Report from the 3rd Annual EuMyoNet Workshop in Stockholm, Sweden 30th-31st of January 2013

Summary

The interest for the meeting has grown and in total 57 participants from 13 different countries joined the 3rd Annual EuMyoNet Workshop that took place at Radisson Blu Royal Park Hotel just outside the city of Stockholm on the 30th and 31st of January 2013. The countries with the highest representation besides Sweden were Czech Republic, the United Kingdom, the Netherlands and Germany but also interested peers from Hungary, France and Italy. The meeting started with the exciting announcement that EuMyoNet is going global with participants from outside of Europe now.
The major part of the discussions evolved around the euromyositis registry, where everyone within the collaboration can have access to clinical outcome measures and follow up data characterizing the phenotype of molecular and epidemiological findings. It was decided essential that the registry is comprehensive and easy to use both when registering the patient data as well as extracting clinical outcome for the multicenter studies conducted. To have good clinical data, standardization of DNA samples, sera sample as well as muscle biopsy assessment standardization will be essential for the continued success of EuMyoNet.

Progress of the genome wide association studies (GWAS) was reported and the strongest signals of single nucleotide polymorphisms (SNPs) are within the human leukocyte antigen (HLA) region of the genome. Overlap between myositis and other autoimmune disorders have also been identified. There are currently 16 projects approved within the EuMyoNet collaboration and the workshop opened up for more centers contributing with samples for the studies which will provide more statistical power to the findings.

Another environmental element that might be a risk factor in myositis was presented. Lung diseases prior to the first reported myositis symptoms have been found to be associated with the disease. This intriguing epidemiological findings needs to be further evaluated with biological data and several centers expressed their interest in participating in such a study.

The search for myositis specific and associated autoantibodies continues and further studies on the cancer related TIF1γ and were presented. Also autoantibodies against proteins associated with interstitial lung disease and necrotizing myopathies was mentioned.

The standardization work on muscle biopsy evaluation is progressing and the 193rd ENMC workshop on pathology diagnosis of IIM has decided on the minimum set of tests, variables to assess and pathological classifications. The work will be continued and a number of centers expressed interest in participating in the follow up workshop that will be arranged later in 2013.

Additional presentations on separate projects and invitations to new collaborations were made. The overwhelming number of participants all actively contributed to lively discussions and jointly expressed interest in the next annual workshop that will be held in Prague, Czech Republic in 2014.

Description of the scientific content and discussion during the event

(Initials: JV-Jiri Vencovsky, IL- Ingrid Lundberg, HC-Hector Chinoy, ILo- Ingela Loell, NSK- Niels Steen Krogh, LW-Lucy Wedderburn, JDB-Jan De Bleecker, LP- Leonid Paduykov, JL- Janine Lamb, SR-Simon Rothwell, SBH-Sevim Barbasso Helmers, GP- Ger Pruijn, OB-Oliver Benveniste, CV-Cornelis Verwei, OK-Olga Krystufkova, MK-Martin Klein, PN-Peter Novota, BM-Brita Maurer)

DAY 1

Introduction of participants and of EuMyoNet

JV held the opening address where he welcomed the impressive number of participants and made a recapitulation of the EuMyoNet history. This year's meeting was not held in Prague as customary since the Czech delegation is organizing another meeting. All the somewhat fifty participants did a quick presentation of themselves.

IL announced that EuMyoNet going global with participants from outside of Europe now which was demonstrated by the participation from China. Our grants come from nine European to support our data base and to establish an interdisciplinary network, collection of longitudinal data and a bio bank with sera and DNA from at least 1300 European patients with myositis. There was a reminder that there are travel grants to facilitate training of young clinician scientists.

ILo addressed the practical issues about the workshop venue and program. Also there was a heads up on the revision of the EuMyoNet website that has been up and running for a while. The registry website need to be more integrated in the network website and there should be no overlapping information on the two sites. The facelift of the website is planned to take place during the latter part of this spring.

