First International Conference on

MYOSITIS

May 8-11, 2015

Radisson Blu Royal Park Hotel, Stockholm Sweden

PROGRAM AND ABSTRACT BOOK

Welcome to the First International Conference on Myositis

Idiopathic inflammatory myopathies or myositis are systemic disorders with many faces often with multi-organ involvement requiring interdisciplinary team care. This is true both for adult and pediatric cases. Current treatment modalities have limited effects, thus there is a high unmet need for new therapies. In order to develop novel treatment strategies we need to understand more of the underlying molecular pathogenesis and to achieve this we need to collaborate between disciplines with expertise in myositis. To facilitate such a multidisciplinary collaboration in research and in the development of clinical care a platform to exchange ideas and experience is needed. This is the main purpose to organize the first international conference on myositis.

The idea of a conference on myositis has developed within the MyoNet network, which was established in 2010, thanks to a 5-year network grant from the European Science Foundation (ESF). During these five years the collaborations have spread making the network international, *www.myonet.eu*. A longitudinal myositis register has been established, with to date more than 3 500 patients, *www.euromyositis.eu*. We feel that it is important to continue to collaborate across borders, geographical as well as disciplinary borders and we hope that this conference will be a start of a continued activity that will stimulate research and clinical trials in myositis.

The target audience for this meeting includes scientists with interest in adult or juvenile myositis active in clinical, epidemiological, translational or basic science. We hope that this will become an important networking event, and that new insights into pathogenesis and treatment will be discussed during the meeting.

Presentations of posters and oral abstracts by young scientists will be at the heart of the conference. World leading experts in the field of myositis will provide a broad perspective of the research field in myosits.

May in Stockholm will be spring time. The weather can be a bit chilly but we can promise beautiful light evenings. The congress hotel is conveniantly located just outside the city centre of Stockholm by a bay of the Baltic sea.

We hope that the First International conference on myositis, will be an interesting and stimulating meeting for you and that you will enjoy your stay.

Finally, we want to thank the Journal of Internal Medicine for a generous financial contribution to this conference.

On behalf of the Scientific Committee,
Stockholm April 7, 2015

Ingrid Lundberg, M.D., Ph.D.
Professor
Rheumatology Unit
Department of Medicine,
Karolinska Institutet,
Stockholm, Sweden

Scientific committee

Ingrid Lundberg, *Chair*	Sweden
Robert Cooper	United Kingdom
Jiři Vencovský	Czech Republic,
Øyvind Molberg	Norway,
Jan De Bleecker	Belgium,
Marianne de Visser	The Netherlands,
Fred Miller	US
Lisa Rider	US
Jens Schmidt	Germany
Olivier Benveniste	France
Lucy Wedderburn	United Kingdom
Guochun Wang	Beijing, China
Victoria Werth	US

Local organizing committee

Ingela Loell
Antonella Notarnicola

Scientific Program

Friday May 8 Pre-conference meetings

14.00 – 15.30 Steering committee meeting for Euromyositis registry.

16.00 – 18.00 WORKSHOPS
a) Genetics workshop – Janine Lamb, UK/Hector Chinoy, UK
b) Euromyositis registry: Interactive workshop on how to use the registry - Niels Steen Krogh, DK

18.30 REFRESHMENTS

19.00 WELCOME – Ingrid Lundberg

19.10 – 19.30 OPENING LECTURE – "Scientific challenges in the development of improved care for patients with myositis" Paul Plotz NIH, US

19.30 GET TOGETHER WITH DINNER at Radisson Blu Royal Park Hotel, Stockholm

Saturday May 9

08.30 – 08.40 OPENING REMARKS – Ingrid Lundberg

08.40 – 10.10 GENES AND ENVIRONMENT
Chairs: Robert Cooper, UK, Lisa Rider, US

- Introduction, what is known about HLA and IIM, link with serology and outcome – Hector Chinoy, UK
- How the GWAS and Immunochip has furthered our understanding of HLA and IIM, use of imputation and current status – Janine Lamb, UK

SELECTED ABSTRACT:

- HLA analysis in idiopathic inflammatory myopathy identifies significant association of classical HLA alleles in polymyositis and dermatomyositis, and amino acids in inclusion body myositis – Simon Rothwell, UK
- Genes and environment – what is the role of HLA in presentation of auto antigens - Hector Chinoy, UK

SELECTED ABSTRACT:

- A genome-wide association study of statin induced myopathy – Ana Alfirevic, UK

10.10 – 10.40 COFFEE

10.40 – 12.10 PATHOGENESIS (1)
Chairs: Lucy Wedderburn, UK, Jens Schmidt, Germany

- T cells in myositis – Vivianne Malmström, Sweden
- Seed and soil model for autoimmunity in myositis – Hitoshi Kohsaka, Japan
- Non-immune mechanisms in myositis – Kanneboyina Nagaraju, US

SELECTED ABSTRACT:

- A new mouse model of spontaneous myositis: NOD mice with disrupted T cell co-stimulatory ICOS pathway - Gwladys Bourdenet, France
- Experimental myositis inducible with transfer of dendritic cells presenting a skeletal muscle C-protein derived CD8 epitope peptide – Naoko Okiyama; Japan

12.10 – 13.10 LUNCH

13.10 – 14.40 PATHOGENESIS (2)
Chairs: Lars Klareskog, Sweden, Britta Maurer, Switzerland

- Muscle specific autoantibodies in Inclusion body myositis - Ger Pruijn, Netherlands
- Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis - Olivier Benveniste, France
- HMGCR and its role in the pathogenesis of inflammatory myopathies - Andrew Mammen, US

SELECTED ABSTRACT:

- Auto-antibodies in necrotizing autoimmune myopathies: from diagnosis to pathogenicity - Olivier Boyer, France
- A novel mouse model of chronic myositis triggers protein aggregation reminiscent of inclusion body myositis (IBM) - Judith Bauer, Germany

14.40 – 15.10 COFFEE AND POSTER VIEWING

15.10 – 16.30 CLASSIFICATION AND DIAGNOSIS OF MYOSITIS
Chairs: Rohit Aggarwal, US, Jan De Bleecker, Belgium

- New Classification criteria for myositis - Ingrid Lundberg, Sweden
- Diagnostic/classification criteria for inclusion body myositis - David Hilton Jones, UK

SELECTED ABSTRACT:

- Increasing incidence of immune mediated necrotizing myopathy, anti-HMGCR antibodies and statin use – single centre experience – Martin Klein, Czech Republic
- Pathogenicity of anti-HMGCR auto-antibodies in necrotising autoimmune myopathy – Cecile Bergua, France

16.40 – 18.00 POSTER SESSION (1) WITH POSTER TOURS
Poster tour leaders: Robert Cooper, UK, Hitoshi Kohsaka, Japan, Kanneboyina Nagaraju, US, Ger Pruijn, Netherlands, Lisa Christopher-Stine, US

Posters # 1- 45

- GENES AND ENVIRONMENT
- PATHOGENESIS (1)
- PATHOGENESIS (2)
- AUTOANTIBODIES
- OUTCOME and OUTCOME MEASURES

18.00 – 18.45 WORKSHOPS
(c) Standards of Treatment for Adults with Myositis and different Phenotypes (STAMP) – Neil McHugh, UK

19.00 DINNER AT RADISSON BLU ROYAL PARK HOTEL, STOCKHOLM

Sunday May 10

08.30 – 10.00 DIAGNOSTIC TOOLS AND OUTCOME MEASURES IN MYOSITIS
Chairs: Neil Mc Hugh, UK, Antonella Notarnicola, Sweden

- Myositis specific autoantibodies – Zoe Betteridge, UK
- Muscle biopsy features and standardization of biopsy evaluation - Jan De Bleecker, Belgium
- Imaging a tool in diagnosis and as an outcome measure in myositis – Marianne de Visser, Netherlands

SELECTED ABSTRACT:

- Evaluation of dysphagia in IBM by novel real-time MRI - Jens Schmidt, Germany
- Biomarkers for Sub-Phenotyping of Juvenile Dermatomyositis - Claire Deakin, UK

10.00 – 10.30 COFFEE AND POSTER VIEWING

10.30 – 12.00 CLINICAL PHENOTYPES AND PATHOGENESIS OF MYOSITIS
Chairs: Paul Plotz, US, Louise Diederichsen, Denmark

- Dermatomyositis clinical and autoantibody features- Victoria Werth, US
- Clinical phenotypes of Juvenile Dermatomyositis- Lisa Rider, US
- Pathogenesis in juvenile Dermatomyositis – Lucy Wedderburn, UK

SELECTED ABSTRACT:

- Cancer and necrotizing immune myopathy: high incidence in anti-HMGCR positive and seronegative patients but not in anti-SRP positive patients - Yves Allenbach, France
- Characterization of autoantibodies directed against transcription intermediary factor 1-gamma (TIF1gamma) in patients with dermatomyositis. - Audrey Aussy, France

12.00 – 13.00 LUNCH

13.00 – 14.00 THE LUNG IN MYOSITIS
Chairs: Øyvind Molberg, Norway, Lisa Christopher-Stine, US

- Clinical features and management of ILD in myositis – Rohit Aggarwal, US
- Lung as a target of the immune activity in myositis – Inka Albrecht, Sweden

14.00 – 14.30 COFFEE AND POSTER VIEWING

14.30 – 16.00 POSTER SESSION WITH POSTER TOURS
Poster tour leaders: David Hilton-Jones, UK, Chester Oddis, US, Øyvind Molberg, Norway, Victoria Werth, US

Posters #46- 84

- DIAGNOSTIC TOOLS AND OUTCOME MEASURES
- TREATMENT
- CLINICAL PHENOTYPES

16.00 – 18.15 INFORMAL DISCUSSIONS

18.45 RECEPTION AT STOCKHOLM CITY HALL
– Bus transfer at 18.00 from Radisson Blu Royal Park Hotel
– Bus transfer back to the hotel at 20.45

Monday May 11, 2015

08.30 – 10.00 UPDATE ON TREATMENT IN MYOSITIS
Chairs: Olivier Benveniste, France, Ingrid Lundberg, Sweden

- Update on pharmacological treatment in adult myositis – Chet Oddis, Pittsburgh, US
- Physical exercise in adult and juvenile myositis- Helene Alexanderson, Sweden
- Chinese multicenter study – Guochun Wang, China

SELECTED ABSTRACT:

- Gene expression profile in muscle tissue before and after immunosuppressive treatment in patients with myositis - Joan Raouf, Sweden

10.00 – 10.30 COFFEE

10.30 – 11.45 IMPROVEMENT CRITERIA AND PATIENT REPORTED OUTCOME MEASURES
Chairs: Marianne de Visser, Netherlands, Victoria Werth, US

- Improvement criteria for juvenile and adult inflammatory myopathies; background on the methodology - Lisa Rider, US
- Results - Jiři Vencovsky, Czech Republic
- Patient reported outcome measures - Lisa Christopher-Stine, US

11.45 – 12.30 OPEN DISCUSSION ON FUTURE PLANS IN MYOSITIS RESEARCH
- Lundberg IE, Rider L and Benveniste O

12.30 END OF MEETING - Ingrid Lundberg

Snacks available

Abstracts

First International Conference on MYOSITIS

1 STATIN-INDUCED MYOTOXICITY - EU PREDICTION-ADR PROJECT

DF Carr [1], T Van Staa [2], H Chinoy, [3], RG Cooper [1], J Fahy [1], A Hanson [1], M Wadelius [4], AH Maitland van der Zee [5], C Palmer [6], M Pirmohamed [1], A Alfirevic [1]

[1] University of Liverpool, UK,

[2] London School of Hygiene & Tropical Medicine, London, UK

[3] University of Manchester, Manchester, UK

[4] University of Uppsala, Sweden

[5] University of Utrecht, The Netherlands

[6] University of Dundee, UK

Background and objectives Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, are highly effective in reducing the risk for major cardiovascular events by lowering low-density lipoprotein cholesterol (LDL-C). Statins are the most commonly prescribed drugs in the US, and the number of patients treated with statins is increasing as a result of the new cholesterol treatment guidelines. However, approximately 5% of patients prescribed statins develop muscle related side effects which can range from mild pain and muscle weakness to rhabdomyolysis with renal failure. Therefore, an effective strategy to predict and prevent these reactions is needed. Genetic variants in several genes involved in statin pharmacokinetics have been associated with statin-induced myotoxicity. However, only the evidence supporting the statin uptake transporter SLCO1B1 polymorphisms in simvastatin-induced myotoxicity is sufficiently strong to be translated into clinical practice. The aim of the statin arm of PREDICTION-ADR is to investigate the contribution of rare genetic variants across the genome to statin myotoxicity, using next generation exome sequencing technologies. Participants and methods Pharmacogenetic research of statin-induced myotoxicity has been hampered by the lack of phenotypic definitions and therefore, we standardised the nomenclature for myalgia, myopathy, rhabdomyolysis and necrotizing autoimmune myopathy to facilitate recruitment1. Our recruitment target is 250 patients with severe phenotypes (defined as CK>4xULN +/- muscle symptoms concurrent with statin prescription) and 500 statin tolerant controls in the discovery cohort. Retrospective and prospective recruitment strategies include identification of eligible patients via the General Practice Research Datalink2, Yellow Card system for spontaneous reporting of ADRs, clinical laboratory registries, muscle clinics and research networks. Replication cohort is being identified via international collaborations. Results For the discovery cohort, a total of 102 statin-myotoxicity patients and 500 statin tolerant controls have been recruited from the UK and Sweden, which fulfil the definition of our standardised phenotype1. Adjudication of all cases is underway. Replication cohorts have been identified via research networks including the cohort of 128 statin myopathy patients, identified and recruited via the General Practice Research Datalink2. Conclusions To study genetic etiology of serious but rare statin myotoxicity, it is necessary to recruit patients using various strategies, including multicenter clinical trials, observational studies, electronic medical records linked to biological repositories and clinical research networks. To facilitate such multicenter research collaborations it is important to use agreed standardized phenotypes. 1. O'Meara H, et al. Br J Clin Pharmacol. 2014 May;77(5):831-8. 2. Alfirevic A, et al. Clin Pharmacol Ther 2014; 96(4): 470-6.

2 HLA analysis in idiopathic inflammatory myopathy identifies significant association of classical HLA alleles in polymyositis and dermatomyositis, and amino acids in inclusion body myositis

Simon Rothwell [1], John Bowes [1], Lucy Wedderburn [2], Robert Cooper [3], Hector Chinoy [1], Janine Lamb [1], UKMYONET , JDRG , EUMYONET, MYOGEN

[1] University of Manchester

[2] University College London

[3] University of Liverpool

Introduction: Results from the Immunochip experiment have revealed that the most associated region in idiopathic inflammatory myopathy is consistently within the major histocompatibility complex (MHC). Due to the complex linkage disequilibrium/haplotype structure in this region, interpretation of causal associations and independent effects using SNPs may be inadequate. Methods: SNP2HLA is a software package that imputes classical human leukocyte antigen (HLA) alleles and amino acids from SNP genotyping information.HLA imputation was carried out on Caucasian myositis samples that had been genotyped on the Immunochip array through the MYOGEN Consortium. Analysis was conducted on clinical myositis subgroups, polymyositis (PM) n=931, adult dermatomyositis (DM) n=879, juvenile dermatomyositis (JDM) n=479, and inclusion body myositis (IBM) n=252, with ancestry-matched shared controls n=15,651. Results: In PM cases, the most associated 4-digit allele was HLA-DRB1*03:01 (p=3.2x10-82). After conditioning on this, there was evidence of an independent association at HLA-B*08:01. In DM, the most associated 4-digit allele is HLA-B*08:01 (p=1.93X10-43). After conditioning on this, there was evidence of independent associations at the HLA-DQB1 locus. In JDM, an association with HLA-DRB1*03:01 was noticeably more modest (p=1.73X10-11) than in DM. The most associated allele in IBM is HLA-DRB1*03:01 (p=4.71X10-44), with strong independent effects at other DRB1 loci. When imputing the amino acids in HLA-DRB1, residues at position 13 and an independent association at position 70 in DRB1 are more significantly associated than a single classical HLA allele in the IBM subgroup. Conclusions: In PM, DM, and JDM, these results are consistent with previous reports that alleles of the 8.1 ancestral haplotype are most strongly associated with myositis. Due to the long range linkage disequilibrium in the MHC, it is hard to tease out which are the causal genes in this haplotype. Although the sample sizes are comparable, associations in PM seem to be stronger than in DM, which is also consistent with previous studies. In IBM, analysis of amino acid residues shows that the association may be driven by certain positions of the DRB1 gene rather than a classical HLA allele, as previously identified in other autoimmune diseases such as rheumatoid arthritis and psoriasis.

3 Long non-coding RNA expression profile in dermatomyositis: a microarray related study

Qinglin Peng [1], Xiaoming Shu [1], Xin Lu [1], Guochun Wang [1]

[1] China-Japan Friendship Hospital, Beijing, China

Background: Long non-coding RNAs (lncRNAs), a class of newfound noncoding RNAs greater than 200 nucleotides in length, are prevalently transcribed in the genome and have been found of crucial functional importance for disease. However, the potential roles of lncRNAs in dermatomyositis(DM) are poorly understood. Objectives: The aim of this study was to determine whether lncRNAs are differentially expressed in DM patients, and to investigate the expression pattern of lncRNAs in relation to mRNA expression profile. Methods: Total RNA was extracted from muscle tissue of 15 DM patients and 5 healthy controls. An lncRNA-mRNA microarray analysis was employed to determine the expression profile of lncRNA and mRNA. Bioinformatics prediction was applied to delineate the functional roles of the differentially expressed lncRNAs. Quantitative real-time PCR (qRT-PCR) analysis was conducted to validate the expression levels of several lncRNAs and mRNAs. Results: Using microarray analysis, we identified a total of 1198 lncRNAs and 1213 mRNAs were significantly differentially expressed in DM patients compared with the healthy control group (fold change2, P0.05, FDR0.05). Among them, 322 lncRNAs and 665 mRNAs were upregulated, while 876 lncRNAs and 548 mRNAs were found to be downregulated. Subgrouping DM patients according to the presence of interstitial lung disease (ILD) and anti-Jo-1 antibody revealed different expression patterns of lncRNAs, suggesting aberrantly expressed lncRNAs may be associated with ILD and anti-Jo-1 antibody. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis for the differentially expressed mRNAs indicated 10 pathways, including Cytokine-cytokine receptor interaction (ko04060), Toll-like receptor signaling pathway (ko04620). LncRNA-mRNA co-expression network was constructed for all significantly changed lncRNAs, which may be used for predicting target genes of lncRNAs. The results of target gene predicting revealed that the expression of 14 lncRNAs was significantly correlated to their nearby coding genes and may probably tareted to these coding genes. Interestingly, we found that the expression of lncRNA p33629 was significantly associated with highly expressed IFN-stimulated gene 15 (ISG15) and ubiquitin specific peptidase 18 (USP18) genes, which contribute to the type I interferon pathway. Conclusions: In conclusion, this is the first study demonstrated the lncRNA expression profile in muscle tissue of DM patients. We identified a series of DM associated lncRNAs, notably several lncRNAs probably invovled in the type I interferon pathway. Our findings of significantly changed expression pattern of lncRNAs indicated potential role of lncRNAs in DM and provided novel insights into the pathogenesis of DM.

4 PREVALENCE OF IDIOPATHIC INFLAMMATORY MYOPATHIES IN SWEDEN IN 2012 – A NATIONAL REGISTER STUDY

John Svensson [1], Marie Holmqvist [2], Anna Tjärnlund [1], Ingrid E Lundberg [1]

[1] Karolinska Institutet, Department of Medicine, Rheumatology Unit

[2] Karolinska Institutet, Department of Medicine, Clinical Epidemiology Unit

Background and Objectives Overall prevalence of idiopathic inflammatory myopathies (IIM) is commonly reported at 10 per 100 000 but worldwide estimates varies between 1 and 25 per 100 000 depending on region, population, sub-diagnosis, methodological considerations and case sources. In this study we aimed at determining the prevalence of IIM in Sweden on January 1st, 2012 using population based registers. Materials and Methods Linking of multiple national registers were possible using each Swedish resident's unique personal identification number. Through this linkage we identified all individuals with an inpatient- or non-primary outpatient visit with ICD-10 code indicating IIM, relevant IIM medication dispensation and registration in the Swedish Rheumatology Quality Register (SRQ). IIM cases were defined by three progressively strict definitions; (1) liberal requiring 1 ≤ relevant specialist1 visit, (2) base case requiring 2 ≤ specialist visits and (3) strict also requiring 30 days between two visits and IIM drug dispensation while SRQ registered cases fulfilled all definitions. Prevalence was calculated overall for respective case definition and stratified by age group, sex, clinical sub-diagnosis and county of residence for the base case definition. Corresponding Swedish population as of January 1st 2012, retrieved from census data at Statistics Sweden, were used in the denominator. Results Overall prevalence varied between 35 (liberal), 19 (base case) and 13 (strict) per 100 000. Overall female to male ratio was 1.4 and varied between 0.6, for inclusion body myositis (IBM), to 2.6, for juvenile dermatomyositis (JDM). Prevalence per clinical sub-diagnosis was 7, 6, 4, 2 and 1 per 100 000 for polymyositis (PM), unspecified, dermatomyositis (DM), IBM and JDM respectively. Prevalence increased by increasing age group: 4, 15 and 48 per 100 000 for 0-14, 15-64 and 65+ years respectively and also varied between the 25 different Swedish counties of residence (between 11 and 24 per 100 000 for Gotland and Västmanland county respectively). Conclusions Calculated base case definition prevalence is higher than what have been historically reported for IIM but corresponds well to recent results from large register studies. One of the greatest challenges with this study was to determine which ICD-10 codes correspond to, primarily IIM, but also to correct clinical subgroup. 1 Rheumatologist, neurologist, internal medicine, pediatric, dermatologist

5 ASSOCIATIONS OF SNPS IN THE BAFF GENE WITH IDIOPATHIC INFLAMMATORY MYOPATHIES IN HLA-DRB1*03 NEGATIVE PATIENTS

Olga Krystufkova [1], Tana Svitalkova [1], Martina Remakova [1], Lenka Plestilova [1], Herman Mann [1], Martin Klein [1], Peter Novota [1], Jiri Vencovsky [1]

[1] Institute of Rheumatology and Department of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Background and objectives: B-cell activating factor of the TNF family (BAFF) plays a role in (auto)antibody production. Patients with idiopathic inflammatory myopathies (IIMs or myositis) have elevated levels of BAFF in the serum which associate with disease activity. We have previously found an association between TTTT haplotype from the four single nucleotide polymorphisms (SNPs) in the promoter region of BAFF gene (rs9514827, rs3759467, rs1041569 and rs9514828) with presence of myositis in our cohort of IIM patients. The HLA-DRB1*03 allele is a well-known genetic risk factor for myositis in Caucasians. In this study we have analysed the possible interference of HLA-DRB1*03 allele with the presence of the particular SNPs of BAFF gene in patients with myositis. Materials and methods: The SNPs (rs9514827, rs3759467, rs1041569 and rs9514828) were analysed by direct DNA sequencing in a cohort of 311 patients with myositis (age 5-80 years, females 74%) and in 113 healthy controls (age 18-79 years, females 69%). The HLA-DRB1 genotyping with PCR using sequence-specific oligonucleotide and sequence based typing technique was available in the subgroups of 297 patients and 103 controls. The ÷2 or Fisher tests for analysis of allelic, haplotype and genotype associations with Bonferroni's correction were used. Results: The four BAFF SNPs were in strong linkage disequilibrium and formed four common haplotypes (TTAC, CTAT, TCAC, TTTT) in both IIM patients and controls, compatible with already reported results. A significantly higher frequency of the TTTT haplotype was present in myositis patients (16%) compared to healthy controls (10%; OR=1.65, 95%CI=1.03-2.65; p0.05). There were no significant differences between patients and controls in the frequencies of alleles and genotypes. 162 IIM patients (55%) and 87 healthy controls (84%) were HLA-DRB1*03 negative and a significant association of the TTTT haplotype in IIM patients was confirmed by a higher frequency (19%) compared to controls (11.5%; OR=1.79, 95%CI=1.04-3.07; p0.05) within the DRB1*03 negative cohorts. The trend for higher frequency of -2701 T allele and TT or AT genotypes (rs1041569) in myositis was more pronounced within the HLA-DRB1*03 negative groups. IIM patients had a significantly higher proportion of -2701 genotypes containing T allele (38%) compared to controls (23%; OR=2.07, CI=1.15-3.75; p0.05). Conclusions: The associations of TTTT haplotype with myositis and a higher frequency of -2701 T allele and TT or AT genotypes in patients with IIM are independent from the presence of HLA-DRB1*03 risk allele. Acknowledgements: MZCR-Institutional support of research organisation-00023728 (Institute of Rheumatology); IMI-funded project BeTheCure-115142-2

6 BsmI B/b and Fok I F/f Vitamin D receptor gene polymorphisms in Bulgarian patients with dermatomyositis

Lyubomir Dourmishev [1], Gyulnas Dzhebir [2], Maria Hristova [3], Alexey Savov [4], Anton Vinkov [5], Radka Kaneva [6], Vanio Mitev [6], Zornitsa Kamenarska [6]

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Background: Historically, vitamin D has been associated with the regulation of bone metabolism. However, increasing evidence demonstrates a strong association between vitamin D signaling and immune responses. The aim of the case-control study was to investigate the association between the Vit D receptor gene (VDR) BsmI B/b (A/G substitution) and FokI F/f (C/T substitution) polymorphisms and the susceptibility to dermatomyositis in Bulgarian patients. Methods: Thirty five patients who met the modified Bohan and Peter's criteria for dermatomyositis as well as 98 unrelated healthy controls were included in this study. The analysis of VDR BsmI B/b (A/G substitution, rs1544410) and FokI F/f (C/T substitution, rs2228570) were performed by using PCR-RFLP genotyping assay. Results: The VDR BsmI Bb+bb genotypes and the b allele were found associated with DM (Bb+bb-p=0.05, OR 2.2, CI 1-4.9; f-p=0.007, OR 2.4, CI 1.2-4.5). An association was found between the Ff+ff genotypes and the f allele and DM (Ff+ff-p=0.04, OR 2.14, CI 0.98-4.7; f-p=0.03, OR 1.9, CI 1-3.6) as well. Conclusion: The results indicate that the VDR BsmI B/b and Fok I F/f polymorphisms might play a role in the susceptibility of DM.

