Summary of the

Ninth International Workshop on Opsoclonus Myoclonus Syndrome Clinical and Basic Science

Abingdon,UK 22nd-24th March 2018

Morag Macleod (Dr. Morag Mackinlay)

SESSION 1 : Updates,Progress and Initiatives

Mike Michaelis, from the OMSLife Foundation, warmly welcomed everyone to the Ninth International Workshop on Opsoclonus Myoclonus Syndrome funded by the DESST and OMSLife.

Jane Stanton-Roberts and Wendy Mitchell reported that the OMS Study group ,which was adopted in February 2014, now has 64 members comprised of parents/patients, clinicians ,researchers and PAMS. This is an increase of 20 since the 2016 workshop. The aim is to continue to increase member numbers.

Andrea Klein informed the delegates of the progress made so far with the OMS registry:
-the hiring of a full-time programme manager at Boston's Children's Hospital
-the protocol for the database has been finalised
-finalisation of the case report forms for data collection
The nemonic POOMAS Registry suggested as a name: Paediatric Onset Opsoclonus Myoclonus Ataxia Syndrome Registry. The plan is to include a retrospective cohort(OMS in the last 10 years) and a prospective cohort which would include patients enrolled within 24 months of OMS onset.
Data would be collected at clinics i.e. there would be no study specific visits so for example those on immunotherapy would have data entered every 3 months. etc etc
Relapse diagnosed if OMS symptoms are present =/> 72 hours with no other explanation.
Additional scales such as the Bayley assessment and IQ could be recorded too.
Initially the database will be at the Boston Children's Hospital then after approval 4 other sites would also be included.

OMS Consensus statement : little progress has been made so it was suggested by Mark Gorman that an alternative approach be taken where a consensus statement is written with lead authors and then circulated for comments and then revamped via conference calls etc which would be much quicker than using the Delphi technique which was previously suggested.

Kitty Petty provided an update on the good feedback received from parents regarding the Family Education School pack. The new proposal is to create a leaflet to cover the transition period for young people moving on to adult health care and education services. There is concern that adult specialists may not recognise or be familiar with OMS relapses, impact from pregnancy and medications etc. The proposed plan is to create a passport like document that could be used for emergency situations when the young person may be unable to explain the condition themselves.

Kumaran Deiva presented a proposal for a new task force for OMS Biological studies. He suggested this should consist of 6 members and initial aims would be the setting up of biobanks which would support or encourage biological projects that might lead to a better understanding of OMS.

SESSION 2 : Trials,Studies and Interventions

Rapporteur Ming Lim

European OMS Trial: updates and amendments
Gudrun Schleiermacher

Dr Schleiermacher provided an overview of the European trial, now familiar to many attendees of the OMS meeting. This trial evaluates the progression of children through a structured three tiered immunotherapy escalation algorithm, with careful attention to the medium and long term outcome. Following many frustrating years for the European team, the study is now underway in 8 nations with Germany opening later in summer of 2018. 65 of the target 100 have been recruited with France, UK and Sweden successfully recruiting the larger proportion of cases.

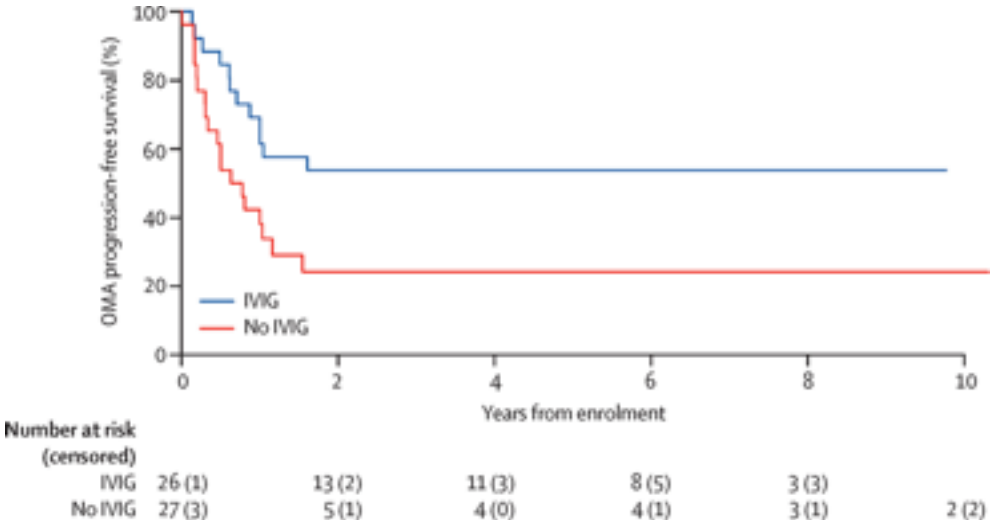
In an interim overview of the 45 cases who have completed the intervention arm of study, it was noted that neuroblastoma was detected in 55%. Children were of mean age 23 months (range 6-72months). 18 serious adverse events (SAEs) have been reported, none of which were Suspected Unexpected Serious Adverse Reaction (SUSARS). Operational aspects of the trial were discussed including intention of study team to extend recruitment until target achieved.