Myositis Registry

NSK: The euromyositis registry is an international collaboration contributing to a research and treatment database for myositis specialists. The numbers of patients entered is now 2500 which are over 25% more than last year. From these patients there are 440 with follow up samples and 1600 with autoantibody data registered and the registry has been used in several projects to this date. To optimize the usage of the registry the procedure needs to be simple and user friendly. Focus areas in the euromyositis registry for the rest of the year are autoantibodies test results, to finalize the juvenile dermatomyositis (JDM) registry and a sprint in Stockholm. The sprint will take place in May and focus on finalizing the data handling, forms and update and integrate the registry site in the EuMyoNet website. Everyone with a special interest in the registry is invited to join the sprint. The security around the online patient registry was presented as robust and trustworthy.

IL: The international myositis classification criteria project intends to validate the criteria collected from 50 centers around the data in the euromyositis data base. The name of the network might be reconsidered since several centers outside of Europe have joined. Suggestions of names are appreciated and so far 'globalmyonet' or 'myonet' has come up. Minimum data to enter in the registry is the core data, clinical data, descriptive, biological data, genetics and an additional extended protocol including follow up visits is available.

IL: When the euromyositis registry is developing requests on collaborating with people outside academia needs to be taken into consideration. This could be an additional way of funding the EuMyoNet networking program. Legal organization is needed and the EuMyoNet steering committee discussed and approved that the register could be based under the heading of the legal organization of Karolinska Institutet (KI; Stockholm, Sweden). If EuMyoNet aspire to collaborate with pharmaceutical companies there is a need for a legal entity which could be provided by KI. Any such agreement with a company will be signed by KI but the steering committee of EuMyoNet will be in charge of the decisions that come within the agreement.

LW: JDM data collection is under standardization, it is suggested to keep it to minimal data registration in order to similar data collection worldwide. There is a separate JDM part integrated in euromyositis registry. It was discussed on how to keep JDM patient data when they become adults. DM and JDM have differences in prognosis especially in regard to malignancies, and longitudinal studies might find an answer using the registry. No decision was made on how to keep the data organized over time.

IL/HC: Basic rules on publication are briefly stated in the collaborative agreement and must be agreed upon from all different centers before submission. A revision of the agreement to make it negative could make progress easier.

Q&A: How can we increase the motivation to include a visitor at least twice – ideas on how to make it easier? Entering data could be clinical work and can be printed as a PDF and filed. As clinicians see the use of the clinical development over the years they will realize that they are helped by registering the data. If considered too time consuming the core data set is the minimum data to enter. The meeting decided that some core data should be mandatory to enter when joining the collaboration.

Q&A: Can we store information on when and why patients leave the registry and a reminder of scheduling follow up visits? The registry can be constructed to contain these options.

Report from the 193rd ENMC international workshop on pathology diagnosis of IIM

JDB: The workshop brought together different sub-specialties involved in diagnostic muscle biopsies to decide on the minimum set of tests, variables to assess and pathological classifications. Basic pathological patterns described. Unanimity along what material to use and pathological features was seen but a wide range of staining used for evaluation was suggested. However, this was a very important first step in biopsy evaluation standardization. The next step is to find out whether there are certain biopsy features that are prognostic and it was decided that another workshop will be arranged during 2013 in order to progress within this field. There were several centers interested in participating in this important project.

DAY 2

Genetics

LP: There are a few publications on genetics in IIM available. Genetic studies will help to understand mechanisms of but many genetic variants are common in generation of risk to autoimmune diseases, thus the need to collect more samples. Different populations in IIM could be studied using meta-analysis and the environmental risks should be studied together with the genetics.