7 PROTEIN-PROTEIN INTERACTION ANALYSIS REVEALS POSSIBLE ROLE OF TRAF6 IN MYOSITIS

Joanna Parkes [1], Simon Rothwell [2], Philip Day [1,3], Neil McHugh [4], Zoë Betteridge [4], Robert Cooper [5], William Ollier [1,] Hector Chinoy [2], Janine Lamb [1] MYOGEN, EUMYONET

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Background and Objectives Little is known about relevant biological pathways in myositis pathogenesis. Myositis specific autoantibodies (MSAs) target proteins which may be involved in these pathways. Immunochip work (unpublished) also highlights SNPs associated with disease. In complex genetic as well as Mendelian disease, it is likely that associated regions have physical interactions between their gene products. This study aims to analyse protein-protein interactions (PPI) between antigens targeted by MSAs and SNP-associated gene products to identify pathways which may be relevant to disease. Materials and Methods The Disease Association Protein-Protein Link Evaluator (DAPPLE) tool was used to create and statistically analyse networks formed by 36 MSA target protein alone and alongside 21 lead SNPs previously identified from the MYOGEN Immunochip analysis of idiopathic inflammatory myopathy (IIM), including the polymyositis and dermatomyositis subgroups. Lead SNPs were defined as the most significantly associated SNP from each locus exceeding a suggestive level of significance (p2.25 x 10-5) and then used by DAPPLE to nominate candidate genes within each locus. 20,000 permutations were used to derive p values. Results Networks formed from MSA targets only and MSA targets combined with myositis associated SNPs had significant direct and indirect connectivity ($p \leq 0.000051$). For MSA targets alone, 21/36 were identified as significant; for the combined analysis 21/57 genes/proteins were significant. TNF receptor-associated factor 6 (TRAF6) was identified as a significant candidate protein derived from a lead IIM SNP. TRAF6 acted as a hub for the direct and indirect networks generated by DAPPLE. TRAF6 brought together five out of eight separate networks generated by analysis of the MSAs alone (TRIM33-TRIM24-TRIM28; UBA2-SAE1; HARS-TARS; GARS-IARS-NARS and the EIF3 network) as well as linking to many of the candidate genes derived from lead SNPs. Conclusions The generation of significant PPI networks from MSAs and myositis associated SNPs highlights several proteins and pathways that could be related to myositis pathogenesis. In particular, the interaction of TRAF6 with other myositis associated gene products and MSA antigens warrants further investigation. TRAF6 mediates the activation of the NF-kB, MAPK and interferon regulatory factor pathways and blocking of TRAF6 has been found to inhibit pro-inflammatory responses. TRAF6 has previously been linked to inflammation and autoimmunity in diseases such as rheumatoid arthritis and systemic lupus erythematosus. Further work including analysis of gene expression and ontology is required to see if these interactions are likely to impact myositis pathology.

8 A novel mouse model of chronic myositis triggers protein aggregation reminiscent of inclusion body myositis (IBM)

Judith Bauer [1], Monika Wolf [2], Thomas Blank [3], Juliane Bremer [4], Regina Reimann [5], Renaud Maire [2], Elisabeth Rushing [5], Veronika Kana [5], Marco Prinz [3] , Adriano Aguzzi [5] , Mathias Heikenwälder [1]

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Introduction: Inflammatory myopathies (IM) show chronic skeletal muscle inflammation accompanied by myopathic changes. However, only entities of autoimmune origin (dermatomyositis and polymyositis) respond to anti-inflammatory therapy (e.g., corticosteroids). In order to elucidate the influence of inflammation on skeletal muscle tissue homoeostasis, we generated a mouse model of chronic myositis. Methods: Samples of human IM patients were analyzed for the expression of LTs and activation of LTbR downstream signaling pathways. Transgenic mouse lines overexpressing lymphotoxin (LT) alpha and beta specifically in skeletal muscle were generated (HSA-LTab). Analyses included histology, RNA and protein expression analysis, muscle function, body and muscle weight and muscle volumetry. HSA-LTab transgenic mice were intercrossed with autophagy deficient mice. Results: Expression of LTa, b and the activation of LTbR downstream target gene expression (e.g. CCL17) were found in samples of human IM. HSA-LTab mice displayed infiltration of immune cells, expression of various cytokines, chemokines and the activation of downstream signaling-pathways similar to IM patients. Reduced body and skeletal muscle weight was found in HSA-LTab mice. Functional analyses revealed decreased muscle function. Notably, upregulation of MHCI on muscle fibers and decreased fiber size was observed in aged animals. Importantly, HSA-LTab mice developed protein aggregates in myofibers reminiscent of human IBM. The appearance of protein aggregates correlated with the induction of autophagy. Additionally, backcrossing with autophagy deficient mice severely aggravated and accelerated the described phenotypes. Discussion: Overexpression of LT, an inflammatory mediator found in IM patients, in murine muscle caused chronic myositis accompanied by protein aggregation. HSA-LTab mice displayed IM, atrophic fibers, and MHCI+ fibers. Chronic inflammation induced the spontaneous aggregation of proteins found in IBM (e.g. ubiquitin, p62 and TDP43). Autophagy was protective in this setting, as backcrossing with autophagy deficient mice aggravated and accelerated the initially observed phenotypes. We therefore demonstrate that chronic myositis triggered by constitutive non-canonical NF-kb signaling suffices to cause myopathic changes including protein aggregation reminiscent of IBM, independent of autoimmune reactions in vivo. Blocking of LT mediated signaling (e.g. by Barminercept) may provide a new therapeutic option for resistant IMs, such as IBM.

9 EXPERIMENTAL MYOSITIS INDUCIBLE WITH TRANSFER OF DENDRITIC CELLS PRESENTING A SKELETAL MUSCLE C PROTEIN-DERIVED CD8 EPITOPE PEPTIDE

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Background and Objectives: It is suggested that polymyositis, an autoimmune inflammatory myopathy, is mediated by autoaggressive CD8 T cells. Skeletal muscle C protein is a self-antigen that induces C protein-induced myositis, a murine model of polymyotitis. The objective was to establish a new murine model of myositis inducible with a single CD8 T cell epitope peptide that derives from C protein. Materials and Methods: Three internet-based prediction systems were employed to identify 24 candidate peptides of the immunogenic fragment of the C protein that bind theoretically to major histocompatibility complex (MHC) class I molecules of C57BL/6 (B6) mice. RMA-S cell assay was performed to observe which peptide(s) had affinity to the H2-Kb molecules. After naïve B6 mice were transferred with mature bone marrow-derived dendritic cells (BMDCs) pulsed with candidate peptide(s), the muscle sections of the recipient mice were graded according to the histological severities of inflammation and immunohistologically stained with anti-CD4 and CD8a antibodies. The mice with experimental myositis were treated with anti-CD8 depleting antibodies or anti-CD4 depleting antibodies. Results: RMA-S cell assay revealed that a HILIYSDV peptide, amino acid position 399 – 406 of the C protein, had the highest affinity to the H2-Kb molecules. Transfer of BMDCs pulsed with HILIYSDV induced myositis in B6 mice 7 days after the transfer. Mice transferred with BMDCs pulsed with 3 other candidate peptides developed no myositis. Furthermore, mice developed myositis with lower incidence and less severity after transfer of BMDCs pulsed with a mixture of HILIYSDV and the 3 candidate peptides than those treated with transfer of the HILIYSDV-pulsed BMDCs. Mice with transfer of the 3 other candidate peptides-pulsed BMDCs barely developed myositis in the same level as those with transfer of unpulsed BMDCs. While both CD4 T cells and CD8 T cells infiltrated in the muscles of the recipient mice with HILIYSDV-induced myositis, which we termed C-protein peptide-induced myositis (CPIM), this myositis was suppressed by anti-CD8 depleting antibodies but not by anti-CD4 depleting antibodies. Conclusions: These results argue that HILIYSDV is a peptide with especial immunogenicity to induce CPIM among the candidate peptides selected by RMA-S assay, and that the three other peptides are not immunogenic, and should have antagonized the effects of HILISDV inducing CPIM. Because CPIM is mediated by CD8 T cells independently of CD4 T cells, it should be a useful tool to investigate pathology of polymyositis and develop therapies targeting CD8 T cells.

10 Interferon-gamma but not interleukin-4 restrains experimental myositis

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Background and Objectives. C protein-induced myositis (CIM) is a mouse model of polymyositis, in which activated antigen-specific CD8+ T cells injure the muscles. Autoimmune animal models examined in the past for the effects of type-1 and type-2 cytokines, interferon (IFN) -γ and interleukin (IL) -4, are all mediated by pathogenic CD4 T cells. In those models, the disruption of IFNγ leads to upregulation of IL-17A, exacerbating the diseases with neutrophil infiltration into the inflammatory sites. The purpose of the study is to study the roles of IFN-γ and IL-4 as well as IL-17A in the absence of IFN-γ in the CD8 T cell-mediated CIM. Methods. IFNγ -null, anti-IL-17A antibody-treated IFNγ -null, IFNγ /IL-17A double-null, IL-4-null, and wild-type C57BL/6 mice were immunized with skeletal muscle C protein fragments to provoke CIM. The muscle tissues were examined histologically. Results. IFNγ -null mice developed myositis with the higher incidence and severity than wild-type mice. Unlike the wild-type mice, they had infiltration of neutrophils into the endomysial sites of the affected muscles. IFNγ-null mice treated with anti-IL-17A antibodies and IFNγ /IL-17A double-null mice developed myositis with the incidence and severity comparable to those of the IFNγ-null mice. Neutrophils infiltrated as in the IFNγ -null mice. IL-4-null mice developed CIM comparable to that of the wild-type mice. Conclusions. IFNγ but not IL-4 has a protective role in the development of CIM. Unlike CD4 T cell-mediated autoimmune disease models, IFNγ prevents factors other than IL-17A from exacerbating myositis and neutrophil infiltration.

11 Injury and Subsequent Regeneration of Muscles Activate Local Innate Immunity to Facilitate Development and Relapse of Autoimmune Myositis

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[Background and Objectives] In the development and relapse of autoimmune myositis, local innate immunity in muscle tissues needs to be activated. The purpose of this study was to discern if injury and subsequent regeneration of the skeletal muscles induce inflammatory milieu that can facilitate development and relapse of autoimmune myositis. [Materials and Methods] The quadriceps of C57BL/6 mice were injured with bupivacaine (BPVC) and evaluated histologically. After 3 days, macrophages in the treated muscles were collected and examined for cytokine expression with reverse transcriptase-polymerase chain reaction. Cytokine production by regenerating muscle fibers and differentiating C2C12 myotubes was evaluated with immunohistochemistry and enzyme-linked immunosorbent assay. Mice were immunized with C protein fragments at the tail bases and right hind footpads (day 0) to evoke systemic anti-C-protein immunity and to induce local myositis in the right hind limbs. The contralateral quadriceps were injured with BPVC or phosphate buffered saline (PBS) at day 7, or after spontaneous regression of myositis (day 42). The quadriceps from the unimmunized mice were injured with BPVC at day 7. The muscles were examined histologically 14 days after the treatments. [Results] The muscles had infiltration of macrophages most abundantly at 3 days after the BPVC injection with emergence of regenerating fibers from 5 days. The macrophages expressed inflammatory cytokines including TNFα, IL-1β and CCL2. In vivo regenerating fibers and in vitro differentiating myotubes also expressed the inflammatory cytokines. The BPVC-injected muscles from the unimmunized mice had regenerating fibers with resolved inflammatory cell infiltration 14 days after the treatment. In contrast, when mice were preimmunized with the C protein fragments, the muscles injured with BPVC, but not with PBS, at day 7 as well as at day 42 accompanied myositis with CD8+ T cell infiltration. [Conclusions] Injury and regeneration could set up inflammatory milieu in the muscles and facilitate development and relapse of autoimmune myositis.

12 ANALYSIS OF THE AUTOANTIBODY REPERTOIRE IN IDIOPATHIC INFLAMMATORY MYOPATHIES USING ANTIGEN BEAD ARRAY

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Background: The Idiopathic Inflammatory Myopathies (IIM), including Polymyositis (PM), Dermatomyositis (DM) and Inclusion Body Myositis (IBM), are a group of rare systemic inflammatory diseases often associated with severe organ manifestations and premature mortality*. The identification of new biomarkers is needed to understand underlying biological pathways, improve diagnosis, predict prognosis and tailor treatment to the single patient. Objectives: We investigated EDTA-plasma samples of IIM patients and healthy controls (HC) to discover new myositis- associated auto-antigens. Methods: Planar antigen microarrays consisting of 5760 human protein fragments were used for the screening of IgG reactivity in 160 samples of patients with Systemic Lupus Erythematosus (SLE)**. A set of 355 antigens (Ag) was selected for verification on suspension bead array using 695 SLE samples and 278 IIM samples. The IIM samples were collected from a cohort of 245 IIM patients (91 DM, 125 PM and 29 IBM) regularly followed at the Rheumatology Unit of the Karolinska University Hospital from January 2003 until March 2014. Twenty-eight IIM patients tested positive for anti- hystidyl-tRNA-synthetase antibodies (anti-Jo-1) and 217 were anti Jo-1 negative. Samples from 41 HC were also analysed. Results: Reactivity towards 70% of the 355 selected Ag was observed in more than 2% of both IIM and HC samples. Comparing the IIM and the HC groups according to the number of samples which showed reactivity towards each single Ag, reactivity towards 3 Ag was discovered with higher frequencies in the IIM samples (Fisher exact test, p0.05). We also compared each IIM subset and HC. A higher number of DM and PM samples versus HC showed reactivity towards 4 and 3 Ag, respectively. No statistically significant difference was observed between IBM and HC samples for any of the 355 Ag. Making 2 group comparisons between DM/PM/IBM subsets, a statistically significant different reactivity profile was found for 1 Ag between DM and PM, 3 Ag between DM and IBM and 4 Ag between PM and IBM. The number of reactive samples towards 5 Ag was significantly higher in the anti-Jo-1 positive compared to the anti-Jo-1 negative patients. Conclusions: Auto-antigen reactivity was present both in IIM and HC samples. IIM and HC samples showed different frequencies of reactivity towards some of the selected Ag. A validation analysis is ongoing to confirm our preliminary results.

13 THE NKG2D PATHWAY AND ITS ROLE IN THE PATHOGENESIS OF INFLAMMATORY MYOPATHIES

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Background/Objectives: NKG2D is a costimulatory receptor on NK and T cells, which has been previously shown to be important in the pathogenesis of several autoimmune diseases. The NKG2D ligands are stress-inducible and can be expressed by various cell types. Through the expression of costimulatory molecules aside from cytokines, chemokines, major histocompatibility complex (MHC) muscle cells actively participate in immune reactions. In this respect we here aim to elucidate the putative pathogenic role of the NKG2D pathway in inflammatory myopathies, especially in polymyositis. Materials and Methods: Primary human myoblasts, blood and muscle biopsy specimens of healthy donors (HD) and polymyositis (PM) patients were investigated by FACS, ELISA, PCR and immunofluorescence staining. Results: NKG2D ligands are expressed on primary human myoblasts. They are found upregulated upon inflammatory stimuli paralleled by reduced production of shedded MICA (sMICA) ultimately leading to diminished inhibition of NKG2D signaling. In vitro co-culture experiments of CD8 T cells and myoblasts revealed an IL-15 dependent upregulation of NKG2D and cytolytic enzymes in CD8 cells. IL-15 pre-stimulated CD8 cells are able to lyse myoblasts in a NKG2D-dependent manner. However, there are no significant changes of sMICA levels or NKG2D expression in the peripheral blood of PM patients compared to HD. In contrast, immunofluorescence staining demonstrated an expression of the NKG2D ligand MICA/B in muscle biopsy specimens of PM patients but not in HD. Conclusions: Muscle cells critically influence immunological processes through NKG2D-mediated interactions with immune cells. The dysregulation of this pathway might be involved in the pathogenesis of PM possibly opening new therapeutic avenues. Further studies are needed to extend our findings to other inflammatory myopathies.

14 OVEREXPRESSION OF MHC I (H-2KB) IN C2C12 MYOTUBES RESULTS IN ER STRESS-MEDIATED SECRETION OF MUSCLE-DERIVED CYTOKINES (MYOKINES)

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Background & Objectives: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare autoimmune disorders, which primarily target skeletal muscle. IIM can be sub-classified into polymyositis (PM), dermatomyositis (DM) and inclusion-body myositis, with further clinical sub-types associated with malignancy and interstitial lung disease. Patients present with symmetrical proximal muscle weakness, elevated serum muscle enzymes and significant immune cell infiltrations into muscle (CD8+, CD4+ T-cells, B-cells and macrophages). Up-regulation of MHC-I in vitro and in vivo is also a characteristic histological finding, and is associated with activation of the Endoplasmic Reticulum (ER) stress response; while pharmacological activation of the ER stress response results in increased expression of pro-inflammatory muscle-derived cytokines (i.e myokines). Based on recent research suggesting that skeletal mu scle can act as a source of diverse cytokines, we interrogated whether induced MHC-I overexpression in myotubes would result in ER stress pathway activation, and release of myokines. Materials & Methods: C2C12 myotubes were transfected using Lipofectamine2000TM with a MHC I (H-2kb) overexpression vector in the presence of Salubrinal, an ER stress response blocker. Successful transfection and upregulation of the H-2kb gene was confirmed by qPCR. Activation of the ER stress response was determined by qPCR and/or western blotting. Cytokine release from transfected C2C12 myotubes was assessed by Luminex mutliplex analysis. Results: Transfection of C2C12 myotubes resulted in increased MHC I gene expression, as well as activation of the ER stress pathway, the latter as evidenced by elevated Grp78, CHOP expression and X-box binding protein (XBP-1) splicing. Elevated levels of IL-6, CCL2/MCP-1, CCL4/MIP1β and CCL5/RANTES were released from C2C12 myotubes following transfection, chang es which were ablated when myotubes were transfected in the presence of Salubrinal. Conclusions: MHC-I overexpression causes activation of the ER-stress response and pro-inflammatory cytokine release from C2C12 myotubes, a process prevented by attenuation of the ER stress response with Salubrinal. These data suggest that MHC I overexpression induces muscle to act as a proinflammatory organ in the absence of immune cells. This MHC-1 induced myokine production may also play a chemotactic role, e.g to encourage immune cell infiltrations into muscle. Attenuation of myokine release may represent a worthwhile therapeutic strategy to minimise inflammatory cell infiltrations into IIM muscle. The authors would like to thank Myositis UK and the University of Liverpool for their generous financial support.

15 Modulation of ER-stress by methylene blue in a model of Inclusion Body Myositis (IBM)

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Objective: Inclusion Body Myositis (IBM) is characterized by a progressive muscle weakness and atrophy. Due to a lack of a precise understanding of the IBM pathophysiology, a sufficient treatment is not available. The pathology includes mononuclear cell inflammation and accumulation of degeneration-associated proteins such as beta-amyloid. Non-adaptive immune mechanisms have been identified to be responsible for skeletal muscle dysfunction. In particular, endoplasmic reticulum (ER) stress might contribute to disease progression. We studied relevant molecular mechanisms of the unfolded protein response and their implications for muscle inflammation. Finally, we tested methylene blue (MB) as a therapeutic strategy that interferes with the ER-pathway. Methods: In vitro, myoblasts and primary human myotubes were exposed to the pro-inflammatory cytokines IFN-gamma + IL-1beta. Using quantitative polymerase chain reaction, the most relevant ER-stress markers, x-box-binding-protein 1 spliced (XBP1s), glucose-related protein 94 (Grp94), phospho-PERK as well as inflammatory markers such as IL-1beta and the degeneration-associated markers APP and beta-amyloid were analyzed. The corresponding proteins were detected by western blot and/or immunocytochemistry. MB, an anti-aggregation and nitric oxide (NO)-modulating drug was applied to the muscle cells. In addition to makers for ER-stress, inflammatory and NO-stress markers including immunocytochemical detection of nitrotyrosine were studied. Results: mRNA expression of the ER-stress markers XBP1s and Grp94 were significantly higher in IFN-gamma + IL-1beta exposed muscle cells compared to controls. At the protein level, IFN-gamma + IL-1beta enhanced the phospho-PERK expression in myoblasts as reflected by Western blot. MB significantly diminished the mRNA expression of XBP1s and the phosphorylation of PERK as identified by Western blot. Immunostaining for major histocompatibility complex I (MHC-I) and intracellular NO-production was diminished. Moreover, amyloid accumulation visualized by thioflavine S-staining was significantly reduced by MB. Conclusions: Using an established cell culture model for myositis, the results demonstrate that ER stress-response induced by inflammation and accompanied by protein accumulation in skeletal muscle is a new major non-immune mechanism of chronic muscle inflammation as in IBM. MB prevented ER-stress as well as amyloid aggregation, NO-stress and inflammation. MB may have a therapeutic potential in patients with IBM.

16 Pathogenicity of anti-HMGCR auto-antibodies in necrotising autoimmune myopathy

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Background and objective. Necrotizing autoimmune myopathies (NAM) constitute a newly recognized group of severe acquired myopathies characterized by pathological features of myofiber necrosis without significant inflammation. NAM may be associated to auto-antibodies (aAbs) against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), notably in statin users. The statins target, HMGCR, is an endoplasmic reticulum membrane-located enzyme involved in cholesterol metabolism. Since its expression is ubiquitous, the role of anti-HMGCR aAbs in NAM remains elusive. We investigated the pathogenic role of anti-HMGCR aAbs in a new in vivo mouse model. Methods. IgGs were purified from the serum of anti-HMGCR aAb-positive patients. These IgGs were transferred to C57BL/6 receiving a single course of cyclophosphamide, or to immuno-deficient Rag-/- mice. Alternatively, mice were immunized with rhHMGCR plus a TLR9 agonist as adjuvant. Clinical status was assessed by grip test performance, locomotor activity and motor performance (Catwalk). Muscle sections were analysed after hematoxylin/eosin staining, or after anti-hIgG or anti-C5b-9 immunofluorescent labeling. Label-free proteomic analysis of muscle protein extracts was performed using Orbitrap. Results. Injection of anti-HMGCR-positive IgGs resulted in a significant decrease in muscle strength whereas IgG-depleted patients' plasma or IgGs from anti-HMGCR-negative control patients had no effect. Histologically, this was associated with moderate myofiber necrosis, and hIgG and C5b-9 deposits on myofibers. The muscle holoproteome at day 8 after transfer was profoundly modified as compared to mice receiving control IgGs, showing increased muscle regeneration- and metabolism-related proteins. Muscle deficiency effect was transient in immunocompetent mice that developed a xeno-immune response against hIgG. In contrast, it was prolonged in immunodeficient Rag-/- animals. Immunization with rhHMGCR also led to impaired muscle strength. Conclusions. Anti-HMGCR aAbs are directly involved in disease pathogenesis. It is unlikely that antibody-dependent cell cytotoxicity plays a significant role in this model since we did not observe inflammatory cell infiltrates. Rather, hIgG and C5b-9 deposits suggest a role for the classical complement pathway. These results support further evaluation of plasma exchange and/or B cell-targeted therapy in anti-HMGCR-associated NAM.