Discussions of the presentation centred on the equipoise of evidence for treatment particularly in light of the ANBLOOP3 study (see later); and the logistics of continuing recruitment despite likelihood of physician enforced deviation from protocol. Finally, the added value of the trial bio-samples collected to date were reported in the genomic profiling of neuroblastoma study by Barbara Hero and collaborators (J Pediatr Hematol Oncol. 2018 Mar;40(2):93-98); and the identification of GluD2 antibodies by the UK group (Neurology. 2018 Aug 21;91(8):e714-e723).

Children's Oncology Group ANBLOOP3 Trial: Results to change in clinical practice
Pedro de Alarcon

This presentation centred on the recently published (see Lancet Child Adolesc Health. 2018 2(1):25-33), randomised, open-label, phase 3 trial where children with neuroblastoma associated opsoclonus myoclonus ataxia syndrome (OMA), were randomized to receive twelve cycles of IVIG (IVIG+) or no IVIG (NO-IVIG) in addition to prednisone and neuroblastoma risk-adapted chemotherapy. An overview of the history of the study design, long course of recruitment (NCT00033293 first registered on 27th January 2003), and lengthy peer reviewed process was provided by Dr Pedro de Alarcon.

Briefly, of the 53 patients enrolled in the study (62% female; 44 low-risk, 7 intermediate-risk, and 2 high-risk neuroblastoma) in which 26 received IVIG, S=significantly higher rates of OMA response were observed in patients randomized to IVIG+ compared to NO-IVIG [21/26=80.8% for IVIG+; 11/27=40.7% for NO-IVIG (odds ratio=6.1; 95% CI: (1.5, 25.9), p=0.0029)]. This was sustained through disease course and below is a Figure from the publication that illustrates this better than words can describe.



Ultimately, this is the first high quality date demonstrating the additional benefit of IVIG compared to prednisone and risk-adapted chemotherapy significantly in improving OMA response rate.

Discussions centred on how this data may be translated to non-tumour cases; its influences on existing trials (like the European one); and how this would be adapted to further treatment regimes, notably raising many further and difficult questions for the OMS community to begin to address in the coming years.

Impact of relapses on cognitive outcomes in OMS
Mark Gorman

This study was conceived by Drs Klein, Pike and Gorman as part of a multi-centre evaluation of cognitive outcome of 81 children with OMS. An overview of the methodology of study was provided; including key definitions utilised of relapses and remission of OMS. The former (relapse) being worsening of OMS symptoms lasting for at least 72 hours following a period of stability or improvement for at least 30 days, or the escalation of immunotherapy as a proxy measure; and the latter (remission) was scoring 0 in the stance, gait, arm and hand function, opsoclonus, and ≤ 1 in behaviour in the OMS scoring category for at least 30 days.

Careful attention was then given to presenting the demographic across the 3 centres, highlighting key differences of US cohort being on more treatment and less likely to be in remission.

The key finding of the first pass univariate analyses was that a lower full scale IQ was significantly correlated with multiphasic compared to monophasic course ($p=0.0012$), higher OMS severity score at last follow up ($p<0.0001$), failure to achieve remission ($p=0.0003$) and higher number of relapses ($p=0.0001$).In a more restricted multivariate analysis of 34 patients, the number of relapses occurring before neuropsychological testing ($p=0.0018$; each relapse was associated with a decrease of 2.4 points in FSIQ) and ongoing OMS symptoms ($p<0.0001$; OMS severity score at last follow-up) were predictors of poor cognitive outcome.
The important negative observation of this study was that time to treatment did not appear to influence outcome.

This presentation sparked many interesting discussion; with many important take home messages, ranging about how we are far from optimising management in OMS through to how important international collaboration will be for rare conditions, as illustrated in this project.

