proximal muscle groups, was going to school and had normal muscle enzymes (Figure 3).

Conclusion: Management of juvenile dermatomyositis is better defined than that of polymyositis in children. It may take a long time for children to recover.

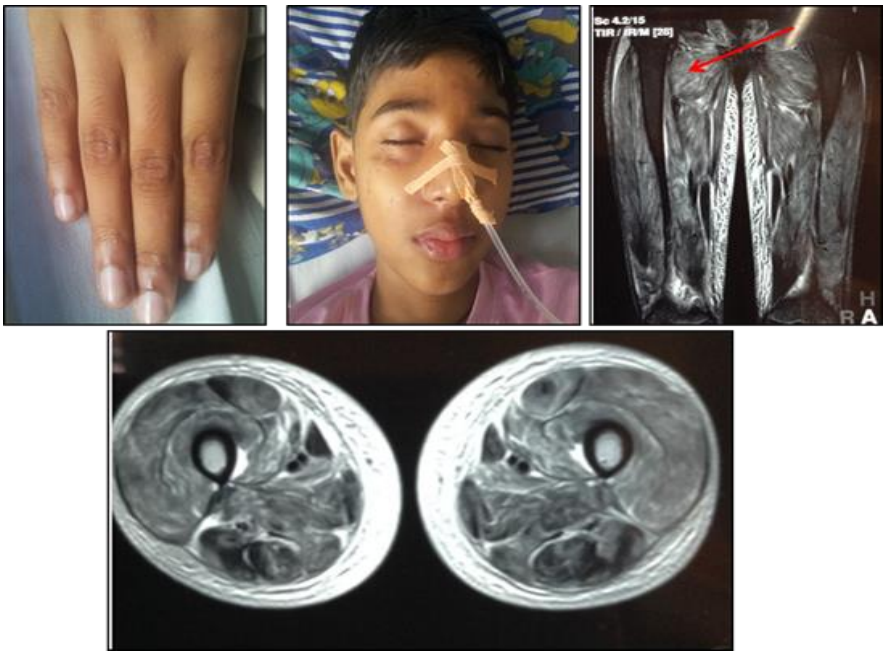

Figure 1: Picture showing no rash, nasogastric tube in situ and MRI changes in inflammatory myopathy.

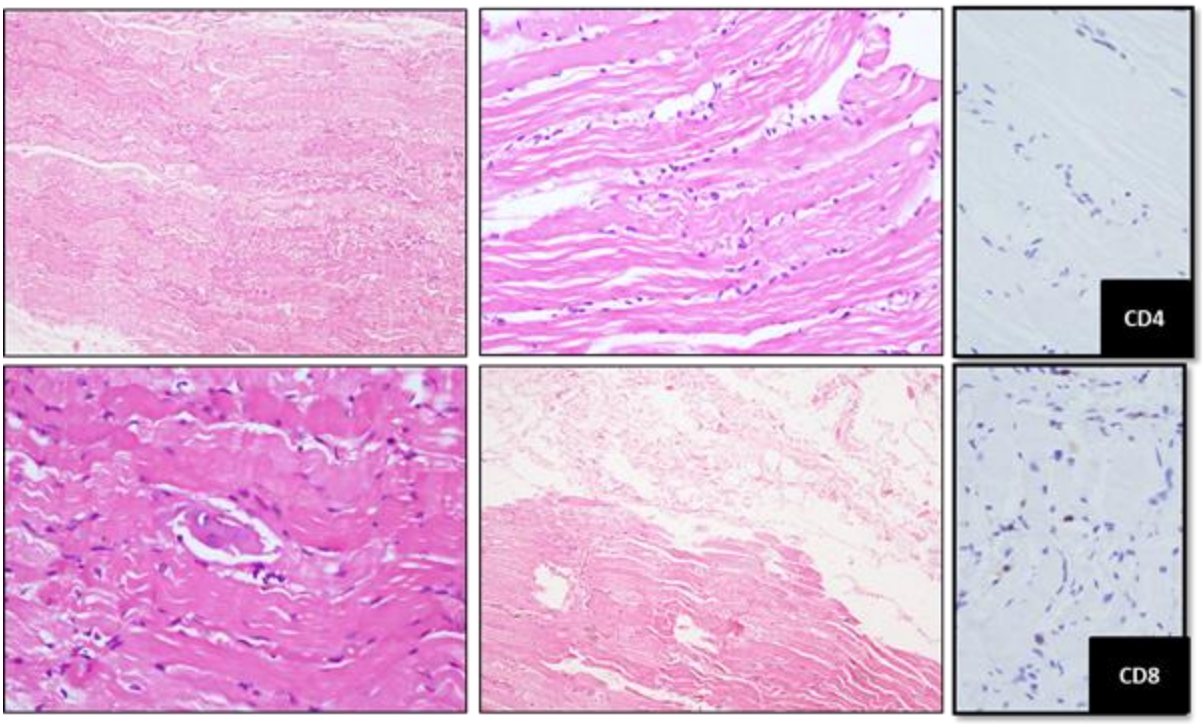

Figure 2: Muscle biopsy showing rarefied muscle fibers, myocyte necrosis, absence of perifascicular atrophy and CD8+ T-cell inflammatory infiltrate.

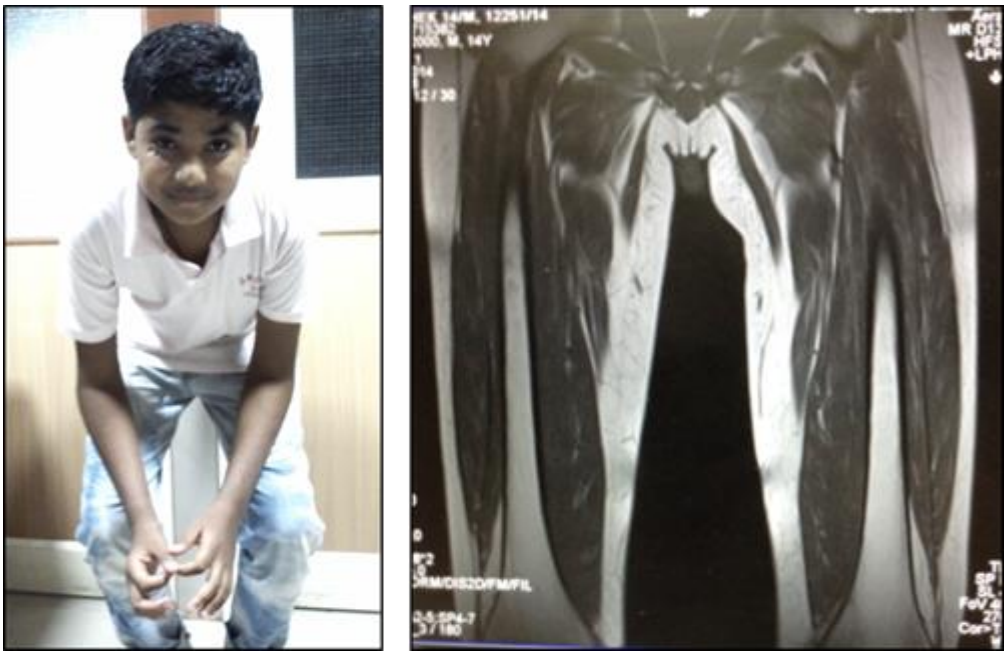

Figure 3: Picture showing normal muscle power and a normal MRI on follow-up.

322 - Myositis Autoantibodies Outperform Clinical Subgroup Classification in Predicting Weakness Levels in Myositis Patients

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Background: Myositis patients may be classified as belonging to one of four clinical groups: dermatomyositis (DM), polymyositis (PM), clinically amyopathic dermatomyositis (CADM) or necrotizing myositis (NM). Alternatively, myositis patients may be classified according to myositis autoantibody status. The aim of this study was to determine whether clinical groups or myositis autoantibodies provide better prognostic categories with regard to muscle involvement in these patients.

Methods: All Johns Hopkins Myositis Center patients with a myositis specific autoantibody collected from 2002 to 2015 were included. Autoantibody groups accounting for less than 2% of the final sample size were excluded. Strength (analyzed as the average of deltoid and hip flexor strength using Kendall's scale) and log transformed CK levels were compared between the different autoantibody groups using multilevel regression models adjusted for age, time from disease onset, sex, race and treatments. Models with different combinations of key variables were compared using the likelihood ratio test to ascertain if autoantibody groups and clinical subgroups provided the same amount of information regarding muscle weakness and CK levels over time.

Results: 483 patients with 4181 visits were included and 9 different autoantibody groups were identified (Table 1). Muscle weakness and CK levels followed a gradient among both antibody and clinical groups. Anti-SRP patients had the greatest weakness, followed by anti-HMGCR, anti-Mi2 and anti-NXP2, and then anti-Jo1. CK levels were highest in anti-HMGCR patients, followed by anti-SRP, anti-PL7, anti-Jo1 and anti-Mi2 (Table 2). Interestingly, strength and CK levels were dissociated in two groups: anti-NXP2 patients had significant weakness with low CK levels and anti-PL7 patients were relatively strong despite high CK levels. Multilevel regression models showed autoantibody groups explained the strength and the CK variability better than the clinical groups (AIC difference>20). Indeed, adding clinical groups to a model using only autoantibodies did not improve the model's ability to predict strength ($p=0.2$) and only mildly improved its ability to predict CK ($p=0.01$). In comparison, adding the autoantibodies to a model using the clinical groups resulted in a marked improvement in predicting both CK and strength (both $p<0.001$) (Table 2).

Conclusion: In patients with myositis, autoantibody status predicts strength and CK levels better than clinical grouping.

Table 1. Percentage of patients by antibody and clinical group

	% (n)
Antibody groups	
Anti-Jo1	23% (111)
Anti-HMGCR	22% (108)
Anti-TIF1g	13% (61)
Anti-NXP2	10% (50)
Anti-Mi2	8% (41)
Anti-Pm/Scl	8% (38)
Anti-SRP	6% (28)
Anti-MDA5	5% (23)
Anti-PL12	3% (12)
Anti-PL7	3% (11)
Clinical groups	
DM	52% (253)
NM	25% (119)
PM	15% (72)
CADM	4% (19)
None	4% (20)
Total	483

Table 2. Ranking of weakness and CK levels according to autoantibody levels and clinical subgroups.

Strength (0-10 scale)		CK levels (log scale)	
	Difference with reference		Difference with reference
Antibody group		**Antibody group**	
Anti-SRP	-	**Anti-HMGCR**	-
Anti-HMGCR	0.7*	**Anti-SRP**	-0.2*
Anti-Mi2	0.9	**Anti-PL7**	-0.6*
Anti-NXP2	1.1	**Anti-Jo1**	-0.7
Anti-Jo1	1.7*	**Anti-Mi2**	-0.7
Anti-PL12	2	**Anti-Pm/Scl**	-1**
Anti-TIF1g	2	**Anti-PL12**	-1.1
Anti-Pm/Scl	2	**Anti-TIF1g**	-1.1
Anti-PL7	2.2	**Anti-NXP2**	-1.1
Anti-MDA5	2.5	**Anti-MDA5**	-1.4*
Clinical group		**Clinical group**	
NM	-	**NM**	-
PM	0.6*	**PM**	-0.4***
DM	1*	**DM**	-0.7***
CADM	1.9	**CADM**	-1.1**

** <0.05; ** <0.01; *** <0.001*

p-values are referred to the previous autoantibody or clinical group.

323 - Clinical Profiles and Prognosis of Patients with Distinct Antisynthetase Autoantibodies

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Background: Antisynthetase syndrome (ASS) is characterized by the presence of anti-amino acyl-RNA synthetase antibodies(ASAs). We conducted this study to investigate the differences between the clinical manifestations and the long-term outcomes of Chinese patients with distinct ASAs.

Methods: One hundred and twenty-five consecutive patients with antisynthetase syndrome (ASS) were investigated retrospectively. Medical records, laboratory results and computed tomography images were obtained.

Results: The ASAs we investigated were anti-Jo1 (n=62), anti-PL7 (n=31), anti-PL12 (n=12), anti-EJ (n=19) and anti-OJ (n=1). ILD is the most common manifestation of ASS, and the overall prevalence of ILD reached 94.4% among study patients. Twelve patients (9.6%) developed rapidly progressive interstitial lung disease (RP-ILD). Eight patients (6.4%) experienced malignancy. Patients with anti-PL7 had a higher frequency of heliotrope rash than those with anti-Jo1 and anti-EJ ($p<0.001$ and $p=0.02$, respectively). Arthritis was more frequently observed in patients with anti-Jo1 than those with anti-PL7 and anti-EJ ($p=0.007$ and $p=0.001$, respectively). RP-ILD was statistically more prevalent in ASS patients with anti-PL7 than those with non-anti-PL7 ($p=0.028$). ASS patients with anti-Ro52 positive experienced higher frequency of RP-ILD than those without anti-Ro52 ($p=0.001$). Furthermore, anti-PL7 positive patients coexisted with anti-Ro52 exhibited more RP-ILD than those without anti-Ro52 ($p=0.001$). ASS patients with RP-ILD had a higher proportion of neutrophils in bronchoalveolar lavage fluid and serum ferritin than those without RP-ILD ($p=0.006$ and $p=0.013$, respectively). Although no differences were observed between the Kaplan-Meier curves of the four ASAs subgroups ($P=0.349$), the survival rate of patients with anti-PL7 decreased more rapidly in the early long-term follow-up compared with those with other ASAs. Finally, RP-ILD, malignancy and elevated serum ferritin were identified to be associated with poor prognosis in ASS patients.

