

Summary of the

The Eighth International Workshop on

Opsoclonus Myoclonus Syndrome

Clinical and Basic Science

Abingdon, UK 7th-9th April 2016

Kindly sponsored by OMSLife, Sparks and the
Dancing Eye Syndrome Support Trust

Morag Macleod (Dr. Morag Mackinlay) May 2016

SESSION 1 Updates, Progress and Initiatives

Rapporteur : Morag Macleod

Nichola Ejaz, chairperson for the Dancing Eye Syndrome Support Trust (DESST) warmly welcomed everyone to the Eighth International Workshop which was kindly funded by DESST , OMSLife and Sparks.

Mike Pike opened the workshop summarising what we know about OMS:

1/ million affected children every year

Neuroblastoma (NB) present in approx 50%

Slightly more females than males affected

HLA-DRB1 association

FH of autoimmune disease in some cases

For diagnosis 3 or more of the following criteria - NB, opsoclonus or flutter, myoclonus, and/or ataxia, behavioural disturbance and/ or sleep disturbance; AND exclusion of any other disorder such as demyelinating disease or encephalitis.

60-100% of affected children have motor, cognitive and /or behavioural sequelae.

Ming Lim (in Mark Gorman's absence) and Marc Tardieu discussed the progress and options regarding the Consensus statement and Registry. The goals for the Consensus statement are :

- 1) To standardise the terminology used in OMS which will facilitate collaboration
- 2) To produce recommendations of care
- 3) To create the foundation for a registry

The Delphi method is to be used and there is currently a working group (WG) of 6 with the number of expert respondents now over 30. IRB approval needed with a proposed base in Boston. The WG will select specific areas focusing on diagnostic criteria, relapse, symptom severity scores, imaging as a tool etc. WG will select the 1st question and send to the expert respondents , responses will be analysed and then the WG will send out a further question until generally 3-5 questions go out in total. From these a Consensus statement will be developed.

There are many unresolved questions including whether the WG should also act as experts? Timeline for this?

Marc Tardieu posed questions regarding the registry for delegates to consider over the course of the workshop with decisions to be reached by the final session.

What form? Based where? National or International? To use information from OMSLife surveys? Orphan disease registries? How much information? Costing? Prospective or retrospective?

A well thought out and packaged Family Education Guide / School Pack has been produced by Joslin Murphy (parent) and Kitty Petty (Special Education Consultant) . This is well laid out with highlighted areas to help inform parents and educators but stressing the individuality of each child requiring tailored support and solutions. Described as a 'work in

progress' delegates were invited to provide constructive comments leading to a final product by the end of the workshop.

The OMS Charter, an informal document with no legal basis, was adopted in February 2014 and currently has 44 members under 4 different categories : clinicians, researchers, parents/patients and PAMS. The aim is to increase membership.

Gudrun Schleiermacher gave the workshop an update on the European trial. The trial is now open in 7 countries out of the proposed 14 with Belgium about to open. There are 37 patients enrolled, running a little behind on accrual as the trial is not open in all countries yet.

This is a prospective trial with outcomes including response to treatment and neurological and neuropsychological outcome at age 5. Biological and immunological samples are collected.

Of the 1st 25 patients 15 had a NB and 10 do not and there have been no adverse effects to treatment to date.

Gudrun reiterated the need to set up a database to record information such as treatment in response to relapses and a Biobank to improve collaboration in research.

Dr. Michael Pranzatelli (US) raised concerns about the design of the European Trial regarding safety and efficacy. He was concerned that the initial 3 month period on steroid monotherapy alone may pose a higher risk of adverse outcomes, such as relapse or insufficient chance of remission, during a time when CNS neuroinflammation has been shown to be rampant. The dose of dexamethasone selected is not based on immunobiomarker data and Dr. Pranzatelli is concerned that the dose may be insufficient to reverse the neuroinflammatory process. Criteria for shortening the time frame before offering additional immunotherapy, at a minimum in severe OMS, and relapse provisions were offered. A discussion ensued.