SESSION 3 : Pablove Grants Holders

Autoantibodies to glutamate receptor delta 2 (GRID 2) in opsoclonus myoclonus syndrome.

Professor Sarosh Irani on behalf of Professor Lang

The main aim of the study was to identify neuronal surface antibodies in opsoclonus myoclonus syndrome (OMS) utilising contemporary antigen discovery methodologies. A brief overview of the method and strategy was explained.
In the first step, blood samples from 6 patients were screened for the possibility of presence of antibodies by probing the patient sera on rat cerebellar sections. Serum of 2 OMS patients sharing similar immunoreactivity (characteristic staining pattern) were selected for antigen discovery. Immunoprecipitation studies with OMS sera from cerebellum of age-equivalent post-natal rat pups identified GluD2, EAAT2 and cerebellin as the putative antigenic targets.
Following identification of putative antigenic targets, antigen-specific live cell-based assays (CBA) were performed in a larger cohort of OMS patients with neurological and healthy controls. Optimised live CBAs for these antigens; alongside CBAs used in current clinical service, evaluated the presence of these autoantigens in 15 OMS patients and 177 controls. 14/16 (87%) of OMS samples were positive for GluD2-antibodies whilst GluD2 positivity was only observed in 5/139 (5%) paediatric disease controls and 1/38 (2.6%) adult healthy controls. Furthermore, the tissue reactivity in OMS patient sera, selected due to larger sample volume availability, co-localised with GluD2 immunoreactivity in similar tissue sections.

This study therefore demonstrates that autoantibodies to glutamate receptor delta 2 (GRID 2) are present in opsoclonus myoclonus syndrome (OMS) patients. Discussions centred on the precise clinical relevance of this finding and how wider collaborations would be planned to confirm the identification of this antibody in other cases of OMS

NB: It is now published in Neurology. 2018 Aug 21;91(8):e714-e723

The Intrathecal B Cell Response in CNS Inflammatory Disease: Antibody Produced by CSF B Cells in Pediatric Opsoclonus Myoclonus Syndrome

Gregory P.Owens

Pediatric opsoclonus-myoclonus syndrome (OMS) is a devastating disorder of unknown cause and without cure. The prognosis of children with this disease is grim, and disease is characterized by dramatic movement abnormalities including chaotic darting eye movement, muscle twitches and impaired gait. Because antibodies produced by CSF B cells may be promoting disease, we utilized single-

cell methods to individually clone OMS CSF B cells and study the antibodies they produce in the laboratory. Presently we have identified antibodies cloned from a single OMS patient that recognizes a protein expressed in cultured neurons and in granule cells of the human cerebellum, a putative target site of disease within the CNS. These antibodies also bind to a 125 kD protein in immunoblots of murine brain tissue. Ongoing goals will identify the nature of this protein, determine if Abs to this protein are made in other OMS patients, and whether these Abs produce disease-like symptoms in animal models of disease.

Autoantigen discovery in OMAS-an innovative multidisciplinary approach
Miriam Rosenberg
Report to follow

Neuroblastoma,immunity and RNA
Franz Blaes
Report to follow

SESSION 4 Immunobiology

Identifying novel antibodies in CNS disorders
Thais Armangue

Search for antibodies in limbic encephalitis first lead to discovery of antibodies against intracellular antigens. Subjects without antibodies responded better to immunosuppression. As antibody-searching techniques improved, surface antibodies were discovered, i.e. anti NMDA antibodies.

Testing serum of interest against rat brain can detect surface antibodies. If this test is negative, a second tear test against live neurons may discover against surface antigens the presence of antibodies.

In movement disorders, surface antigen targeted antibodies are pathogenic, while antibodies against intercellular antigens are markers. Examples are anti gaba antibodies in Opelia Syndrome, anti mGluR5 antibodies in memory loss syndrome in Hodgkin Lymphoma.

Study of adults with OMS showed 13% of 114 patients with intracellular antigen targeted antibodies and 11% with surface antigen targeted antibodies (glycine antibodies). In 30 children studies so far, no common antibodies yet found.