Conclusion: Our study investigates the clinical phenotypes and outcomes of ASS patients with distinct ASAs and highlights the link between the anti-PL7 antibody and RP-ILD.

324 - A Longitudinal Study of Cutaneous Dermatomyositis

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Background: Previous studies have described the course of dermatomyositis (DM) using muscle weakness and enzymes as their primary endpoints. Limited studies have described the course of cutaneous disease in DM.

Methods: A retrospective cohort study included patients 18 years or older with clinical or histologic evidence of DM who had the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity subscores recorded for at least 2 years from baseline. Statistical methods were used to determine average disease activity, overall disease progression, disease course, and variability. Disease progression was classified into improved, worsened, or stable based on criteria combining the net area under the curve per unit time relative to baseline CDASI score and a fitted linear slope. Disease course was classified into monophasic (significant skin improvement without a flare), polyphasic (significant skin improvement with at least one flare), or chronic (significant skin worsening without a significant improvement) based on the literature. Subjects were divided into mild and moderate-severe disease severity at baseline. Outcome measures were compared between groups.

Results: Our final cohort consisted of 40 DM patients, the majority of whom were female (90%) and Caucasian (95%), with a mean age of 52.9 years at baseline. Disease subtype was classified as classic (52.5%) and skin predominant (47.5%). Mean follow-up time was 3.50 years. More patients had moderate-severe disease activity at baseline (N=24, 60%) compared to mild disease activity at baseline (N=16, 40%). Average disease activity over time was significantly different between the mild and moderate-severe groups (9.10 vs. 14.96; P = 0.004). The majority of DM patients experienced an improvement in disease activity (N=23, 57.5%) compared to a worsening (N=8, 20%) and stable (N=9, 22.5%) progression. Within the mild subgroup, a majority of the patients' disease activity remained stable (N=8, 50%) while in the moderate-severe group a majority showed improvement in disease activity (N=20, 83%). The majority of DM patients had a polyphasic disease course (N=33, 82.5%) compared to monophasic (N=5, 12.5%) and chronic (N=2, 5%) courses. Variability in disease activity over time, evaluated by calculating the average flares/yr, was independent of baseline disease activity.

Conclusion: The majority of our patients had moderate-severe disease activity at baseline that tended to improve with a polyphasic course while those with mild baseline activity scores tended to remain stable with a polyphasic course. Baseline CDASI activity score is associated with particular patterns of disease progression and disease course in patients with cutaneous DM.

325 - Evaluation of Bone Fracture Risk in Patients with Idiopathic Inflammatory Myopathies

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Background: Idiopathic inflammatory myopathies are chronic, heterogeneous systemic autoimmune diseases with symmetrical proximal muscle weakness. With the progress of the disease, osteoporosis and bone fractures are more common compared to the healthy population, which can be explained by the chronic inflammation, immobilization, spontaneous falls and steroid treatment, and affect crucially the patients' quality of life. Recently, a WHO fracture risk calculation tool, FRAX score is available, to measure the 10-year probability of osteoporotic fractures. It takes into account relevant clinical risk factors, such as rheumatoid arthritis, however myositis does not exist among the risk factors.

Methods: FRAX score was determined in 71 patients with idiopathic inflammatory myopathies and results were compared with the data from 50 age, sex and BMI matched patients with rheumatoid arthritis. Moreover, osteoporosis related biomarkers, disease related fractures and bone mineral densities were determined using DXA examinations. Statistical analysis was performed with IBM SPSS 20.0 software.

Results: There were no significant differences between the demographical data, biomarkers (Ca, Vitamin D, parathormone level) of the two groups. Disease duration and cumulative steroid dose were higher in the myositis group. Results of the FRAX score without BMD were significantly lower in the patients with myositis, in both fracture risk: major osteoporotic (8.61±6.36% vs. 15.59±12.66%; p=0.002) and femur neck (2.66±3.24% vs. 6.34±9,018; p=0.003). T score results of the DXA examination were not significantly different between the two populations (Lumbar1-4 = -0.9±1.43 vs.-0.829±1.38; p=0.829; Femoral neck: -1.4±1.08 vs. -1.02±1.08; p=0.93), but the presence of osteopenia (60% vs. 39.5%) and osteoporosis (13.5% vs. 7%) were more frequent in the myositis group (p=0.045). Disease-related fracture was associated with disease duration in the myositis group and with antibody (RF, ACPA) presence in the RA group. FRAX score with BMD results showed no significant differences between the two populations (Major osteoporotic: 9.44±6.72 vs. 13.25±9.43; p=0.053; Hip: 2.77±3.01 vs. 3.57±5.08; p=0.811).

Conclusion: As far as we know, this is the first study, which examine the fracture risk using FRAX score in patients with idiopathic inflammatory myopathies. According to our data, we can conclude that existence of myositis might indicate similar, independent risk factor in fracture probability, like rheumatoid arthritis. Evaluation of fracture risk should be done with DXA result in patients with IIM, otherwise risk could be underestimated. The exact value of the "myositis related risk" could be determined by a 10-year prospective study.

326 - A Prospective, Natural History Study of Sporadic Inclusion Body Myositis: 1-Year Results

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Background: Sporadic inclusion body myositis (sIBM) is a rare and debilitating muscle wasting disease characterized by the slow, progressive asymmetric atrophy and weakness of muscles, typically affecting people aged >50 years. Limited data are available on the longitudinal characterization of functional impairment, patient burden, and economic impact of sIBM across multiple countries. This study will characterize the natural clinical progression and functional impact of sIBM in patients over time.

Methods: This is the largest, longitudinal, multicenter, prospective study, in which 184 patients were recruited; of these, 11 patients were non-ambulatory. Demographics, medical history, and functional assessments were recorded at baseline and 1-year after study initiation. Patient-reported outcomes were collected using a brief patient assessment each month and in more detail every 6 months. sIBM physical functioning assessment (sIFA) for patient-reported functional impact was the primary outcome. Other functional performance measures were 6-min walk distance (6MWD) and quantitative muscle testing (QMT). The detailed characterization of muscle structure and composition was assessed in a subset of patients using magnetic resonance imaging (MRI).

Results: At baseline (data cutoff date: July 31, 2015; n=137), significant correlations between the sIFA total score and 6MWD (R=-0.79) were observed. Correlations were also observed between the sIFA total score and the level of muscle atrophy (R=-0.63), and the sIFA total score and fat infiltration (R=0.35) in the thigh, as assessed by MRI. The most recent results from the 1-year longitudinal data analysis will be presented at the congress.

Conclusion: Findings from this study will help provide data on the clinical progression, functional impact, and economic and humanistic burden of sIBM over time.

327 - Development and Validation of a Composite Disease Activity Score for Juvenile Dermatomyositis

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Background: JDM is a multisystem vasculopathic disease that primarily affects skin and muscles. Most tools for assessment of disease activity in JDM are lenghty, complex, and centered on physician's evaluation. We aim to develop a composite disease activity score for JDM and provide preliminary evidence of its validity.

Methods: A panel of experts devised the new score, named Juvenile DermatoMyositis Activity Index (JDMAI), based on their clinical experience and a literature review. The JDMAI is composed of 4 clinical domains: 1) physician's global assessment of overall disease activity on a 0-10 visual analog scale (VAS); 2) parent's/child's global assessment of child's wellbeing on a 0-10 VAS; 3) muscle strength/endurance; 4) skin disease activity. Six versions of the JDMAI were tested, which differed in the tools used to assess items 3 and 4. For item 3, two versions included the hybrid MMT/CMAS (hMC) with score in deciles (0-10), two the MMT-8 with score in deciles (0-10), and two the CMAS with score in deciles (0-10). For item 4, three versions included physician's global rating of skin disease activity on a 0-10 VAS and three included the cutaneous domain of the Disease Activity Score (DAS) (0-9). Validation was conducted on 294 patients included in a multinational dataset, evaluated at baseline and at 6, 12, and 24 months. *Construct validity* was assessed by calculating *between-subject* and *within-subject correlations* with JDM outcome measures not included in the JDMAI; *internal consistency* was assessed with Cronbach α and *responsiveness to change* with standardized response mean (SRM). *Discriminant ability* was determined in a different multinational dataset of 142 patients, by assessing the JDMAI score in patients rated in remission, low, moderate, or high disease activity by the attending physician, and in remission, continued activity or flare by the parent.

Results: In *between-subject* exercise, all JDMAI versions showed strong (r>0.7) correlations with CHAQ (0.77-0.78), muscle VAS (0.84-0.87), muscle DAS (0.81-0.83) and total DAS (0.83-0.90), and moderate correlations (r=0.4-0.7) with pain VAS (0.56-0.57) and Myositis Damage Index (MDI) (0.58-0.60). Owing to the interrelatedness of longitudinal data from an individual patient, *within-subject correlations* were higher and were all strong (r=0.81-0.97). SRM was good (1.56-1.67) for all JDMAI versions. Cronbach's α was fair to moderate (0.68-0.72) for the 6 different versions. All JDMAI versions discriminated strongly between patients in different disease activity states (Kruskal-Wallis test, $p < 0.001$).

Conclusion: The JDMAI is the first composite disease activity score for JDM. JDMAI calculation is simple and quick. All 6 JDMAI versions revealed similar measurement properties in validation analyses. The final version of the new outcome measure will be selected thanks to its future prospective validation.

JDMAI 1	JDMAI 2	JDMAI 3	JDMAI 4	JDMAI 5	JDMAI 6
Phy's VAS	Phy's VAS	Phy's VAS	Phy's VAS	Phy's VAS	Phy's VAS
Par's VAS	Par's VAS	Par's VAS	Par's VAS	Par's VAS	Par's VAS
hMC in deciles	hMC in deciles	MMT-8 in deciles	MMT-8 in deciles	CMAS in deciles	CMAS in deciles
Skin VAS	Skin DAS	Skin VAS	Skin DAS	Skin VAS	Skin DAS
0-40	0-39	0-40	0-39	0-40	0-39

328 - Daily Physical Activity Monitoring as a Promising Outcome Measure in Patients with Idiopathic Inflammatory Myopathies

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Background: Outcome measures for idiopathic inflammatory myopathies (IIM) are crucial. The current consensus for the assessment of IIM severity and treatment efficacy relies on a core set of outcome measures combining manual muscle testing (MMT8), creatine kinase (CK) level, physician's and patient's reported disease activity, and patient-reported quality of life questionnaires. CK level is a sensitive measure for assessing disease activity but it does not correlate with symptom severity in every subtype of myositis. MMT8 is operator-dependent and semi-quantitative resulting in poor inter-reliability and poor sensitivity to changes. Disease burden may be overlooked when using self-reported questionnaires. Floor and ceiling effects associated with these metrics are major concerns.

Wrist-worn accelerometers are used for the objective assessment of physical activity energy expenditure in daily life.

We aimed at testing accelerometer measurements to assess the changes in global physical activity of IIM patients after treatment initiation.

Methods: Five newly diagnosed IIM patients were enrolled. Patients wore a device (GENEActiv®) for fourteen consecutive days, every month during six months after treatment initiation. The Euclidean norm of the three raw acceleration signals minus 1, referred to as ENMO, was used to estimate daily physical activity energy. Results were to MMT8 score (max 150), CK level, physician and patient global activity scores (visual analogue scale; max 10) and Health Assessment Questionnaire (HAQ).

Results: Median age of the patients was 51 years (Dermatomyositis=1; Necrotizing myopathy=3; Anti-synthetase syndrome n=1). At M0, all patients received corticosteroids 1 mg/Kg/d associated with an immunosuppressant and IVIg. At M0, the median MMT8 score was 126 [104-135] and the median CK level was 3225 [1375-6366] UI/L. The median ENMO was 15.6 [14.3-22.5] m*g*.day^{-1}. Median physician and patient global disease activity scores were 7 [4-8] and 6 [4-10], respectively. The median HAQ score was 2 [2.65-0.375].

At M3 CK levels was dramatically decreased, 3 patients at normal value and two patients had doubled normal values. At M6, all patients had increased in MMT8 score with a median percentage of improvement of 19 [11-40] %. Along that line, the median percentage of improvement in ENMO was 75 [15-188] %. Interestingly, two patients displayed increase in ENMO after plateauing of MMT8. At M6 physician and patient global disease activity scores as well as HAQ scores attested that patients were in remission. The median dose of corticosteroids was 12.5 mg/d [8-15] at M6.