SESSION 2 Trials, Studies and Interventions

Rapporteur : Gudrun Schleiermacher

Pedro de Alarcon presented the final results of the COG ANBLOOP3 Trial. This was a randomised clinical trial for the treatment of neuroblastoma associated OMS. The trial was activated in March 2004 and closed in February 2013 with 52 patients in total (53 initially but one withdrew) and an accrual rate of 6/year.

Primary aim was to determine if treatment of NB associated OMS with prednisone and cyclophosphamide was effective and whether the addition of IV Immunoglobulin improved outcome.

Secondary objectives regarding functional outcome , motor function.

27 patients had prednisone + cyclophosphamide (1 withdrew)

26 patients had prednisone + cyclophosphamide + IVIG

Female : Male ratio 33:20

RESULTS

V low incidence of toxicity from treatment (one death in a child with Stage IV NB with stem cell rescue who died from adenovirus infection)

Response was assessed by OMS scoring based on clinical assessment.

81% responders in the chemo + IVIG group

42% responders in the chemo alone group

At 2 years follow up this remained statistically significant.

49% were seen at 6/12 follow-up

38% at 1 year

36% at 2 years

There were 6 amendments from the start of the trial and cross-overs were permitted if there was no response to treatment within 4-8 wks.(those not receiving IVIG were given it and those on IVIG were given ACTH)

21% relapsed after completing treatment.

CONCLUSION

IVIG showed a significant difference in the short-term. Longer term follow-up continues with results pending from biological samples, MRI results and neuropsychological testing.

Next Holly Bridge and Geetha Anand presented further results from their OMS Brain Imaging Study.

The aim was to look for structural and functional changes in MRI scans of affected individuals. The study itself is well-described in the previous workshop summary.

Essentially, there were 9 OMS participants and 10 age-matched controls. The findings showed that there was a greater reduction in cerebellar volume (vermis in particular) in more symptomatic individuals. The cerebral cortex was also shown to be thinner across the motor and visual areas suggesting damage beyond the cerebellum.

Since their last presentation they have used the SUI template to further assess the MRI scans. This identifies more specific areas of the cerebellum that are affected and has shown that in fact the areas affected are bilateral.

Looking at resting state functional MRI revealed DIFFERENCES between the OMS participants and controls. The controls showed a strong correlation between the cerebellum and areas of the motor cortex involved in eye and facial movements whereas the OMS group showed a stronger correlation between the cerebellum and the suboccipital/parietal areas which are involved in saccadic eye movements.

The original paper had shown SIMILAR connectivity between the 2 groups.

Brain connectivity however, is not fixed and can vary depending on the state of the brain.eg resting or performing tasks. e.g. abnormal connectivity in migraine is linked to time since attack.

Areas for future research include

- paired sequential functional imaging studies (rest and task) ? during relapse and remission
- during different tasks-fine motor tasks, visual,motor ,cognition etc
- link to different treatments

The final presentation in this session came from Michael Pranzatelli regarding **Immunobiomarkers in OMS**.

A fresh look is needed to find biomarkers of biological activity as routine studies of CSF from over 420 patients have not revealed an answer. There are many different types of biomarker depending on what you are looking for.

e.g. prognostic, predictive, diagnostic, disease activity, treatment response.

Why CSF biomarkers?

Many reasons : proximity to the CNS parenchyma

: to evaluate neuroinflammatory disease

: what would we study instead?

: so far there are no known autoantibodies

: no animal models

: no brain tissue

: no surrogate radiological markers

Dr. Pranzatelli introduced the use of the CSF flow cytometric 'immunophenotype' of lymphocytes in CSF and blood in OMS 12 years ago. Flow cytometry (which can be carried out in most hospitals) to look at CSF showed an increase in the frequency of activated T cells and B cells, and a decrease in the CD4:CD8 cell ratio in the CSF of OMS patients which was linked to symptom severity as per a 12 point OMS severity score. (video-taping of patients recommended). The frequency of B cells was shown to increase with the clinical severity and decrease with disease duration and to be unaffected by steroid treatment. Neither the presence of a neuroblastoma nor chemotherapy made any difference.

