

Report on

THE SEVENTH INTERNATIONAL WORKSHOP
ON OPSOCLONUS MYOCLONUS SYNDROME
CLINICAL AND BASIC SCIENCE

By Morag Macleod (Dr. Morag Mackinlay)

Abingdon, Berkshire, UK

6th -8th February 2014

SESSION 1

Rapporteur : Peter Beverley

The Seventh International Workshop was opened with a warm welcome from **Joslin Murphy** on behalf of **Tony Tzoubris** of the **Pediatric OMS Research Fund** (from the US) which has funded the majority of the workshop.

Mike Michaelis from the **OMSLife Foundation** in the US gave an inspiring opening presentation on data collected from his Family Forum Surveys between 2011 and 2014. He started these in 2011 after OMSLife began in response to his grand-daughter developing OMS.

OMSLife has a registry of over 450 OMS warriors in 39 different countries with information provided for the surveys from a group of 200 main participants.

The majority of the respondents are on closed facebook sites such as OMSLife, OMSLife (Espagnol) and the DESST. Others from the OMSLife Teddy Bear drive, (which is public), direct contacts, adult OMS patients and referrals from other families.

Mike showed results about treatment options, treatment side effects, time from initial symptoms to treatment, who had made the diagnosis etc etc-a wealth of data.

The most important and vital question he asked the workshop participants:

What information can we get to you that you need?

Mike also presented some of the aims for OMSLife for the future;

Raising awareness at grassroots level (A&E personnel, general paediatricians etc)

Planned OMS family conferences for 2014

Help for OMS sufferers in Latin America

Guidelines and contacts for adults with persisting or relapsing Paediatric OMS

Beth Lang gave us an immunology update with the help of information from **Josep Dalmau** who unfortunately was unable to attend the workshop.

There are a number of factors that provide support for an immune mechanism in OMS:

-a response to immunotherapy eg steroids, IVIG etc

-lymphocytic infiltration of neuroblastoma tumours

-CSF B-cell expansion

- an association with HLA-DRB1 and the finding that 16% of close relatives of children with OMS have an autoimmune disorder

Beth Lang explained there are two kinds of autoantibodies-those which recognize **intracellular** antigens and those which recognize **extracellular** antigens. It is the autoantibodies to extracellular antigens that have the POTENTIAL to be pathogenic (disease-causing).

A number of different groups have demonstrated the presence of autoantibodies in patients with paediatric OMS.

Antibodies to intracellular antigens include neurofilament 210KDa, Ri (ANNA2) , Hu (ANNA1) and glutamic acid decarboxylase (GAD) whilst antibodies to extracellular antigens include those to NMDAR, GABAb and GABAa receptors.

Josep Dalmau looked at a group of 249 adult patients with teratoma associated encephalitis and found that the majority were NMDAR antibody positive and had a classical clinical picture of NMDAR encephalitis but that 38 patients ,who were mainly younger and female, were NMDAR antibody negative and 45% of those had clinical OMS. These patients had a good rate of recovery following tumour removal and immunotherapy. He concluded that although teratoma is the common tumour between anti-NMDAR encephalitis and the group of cases with OMS, **the neurological symptoms may come from autoantibodies to different entities.**

Josep summarised that in adults and children OMS may result from a number of different immune responses and antibodies and that there is not yet a 'single' autoantibody that would explain the majority of patients with OMS.

Mark Gorman, Marc Tardieu and **Hugh Perry** then introduced the proposed plans for an OMS Charter, OMS Consensus statement and OMS Registry so that discussion could take place during the workshop with decisions being made on how to progress with these in the final session. Summaries had been provided to delegates in advance.

SESSION 2

Rapporteur: M. Tardieu

This session focused on trials and studies in OMS.