Conclusion: These data clearly emphasize the high potential of objective physical activity energy expenditure estimates from wrist-worn accelerometers raw signal analysis for evaluating disease burden and treatment-induced changes in physical activity behaviour in IIM. A common effort must be carried out to implement this low-cost approach in large-scaled studies to improve the evaluation of treatment efficacy toward enhanced clinical decision-making.

329 - Characterizing Muscle Performance in Subjects with Juvenile Idiopathic Inflammatory Myopathies: What is the Utility of Isokinetic Testing?

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Background: Children with juvenile idiopathic inflammatory myopathy (JIIM) have muscle weakness and difficulty with functional activities. The objective of this work is to determine which impairment and functional performance measures can discriminate between individuals with JIIM and healthy controls, and to identify if isokinetic or isometric testing has a stronger association with functional performance tasks.

Methods: As part of a NIH intramural NIEHS natural history study, 44 subjects participated in the study (21 patients with JDM, 1 patient with JPM and 22 healthy gender- and age-matched control subjects; age range: 7-32 years). Standardized impairment and functional testing were performed over a 3-day period. Isokinetic and isometric tests for the dominant lower extremity (LE) were performed 24-48 hours apart. Impairment measurements included isokinetic peak torque and power, and maximum voluntary isometric contractions assessed by Quantitative Muscle Assessment (QMA). Functional measurements included the Childhood Myositis Assessment Scale (CMAS; total and lower extremity, LE score), six-minute walk test (6MWT), repeated stair step-up and repeated chair squats. Group differences in physical performance were examined with independent t-tests or Mann-Whitney U tests. Spearman correlations were used to examine relationships between impairment and functional measures for subjects with and without JIIM.

Results: All impairment measures of muscle performance significantly discriminated between the JIIM and control group (p = 0.001-0.012). While the CMAS, full squat, and chair squat tests significantly discriminated between the JIIM and control group (p = 0.001-0.004), stair power and 6MWT performance did not differ between the groups (p> 0.05). The relationship between weight-adjusted muscle performance and functional performance varied across groups, but the strongest associations were observed with the full squat and chair squat tests (Table 1).

All strength values demonstrated a robust ability to identify differences between JIIM and control subjects. Only functional measures associated with endurance, the 6MWT and stair power, failed to discriminate between children with and without JIIM. Isokinetic and QMA values differed in their significant associations with functional measures.

Conclusion: Isokinetic testing is a viable option to quantify impaired knee extension strength in patients with JIIM, but QMA testing for multiple muscle groups has utility across a range of functional tasks. Additional muscle groups will need to be tested to fully evaluate the value of isokinetic testing in patients with JIIM.

Patient	CMAS	CMAS LE	6MWT	Stair Power	Chair Squat	Full Squat
PT 180°	0.16	0.43	-0.02	-0.08	0.29	0.56†
PT 60°	0.24	0.37	-0.07	-0.16	0.39	0.81‡
Power 180°	0.35	0.42	0.20	-0.03	0.13	0.60†
QMA Knee	0.18	0.43	-0.22	0.05	0.59‡	0.38
QMA LE	0.44†	0.48†	0.00	-0.01	0.75‡	0.46
Control						
PT 180°	0.32	0.20	0.43	0.00	0.28	0.63‡
PT 60°	0.34	0.15	0.32	0.06	0.22	0.65‡
Power 180°	0.39	0.13	0.37	0.05	0.25	0.62‡
QMA Knee	0.16	-0.13	0.45†	0.03	0.28	0.72‡
QMA LE	0.05	-0.18	0.45†	-0.06	0.28	0.51†

CMAS = Childhood Myositis Assessment Scale; LE = Lower Extremity, 6MWT = Six minute walk test ; PT = Peak torque; QMA = Quantitative Muscle Assessment
Spearman Correlations, Significance Level: † $p \leq .05$, ‡ $p \leq .01$

330 - Quantitative Fixed Frame Maximum Voluntary Isometric Contraction Testing is Reliable in Patients with Idiopathic Inflammatory Myopathies

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Background: There is a need for valid and reliable outcome measures to assess muscle strength in patients with idiopathic inflammatory myopathies (IIM). Manual muscle testing (MMT) has been established as a myositis disease activity core set measure and maximum voluntary isometric contraction testing (MVICT) as an extended set measure by the International Myositis Assessment and Clinical Studies Group (IMACS). Fixed frame MVICT (FFMVICT) techniques have been shown to be highly reliable for persons with ALS, FSH and Duchenne dystrophies, LMN syndrome, and multiple sclerosis. We found only 3 papers that evaluate MVICT reliability in IIM, but interpretation of their data is limited due to differences in technique and testing of only half of the suggested MMT-8 core set muscles. The objectives of this study are to examine FFMVICT inter-rater reliability in persons with IIM for the 8 muscle groups listed by IMACS as a core set MMT-8 measure, examine inter-rater and intra-rater reliability for a more comprehensive set of 16 muscles in 10 healthy individuals, and explore relationships between MMT-8 and FFMVICT-8 measurements.

Methods: As part of a NIH intramural NIEHS natural history study, study participants included 10 healthy males and 15 IIM patients (3 males; 8 with polymyositis, 3 with dermatomyositis, and 4 with juvenile dermatomyositis). The design of the study is a repeated measures design, with inter-rater and intra-rater reliability assessment. Testing procedures included 2 MVIC trials (5s) with 30s rest periods for each muscle tested on consecutive days by Rater 1 and 2, and 1 week later by Rater 1, for healthy subjects. FFMVICT-8 unilateral muscle groups were tested on all participants and 8 additional unilateral muscle groups tested on healthy participants. In addition, Kendall 10-point MMT-8 was completed on IIM patients. MVIC reliability was assessed by intraclass correlation coefficient (ICC) and standard error of the measurement (SEM) for max of 2 and average of 2 trials.

Results: Inter-rater FFMVICT measurements are highly reliable for the total composite-8 muscles in IIM and for inter-rater and intra-rater measurements for total composite-8 and total composite-16 muscles in healthy subjects. The individual muscle group ICCs demonstrate high to very high reliability in IIM (0.83-0.97), and in healthy participants (0.76-0.99). Averaging FFMVICT measurements improves reliability compared to using a maximum value. FFMVICT composite-8 identifies strength deficits that are 32% greater compared to MMT-8 in subjects with IIM with knee extension and elbow flexion having the greatest disparity. The pattern of weakness seen in our IIM patients is consistent with other reports.

Conclusion: FFMVICT is a very reliable method of assessing strength in IIM patients, and appears to be more sensitive in detecting weakness than MMT. We suggest future studies correlate this data with functional performance testing in patients with IIM.

331 - The Myositis Activity Profile – Reliability and Validity of the German Version

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Background: The Myositis Activity Profile (MAP) is the only disease specific questionnaire to assess limitations of activities of daily life in patients with inflammatory myopathy (IM). To the best of our knowledge, there is no validated version available for German speaking patients. Thus, the aim of this study was to translate and cross-culturally adapt the MAP into German and to determine reliability and validity.

Methods: A cross-cultural adaptation of the English version of the MAP into German was performed following international guidelines. To assess reliability, participants filled out the MAP twice within one to two weeks and linear Kappa was evaluated. For construct validity, the correlation between the MAP and the Stanford Health Assessment Questionnaire Disability Index (HAQ), the SF36, the Manual Muscle Test (MMT8), the Hand Held Dynamometry (HHD) and the Functional Index in Myositis (FI-2) were analyzed with the Spearman correlation coefficient. Additionally, for discriminative validity differences between patients and age- and gender-matched healthy controls were analyzed using the Mann-Whitney- U Test.

Results: Forty-eight German-speaking patients with a diagnosis of acute (18%), subacute (18%) or chronic (64%) myositis were included. Participants were 57 ±14 years old and 76% of them were female. Reliability was substantial for the MAP subscales (linear Kappa between 0.65 and 0.71) and moderate to substantial for the single items (linear Kappa between 0.57 and 0.77). The total score of the German MAP correlated good with the HAQ (0.81), the physical component score of the SF36 (0.77), the FI-2 shoulder flexion (0.84); moderate with the FI-2 hip flexion (0.54), the FI-2 total score (0.69), the QMT total score (0.61) and the MMT8 (0.63); and poor with the mental component score of the SF36 and with pain. The healthy control group had significant lower scores (single items, subscales and total score) than IM-patients ($p \leq 0.05$).

Conclusion: The German version of the MAP seems to be a reliable and valid tool to assess limitations of activities of daily life in IM patients. However, further research is required to confirm this results and to evaluate responsiveness.

332 - Comparison of Motor Performance Measures in Individuals with Myositis

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Background: Individuals with idiopathic inflammatory myopathies (IIM) present with muscle weakness, resulting in difficulties with motor performance and endurance-based skills. The 213th European Neuromuscular Conference on outcome measures for myositis trial readiness proposed a number of performance-based assessments of muscle function, such as the Childhood Myositis Assessment Scale (CMAS) and the Motor Function Measure (MFM), be examined for use in therapeutic trials. The CMAS, a 14-item instrument assessing motor performance with three endurance tasks, has been validated in children with IIM, with high inter and intra-rater reliability, but has not yet been validated for adults with IIM. The MFM, a 32-item standardized assessment developed to measure motor performance in neuromuscular diseases, has been validated in children and adults (6-60 years old), but has not yet been examined in IIM. The MFM assesses skills in supine, sitting and standing, within three domains including D1(Standing and transfers), D2 (axial and proximal function) and D3 (distal motor function). The objective of this study is to compare the CMAS and MFM to determine their utility and effectiveness in children and adults with IIM.

Methods: Our cohort included 23 individuals diagnosed with IIM, including dermatomyositis (17), polymyositis (5) and inclusion body myositis (1) as part of a NIH intramural NIEHS natural history study, including 8 males and 15 females ranging from 6 to 72 years, with the mean age of 21.7 years. We administered the CMAS, MFM, and manual muscle test (MMT) within a 2-day period to each patient. All assessment scores were converted into percentages of the total potential score. The three CMAS endurance tasks and eleven functional tasks as well as the 3 domains of the MFM were examined separately and in total. Wilcoxon signed rank tests were used to compare median scores and spearman rank was used to examine correlations among CMAS (total, endurance and functional skills), MFM (total, D1, D2 and D3 domains), and MMT scores.

Results: Descriptive statistics are presented in Table 1. CMAS total and subscores were lower than MFM and its domain scores, and also lower than MMT scores. Spearman correlations between the CMAS and MFM, MMT28 and MMT8 scores ranged from 0.66 to 0.90, $p<0.01$, but were lower for subdomains D2 and D3 of the MFM

Conclusion: In this highly functional cohort of individuals with IIM, the CMAS more effectively identified functional impairments. These data also show the subjects had more difficulty with the three CMAS endurance tasks. We plan to further examine the CMAS and MFM, especially the D1 domain, in IIM cohorts with a wider range of functional abilities. The examination of additional performance-based measures that include sustained or repeated tasks, i.e. Functional Index 2, Adult Myopathy Assessment tool, Extended CMAS, may be useful for patients with IIM.

Table 1 Descriptive statistics of muscle function and strength outcome measures in 23 IIM patients.

	Minimum	Median	25th percentile	75th percentile	Maximum	Correlation with CMAS
CMAS	33	90	69	94	100	
CMAS.endurance tasks	29	71	57	79	100	0.77**
CMAS.functional tasks	16	97	71	100	100	0.90**
MFM	81	99	92	100	100	0.66**
MFM - D1	62	100	87	100	100	0.77**
MFM - D2	72	100	100	100	100	0.28
MFM -D3	86	100	95	100	100	0.02
MMT28	75	92	9.5	75	100	0.80**
MMT-8	66	90	12	66	100	0.83**

Values are presented as percentages of potential total scores
**Spearman correlations significant at the 0.01 level

333 - Qualitative Study by Individual Interviews of the Consequences of Myopathies on the Quality of Life

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Background: Idiopathic inflammatory myopathies (IIM) significantly impairs patients' quality of life and can be life threatening. Social and psychological consequences of muscular involvement are indeed important and widely underestimated. Generic Patient Reported Outcomes (PRO) may not be sufficient to exhaustively represent the burden of the disease on patients' daily living. This study aimed to describe the experiences and perspectives of adults living with IIM, as well as to highlight patients' preoccupations not covered by existing PRO or ignored by caregivers.

Methods: In 2015, consecutive patients were included in 2 tertiary centers. IIM was defined according to Trojanov and Hoogendjik criteria. A semi-structured interview with a sociologist was conducted, with a free duration (median: 60 min, range: 32-80). Each interview was recorded, adapted and analyzed by a single interviewer. Interview transcripts were coded and analyzed using Modalisa Software to facilitate the reporting of recurrent themes and supporting quotations. New codes were added when necessary, until theoretical saturation was achieved (25 interviews were necessary).