17 A new mouse model of spontaneous myositis: NOD mice with disrupted T cell co-stimulatory ICOS pathway

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Background and objectives: The lack of animal model of spontaneous myositis has hampered pathophysiological studies and therapeutic development. T cell activation requires cognate recognition of peptide-MHC complexes by the TCR (signal 1) and co-stimulation through pathways such as CD28/CD80 or ICOS-ICOSL (signal 2). NOD mice spontaneously develop an auto-reactive response toward pancreatic islets and provide a canonical model of auto-immune diabetes. We observed that, when invalidated for the ICOS-ICOSL pathway, NOD mice became protected from diabetes but secondarily developed a severe disease affecting the neuromuscular system. The aim of this study was to characterize muscle disease in this model and establish whether it may represent a new paradigm of myositis. Materials and methods: Clinical status was assessed by grip test performance and behavioral analysis (Catwalk), permitting to measure both forced and spontaneous locomotor activities. Histological sections of muscle were analyzed after hematoxylin/eosin staining or CD4, CD8, CD11b, H-2Kd immunofluorescent labeling. Adoptive cell transfer was performed by injecting Icos-/- NOD splenocytes or subsets into NOD.scid recipients. Auto-antigen discovery was attempted by incubating Icos-/- or Icosl-/- NOD serum with either Icos-/-, Icosl-/- NOD or NOD membrane-transferred 2D-gel separated muscle protein extracts followed by MS/MS identification. Results: Muscle grip strength was significantly decreased in both Icos-/- and Icosl-/- NOD mice, as compared to age-matched NOD controls. Because the grip test only assesses forced activity, a more thorough behavioral analysis was performed using a Catwalk apparatus. This confirmed locomotor disability with impaired cadence. Muscle damage initially affected the front paws, with significantly lower paw contact intensity and print area. Pathological analysis revealed the presence of necrotic myofibers, important inflammatory infiltrates (CD4+, CD8+ T cells, myeloid cells) and MHC class I re-expression, three hallmarks of human myositis. Disease was conferred to NOD.scid recipients by T cell adoptive transfer. Because human myositis may involve cellular but also humoral auto-immunity, auto-antibodies were sought for. MS/MS analysis of immuno-reactive proteins recognized by both Icos-/- and Icosl-/- NOD mouse serum allowed identification of four potential auto-antibodies. Conclusions: Muscle deficit and pathological findings closely resemble those observed in human myositides such as polymyositis or dermatomyositis. Icos-/- and Icosl-/- NOD mice offer a unique model of spontaneous myositis that should be instrumental to help decipher the pathophysiological mechanisms of disease. Since they do not rely on immunization with selected auto-antigens, they are not antigenically biased. We believe that they represent good candidates to discover new therapeutic targets and evaluate candidate therapies.

18 Evidence for the involvement of NK cells and NKp30 natural cytotoxicity receptor in Antisynthetase Syndrome

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Antisynthetase syndrome (aSS) is characterized by the association of interstitial lung disease and myositis with anti-tRNA-synthetase autoantibodies. Its pathogenesis remains unknown, especially regarding the involvement of NK cells. We describe the first phenotypic and functional characterization of NK cells in aSS: twenty patients with inactive and active aSS were included (women/men =9, median age=50 years) and compared to 20 controls. Freshly isolated NK cell phenotype was performed by flow cytometry. Polyfunctionality assays were performed to measure degranulation and intracellular production of TNFα and IFNγ, spontaneously or after stimulation by IL12 and IL18, in the presence of K562 or P815 target cells. Immunohistochemistry with anti-NKp46 antibody was used to locate and quantify NK cells in target tissues. NK cells from inactive patients showed normal phenotype, whereas active aSS revealed a di fferentiated NK cell profile, as indicated by a slight increased level of CD57 (p=0.09) and significantly increased ILT2 (p=0.02) associated with decreased CD161 (p=0.05) and NKp30 (p=0.009), compared to healthy controls. This is consistent with the inability of circulating NK cells of active aSS patients to produce IFNγ (p=0.002) after IL12+IL18 stimulation. The NKp30 down-modulation strongly correlated with the loss of NK cell functions against K562 (p=0.009). Furthermore, redirect killing assays against P815 target cells in the presence of activating anti-NKp30 antibody showed a significant decrease of IFNγ producing NK cells in aSS patients as compared to the controls (p=0.03). Histological studies reveal the presence of small numbers of NK cells in the muscles, as well as a massive presence of NK cells inside the lungs of aSS patients (148 vs 10/mm2). Taken together, these data argue for key role of NK cells and NKp30 in aSS pathogenesis.

19 From Immune mediated necrotizing myopathies to humoral mediated necrotized myositis: study of 44 anti-SRP and anti-HMGCR muscle biopsies

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Background and objectives: Immune mediated necrotizing myopathy (IMNM) has been recently added as a new entity among dermatomyositis, polymyositis and sporadic inclusion body myositis. IMNM is morphologically defined by predominant muscle fiber necrosis and no or few inflammatory infiltrates. Two auto-antibodies are held to be specifically associated with IMNM: the anti-signal recognition particle antibody and anti hydroxymethyl-3-glutarylCoA reductase (HMGCR). The clinical phenotype of anti-SRP and anti-HMGCR patients is characterized by severe proximal weakness of skeletal muscles, whereas extra-muscular manifestations are uncommon. However, it is unknown to which extent pathological features are similar and muscular immune mechanisms especially those involved in the necrosis are largely unknown. It is of outmost importance to gain insight in pathophysiology of the disease regarding its severity and refractory course. Thus, we aim to precisely describe the morphology of skeletal muscle alterations of both conditions in a series of SRP+ and HMGCR+ patients, and analyze molecular immune mechanisms at the muscular level. Material and methods: A total seventy five muscle biopsies were analyzed. Forty four muscle biopsies from SRP (n=25) and HMGCR (n=19) patients were analyzed and compared to myositis patients (Jo-1; n=21 and dermatomyositis; n=10). Results: SRP patients showed the highest proportion of necrotic fibers and strikingly this proportion was similar in HMGCR and Jo1 patients. However, necrosis occurred in perifascicular regions only in Jo-1 patients, whereas it was randomly distributed in SRP and HMGCR patients. Creatine kinase levels correlated with proportion of necrotic fibers. Regeneration of fibers also correlated with necrosis and occurred much more frequently. Inflammation was regularly met and in a quarter of cases in the same range as myositis controls. Classically activated macrophages in a Th-1 immune environment were involved in myophagocytosis. In addition, humoral immunity with activation of the classical pathway of the complement cascade was observed. This was accompanied by a sarcolemmal immunoglobulin deposition and alternatively activated macrophages. Conclusions: Based on these results, we propose a new definition of IMNM in which inflammation and complement deposition are no exclusion criteria and emphasized the role of humoral immunity.

20 DYSREGULATION OF SIGNAL TRANSDUCTION PATHWAY IN JUVENILE DERMATOMYOSITIS

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Background and Objectives: Juvenile dermatomyositis (JDM) is a childhood idiopathic inflammatory myopathy of unknown origin, but immunological mechanisms are strongly implicated in its pathogenesis. Our objective was to investigate the signal transduction pathways involved in this chronic immune-mediated inflammatory process. Materials and Methods: Patients recruited to the UK JDM Cohort & Biomarker Study who fulfil Bohan-Peter criteria for JDM were included and clinical and laboratory data were collected. PBMC from JDM patients and adult healthy controls were stimulated with 10U/ml of IFNγ or IL-6 to investigate, respectively, STAT1 or STAT3 phosphorylation. Phosphorylation levels of STAT1 and STAT3 were analysed by flow cytometry. For each sample, phosphorylation levels were compared to an unstimulated sample and fold change was calculated. Results A total of 10 patients were included, of whom 70% were female and 80% were Caucasian. The median [IQR] age at diagnosis was 6.67 years [2.7-8.5], with median disease duration at sample collection of 4.07 years [2.9-5.15] and current disease duration of 14.2 years [3.78-15.82]. There was a trend (p=0.08) towards higher STAT3 phosphorylation in response to IL-6 stimulation in T cells of active JDM patients (median fold-change 2.7 [1.79-9]), compared to healthy controls (median fold-change 1.79 [1.28-3.94]). When STAT3 phosphorylation levels were stratified according to presence or absence of calcinosis, higher STAT3 levels appears to be associated with the presence of calcinosis (median fold-change 6.175 [2.735-8.400] vs 2.280 [1.303-3.043], respectively), but this was not statistically significant (p=0.07). STAT1 phosphorylation levels were similar between JDM and healthy controls. Conclusion There is a trend towards higher levels of STAT3 phosphorylation in response to IL-6 stimulation within T cells of JDM patients compared to healthy controls. In addition, these preliminary results suggest that after IL-6 stimulation, higher T cell STAT3 phosphorylation levels may be associated with the development of calcinosis. These findings provide evidence for dysregulation of IL-6 signaling as a potential mechanism underlying the pathogenesis of calcinosis indicating that IL-6 could be a target for treatment in these patients.

21 Dermatomyositis with or without anti-MDA5 antibodies: common Interferon signature but distinct NOS2 expression

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Background and objectives: To define the histological pattern and the intrinsic immune response in anti-MDA5 positive DM patients. The anti-Melanoma Differentiation-Associated protein 5 (MDA5) auto-antibody is held to be specifically associated with dermatomyositis (DM). Nevertheless anti-MDA5-positive patients suffer from characteristic symptoms distinct from classical DM including severe signs of extra-muscular involvement, while clinical signs of myopathy are mild or even absent. Material and methods: Ten biopsies taken for diagnosis purpose before any immunosuppressive treatments from 9 anti-MDA5 patients were compared to 8 classical DM patients. Muscle specimens were subjected to histopathological analysis to describe fiber and vessel pathology. Morphological analysis of vessels was performed on digitally completely scanned slides and by electron microscopy. A panel of interferon stimulated genes, involved in IFN-associated immune responses was tested in muscle biopsies. Results: Muscle biopsies from anti-MDA5-positive patients did not present the classical feature of perifascicular fiber atrophy and MHC class I expression. They did not show significant signs of capillary loss, and tubulo-reticular formations were observed less frequently. Inflammation was focal, clustering around single vessels but significantly less intense. Expression of interferon (IFN) stimulated genes was up-regulated in anti-MDA5 positive patients, however, the IFN-score was significantly lower. Numerous muscle fibers showed strong NO synthase (NOS2) immunoreactivity. Sarcoplasmic co-localisation of NOS2 with markers of immaturity was exclusively found in anti-MDA5 positive patients. Conclusions: Anti-MDA5 positive patients demonstrated a morphological pattern distinct from classical DM. This included strong NOS2 expression in skeletal muscle fibers, and a less relevant IFN signature.

22 ERK-Inhibition diminishes amyloid formation and reduces autophagy in an in-vitro-model for IBM

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Inclusion body myositis (IBM) is the most common acquired myopathy in patients over 50 years. The pathology involves an inflammatory response and β-amyloid deposits in muscle fibers. It is believed that MAP kinases such as ERK, JNK and p38 signaling pathways mediate the inflammatory signalling in cells. There is evidence that autophagic activity plays a crucial role in the pathogenesis of IBM. Using an in vitro model of IBM, transcription factors, such as MAP kinases, the autophagic pathway and accumulation of β-amyloid were examined. Rhabdomyosarcoma cells were exposed to the cytokines IFN-γ and IL-1β for 24 and 48 hours. In addition, the cells were treated with various MAP kinase inhibitors. The protein expression of IL-1β, CXCL9 and of phosphorylated and non-phosphorylated forms of the different MAP kinases was determined by western blotting. The effects on autophagy were analyzed using stably transfected GFP-LC3-rhabdomyosarcoma cells. β-sheet aggregates were visualized by immunocytochemistry. Cell death was determined via propidium iodide staining. Stimulation of muscle cells with IL-1β and IFN-γ led to an increased phosphorylation of ERK, but neither JNK nor p38. The ERK inhibitor PD98059 diminished the expression of pro-inflammatory markers as well as the accumulation of β-amyloid. Immunocytochemical analysis of GFP-LC3 muscle cells showed that IL-1β and IFN-γ led to an increase of autophagic activity, upregulation of APP and subsequent accumulation of β-sheet aggregates. Cytokine-induced cell death could be prevented by inhibition of autophagic activity as revealed by propidium iodide staining. Taken together, these data demonstrate that MAP kinases, such as ERK are of importance for the formation of β-amyloid and the regulation of autophagic activity in an in vitro model of IBM, especially under conditions of pro-inflammatory cell stress. Thus, ERK could provide an important link between inflammation and protein deposition in IBM muscle. This study helps to better understand the pathology of chronic muscle inflammation as in IBM.

23 Interleukin-35 in idiopathic inflammatory myopathies

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Background: Interleukin-35 (IL-35) is a newly described heterodimeric cytokine that belongs to the IL-12 family and consists of p35 (IL-12a) and EBI3 (IL-27b) subunits. IL-35 exerts immunomodulatory activities in several human autoimmune inflammatory diseases. Objective: to assess IL-35 expression in muscle tissue and serum levels of IL-35 in myositis patients compared to healthy controls and characterise its potential association with myositis disease activity. Methods: The expression of IL-35 was studied by primary rabbit anti-human EBI3 polyclonal antibody and mouse anti-human p35 monoclonal antibody in a series of 19 muscle biopsy samples of idiopathic inflammatory myopathies (9 dermatomyositis/DM, 10 polymyositis/PM) and 10 cases of non-inflammatory myopathies and 10 control muscles biopsies. Serum levels of IL-35 were determined in 28 DM, 26 PM and 17 cancer associated myositis patients as well as in 40 healthy controls. Disease activity was evaluated by the score of the Myositis Disease Activity Assessment Tool (MYOACT), including both extramuscular, muscular and the physician's score of overall disease activity. Results: Both IL-35 subunits were found in immune cells of the inflammatory infiltrates in idiopathic inflammatory myopathies, but not in muscle cells. No immunoreactivity was observed in muscle tissue of healthy controls and in non-inflammatory myopathies. IL-35 serum levels were increased in all myositis patients compared to healthy controls (p 0.001). There were no differences in IL-35 serum levels among myositis subgroups. In patients with PM, but not DM, serum IL-35 levels correlated with MYOACT score (r=0.548, p=0.023), lactate dehydrogenase (r=0.621, p=0.024), CRP (r=0.632, p=0.009) and physician's score (r=0.514, p=0.042). Conclusion: IL-35 subunits are overexpressed in inflamed muscle tissue and elevated circulating IL-35 levels are associated with several disease activity parameters in polymyositis patients. These data suggest potential role of IL-35 in the pathogenesis of inflammatory myopathies. Supported by: MHCR support for conceptual development of a research organization (023728) and BTCure (115142-2)

24 Loss of TLR2 increases fatigue resistance in mouse skeletal muscles

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Background and Objectives: TLR2, classically expressed in immune cells, is also expressed in non-immune cells including skeletal muscles. In this study we investigated the role(s) of TLR2 on skeletal muscle contractile properties. Materials and Methods: In animal studies enzymatically dissociated skeletal muscle fibers were used to investigate the effects of TLR2 ligands on muscle functions. And mechanically dissected skeletal muscle fibers were used to decide the calcium release and force production in TLR2 gene knock out (-/-) mice and wild type (WT) mice. Immunohistochemistry were performed on muscle tissues from patients with idiopathic inflammatory myopathies (IIMs) to investigate the expression of TLR2. Results: Firstly, we found that presence of TLR2 ligands accelerated development of muscle fatigue during repeated tetanic stimulation of dissociated muscle fibers. Secondly, muscle fibers from TLR2-/- mice were more fatigue resistant, and tetanic [Ca2+]i was greater in muscle fibers from these mice than WT. We observed no difference between TLR2-/- and WT muscle in mitochondrial oxidative capacity or glycogen content. However, the expressions of the antioxidant proteins superoxide dismutase 1 and 2 were significantly higher in TLR2-/- than in WT muscle. Finally, we found that TLR2 was expressed in muscle fibers of patients with IIMs and in contrast to healthy controls, muscles of IIMs patients also express one of the most important endogenous ligands of TLR2, high mobility group box protein (HMGB) 1. Conclusions: In conclusion, TLR2 signaling may impair muscle contractile function and could play a role in the induction of muscle weakness in muscle disorders, such as IIMs. Therefore, therapies aimed at modifying TLR2 signaling may be used to counteract pathological muscle weakness.

25 INTERFERON-BETA INDUCED REACTIVE OXYGEN SPECIES PARTICIPATE IN MUSCLE INFLAMMATION AND MITOCHONDRIAL OXYDATIVE PHOSPHORILATION DEFECTS CONTRIBUTING TO DERMATOMYOSITIS MUSCLE IMPAIREMENT

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Background: Dermatomysoitis (DM) has been related to high type-I-interferon (IFN-I) signaling in skeletal muscle which is thought to play a pivotal role in muscle inflammation and impairment. However, the mechanisms by which muscle dysfunctions occurred remain unknown. Objectives: We assessed the involvement of mitochondria in the muscle of recent onset untreated DM patients using transcriptomic, morphological and in-situ functional studies. We also unraveled the link between inflammation, reactive oxygen species (ROS) and mitochondrial dysfunctions using animal model and cell system. Methods: Ten early (6 months) and untreated DM (according to ENMC) patients were prospectively included and compared to controls. C2C12-cells were exposed to IFN-β in the presence and the absence N-acetyl-cystein (NAC), a potent ROS-scavenger. BALB/c-mice were immunized with PBS (controls) or myosin (EAM) emulsified in CFA. The treated group received 300 mg/kg/day of NAC until sacrifice. We recorded aerobic capacity in patients and muscle strength in animals. Transcriptomic analysis were confirmed using qPCR. Mitochondria was further assessed by oxygraphic oxygen consumption recording, histoenzymological staining of oxidative enzymes and electronic microscopy (EM). Reactive oxygen species (ROS) production was quantified using electron paramagnetic resonance spectroscopy or H202 detection with spectrofluorometry. Results: The main up-regulated cluster of transcripts in DM patients (n=3) was composed of genes encoding proteins involved in inflammatory responses (especially IFN-I induced genes) while the first cluster of the down-regulated transcripts was composed of genes encoding proteins involved in mitochondrial integrity and functions. Numerous mitochondrial abnormalities were found on EM and abnormal histochemical staining of oxidative enzymes was noted in all DM muscles (n=10). In situ oxygen consumption of DM muscle samples (n=10) was about 40% decreased whatever the mitochondrial substrate used while H2O2 production was increased (p0.01). Oxygen consumption in the muscle correlated with maximal aerobic capacities on cycle ergometer (Spearman r=0.90). After 24 hours exposition, IFN-β induced a 30% decrease in mitochondrial respiration of cells that was prevented by ROS scavenging with NAC (p0.05). Muscle of EAM-animals exhibited 2-fold increase in ROS production and about 1.5-fold decrease in mitochondrial respiration that was partially prevented by NAC. NAC also prevented EAM-muscle weakness (p0.05) and the increase of muscle transcripts of several genes implied in inflammation including IFIT3 (p0.05). Conclusions: Mitochondrial dysfunctions, contributing to poor aerobic capacity, occur early in DM muscle and might be mediated by high ROS production triggered by IFN-β. In turn, ROS might participate in IFN-I inducible genes expression and inflammation, which can become self-sustained.

26 VITAMINE D SERUM LEVEL CORRELATES WITH QUADRICEPS MUSCLE STRENGTH IN INFLAMMATORY MYOSITIS

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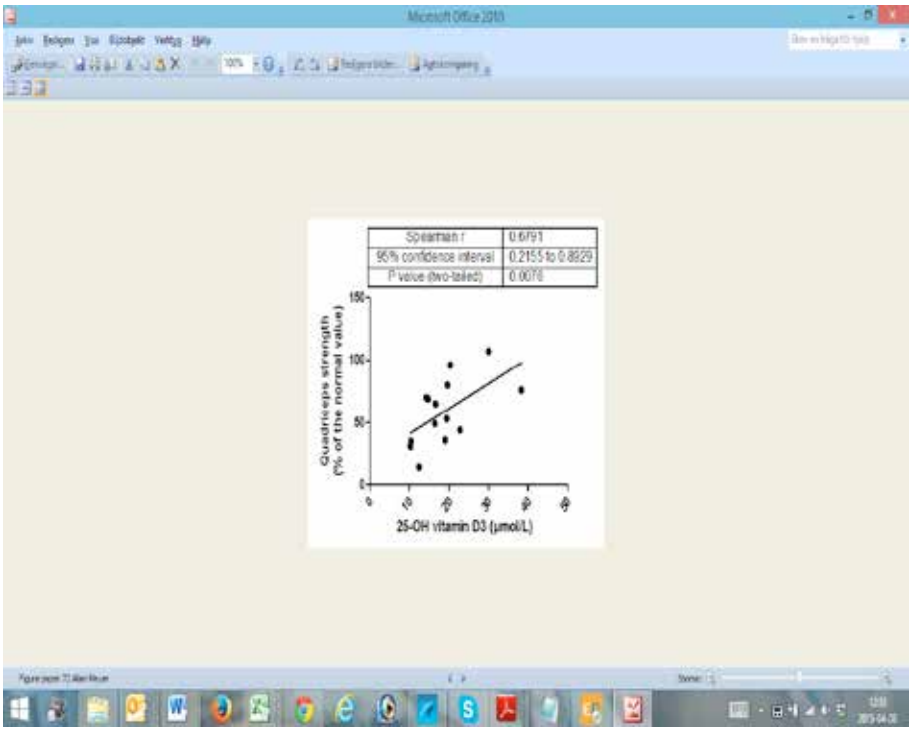
Background: Vitamin D has been involved in both inflammation and muscle strength. Inflammatory myopathies are characterized by muscle inflammation and weakness. Objectives: We assessed whether vitamin D serum level is linked to muscle strength during inflammatory myopathies. Methods: Fourteen consecutive patients with inflammatory myopathies (with the exclusion of inclusion boy myositis) were prospectively included. Muscle strength was recorded on dominant quadriceps using hand held dynamometer. 25-OH-vitamin D3 level was measured on a blood sample at the same time. Results: Characteristic of the patients: 9 women and 5 men with a median age of 53.5 (13-71) were included. Duration of mysoitis at the time of muscle strength was 29 months (3-68). 11 patients were treated at the time of quadriceps strength measurements (corticosteroids n=11, methotrexate n=9, mycophenolate mofetil n= 2, intraveinous immunoglobulin n=5). Vitamine D levels and quadriceps muscle strength: median 25-OH-vitamine D3 level was 17.80µg/L (10.2-38.3) and median quadriceps strength (expressed as the percentage of the mean value recorded in healthy volunteers of the same age and sex) was 65% (14-107). 25-OH-vitamine D3 correlated with quadriceps muscle strength (figure: Spearman R = 0.68, 95%CI: 0.22-0.89, p 0.01). Conclusions: Our data suggests that vitamin D is involved in muscle strength during inflammatory myopathies. 25-OH-vitamin D3 might be monitored in these patients not only with the aim of protecting bone during corticosteroids treatments but also with the objective of improving muscle strength.