The cellular immunology of autoantibody mediated encephaltidies: relevance to OMS

Sarosh Irani

Circulating B cells generate antigen-specific antibodies in CNS autoantibody-mediated conditions

Autoantibodies to aquaporin-4 are pathogenic in Neuromyelitis optica (NMO), and those which target N-methyl, D-aspartate (NMDA)-receptors cause a characteristic encephalitis. However, the lymphocytes which make the major contributions to serum autoantibodies are unknown. We sought to understand the relative capacity of peripheral plasmablasts and circulating precursor B cells to the generation of the pathogenic autoantibodies using live cell based assays from human lymphocyte cultures. From 20 patients with these diseases, factors known to sustain plasmablasts in unfractionated peripheral blood mononuclear cells, such as IL-6, APRIL and BAFF, failed to generate detectable disease-related autoantibodies in culture supernatants. Hence, we explored whether circulating non-secretory B cells had the capacity to generate disease-specific autoantibodies by differentiating these B cells into antibody-secreting cells, without addition of exogenous antigen. A variety of combinatorial factors, typically mimicking T cell-derived cytokines such as IL-2, IL-21 and CD40 ligand, generated a mean of 25% $CD27^{++}CD38^{++}$ antibody-secreting cells of all $CD19^{+}$ in vitro (range 1-56%). From 20 unselected patients with serum AQP4-antibodies and NMDAR-antibodies, these cytokine-driven PBMC cultures led to the generation of antigen-specific antibodies in 17 (85%). Overall, these autoantibodies were produced from more culture conditions, and at higher cumulative levels, from patients with the higher levels of serum autoantibodies ($r=0.80$, $p<0.001$). They were not observed in cultures from 20 age-matched healthy controls. Furthermore, these optimised culture conditions were employed to amplify the resident B cells within ovarian teratomas of patients with NMDAR-antibodies. These intra-tumoural lymphocytes generated NMDAR-antibodies in vitro. Taken together, these human cell-culture experiments demonstrate that preformed B cells, rather than ex vivo circulating antibody-secreting cells, possess AQP4 or NMDAR-reactivities. Their differentiation and autoantibody secretion is preferentially driven by select cytokines and these cells may make the dominant contribution to serum autoantibodies. This was also true of ovarian teratoma-resident B cells. This study has implications for understanding cellular mechanisms of disease perpetuation and for rational choice of targeted immunotherapies in antibody-mediated diseases. Anti N-methyl-D-aspartate encephalic NMDA – good response to immune therapies.

In simple terms ,conventional immunology tells us that cells come out of bone marrow and are exposed to antigens in blood then transform to memory cells or antibody producing cells and back to marrow.

However, in some patients IgM antibodies are produced.
The persistence of IgM antibodies suggest germinal center involvement and t-cell mediation.
Auto immunity may not be a plasma cell only process – do not forget the T-cell.

Identifying biomarkers in OMAS to predict durable response to Immunotherapy
Angela Waanders

Creating a tumor/tissue bank/repository. This needs an open access platform.

Brain tumor consortium is a good model.
The Children's Hospital of Philadelphia has created an infrastructure with informatics, clinical research, bio specimen unit and molecular diagnostics.
There is a genomic repository in the cloud.
The study of media vision of OMS requires the development of a complex model with both T & B cell interaction. There is a need to characterize the genome and the transcriptome in OMS.

SESSION 5: OMS through lifespan

Rapporteuse: Miriam Rosenberg

OMS Patient Registry: Neuroblastoma and precocious puberty survey
Mike Michaelis

OMS Life has partnered with NORD (National Organisation of Rare Disorders) in the US, to establish a registry of patient and caregiver derived information and survey data.

The first set of surveys developed for the OMS registry at NORD were aimed at capturing caregiver and patient reports of several important aspects of OMS disease:

1) Demographic, clinical, and treatment characteristics of the OMS-affected population
2) Triggers of OMS and onset of disease relative to diagnosis
3) Diagnosis process: who, how, where and when

4) Frequency of OMS-related issues and therapeutic approach to resolving them
5) Catalogue drug therapies in use and the longitudinal pattern of care
6) Identify patients interested in clinical studies
7) Develop quality of life metrics based upon treatment protocols established

This registry is designed to serve a number of entities interested in OMS:

- Caregivers/patients: provide a reference database of patient experience, organised and annotated for easy search and use, for use in insurance disputes, and to get help understand range of possible disease outcomes
- Clinicians: provide patient reports to supplement textbook learning; provide reference material about protocols in use by other physicians
- OMS Specialists: Provide means to survey extensive patient population
- Researchers: Provide lists of potential clinical study participants

Registry is supported by 5 year joint FDA/NORD grant. Data are housed at NORD, protected by standard US privacy regulation compliant parameters. Data collection forms and outputs reviewed by Hummingbird IRB. Data presented were collected from Feb 2017- December 2017.