Pedro de Alarcon gave the preliminary results of the COG trial. This is the first formal therapeutic trial in OMS. It evaluated children with newly diagnosed OMS and neuroblastoma, who had not had prior chemotherapy. All children were treated with steroids and cyclophosphamide with one group being randomly allocated to additional treatment with IV Immunoglobulin. 53 children were included in the trial after 8 years of accrual. The main end-point was the outcome after treatment. Although the results are still preliminary, the initial results suggest an improved outcome, in the short term, in those children who were given immunoglobulins. Safety and toxicity results appear reassuring. More detailed results concerning MRI, neuropsychology, cross-over and analyses of relapses are still pending.

Barbara Hero and **Gudrun Schleiermacher** then described the features of the European trial. This is a non-randomised trial which incorporates an escalation in treatment from dexamethasone only to dexamethasone plus Cyclophosphamide, to the addition of Rituximab according to persistence or not of OMS symptoms. Children will be enrolled who are aged 6 months-8 years who fulfil the diagnosis of OMS based on the presence of 3 out of the 4 criteria: of ataxia, irritability, opsoclonus and neuroblastoma. The endpoint is response to treatment at 24 months. This is assessed by standardised scoring of different modalities including gait and opsoclonus. Secondary endpoints will look at treatment burden and neuropsychological outcome at 2 years and 5 years.

Six children have been enrolled in France (1 without neuroblastoma) since it opened there in April 2013. The trial is now open in several other European countries.

Lim Ming described the results of a worldwide survey of the use of Rituximab in children. The paper, now accepted for publication in Neurology, reports the safety, tolerance and adverse events related to the infusion of Rituximab in 144 children. Most children below 3 years of age had OMS (n=32) while older patients had NMDAR encephalitis (n=39), NMO (n=20), neurolupus (N=18) and other inflammatory diseases of the CNS. Altogether 12.5% of children had an infusion related adverse event, in the majority an anaphylaxis reaction, and 7.6% developed infections. Two children died and 2 had a very severe event that led to permanent

disability, all four had NMDAR encephalitis and were in a very poor condition prior to Rituximab treatment. Low IgG was observed in 22% of children. The survey also evaluated efficacy and suggested that Rituximab improved symptoms in the majority of patients.

Michael Absoud presented details of PUDDLs (Paediatric UK Demyelinating Disease Longitudinal Study) to illustrate the potential difficulties and pitfalls for a future OMS network. The study strongly advocated for registries and focus groups using input from affected families. The Healthtracker programme was used to organise on-line questionnaires to parents/children so that information on symptoms etc could be entered onto a database for clinicians to access. It also promoted imaging centralization. Definitions are also very important as is a catchy acronym!

Finally **Dido Green** described the results of a pilot project on the prevalence of sensory symptoms in OMS children. This project involved an anonymous questionnaire to 16 participants (6<5yrs of age, 5> 10yrs). It evaluated the regulation of response to sensory inputs in a graded manner (over- or under-responsivity and sensory seeking-craving). 50% of respondents had symptoms of sensory processing disorders. The links with anxiety were discussed. These symptoms are important to consider in behavioural and pharmacological interventions.

SESSION 3

Rapporteur : Bethan Lang

Gudrun Schleiermacher and **Michaela Semeraro** gave interesting presentations in this session opening with a presentation on recent advances in genetic alterations in Neuroblastoma. NB, although rare, is the most frequent solid extracranial tumour of childhood and occurs in between 1 in 8000 to 1 in 10000 births. There is marked clinical heterogeneity with some tumours spontaneously regressing and others showing aggressive tumour progression. It is difficult to predict outcome.

In looking for genetic clues to prognosis, studies have considered familial NB (occurs in <1% of cases) and identified mutations of 2 genes, ALK and Phox2B.

GWAS (genetic w association studies) by John Maris have identified several genetic polymorphisms that are associated with both low and high risk NB.

However, it is often from the genetics of the particular NB tumour itself, that prognostic indicators can be found. For example, the somatic genetic alteration of amplification of MYCN is associated with a poor prognosis.