JL: GWAS on altogether 1178 adult and juvenile DM cases, genotyped on illumine SNP assays. Strongest signal in MHC region, no other SNP reached genome wide significance. Strongest non MHC association on CHR2 in phospholipase c like 1. 140 SNPs identified (end of 2010) associated with other autoimmune disorders. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohns disease and type 1 diabetes overlap with dermatomyositis. Sixteen projects currently approved including IFN SNPs and signature, calcinosis, gene x gene and gene x environment interactions, etc. Submit myogen collaborative agreement form to Fred Miller, a brief overview of proposed research and submit data access approval from principal investigator to join.

SR: GWAS provided evidence for DM association with a number of genes previously identified as risk factors in other autoimmune diseases. Remarkable genetic overlap of susceptibility across 12 autoimmune diseases. Not genome wide, focus on smaller loci for autoimmune disease; 186 loci. In myositis now 3000 samples approximately, DM, JDM and PM. Extra 1000 samples are needed to increase power. Matched shared controls from US, UK and a MS control cohort. Genotyping is undertaken in the US and in the UK. Analysis made in Manchester will probably start in April.

Q&A: Are there still chip available? Yes, there is capacity for sending samples within a month since genotyping will need to be ready by end of March. Focus on Caucasians; other ethnicities are not enough to give statistical power.

Environmental factors

SBH: Smoking, infections, UV-light, vitamin D deficiency, are risk factors for onset of myositis. An epidemiological study containing 100 adult and 6 matched controls per case, aimed to study the role of infections in lung as a risk factor of myositis. It was found an association between lung infections before the first reported symptoms of myositis thus inflammatory lung disease may be a risk factor for myositis. A discussion on whether differences between patients having lung diseases in their childhood compared to adult age should be investigated. No biological samples available in this cohort.

A questionnaire has been distributed to collect environmental exposure in patients where biological samples already are available. At least 1200 cases are needed in order to study gene and environment interactions. The importance of capturing newly diagnosed cases was stressed as individuals tend to change their habits after disease onset. Around ten centers were interested in contributing to such a study.

Autoantibodies

IL presented on behalf of Zoe Betteridge results from immunoprecipitation studies in EMN where sera from 1800 EuMyoNet samples are analyzed. TIF1γ reported in 26% patients with (ever) cancer. 140kDa autoantibodies NXP2, MDA5 and TIF1 (α, β and γ). TIF1α is the 140 and TIF1 γ is the 155 kDa protein. Setting up TIF1α and β antigen for ELISA ongoing. NXP2 directed against MORC3. Also 140kDa protein first reported in JDM. 186 patients ran ELISA, 30 pat were positive for NXP2. Significant association with HLA-DRB1*11. MDA5 140kDa, melanoma differentiation associated gene 5, associated with ILD and rapidly progressing ILD. Hmgcr 100 and 200kDa band on IPP associates with statin induced necrotizing myopathy. For the future: IPP on remaining samples, full validation off NXP2, MDA5, and TIF1g + α and β ELISA for diagnostic use.

GP: Investigation whether anti mup-44 is an IBM autoantibody. Autoantibodies are believed less common in IBM but plasma cells in infected muscles has been reported and mup44 has been found in several sIBM patient sera. Mup44 found in several sIBM patient sera. Skeletal muscle specific protein not detectable in cultured cells. cN-IA peptide ELISA in IBM. Low reactivity in PM and DM and in controls but high in IBM. Neither ELISA nor IPP are optimal in detecting these antibodies. Three cN-1A epitopes targeted by IBM sera have been identified and peptides containing these epitopes can be used in ELISA to detect anti mup44 antibodies. Not IBM specific.

OB: A report from the French myositis network on Immune mediated necrotizing myopathy. A group of patients were positive for anti-HMGCoAR autoantibodies displaying correlation with CK levels and weakness. IMNM is rapidly progressive and almost half of the patients are resistant to immunosuppressive treatment. Other centers were invited to participate.