Four Major study forms/surveys so far:

1) Neuroblastoma
2) Onset and Diagnosis
3) Treatments
4) Non-pharmacological interventions and therapies

Summary of some of the data:

- Female bias in OMS morbidity: 53% female/47% male
- 51% of patients report no tumor found, 36% NB, 5% ganglioneuroma, 8% ganglioneuroblastoma
-
- Age at OMS diagnosis: median- 18 months old, 1 month to diagnose
  mean- 25.9 months old, 6.3 months to diagnose
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- Age of tumor Dx: median- 18 months, 1 month to diagnose
  mean- 23.5 months old, 4.9 months to diagnose
-
- 34/85 respondents used ACTH, 44/85 dexamethasone, 31/85 prednisone, 18/85 prednisolone, 8/85 methylprednisolone
- Mean times on each treatment (months): 18 ACTH, 16.8 dexamethasone, 12 prednisone, 17.4 prednisolone, 16.6 methylprednisolone
- Precocious puberty? 15% yes, 85% no
- Age at onset :(119 respondents): 86% of patients were ≤36 months at symptoms onset; median age of pediatric onset was 19 months

- Symptoms at onset **:**
  Ataxia: 85%
  Myoclonus: 63%
  Opsoclonus: 59%
  Tremors: 49%
  Sleep disturbance: 45%
  Temper tantrums: 37%
  Vomiting: 27%
  Other*: 14% (includes: head tilt, drooling, depression, hypotonia, loss of appetite, nystagmus, seizures, spaced out, diarrhoea, clinginess)
  Fever: 11%
  Headache: 9%
- OMS severity at onset (118 respondents): range on Mitchell-Pike scale from 5-18
- OMS severity scores seem to be trending downward, depending on date of diagnosis (severity scores pre-2010 Dx were highest, median=16 vs now: median=12)
- Non-pharmacological therapies (83 respondents)**:** 65/83 patients used speech and physical therapies; 57/83 tried occupational therapy; 24/83 tried behavoral therapy.
  Beneficial? (yes answers) 95% yes Speech 97% yes physical 100% yes occupational 96% yes behavioral
- Approximately 50% of patients continue these therapies >36 months

Goals: 2018: 5 additional surveys completed, 150 patients each
2019- Predictive quality of life models!

Transition - What can we learn from other conditions?

Susan Byrne

Transitional care is not just a baton that can be (or is effectively) passed from a pediatric physician to an adult one.
The transition period from 10/12 y.o. to early 20's is an important one with challenges for maintaining and transitioning care.

Skinner 2011
Metrics of successful transition: (other conditions that serve as reference examples)

1) Renal medicine: kidney function, non-rejection of transplant
   Increase in positive outcomes corresponding to successful transitions,
   COMPLIANCE is critical

2) Diabetes: 80% of disease associated costs associated with complications
Cheaper, better outcomes with effective transition care

What would be good for OMS for successful transition?

Ex. Kidney health: statement; delivering excellence

STEP 1: Make a public statement. "We need this!"

KEYS: Mercy Hospital, Kansas Education, age appropriate variants

Example 2: Diabetes Best Practice Tariff

27,000 Young diabetes patients in the UK
NHS commissioned transition service in 2016
To be a certified center, you need TRANSITION SERVICE

CQUIN goals/metrics

Epilepsy: Benson et al 2015
Temple street study
"TEMPLE STAR MODEL OF CARE"

https://www.epilepsybehavior.com/article/S1525-5050(15)00396-0/abstract

Kids and parents separate;
Kids: how to talk to peers
Parents: How to let go

Direct questions to adolescents

"READY, STEADY, GO"
Nagra et al…. Salmon (Not disease specific)
https://www.ncbi.nlm.nih.gov/pubmed/26063244

Personal care folder: something that each patient can keep with them, detailing personal care details, treatment history; this can be taken to each new treating physician, allow the doctor to get an overview and help maintain continuity of standard of care;
Also, possible contacts for new physician for reference, to old physician? Important for rare diseases, where expertise may not be as widespread.

Additional reference material cited in talk:
Arch Dis Child Educ Pract Ed. 2015 Dec;100(6):313-20. doi: 10.1136/archdischild-2014-307423. Epub 2015 Jun 10.

Implementing transition: Ready Steady Go.

Nagra A[1], McGinnity PM[2], Davis N[3], Salmon AP[4].