27 Autophagy May Contribute to Glucocorticoid Resistance in Patients with Myositis by Maintaining T Lymphocytes Homeostasis in the Muscles

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Background and Objectives: T cells often persist even after glucocorticoid (GC) treatment in the muscles of patients with myositis. Autophagy helps cells to survive under variable cellular stresses. Beclin1 can induce autophagy by binding high mobility group box protein (HMGB) 1. In this study, we investigated whether autophagy initiated by Beclin1-HMGB1 binding can contribute to T cell survive in the muscles of patients with myositis, and whether this homeostasis of T cells are related with GC treatment resistance. Materials and Methods: Muscle biopsies were obtained from poly- and dermatomyositis patients with good response to GC. Clinical response was evaluated by functional index (FI) and serum creatine kinase (CK) level. Muscle biopsies were investigated by immunohistochemistry for macrophages (CD163, CD68), T cells (CD3), HMGB1 and Beclin1. Computer image analysis was performed for each marker. Co-localization of HMGB1, Beclin1 and T cells was done by consecutive section staining and was confirmed by double fluorescence staining. Results: HMGB1 and Beclin1 were expressed in muscle tissues of patients with myositis; furthermore, their expressions co-localized to the infiltrating T cells in muscles as demonstrated by both consecutive section staining and double fluorescence staining. The expression of Beclin1 correlated positively with HMGB1 and T cells but not with macrophages. Moreover, Beclin1 was also correlated with FI negatively. Finally, in the patients with good response to GC, both HMGB1 and Beclin1 expression were decreased after treatment, so was a trend for T cells. Conclusions: Autophagy initiated by HMGB1-Beclin1 binding may contribute to T cell survival in the muscles of patients with myositis. And this homeostasis in T cells could be a factor that contributes to the GC resistance. Thus, targeting this pathway might benefit the patients in the future.

28 Nuclear actin aggregation is a hallmark of anti-synthetase syndrome-induced dysimmune myopathy

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The aim of this study was to analyze Antisynthetase syndrome (ASS)-associated myositis by modern myopathological methods and to define its place in the spectrum of Idiopathic Inflammatory Myopathies (IIMs). Skeletal muscle biopsies from ASS-associated myositis and other IIMs from different institutions worldwide were analyzed by histopathology, quantitative polymerase chain reaction and electron microscopy. Myonuclear actin filament inclusions were identified as a unique morphological hallmark of ASS-associated myositis. Nuclear actin inclusions were never found in dermatomyositis, polymyositis, sporadic inclusion body myositis, autoimmune necrotizing myopathy associated with SRP or HMGCR autoantibodies, or nonspecific myositis associated with other systemic diseases, harboring myositis-associated autoantibodies and presenting myofiber necrosis. We show that molecules involved in actin filament formation and actin shuttling mechanisms are altered in ASS, and may thus be involved in pathological myonuclear actin aggregation. In addition, we have identified a typical topographic distribution of necrotic myofibers predominantly located at the periphery of muscle fascicles accompanied by inflammation and destruction of the perimysial connective tissue. ASS-associated myositis is characterized by distinctive myonuclear actin filament inclusions, including rod formations and a typical necrotizing perimysial myositis. This supports the hypothesis that ASS-associated myositis is unique and should not be grouped among DM, PM, sIBM, NAM or nonspecific myositis.

29 Autoantibody specificities and type I interferon pathway activation in Idiopathic Inflammatory Myopathies

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Objective To test the hypothesis that autoantibodies directed against RNA-binding proteins in myositis patients are associated with a type I Interferon (IFN) signature. Methods Two cohorts of myositis patients were included. Autoantibody status was analyzed using a validated line immunoassay system and immunoprecipitation. Type I IFN activity in serum was determined using a reporter cell assay (cohort 1) and in whole blood using direct gene expression analysis (cohort 2). Clinical characteristics were obtained according to the International Myositis Assessment and Clinical Studies (IMACS) Group's criteria. Results Patients were categorized into IFN high and IFN low based on an IFN score in both cohorts. The frequency of antinuclear antibody positive patients was significantly higher in the IFN-high group compared to the IFN-low group (cohort 1). The IFN score in myositis patients was related to autoantibody multi-specificity and to autoantibodies against RNA-binding proteins (cohort 2). Myositis patients with autoantibodies against RNA-binding proteins had a higher IFN score and had an IFN signature to a higher extent (cohort 2), compared to patient without those antibodies. In patients with dermatomyositis (DM), the IFN score was correlated to disease activity (Physician's global disease activity assessment). Patients with DM were overrepresented in the IFN-high group (cohort 1) or had higher IFN score (cohort 2) than the other subgroups. Conclusions This study suggests that there is heterogeneity among myositis patients in the context of type I IFN. The IFN score was significantly higher in myositis patients with autoantibody multi-specificity and in patients with autoantibody mono-specificity against RNA-binding proteins. Another clinical subgroup with an IFN signature is DM, regardless of antibody profile, where we could see a correlation between IFN score and disease activity. These patient categories could possibly benefit from IFN-blocking agents.

30 Necrotising autoimmune myopathy: diagnostic value of anti-HMGCR auto-antibodies and their role in pathogenesis

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Background and objective. Necrotizing autoimmune myopathies (NAM) constitute a newly recognized group of severe acquired myopathies characterized by pathological features of myofiber necrosis without significant inflammation. Because of the lack of appropriate biomarkers, these diseases have been long misdiagnosed as atypical forms of myositis. NAM may be associated to auto-antibodies (aAbs) against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), notably in statin users. The statins target, HMGCR, is an endoplasmic reticulum membrane-located enzyme involved in cholesterol metabolism. Since its expression is ubiquitous, the role of anti-HMGCR aAbs in NAM remains elusive. We developed a quantitative assay of anti-HMGCR aAbs and investigated their pathogenic role in an in vivo mouse model. Methods. Recombinant human HMGCR (rhHMGCR) was coupled to fluorescent beads and used to measure aAbs level of human serum by Luminex. IgGs purified from anti-HMGCR aAb-positive patients sera were transferred to C57BL/6 or Rag-/- mice. Alternatively, mice were immunized with rhHMGCR plus a TLR9 agonist as adjuvant. Results. Luminex immunoassay in patients with suspicion of NAM revealed that patients anti-HMGCR aAbs were mostly females and that only 40% had been exposed to statins. Anti-HMGCR aAbs were almost exclusively IgG1and their titres were highly variable between patients, with a correlation with creatine kinase levels at a population level. In mice, injection of anti-HMGCR-positive IgGs resulted in a significant decrease in muscle strength whereas IgG-depleted plasma or anti-HMGCR-negative IgGs had no effect. Histologically, this was associated with moderate myofiber necrosis, and hIgG and membrane attack complex deposits on myofibers. The effect was transient in immunocompetent mice that developed a xeno-immune response against hIgG. In contrast, it was prolonged in immunodeficient Rag-/- animals. Immunization with rhHMGCR also led to impaired muscle strength. Conclusions. Anti-HMGCR aAb assays are helpful for the diagnosis of a necrositing myopathy: a positive result allows ascribing patients to an auto-immune form. An absence of statin exposure should not eliminate the diagnosis of NAM. Anti-HMGCR aAbs are directly involved in the disease pathogenesis. It is unlikely that antibody-dependent cell cytotoxicity plays a significant role in this model since we did not observe inflammatory cell infiltrates. Rather, hIgG and C5b-9 deposits suggest a role for the classical complement pathway. These results support further evaluation of plasma exchange and/or B cell-targeted therapy in anti-HMGCR-associated NAM.

31 Antibodies against TIF1gamma in cancer associated myositis precede cancer symptoms and persist after cancer removal

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Background: Antibodies against TIF1gamma have been detected in patients with cancer associated myositis (CAM). It is not known whether the antibodies precede the symptoms of cancer or if the antibodies persist after successful treatment of a malignancy. It is furthermore unknown if the level of positivity plays a role in the prognosis of patients with CAM. Objectives: To analyse the levels of TIF1gamma antibodies in longitudinally collected sera taken before cancer diagnosis and after treatment of the malignancy in patients with CAM. Methods: From our local myositis register including 170 myositis patients we found 54 cases of CAM. Serum levels of anti-TIF1gamma antibody were tested by ELISA using a commercially available purified recombinant protein (OriGene, Rockville, MD). Results: Sera from 16 (29.6%) patients with cancer (13 females and 3 males) were positive for anti-TIF1gamma antibodies in at least one serum sample. Of the 16 positive patients 12 had developed cancer within 3 years from myositis diagnosis, 4 after 3 years. 15 patients had solid tumors; the most frequent were 4 ovarial cancers, 2 breast cancers, and 3 lung cancers. Of the total 16 TIF 1 gamma positive patients serum samples taken before cancer diagnosis were available from 5 patients. One of these patients had detectable anti-TIF1gamma antibodies up to 5 years before cancer diagnosis. Of the 16 patients positive for anti-TIF1 gamma, 12 patients had died at time of our study, 7 within 1 year from cancer diagnosis. The 7 patients who died within one year had a mean antibody level of 1976 +/- 304 au, the 5 patients who died after more than 1 year had a mean antibody level of 1036 +/- 555 au (p=0.003). None of the patients that died became negative in the antibody test after cancer diagnosis. Four patients were still alive at time of the investigation, between 2-13 years after cancer treatment. They were all in remission from cancer disease and 2 of them became negative for anti-TIF1gamma antibodies. Conclusions: Anti-TIF1gamma antibodies can be detected before clinical symptoms of cancer and may thus become a helpful marker to alert for cancer in patients with myositis. The levels of anti-TIF1gamma antibodies seem to be a prognostic marker for survival in CAM. In addition the TIF1gamma antibodies may persists after cancer treatment even in patients without clinical sings of a persisting malignancy. The clinical relevance of this observation will need further investigation.

32 The clinical phenotype of anti-SRP antibodies associated polymyositis patients

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Objective: To study the prevalence of anti-SRP antibodies and their association with clinical and muscle pathological characteristics in a large Chinese dermatomyositis(DM) and polymyositis(PM) cohort. Methods Sera from 106 DM patients and 42 PM patients were detected for anti-SRP antibodies by immunoblotting test. Clinical and muscle pathological characteristics were collected by review of medical records. Follow-up study and systemic literature review was also completed. Results Sera from 9 PM patients out of the 148 patients were positive for anti-SRP antibodies (6.08%), while the positive rate in PM patients was 21.43%. Compared with antibody negative patients, high incidence rate of dysphagia (P=0.005) and low incidence rate of CRP elevation (P=0.04) in the positive group were the main findings. Patients with anti-SRP antibodies had low incidence of serious cardiac damage and no obvious correlation with ILD. Muscle pathological features were scattered muscle fiber degeneration, atrophy and necrosis, positive expression of MHC class-I molecules, scattered or focal infiltration of T lymphocytes, but with no infiltration of B lymphocytes. The mean follow-up period was 20.6 months, while remission rate was 87.5%. Conclusion Anti-SRP antibodies were relative specific antibodies of PM. They had a remarkable correlation with dysphagia, but low frequency of serious cardiac damage. The infiltration of T lymphocytes existed in muscle tissues of the myositis subtype.

33 ANTI-CN-1A ANTIBODY STATUS AND CLINICAL CHARACTERISTICS IN INCLUSION BODY MYOSITIS

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Background and objectives: Muscle specific antibodies, such as anti-Jo1, seem not to occur in sporadic inclusion body myositis (sIBM). However, sIBM has a strong association with the HLA-B8-DR3 ancestral haplotype and concomitant autoimmune diseases, so the existence of a sIBM-specific antibody remained plausible. A few years ago two independent research groups discovered a specific antibody against cytosolic 5'-nucleotidase 1A (cN-1A). We detected anti-cN-1A in about 36% of sIBM patients. Whether the presence of anti-cN-1A correlates with specific clinical features, is unknown. Materials and methods: The clinical features of 56 sIBM patients (21 females and 35 males) who met the Hilton-Jones diagnostic criteria were retrospectively assessed by an investigator blinded for anti-cN-1A status. The presence of anti-cN-1A antibodies was evaluated by enzyme-linked immunosorbent assay with three synthetic peptides containing cN-1A autoepitopes previously identified by overlapping peptide microarray analyses. Results: General features - 42% of the evaluated patients showed high anti-cN-1A reactivity. No significant differences were found between anti-cN-1A positive and negative patients regarding gender, concomitant autoimmune diseases and the presence of autoantibodies (ANA, ANCA, anti-SSA, anti-SSB, anti-SM, anti-RNP, ENA, anti-dsDNA), previous statin use and presence of cardiovascular diseases or malignancies. Clinical features - The age at onset of weakness was similar in both groups (mean age at onset antibody positive 60 ± 1.7 years vs. negative 57.7 ± 1.6 years). Asymmetric proximal weakness and muscle atrophy at onset was seen in the majority of patients in both groups. At last follow up (mean period of 7.5 years after diagnosis) no differences were seen in the pattern of weakness, the presence of dysphagia, the number of falls a year and the use of a walking aid. Progression - The anti-cN-1A positive patients do not progress faster to the need of a walking aid or wheelchair. 34 patients died during follow up. Survival in anti-cN-1A positive patients was significantly shorter than in anti-cN-1A negatives (p 0.03), but this difference subsides after correction for age (p = 0.06). Conclusions: This retrospective assessment shows no differences in clinical characteristics between anti-cN-1A positive and negative sIBM patients, except a trend to shorter survival in anti-cN-1A positive patients.

34 Anti-Tif1-gamma antibodies are markers of paraneoplastic myositis but not paraneoplastic arthritis and paraneoplastic Raynaud's syndromes

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Background and Objectives An association between cancer and idiopathic inflammatory myopathies, referred to as cancer associated myositis, has been intensively discussed in the scientific literature. The overall cancer risk in these patients is higher than that in the general population, particularly during the 3 years following the diagnosis of myositis. It is believed that nearly one fourth of DM cases develop as a paraneoplastic phenomenon. Due to that patient with inflammatory myopathies usually undergo an extended examination for cancer. A novel anti-TIF1-gamma autoantibody (Ab) was proposed to have high sensitivity and specificity for predicting malignancy in patients with DM. Conclusion were drawn from small individual reports lacking proper control groups. Thus the true predictive value is not known. Here we aim to compare frequency of anti-TIF1-gamma Ab in cohorts of paraneoplastic myositis, paraneoplastic arthritis and paraneoplastic Raynaud, cancer patients without rheumatological disease and healthy controls. Materials and Methods Patients presented with myositis, arthritis and newly developed Raynaud's syndrome 3 years before or after cancer diagnoses as well as patients with diagnosis of solid cancer and healthy controls were included in this study. Commercially available recombinant Tif1-gamma protein was used for ELISA to detect the frequency of anti-Tif1-gamma Ab in sera of paraneoplastic myositis (n=16), paraneoplastic arthritis and paraneoplastic Raynaud (n=76), solid cancer patients (n=76) and healthy controls (n=76). Cut off value was set up on 98th percentile among 76 healthy controls. Results Positivity for anti-Tif1-gamma in the groups of paraneoplastic myositis was 94%, paraneoplastic arthritis and Raynaud 2,6%, cancer patients 5,2% and healthy controls 2,6%. Sera antibody levels were also significantly higher in paraneoplastic myositis group if compared to paraneoplastic arthritis and Raynaud (P 0,0001), cancer patients (P 0,0001) and healthy controls (P 0,0001). There was no significant difference between paraneoplastic arthritis and Raynaud, cancer patients and healthy control groups. Conclusions Anti-TIF1-g antibodies could be considered as serological marker for paraneoplastic myositis but not other paraneoplastic rheumatic inflammatory syndromes. Since TIF-1 proteins have significant roles in oncogenesis, these antibodies may be produced during misdirected antitumor immunity.

35 CHARACTERIZATION OF ANTI-JO1 AUTOANTIBODIES IN MYOSITIS

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Background and Objectives: Anti-histidyl tRNA synthetase (Jo1) autoantibodies are the most common type of myositis specific autoantibodies, being present in 15-30% of the patients. When myositis patients develop simultaneous interstitial lung disease the percentage of patients positive for anti-Jo1 autoantibodies can reach approximately 70%. These individuals are generally characterized by a condition called anti-synthetase syndrome known to present a particular clinical phenotype affecting the muscles, lungs, joints and skin. Little is known about the functional role of anti-Jo1 autoantibodies. The aim of this study was to purify anti-Jo1 IgG from blood of myositis patients, determine the proportion in circulation and further characterize any molecular effects of these autoantibodies. Materials and Methods: Sera (n=42) samples from anti-Jo1 positive myositis patients were collected and used to affinity purify anti-Jo1 IgG. Recombinant human Jo1 (rJo1) was over-expressed in E.coli competent cells, purified from the cytosolic fraction using hydroxyapatite followed by strong anion exchange chromatography and coupled to an NHS activated pre-packed sepharose column. Anti-Jo1 IgGs were isolated from total IgGs extracted from pooled myositis sera using a ProteinG column and further purified using the Jo1 column. The abundance of anti-Jo1 IgG in serum from myositis patients was estimated by measuring the absorbance at 280 and 595 nm. Recovery/purity and reactivity against rJo1 was analyzed by SDS-PAGE and western blot, respectively. Results: Anti-Jo1 IgGs were successfully purified from myositis serum using an in-house developed Jo1 affinity column. Among the total percentage of IgG 1.5% were Jo1 reactive (anti-Jo1 IgG). The total concentration of anti-Jo1 IgG in myositis serum was estimated to be 180 μg/ml. Anti-Jo1 IgG recognized both the monomer and the dimer structure of the enzyme. Conclusions: Anti-Jo1 IgGs were efficiently purified from myositis serum and the proportion and concentration was estimated. Affinity purified anti-Jo1 autoantibodies are currently being used as molecular tools in in vivo and in vitro experiments for the characterization of functional effects and antigen/autoantibody dynamics in myositis.

36 Expression of the cN-1A autoantigen in skeletal muscle from patients with inclusion body myositis and controls with non-neuromuscular disorders

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Background and Objectives: Recently, the cytosolic 5'-nucleotidase 1A (cN-1A) was identified as a target of autoantibodies in sporadic inclusion body myositis (IBM). cN-1A is a 5'-nucleotidase, which catalyses the hydrolysis of adenosine monophosphate (AMP) and is highly expressed in skeletal muscle. Therefore, the identification of this novel autoantibody-autoantigen system raises the question of whether the anti-cN-1A immune response is mediated by changes in the expression or activity of the target enzyme in skeletal muscle tissue, possibly differentiating IBM from other types of myositis. Therefore, we aimed to determine the distribution of cN-1A in skeletal muscle of IBM, other types of myositis and controls. Materials and Methods: Histological analyses, including muscle fibre typing were performed on diagnostic muscle biopsy tissue from 8 IBM, 8 PM and 6 DM patients and from 5 individuals with non-neuromuscular diseases. Results: In all patient groups, cN-1A distribution was characterized by a mosaic pattern of distribution strongly correlating with muscle fibre type and perinuclear accumulation was also observed in all muscle tissues. The most intense staining for cN-1A occurred in type 2a/b fibres followed by intermediate type 2c fibres and type 1 fibres. In muscle biopsies from myositis patients, we observed elevated levels of cN-1A in small type 2 muscle fibres, particularly in those with signs of inflammation and internal nuclei, but this was not specific for IBM. In sections containing longitudinal fibres, cN-1A co-localised with alpha-actinin to the Z-disc of the sarcomere, suggesting a possible role of cN-1A in muscle contraction. We observed the presence of both cN-1A and p62 in the same muscle fibres and, although there was evidence of perinuclear co-localisation of these proteins, this was inconsistent and restricted. Conclusions: Our findings suggest that cN-1A expression is increased in the muscle fibres of patients with myositis compared with controls, but the question as to whether changes in cN-1A could be specifically associated with IBM requires further study.

37 Deficiency of Ro52/TRIM21 in different subsets of peripheral blood mononuclear cells from patients with inflammatory myopathies

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Backgrounds and Objectives: The analysis of the Ro52/TRIM21 expression of and its association with autoimmune disease is important, especially where there have been correlations with a worse prognosis and severe clinical manifestations. However, the information about the expression of Ro52/TRIM21 in T cells and its role as a regulator of innate immunity is scant. Therefore, the aim of this study was to evaluate the expression of Ro52/TRIM21 in subsets of peripheral blood mononuclear cells (PBMCs) of patients with idiopathic inflammatory myopathies (IIM). Materials and Methods: We included 18 active patients with recent onset diagnosis of IIM, seen at a tertiary care center from March 2013 to April 2014. PBMCs were isolated by Ficoll-Hypaque method and different subsets of PBMCs (CD4+, CD8+, CD14+) were purified by magnetic selection. The expression of Ro52/TRIM21 in different PBMC subsets of patients with IIM and healthy donors was evaluated by Western-Blot. We assessed the presence of myositis-specific and associated autoantibodies (MSAs, MEAs) by ELISA. The cytokine expression was evaluated in the supernatant cultures of stimulated (anti-CD3 or LPS) and resting T CD4+ and CD14+ lymphocytes in 4 patients con IIM and 4 healthy controls matched by age and gender. The cytokine quantification was performed with the equipment Human cytokine (Milipore) of the following cytokines: IL-4, IL-8, IL-6, INF-γ, TNF-α. Results: We included 3 patients with polymyositis (PM), 3 with anti-synthetase syndrome (AAS) and 12 with dermatomyositis (DM) as well as 18 healthy controls. DM was the predominant IIM (66.6%), 61% were female, with a mean age of 46 (34-57) years; CPK levels at diagnosis of 804 (392-4695) UI/L and lymphocyte count of 1021 (683-1526) cells/μL. Anti-Ro52 was present en 25% of DM and 33.3% of PM and AAS. All patients with IIM showed decreased protein expression of Ro52/TRIM21 in comparison to healthy controls in PBMC (0.9713±0.6037 vs 1.8493±0.9274 p=0.016), CD4+ lymphocytes (0.7973±0.5404 vs 2.4134±0.7868 p=0.017), and monocytes (0.8751±0.3586 vs 1.8908±0.2092 p0.001). There were no significant differences among IIM groups. There was an increased production of IL-6 in the supernatants of T CD4 stimulated (anti-CD3) cells of MII in comparison to healthy controls (6300.9 ± 562 vs, 2942 ± 782, p=0.011). Conclusion: Patients with IIM are characterized by deficient expression Ro52/TRIM21 in different PBMC subsets (CD4+ lymphocytes and monocytes) and a higher expression of IL-6. Further insights into the function of this protein will have profound implications for the understanding of its role in IIM.

38 Characterization of autoantibodies directed against transcription intermediary factor 1-gamma (TIF1gamma) in patients with dermatomyositis

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Background and objectives: Anti-TIF1γ auto-antibodies (aAbs) have been described to be associated with paraneoplastic dermatomyositis (DM). Yet, these aAbs have been poorly characterized to date. The objective of this study was to determine the main biological characteristics of anti-TIF1 γ aAbs and the clinical profile of DM patients harbouring these aAbs. Patients and Methods: Sera from 116 patients with DM were analysed. Recombinant TIF1γ protein was coupled to fluorescent beads and used to measure aAb level by ALBIA (Luminex) using class- or subclass-specific anti-human immunoglobulin G (IgG) antibodies. Avidity of anti-TIF1γ aAbs was evaluated by elution with increased concentrations of ammonium thiocyanate. Anti-TIF1γ positive sera were analysed by indirect immunofluorescence on HEp2 cells and immunoprecipitation. Results: The ALBIA-TIF1γ immuno-assay revealed sensitive, i.e. detecting Ab concentrations as low as 0,8ng/mL. At a 4AU/mL cut-off (mean+3SD of negative control values), the test had 100% sensitivity and 97% specificity. Nineteen patients (16%, 16 adults, 3 children) were positive with aAbs levels ranging from 10 to 535AU/mL. ALBIA-TIF1γ revealed more sensitive than commercial immunoblot (Euroimmun). Most anti-TIF1γ aAbs were of IgG1 isotype. Positive sera immuno-precipitated the TIF1γ protein. IFI on HEp2 cells revealed a finely granular nuclear fluorescence with nucleoli exclusion that was inhibited by free recombinant TIF1γ. The 16 anti-TIF1γ positive adults (6 male, 10 female) were 62±15 years old. Four of them had amyopathic DM, all with associated neoplasia. In patients with associated cancer (n=7), aAbs levels were higher (170AU/mL)(p0.05) than in those without cancer (53AU/mL). In 5 cases, discovery of cancer was concomitant to DM diagnosis and aAb were t hen of low/medium avidity for TIF1γ. The two patients with the highest aAb avidity were those with neoplasia having preceded DM by several years. Conclusion: ALBIA-TIF1γ is sensitive and specific for detecting anti-TIF1γ aAbs in DM patients. Anti-TIF1γ positive patients with cancer often present with amyopathic DM and have higher aAb levels. High avidity of aAbs seems to be associated with duration of exposure to cancer, suggesting affinity maturation by tumoural auto-antigen.