Various aspects + further planned projects

CV:, role of IFN biomarkers hypothesis IFN signatures in IIM are related to the presence of autoantibodies directed against RNA binding proteins as in SLE. Investigate IFN signature. RNA and serum samples from 94 patients included autoantibody test, ANA and myositis specific and associated antibodies. Line blot and immunoblot assay. IFN signature correlates with serum IFN bioactivity at 4hrs and associates with mono specificity against RNPs. Whole blood IFN signature in IIM patients is associated with presence off anti RNP autoantibodies and multi specific autoantibody profiles. Underlying mechanism for the induction of an IFN signature in IIM might be similar to SLE. Investigate the regulation of IFN response activity in IIM. Investigate the (epi-) genetic background of the IFN response activity in IIM.

OK: presented B cell activating factor (BAFF) project and invited participating centers for collaboration. MK: Arthritis is a common feature in IIM, 50% presence of tender and/or swollen joints at examination which is associated with the presence of anti-Jo1 autoantibodies and arthritis. IL presented classification criteria, and the evaluation of the different models based on statistical calculations. For the future, analyses on patient subgroups and validation of the criteria are needed before dissemination and implementation can be carried out. PN: genetic differences between PM and DM in a single center study. HLA-DRB frequency significantly increased in patients compared to controls. DRB1*03 in PM *16 in DM.

Final discussion

IL: Johan Rönnelid from KI will take over the work of Peter Charles'. In the future it was considered better to store the sera samples at the rheumatology department at KI, where there is available staff that can aliquot the samples.
BM raised the question whether the workshop in the future also could include discussions on basic science in addition to clinical projects. This was agreed upon and will be included for next workshop.
IL: budget some money for study visit announcement. New annual workshop 2014 in Prague. End of January/beginning February. Thursday-Friday decided. Partly support a new biopsy workshop during 2013 together with ENMC. Proposal on a new genetic workshop in Manchester, when is depending on results. Might be combined with the Prague workshop? American colleagues will be invited.

Assessment of the results and impact of the event on the future directions of the field

The aim of the EuMyoNet workshop was to bring together parties interested in clinical care and research of patients with IIM. This meeting did not only hold participants from Europe but also interested colleagues from China and the network keep on growing. In this setting, the ongoing projects were updated and future projects created. The participants from several different medical specialties (rheumatology, neurology and immunology) were all very involved in the discussions and there was a great interest for new centers to join ongoing projects.

The myositis registry is the core of the EuMyoNet collaboration and it is of utter importance to have outcome and follow up data to include in the studies. An additional very important matter is that the registry is routinely used for data extraction. For every new collaboration project the registry should be used for outcome measures and the registry should be modified in order for the end user to filter the data easier. The registry also need to be more visible on the website, thus a revision of the network website will be undertaken.

Having a registry of this magnitude will attract pharmaceutical companies. This could, in addition to improve patient therapy also be a future source of funding for the network. Collaborations with pharmaceutical companies will raise both legal and ethical questions and it is advisable that the network engage a business consultant for advice.

The genetic studies are growing and the strongest signals are seen within the HLA regions. Also, an overlap between IIM and other autoimmune diseases are seen. More centers are entering in order to increase the power of the studies.

New autoantibodies are being investigated and might be used for predicting outcome in the future.

Lung infection as a contributing factor for developing myositis should be further investigated and possible differences between having lung diseases during childhood or in adult age should be explored.

It was agreed that the progress and expansion of the network was valuable for the participants and the enthusiasm for a similar meeting, with the addition of basic science discussions was well noted. Next meeting was decided to take place around the same time next year in Prague, Czech Republic.

MYOSITIS WORKSHOP FOR EUROPEAN MYOSITIS NETWORK (EuMyoNet)
30-31 January, Stockholm, Sweden
Radisson Blu Royal Park Hotel
Frösundaviks Allé 15 , P.O Box 3005, S-169 03 Solna, Sweden

PRELIMINARY PROGRAMME

Wednesday, 30 January 2013

Arrivals, registration.