The overall genomic profile adds prognostic information to clinical parameters and may then be able to help influence treatment of the NB.

Identification of a mutated gene also provides a therapeutic target, indeed Phase 1/2 trials in the use of Crizolinib to target ALK are in progress.

Gudrun summarised that NB is a genetic disease but one with few somatic mutations. The tumour also has the ability to undergo genetic changes after initial therapy so re-sampling in recurrence is essential.

Michaela discussed neuroblastoma immunology explaining that there is a combination of the effects of immunosuppression and immunogenicity which contribute to the development of OMS and to regression of the tumour in those affected individuals. There is evidence for involvement of both B and T cells . NB is the only solid tumour of childhood in which immunotherapy is part of the treatment.

SESSION 4

Rapporteur: Mike Pike

This session focused on Behaviour and Education and was opened by **Jeremy Turk** giving a very helpful and practical survey of sleep difficulties in children and young people with developmental disabilities, and their management.

Sleep difficulties are relatively common in this group and take on a variety of forms: difficulties of sleep settling, recurrent night-time waking, early morning waking and parasomnias such as nightmares and night terrors.

These have a significant impact on the child in terms of daytime behavioural and learning problems and on the rest of the family. Parental depression and maternal stress as well as parental separation are more common.

Management can also be difficult with limited health professional training in sleep difficulties.

Good sleep hygiene or routines such as avoiding TV in the child's bedroom or a relaxing environment help but there is also a place for medications.

Melatonin helps with sleep settling, clonidine is helpful for sustaining sleep so a combination can be good. Antihistamines and chloral are not particularly helpful.

Clonidine is also helpful in reducing anxiety, improving symptoms in ADHD and Tourette's syndrome.

Paramala Santosh discussed the issues involved in using pharmacotherapy for behavioural problems. This stemmed from looking at children with acquired brain injury but was of clear relevance to children with OMS. Behavioural problems are very important to parents as they can lead to stress, social isolation and difficulties with school.

He very importantly pointed out that we should look closely at any medication the child is taking in case it is contributing to the behavioural problems – for example clonidine, antireflux and antispasticity drugs can sometimes affect mood.

Risperidone and aripiprazole are valuable mood stabilisers. B-blockers are helpful in anxiety and fluoxetine or other SSRIs help low mood and depression symptoms.

What is vital is to tailor treatment to the individual and to start at 1/6-1/10 of the therapeutic dose and build up gradually with careful monitoring. Monitoring can be via the telephone every 3-7 days or by using Health Tracker or other web-based programmes which allow the patient and their family to fill in tick box questionnaires which their clinician can access and then direct treatment.

Andrea Klein and **Mark Gorman** gave the report from the **Boston/Oxford/Zurich OMS Neuropsychology Study**. The data is still a work in progress and has not yet been fully analysed. However, it is really encouraging that transcontinental studies of this kind are possible and important.

81 children over the 3 sites have been evaluated with a view to discovering what factors influence outcome in OMS. A number of factors were hypothesized. Evidence suggests that the data is generalisable to the wider OMS population.

The key points were that age of onset, OMS severity at onset, presence of neuroblastoma, gender, or time to first therapy had no effect on full-scale IQ (FSIQ). Outcome was worse if the disease was multiphasic, the latest OMS severity score worse, there was no remission and there were an increased number of relapses.

Overall the mean FSIQ is in the low normal range but with a wide spectrum of scores.

More data is awaited.

The final presentation in this session was from **Catherine (Kitty) Petty** on educational issues and school liaison priorities.

Kitty gave a wonderfully sensitive and practically helpful talk about her role with OMS families in Boston. She provides emotional, social and especially school support for

the Boston OMS families and other children seen at the Boston Children's Hospital. Families are referred to her and seen at the Dr. Gorman's clinic.

Kitty, also a former special educator, reviews the results of neuropsychological evaluations of patients with their parents. Significant follow-up is by telephone contact and email.