39 Jo-1 patients with anti-synthetase syndrome show a characteristic necrotizing perifascicular myositis

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Background and objectives: Idiopathic inflammatory myopathies (IIM) can be classified in five categories: polymyositis (PM), dermatomyositis (DM), immune mediated necrotizing myopathy (IMNM), sporadic inclusion body myositis (sIBM) and non-specific myositis based on five different histological patterns. To date, there are more than 15 myositis-specific-autoantibodies (including the anti-Jo-1 antibody which is the most prevalent one) that possibly define more homogenous groups than histological classifications do. Nevertheless, anti-Jo-1 antibody positive patients are classified either among PM or DM groups suggesting overlapping pathological features between both entities. We aimed to determine if myopathy occurring in anti-Jo-1 antibody positive patients is associated with a specific morphological phenotype different from the five known histological patterns. Material and methods: A first series of 53 muscle biopsies of anti-Jo-1 antibody positive patients was analyzed morphologically. Relevant descriptive criteria defining a characteristic morphological pattern were identified. In a blinded analysis, the selected criteria were tested in a second series of anti-Jo-1 antibody positive patients (n=19) and compared to 69 biopsies from patients suffering from idiopathic inflammatory myopathies (DM, IMNM and sIBM). Results: In anti-Jo-1 antibody positive patients, necrotic fibres, which strongly clustered in perifascicular regions, were very frequently observed (86.8%). Clustered atrophic myofibres in perifascicular regions occurred less frequently (58.8%). Sarcolemmal complement deposition was detected specifically in perifascicular areas (75%). Inflammation was mainly located in the perimysium and around vessels in 90.6% with endomysial extension. Perimysial fragmentation was observed in 90% of cases. MHC-I staining was diffusely positive in 92.2%, with a perifascicular reinforcement in 58.8%. Multivariate analysis showed that criteria defining a perifascicular pathology: perifascicular necrosis (32.1 [5.7-181.1]), atrophy (60.9 [4.2-890.3]) and perimysial fragmentation (6.4 [1.2-33.7]) allow the distinction of anti-Jo-1 antibody-positive patients among patients suffering from other idiopathic inflammatory myopathies. According to the clinico-pathological classification, diagnosis of DM (including 'DM sine dermatitis') was achieved in 77.3% of cases. Since the pathology also occurred in perifascicular regions in DM patients, we tested whether vasculopathy, commonly observed in DM, occurs in anti-Jo-1 antibody-positive patients. Membrane attack complex deposits in capillaries, capillary:fibre ratio and capillary density were not different in both groups. Finally, we showed that anti-Jo-1 antibody-positive patients displayed perifascicular necrosis (79% vs. 35%, p=0.007) whereas DM patients exhibited perifascicular atrophy more frequently (85% vs. 63%, p=0.04). Conclusion: necrotizing perifascicular myositis is a new pattern characteristic for anti-Jo-1 antibody-positive patients, and is different from the one observed in DM patients.

40 The anti-Mup44 autoantibody target cN-1A accumulates in cytoplasmic aggregates in cultured human cell lines

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Background and Objectives: Sporadic inclusion body myositis (IBM) is the most common acquired muscle disease in people over 50. The underlying cause of the disease is still unknown. Recently, cytosolic 5'-nucleotidase 1A (cN-1A) was identified as a frequent target of autoantibodies in IBM but not other forms of myositis, or other neuromuscular and inflammatory diseases [1; 2]. cN-1A, a member of the 5'-nucleotidase family, catalyses the conversion of adenosine monophosphate to adenosine and phosphate. However, the subcellular localisation of cN-1A has not been well characterized. Therefore, we aimed to characterise the localisation of cN-1A in established cell lines. Materials and Methods: Expression of cN-1A was analysed in various transfected and non-transfected cell lines. For transfection three different cN-1A constructs were used: 1) pEGFP-cN-1A, encoding a fusion protein of cN-1A and EGFP, 2) pcDNA4-cN-1A and 3) pcDNA4-[D211A]cN-1A, encoding a mutant with a substitution of a highly conserved residue in the predicted catalytic site. Expression in cells transfected with constructs 2 and 3 was induced by the addition of doxycycline. To further investigate the relationship between cN-1A localisation and that of proteins associated with IBM inclusion bodies and rimmed vacuoles (e.g., p62 and TDP-43), we performed co-localisation studies. Results: Endogenous cN-1A was not detectable in HeLa cells, but a diffuse staining pattern was observed in the cytoplasm of HEp-2 and T-Rex HeLa cells. Interestingly, in cells transfected with pEGFP-cN-1A we observed structures resembling previously described 'Rods and Rings' (RR) [3]. However, comparison of EGFP-cN1A with RR in HEp-2 cells in which RR were induced by Ribavirin treatment, we observed no co-localisation of EGFP-cN-1A and the RR marker IMPDH2, although the structures showed similar morphologies. Overexpression of cN-1A in T-Rex HeLa cells resulted in the accumulation of cN-1A at specific sites in the cytoplasm but did not lead to RR-like structures. In these cells, some co-localisation of cN-1A and IBM inclusion body proteins was observed, but the majority did not co-localise with cN-1A. The mutant cN-1A[D211A] accumulated in perinuclear web-like structures, which were different from the accumulations observed for the wild-type protein. Conclusions: Our studies show that EGFP-tagged cN-1A expression leads to the deposition of structures which resemble, but are not the same as, previously described RR structures. Further, in cultured cells overexpressing cN-1A, cN-1A co-localised with IBM inclusion body-associated proteins only to a limited degree. Additional studies will be required to determine whether the cytoplasmic accumulations of cN-1A are physiologically relevant.

41 **Abstract no 41 withdrawn**

42 Psychometric Evaluation of the Sporadic Inclusion Body Myositis (sIBM) Physical Functioning Assessment (sIFA)

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BACKGROUND AND OBJECTIVES: Patient-reported outcomes (PROs) provide an assessment of disease impact directly from the patient's perspective. To assess self-reported physical functioning in patients with sIBM, the sIFA was developed in line with rigorous questionnaire development recommendations outlined in the Food and Drug Administration's (FDA's) PRO guidance. The objective of this research is to establish the validity, reliability and responsiveness of the sIFA using psychometric analyses in accordance with this guidance. METHODS: Data from three small, non-interventional, observational studies of 102 sIBM patients in the United States were analyzed to assess the psychometric properties of the sIFA. A subset of 31 patients were longitudinally characterized over 1 year. Patients completed the sIFA either electronically or on paper forms. Other measures of physical function such as the 6-Minute Walk Distance (6MWD) and the Short Physical Performance Battery (SPPB), as well as the Improved Health Assessment Questionnaire (IHAQ) and Swallowing Quality of Life Survey (SWAL-QOL) were included to evaluate construct validity. Reliability (Cronbach's alpha, test-retest intraclass correlations), construct validity (correlations, analyses of variance), and responsiveness (effect size estimates) were performed. RESULTS: Cronbach's alpha (range 0.86 – 0.91) as well as test retest reliability were highly satisfactory (0.91). Hypothesized correlations with other measures such as IHAQ total score and 6MWD provided evidence of convergent validity. sIBM patients able to walk without assistive devices scored significantly better (sIFA score [36 – 47] than those requiring power mobility or wheelchairs (55-71; p0.01) demonstrating the discriminative ability of the sIFA. Although effect size estimates of responsiveness were small suggesting mild functional progression, preliminary evidence suggests that the sIFA can be used to detect functional change in sIBM patients. CONCLUSIONS: The initial psychometric analyses of the sIFA indicate good reliability, validity, and responsiveness, as well as its value in assessing the impact of sIBM on patient-reported physical function. The sIFA has the potential to facilitate a more comprehensive evaluation of treatment benefit in sIBM patients.

43 Outcome of Muscle impairment and quality of life in patients with polymyositis and dermatomyositis five years following diagnosis

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Background Muscle function in adult Polymyosit (PM) and dermatomyosit (DM) is usually assessed by the manual muscle test (MMT)-8 muscle groups. The use of the disease-specific muscle endurance measure Functional Index-2 (FI-2) has indicated severely impaired muscle endurance in adult PM/DM and a majority of patients might not improve clinically relevant in muscle endurance one year after diagnosis. It is not known how muscle endurance develops over a longer period. Aim of study To study how muscle strength, muscle endurance and quality of life change over five years after diagnosis, and to investigate possible relationships between muscle impairment and quality of life in patients with adult PM/ DM at 5-year follow-up. Methods: Data of muscle strength (MMT-8), muscle endurance (FI-2), and quality of life (SF-36, 0-100, 100 = good health) were retrieved from the Swedish Myositis Register (SweMyoNet) on patients followed at Karolinska University Hospital at one year (n=49) and five years (n=44) after PM or DM diagnosis. Results On a group level muscle endurance (FI-2) was unchanged at 5 years; median 27 (q1-q3 6-72) % of maximal score compared to 1-year follow-up 29 (17-61). Also, muscle strength (MMT) was unchanged at 5 years; 98 (86-100) % of maximal score compared to 1-year 96 (88-99) %. Six out of 26 patients improved in FI-2 20% (of whom 4 70%) and 11/26 patients worsened 20% (of whom 6 50%, of whom 4 70%) at 5 years. 1/28 patients improved in MMT-8 20%, while none worsened. The group (n=33) had significantly more pain (SF-36 Bodily pain), 51 (41-84) at 5 years compared to 1-year, 74 (51-84) (p0.05) while the remaining domains were unchanged. FI-2 correlated strongly to SF-36 Physical Function (PF) (rs=0.80) and moderately to Role-Physical (RP) (rs=0.50), Social function (SF) (rs=0.52) and Role Emotional (RE) (rs=0.54). The MMT correlated equally strong to PF, with moderate correlations to General Health (rs=0.63), SF (rs=0.58) and RE (rs=0.54). Conclusion Forty-two % of patients worsened in muscle endurance while 23% had a clinically relevant improvement while most patients remained unchanged in muscle strength between one and five years after start of immunosuppressive treatment. Patients scored worse pain after 5 years compared to one year post treatment-start. The objective assessments FI-2 and MMT correlated strongly to self-reported physical function. These data are preliminary due to large number of missing data, but raise concern and the need for systematic follow-up in larger cohorts of myositis patients.

44 Work ability in patients with polymyositis and dermatomyositis: an explorative and descriptive study

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OBJECTIVES: This study aimed to investigate the work situation, work ability, work-related risk factors, and influence of the physical and psycho-social work environment in patients with polymyositis (PM) and dermatomyositis (DM). METHODS: Patients with PM/DM were assessed using the Work Ability Index (WAI), and the Work Environment Impact Scale (WEIS). RESULTS: Forty-eight patients (PM n=25 and DM n=23) participated (women/men: 29/19) with a mean age of 54 years (range 28-67 years, SD.10) and mean disease duration of nine years (SD.9). Forty-four percent worked full-time, 31% part-time and 25% were on full-time sick leave. More than 50% self-rated work ability as “poor” or “less good”. Physically strenuous work components were present “quite to very often” in 23-79% and more in patients on sick leave ≥2 years. For those working, the interfering factors in the work environment concerned task and time demands. Supporting factors concerned meaning of work, interactions with co-workers and others. Self-rated work ability correlated moderately–highly positive with percentage of full-time employment, work-related risk factors and opportunities and constraints in the work environment. CONCLUSIONS: Poor self-rated work ability is common in patients with PM/DM indicating a need to identify interfering risk factors and support patients to enhance work performance.

45 Fatigue in adult idiopathic inflammatory myopathies

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Background Patients with adult polymyositis (PM), dermatomyositis (DM) and inclusion body myopathies (IBM) have reduced quality of life. Fatigue is a disabling symptom in other rheumatic diseases, however the contribution of fatigue on quality of life in patients with myositis is largely unknown. Objectives To evaluate fatigue severity in PM, DM and IBM and to compare with population-based reference values, to evaluate a possible difference in fatigue between the myositis entities and gender, to evaluate correlations between fatigue and muscle function, disease activity and other aspects of quality of life and to study how fatigue develops over time. Methods All patients registered in the Swedish Myositis register at the Karolinska University Hospital, n=80 (PM, n=46, DM, n=27, IBM, n=7) (55 women/ 25 men) who had completed the SF-36 survey during 2013 during a yearly check-up were included in this study. They had median age 62 (q1-q3 54-70.5) years, median diagnosis duration 8 (4.5-15.5) years and median disease activity 6 (0-15) mm (VAS physician's global assessment). Data on fatigue (SF-36 Vitality, 0-100 where 100 equals no fatigue), and muscle endurance (Functional Index 2, FI-2) were also collected. All patients who had completed the SF-36 survey at both 2009 and 2013 (n=41) were included to study how fatigue changes over time. Results Patients had worse fatigue on the SF-36 Vitality, (median 50 (30-70)/mean 50 + 26) compared to population-based reference values (mean 67 + 20) (p0.001). There was no difference in fatigue between patients with PM, DM and IBM (medians 48 (30-70), 50 (35-80) and 45(35-50), respectively or between men, 50 (30-80) and women 50 (35-70). Correlations between the SF-36 Vitality and the other SF-36 domains varied between rs=0.54-0.75 with highest correlations to Mental health (rs=0.75) and Social function (rs=0.66). Correlations between the SF-36 Vitality and the FI-2, the HAQ and the physician VAS varied between rs=0.46-0.48 with lower correlations to prednisolone dose, diagnosis duration and age (rs=0.35, 0.01, 0.01, respectively). There was no significant change in fatigue over five years, median 50 (35-72.5) compared to 45 (20-60). Conclusion Patients with PM, DM and IBM have significantly worse fatigue than reference values, with no difference between sub-diagnosis and gender. Fatigue correlated best to mental health and social function. Fatigue scores were unchanged over five years. Fatigue seems to have an impact on quality of life and function in adult myositis and needs to be addressed in clinical care and future research.

46 Evaluation of dysphagia in IBM by novel real-time MRI

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OBJECTIVE: To demonstrate real-time MRI (RT-MRI) as alternative to X-ray-video-fluoroscopy for assessing dysphagia. BACKGROUND: Inclusion-body-myositis (IBM) is a relentlessly progressive muscle disease. Patients can suffer from dysphagia with subsequent aspiration pneumonia and death. Longitudinal swallowing-evaluation is highly desired for clinical trials and daily practice. MATERIAL & METHODS: IBM patients (N=17) were assessed by Sydney-swallow-questionnaire (SSQ) and swallowing-quality-of-life (SWAL-QoL). Technical outcome-measures included flexible-endoscopic-evaluation-of-swallowing (FEES), video-fluoroscopy (VF) and 45s RT-MRI-assessment of swallowing 5ml pineapple-juice, resulting in a bright image appearance due to natural paramagnetic manganese. Clinical parameters included IBM-functional-rating-scale (IBM-FRS), sIBM-specific-functional-assessment-scale (sIFA) and MRC-sum-score. RESULTS: Patients displayed typical clinical deficits reflected by IBM-FRS, sIFA and MRC-sum-score, all significantly correlating with each other. Impaired swallowing was present in 15/17 (88%) patients and 11/17 (65%) displayed a relevant dysphagia per SSQ. SWAL-QoL was impaired compared to published values of healthy elderly individuals. All swallowing questionnaires correlated significantly with each other and FEES. RT-MRI was well tolerated by all patients without aspiration. Quantitative assessment of transit-times in pharynx/upper esophagus displayed significant abnormalities compared to healthy controls previously studied by our group. VF and RT-MRI significantly correlated with each other and all swallowing scales. In patients with severe dysphagia, a propulsion of the cricopharyngeal muscle was readily detected by RT-MRI and VF, yet only RT-MRI allowed distinction of soft-tissue. CONCLUSIONS: Dysphagia is present in the majority of IBM patients and is equally detected by RT-MRI and VF. Compared to VF, RT-MRI facilitates longitudinal assessments and provides a superior distinction of soft-tissue. This novel tool will be of high clinical relevance for assessing dysphagia in IBM as well as in many other conditions. FUNDING: The study was support by an unrestricted research grant from Novartis.

47 **Abstract no 47 withdrawn**

48 ROLE OF MRI IN THE FOLLOW-UP OF PATIENTS WITH MYOSITIS

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Background: Muscle edema on MRI STIR sequences is thought to reflect active inflammation in myositis. However, it is unclear how useful MRI is in following up patients with myositis, in particular which is its sensitivity to change after treatment onset or intensification. Objectives: To assess changes in MRI muscle edema and to correlate MRI edema score with serum creakine kinase (CK) and muscle strength in a cohort of patients with myositis at their first presentation to our centers (T0) and at follow- up after onset/intensification of immunosuppressive therapy (T1). Methods: We enrolled in 2 Rheumatology centers 36 patients, 17 with dermatomyositis (DM) and 19 with polymyositis (PM). In all patients, CK (upper limit of normal 190 U/l) was measured, manual muscle test (MMT) was performed and MRI sequences were acquired within a week. MRI edema (1= present, 0= absent) was assessed bilaterally in 17 thigh and pelvic floor muscles. An MRI composite edema score (0-17) was calculated as described elsewhere (1). The (single measures) intraclass correlation coefficient (ICC) between the Radiologists involved was 0.78. Muscle strength was measured by MMT and graded according to the Medical Research Council extended scale (0-5). The ICC between the 2 physicians performing the MMT was 0.8. Results: Mean age (years±SD) was 54±15. The ratio F:M was 31:5. MRI was positive (edema score 31) in 26 (72%) patients at T0 and in 18 (50%) at T1. Mean MRI edema score was 5±5.2 (mean±SD) at T0 and 2.4±4.5 at T1 (p=0.002). Median and interquartile range (IQR) of MRI edema score were 3.5 (8) at T0 and 0.5 (4.5) at T1. CK was elevated in 22 (61%) patients at T0 and 10 (28%) at T1. CK was 1,816±3,560 at T0 and 531±1,536 at T1 (p=0.002). MMT score was 4.4±0.44 at T0 and 4.6±0.40 at T1 (p=0.02). MRI edema score did not correlate with CK or MMT scores neither at T0 nor T1. Eleven patients had a normal CK but a positive MRI at T0. In 5 of these patients, MRI became negative at T1. In the 11 patients with a normal CK but positive MRI at baseline, MRI edema score decreased from 6.7±5.3 at T0 to 2.4±2.7 at T1. Conclusions: MRI is a useful tool to monitor patients with myositis, and might particularly have a role in monitoring disease activity in patients with a normal serum CK at baseline. Larger studies are required to confirm our findings.

49 **Abstract no 49 withdrawn**

50 Resource Utilization in a US-based Sample of Patients with Sporadic Inclusion Body Myositis (sIBM)

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Background sIBM is a progressive, idiopathic inflammatory myopathy characterized by atrophy and weakness of proximal and distal muscle groups (e.g., knee extensors, wrist/finger flexors) and dysphagia. Progressive weakness results in the need for assistive devices, loss of independence and supportive care. There is a lack of information on the socioeconomic burden of sIBM in the United States (US). Objectives To better characterize the socioeconomic burden of individuals with sIBM in the US. Methods Registered participants of The Myositis Association (TMA) 2013 and 2014 annual patient conferences with a clinical diagnosis of sIBM were invited to participate. A repeated cross-sectional study was conducted at both TMA meetings; participants completed either a paper or web-based version of the Skeletal Muscle Activity and Resource Tool for Sporadic Inclusion Body Myositis (SMART-sIBM), a measure of self-reported resource utilization designed to characterize direct and out-of-pocket expenses including items not reimbursable via US third party payers. A subset of participants participated in both cross-sectional assessments. Results In total, 102 sIBM patients participated in 2013 and 2014 data collection with 71 assessed once and 31 for both years. Overall, mean age was 67.2 years (range 49 – 88), and most (62%) participants were male, Caucasian (94%), and well educated (72% with at least some college). Average number of years since diagnosis and years since first symptoms was 5.3± 4.3 (range 0 – 18) and 11.3±6.4 (range 1 – 35), respectively. Approximately one-third of participants reported being ambulatory without an assistive device; 37% noted use of an aid/brace; 17% used power mobility for long distances; 7% used power mobility most of the time; and 4% noted an inability to walk or stand. Average number of falls per month and healthcare visits because of falls was 1 (range 0 – 4) and 0.71±1.8 (range 0 – 12), respectively. Participants reported a need for frequent health care visits with over half (56%) visiting specialists, and 80% indicated a need for out of pocket house/vehicle modifications and purchase of assistive equipment to accommodate sIBM-related disabilities. More than one-third (36%) of participants required paid help with household tasks, and 60% relied on help from unpaid caregivers (87% spouse). Nearly half (42%) reported a change in job status because of sIBM-related functional limitations. Conclusions This study provides socioeconomic data for the first time in a US-based sample of mostly ambulatory patients with sIBM, indicating the important out-of-pocket financial burden experienced by patients.

51 DOES MRI PROVIDE AN ADDED VALUE OVER SERUM CREATINE KINASE MEASUREMENT IN MYOSITIS?

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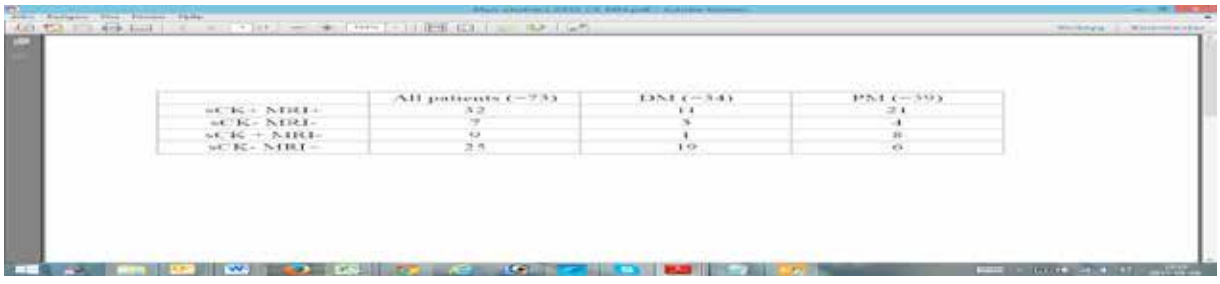
Background: MRI is widely used to evaluate muscle inflammation in myositis. Muscle edema on STIR MRI sequences is thought to reflect active inflammation. However, it is unclear whether MRI has an added value over the cheaper measurement of serum creatine kinase (sCK) levels. Objectives: To assess the concordance between sCK and MRI edema in a cohort of patients with myositis at their first presentation to our centers. Methods: We enrolled in 2 Rheumatology centers 73 patients, 34 with dermatomyositis (DM) and 39 with polymyositis (PM) diagnosed according to Bohan and Peter criteria. 33% of patients were untreated. In all patients, sCK were measured and MRI sequences were acquired at the same time. MRI edema (1= present, 0= absent) was assessed bilaterally in 17 thigh and pelvic floor muscles. An MRI composite edema score (0-17) was calculated by adding the separate scores bilaterally and dividing them by two as described elsewhere (1). sCK was considered positive if values were above the upper limit of normal (190 U/l), while MRI was considered positive if the edema score was at least 1. The (single measures) intraclass correlation coefficient (ICC) between the Radiologists involved was 0.78. Muscle strength was measured by MMT (manual muscle testing) and graded according to the Medical Research Council extended scale (0-5). The ICC between the 2 physicians performing the MMT was 0.8. Results: sCK and MRI were discordant in 47% of patients with myositis, more frequently in DM (59%) than in PM (39%). 56% of patients with DM, but only 15% of those with PM had a positive MRI with normal sCK. There was a significant correlation between MRI score and muscle strength of the hip flexors (Spearman's rho 0.26, p 0.028) but not between MRI score and overall muscle strength. MRI scores did not correlate with sCK. No significant differences were found between treated and untreated patients for any study variable (Mann-Whitney test, p0.05). Conclusions: MRI is a useful tool to assess disease activity in myositis, especially in DM, where it can be identify a sizeable number of patients who have normal sCK. Further studies of larger cohorts are warranted to confirm our findings. References: Clin Exp Rheumatol 2012; 30:570-3



	All patients (=73)	DM (=34)	PM (=39)
sCK+ MRI+	32	14	21
sCK- MRI-	7	5	4
sCK + MRI-	9	1	8
sCK- MRI+	25	19	6