12.00-15.30 **EUMYONET STEERING COMMITTEE MEETING**
15.30-16.00 **Registration coffee**

EUMYONET, EUROMYOSITIS REGISTRY Chair: Jiri Vencovsky
16.00 - 16.15 Welcome – and introduction of participants and of EUMYONET *(Ingrid Lundberg, Sweden, Jiri Vencovsky,Czech Republic)*
16.15 – 16.25 EuMyoNet – practical issues & website (*Ingela Loell, Sweden*)
16.25 - 16.40 Euromyositis registry – update *(Niels Steen Krogh, Denmark)*
16.40 - 17.00 Euromyositis registry - access, legal aspects, terms of usage, publication policy *(Hector Chinoy and Ingrid Lundberg)*
17.00 – 17.10 Juvenile Dermatomyositis in Euromyositis *(Lucy Wedderburn)*
17.10 – 17.40 Discussion (A*ll*)

17.40 – 18.10 **Break**

MUSCLE BIOPSIES Chair: Marianne de Visser
18.10 – 18.30 Report from Muscle biopsy and standardisation workshop (*Jan de Bleecker, Belgium*)
18.30 – 19.00 Discussion *(All)*

19.30 **Dinner at the hotel**

Thursday, 31 January 2013

GENETICS Chair: Janine Lamb
8.30 – 8.45 Introduction genetics (*Leonid Paduykov, Sweden)*
8.45 – 9.00 Update Myogen – EuMyonet Genetic studies *(Simon, UK),*
9.00 – 9.15 Future directions – HLA and Immunochip (*Hector Chinoy, UK)*
9.15 – 9.40 Discussions around genetics, future strategies, practical issues, logistics (*All)*

ENVIRONMENTAL FACTORS Chair : Hector Chinoy
9.40 – 10.00 Environmental factors known in RA *(Lars Alfredsson, Sweden)*
10.00 - 10.20 Environmental factors in myositis *(Sevim Barbasso Helmers, Sweden)*
10.20 -10.40 How to proceed within the EuMyoNet Discussion (All)

10.40 - 11.00 **Coffee**

AUTOANTIBODIES Chair: Jan de Bleeker
11.00 – 11.20 Immunology, autoimmunity, T cells & HLA *(Vivianne Malmström, Sweden)*
11.20 – 11.40 Current status of autoantibody screening in European Myositis Network (*Ingrid Lundberg, Sweden)*
11.40 – 12.00 Recent results on anti-Mup44 autoantibodies *(Ger Pruijn, the Netherlands).*
12.00– 12.20 anti-HMGCoAR+ patients (*Olivier Benveniste, France*)
12.20 – 12.40 Next steps. Discussion on autoantibodies (*all*)

12.45 – 13.40 **Lunch**

VARIOUS ASPECTS + further planned projects Chair: Lucy Wedderburn

13.30 – 13.45 Type I Interferon Signature is Associated with Autoantibody Profiles in Patients with Myositis (*Cor Verweij, the Netherlands*)

13.45 – 15.00 Reports on the ongoing activities and new plans
1) EuMyoNet plans for 2013- 2013 *(Ingrid Lundberg, Sweden)*
2) Genetic workshop (*Ingrid Lundberg, Sweden*)
3) Invite for cooperation - Genetic variation in promoter sequence of B-cell-activating factor of the TNF family (BAFF) gene in myositis *(Olga Kryštofková, Czech republic)*
4) Arthritis in patients with idiopathic inflammatory myopathies (*Martin Klein, Czech republic*)
5) Update on New classification criteria for IIMs (*Ingrid Lundberg, Sweden)*
6) Different genetic background of dermatomyositis and Polymyositis in Czech patients (*Peter Novota, Czech republic*)

GENERAL DISCUSSION Chair: Ingrid Lundberg
15.15 – 16.00 General discussion and future plans *(All)*

16.00 Coffee and end of the meeting

EuMyoNet workshop Stockholm 2013 Participants List

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