Dr. Pranzatelli reported on a "Phase I Clinical trial of Rituximab for Pediatric Opsoclonus-Myoclonus Syndrome", which looked at immune cell responses (Clinical Trials.gov NCT 00244361). The CSF B cell percentage dropped sharply into the normal range and stayed there for at least 12-18 months with clinical improvement. Rituximab has its effect in the blood where it depletes B cells and appears to interrupt trafficking of B cells from the blood into the CSF.

He also found that 58% of untreated OMS patients had positive oligoclonal bands and suggested that these should be looked for as part of the standard immunodiagnostic studies.

Dr. Pranzatelli postulated that measurement of oligoclonal bands could be used as a monitoring tool for patients after treatment.

Dr. Pranzatelli presented summary data from 9 publications on chemokines and cytokines, which occur in CSF or blood, as possible biomarkers of OMS disease activity. Some have been shown to increase in the CSF depending on clinical severity (CXCL13, CXCL10, BAFF) and one (CXCL12) decreases. Serum BAFF can be used as a monitor for response to rituximab and APRIL to monitor response to IVIG.

Dr. Pranzatelli concluded that there are abundant data on putative immunobiomarkers in OMS. B cells, chemokines and cytokines are all potential biomarkers that could be used to monitor disease severity, response to treatment, relapse, and to identify specific immunotherapeutic agents to use as treatment in particular individuals.

Oligoclonal bands and the CSF phenotype are recommended immunological tests in OMS. As to a recommended panel of other immunological tests, Dr. Pranzatelli is analyzing data and working on manuscripts to develop an algorithm or decision tree to develop a treatment

proposal which would allow chemokine targeted therapies based on specific biomarker profile.

SESSION 3 Pablove Grants

Rapporteur : Sarosh Irani

Range of autoantibodies directed against intracellular and extracellular antigens have already been identified in a few patients with OMS +/- NB – not consistently. These include Hu, Ri and the GABA_B, GABA_A NMDA receptors.

There are other reasons to believe OMS has an autoimmune basis: HLA-association, lymphocytic infiltrates in NB, and response to immunotherapy.

In Oxford, Dr Lang and colleagues immunoprecipitated brain antigens using autoantibodies from patients with OMS, and identified their targets using mass spectrometry. They found that 12 membrane proteins were immunoprecipitated by the index patient's IgG. One of these proteins were expressed in HEK cells and was bound by the serum IgG from several OMS patients. The other 11 potential antigenic targets are being investigated.

An alternative approach to the study of the humoral response in OMS was to clone the recombinant antibodies from B cells and the antibody-secreting plasma cells found in the CSF of patients with OMS. A similar approach in neuromyelitis optica and multiple sclerosis has generated recombinant antibodies which can mimic aspects of these diseases in rodent models. There is a need to share further CSF samples to progress this research.

Drs Panzer and Rosenberg showed that a small number of IgGs from patient with OMS bind to neurons cultured from cerebellar-brainstem localisations. These neuronal-bound antibodies can be immunoprecipitated and targets identified. Also, they are trying to profile NB markers which will allow differentiation of patient subsets. What is different about the tumours in those with OMS? These may allow for the development of immune profiles which can be sought in CSF, blood and correlated with prognosis.

Finally, Dr Blaes suggested a potential caveat to the above studies in that extracellular mRNA may alter the nature of the extracellular epitopes in OMS. This suggests that perhaps a modified antigen is the most likely patient autoantibody epitope.

SESSION 4 OMS Issues across Lifespan

Rapporteur : Joslin Murphy

Jeremy Turk and Iris Rathwell discussed CHALLENGING BEHAVIOURS and associated problems of anxiety, attention disorders and neuropsychological difficulties. Socially inappropriate or unacceptable behaviour can involve aggression, self-injury, tantrums, hyperactivity, stubborn refusal, passive resistance, damage to property, etc.