Results: We included 26 patients (9 men, 17 women, median age 58, 24-85): 9 dermatomyositis (35%), 7 overlap myositis (27%), 7 immune-mediated-necrotizing myopathies (27%) and 3 inclusion body myositis (12%). Median disease duration was 30 months (0-228). IIM was active in 14 (54%) or inactive in 12 (46%) patients. An actual muscular weakness was recorded in 13 (50%) and a pulmonary involvement in 11 (42%) patients.

Themes revealed by analysis included a body image alteration (weakness, fatigue, rash, weight variation) inducing a loss of self-confidence sometimes affecting family or couple life. IIM had important consequences on social relationships (being afraid to go out, being afraid of revealing disabilities to relatives). Difficulties due to the unpredictiveness of the disease were frequently expressed by the patients, limiting the ability to plan for the future or simply to organize leisure activities such as travelling. Professional activities are frequently impacted, resulting in absenteeism. Patients frequently reported difficulties due to the incomprehension of colleagues or supervisors. Patient also have to face with financial difficulties due to the professional consequences of the disease. The psychological impact of the disease and the lack of social support often result in anxiety and rarely in a solitude feeling or depression.

Importantly, difficulties in patient-physician relationship are reported in all steps of the care pathway, noticeably incomprehension of caregivers before the diagnosis, psychological trauma due to diagnosis. Moreover, the multiplicity of actors and the lack of communication between GP and specialists is a frequent complaint of patients.

Conclusion: IIM may impact all aspects of the patient's life, noticeably social relationships and professional activities. Some specific problems of the patients are not explored by existing generic PRO. The results of this qualitative study may be useful for the development of disease-specific PRO in IIM.

334 - Reduced Hand Function Affects Activity Performance and Quality of Life in Persons with sIBM.

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Background: Reduced hand function is one characteristic features of sporadic inclusion body myositis (sIBM). There is limited information regarding how hand function deficits affect activities of daily living and quality of life (QoL). The aims of this study were to investigate different aspects of hand function, QoL and activity limitation in persons with sIBM and to compare these variables to reference values.

Methods: A total of 36 persons (women n=14, men n=22) with sIBM participated in this cross-sectional study. Jamar dynamometer was used to measure grip strength, Purdue Pegboard to measure dexterity, the SF-36 to measure QoL and activity limitation was measured by the Disability of the Arm, Shoulder and Hand (DASH) and the disease specific questionnaire Myositis Activity Profile (MAP). Reference values from the literature were available for grip strength, dexterity, QoL and activity limitation. Nonparametric tests have been used in the statistical analysis.

Results: Grip strength was reduced in right and left hand in both women ($p < 0.001$) and men ($p<0.0001$) when compared to gender and aged matched population based reference values. The dexterity was likewise reduced in both right and left hand ($p<0.001$) when compared to reference values based on a convenience sample. Persons with sIBM had significantly more activity limitation when compared to population based reference values ($p<0.001$). Activities of moving around (very difficult) followed by movement, recreation and household activities (somewhat difficult) were most limited. The participants reported lower QoL dimensions Physical Function, Role Physical, General Health, Vitality and Social Functioning compared to reference values ($p<0.001$). The reduced grip strength correlated moderately to QoL dimensions Physical Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health ($Z \geq 4.5$; $p<0.001$). The reduced grip strength additionally correlated moderately to activity limitation measured by DASH ($Z=-0.45$; $p<0.006$) and all subgroups of the MAP ($Z \geq 4.2$; $p<0.001$).

Conclusion: Persons with sIBM have reduced hand function, lower self-reported QoL and more activity limitation compared to reference values. The activities that are affected include both physical aspects such as moving around but also recreation and household activities. The reduced hand function affects most activities of daily living and QoL. This indicates the importance of developing interventions to improve hand function and grip ability to enable daily activities.

335 - Construct Validity of the Inclusion Body Myositis Functional Rating Scale

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Background: The Inclusion Body Myositis Functional Rating Scale (IBMFRS) is a 10-item disease specific survey that is designed to assesses the ability to perform selected activities of daily living in sIBM patients[1]. However, the construct validity of the IBMFRS has not yet been evaluated. Therefore, the purpose of this study was to evaluate the validity of selected constructs in the IBMFRS.

Methods: Twenty-two sIBM patients (69.0±5.6 years) filled in the IBMFRS and the SF-36 health survey and completed a series of functional capacity tests (2-min Walk test, Timed Up & Go test, 30-sec Chair stand test) and testing of maximal knee extensor muscle strength. Ten hypotheses were defined a priori (#1-10, Table 1), evaluating the relationship between the IBMFRS and the additionally collected outcomes. The hypotheses evaluate both convergent and discriminant validity. The Spearman rank order correlation was used for the analyses and cut points for strength of relationships were defined as: low ($r \leq 0.3$), moderate ($0.3 < r \leq 0.7$) and high ($r > 0.7$).

Results: As hypothesized the sum of items 5,6 & 8-10 was a stronger predictor (#3, r=0.72) of SF-36 *physical function (PF)* domain than the full composite IBMFRS score (#1, r=0.60). Also, the initial hypothesis that IBMFRS score would correlate weakly to SF-36 *mental health (MH)* was verified (#2, r=0.29). IBMFRS items 8 and 9 were not highly correlated (#4, r=0.66 & #5, r=0.62, respectively) to their respective functional test (2-min Walk test & 30-sec Chair stand test) as we had hypothesized. However, summed score of item 8 & 9 was only moderately towards weakly correlated (#6, r=-0.35) to the Timed Up & Go test. We hypothesized item 8 and item 10 to be strongly correlated to maximal knee extensor muscle strength, which was also the case for item 8 (#9, r=0.73) but not item 10 (#9, r=0.46).

Conclusion: The present data suggest that IBMFRS are moderately-to-strongly associated with general physical function (SF-36 *PF*) in sIBM patients. Notably, selected single IBMFRS item scores involving the lower extremities were stronger predictors of SF-36 *PF*, than the full IBMFRS score including the upper body tasks. The individual items of the survey were only moderately related to objectively measured physical function. One item (chair rise) correlated strongly to knee extensor muscle strength.

This small-sized study suggests that the IBMFRS can be used to assess everyday physical function in sIBM patients. However, we suggest that the construct validity of the IBMFRS should be investigated further in larger and more thorough studies involving more sIBM patients.

Reference

1. Jackson CE, Barohn RJ, Gronseth G, Pandya S, Herbelin L, Muscle Study G. Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve 2008;37(4):473-476.

Table 1: Construct validity of the IBMFRS - A priori defined hypotheses and regression analyses

Hypothesis Number	Hypothesis description	Regression result
#1	*Total IBMFRS score correlates moderately (0.30< r <0.70) to SF-36 PF score.*	R = 0.60. True
#2	*The total IBMFRS score correlates weakly (r<0.30) to SF-36 MH score.*	R = 0.29. True
#3	*Summed scores of item 5, 6, & 8-10 (lower extremity function) of the IBMFRS correlates better to SF-36 PF than Total IBMFRS score.*	R = 0.72. True
#4	*IBMFRS item 9 score (gait function) is highly correlated (r>0.7) to 2-min Walk test performance.*	R = 0.62. Not true
#5	*IBMFRS item 8 score (chair rise function) is highly correlated (r>0.7) to 30-sec Chair Stand performance.*	R = 0.66. Not true
#6	*IBMFRS item 8 & 9 score summed (chair rise + gait function) is highly correlated (r>0.7) to Timed up & Go performance.*	R = -0.35. Not true
#7	*IBMFRS item 1 score (dysphagia) is weakly correlated (r<0.3) to Timed Up & Go, 2 min Walk and 30-sec Chair stand performance.*	R = 0.02. 0.02 & 0.31 True (2 out of 3)
#8	*Summed score of item 2-4 score (upper extremity function) of the IBMFRS is moderately correlated (0.3< r <0.7) to Timed up & Go test, 2 min walk test and 30-sec chair stand performance.*	R = 0.06. 0.38 & 0.24 True (1 out of 3)
#9	*IBMFRS item 8 (chair rise function) & 10 (stair climb function) score is highly correlated (r>0.7) to Maximal knee extensor muscle strength.*	R = 0.73 & 0.46 True (1 out of 2)
#10	*IBMFRS item 7 score (turning in bed) is weakly correlated (r<0.3) to Maximal knee extensor muscle strength.*	R = 0.3 True

IBMFRS: Inclusion Body Myositis Functional Rating Scale: *SF-36:* Short form (36) health survey; *PF:* Physical function domain: *MH:* Mental health domain

336 - Muscle Fiber Dysfunction Contributes to Clinical Muscle Weakness in Inclusion Body Myositis

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Background: Inclusion body myositis (IBM) is the most common acquired muscle disorder in adults over 50 years old. It is characterized by progressive muscle weakness and marked muscle atrophy, most prominent in the finger flexors and quadriceps muscle. In addition to atrophy, fatty replacement of muscle tissue contributes to clinical muscle weakness and functional decline. This study aims to investigate the contractile performance of residual muscle tissue.

Methods: We included 8 participants with IBM and 12 healthy controls. We measured individual health-related quality of life, functional performance and muscle strength. In all participants, muscle contractile capacity was measured both in vivo, using quantitative muscle testing and MRI imaging, and ex vivo, using single fiber studies of the vastus lateralis as well as tibialis anterior muscle biopsies. Quadriceps specific force was calculated by correcting the voluntary maximum force (N) for the contractile cross-sectional area (CCSA). CCSA was calculated by multiplying the total cross-sectional area by the muscle fraction on MRI.

Results: Voluntary maximum force generation of the quadriceps muscle was significantly reduced in IBM participants (216.9 ± 57.6 N vs. 572.1 ± 53.1 N, $p < .001$). Quadriceps specific force was reduced in IBM participants. Muscle fiber specific force was also reduced in IBM patients compared to healthy controls (type 1 fibers: 158.3 ± 4.1 mN/mm² in IBM vs. 178.9 ± 3.4 in controls, type 2 fibers: 180.3 ± 7.2 mN/mm² in IBM vs. 213.7 ± 4.2 in controls, $p = .036$). Reduced muscle fiber specific force was present in vastus lateralis as well as tibialis anterior muscles ($p = .554$).

Conclusion: Contractile performance of residual muscle tissue is impaired in IBM patients, both *in vivo* and *ex vivo*. We conclude that sarcomeric dysfunction contributes to clinical muscle weakness in IBM.

337 - Intravenous Cyclophosphamide According to the Euro-Lupus Nephritis Protocol for Progressive Interstitial Lung Disease in Patients with Polymyositis/Dermatomyositis

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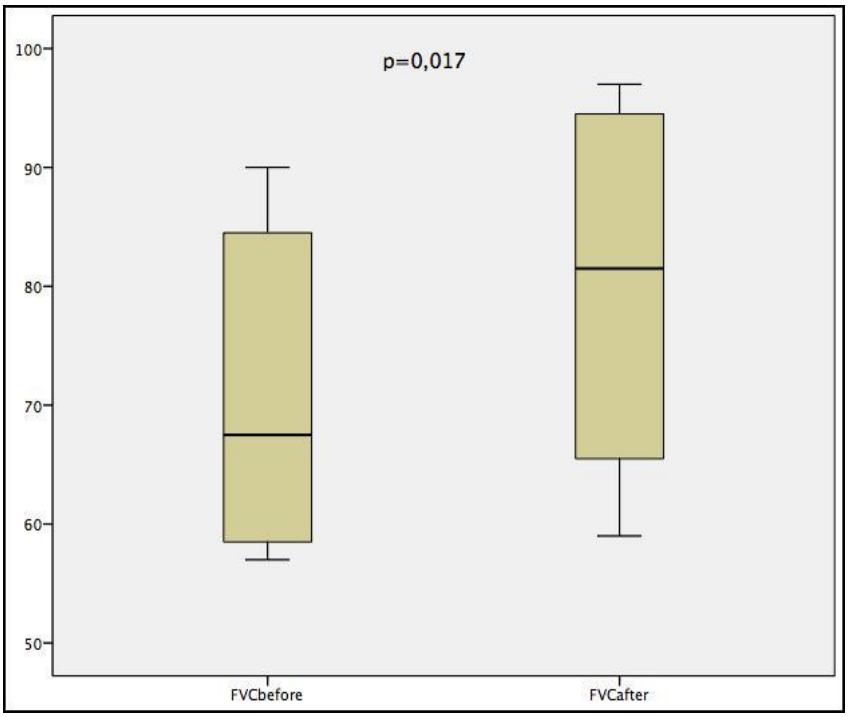
Background: Interstitial lung disease (ILD) affects 30-70% of patients with Polymyositis (PM) and Dermatomyositis (DM) and is one of the major contributors of morbidity and mortality. **Objective:** To study the efficacy and the safety of intravenous cyclophosphamide (IVCYC) according to the Euro-Lupus nephritis protocol for ILD in PM/DM patients.