52 DO DERMATOMYOSITIS AND POLYMYOSITIS AFFECT DIFFERENT THIGH MUSCLE GROUPS? A COMPARATIVE MRI-BASED STUDY

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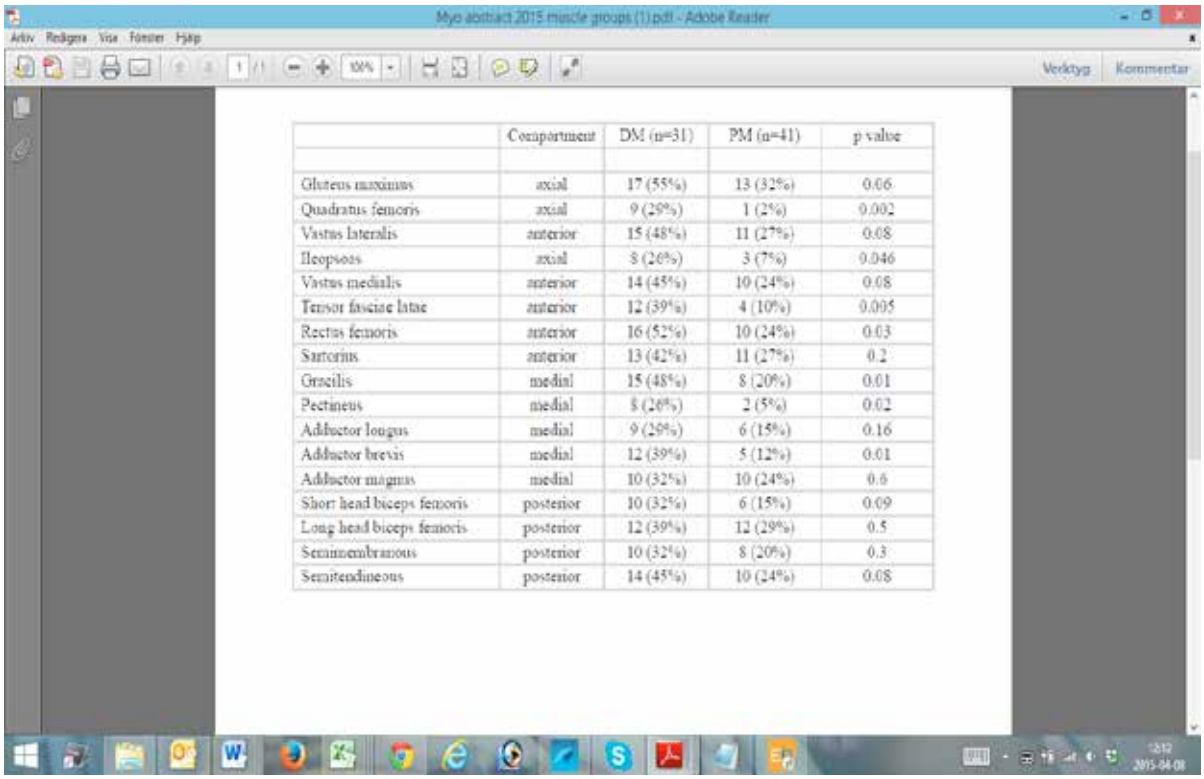
Background: MRI is often used to assess muscle inflammation in myositis. Muscle edema on short tau inversion recovery (STIR) sequences is thought to represent active inflammation. Dermatomyositis (DM) and polymyositis (PM) affect very frequently thigh muscles. However, it is unknown whether DM and PM differ in the respective involvement of the various thigh muscle groups. Objectives: To assess which thigh muscle groups are preferentially affected by DM and PM, respectively Methods: We analysed 72 patients from 2 Rheumatology centers, 31 with DM and 41 with PM diagnosed according to Bohan and Peter criteria. MRI edema (1= present, 0= absent) was assessed bilaterally on STIR sequences in 17 thigh/pelvic floor muscles. An MRI composite edema score (0-17) was calculated by adding the separate scores bilaterally and dividing them by two as described elsewhere (1). The (single measures) intraclass correlatio n coefficient (ICC) between the Radiologists involved was 0.78. Fisher's exact test was used for comparison of binomial data. Results: Age (years, mean±SD) was similar in patients with DM (53 ± 16) and PM (56 ± 16). The F:M ratio was similar in DM (23/8) and PM (32/9). Disease duration (months, mean±SD) was longer (20±31) in DM than in PM (52±68) (p=0.02). The frequency of the thigh muscle groups involved in DM and PM is shown in the Table below. TABLE. Prevalence of involvement of thigh muscle groups in DM and PM. Conclusions: Compared with PM, DM affects more frequently some muscle groups. Posterior muscle groups appear to discriminate poorly between DM and PM. These findings may be useful for differential diagnostic purposes in patients with histological features of DM without the typical skin rash as well as to target physiotherapy on more frequently affected muscles. Larger studies are needed to confirm our preliminary findings. References: Clin Exp Rheumatol 2012; 30:570-3



	Compartment	DM (n=31)	PM (n=41)	p value
Gluteus maximus	axial	17 (55%)	13 (32%)	0.06
Quadratus femoris	axial	9 (29%)	1 (2%)	0.002
Vastus lateralis	anterior	15 (48%)	11 (27%)	0.08
Iliopsoas	axial	8 (26%)	3 (7%)	0.046
Vastus medialis	anterior	14 (45%)	10 (24%)	0.08
Tensor fasciae latae	anterior	12 (39%)	4 (10%)	0.005
Rectus femoris	anterior	16 (52%)	10 (24%)	0.03
Sartorius	anterior	13 (42%)	11 (27%)	0.2
Gracilis	medial	15 (48%)	8 (20%)	0.01
Pectineus	medial	8 (26%)	2 (5%)	0.02
Adductor longus	medial	9 (29%)	6 (15%)	0.16
Adductor brevis	medial	12 (39%)	5 (12%)	0.01
Adductor magnus	medial	10 (32%)	10 (24%)	0.6
Short head biceps femoris	posterior	10 (32%)	6 (15%)	0.09
Long head biceps femoris	posterior	12 (39%)	12 (29%)	0.5
Semimembranous	posterior	10 (32%)	8 (20%)	0.3
Semitendineous	posterior	14 (45%)	10 (24%)	0.08

53 Auto-antibodies in necrotizing autoimmune myopathies: from diagnosis to pathogenicity

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Background and objectives. Necrotizing autoimmune myopathies (NAM) are a newly recognized group of severe acquired myopathies, characterized by prominent myofiber necrosis without significant inflammation. Because of lack of biomarkers, they have been long misdiagnosed as atypical forms of myositis or muscular dystrophies. NAM may be associated to auto-antibodies (aAbs) to signal recognition particle (SRP) or to the statins target 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). We developed quantitative assays of these aAbs and investigated their possible pathogenic role in mice. Methods. Recombinant human SRP or HMGCR was coupled to fluorescent beads and used to measure aAb level by ALBIA (Luminex) with class- or subclass-specific anti-human immunoglobulin G (IgG) Abs. NAM patients were compared to different inflammatory/autoimmune diseases and healthy controls. Reactivity of anti-SRP Abs against muscle was determined. IgGs from aAb-positive patients were transferred to C57BL/6 receiving a single course of cyclophosphamide, or to immuno-deficient Rag-/- mice. Grip strength, locomotor activity and motor performance (Catwalk) was assessed. Frozen muscle sections were analysed after hematoxylin/eosin staining, or after anti-hIgG or anti-C5b-9 immunofluorescent labeling. Label-free proteomic analysis of muscle protein extracts was performed using Orbitrap. Results. Both Luminex assays revealed sensitive and specific. IgG1 was the predominant (anti-SRP) or exclusive (anti-HMGCR) isotype. Only 40% of anti-HMGCR positive patients had been exposed to statins. Titers of aAbs correlated with creatine kinase levels. Incubation of muscle sections with anti-SRP Abs revealed a punctuated intracellular staining with peripheral reinforcement which disappeared upon preincubation with excess recombinant SRP54. Immunogold electron-microscopy revealed immunoreactivity to the endoplasmic reticulum. Anti-SRP positive plasma was toxic to myotubes in vitro. Injection of anti-SRP positive IgGs to mice resulted in decrease in muscle strength. The effect was transient in immunocompetent mice (with production of anti-human IgG Abs) and prolonged in immunodeficient Rag-/- animals. Similar results were found after transfer of anti-HMGCR positive IgGs. As compared to mice receiving control IgGs, the muscle holoproteome was profoundly modified after transfer of anti-HMGCR positive IgG with increase of muscle regeneration- and metabolism-related proteins. Conclusion. Anti-SRP and anti-HMGCR aAb assays are helpful for the diagnosis of a necrositing myopathy: a positive result allows ascribing patients to an auto-immune form. An absence of statin exposure should not eliminate the diagnosis of anti-HMGCR associated NAM. Our experimental results suggest a direct pathogenic role of anti-SRP and anti-HMGCR aAbs through activation of the classical complement pathway, and prompts to evaluate plasma exchanges and/or B cell targeting therapies in NAM.

54 GALECTIN-9 IS A ROBUST BIOMARKER FOR DISEASE ACTIVITY IN JUVENILE DERMATOMYOSITIS AND ACTS AS A T CELL ACTIVATOR

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Background and objectives Juvenile dermatomyositis (JDM) is a rare, but severe chronic systemic autoimmune disease in children, characterized by muscle weakness and a typical skin rash. Clinical evaluation of disease activity remains challenging. Recently, we identified a protein that highly correlates with disease activity in a Dutch JDM cohort: galectin-9 (gal-9). The immunobiological role of gal-9 in autoimmune diseases is still controversial. On the one hand it is known for its immunosuppressive effects by inducing apoptosis in T-helper (Th) 1 and Th17 cells and activating regulatory T cells, on the other hand it has been implicated in T cell activation and Th1 skewing. We wanted to validate the potential of gal-9 as a biomarker in JDM and investigate its immunobiological effects on T cell skewing and activation. Materials and methods Gal-9 was measured in patient's serum of an independent JDM cohort by multiplex immunoassay. For functional experiments, naive CD4 T cells were isolated and stimulated with different concentrations of gal-9, plus anti-CD3 and antigen presenting cells. To test specificity, a gal-9 blocking agent (TIM-3 fusion protein) as well as a control from the galectin family (galectin-8) were included. Flow cytometric analysis of proliferation and T cell activation markers was performed on day 3 and 5 of culture. Cytokines TNFα, IFNγ, IL-13, IL-17 and IL-10 were measured in the culture supernatants until day 7 by multiplex immunoassay. Results Measurement of gal-9 in serum confirmed its high discriminative value for active disease versus remission (P=.0001; AUC 0.894; OR 9.17) even under medication, as well as a strong correlation with the clinical disease activity scores CMAS and Physician's Global VAS. On a functional level, the presence of gal-9 induced a slight but significant increase in naive CD4 T cell proliferation after 3 days of culture. The T cell activation markers CD25, CD69 and TIM-3 showed the same pattern. Gal-9 also increased production of IFNγ, TNFα and IL-10, mainly at day 7. These effects were not seen in the control conditions. Conclusions We confirmed the potential use of a very robust biomarker, galectin-9, that highly correlates with disease activity in juvenile dermatomyositis. Introduction of this biomarker into clinical practice will help to personalize treatment. Functionally, we found that gal-9 is a T cell activator, causing increased proliferation, cytokine production and expression of T cell activation markers. The high levels of circulating gal-9 in JDM patients may therefore contribute to the immunopathogenesis of JDM.

55 DEVELOPMENT AND PRELIMINARY VALIDATION OF A NEW COMPOSITE DISEASE ACTIVITY MEASURE FOR JUVENILE DERMATOMYOSITIS

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Background: Juvenile dermatomyositis (JDM) is a multisystem disease that primarily involves the skin and muscles, but may affect many other organs. The global tools that are currently available for the assessment of disease activity in JDM are centered on physician's evaluation, whereas parent's or child's views are neglected. Furthermore, existing instruments are lengthy and complex. There remains the need for a concise and easily administered score tool that provides an absolute measure of disease activity. Methods: The JDM activity index (JDMAI) includes 4 measures: 1) physician global assessment of disease activity (0-10 visual analog scale (VAS)), 2) parent/patient global assessment of well-being (0-10 VAS), 3) muscle strength assessment, and 4) cutaneous disease activity. Validation analyses were conducted on 140 patients included in a multi-national study. Four versions of the JDMAI were tested, three of which included the hybrid MMT/CMAS as measure of muscle strength (hMC, scores were reversed and divided by 10), together with distinct measures of skin activity: JDMAI-1 included the cutaneous domain of the DAS (0-9), JDMAI-2 the cutaneous VAS (0-10) and JDMAI-3 the skin involvement type and distribution items of the DAS (0-7). A fourth version of the score (JDMAI-4) was identical to JDMAI-3 but the muscle domain was limited to the 3 CMAS items of the hMC (0-20). Results: Construct validity: Spearman's correlations of all JDMAI versions were: strong (r0.7) with total DAS (0.8-0.9), and CHAQ (0.72 to 0.80); moderate (r 0.4-0.7) with CMAS (-0.63 to -0.65, -0.80 for JDMAI-4), pain VAS (0.55 to 0.60), fatigue VAS (0.62 to 0.70), Pediatric Rheumatology Quality of Life Scale (PRQL) (0.66 to 0.70), and MyoFun (0.68 to 0.70); poor (r 0.4) with LDH (0.27 to 0.32), AST (0.33 to 0.35), and ESR (0.35 to 0.38). Responsiveness to change between 2 consecutive visits in those patients who were defined as improved at the second visit: SRM ranged from 0.72 to 0.78. Discriminant validity: all JDMAI versions discriminated between patients rated in remission, continued active disease, and flare by the physician (p0.001) and by the parent (p0.001), and between patients with high, moderate, or low disease activity according to the physician (p0.001). Conclusions: All JDMAI versions showed good construct validity and responsiveness to change, and excellent discriminant validity. The most effective and feasible version of the tools will be selected in future prospective studies, with a view to application in standard clinical care, and clinical trials including treat-to-target.

56 PET-CT WITH 18F-FDG IN THE DIAGNOSTIC OF NEOPLASIA ASSOCIATED WITH INFLAMMATORY MYOPATHIES

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Objectives: The inflammatory myopathies (IM), especially dermatomyositis, are frequently paraneoplastic and diagnosis of the malignancy underlying capital. The aim of our study was to evaluate the additional diagnostic value of PET-CT with 18F-FDG in this indication. Methods: we conducted a single-center retrospective study of 2008 to 2014 for patient monitoring for MI and having been explored by PET-CT with 18F-FDG whole body to look for a not yet detected neoplasia or to specify the extension previous diagnosis of cancer on a conventional radiological imaging (CT abomino thoraco-pelvic and breast screening). Results: of 32 patients with IM (including 16 dermatomyositis), 5 IM were associated with neoplasia already documented previously. PET-CT with 18F-FDG did not identify neoplasia when conventional radiological assessment was negative. PET-CT with 18F-FDG modified the staging for 2 of them. When the conventional radiological assessment suspected paraneoplastic origin, PET-CT with 18F-FDG helped rule out this hypothesis in 5 cases (lung nodules, mediastinal lymph nodes). Conclusions: in IM patients, PET-CT with 18F-FDG has similar sensitivity and better specificity for the diagnostic of associated neoplasia as compared with conventional radiological assessment.

57 DEVELOPMENT OF AN INTERNATIONALLY AGREED MINIMAL DATASET FOR JUVENILE DERMATOMYOSITIS (JDM) FOR CLINICAL AND RESEARCH USE

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Background and objectives: Juvenile dermatomyositis (JDM) is a rare disease associated with significant morbidity. International collaboration is essential to collect sufficient patients for research. This requires standardised data collection suitable for both clinicians and research. A provisional data set has been produced from existing clinical registries [1]. Our objective is to develop the provisional dataset into a consensus-approved minimum core dataset tested in a wider setting, with international agreement. Materials and Methods: A two-stage Delphi-process will engage the opinion of a large number of key stakeholders by e-mail distribution via established international paediatric rheumatology and myositis organisations. Consensus that each outcome should be included in the minimal dataset is defined by ≥70% of participants scoring 'critical for decision making',, but all outcomes will be considered. This, together with a formalised patient / parent participation process will help inform a consensus meeting of international experts. Agreement of ≥80% consensus of all attendees is required for each variable to be included. The resulting proposed minimal dataset will be tested for feasibility within existing database infrastructures. The developed minimal dataset will be sent to all internationally representative collaborators for final comment. Results: The proposed minimal dataset from a consensus meeting of 17 internationally representative myositis experts in March 2015 will be available for presentation. Data from Delphi round 1 (n=171 responses) and round 2 will be used to define the opinion of clinicians representative of paediatric rheumatology/ myositis organisations. Patient and parent opinion will be collated from questionnaires to help inform the consensus process. Conclusions: An internationally agreed minimal dataset has the potential to significantly enhance collaboration, allow effective communication between groups, provide a minimal standard of care and enable analysis of the largest possible number of JDM patients to provide a greater understanding of this disease. The final approved minimum core dataset could be rapidly incorporated into national and international collaborative efforts. References: 1. McCann LJ, Arnold K, Pilkington CA, Huber AM, Ravelli A, Beard L, Beresford MW, Wedderburn LR, UK Juvenile Dermatomyositis Research Group (JDRG). Developing a provisional, international Minimal Dataset for Juvenile Dermatomyositis: for use in clinical practice to inform research. Pediatric Rheumatology 2014.12:31 Acknowledgements: We wish to thank all collaborative groups including Euromyositis, JDRG, IMACS, CARRA, PRINTO, PReS, COMET, OMERACT, NIHR Clinical Studies Group consumer representatives, BSPAR Parent Group, NIHR Young Person,s Advisory Group, UK JDM Young Person,s Group, Cure JM, Myositis UK. Funding body: Arthritis Research UK.

58 Biomarkers for Sub-Phenotyping of Juvenile Dermatomyositis

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Background and Objectives: Juvenile Dermatomyositis (JDM) is a rare and severe autoimmune condition characterised by rash and proximal muscle weakness. It can encompass a heterogeneous spectrum of symptoms, and possible serious complications can include calcinosis, gastrointestinal ulceration, interstitial lung disease and even death. Existing treatment consists of long-term management involving steroids and immunosuppression, and while some patients are responsive and able to come off treatment by 2 years, others fail to respond. In order to improve management of JDM, there is an imperative to define clinical sub-phenotypes that are identifiable by unique biomarkers, and to investigate biological mechanisms underpinning these subtypes. Previously, associations have been identified between certain clinical features and expression of the autoantibodies anti-MDA5, anti-NXP2 and anti-TIF1[gamma]. We hypothesised that JDM patients with known autoantibodies would display distinct pathological phenotypes on muscle biopsy. Materials and Methods: Longitudinal clinical data was collected for patients included in the multi-centre UK Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS; n=468). Plasma or serum samples (n=285) were screened for the presence of autoantibodies by immunoprecipitation and confirmed by ELISA. Muscle biopsies (n=101) were stained and scored using the JDM muscle biopsy score tool, which measures the severity of muscle pathology. Principal component analysis (PCA) was used as a clustering technique in order to define JDM sub-phenotypes. Results: PCA identified two distinct clusters that correlate with the autoantibodies anti-MDA5 and anti-Mi2, reflecting mild and severe histological changes, respectively. Biopsy features in the inflammatory and muscle fibre domains of the score tool accounted for the greatest proportion of variance giving rise to the difference between these clusters. Conclusions: These analyses represent the first step towards identification of JDM sub-phenotypes that correlate with potential biomarkers, and may enable a better understanding of disease mechanisms and a more targeted therapeutic approach.

59 Seropositivity for NT5c1A Antibody in Sporadic Inclusion Body Myositis Predicts More Severe Motor, Bulbar and Respiratory Involvement

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Objectives: To explore phenotypic differences between individuals with sporadic inclusion body myositis (sIBM) who are seropositive for the NT5c1A antibody compared to those who are seronegative. Methods: Cross-sectional clinical, serological and functional analysis in 25 consecutive subjects with sIBM. Results: All subjects met criteria for clinically defined or probable sIBM. 18 of 25 sIBM subjects (72%) were seropositive for the NT5c1A antibody. Females have higher odds of being seropositive (OR=2.30). Seropositive sIBM subjects took significantly longer to get up and stand (p=0.012). There were no significant differences between the two groups in terms of distance covered on a 6-minute walk. Seropositive subjects were more likely to require assistive devices such as a walker or wheelchair for mobility (OR=23.00; p=0.007). A number of secondary (exploratory) outcomes were assessed. NT5c1A seropositive sIBM subjects had lower total MRC sum score and MRC sum score on the right (p=0.03 and 0.02 respectively), Subjects with the NT5c1A antibody were significantly more likely to have complaints of dysphagia (OR=10.67; p=0.03) and reduced forced vital capacity (p=0.005). Facial weakness occurred in 50% of seropositive subjects while it was only seen in 14% of seronegative subjects. Conclusion: In sIBM, seropositivity to the NT5c1A antibody is associated with greater motor and functional disability. Our cross-sectional study also suggests more prominent bulbar, facial and respiratory involvement in subjects positive for NT5c1A antibodies.

60 Effect of abatacept treatment on inflammatory cells in muscle tissue in polymyositis and dermatomyositis patients – A pilot study

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Background: Abatacept, a T cell blocking agent, has been shown to be a potential biological drug for a number of autoimmune diseases. Some small studies have been performed in myositis patients, however, none has evaluated abatacept mode of action in muscle tissue. Methods: Six patients (2 polymyositis and 4 dermatomyositis) were included in this 6 month open pilot study. Abatacept was given as intravenous infusions 10mg/kg at the following time-points 0, 2, 4, 8, 12, 16, and 20 weeks. Muscle biopsies were taken before and after 24 weeks of therapy. Frozen biopsies were sectioned and immunohistochemically stained for different cell markers (CD3, CD4, CD8, CD68, CD163, CD19, CD20, CD31, CD244, CTLA-4, and DC-LAMP-PE) and cytokines (IL-1α, IL-1β, IL-15, and TNF-α). Each tissue section was evaluated coded and the degree of inflammation was scored on 4-grade scale. A change of expression was defined as a change of one score on the 4 graded scale. Responders to abatacept treatment were defined as improved according the IMACS criteria. Muscle strength was measured by MMT-8 and muscle endurance was measured by Functional Index (FI)-2. Results: After 6 month's treatment, 2 patients were responders to abatacept, 4 patients were non-responders. The muscle strength as measured by MMT-8 increased from mean 68.5 to 72.5 in the two responders. In the non-responders, the muscle strength increased from mean 67.5 to 71. The expression of CD3, CD4, CD8, CD68 and CD163 decreased by one grade of the score in one responder while no change was found in the other. The expression of TNF-α increased in both responders. In the 4 patients who were non-responders 3 had higher overall expression of CD3, CD4, CD8 and IL-15 in the follow up biopsy, and the fourth patient did not show any changes. Conclusions: Abatacept may have an effect on inflammatory cells in muscle tissue of patients with polymyositis and dermatomyositis. However, we could not find any correlation between clinical responders and the expression of inflammatory cells in muscle tissue in this pilot study, but more detailed analyses are ongoing.

61 IVIG Usage in the U.S. for the Treatment of the Inflammatory Myopathies: Interim Analysis of the Ig Treatment Outcomes Assessment and Clinical Guidelines Study (the "INSIGHTS Study"):

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OBJECTIVE: To collect clinical data and intravenous immunoglobulin (IVIG) prescribing regimens, and to examine correlation of clinical features with treatment outcomes. BACKGROUND: IVIG is considered standard of care for several neuromuscular disorders, and is FDA-approved for two of these conditions. Despite being off-label IVIG is frequently prescribed for the inflammatory myopathies. However, prescribing regimens vary widely. As part of a larger physician led quality improvement study we have collected prospective data on 55 patients with inflammatory myopathies who have received IVIG over the past three years. DESIGN/ METHODS: The INSIGHTS database captures background clinical and electrophysiologic data from patients referred to NuFactor's home-infusion services. Independent analysis by neuromuscular experts and outcomes are entered into the RedCap database housed at Kansas University. Quality-of-life measures, patient global impressions of change, and follow up assessments are compared with diagnosis, clinical and electrodiagnostic findings, and dose of IVIG. Data from 55 patients with inflammatory myopathies is presented. RESULTS: 19 patients had dermatomyositis (DM), 29 patients had polymyositis (PM), and 6 patients had non-specified myopathy. The average dose of IVIG was 1.8 gm/kg/month. Patients averaged 10 months of therapy. 50/55 patients were on concomitant immunosuppressants with 25/50 on steroids alone, 19 on other immunosuppressives alone, and 6 on combination of steroids and other agents. IVIG was well tolerated with only 12 major adverse drug reactions (ADRs: headache, n=4; TIA, n=1; flulike symptoms or nausea, n=8). There were a total of 155 ADRs in the group with headache being the most common (n=61). Analysis of Patient Global Impressions indicate that 24/55 patients improved with IVIG therapy, 6 patients worsened, and 25 had no change. CONCLUSIONS: The interim data indicate that IVIG is often used as a therapeutic option in U.S. patients with inflammatory myopathy. The average dose used was 1.8 gm/kg/month. IVIG was well tolerated with few major ADRs. Although not controlled, the response rate was similar between DM and PM patients (for each approximately 40% improved). However, a majority either did not change or worsened with IVIG. The INSIGHTS study will continue to enroll patients but we believe the data suggest a controlled trial of IVIG in IIM is indicated.