It is thought to be experienced by approximately 7% of the adolescent population; in approximately 11-12% of adolescents with Diabetes or IBD; in approximately 33% of adolescents with OMS; and approximately 50% of adolescents with an IQ <50.

Behaviour of this nature may be perceived as abnormal, unusual, and troublesome, and can be functionally disabling; often magnified or entrenched by early and maladaptive learning experiences. The severity, duration and frequency of this behaviour increases in adolescents with greater intellectual disability, those on the autism spectrum, and those with social, language or communication disorders.

A number of factors may contribute to this behaviour :

The Environment: An environment that is noisy, lacking routine, un-empathetic or abusive, too warm or too cold, or presenting other more subtle sensations may contribute to such behaviours.

Undiagnosed Condition: Epilepsy, diabetes, asthma, fever, angina and other undiagnosed conditions may contribute.

Medication: Antihistamines, ACTH, corticosteroids, anti-asthmatics, polypharmacy may contribute.

Physical Discomfort: Life events, abuse, PTSD, mood disorder may contribute.

ANXIETY

- can be common ,difficult to assess ,easily missed and can trigger challenging behaviours.
- increased incidence in children with neurodevelopmental disorders and intellectual disability (10-22%) . This is believed to be related to the presence of communication, cognitive and sensory processing difficulties, lower adaptive and coping skills, and co-morbid conditions among this population.
- in these NDD/ID groups there are also a lack of anxiety screening/diagnostic tools
 - 30% of Adolescents with Autism Spectrum Disorder (“ASD”) experience anxiety .It is interesting that both anxiety and ASD have a shared neurobiological dysfunction-is similar areas of the brain are affected. ASD features include social difficulty, bullying, social anxiety, repetitive behavior, resistance to change, and differences in sensory processing. Anxiety may lead to “meltdowns.” In response, it is recommended that caregivers anticipate known triggers, maintain awareness of early warning signs, and remain calm and assertive. Rewarding challenging behavior (such as removing the child from the location) should be avoided; the STAR model implemented (Setting, Trigger, Action, Results)

Recommended BEHAVIOURAL MODIFICATIONS seek to reduce undesirable behaviour and enhance that which is desirable.

- Assessments such as KINDL (for the child)
- the Sheffield Scale (for parents)
- the ABC approach – awareness of Antecedents, observing Behaviour, and implementing Consequences. Common antecedents include attention seeking, solitude seeking, boredom, being overwhelmed, under stimulation.
- Pharmacological therapies e.g. methylphenidate or clonidine for ADHD/ADD
Melatonin for sleep disorders, haloperidol for self-harm

OMS CASE STUDY

Alison R¹ spoke very compellingly of her family's difficult experience following her daughter Isla's diagnosis with OMS in 2007 at the age of 3.5. Isla received treatment for the next six years. At first, she was treated with prednisone and IVIG, with relapse on weaning. Thereafter, Azathioprine, pulse Dexamethasone and Rituximab were tried.

Presently, she is doing well academically, with no apparent learning difficulties. However, at the age of 4, she was unable to wear shoes or be in her car seat, and in her first year at school she experienced anxiety. During this time, she suffered from one or two relapses, and her anxiety and sensory processing issues increased. At the age of 6, despite desperately wanting to Isla was unable to wear clothing other than a leotard, leggings and body warmer. School personnel were unsympathetic. Eventually, Isla was unable to touch her bed, and slept on the floor. This worsened to the extent that at age 9 she was unable to withstand touch.

This was both exhausting and severely distressing to Isla and her family. It was a battle to get her to school, and she became isolated and unable to do the things that she had previously enjoyed, such as dancing. Isla began to scratch her skin, and was at that point referred to a psychiatrist and diagnosed with anxiety disorder. It was very difficult to get Isla to these appointments, and inpatient admission was considered. It was then that Isla saw a second psychiatrist who prescribed Sertraline (SSRI antidepressant). She was also referred to an art centre which became a sanctuary for Isla.