Kitty acts as a practical facilitator between patients and schools who may well be in other states of the US. She stressed the importance of providing the OMS diagnosis to special educational personnel at the child's school. Kitty highlighted a number of vital issues; not falling out with the school, contact with the school nurse (in the US setting) and consistency of approach at home and at school and between home and school.

SESSION 5 – Cerebellum and Function

Rapporteur: Mark Gorman

Catherine Limperopoulos discussed the consequences of early cerebellar injury in both the preterm and term infant. The cerebellum is particularly vulnerable in the preterm infant because major development of the cerebellum occurs during the 3rd trimester. Growth failure and haemorrhagic injury to the developing germinal matrices is more likely at this time. She presented a longitudinal study involving preterm babies born weighing less than 1500g. The study looked solely at cerebellar injury, using MRI imaging, and excluded any infants who had suffered cerebral injury. It was a longitudinal study from 2000-2010 comparing subjects and controls with standardised functional outcome testing at pre-school age.

Gross motor function, fine motor function, cognition, receptive and expressive language and behaviour were assessed.

Anatomical area affected was also recorded-unilateral,bilateral,+/- vermis involvement

The study showed that function in all modalities declined from unilateral hemisphere involvement to unilateral involvement with vermis to bilateral hemisphere involvement to bilateral with vermis. In particular, none of the children with unilateral hemisphere involvement were diagnosed with Autistic Spectrum Disorder but 60% of those with additional vermis involvement and 100% of those with bilateral hemisphere damage plus vermis had an ASD diagnosis.

The traditional view has been that the cerebellum is largely a motor centre with injury resulting in impairment to motor functions. However, this study has identified that the cerebellum has a much more extensive role and damage results in a 'Cerebellar

Cognitive Affective Syndrome' which is a syndrome of higher order dysfunction with executive, visual-spatial, linguistic and affective impairment. 29% of the children had a diagnosis of ASD and 40% had another psychoaffective disorder eg ADHD, Compulsive disorder, Anxiety disorder, Mood disorder, Selective mutism and Aggression disorder.

The study also revealed that unilateral cerebellar injury results in decreased contralateral cerebral volume ie growth impairment with an effect on function. The links of the cerebellum to the cerebral cortex would explain the impaired outcomes of these children.

Term infants showed a similar although less severe pattern of impaired function.

She suggested there may therefore be a window of opportunity to limit secondary remote cerebral damage by early intervention.

Continuing on the subject of the integrative role of the cerebellum in both motor and non-motor function **Peter Tsai presented** a very illuminating study investigating the role of the cerebellum and Autistic Spectrum Disorder (ASD).

In sufferers of ASD there are both pathological and functional changes demonstrable in the cerebellum. Dr.Tsai's hypothesis was that

'Cerebellar dysfunction contributes to and is sufficient for the pathogenesis of ASDs '

The mouse was chosen as the best fit animal model because of a number of factors:

facile genetics,

easier to house,

behavioural evaluations are possible

previous studies using mouse models have shown that ASD clustered genes are expressed in the cerebellum(Menasha et al 2013)

there are mouse models with cerebellar abnormalities

He used TSC (Tuberose Sclerosis Complex) as the model system (the result of a mutation in TSC1 or TSC2) because autism occurs in 50% of cases, cerebellar involvement is associated with ASD in TSC and abnormal function of the cerebellum occurs in patients with TSC and ASD.

The mice with the mutated TSC1 gene demonstrated abnormal social behaviours and social impairment. Pathology revealed loss of Purkinje cells in the TSC1 mutant mice.

Next Dr.Tsai asked **'What underlies these ASD-like behaviours? '**

-cerebellar or extracerebellar mechanisms?

ie. inherent function or impaired connectivity?

‘Would intervention with Rapamycin (MTOR inhibitor) at Day 7 improve the behaviour and pathological abnormalities in the TSC1 mutant mice? ‘

[Rapamycin is an immunosuppressant used in patients following organ transplantation to prevent rejection]

YES, it reverses these behaviours!