62 LONG-TERM EFFICACY OF ALEMTUZUMAB IN A PATIENT WITH POLYMYOSITIS

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Background/Objectives: Polymyositis is an idiopathic inflammatory myopathy causing symmetrical proximal muscle weakness characterized by an endomysial mononuclear cell infiltrate, mainly composed of CD8 T lymphocytes and macrophages. Current therapeutic options of polymyositis consist of corticosteroids, intravenous immunoglobulines and immunsuppressants such as azathioprine or methotrexate. However, these therapies are mainly non-specific and often show limited efficacy. Materials and Methods: We here present a case report of a patient suffering from a severe disease course of polymyositis refrectory to standard therapy, who was treated with a single treatment cycle of alemtuzumab and followed up for 3 years. Results: A male Caucasian patient presented was diagnosed with polymyositis after suffering progressive symmetrical muscle weakness and myalgia at the age of 52. The diagnosis was established based on typical clinical presentation, elevated creatine kinase levels, myopathic changes in the electromyogram and muscle biopsy. Therapy with oral prednisolone and azathioprine first resulted in a good treatment response but had to be withdrawn due to severely elevated liver enzymes. Subsequently, the patient was refractory to treatment with ciclosporin, cyclophosphamide, intravenous immunoglobulines and methotrexate. After giving informed consent the patient received alemtuzumab (one cycle at 5x30 mg) leading to clinical improvement, a decrease of CK levels and prolonged walking distance. The patient remained stable for a follow up period of three years. Conclusions: We present the first long-term follow-up case of an adult patient with polymyositis effectively treated with alemtuzumab. Randomized and controlled trials are required to draw definite conclusions.

63 Interim Analysis of Pilot Trial Of Natalizumab in Inclusion Body Myositis

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Background: Inclusion Body Myositis (IBM) is the most common form of inflammatory myopathy in people over age 50. Yet in contrast to polymyositis or dermatomyositis, there are no effective therapies for IBM. The muscle biopsies of patient with IBM show a T cell predominant inflammatory infiltrate suggesting a novel agent that prevents t-cell emigration out of the vasculature may be beneficial in the therapy of patients with IBM. Objectives: Natalizumab is a synthesized monoclonal antibody that blocks the interaction of VLA-4, found on leukocytes and VCAM-1 found on the endothelial surface of the blood vessels. Natalizumab is approved for the treatment of patient with relapsing remitting MS and is very effective in preventing the migration of leukocytes out of the blood vessels. We proposed a phase I trial to look at the safety of Natalizumab in patients with IBM with the hypothesis that blocking the interaction of VLA-4 with VCAM-1 would result in the inability of lymphocyte translocation across the endothelium. This would abolish T-cell infiltration in muscles and improve the course of the disease for patients with IBM. Methods: This is a small phase 1 trial of Nataluzumab in patients with IBM. Natalizumab was delivered intravenously at 300 mg monthly. To date 2 patients have received 3 monthly infusions with no significant side effects. Manual muscle testing, dynomometry, and quality of life measures are assessed at baseline and monthly for six months. Muscle biopsies are performed at baseline and after six months. Results: At three months both patients demonstrated improved strength on the Manual Muscle Testing. MMT 26 improved by 13.7% and 11.8%). Patient 1 reported subjectively feeling stronger with fewer falls and handheld dynomometry showed a 24% improvement in knee etension. By the time of the meeting both patients will have completed six months of therapy and have had pre and post muscle biopsies and this data will be presented as well. Discussion: Although this is an interim analysis on a small number of patients we believe the data suggests that a larger Phase 2 trial of Natalizumab in IBM may be indicated. The ability to present and study the effects of Natalizaumab on the muscle biopsies may help elucidate the underlying mechanisms involved in the improvement with therapy.

64 Acthar in Dermatomyositis and Polymyositis Treatment Registry: An Interim Analysis

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Background: Despite numerous different therapeutic agents used to treat patients with dermatomyositis and polymyositis, only corticosteroids and Acthar have FDA indications for these diseases. 50% of patients do no respond to commonly used medications or have intolerable side effects. Therefore a more effective, better tolerated treatment option is needed. Adrenocorticotrophic hormone gel (H.P. Acthar Gel) s a long-acting formulation of the full sequence ACTH that may include other pro-opiomelanocortin peptides. ACTH is known to cause the release of endogenous coritcosteroids ands also acts through a system of melanocortin receptors which are widely distributed throughout the immune system, muscle, endothelial cells and other tissues. This registry was undertaken to study the patient demographics, dosing, side effects, and efficacy of Acthar in patients with dermatomyositis and polymyositis. Methods: Adult patients with refractory polymyositis and dermatomyositis in whom the treating physician decided to use Acthar to treat their muscle weakness were included. Muscle biopsy slides were reviewed by a blinded myopathologist. Demographics, laboratory data, strength measurements, as well as validated quality of life scores were collected at baseline, 3,6,9, and 12 months. Results: To date 28 patients have been enrolled into the registry. 9 patients had DM and 19 had PM. The median age was 58 with 18 patients being female and 10 being male. The patients had an average of 3.6 years since their diagnosis and treated with an average of 3.8 medications before being prescribed Acthar. 26/28 patients had been treated with corticosteroids previously and 7 patients were on concomitant steroids at the time Acthar was prescribed. All 28 patients were started on 80 units of Acthar subcutaneously twice a week. 17/28 patients had an increase in muscle strength by 3 months. Positive predictors of response were evidence for disease activity as manifested by elevation in muscle enzymes at baseline and a recent objective decline in muscle strength. There were no serious adverse events. Adverse events included worsening of glycemic control in patients who were previously known to be diabetic, lower extremity edema, rash, and vertigo. Conclusion: This is an interim analysis with a target enrollment of 100 patients. To date, Acthar at 80 units twice a week seems to be well tolerated in patients with dermatomyositis and polymyositis. In 28 patients studied to date there have been no serious adverse events. The patient population was very refractory to previous therapies and 60% of the patients responded within three months.

65 SUBCUTANEOUS IMMUNOGLOBULIN IN INFLAMMATORY MYOSITIS: DIRECT PROTOCOL OF ADMINISTRATION

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Background and Objectives Subcutaneous immunoglobulin (SCIg) is a blood product containing immunoglobulin G from normal subjects, initially used in primary immunodeficiency diseases. More recently their efficacy has been reported in several immune-mediated disorders or neurological conditions, such as idiopathic inflammatory myositis (IIM). We here report the efficacy of a direct protocol using 20% SCIg in seven patients (five females and two males, mean age 55 years) with IIM. Material and methods: In our clinic we used SCIg in patients with IIM according to two different schedules of administration: 1) the sequential protocol in which 20%SCIg (Hizentra ®, CSL Behring) is employed as maintenance treatment after a 6-month therapy with intravenous immunoglobulin (IVIg) in case of severe disease (dysphagia, head drop…); 2) the direct SCIg protocol in patients with moderately active PM/DM having either a new onset, recently relapsed disease or refractory PM/DM. In this case SCIg are used as add-on treatment to glucocorticoids. Results In each patient, SCIg was infused at a weekly dosage of 0.2-0.8 g/kg. After a mean follow up of 18 months in all of the patients we documented an improvement of muscle strength, assessed by the modified MRC muscle score and Rankin modified score, and a reduction of serum CK levels and of the daily prednisone dose. Among the two patients, being treated with an immunosuppressive agent, one was able to stop it and the other to reduce the daily dose.

66 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) is one of the major contributors to morbidity and mortality of polymyositis (PM) and dermatomyositis (DM)*. Objectives: To study the efficacy and the safety of intravenous cyclophosphamide (IVCYC) according to the Euro-Lupus nephritis protocol** (500 mg IVCYC every other week with a minimum of 6 doses) for progressive ILD in PM and DM patients. Methods: Twelve PM/DM patients with progressive ILD (mean age 54 years ± SD 8) were treated with 500 mg IVCYC according to the Euro-Lupus nephritis protocol as first line treatment between October 2007 and December 2014. IVCYC was given in combination with oral prednisolone 0.75- 1.0 mg/kg/day for 4 weeks, then gradually tapered. At start of treatment the median disease duration was 4 months ± IQR 11.Exertional dyspnea, dry cough, need for supplemental oxygen, pulmonary function tests (PFTs), high-resolution computed tomography (HRCT), were recorded at start of treatment and after a median follow-up of 5 months ± IQR 5. Results: Before therapy, all patients had exertional dyspnea, 11 of 12 complained of dry cough and 1 required supplemental oxygen, the median 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 57± IQR 25, 67± IQR 20, 63± IQR 25, 64± IQR 17, 57± IQR 25, respectively. The patients received a total mean of 4.6 gr ± SD 1.4 IVCYC. At follow-up, 8 of 12 patients showed regression of both exertional dyspnea and dry cough. One patient kept requiring supplemental oxygen. The median values of PFTs improved; the difference between baseline and follow- up FVC% and VC% median values was statistically significant (p=0,01 and p=0,02, respectively). Five of 12 patients showed 10% improvement of TLC% and 3 of 12 had 15% improvement of DLCO%. The HRCT showed no signs of progression in 8 of 12 patients, the extent of abnormal lesions decreased in 5 and remained unchanged in 3. No adverse events or drug toxicity were observed during the study period. Conclusions: Our preliminary data suggest that the Euro-Lupus nephritis IVCYC protocol improved PFTs and HRCT findings in PM/DM patients with progressive ILD and it was not associated with adverse events or drug toxicity. Longitudinal controlled studies are needed to confirm the efficacy and the safety of this treatment protocol.

67 Toll-like Receptor Antagonism as a Novel Treatment Approach for Dermatomyositis

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Background: Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy characterized by muscle weakness, skin rash and/or calcinosis, fatigue, elevated muscle enzymes in serum, and histological characteristics including mononuclear cell infiltration and myofiber degeneration. Toll-like receptors (TLRs) are a key component of the innate immune system, and are involved in regulating inflammation and adaptive immunity. In DM, damaged tissues release damage associated molecular patterns (DAMPs), which activate TLR signaling leading to induction of the inflammatory cascade. As a consequence, a self-sustaining autoinflammatory response contributes to chronic inflammation in affected tissue. Targeting TLRs to block inflammation is a novel therapeutic approach for DM that has the potential to reduce chronic inflammation and improve clinical symptoms. Here we propose the therapeutic rationale for TLR antagonism in DM, as well as preliminary plans to advance an investigational TLR antagonist candidate into a proposed Phase 2 multicenter, randomized, double-blind, placebo-controlled clinical trial in DM subjects. Results: Multiple lines of evidence have been assembled to suggest the role of TLRs in the pathogenesis of DM. A retrospective study evaluating muscle biopsy samples showed that TLR9, TLR4 and TLR2 were significantly over-expressed in skeletal muscle and infiltrating cells in DM subjects compared to controls. Cellular sources of TLR expression in DM subjects included infiltrating CD4+ T cells, CD20+ B cells, and CD68+ macrophages. Cytokines such as IFN-γ, IL-4, IL-17 and TNF-α were over-expressed, suggesting involvement of the NF-κB signaling pathway. Expression of these cytokines had significant positive correlations with expression of TLR9 and TLR4. In addition, several other studies have shown TLR over-expression in DM muscle biopsies. In preclinical studies in mouse models of skin inflammation, TLR antagonist candidates blocked IL-17, IL-6, IFN-γ and IL-1. In clinical studies in patients with psoriasis, an autoimmune disease in which TLRs are implicated, TLR a ntagonist candidates were generally well tolerated, blocked induction of the IL-17 pathway, and demonstrated clinical activity. Conclusions: DM is a severe and chronic inflammatory myopathy. TLRs are key drivers of inflammation and have been shown to be significantly over-expressed in DM muscle biopsies. In DM subjects, TLR expression has been correlated with expression of key cytokines. TLR antagonist candidates have demonstrated preclinical and clinical activity in models of skin inflammation and patients with psoriasis, respectively. Collectively, these data support advancing a TLR antagonist drug candidate into a Phase 2 proof-of-concept trial in DM subjects.

68 Efficacy of Rituximab in Refractory Inflammatory Myopathies Associated with Anti- Synthetase Auto-Antibodies: an Open-Label, Phase II Trial

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Background and objectives: Anti-synthetase syndrome (anti-SS) is frequently associated with myositis and interstitial lung disease (ILD). We evaluated prospectively, in a multicenter, open-label, phase II study, the efficacy of rituximab on muscle and lung outcomes. Material and methods: Anti-SS patients refractory to conventional treatments (prednisone and at least 2 immunosuppressants). They received 1 g of rituximab at D0, D15, and M6. The primary endpoint was muscular improvement based on manual muscular testing (MMT10, Kendall score in 10 muscles) at M12. Secondary endpoints were normalization of creatine kinase (CK) level, ILD improvement based on forced vital capacity (FVC), and a decrease in treatment. Results: Twelve patients were enrolled, and 10 completed the study. Seven patients had an increase of at least 4 points on MMT10. CK level decreased from 1331.5 IU/L (range, 48-11,718] to 74.5 IU/L (range, 40-47,857). Six patients had a decrease in treatment. Corticosteroid dose decreased from 52.5 mg/d (range, 10-70) to 9 mg/d (range, 7-65). At baseline, all 10 patients presented with ILD. At M12, improvement of FVC was observed in 5 of 10 patients, stabilization in 4 of 10, and worsening in 1. Conclusions: In patients with refractory anti-SS, rituximab treatment is associated with improvement in muscular and pulmonary parameters in approximately 50% of them. Rituximab should now be evaluated in a larger, controlled study for this homogenous group of patients.

69 ABATACEPT IN THE TREATMENT OF ADULT DERMATOMYOSITIS AND POLYMYOSITIS: ARTEMIS, A RANDOMIZED, TREATMENT DELAYED-START TRIAL

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Background and Objectives The predominance of T cells in inflammatory infiltrates in affected myositis muscle, and associations with certain HLA class II alleles, indicate a role for T cells in the disease process in dermatomyositis (DM) and polymyositis (PM). Their role may be direct as mediators of muscle fiber necrosis and as producers of molecules that may have negative effect on muscle fiber contractility. The objective of the study was to assess the clinical efficacy of Abatacept, an agent blocking T cell co-stimulation, on disease activity in adult DM and PM patients in a randomized treatment delayed-start trial. Materials and Methods DM and PM patients with persisting signs of active disease after treatment with glucocorticoids and ≥1 immunomodulating drug for ≥3 months were randomized to receive either immediate active treatment with Abatacept intravenous (10 mg/kg) infusions or a delayed start after 3 months. The primary endpoint was the number of responders, defined as improved according to the IMACS definition of improvement (DOI), after treatment for 6 months. The secondary endpoint included the number of responders in the delayed onset arm compared to the active treatment arm at 3 months, and the efficacy after 6 months treatment on the components of the IMACS core set measures for disease activity, and health-related quality of life assessed by SF-36. Results Among 20 randomized patients (9 DM, 11 PM; 13 female, 7 male), 17 were included in the analyses and 8 (47%) achieved the DOI after 6 months of active treatment. No differences between DM and PM, or female and male patients were seen. Three months after study start, 5/10 (50%) patients in the active treatment arm were responders compared to 1/7 (14%) patients in the delayed onset arm. After active treatment for 6 months, significant improvement was seen in muscle strength, assessed by MMT-8, from (median) 70 to 73 (p=0.0082), in gastrointestinal disease activity from 3 to 0 (p=0.0156), and in muscle disease activity from 18 to 10 (p=0.0133). SF-36 physical was significantly improved from median 31 to 36 (p=0.0054). There were 36 adverse events (AE) reported. Eight AE (infections, flank pain and dizziness) were judged as related to the drug (4 mild and 4 moderate). Conclusions Treatment of PM and DM patients with Abatacept resulted in improved muscle performance and health-related quality of life in half of the patients, and warrants further investigation. Acknowledgement This research received funding support from Bristol-Myers Squibb.

70 WORKING TOWARDS STANDARDS OF CARE FOR PATIENTS WITH MYOSITIS: RESULTS OF A SERVICE EVALUATION QUESTIONNAIRE

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INTRODUCTION Idiopathic inflammatory myopathy negatively impacts the lives of around 10,000 UK sufferers. Care provision is hampered by a lack of best practice guidelines. To date, only the Arthritis and Musculoskeletal Alliance have defined standards of care for patients with connective tissue diseases. No statement addressing specific needs of those with myositis exists. METHODS A questionnaire was produced by the authors (JBL, HC). Items surveyed were informed by outcomes of a patient focus-group at the Myositis UK annual meeting (July 2014) and included; pathway to diagnosis, care arrangements, treatments offered and access to local services. The questionnaire was distributed to all members of Myositis UK (n≈200). RESULTS 76 completed questionnaires were returned (response = 38%). Average age was 58 years. 70% were female. The proportion of respondents with DM, PM and IBM was 36%, 28% and 36% respectively. Most respondents presented to their general practitioner (GP) and were referred to a specialist (75%). Most waited at least 1 month before this referral (62%). Respondents with DM were most commonly initially referred to dermatology (46%), PM to rheumatology (62%) and IBM to neurology (56%). The median wait to diagnosis from point of first specialist review was 3 months (range 0-84). 49% were initially given an incorrect diagnosis. Rheumatologists oversee the care of most respondents with DM and PM (64%, 90%). Most with IBM are cared for by neurologists (63%). 21% of those with IBM indicated that they were not under specialist follow-up. Overall, 34% felt at least "satisfied" with access to a myositis specialist nurse. None with IBM, and only 25% overall, felt at least "satisfied" that psychological aspects of disease were adequately managed. Of those receiving any treatment, 52% felt at least "satisfied" that they had received adequate side-effect counselling and 17% with access to a specialist pharmacist. CONCLUSIONS Key unmet needs and variation in provision are highlighted. In particular misdiagnosis and delayed diagnosis is common and low satisfaction is reported with access to specialist nurses, pharmacists and regarding side-effect counselling and management of psychological aspects of disease. A high proportion of patients with IBM are not under active specialist follow-up, preventing their participation in ongoing clinical trials. These results will inform the production of a 'Standards of Care' statement specifically tailored to the needs of patients with myositis. By defining minimum expected standards of care we aim to help address identified unmet needs and promote consistent good practice.

71 Gene expression profile in muscle tissue before and after immunosuppressive treatment in patients with myositis

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Background: Polymyositis (PM) and dermatomyositis (DM) are autoimmune muscle diseases, characterized by infiltration of inflammatory cells, production of cytokines as well as the expression of major histocompatibility complex (MHC) class I on skeletal muscle fibers. Patients are conventionally treated with high doses of glucocorticoids in combination with additional immunosuppressive drugs. Nevertheless, many patients have persisting muscle weakness even after prolonged treatment. Objectives: To investigate the effect of conventional immunosuppressive treatment on gene expression profiling in skeletal muscle biopsies from patients with PM and DM, taken before and after treatment in order to develop further understanding of molecular mechanisms that might contribute to the persisting compromised function. Methods: Biopsies (vastus lateralis muscle) from six newly diagnosed, untreated patients with PM (n=2) or DM (n=4) before and after a median of 8.5 months of immunosuppressive treatment were examined by gene expression microarray analysis. Functional associations were analyzed by using Ingenuity Pathway Analysis. Tissue sections from corresponding biopsies were evaluated for MHC class I molecule expression, inflammatory infiltrates, and signs of fiber regeneration/degeneration. Selected genes that displayed changes in expression were validated by western blot (WB). Results: Evaluation of the biopsies taken after a median of 8.5 months of treatment showed MHC class I staining in muscle fibres, presence of CD3 positive cells (few positive cells scattered throughout the tissue) and CD68 positive cells (ranging from scattered mononuclear cells to infiltrates). By microarray analyses alterations were observed in the overall gene expression in muscle tissue. As expected most of the genes related to immune response such as interferon (IFN) pathway and inflammasome (e.g., AIM-2 and Caspase-1) were down-regulated. In addition alterations were seen in the expression of genes involved in muscle tissue remodeling (e.g., FKBP5) suggesting protein breakdown as well as muscle regeneration. Validation of gene expression by WB confirmed changes in protein expression; AIM-2 ($p=0.044$) and Caspase-1 ($p=0.035$) were significantly down-regulated, while FKBP5 ($p=0.020$) was up-regulated after glucocorticoid treatment. Conclusion: Together, these data indicate that during conventional immunosuppressive treatment of myositis patients; transcriptional modifications in genes involved in muscle tissue inflammation and remodelling are taking place; their changes could be validated by protein expression. The alteration indicate that besides the beneficial down-regulation of inflammatory pathways there are signs of protein breakdown which may have a negative consequence in muscle repair and could contribute to a defect recovery of muscle strength that might be seen in patients with PM/DM despite treatment.

72 Altered serum fatty acid profiles in patients with polymyositis or dermatomyositis compared to healthy individuals and in relation to immunosuppressive treatment

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Background Polymyositis (PM) and dermatomyositis (DM) are chronic autoimmune diseases, characterized by muscle fatigue and low muscle endurance. Histopathological characteristics of muscle biopsies are infiltration of inflammatory cells, muscle fiber degeneration and regeneration. Conventional treatment includes high doses of glucocorticoids and immunosuppressive drugs, however, only a limited number of patients recover muscle function. Our group has recently found that immunosuppressive treatment has significant effects on gene expression related to lipid and fatty acid (FA) metabolism that may contribute to the persistent muscle weakness often seen in myositis patients. Lipid dysregulation might lead to generation of lipotoxic mediators which contribute to cell dysfunction or death. Furthermore, a number of studies have confirmed the important effects of FA on skeletal muscle growth, strength and inflammation. However the involvement of lipids and FA in the pathogenesis of polymyositis and dermatomyositis has not been clarified. Objectives To analyze lipid and FA profiles in sera from patients with polymyositis or dermatomyositis in comparison to healthy individuals and in relation to immunosuppressive treatment. Methods Serum samples were obtained from 14 patients with established PM or DM and 12 healthy individuals. Serum lipids were extracted by using liquid-liquid extraction (LLE). FA composition of total lipids was determined by gas chromatography flame ionization detector (GC-FID). FA composition of several lipid classes e.g., triacylglycerols, phospholipids, sphingolipids and lysophospholipids was analyzed by using liquid chromatography tandem mass spectrometry (LC-MS/MS). In addition, serum samples from 8 myositis patients before and after 6 months of immunosuppressive treatment was extracted by LLE and analyzed by LC-MS/MS. Results Our preliminary results suggest that FA composition of total serum lipids was different in myositis patients compared to healthy donors; the levels of palmitic16:0 acid was significantly higher (0.05) in myositis patients whereas the levels of arachidonic 20:4(n-6) acid was significantly lower (p=0.05). Immunosuppressive treatment did not affect the total levels of lipid classes in the serum from myositis patients. However, the levels of phosphatidylcholine (PC) PC(32:1) , phosphatidylethanolamine (PE) PE(36:5) and lysophosphatidylcholine (LPC) LPC(16:1) were all significantly higher (p0.05) in myositis patients after 6 months of immunosuppressive treatment. Conclusions FA composition of total serum lipids is altered in myositis patients compared to healthy controls. Immunosuppressive treatment resulted in changed FA composition of serum PC, PE and LPC. These findings indicate that FA metabolism might be deregulated in PM and DM patients and may be further affected by immunosuppressive treatment.