Methods: Twelve patients with PM/DM (mean age 54± SD 8), who received 500 mg IVCYC every other week, up to 12 times according to the treating physician, as first line treatment, were retrospectively studied. Six patients had anti-Jo1, 4 anti-PL7, 1 anti-PL12, and 1 anti-MDA5 auto-antibodies. The median (IQR) disease duration before IVCYC was 4 (10.8) months. High doses of prednisolone were given for the first month and then gradually tapered. Response to treatment after a median (IQR) follow-up of 5 (2,8) months was based on pulmonary function tests (PFT) and high-resolution computed tomography (HRCT). The extent of pure ground-glass opacity (pGGO), pulmonary fibrosis (PF), honeycomb cysts (HCs) and emphysema was scored (0=0%, 1=1-5%, 2=6-15%, 3=16-20%, 4=21-25%, 5=26-50%, 6=51-75%, 7= >75%) in the upper, middle and lower lung zones before and after therapy. The total score for each finding was calculated as the sum of the scores of the 3 zones.

Results: The mean IVCYC total amount was 4.75 ± SD 1.4 gr. Before IVCYC, the median (IQR) values of forced vital capacity (FVC)%, forced expiratory volume in 1 second (FEV1)%, vital capacity (VC)%, total lung capacity (TLC)% and diffusion capacity of the lung for carbon monoxide (DLCO)% were 67 (26), 60 (14), 63 (11), 63 (12) and 57 (25), respectively. After therapy, the median (IQR) values became 74 (29), 80 (18), 80 (24), 77 (19) and 68 (27), respectively. The difference between baseline and follow-up TLC%, FVC% (fig.1) and VC% median values was statistically significant (p<0,05). FVC% and TLC% improved >10% in 6 and 5 patients, respectively; DLCO% improved >15% in 3 patients. Before IVCYC, the median (IQR) scores of pGGO and PF were 12,5 (9) and 12 (7), respectively. After IVCYC, they decreased (7 (6) and 9 (12), respectively). In the group of anti-Jo-1 positive patients, the difference was close to the statistically significance (from 13,5 (10) to 7,5 (15), p=0,06 and from 9,5 (10) to 4,5 (16), p=0,07, respectively). The median (IQR) pGCO scores of anti-Jo-1 negative patients improved (from 11,5 (11) to 8,50 (17)), while the median (IQR) PF scores were unchanged (from 13,5 (4) to 14 (10)). At baseline and follow up, the median scores of HCs and emphysema were 0. No statistically significant correlations were found between PFT values and HRCT scores. The difference of PF extent was negatively correlated with the disease duration before the first IVCYC (r=-0,56, p=0,056). No adverse events or drug toxicity were observed.

Conclusions: After IVCYC according to the Euro-Lupus nephritis protocol PFT and HRCT findings improved in PM/DM patients with ILD without any adverse events or drug toxicity. Longitudinal controlled studies are needed to confirm the efficacy and the safety of this treatment protocol.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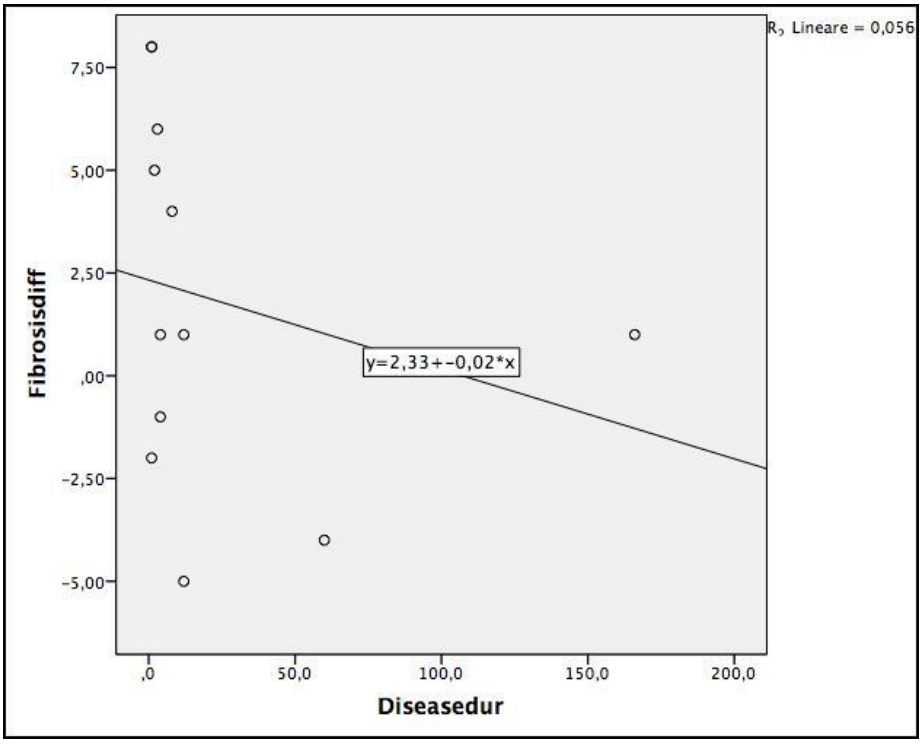
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338 - High-Dose Cyclophosphamide (HiCy) Without Stem Cell Rescue in Severe Idiopathic Inflammatory Myopathy

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Background: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by muscle weakness and inflammation. While most patients respond to standard immunosuppressive therapies, a subset will develop refractory disease.

Methods: Seven patients with severe refractory IIM who were treated with high-dose cyclophosphamide (HiCy) without stem cell rescue were identified. Their medical records were reviewed to assess demographic, clinical, histologic characteristics as well as response to therapy.

Results: The mean follow-up time after HiCy therapy was 38 ± 25 months. Three out of seven patients demonstrated substantial response, evidenced by improved muscle strength and decreased muscle enzymes after HiCy therapy. Two of three patients with anti-SRP antibody showed progressive improvement in muscle strength and function; the third patient who did not fully respond also had anti-Ro antibodies. Five patients experienced febrile neutropenia after HiCy therapy, one of which required a prolonged ICU stay for infectious complications, from which they eventually recovered.

Conclusion: These data suggest HiCy therapy without stem cell rescue may be considered as an alternative for the treatment of refractory IIM in anti-SRP positive IIM.

339 - Development of Training Guidelines in Patients with Inflammatory Myopathy

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Background: Physical exercise seems to be a safe and effective intervention in adult patients with inflammatory myopathy (IM). However, there is no expert consensus on the most appropriate training methodology. Thus, the aim of this study was to develop training guidelines for all stages of IM.

Methods: A systematic literature review including all studies, which assessed training or exercise interventions in IM patients was performed. The MEDLINE/PreMEDLINE, COCHRANE LIBRARY, and EMBASE database were searched up to June 2015. Information was extracted on the number of participants, study design, IM subtype, disease activity, form of intervention and training components (intensity, frequency, modality and time). Based on these results and our clinical experience, training guidelines stratified by disease activity were determined.

Results: Twenty-four studies with a total of 219 IM patients (57 with active and 162 with chronic disease activity) were included. Fourteen publications evaluated resistance training, 4 endurance training and 6 combined training strategies. Six studies reported complete and comprehensible training protocols with all training components (intensity, frequency, modality and time). In contrast, our newly developed training guidelines combine resistance and endurance training for recent-onset, active and chronic disease activity. Patients with recent-onset IM are recommended to exercise daily. Each resistance exercise is advised to perform 5-10 times with an absolute load of ≤ 20%VRM (voluntary repetition maximum). Additionally, walking or cycling at 50-60% HRmax (estimated maximal heart rate) is recommended. Patients with active or chronic IM can increase intensity and decrease frequency. These patients are currently recommended to perform 2-3 series of each exercise 2-3 times a week. Patients in an active stage can exercise with an absolute load of 20-50% VRM and patients in a chronic stage with 40-80%VRM accompanied by 15-30 minutes of cycling, walking or treadmill exercise at 60-80% HRmax.

Conclusion: First results in our local IM cohort show that these training guidelines are useful and safe in daily routine to optimize exercise programs in IM patients. Further studies in larger cohorts are needed to evaluate the overall applicability and effectiveness of these training guidelines.

340 - Effect of Abatacept Treatment on T Cells in Peripheral Blood in Polymyositis and Dermatomyositis Patients

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Background: Abatacept (CTLA4-Ig), a blocking agent for T cell co-stimulation, has been proven beneficial in several autoimmune diseases. The aim of the study was to screen the T cell subset landscape in peripheral blood of myositis patients by mass cytometry (CyTOF) and modulations following abatacept therapy after 6 months of treatment.

Methods: 12 patients (6 PM and 6 DM) were included in this exploratory substudy of a 6 months' treatment delayed-start design trial (ARTEMIS). Abatacept was given as intravenous infusions 10 mg/kg monthly, in total 7 times. Responders to abatacept treatment were defined as improved according to the IMACS criteria. Blood samples were taken before and after 6 months of active therapy, using either heparin or EDTA as anti-coagulant. Frozen PBMCs from the two time points were analyzed by mass cytometry employing a 29-antibody panel focusing on T-cell features. The resulting data was analysed using ACCENSE software which maps it to a 2D representation by t-SNE, as well as by counting cells by known marker combinations for different T cell subtypes.

Results: Following 6 months' treatment, 4 out of 12 patients were responders. Overall the T cell compartment was stable, with subtle changes in CD4+ regulatory T cells, which increased by 15% on average (-6% in responders, +25% in non-responders), although not statistically significant. Among the regulatory T cells, several clusters could be identified in the t-SNE map, some more distinct than others. Amongst these, 2 clusters out of 25 clusters changed significantly ($P<0.05$, FDR=0.40) after 6 months of abatacept treatment. Cluster 4 (CCR6+CD45RA+CD27+CD38+) increased 29% relative to total number of Tregs after treatment. Out of these markers, CCR6 was the unique marker of the cluster. Cluster 14 (CD39+CCR4+) decreased 25% relative to total number of Tregs after treatment, with CD39 being the signature marker.

Conclusion: Following abatacept treatment of poly- and dermatomyositis surprisingly few alterations were observed in the T cell landscape corroborating the notion that this treatment regime is 'physiological' in its action. We noted possible changes amongst regulatory FOXP3+ T cells. These changes did not correlate with therapeutic response, but represent the power of mass cytometry in redefining cellular subsets.

341 - Design of a Randomized, Double-blind, Placebo-controlled Phase 2 Clinical Trial of the Toll-like Receptor Antagonist IMO-8400 in Patients with Dermatomyositis

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Background: Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy characterized by an auto-inflammatory immune response in muscle and skin. Multiple lines of evidence suggest Toll-like receptors (TLRs), a key component of the innate immune system, play a critical role in DM pathogenesis. Retrospective studies evaluating muscle biopsy samples have shown that TLRs were over-expressed in skeletal muscle and infiltrating cells in DM subjects compared to controls. Type I and II interferons and other cytokines were also over-expressed, and expression of certain cytokines were correlated with TLR expression. IMO-8400 is an investigational oligonucleotide-based antagonist of endosomal TLRs 7, 8, and 9 that has demonstrated activity in preclinical models of autoimmune disease and in patients with psoriasis. Here we describe the design of a recently initiated Phase 2 clinical trial of IMO-8400 in DM patients.

Methods: As skin manifestations are among the most severe disease components and have a large impact on quality of life, we selected the Cutaneous Dermatomyositis Disease Area and Severity Index activity subscore (CDASI) as the primary endpoint. Using longitudinal CDASI natural history data for 115 unique DM patients seen at the Stanford University outpatient dermatology clinic, we modeled change over time to estimate sample size. Data were classified into baseline, 12-, and 24-week visits, and estimates of change over time and correlation of CDASI scores were assessed and used to calculate the sample size needed for a clinical trial.

Results: Over 24 weeks, patients with baseline CDASI <15 and CDASI ≥15 had a mean (SD) change from baseline of -1.75 (2.63) and -8.40 (10.49) points, respectively. In general, patients with low baseline scores reported small magnitudes of change, supporting selection of a clinical trial population with moderate to severe skin disease (baseline CDASI ≥15) consistent with the cut-off score range reported in the literature. Over the same timeframe, a 4-point or greater decrease in CDASI activity score was observed in 70.6% of patients with a baseline CDASI ≥15. Due to the large proportion of patients who achieved a clinically meaningful change with standard of care therapy, we decided to target a larger threshold of improvement for the drug under study, i.e., a mean change in the treated group of 7 points better than the placebo group. Sample size calculations resulted in 10 patients per treatment group, assuming a standard deviation of 8.5 points over 24 weeks using a Repeated Measures Mixed Model analysis assuming monthly CDASI assessments (>80% power on a 1-sided test; alpha=0.05).