The hypothesis is proved - in mice Purkinje cell dysfunction is sufficient to generate autistic-like behaviours in mice which can be prevented by treatment with Rapamycin.

However, there is still so much we don't really know-how does cerebellar dysfunction lead to these complex behaviours? Can we extend this to humans?

In both children with OMS and children with cerebellar disorders at least 50% have cognitive and behavioural sequelae. Further research, using mouse models, offers an opportunity to help these children.

The final presentation in this session was by **Geetha Anand** and **Holly Bridges** who presented their **OMS Brian imaging study**. The aim of this study was to determine structural changes that may underlie the variety of cognitive/behavioural and motor symptoms of OMS using detailed neuroimaging.

The study group were children/young adults aged between 10 and 40 years with a history of Paediatric OMS. They were recruited from Oxford University hospitals and through the Dancing Eye Syndrome Support Trust (DESST). Age-matched controls were recruited mainly from siblings.

There were 9 OMS participants with a median age of 14 years, 8 females and 1 male. Pre-OMS development had been normal in all 9 and the mean age of OMS symptom onset was 18/12. In 4/9 a neuroblastoma was present and 8/9 had a multiphasic pattern of illness.

The standard proforma also recorded the symptom severity score at the time of the scan using the Genoa OMS severity score, details of previous and current treatment and educational details.

4 were asymptomatic at the time of the scan and all of them were in unsupported mainstream education.

5 were symptomatic and they all required either support in mainstream school or attended a special school.

In all 9 cases the behavioural issues associated with OMS had settled with time.

The controls had a median age of 12.5 years and were all in mainstream education.

Methods summary-

T1 weighted structural scanning to analyse - cerebellum integrity

- group differences in grey matter volume

- quantification of cortical thickness in visual and motor areas

Diffusion Weighted Imaging to look at the white matter tracts

MRSpectroscopy to look at the neurochemistry in the cerebellum

Resting state functional MRI to correlate activity in the brain

Preliminary results have shown that there is cerebellar grey matter loss, particularly in the vermis area, in symptomatic individuals compared to asymptomatic participants and controls. The cortex appears thinner across the motor and visual areas suggesting involvement beyond the cerebellum. There are small differences in metabolites between the two groups and there are also resting state abnormalities in the symptomatic group.

This study, albeit with small numbers, **has** shown a relationship between symptom severity and imaging findings in OMS sufferers.

Longitudinal studies and task-related functional MRI would be a useful follow-on from this very interesting and illuminating study.

SESSION 6

Rapporteur: Jane Stanton-Roberts

This session concentrated on Teenagers and Young adults with OMS.

Wendy Mitchell gave us an update on OMS neurodevelopmental outcome and posed the question “**Does more aggressive treatment improve outcome?**”

Wendy had previously reported on children with OMS who were reevaluated with comprehensive neurodevelopmental testing in 1999-2004. All of these children had been treated with ACTH /oral steroids or both, most had received IVIG and NONE were given rituximab. The results were discouraging with the majority having chronic learning disabilities, speech and language difficulties, behavioural problems etc.

15 children with OMS who were treated from 2004-2013 were enrolled in a new study. 9 had a neuroblastoma, in 6 no NB could be found. Treatment started very

quickly after diagnosis. The children were graded by an OMS rating scale 0-3 (zero-no symptoms, 3 most severe symptoms) in 6 areas: stance, walking, hand function, opsoclonus, mood/behaviour, speech.

The children were all treated with ACTH and IVIG and 13 had rituximab either as part of the initial treatment or if non-response or relapse.

The 2 groups were compared using IQ/DQ testing, Adaptive Behaviour Scale, Motor testing etc using standardised assessment tools.

There were significant differences between the groups with the 'new' group achieving much higher scores in all modalities and in particular the 'new' group showed NO apparent decline with increasing age which the 'old' group had done.

“What did we do differently?”