73 Developing Standardised Treatment for Adults with Myositis and different Phenotypes (STAMP)

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Background: The evidence base for treatment of idiopathic inflammatory myopathies (IIM) is extremely limited and development of treatment guidelines is further hampered by significant heterogeneity between IIM subtypes. As part of the STAMP project we aimed to establish current prescribing practices used to treat adults with IIM. Methods: An electronic survey based on 8 clinical scenarios designed to reflect different IIM subtypes was distributed internationally to experts and non-experts involved in the treatment of IIM via special interest groups and within the UK via the British Society for Rheumatology. Participants were asked to select first-line treatment preferences in each situation (defined as one of their top three choices). Scenario 6 was later excluded due to the wide range of responses, which we felt suggested a lack of clarity of the case vignette. Results: 107 survey responses were received, 52 of which were from UK based clinicians, (19 who considered themselves an expert in IIM and 33 who did not). Only 13 of the 55 non-UK based respondents considered themselves non-expert in myositis. Analysis of UK data demonstrated that, while overall there was general agreement on first-line DMARD treatment preferences within and between expert and non-expert groups, agreement was greater between experts where 75-100% selected the most popular first-line treatment for each scenario. In all scenarios, experts selected a more limited range of first-line DMARD treatments than non-experts (mean average 6.1 vs 10.8, p=0.002). Furthermore, non-experts chose more expensive (Rituximab, Immunoglobulin) and more toxic (Cyclophosphamide) drugs. Internationally, first-line treatment preferences were also similar suggesting comparable treatment approaches. Scenario 5 (inclusion body myositis [IBM]) showed the greatest disparity in suggested treatment; 1 in 4 respondents recommended no pharmacological treatment, and experts were less likely to recommend pharmacological treatment than non-experts (68% vs 80%, p=0.07). Conclusions: In most scenarios assessed, comparable treatment approaches were suggested by survey respondents despite a lack of robust evidence -based or treatment guidelines. In some scenarios, namely IBM, the treatment approach varied considerably. We speculate that this may reflect a desire to try ‘something’ that may help, or a lack of diagnostic certainty. Based on UK data, self-reported experts appear to have a more uniform treatment approach. The increased range of drugs selected by non-experts, including more expensive and potentially toxic treatments, highlights a requirement for clear treatment guidelines. More data is required from non-UK physicians and is currently being collected.

74 Increasing incidence of immune mediated necrotizing myopathy, anti-HMGCR antibodies and statin use – single centre experience

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Objectives. Immune mediated necrotizing myopathy (IMNM) is a member of a group of idiopathic inflammatory myopathies (IIM) and it is characterized by predominant presence of necrotic muscle fibres and absence of inflammatory infiltrate in muscle biopsy and variable response to immunosuppressive treatment. We have analysed the incidence of IMNM in our centre over the last ten years and explored the role of statins as possible causative agents. Methods. A retrospective evaluation of muscle biopsy results, clinical and laboratory data including antibody associations of all patients with IIM newly diagnosed between 2004 and June 2014 was performed. Available sera were tested for the presence of anti-HMGCR autoantibodies. Results. Out of 357 biopsied patients, 233 fulfilled criteria for inflammatory/immune mediated myopathy, including 27 (11.6%) classified as IMNM. There were no patients with IMNM diagnosed between 2004 and 2007; subsequently 2-3 cases of IMNM per year were seen during the period of 2008 to 2011 with a substantial increase to 18 cases (66.6% of all IMNM biopsies) in 2012-2014. This rapid change represents a significant increase compared with previous years (p0.0001). 217 available serum samples were tested for anti-HMGCR and 15 (6.9%) were identified to be positive; 11 of them had necrosis in biopsy. Thirteen out of 27 IMNM patients (48%) had a history of statin use; eleven (85%) of them had anti-HMGCR antibodies. There were no patients with positivity of anti-HMGCR antibodies without prior exposure to statins. Conclusions. Our data show an increasing incidence of IMNM, which is mainly accounted for by anti-HMGCR positive IMNM associated with use of statins.

75 SKIN ACCUMULATION OF ADVANCED GLICATION ENDPRODUCTS (AGES), INSULIN RESISTANCE AND MONOCYTE CHEMOATTRACTANT PROTEIN-1 ARE EARLY MARKERS OF CARDIOMETABOLIC RISK IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background/Objectives: Many data suggest that AGEs and insulin resistance (IR) play an important role in the development of atherosclerosis and cardiovascular (CV) diseases. Homeostatic metabolic assessment (HOMA) index is a validated method to assess IR. Monocyte chemoattractant protein-1 (MCP1) is a chemokine involved in the recruitment of monocytes to inflammatory sites. Since AGEs, MCP1 and IR are altered during chronic inflammation, abnormalities of these parameters may be hypothesized in idiopathic inflammatory myositis (IIM). The primary aim of this study was to evaluate whether AGEs, HOMA index and MCP1 are increased in patients with IIM; the secondary aim was to explore whether these markers are related to clinical and epidemiological data, disease activity and a measure of subclinical atherosclerosis (intima media thickness - IMT) measured at carotid level. The last aim was to evaluate the correlations between AGEs, HOMA index and MCP1. Methods: Twenty-seven IIM patients (F/M 19/8; mean age 56.7±12.3; mean disease duration 8.8±7 years, 13 polymyositis and 14 dermatomyositis) fulfilling the Bohan and Peter criteria were enrolled and compared with 12 control subjects (CT) matched for age, sex and CV risk factors (smoking habits, hypertension, family history of CV disease, body mass index). AGEs were determined by skin autoflorescence (SAF), a validated noninvasive measure AGEs, at level of left forearm. In IIM group AGEs levels were analyzed vs demographic data, disease activity parameters according to IMACS activity criteria, disease duration, cumulative corticosteroids dose. IMT was measured on B-mode ultrasound image sequences of right common carotid artery. Serum levels of MCP1 and insulin concentration (FPI) were measured through ELISA kit; HOMA was calculated as (FPI X glucose)/22.5. Results: IIM patients had higher subcutaneous AGEs (mean 2.83± 0.6360 vs 2.187±0.477 p0.002) and HOMA values (mean 5.069±5.425 vs 2.431±1.749 p0.05) than CT. However, carotid IMT was similar while MCP1 concentrations tended to be higher than in CT (195pg/ml±111 vs 152±65) although not significantly different. AGEs was not associated with myositis duration, cumulative corticosteroid dose, disease activity parameters. In the whole cohort, AGEs increased with age (p=0.011) and were directly correlated with IMT (p0.02) and MCP-1 (p0.02). A mild correlation, although not statistically significant between SAF and HOMA-IR was also reported (p=0.09). Conclusions. These preliminary data show that IIM patients are at higher risk of subclinical CV involvement and suggest that AGEs may represent an early marker of CV disease in myositis. Data on wider populations are needed to confirm these observations.

76 Clinical and immunological predictors of malignancy for adult Japanese dermatomyositis patients with anti-transcriptional intermediary factor 1 (TIF1) autoantibodies

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Objectives. Malignancy is a representative complication and a prognostic factor for patients with dermatomyositis. Previous reports revealed that malignancy is associated with anti-transcriptional intermediary factor 1 autoantibodies (anti-TIF1), which are one type of myositis-specific autoantibody. However, factors associated with malignancy in patients with anti-TIF1 have not been elucidated. In this study, we aimed to identify factors predictive of malignancy in patients with anti-TIF1. Methods. A total of 24 adult Japanese dermatomyositis patients with anti-TIF1 who visited Kanazawa University Hospital from 2001 to 2013 were enrolled in this study. Anti-TIF1 was identified by immunoprecipitation assays. Clinical and immunological factors associated with malignancy were examined by logistic analyses. Results. In this cohort, 15 of 24 (63%) dermatomyositis patients with anti-TIF1 had malignancy. No significant trend was observed concerning the type of malignancy. Age at onset of patients with malignancy (66 } 13 years) was significantly older than for those without malignancy (54 } 14 years) (P = 0.02). Our multivariate analyses revealed that male gender (OR = 6.1e+7, 95% CI 2.0 - uncalculated, P = 0.0171) and serum creatine kinase greater than 583 (OR = 1.7e+8, 95% CI 3.8 - uncalculated, P = 0.0053) were independent factors associated with malignancy. The overall cumulative rate of survival from the time of dermatomyositis in all 24 patients with anti-TIF1 was 67% at 5 years. The survival rate for patients with malignancy was significantly decreased compared with that for those without malignancy (47% vs. 100%, P = 0.0116 by log-rank test). Conclusions. As reported previously, anti-TIF1 is associated with malignancy. In addition, male gender and a higher serum creatine kinase level are factors independently predictive of malignancy in dermatomyositis patients with anti-TIF1.

77 Analysis of anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies in idiopathic inflammatory myopathies

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Objective. The objective of this study was to detect anti-HMGCR antibodies in Chinese IIM patients and to analyze their potential clinical associations. Methods. The sera of 355 patients with IIM and 255 controls (30 healthy subjects, 30 with primary Sjögren¡¯s syndrome, 15 with ankylosing spondylitis, 55 with systemic lupus erythematosus, 50 with rheumatoid arthritis, 5 with systemic sclerosis, 20 with hyper-CK-emia, 35 with other connective tissue diseases, 15 with metabolic myopathies) were tested for anti-HMGCR antibodies using the method of ELISA. Anti-HMGCR levels, creatine kinase (CK) levels, muscle strength, muscle biopsy and efficacy of treatment were assessed in anti-HMGCR positive patients. Results. Twenty out of 355 patients (5.6%) were found to be anti-HMGCR positive in IIM patients. Their mean age was 41.6 ¡À 13.8 years and the group was predominantly female (85%). Statin-exposure was recorded in only 10% of anti-HMGCR positive patients, most of those (90%) was statin-naïve. Sixteen patients had a muscular deficit (80%) and 14 patients had myalgia (70%). Progressive onset (6 months) was noted for most of them (70%). Dysphagia was observed for 10 patients (50%), and skin rash was also noted in 35% of them. Besides weight loss (25%), interstitial lung disease (ILD) (15%) and arthralgia (25%) were observed. Electromyography (EMG) of an involved muscle reveals an irritable myopathy in most cases (80%) and a non-irritable myopathy in a few. Hyperlipidaemia (60%), osteoporosis (40%) and hypopotassemia (25%) were common complications. The mean CK level was higher (5184.4 ¡À 5366 IU/L) than that of patients with negative antibody. Anti-HMGCR antibodies titers were corre lated with initial CK levels (r = 0.504; p 0.05). A few of patients (33.3%) did not respond to treatment. Anti-HMGCR antibody levels did not normalize in 83.3% patient. Most of patients (81.8%) had a prominent myofiber necrosis without or with little inflammatory on muscle biopsy. Conclusion. This study confirms the observation and description of anti-HMGCR antibody associated with necrotizing autoimmune myopathy (NAM) and the majority of patients were statin-unexposed.

78 **Abstract no 78 withdrawn**

79 HEART INVOLVEMENT IN INFLAMMATORY MYOSITIS: A BRIEF REPORT OF OUR EXPERIENCE

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Background and Objectives: Heart involvement in idiopathic inflammatory myositis (IIM) constitutes a major prognostic factor. It has a frequency between 6 and 75%, depending on whether clinical manifestations or subclinical involvement are considered, and is described as cause of death in 10-20% of cases. We here report our data about patients with IIM complicated by heart disease. Material and methods All medical records of patients with IIM followed in our center of Clinica Medica from January 1995 to December 2014 were retrospectively analyzed according to a standardized protocol. 16/102 patients with IIM, diagnosed according to Bohan and Peter criteria (6 PM class I, 5 DM class II, 3 PM class V and 2 DM class III), and heart involvement were identified. The median age at diagnosis was 59.3 years. Results An asymptomatic cardiac involvement was reported in most of patients, while only 6/16 patients (38%) had symptoms. The more frequent manifestations included: valvular heart diseases (43.7%), cardiomyopathies (50%) and conduction defects (43.7%). The most of patients (62.5%) had concomitantly 2 or more cardiac alterations. Data from ECG, echocardiography and magnetic resonance of the heart confirmed the heart involvement. We did not detect any correlation between the course of the heart disease and skeletal muscle involvement. Death occurred in 4/16 patients. In one case it was due to heart failure complications. Conclusions Cardiac involvement is an important cause of morbidity and mortality in patients with IIM. It can manifest as cardiomyopathies, valvular diseases, arrhythmias, pericardium diseases, conduction defects. Because most of patients are asymptomatic an early clinical and instrumental assessment of the heart is mandatory in all patients with IIM.

80 Cancer and necrotizing immune myopathy: high incidence in anti-HMGCR positive and seronegative patients but not in anti-SRP positive patients

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Background and objectives: Twenty percents of inflammatory myopathy are associated with a synchronous cancer occurring ±3 years around the diagnosis of the myopathy. Malignancy is a major cause of mortality in inflammatory myopathy. The association between cancer and myositis is mainly reported in dermatomyositis patients. It has been clarified that DM patients positive for either anti-TIF1γ or anti-NXP2 myositis specific have increased risk of cancer. Some reports showed that malignancy could also occur in patients with necrotizing myopathies (NAM). We aim to analyse the incidence of cancer in a large cohort of NAM with or without the myositis specific anti-SRP or anti-HMGCR auto-antibodies. Material and methods: One hundred four-teen NAM patients were analysed. SRP patients (n=48) and HMGCR patients (n=52) were enrolled based on positive immune tests. Fourteen patients suffering from NAM, based on pathological definition, without any myositis specific antibody were identified. Results: The mean age of the diagnosis 51.8±16 years old in seronegative NAM patients, 48.8±23 years old anti-HMGCR patients and 45.4±16.7 years old in anti-SRP patients was not different (p=0.5), and in sex ratio as well. The mean follow-up time was not different (seronegative: 4.8±5 years, HMGCR: 6.2±5.6 years and SRP: 8.3±13 years; p=0.49). Malignancy occurred in 28.5% of seronegative NAM patients and in 17.3% of HMGCR patients compared to 6.1% in SRP patients (p=0.04). The median time between the diagnostic of malignancy and the myopathy was 4.9±21 months in seronegative NAM patients, 25.1±58 months in HMGCR patients and 80.1±76.2 months in SRP patients. Synchronous malignancy was diagnosed in 21.4% of seronegative NAM patients, 11.5% of HMGCR patients and 4% of SRP patients (p=0.03). The mean age at the diagnosis of cancer was not different in the three groups (69 years old). Types of synchronous malignancy were breast and gynecologic cancers (breast n=3, ovarian n=1), gastrointestinal cancers (oesophageal n=1, gastric n=1, liver=2 and anal n=1), urologic cancer (kidney; n=1) and skin cancer (melanoma n=1). Only two cancers were diagnosed with metastasis whereas other were localised. Survival analysis showed no significant difference depending on serological status. However, patients suffering from a synchronous cancer had a poor out-come with a median survival of 57.2 years (p=0.0001). Conclusion: Seronegative NAM and anti-HMGCR patients have a high frequency of synchronous malignancy compare to anti-SRP patients. The presence of cancer is associated with a poor survival. Cancer screening is necessary in seronegative and in anti-HMGCR NAM patients.

81 Myocarditis in patients with antisynthetase syndrome: prevalence, presentation and outcomes

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Objectives: Antisynthetase syndrome (aSS) corresponds to an overlapping inflammatory myopathy identified by various myositis-specific autoantibodies (directed against tRNA-synthetases). Myocardial involvement in this condition is poorly described. Methods: From a registry of 352 aSS patients, 12 cases of myocarditis were retrospectively identified on the basis of an unexplained increase in troponin T/I levels associated with either suggestive cardiac magnetic resonance imaging (MRI) findings, non significant coronary artery abnormalities or positive endomyocardial biopsy. Results: The prevalence of myocarditis in aSS is 3.4% and was not linked to any autoantibody specificity: anti-Jo1 (n=8), anti-PL7 (n=3) and anti-PL12 (n=1). Myocarditis was part of the first aSS manifestations in 42% of the cases and was asymptomatic (n=2) or revealed by an acute (n=4) or a subacute (n=6) cardiac failure. It should be noted that myocarditis was always associated with an active myositis. When performed (n=11), cardiac MRI revealed a late hypersignal in the T1-images in 73% of the cases (n=8). Half of the patients required intensive care. Ten patients (83%) received dedicated cardiotropic drugs. Steroids and at least one immunosuppressive drug were given in all cases. After a median follow-up of 11 months (range 0-84) nine (75%) patients recovered whereas three (25%) developed a chronic cardiac insufficiency. No patient died. Conclusions: The prevalence of myocarditis in aSS is similar to that of other inflammatory myopathies. Although the prognosis is relatively good, myocarditis is a severe condition and should be carefully considered as a possible manifestation in active aSS patients.

82 CANCER RISK ACROSS A COMPLETE AND UNSELECTED IDIOPATHIC INFLAMMATORY MYOPATHY COHORT FROM SOUTH-EAST NORWAY

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Background and Objective; To utilize a exposed/ unexposed cohort strategy for cancer risk assessment across unselected and complete cohorts of patients with Idiopathic Inflammatory Myopathy (IIM) resident in South-east Norway (denominator population 2.6 million), between 2003-12. Materials and Method: IIM cases were identified by comprehensive searches through patient administrative databases followed by manual chart review. Polymyositis (PM) and Dermatomyositis (DM) cases were classified by the Peter and Bohan and/or Targoff diagnostic criteria and sporadic Inclusion Body Myositis (sIBM) by the European Neuro-Muscular Centre (ENMC) criteria from 1997 and/or 2011. Every patient was matched with 15 unexposed controls drawn from the Norwegian population registry. For rarer cancer types additional life-tables were utilized. Results: Total cancer frequency in the IIM study cohort was 24.2% (79/326). Standardized Incidence rate (SIR) was higher in DM (2.0) than PM (1.3) and sIBM (1.0).Univariate analysis identified the following cancer risk factors in PM; age at diagnosis (calculated in 10 year intervals) with a Hazard Ratio (HR) of 2.1flu-like symptoms at disease onset (HR 3.49) and a predicted Diffusing e capacity of the lung for carbon monoxide (DLCO) 60% (HR 4.34). The presence of swallowing difficulties (HR 0.40); and dynamic X-ray showing oesophagus dysmotility (HR 0.75) appeared to reduce cancer risk in PM. In DM, age at diagnosis was associated with increased risk (HR 1.97), while positive Myositis Associated Autoantibody (MAA) test was protective (HR 0.43). Notably, TIF-g and NXP antibodies were not included among the MAA in this study. In sIBM, age at diagnosis was associated with increased risk of cancer (HR 2.49) while findings compatible with active myositis on Magnetic Resonance Imaging (MRI) of thigh muscles were protective (HR 0.11). Multivariate cox regression analysis using a manual backward elimination procedure showed that the most significant risk factors were age at diagnosis across all of the three IIM; PM; (HR 2.27, 95% CI: 1.11, 4.64, P0.026), DM (HR 1.97, 95% CI: 1.46- 2.66,P0.001) and sIBM (HR 1.80, 95% CI:1.10- 3.00, P0.025). Oesophageal dysmotility was protective in PM (HR 0.45, 95% CI: 0.01-0.44, P0.008) and active myositis on MRI of thigh muscles were protective in sIBM, (HR 0.11, 95% CI: 0.03-034, P0.001). Conclusion: Our findings suggest that the strongest risk factors for cancer across all of the IIM subtypes are age at diagnosis. Unexpectedly, we found that pathology on radiological studies of the oesophagus and on MRI of thigh muscles was protective in PM and sIBM, respectively.

83 Juvenile dermatomyositis: is periodontal disease a risk factor for dyslipidemia ?

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INTRODUCTION: Dyslipidemia was previously demonstrated in active JDM children and adolescents. In adult population periodontitis is associated to increased risk of dyslipidemia and cardiovascular diseases. Dyslipidemia and periodontitis may be associated with chronic inflammation and drugs, however the association of both conditions have never been studied in JDM patients. OBJECTIVE: To evaluate the frequency of periodontitis and dyslipidemia in JDM and healthy controls and to assess the possible association between periodontitis and lipids profile in JDM patients. METHODS: 25 JDM patients were compared to 25 healthy controls according to demographic data, body composition, muscle enzymes, clinical orofacial characteristics, fasting lipoproteins, serum lipid profile, glycemia, insulin and anti-LPL antibodies. The following JDM scores were assessed: Disease Activity Score (DAS), Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing (MMT), Myositis Disease Activity Assessment Analogue Scale (MYOACT) and Myositis Intention to Treat Activity Index (MYTAX). RESULTS: JDM patients and controls were comparable regarding mean age (11.5 ± 3.8years, p=0.7), female gender (56 vs 52%, p=0.5), median body mass index (19.1 vs 17.1Kg/m2, p=0.5), fat percentage (27.5 vs 22.5%, p=0.23), fat mass (10.7 vs 6.7Kg, p=0.27) and lean mass (24.8 vs 25.4Kg, p=0.6). Abnormal lipid profile was found in 9 (36%) JDM patients and 4 (16%) controls (p=0.2). JDM patients demonstrated higher levels of triglycerides (TG) [80 (31-340) vs. 61 (19-182)mg/dL, p=0.01] and higher frequency of abnormal levels of high density lipoproteins (HDL) (28 vs. 4%, p=0.04) when compared to controls. Regarding periodontal assessment, JDM patients presented higher gingival bleeding index (GBI) [24 (4-69) vs. 11 (0-66)%, p=0.001] and higher probing pocket depth (PPD) [1.7 (0.6-2.4) vs. 1.4 (0.2-12)mm, p=0.006] in comparison to control group. Further analysis of gingival parameters and lipid profile in JDM group, a significant correlation was observed between total cholesterol and plaque index (r=0.498, p=0.011) and between low density lipoproteins (LDL) and plaque index (r=0,421, p=0.036). No differences were observed between patients with higher vs. GBI, as well as higher vs. lower PPD, regarding body mass index, body composition, lipodystrophy, lipid profile, anti-LPL antibodies, JDM activity index scores and treatment (current and cumulative doses of prednisone, methotrexate and cyclosporin) (p0.05). CONCLUSIONS: Dyslipidemia in JDM was characterized by increased levels of TG and low levels of HDL. There is a possible association between a subclinical gingival inflammation and dyslipidemia in JDM patients.

84 Illness Onset Features and Misdiagnosis in Juvenile Idiopathic Inflammatory Myopathies (JJIM) Differ Among Clinical and Autoantibody (Ab) Subgroups

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Background/Purpose: To evaluate features of JIIM clinical and Ab subgroups at illness onset. Methods: Physician-completed questionnaires illness onset features were reviewed in 465 JIIM pts (381 JDM, 33 JPM, and 51 JCTM) meeting probable or definite Bohan and Peter criteria. Myositis Abs were tested by standard immunopreciptation methods. Univariate analysis was performed using GraphPad Prism 5.0. Results: The first weakness was proximal in all clinical and Ab subgroups (86-90%). Gottron's papules were most often the first rash in JDM and JCTM (48% and 47%), followed by heliotrope (45% and 29%), and malar rash (30% and 14%). Gottron's papules were also the first rash in 57% of anti-p155/140, 50% of anti-Mi2, 40% of anti-MJ and 32% of pts with anti-ARS Abs (P 0.04). Heliotrope was most often the first rash in pts with anti-MJ (52%) and anti-ARS (47%). Both Gottron's papules and heliotrope were present at diagnosis in 72% of JDM and 58% of JCTM pts. Gottron's papules or heliotrope alone were seen in 18% and 9% of JDM pts at diagnosis, yet 1.7% of JDM patients did not have either rash at diagnosis. 81% of pts with anti-p155/140 Abs had both Gottron's and heliotrope at diagnosis. Rash before weakness was seen in 54% of JDM and 74% of JCTM pts. Weakness before rash was seen in 23% of JDM and 14% of JCTM pts; 23% of JDM and 12% of JCTM pts developed rash and weakness simultaneously. Rash before weakness was observed in 73% of anti-p155/140, 67% of anti-Mi2, 39% of anti-MJ, and 39% of anti-ARS Ab pts (P 0.04). Weakness before rash was observed in 33% of anti-ARS, 31% of anti-MJ, 17% of anti-Mi2 and 12% of anti-p155/140 pts (P 0.02). 23% of JIIM pts had one and 5.7% had ¡Ý 2 misdiagnoses: infections (9.6%), other autoimmune diseases (4.6%), musculoskeletal (2.4%), dermatologic (17.6%), neurologic (1.5%), psychologic (0.7%) disorders. JPM and pts with anti-SRP Abs were often misdiagnosed with hepatitis (15.2-28.6%), neurologic conditions (9.1%) including Guillain-Barre (3-14%). Pts with JDM and JCTM, including those with p155/140 and MJ Abs, were often misdiagnosed with eczema (11-21%). Conclusion: JIIM clinical and Ab subgroups vary in their type of rash and weakness and misdiagnosis at illness onset. Most present with rash before weakness, and with Gottron¡¯s papules first. Better recognition of these varied presentations of illness should enhance recognition of JIIM phenotypes and help decrease delay in diagnosis and therapy.

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