Conclusion: Based on these analyses, we initiated a double-blind, placebo-controlled, 24-week Phase 2 clinical trial in DM patients (NCT number: NCT02612857). Key entry criteria include adults with DM aged 18-75 years, CDASI activity score ≥15, clinical symptoms of active muscle disease, and abnormal serum CK or ALD, EMG, muscle biopsy or MRI. Additional outcome measures include MMT-8, timed function tests including 10-meter run walk, and exploratory biomarkers of disease activity.

342 - Overexpression of IFNα and Derived Diseases: Innovative Approach with a Therapeutic Vaccine IFNα Kinoid

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Background: Interferon α kinoid (IFN-K) is a therapeutic vaccine developed to treat the deleterious effects of over-expressed IFNα. IFN-K is composed of inactivated IFNα coupled to a carrier protein, keyhole limpet hemocyanin. Administered intramuscularly with ISA 51 VG adjuvant, IFN-K elicits polyclonal neutralizing antibodies directed against IFNα. Therefore, IFN-K may address diseases mediated by IFNα over-production, such as systemic Lupus erythematosus (SLE) and dermatomyositis (DM). DM is a rare, systemic autoimmune idiopathic inflammatory myopathy characterized by progressive symmetrical muscle weakness and cutaneous lesions. Numerous studies in DM patients have led to the identification of a cluster of type I IFN-inducible genes, known as the IFN signature, that are upregulated in the peripheral blood[1,2,3,4] in muscle[5,6,7] and in skin[8] of DM patients. This upregulation was found to correlate with disease activity, whereas downregulation occurred when the disease was controlled by treatment[9,14].

Methods & **Results:** As previously reported in patients with SLE, IFN-K was immunogenic and all treated patients developed anti-IFNα binding antibodies including neutralizing antibodies at the highest doses[10,11]. A significant correlation of immune response with the down-regulation of IFN gene signature was observed. Today, more than 120 patients were treated with the study product in two SLE trials and IFN-K was well tolerated at all doses including those eliciting neutralizing anti-IFNα antibodies. Three of the 13 serious adverse events reported in the two SLE trials were related to the study product, one SLE flare, one colon cancer and one Kaposi varicelliform eruption. Results from these SLE studies led the company to design a Proof of Concept (PoC) study (IFN-K-005-DM) in 30 adult patients with DM. The study is single-blind, placebo-controlled, randomized study to evaluate the safety, immunogenicity, clinical and biological efficacy of IFN-K. Eligible are patients with newly diagnosed or relapsing DM, with 'probable' or 'definite' DM based on ENMC criteria[12]. Patients should be treated with corticosteroids (CS), and naïve for immunosuppressant, in order to avoid impact on the IFN-K immune response. This ongoing Poc study is designed using two cohorts of patients, which will be enrolled sequentially:

In Cohort 1, 10 patients will receive IFN-K (emulsified in ISA 51 VG). Immunogenicity induced by IFN-K, and safety will be evaluated in order to confirm the immune response in patients receiving high doses of CS. In Cohort 2, 20 patients will be randomized in a 1:1 ratio to receive IFN-K or placebo (both emulsified in ISA 51 VG). Immunogenicity induced by IFN-K, biological effect on the IFN gene signature in blood and muscle/skin biopsies, clinical response to treatment (MMT8, MMT5, accelerometer for daily activity, CDASI) and safety will be evaluated in both cohorts.

Conclusion: The results from this ongoing study should provide supportive data to design the pivotal study.

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343 - Analysis of Real-World Oral Prednisone Usage in Patients with Dermatomyositis Supports the Unmet Need for Additional Corticosteroid-sparing Agents

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Background: First-line treatment of dermatomyositis (DM) typically involves high dose oral prednisone. Adverse events associated with prednisone include muscle atrophy, hypertension, glucose intolerance, fluid retention and weight gain, cataracts, infection, and osteoporosis. Clinical and laboratory responses are typically seen within 3 to 6 months, after which prednisone is usually tapered to a minimally effective dose. However, anecdotal evidence suggests many patients are not able to reduce or stop high dose prednisone treatment and maintain disease control, despite the addition of current second-line immunomodulatory agents. IMO-8400 is an investigational Toll-like receptor antagonist with a novel mechanism of action currently in clinical development with the potential to treat persistent disease and reduce corticosteroid burden. Our objective was to assess the real-world use of oral prednisone via commercial and Medicare supplemental claims databases to understand the unmet need for new corticosteroid-sparing agents and inform IMO-8400 clinical development planning.

Methods: We acquired longitudinal claims data for ~148 million unique commercial and Medicare supplemental enrollees. From this dataset, we extracted "reliable" DM patients defined as having the ICD-9 diagnostic code for DM (710.3) noted ≥3 separate months in their history. Patients with ≥12 months of history before and after first use of the DM ICD-9 code were included in the analysis (N=3,238); max follow up was ±60 months. Longitudinal use of oral prednisone or equivalent was evaluated, with a cut-off of 10 mg per day separating low and high dose regimens.

Results: 1,858 (57%) had at least one high dose prednisone prescription in their history. About 1/3 of patients received high dose prednisone immediately following diagnosis. After 12 months, high dose prednisone use declined but remained constant in the range of 10-20% of the population through the end of the follow up period. The median duration of high dose prednisone use was 34 days, with 25% of patients on therapy for 268 days or longer. 1,246 (38%) of patients required a dose spike after diagnosis, defined as a ≥10 mg per day increase, with a mean spike of 30 mg per day. The mean number of spikes per patient after diagnosis was 4, with 25% requiring 1 spike per year and some as many as 4 per year. Among patients who discontinued high dose prednisone for at least 30 days, 856 (47%) had to resume treatment with ≥10 mg per day presumably to treat a disease flare.

Conclusion: Results demonstrated that DM patients are treated with chronic and repeat high-dose prednisone. This supports the need for additional corticosteroid-sparing agents to reduce the burden of prednisone use. Most DM patients were treated with high dose prednisone at least once, 10-20% were unable to reduce treatment below 10 mg per day at any given time point, and nearly 40% required ≥1 dosing spikes to control their disease. Future analyses may evaluate the incidence of corticosteroid-related adverse events and the limitations of currently used corticosteroid-sparing medications. Overall, these data support development of IMO-8400 as a potential corticosteroid-sparing agent.

344 - Efficacy and Adverse Effects of Methotrexate Compared with Azathioprine in the Antisynthetase Syndrome

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Background: Methotrexate and azathioprine are two of the most widely immunosuppressant drugs most used in the antisynthetase syndrome, but their efficacy to treat the different manifestations of the disease, secondary effects, and their comparative efficacy as steroid-sparing drugs is, to a large extent, unknown. Our main objective was to study the differences in pulmonary function, muscle strength and changes in the dose of corticosteroids between patients with antisynthetase syndrome (AS) treated with azathioprine (AZA) or methotrexate (MTX) at any point in the course of their disease. Complete data on arthritis outcomes was lacking and therefore not assessed. The secondary objective was to assess the profile of adverse effects of AZA compared to MTX in myositis patients

Methods: We included all patients from a single myositis center cohort from 2002 to 2015 who were positive for anti-Jo1, anti-PL7, anti-PL12, anti-OJ or anti-EJ AS autoantibodies. All the treatments administered at each clinical evaluation were recorded, and those visits where the patients were treated exclusively with corticosteroids plus AZA or MTX were included for analysis.
The change in pulmonary function tests (PFTs), strength (using the using the Medical Research Council scale), CK and dose of corticosteroids during the period that patients were exposed to the different treatments were analyzed using multivariate regression models adjusted for age at onset, sex, race, dose of corticosteroids, type of antisynthetase antibody and time from the onset to the clinical evaluation

Results: Of a total of 169 AS patients, 450 visits from 102 patients fulfilled the above-mentioned inclusion criteria and were included in the study. Twenty-two of those patients were treated with MTX, 63 were treated with AZA, and 17 were treated with both drugs at different time points. The mean dose of MTX was 20 mg/week and 136 mg/day of AZA. Comparing azathioprine with methotrexate, there were no significant differences in the rate of muscle strength recovery, corticosteroid tapering or CK decrease. Alternatively, and even if the number of patients with ILD treated with methotrexate was too low to draw definitive conclusions (7 patients), during the period that patients were treated with MTX, the FVC decreased significantly faster (13%/year) than in those patients treated with AZA (p=0.05). Twenty-nine per cent of all the patients that were treated with azathioprine showed adverse effects to this drug compared with 25% of the patients that were treated with methotrexate, however, the difference did not reach statistical significance. The most common adverse effects with both drugs were the elevation of liver function tests (46% AZA vs. 29% MTX), gastrointestinal symptoms (26% AZA vs. 19% MTX) and cytopenias (15% AZA vs. 15% MTX).

Conclusion: Compared with AZA, MTX did not show any advantage in terms of adverse effects, faster recovery of strength, decrease of CK or taper of corticosteroids. Alternatively, we found a trend towards worsening evolution of lung involvement in those patients treated with MTX. Consequently, our analysis suggests that, when possible, AZA should be chosen over MTX in the management of the AS.

345 - Systemic Treatment for Clinically Amyopathic Dermatomyositis: A Retrospective Cohort Study at Four Tertiary Care Centers

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Background: Clinically amyopathic dermatomyositis (CADM), characterized by pathognomonic cutaneous findings without muscle weakness, is an important subset and accounts for 20% of patients with DM. In patients with CADM, limited literature exists regarding treatment specifically for cutaneous disease as most studies have focused on pulmonary disease outcomes. In addition, skin disease outcomes in patients with classic dermatomyositis are often challenging to assess given concomitant therapies aimed at treating muscle disease. Therefore, our study investigated the use of systemic therapy for skin disease in CADM at 4 tertiary care centers.

Methods: A search of the Partners Healthcare and New York University medical record systems between 2000 and 2016 was conducted. CADM is not included in the ACR diagnostic criteria for DM, but was defined by the presence of 3 major cutaneous criteria (heliotrope eruption, Gottron papules, and Gottron sign), or 2 major and 1 minor criteria (e.g. violaceous erythema, calcinosis) along with a compatible skin biopsy, and absence of clinical evidence of myositis within 6 months of disease onset. A total of 117 patients with CADM were identified. We excluded all patients for whom treatment was prescribed for a systemic disease manifestation rather than specifically for cutaneous disease. Data collected included demographics, laboratories, medications used, and outcomes. Continuous variables are reported as mean ± SD. The percentages of patients receiving each treatment type were compared by provider type, and the statistical significance of differences was assessed via Fisher's exact test. A P-value < 0.05 was considered significant.

Results: Of the 117 patients identified, 96 were amyopathic and 21 were hypomyopathic. The mean age of diagnosis was 49.8 years. Most patients were referred from dermatologists (46%) and rheumatologists (30.1%). Antimalarial agents were the most commonly used treatment type (77%), but achieved good control of skin disease in only 11% of cases. In addition, 26.7% of patients developed a cutaneous hypersensitivity reaction to HCQ. Of the entire cohort, only 19.7% of patients were treated with antimalarials and topical therapy alone, while 80.3% required at least one immunosuppressive therapy to control their cutaneous disease. Furthermore, patients tried a mean of 3.6 (SD = ±1.9) treatments prior to achieving skin disease control. Among these additional therapies, MTX (53.8%) and MMF (39.3%) were the most commonly used, followed closely by IVIG (29.1%). Notably, 13 patients were followed exclusively by a rheumatologist, and none of these patients received IVIG (32.7% vs 0%, p=0.02).

Conclusion: In this cohort of CADM patients, which is the largest reported to date, cutaneous disease was largely refractory to antimalarial agents. This study emphasizes the recalcitrant nature of DM skin disease, and highlights that aggressive therapy is often warranted on the basis of cutaneous involvement alone. As existing data supports the concept that IVIG is likely the most effective treatment of skin disease in DM, the difference in treatment approach between rheumatologists and dermatologists may impact patient outcomes.

346 - Long-term Observational Study of Patients with Inclusion Body Myositis (IBM) Receiving Intravenous Immunoglobulin (IVIG)

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Background: IBM is characterized by a relentlessly progressive muscle weakness. Controlled clinical trials with IVIG for 3 months failed to demonstrate efficacy. By contrast, several recent case reports and retrospective series with clinical observation for several years suggest positive effects, at least in selected patients. In the present study, we assessed the long-term effects of IVIG in the course of IBM compared to no pharmacological treatment.

Methods: 73 patients from the Dept. of Neurology at the University Medical Center Göttingen in Germany fulfilled the ENMC criteria of IBM. 57 of these patients provided sufficient clinical data for a retrospective analysis with at least two visits over one year. All patients had received a full neurological examination including an MMT6 and most patients had also received hand grip dynamometry, walk tests, and patient-based questionnaires for daily life activities (IBM-functional rating scale, IBM-FRS) and swallowing (swallowing-related quality of life scale, SWAL-Qol).