¹ Alison's surname has been omitted to maintain confidentiality.

Isla's condition was not supported nor understood at her primary school, which was extremely difficult for Isla and her family. At school, she was discriminated against and bullied. Despite this, Alison described her daughter as strong and determined.

Moving to secondary school has been good for Isla. Her therapist made a presentation to staff at the school prior to her starting which was very helpful. She is now attending school, able to wear 'her uniform' and is back to dancing and cheerleading.

Alison described this experience as horrendous for the family and very isolating. However, despite this the family is stronger than before and positive about the future.

OMS CASE STUDY IN PREGNANCY

Nichola E. discussed her experience with OMS in pregnancy. She identified triggers that she believes have contributed directly or indirectly to her symptoms of relapse in the past. These include infection, stress, contraindicated medicines, puberty, and pregnancy/lactation.

Nichola has identified six young women with OMS via social media and asked them about their experience in pregnancy. Two women experienced relapse during pregnancy, and one during breastfeeding. One woman experienced an improvement in her OMS during her pregnancy but subsequently suffered chronic relapses again following the pregnancy. Two other women had no OMS symptoms either during pregnancy or in the post-partum period. There are three further case studies on-line of OMS occurring in late pregnancy.

Nichola has had two pregnancies. In her first, she experienced mild OMS symptoms that became increasingly severe. Despite treatment for PID at 7 weeks gestation, her OMS symptoms rapidly increased. She miscarried at 11 weeks gestation and her OMS symptoms disappeared.

In her second pregnancy, Nichola again observed a flare up of some of her OMS symptoms. Her symptoms were persistent but fluctuated daily. At 25wks she developed intermittent opsoclonus. At 27.5 weeks gestation, she experienced a full relapse, described as the appearance of ataxia, a decline in vision, and opsoclonus. She was hospitalized and given antibiotics. After a month she was released from the hospital in poor condition. Whilst in hospital she had received anti-D as per routine protocol for Rhesus negative mothers. She described her symptoms of relapse as ataxia, tremor, unsteady gait, weakness, vertigo, opsoclonus, visual disturbances ("floaters, sparkles, blurry moving objects), and photo-sensitivity. Nichola was no longer able to walk or support herself. In hospital, she requested but was denied IVIG.

During the birth of her child, Nichola described her water breaking, but having no contractions in the following 24 hour period. She was administered anti-D, again as per routine protocol and admitted for induction. Nichola was given a 'customised' epidural

containing Bupivacaine and Alfentanil. She believes this caused some eye disturbance. Her lovely, healthy baby girl was delivered vaginally. During postpartum recovery, Nichola observed a significant change in her OMS symptoms and required antibiotic treatment for septicemia. In hindsight, Nichola believes that IVIG during and upon the birth may have been vital to avoid complications from infection and septicemia.

5 ½ months after her daughter's birth, Nichola experienced another relapse. She believes this relapse occurred in connection with wisdom tooth infection, followed by bronchiolitis. After a five day course of prednisone and antibiotics her symptoms disappeared.

Nichola has not relapsed since 2014, however she has experienced increased OMS symptoms, including double vision, tremor and clumsiness, with infections. She believes that if not treated promptly, these symptoms would increase and result in relapse.

In conclusion, Nichola offered her view that

- (1) data indicates that relapses tend to occur later in pregnancy and/or during the postpartum period, unless otherwise triggered by infection
- (2) 50% of pregnant women with OMS may relapse
- (3) a treatment protocol including consideration of IVIG and steroids should be prepared.

SESSION 5 Registries and their use in Research

Rapporteur : Pedro de Alarcon

Early Life Epilepsies: Creating a Rare Disease Network: Anne T. Berg

Rare Diseases Research: The Journey

During this session Dr. Berg cover the pertinent issues of research in rare diseases and the use of registries for this purpose.

A rare disease is a disorder with frequency of < 1 case per 2000 population in the US or <1 case per 2000 population in Europe. But if you compound all rare disease, rare diseases become a frequent disease as a group. Approximately 10% of the population have a rare disease.