Author information

Abstract

There is good evidence that morbidity and mortality increase for young persons (YP) following the move from paediatric to adult services. Studies show that effective transition between paediatric and adult care improves long-term outcomes. Many of the issues faced by young people across subspecialties with a long-term condition are generic. This article sets out some of the obstacles that have delayed the implementation of effective transition. It reports on a successful generic transition programme 'Ready Steady Go' that has been implemented within a large National Health Service teaching hospital in the UK, with secondary and tertiary paediatric services, where it is now established as part of routine care.

KEYWORDS:

Adolescent Health; Cardiology; Cystic Fibrosis; Diabetes; Nephrology; Patient empowerment

Comment in

- The evidence base for transition is bigger than you might think. [Arch Dis Child Educ Pract Ed. 2015]

SESSION 6 : Long term neurodevelopment and neuropsychiatric sequelae

Rapporteuse: Morag Macleod

Emotional Behavioural Autonomic Dysregulation (EBAD): Management in rare diseases.

Paramala Santosh

Causes of EBAD are complex including brain pathology, hormonal imbalance, side effects of medication, intellectual and developmental impairment. EBAD symptoms are often missed or not assessed as they don't fall under one specific specialty and there is a lack of research.

There is some on-going research exploring mental health following acute brain injury(ABI) which may shed some light and it is of significance that:

1 in 10 of the normal paediatric population will have contact with Mental health services
20% of those who have chronic non-brain injury and
40% of those where disease involves the brain.

ABI can result in Autism Spectrum Disorder,ADHD,ODD,Anxiety and Mood problems, hallucinations, delusions and rarely severe psychosis.Best care and

practice results from personalised care and monitoring which can be done very effectively by web-based programmes such as Health Tracker where children and clinicians participate to monitor symptoms and tailor treatment.
In ASD there is evidence of improvement in repetitive behaviours with social awareness training.
Medication can improve symptoms in ADHD, depression, anxiety,OCD and ODD.
There is currently a trial into the use of propranolol to help with the social communication difficulties in children with ASD.
Risperidone in minute doses can lead to significant improvements in ASD and ODD.
There has also been evidence to show improvement in ASD ratings using microbiotica transfer therapy where faecal material from non-affected children was given in capsules.

Outcomes of children with neuroblastoma associated OMS: The Memorial Sloan Kettering Cancer Experience 2000-2016
Yasmin Khakoo

- 5/15 patients had immunisations 2 years post treatment without any ill effects

Various medications can have an effect :
Melatonin can make neuroinflammation worse
Trazodone should not be used as it can result in priapism
Valproate and possibly high doses of Vitamin E

SESSION 7 :Task Force Feed Back

OMS School Pack - Excellent resource -following feedback Catherine Petty will expand the section on Speech and Language problems.

OMS Best practice/Consensus Statement - Plan is for 2 tandem papers with a writing group to formulate these on behalf of the study group . PAEDIATRICS journal is to be contacted regarding commissioning.Parent /family involvement will be encouraged.
The plan is for the first circulating draft to be ready October 2018.
The two parts of the statement are to be :
1) Acute phase
2) Disease course and outcome

Next steps are to circulate topics, select leads and for the final document to be sent to the study group for approval.

OMS Registry - Progressing but money will be needed for the main set up, for each country ,for maintenance and for a central coordinator.

OMS Clinical trials - much discussion ensued and more will take place over the next few months.

OMS Biological Studies- a biological task force will be established to look at this.

SESSION 8 : Summing up

There has been significant progress made since the last workshop in 2016.

- the OMS study group is growing and it is hoped that it will continue to do so to raise awareness among the wider scientific and clinical communities as well as the wider world.
- the Registry now has a suggested name and the appointment of a full-time manager at Boston's Children's Hospital.
- a new approach is to be taken on the Best Practice/Consensus statement
- the COG Anbloop3 trial results have now impacted on clinical practice with the inclusion of IVIG in treatment protocols
- the European trial is progressing well
- the Pavlove Foundation recipients are making progress with their research projects
- the group behind the School pack are now working towards producing a Transition passport with the help of new personnel
- relapses are significant as they have been shown to impact on cognitive function
- plans are being developed to set up a biobank where biological specimens can be stored and accessed for research into biomarkers
- OMSLife and NORD have set up a registry of patient and caregiver derived information
- Health Tracker is a web-based programme that can help personalise care and monitoring of individual patients so that treatment and interventions can be tailored to that individual. This could be very helpful in OMS as symptoms can vary significantly between individuals. Both children, parents and clinicians contribute to monitoring.

The success of the workshop is in part due to strengthening of existing bonds between clinicians ,scientists, parents and patients and the creation of new links with increasing world-wide awareness of OMS.