Results: Patients were observed for a mean of 6 years (range 1-9 years). 72% of the patients were male. The mean age at disease onset was 59.5 years. 33% of the patients were positive for the cN1A autoantibody. 65% of the patients suffered from dysphagia, 77% of the patients used walking aids and one third was wheelchair dependent. 22 patients had received IVIG for at least 50% of the time and 16 patients had received no pharmacological treatment. Patients with IVIG treatment displayed a significantly ameliorated decline of the mean MMT6 per year (mean +/-SD: -1.175+/-0.49) compared to untreated patients (-2.815+/-0.59; $p<0.05$). IVIG treated patients depended significantly later on a cane compared to untreated patients (3.6 years vs. 7.6 years; $p<0.05$). In daily life activities as measured by IBM-FRS, the IVIG group showed a better performance, which did not reach statistical significance. The maximum walk distance declined in IVIG-treated patients by a mean of 13 meters per year compared to 98 meters in untreated patients. No difference was noted in the SWAL-QoL value. No difference of any clinical parameter was noted when comparing presence or absence of anti-cN1A antibodies. Additional clinical parameters and a subgroup analysis of the different walking aids will be presented.

Conclusion: IVIG treatment improved relevant clinical parameters in the long-term course of IBM compared to patients without pharmacological treatment. The data support a treatment attempt with IVIG in selected patients and call for a placebo-controlled clinical trial in IBM with IVIG treatment for one year.

347 - Whole-body Vibration Exercise Is Safe and Could Improve Physical Function in Patients with Sporadic Inclusion Body Myositis

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Background: Sporadic inclusion body myositis (sIBM) is a rare idiopathic inflammatory myopathy presenting with muscle weakness and muscle atrophy. There is no effective medical treatment and patients develop severe disability over time. Adapted exercise is safe, however knowledge of effects of exercise on muscle strength and physical function in these patients is limited. The objective was to evaluate the effects of whole-body vibration (WBV) exercise on muscle strength, physical function, disease activity and urine levels of prostaglandin metabolites (PG-M) in patients with sIBM.

Methods: Four males with sIBM (age: 67-73 years, diagnosis duration: 3-7 years) were included in this Single Subject Experimental Design study. All were ambulant (two using a cane) and without medical treatment for their sIBM. During a 6-week A-phase without any intervention, participants (P) were assessed every other week as to muscle strength (hand-held myometer, Newton), physical capacity (30-meter walking test, Sit-to-stand test, heel-lift test), grip strength (Grippit), physical function (HAQ) and urine PG-M levels as an index of systemic PG production (LC-MS/MS). Disease activity (6-item core set; physician/patient global, the MMT, the HAQ, CK-levels, extra-muscular disease activity) was assessed twice, before and after exercise. During the 12-week interventional B-phase, knee extensors, plantar-flexors of the feet and finger/wrist flexors were exercised on the whole-body vibration platform twice a week. Assessments continued every other week through the B-phase. Exercise intensity and duration started on 30 Hertz (Hz) in two 30-sec sets, increasing to 45 Hz, in four 300-sec sets per muscle group. Two consecutive assessments in the B-phase above or below the A-phase mean + 2SD represented a statistically significant change. > 20% improvement in 3/6 disease activity items with worsening > 25% in no more than 2 (not including the MMT) represented a responder in disease activity. mPGES-1 and COX expression was evaluated by immunohistochemistry in muscle tissue from 6 other patients with sIBM.

Results: P1 stopped after 8 weeks (exercise uncomfortable), P2 exercised for 10 weeks (stopping for personal reasons). P3 and P4 completed the 12-weeks. All Ps completed all assessments. P1 remained unchanged in all parameters. P2 improved statistically significant in number of heel-lifts and in 30-meter walk, and responded with reduced disease activity (>20% reduced physician global, HAQ, extra-muscular VAS). P3 improved significantly in sit-to-stand test and right wrist flexor strength. P4 improved significantly in sit-to-stand test and in right knee extensor strength. No P worsened statistically significant in any variable and systemic production of PGE2 and PGD2 remained unchanged in response to exercise. The COX/mPGES-1/PGE2 pathway was markedly up-regulated in muscle tissue from sIBM patients.

Conclusion: The WBV exercise was well-tolerated and resulted in mainly improved ability to walk and stand up from sitting. This program was safe with stable prostaglandin levels and reduced or unchanged disease activity throughout the study.

348 - Nonretinal Ocular Complications Associated with the Use of Anti-Malarial Drugs: Case Report and Literature Review

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Background: Antimalarials (AM), including hydroxychloroquine (HCQ) and chloroquine (CQ) are often used in lupus (SLE), rheumatoid arthritis (RA) and dermatomyositis (DM). AM ocular adverse events (AEs) are common and include retinal pathology, corneal deposits and ciliary body dysfunction. Because retinal pathology from AM can result in permanent damage, specific guidelines exist to prevent and detect potential damage early before permanent eye damage occurs, yet little is known about non-retinal AEs.

Methods: We report a case where the use of HCQ in a woman with chronic active SLE-DM resulted in significant ciliary body dysfunction and review the literature on non-retinal ocular problems occurring with AM. Review search terms included "antimalarial, HCQ, CQ, eye, visual, ocular and ophthalmologic", and included PubMed, FDA and Google searches.

Results: Patient characteristics with HCQ challenge, dechallenge, rechallenge and re-dechallenge are summarized in the table below. The fact that the patient developed visual problems after taking HCQ and the symptoms resolved when HCQ was stopped on 2 separate occasions strongly implicates HCQ as the cause of her ocular problems, which was diagnosed as probable ciliary body dysfunction.

Non-retinal AM eye problems are stated as relatively common in the literature and labeling of these drugs, but data documenting the frequency and significance of non-retinal eye problems are sparse. Reviews generally report a higher frequency of eye AEs with CQ compared to HCQ, and drug dosage, duration and patient age may be contributing factors. Non-retinal eye problems are thought to remit with cessation of the drug.

In one of the few studies with AM AE frequencies, Jover et al. 2012 Clin Exp Rheumatol, retrospectively assessed 778 rheumatic disease patients on long-term AM and found that 52% of treatment discontinuations were due to AEs, of which 45.5% were ophthalmologic events. Of the 110 ocular AEs, 9 [8.2%] were due to AM retinopathy. There were 32 cases of corneal deposits and 10 non-permanent, unilateral scotomas where visual acuity was not affected, and which remitted with drug discontinuation. There were 62 cases of ocular comorbidity not related to AM and not further specified. Factors related to ocular AEs included female sex, use of CQ versus HCQ, age, using both AMs together, and the diagnosis of SLE and scleroderma compared to RA.

Conclusion: Nonretinal ocular AEs resulting from AMs can cause significant problems for patients, are important contributors to AM discontinuation, and are often under-recognized, under-reported, or minimized as to their significance. More information is needed to fully understand the significance and mechanisms of AM AEs, which can be serious.

Age	Current drugs	HCQ dose	HCQ duration	Eye problem	Effect of stopping drug	Visual Exams
45	NSAIDS, prednisone, azathioprine	200 mg daily	5 months	Blurred vision that continued to worsen, affecting visual acuity and the ability to read and drive	Symptoms completely resolved over 4 weeks	Recommended eye exams [visual acuity, color, visual fields, pressures, slit lamp] before starting HCQ showed no pathology. Repeat exams after stopping HCQ and cessation of symptoms again showed no pathology
62	Methotrexate, mycophenolic acid, prednisone	300 mg daily	4 weeks	Severely blurred vision with more rapid onset than in previous episode	Symptoms completely resolved over 4 weeks	Recommended eye exams before starting HCQ showed no pathology. Repeat exams after stopping HCQ and cessation of symptoms again showed no pathology

349 - Efficacy and Safety of Cyclophosphamide Treatment in Severe Juvenile Dermatomyositis Shown by Marginal Structural Modelling

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Background: In patients with severe or refractory juvenile dermatomyositis (JDM), second-line treatments may be required. Cyclophosphamide (CYC) is used to treat cancer and severe cases of severe systemic lupus erythematosus and vasculitis, but evidence of efficacy in JDM is limited. The aims of this study were to describe clinical improvement in patients treated with CYC and to model efficacy of CYC in patients who were or were not treated with CYC.

Methods: Clinical data were analysed from n=200 patients recruited to the Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS), of whom n=56 were treated with CYC. Skin, global and muscle disease activities were assessed using the modified disease activity score (DAS) for skin, physician's global assessment (PGA) and the Childhood Myositis Assessment Scale (CMAS), respectively. Descriptive analysis of improvement in just the patients treated with CYC was performed using Friedman's test for non-parametric repeated measures ANOVA. Marginal structural modelling (MSM) was used to longitudinally model treatment efficacy in patients who received CYC within the last 6 months, 6-12 months ago and over 12 months ago, relative to patients who had never or not yet received CYC while adjusting for confounding by indication.

Results: Patients treated with CYC had higher global and muscle disease activities at baseline than patients who were not treated with CYC ($p=7.4\times10^{-4}$ and $p=9.1\times10^{-5}$, respectively). Distribution of myositis-specific autoantibodies did not differ between treatment groups (p=0.66). Descriptive analysis showed reductions at 6, 12 and 24 months in skin disease ($\chi^2(3)=49.0$, $p=1.3\times10^{-10}$), global disease ($\chi^2(3)=38.3$, $p=2.4\times10^{-8}$), and muscle disease ($\chi^2(3)=45.3$, $p=8.0\times10^{-10}$) compared to baseline. Median [IQR] modified DAS reduced from 4.5 [3-5] at baseline to 2 [0-4] at 6 months ($p=3.5\times10^{-5}$), 1.5 [0-3] at 12 months ($p=2.6\times10^{-6}$), and 0 [0-3] at 24 months ($p=6.2\times10^{-7}$). Median PGA reduced from 6.4 [4.0-8.0] at baseline to 1.7 [1.0-3.0] at 6 months ($p=5.8\times10^{-7}$), 0.7 [0.4-2.0] at 12 months ($p=2.8\times10^{-6}$), and 0.8 [0.0-1.5] at 24 months ($p=3.8\times10^{-7}$). Median CMAS increased from 19.5 [5.75-38] at baseline to 45.5 [42-50] at 6 months ($p=2.0\times10^{-6}$), 48 [44-52] at 12 months ($p=4.0\times10^{-6}$), and 51.5 [46.75-52] at 24 months ($p=8.3\times10^{-6}$). MSM analysis showed reduced global disease and skin disease in patients treated with CYC over 12 months earlier, relative to CYC-naïve patients. In these patients, modified DAS was 1.19 units lower (p=0.0085) and PGA was 0.66 units lower (p=0.027), compared to patients never or not yet treated with CYC. MSM analysis did not indicate improvement in muscle disease. Minor adverse events (3 respiratory infections, 1 episode of mouth ulcers) were reported in 3 patients within 1 year of stopping CYC.

Conclusion: CYC is efficacious in JDM with no short-term side-effects. Improvement was observed in skin disease, global disease and muscle disease. MSM analysis showed reduced skin and global disease activity in patients who had been treated with CYC over 12 months ago, relative to patients who had never or not yet been treated with CYC. Further studies are required to evaluate longer-term side-effects.

350 - Efficacy and Safety of Tumour Necrosis Factor Antagonists in a Large Cohort of Juvenile Dermatomyositis Patients

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Background: Some patients with juvenile dermatomyositis (JDM) have a disease course which is refractory to multiple drug treatments. There is evidence that prolonged disease activity is associated with increased mortality and morbidity. High levels of TNFα have been reported in JDM patients with a long disease course, suggesting it may play a significant role in refractory disease. There are no published clinical trials of this therapy but some are in progress. The aim of this study was to evaluate the efficacy and safety of anti-TNF treatment in UK JDM Cohort and Biomarker Study patients.

Methods: Data were analysed from children who were recruited to the UK JDM Cohort and Biomarker Study, met Bohan-Peter criteria and were on anti-TNF treatment at the time of analysis, and had had at least 3 months of therapy. Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing (MMT8), muscle enzymes and physician's global assessment (PGA) were recorded. Skin disease was assessed using modified skin Disease activity score (DAS).

Results: 67 patients with JDM actively treated with anti-TNF agents were analyzed. 41 patients were female (61%). The median [IQR] age at disease onset was 5.2 [3.4-9.5] years and the median age at beginning of anti-TNF was 10.1 [6.5-14] years. The median disease duration at beginning of anti-TNF was 3.2 [1.8-5.3] years and the median duration on anti-TNF was of 2.55 [1.5-3.9] years. Muscle involvement significantly improved, with median [IQR] CMAS and MMT8 values at initiation of anti-TNF therapy of 45.50 [39.75-52.25] and 74 [59.5-79.5] respectively, and at current evaluation (or date of anti-TNF treatment completion) of 53 [50-53] and 79 [74.580] ($p<0.0001$ and $p=0.0097$; Mann Whitney test), respectively. For skin involvement the initial modified DAS was 4 [2-5] and final 1 [0-3] ($p<0.0001$; Mann Whitney test). Assessing global disease activity the initial PGA was 2.9 [1.3-4.3] and final 0.5 [0-1.45] ($p<0.0001$; Mann Whitney test). Sixteen patients (24%) switched their anti-TNF treatment. 62.5% of the switches were due to therapy failure, 25% due to adverse events and 12.5% for patient preference in subcutaneous administration. Of 31 adverse events registered (13.3 adverse events per 100 patient-years), 12 were considered severe. One patient died due to small bowel perforation (not felt to be related to the use of TNF antagonists). The remaining adverse reactions were not severe and 79% (n=15) of them were due to infections causes. In 5 of the mild to moderate adverse reactions the drug had to be discontinued and switched to another TNF antagonist, while in the remaining patients temporarily withholding the drug proved sufficient. No malignancies or tuberculosis were reported.