She used two examples: The Pediatric Epilepsy Research Consortium (PERC) and The National Infantile Spasms Consortium (RIKEE) as examples of rare diseases that have come together to develop a registry. These registries have brought together several centres to be able to gather information on hundreds of subjects with early childhood epilepsy making the population available for research purposes. However, to develop an effective registry you need to fulfil certain parameters:

Most importantly

YOU NEED TO KNOW WHERE YOU ARE GOING AND WHY.

The process of establishing a registry is a journey beginning with

1. Defining your purpose: hypothesis, goals
2. Define your design. What is the structure of data: observations, trials done, sampling, what your data collection forms are and why such data is included
3. Data collection: It can be two types, opportunistic which is cheaper but limited, i.e.: information in medical records, or collect what you want which can be more expensive but more accurate and consistent. Regardless of the approach the data needs to be consistent, complete and accurate. The design is important to avoid sampling bias
4. Data analysis: You begin with your hypothesis and science but need to have the proper statistics. You need statistical support and clear research methodology. Science drives the effort but proper analysis is what delivers the product
5. Data base: it is not the research but the vessel that contains the information. To have a proper data-base you must have
 - a. An organized repository
 - b. Rules for gathering data and storage
 - c. Proper forms to gather the data
 - d. Communication
 - e. IT infrastructure:
6. There are two available infrastructures that Dr. Berg has experience with and that are available for reasonable cost
 - a. REDCap: Has well designed CRF forms that can be adapted to the specific requirements to define the fields of the data-base. It is easy to use. It exports easily to other data bases and statistical programs. It is good for relatively simple studies and very nicely displays parts of the data at a time.
 - b. CLIRINX is a more complex data base. It is more of a software to create your own data-base vs REDCap that provides the CRF to be tailored. This would be more expensive.
 - c. There are other data-bases that are available for example NIH Toolbox, NINDS common data set .However, Toolbox only provides some instruments/forms for download which you can then incorporate into your database(they can be downloaded directly into REDCap or CLIRINX).
7. Data quality: This is an essential and ongoing process that begins with the appropriate definition of the data fields and the processes defined a priori
8. Data cleaning processes: This is an absolute requirement constantly looking for missing data, consistency of date, accuracy. It is essential to train the individuals entering data or using data. Training is best in person. Need meetings, phone meetings, practice exercises. It is paramount that rules be followed. **DO NOT COLLECT HUMAN SUBJECT DATA WITHOUT APPROPRIATE APPROVALS.** All subjects need consent. Likely all institutions need IRB approval.
9. Team data and procedures: These need to be defined including authorship of manuscripts

It sounds hard but it is doable and very worthwhile.

OMS Registry: Dr. Marc Tardieu

Dr. Tardieu presented the choices and decisions we need to take regarding an OMS Registry.

Should we use the European trial as a registry?

The comments from the session stated that the trial is not a registry but a very specific clinical trial with a termination date. Therefore it CANNOT be used as a registry

What do we want to do?

The goal of the registry should be a prospective and not retrospective registry. It should focus on natural history, treatment data and cognitive outcome

Secondary endpoints

Assessment of incidence

Registry Do's

- 1) Should follow recommendations of regulatory agencies
- 2) Primary endpoint should be the natural history under presently accepted treatments with a main emphasis on cognitive outcome
- 3) Secondary endpoint : any metrics for future assessment eg a rough evaluation of incidence
- 4) Should be prospective
- 5) Have financial support

Registry Don'ts

- 1) Should NOT be highly centralised
- 2) Be only retrospective
- 3) Have no primary or secondary endpoints or only vague ones
- 4) Have too much information

Proposal :

Use the information on the European trial: as stated before , the trial is not a registry and the data cannot be used for a registry. It has a finite end and at that point data acquisition stops.

In addition have a North American registry with the same questions: the North American trial cannot be used as a registry.

A registry will need to be an independent process on both sides of the ocean.

OMS Patient Registry Proposal : Mike Michaelis

Purpose

Is it for the researcher?

is it for the clinician?

Is it for the caregiver?

Each has different needs

Is it for the clinician or care giver?

1. Children have different needs.

2. Children are looking for where to be cared and find a doctor.

Is it for the researcher?

1. Acquiring hypothesis driven data
2. Research samples
 - a. Tissue
 - b. Blood
 - c. Other
3. Strict controls
4. Must go through IRB
5. Must be carefully screened
6. It does not help parent directly
7. Needs funding

A parents driven “registry” serves for:

1. Dissemination of treatment options
2. Dissemination of guidelines eg educational guidelines, vaccine policy
3. A forum for parents to connect
4. Inform care providers about OMS

Recommendation:

Develop two approaches :

1. Fast track: focused on caregivers and clinicians
2. Slow track: scientific

Slow track:

1. Well designed data-base
2. Hypothesis driven
3. Strict data quality
4. IRB approved
5. Long term development

Fast Track:

1. CAREGIVER drive
2. With a guidance committee
3. Short term development
4. Less costly
5. Funding is available
6. Governance: open ownership
7. Provides recommended guidelines and best practices

We will pursue both strategies:

1. Mike Michaelis to develop fast track initiative to be clinician and patient focused
2. Marc Tardieu to develop slow track initiative to be science based hypothesis driven

SESSION 6 Clinical Immunology and new therapies

Rapporteurs : Kumaran Deiva and Morag Macleod

Dr Jeremy Chattaway presented results of a study where old drugs such as statins were used in treating progressive Multiple Sclerosis (MS). MS is a neurodegenerative disease affecting mostly young adults and also children. The commonest form of the disease evolves as a relapsing remitting form, which despite treatment and improvement of several relapses, in 50 % of cases deteriorates to a progressive disease which results in increasing disability.

Simvastatin, is a drug that is used in the treatment of hyperlipidemia or hypercholesterolaemia and for cardiovascular disease prevention. By modifying the cholesterol pathways, it may have an anti-inflammatory effect.

The trial, which was charity funded, involved 100 patients and was a blinded placebo controlled trial. Patients were given 80mg of simvastatin with the controls receiving placebo. The treatment was well tolerated and compliance was 100%.

Primary outcome was measurement of brain atrophy by MRI volumetric BBSI (colour overlay) at 1 month and 2 years after treatment. There was a significant reduction in the annualized rate of whole brain atrophy in the treated group by 43%.

Secondary outcome was level of disability and this showed LESS progression.

Immunological parameters were similar in both groups. This suggested a role for simvastatin in neurological autoimmune/inflammatory diseases.

His group are now looking for funding for a trial involving 1000 patients.

Dr. Chattaway proposed that other repurpose drugs e.g. amiloride or riluzole could be used as treatments and indeed the MS-SMART trial is looking at repurpose drugs.

The Stampede trial is a multi-arm multi-stage trial which looks at more than one treatment at a time saving time, money and bureaucracy. He suggested that this may be a way forward for trials into the treatment of OMS.

Dr Pedro de Alarcon then presented a discussion on new therapies. Children who present before 18 months do better than older children regardless of stage of disease. And yet many children who present with OMA and NB (more than 50%) do much better from the NB point of view. In vitro serum from OMA subjects is cytotoxic to NB cells. He posed the question:

Can understanding of OMA contribute to the therapy of NB?

Immunotherapy can lead to increased survival from NB. Novel therapies are needed to improve treatment of high grade NB for example Anti-PD-1 (NB cell surface is rich in PD-1), CAR and IgGD2.

The COG trial closes in 3 years-what next?

Dr. Pranzatelli suggested a newer model for Orphan diseases trials (with newer statistical designs) which involve multiple arms, shorter duration and use smaller numbers of patients-this could be the way forward. The US FDA is moving this way for orphan diseases, which is a major departure from the standard RCT format. What to avoid in OMS trials is encumbering patients with agents that are not disease-targeted and prove obsolete by the time the lengthy trial ends. All such trials should avail themselves of immunobiomarker monitoring to verify that the neuroinflammation is actually being eradicated, and not rely solely on clinical endpoints.