Conclusion: This study is one of the largest to explore the efficacy and safety of TNF antagonist treatment in a large independent cohort of JDM patients. Both muscle and skin involvement appeared to improve after anti-TNF treatment.

351 - The Effectiveness of Rituximab in Treatment of Juvenile Dermatomyositis

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Background: Initial case reports of the use of rituximab, a monoclonal antibody directed against CD20, in JDM patients showed promising results. This success led to conducting a large multi-center randomized clinical trial to evaluate the effectiveness of rituximab in refractory myositis patients. Although the primary endpoint was not achieved, the study found that the JDM early treatment group responded faster than the late treatment group. However, the study was not powered to allow for JDM subgroup analysis and patients without myositis specific antibodies were included in the study. To investigate if rituximab is effective in JDM patients, we conducted this study.

Methods: This was a retrospective study conducted at CureJM Center - Ann & Robert H. Lurie Children's Hospital of Chicago between 2012 and 2016. We included all JDM patients who received rituximab infusions as part of their treatment plan and who had documented follow-up data for at least one year. 9 subjects met inclusion criteria and their data were analyzed to evaluate their response to rituximab therapy. We defined positive response as: improvement of the disease activity score (DAS) by at least 2 points in two consecutive visits. IRB approval was obtained before conducting this study. Myositis specific antibody (MSA) was performed at the Oklahoma Medical Research Lab by Immunoprecipitation

Results: Complete B cell depletion was achieved in all study subjects. All subjects had skin involvement before rituximab treatment except one, while 4 out of 9 subjects had muscle involvement. Two third of the study subjects showed a clear response to therapy. However, the disease relapsed in 50% of the responders (time to relapse ranges from 9 to 30 months). The majority of the patients needed more than one course of rituximab therapy to maintain B cell depletion. Of note, parents of subject number 5 refused to continue rituximab therapy. Patients with anti-Mi-2 and anti-MJ antibodies responded to rituximab without relapse.

Conclusion: Rituximab is an effective therapy for skin manifestation of JDM especially if the patients have known myositis specific antibody. More than one course of rituximab therapy should be considered, especially if the patient had a good response to the initial therapy.

Gender	Race	Age at Onset (y)	Age at 1st Rituximab	No. of Doses	Disease Manifes-tations	Response	Duration of Resp. (mo)	Duration of Obs-ervation (mo)	Relapse	MSA ever
F	W	2.5	12.3	5	S	Yes	30	50	Yes	Ro ind, P155/140+
F	W	8.4	16	3	S	Yes	19	19	No	Ro+, Mi-2+, P155/140+
M	W	6.1	12.4	2	S	Yes	9	20	Yes	P155/140+
F	W	2.3	15.9	2	S	No	N/A	12	N/A	Ro ind, P155/140+
M	W	5.7	12.4	1	S	Yes	20	20	No	U1RNP+, MDA5+, P155/140 ind
M	B	8.8	14.7	2	Mu	Yes	12	12	No	MJ+
F	W	9.7	17.2	3	S + Mu	Ind	N/A	26	N/A	Ro+, P155/140+
F	H	2.3	11.2	3	S + Mu	Ind	N/A	21	N/A	P155/140+
F	W	14.7	17.8	2	S + Mu	Yes	11	15	Yes	P155/140+

F= Female, M= Male, W= White, H = Hispanic, B = Black, yr = years, m = months, S = Skin, Mu = Muscle, Ind = Indeterminate.

352 - Intravenous Immunoglobulin in Combination with Intravenous Methylprednisolone in the Treatment of Calcinosis Associated with Juvenile Dermatomyositis (JDM)

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Background: Calcinosis is one of the hallmark complications of juvenile dermatomyositis (JDM), and is associated with long-term damage, functional disability, and poor quality of life. There is no known effective treatment of calcinosis and current treatment protocols have been limited to anecdotal retrospective studies. Two published case reports showed improvement of calcinosis in JDM patients treated with Intravenous Immunoglobulin (IVIG). We assessed the response of IVIG in combination with Intravenous Methylprednisolone (IV MPD) in five JDM patients with calcinosis.
Methods: Retrospective medical record review of over 200 JDM patients seen from 2008-2016 at The George Washington Myositis Clinic was performed. 53 (26.5%) of JDM patients developed calcinosis, 15 had at least one follow-up visit and 5 were identified, 4 of whom were on background immunosuppressive therapies, that received IVIG and IV MPD treatment for calcinosis. The number of anatomic areas (bilateral upper extremities, lower extremities, axilla, chest, back, abdomen, head, and buttocks), limitation of joint range, type of calcinosis (plaque, nodular), consistency, extent, signs of inflammation, and progression were used to assess response to treatment.
Results: The median age at baseline was 14.8 years [13.7-17.7], 4 patients were male, and 3 were Caucasian, 2 Hispanic. Median disease duration at baseline was 5.5 years [2.9-10.0]. The median duration of IVIG treatment from baseline to clinical improvement in calcinosis was 9.0 months [5.0-13.0], with a dose ranging between 1g/kg- 2g/kg per month. Patients also received IV MPD ranging from 100 mg to 1,000 mg at the time of the IVIG infusion; 4 patients also received oral prednisone and MTX, 1 patient infliximab and 1 patient rituximab, among other therapies (Table). The median Childhood Assessment Questionnaire score (CHAQ) was 1.6 [0.17-2.6] pre-treatment and 0.0 [0.0-1.1] at follow-up after treatment. Median Childhood Myositis Assessment Scale score (CMAS) was 48.5 [20.8-50.8] pre- and 51.0 [38.0-51.5] post-treatment, median Manual Muscle Testing (MMT) was 138.0 [127.0-145.0] pre- and 150.0 [128.0-150.0] post-treatment. Median number of anatomic areas involved with calcinosis was 6.0 [1.5-7.5] pre- and 6.0 [1.0-8.0] post-treatment, the median number of restricted joints was 5.0 [1.5-8.0] pre- and 0.0 [0.0-6.5] post-treatment (Table).
Conclusion: Major clinical benefit was seen after the initiation of IVIG and IV methylprednisolone in this small case series of JDM patients with refractory calcinosis. All patients exhibited a late response to IVIG therapy. Larger, controlled studies are needed to determine the effectiveness of immunosuppressive and immunomodulatory therapies for treatment of calcinosis associated with JDM.
Table: Five patients with juvenile dermatomyositis and their response to intravenous immunoglobulin and IV Methylprednisone therapy for calcinosis.

	Background therapy	IVIG and IV MPD duration (mo)	IVIG dosing (mo)	IV MPD dosing (mo)	CHAQ (0-3)	CMAS (0-52)	MMT (0-150)	Anatomic areas	Restricted joints	Calcinosis description
Patient 1 Baseline:	INFLX, MTX, PRED	0	-	-	0.657	51	140	1	1	Large painful firm plaque.
Evaluation visit:	IVIG, IV MPD, INFLX, MTX, PRED	9	2g/kg	250mg	0	51	150	1	0	Softening, non-tender, decreased size on exam, edema surrounding lesions decreased on MRI, decrease number of lesions.
Patient 2 Baseline:	IVIG, IV MPD, CS, MTX, PRED, HCQ, ALD	0[1]	1g/kg	500mg	2.66	-	96	2	8	Tender large plaques.
Evaluation visit:	CS, MTX, PRED, HCQ, COL	14	2g/kg	1000mg	0.125	48	141	1	0	Softening, decrease size on exam, non-tender, decrease number of lesions.
Patient 3 Baseline:	IVIG, IV MPD, MTX, PRED, HCQ, RTX, ALD	0[1]	1g/kg	100mg	0	47	138	6	2	Multiple small nodules, large warm plaques.
Evaluation visit:	IVIG, IV MPD, MTX, PRED, HCQ, ALD	9	2g/kg	1000mg	0	52	150	6	0	Softening, decrease size on exam, some lesions are no longer palpable, warmth resolved.
Patient 4 Baseline:	Aluminum hydroxide, Amlodipine	0	-	-	-	50	150	7	5	Multiple large plaques.
Evaluation visit:	None	15	2g/kg	500mg	0	51	150	8	5	Decreased size of calcinosis, DEXA/X-ray showed improvement in quantity of calcinosis.
Patient 5 Baseline:	PRED, MTX	0	-	-	-	12	125	8	8	Multiple tender nodules.
Evaluation visit:	IVIG, IV MPD, HCQ, MTX, PRED, AZA, PMD	57	1g/kg	500mg	2.125	28	115	8	8	Softening, non-tender, size and number of lesions decreased on exam.

[1]Patient 2 & 3 IVIG dose was increased at baseline evaluation
Body was divided into 11 anatomic areas: Right arm, Left arm, Right axilla, Left axilla, Right leg, Left leg, Buttocks, Chest, Back, Abdomen, and Head.
Abbreviations: IVIG: Intravenous Immunoglobulin, IV MPD: Intravenous Methylprednisolone. INFLX: Infliximab, CS: Cyclosporine, PRED: Prednisone, MTX: Methotrexate, HCQ: Hydroxychloroquine, COL: Colchicine, ALD: Alendronate, PMD: Pamidronate, RTX: Rituximab.
CHAQ: Childhood Assessment Questionnaire, CMAS: Childhood Myositis Assessment Scale, MMT: Manual Muscle Testing.
mo: months

353 - Intravenous Immunoglobulin Treatment is Associated with Improvement of Calcinosis in Juvenile Dermatomyositis Patients: A Case Series

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Background: Juvenile dermatomyositis (JDM) is a rare autoimmune disease characterized by chronic inflammation of striated muscle and skin. Many children experience complications of their disease, such as contractures, weakness, skin lesions, and painful calcinosis. There has been evidence that calcinosis may be minimized by aggressive and early treatment. Much is unknown about the pathophysiology of calcinosis and there is no universally standardized treatment.

Methods: Here we present three cases of JDM where initiation of treatment with IVIG led to improvement of calcinosis. These patients presented to the Pediatric Rheumatology service at Children's National Medical Center over the period of 10 years.

Results:

Case 1

A 5-year-old previously healthy female presented for evaluation of nodular skin lesions. Imaging showed right leg soft tissue calcification and semitendinosus edema. On exam, she had nodules on her fingers and elbows and a calcific lesion on her right knee, causing a 20-degree reduction of extension. She was diagnosed with JDM and started on monthly IV Methylprednisolone and IVIG. After 7 rounds of infusions, she had full extension of her right knee and infusions were discontinued. Two years later, she presented with muscle weakness and calcinotic tumors on her right hip and scapula. She was restarted on IVIG, IV Methylprednisolone, and Infliximab. Over the next 6 months she had decreasing calcinosis in her right thigh, hip, and shoulder. IVIG was removed from her treatment regimen. After 4 months, she had interval worsening of calcinosis. She was restarted on IVIG infusions for 1.5 years and repeat imaging showed significant improvement of calcinosis.

Case 2

A 13-year-old male presented for second opinion of JDM management. He was previously healthy until diagnosis at age 9. At presentation, he was receiving monthly Methylprednisolone infusions; however, he continued to have significant weakness and calcinosis behind his bilateral knees and on the extensor surface of his elbows. MRI demonstrated the presence of fluid in his right leg suggesting liquefaction of his calcinosis. The lesion was drained and he was continued on IV Methylprednisolone with the addition of IVIG. After 6 months of therapy, his calcinosis resolved and his infusions were discontinued. About 3 months later, he redeveloped calcinosis posterior to his right knee. He was unfortunately lost to follow up at this time.

Case 3

A 13-year-old male presented to the hospital with a 5-year history of arthralgia, muscle weakness, and calcinotic lesions on his buttocks and over his right axilla. He was diagnosed with JDM and started on Methotrexate, IV Methylprednisolone, and IVIG. After 7 rounds of infusions, he showed significant improvement in his calcinosis as evidenced by imaging. After 2 years of infusions, he had resolution of myositis and calcinosis of his lower extremities.

Conclusion: These three cases illustrate improvement of calcinosis after treatment with IVIG. Although we cannot draw the conclusion that IVIG alone caused resolution of calcinosis, there is evidence in 2 patients of worsening calcifications after discontinuing only IVIG infusions. Further investigation of this association is warranted.