SESSION 7 Registry, Best practice and Family Education Guide

Rapporteur : Jane Stanton-Roberts

Marc Tardieu started this session by explaining that 3 task forces were set up 2 years ago and there now needs to be clear milestones and decisions made on new task forces.

School Pack

Joslin Murphy thanked everyone for the suggestions made after the introduction of the school pack during the first session. Together with Kitty Petty the language has been made more comprehensible.

Additions to be made:

- emotional symptoms – maybe needing assessment for sensory processing.
- Autistic traits – not necessarily on spectrum
- Functional behaviour improvement.
- Puberty can cause relapse
- Recommendation of an educational strategy
- Mention vulnerability to disease especially during treatment and soon after. Strict hygiene should be observed.
- Likelihood of bullying.
- Opportunity to give feedback as to the usefulness of the guide and how user-friendly it is.

The section about 'statementing (IEP) will be in a box, the contents of which can be altered according to the country it is being used in. Every country has a different name for it and this changes over time too.

A separate publication for primary and secondary education. In the secondary one there should be something about transition.

Versions should be dated.

Translation into different languages eventually.

Milestone – make changes in 2 weeks, submit to Study Group for feedback within 30 days.

Best Practice

Ming Lim, standing in for Mark Gorman, explained that it would be the Delphi system with advice from Nicola Ruperto, a rheumatologist with experience of setting this up. A work force is in place and suggestions for an expert panel (EP) listed. Ideally the workforce should be different people to those in the expert panel.

Points already on the draft questionnaire are diagnostic criteria, symptom severity, screening inactive disease. Suggestions for additional questions – transient treatments (like statins), behavioural phenotype, vaccines, role of CSF immunotyping for diagnosis and monitoring, pharmagenetics.

Suggestions that the EP should include a parent, psychologist, psychiatrist. Members can opt out of questions not relevant to their expertise.

Dravet syndrome offered an honorarium for return of completed forms.

Suggest creating a group email for members of workforce to access.

Milestones – confirm the members of EP in 4 weeks

1st questionnaire sent to EP in summer 2016

Working group to prepare final report to circulate to EP to assess final report summer 2017.

Work group to present report in 2018.

Registry

Anne Berg gave a lot of practical advice in her talk. There needs to be very clear goals. Data entry needs to be done accurately so parameters should be simple. The registry will be long – lasting unlike a trial which has an endpoint. There will need to be a coordinator in each country. Ethical approval for every state/country needs to be current all the time because the occurrence of a case of OMS is intermittent. Separate national databases can be set up and then entered on to an international database. The international database will need to be set up ready for this.

Funding is a big issue. REDCap software is free but would need an administrator. CLIRINX would cost money but could be tailored to cope with the complexities. An administrator's wages would need to be found.

Milestone – put together a proposal in 3 months with clear goals. Anne Berg will advise. Taskforce to include Mark Gorman, Pedro de Alarcon, Marc Tardieu, Wendy Mitchell. Representatives of separate countries- Barbara Hero (Germany), Andrea Klein (Switzerland), Gudrun Shleiermacher (France).

The separate care givers registry will proceed. Mike Michaelis has a grant application with Nord.

SESSION 8 Summing Up

Rapporteur : Morag Macleod

Progress has been made with results now available from the COG trial and from the Brain Imaging study.

The European trial is recruiting well and research projects are underway with financial support from many bodies including the Pavlove Foundation.

The School and Family pack has reached its final draft and will be available within a few weeks.

The Consensus statement process will start in the next few months and work on a registry is underway.

Through presentations and discussions at the workshop new approaches to trials and suggested research has been proposed with an emphasis on shorter term results.

International collaboration is essential for this and the willingness for this was very apparent at the workshop.

At the heart of this we must remember that 'OMS warriors are continuing the battle all the time' day by day and through all the stages of life as this is not just a disease of childhood.