- More aggressive immunosuppression
- Early addition of rituximab
- High dose ACTH/steroids in all, increased even with minor signs of relapse
- Bolus IV dexamethasone with IVIG to help with weaning from steroids

The dominant attitude of the 1980s-1990s of 'wait and see' with regards to treatment has been firmly disproved. In the last 7-10 yrs it has increasingly been recognised that rituximab is helpful although we are probably still using it too cautiously.

However, at least developmental and behavioural outcome is improving for children with OMS.

“Where are we going?”

Dr. Mitchell suggests that we probably need to use 'triple therapy' ACTH/steroids + IVIG + rituximab early on and possibly repeat the rituximab at 6-9 month intervals.

Morag Macleod then reported on the findings from a questionnaire sent to children and young adults aged 13 and above who have suffered from OMS. The participants had been identified from the DESST, OMS Life contacts and via facebook. The aims of the questionnaire were:

- 1) To raise awareness that OMS/DES exists beyond childhood
- 2) To give a voice and platform to these young people
- 3) To highlight the lifelong support required to help these young people

The questions were both closed and open and covered diagnosis, symptoms, relapses, education, family life, relationships, leisure activities and employment.

There were 23 respondents, a response rate of approximately 43%. 20 females and 3 males, with an age range from 13-30 years. Some responses supported other studies eg majority of children were aged <2 years at diagnosis and approx 56% had had a neuroblastoma.

However, the questionnaire also highlighted a number of other areas:

- 91% have suffered one or more relapses-with detailed descriptions of individual's symptoms
- Nearly ALL respondents STILL have symptoms to varying degrees
- 77% of school leavers went on to further education but many didn't complete their courses and felt OMS was a major factor in this
- Only 33% of those eligible to work were in paid employment with 22% working as volunteers

On a brighter note many respondents when asked if there were any good things that have occurred as a result of having OMS answered that:

- 'I am more determined' 'more compassionate' 'stronger person'

The questionnaire also asked about pregnancies and parenthood which, although only small numbers were involved, showed that there may be a relationship between relapses and both pregnancy and postpartum problems.

In summary, the questionnaire identified that

- we need a SEAMLESS transition from children to adult services
- OMS needs to be highlighted to many other healthcare specialists eg obstetricians
- sufferers need on-going psychological support
- follow-up is vital

A more detailed report will be available on the DESST and OMS Life websites.

Victoria Bartholomew then gave a fantastic presentation of her experience of OMS. Victoria is now aged 20 and had developed symptoms at the age of 13 months. She started school just after coming off medication and felt that she was always trying to 'catch-up' with her peers both academically and socially. Unfortunately, like many children with OMS she was bullied. Victoria is dyslexic and found subjects like PE very hard.

However, with the support of her family and extra help from a tutor once a week Victoria completed an HND with distinction and now works as an Insurance administrator.

Victoria feels that she is a much more determined person as a result of what she has gone through. She passed her driving test over a very short time scale so that she could be a helper at the Para-Olympic Games in London-a fantastic achievement and experience.

This was a very honest and inspirational presentation.

SESSION 7

Rapporteur: Mike Pike

Registry

Mark Gorman and Pedro de Alarcon will take forward the issue of an International OMS registry. This process will include:

- a) Eliciting views as the priority information which should be registered, starting small – i.e. with fewer items.
- b) Identifying a centre which would host this registry
- c) Costing this process.
- d) Determining the governance issues including confidentiality and access.
- e) Feeding back to the Steering committee and then the wider membership.

Consensus

Mark Gorman has identified a core group and expert group to take forward a Delphi consensus process for OMS. He anticipates completing this process within 3-6 months.

Charter

There was a discussion about the Charter of the proposed International OMS Study Group (OMS SG) including particular comments with respect to the purpose of the OMS SG as an international focus of advocacy and collaboration, membership, membership categories, representation on the Steering committee. A vote was taken of all present on the proposal that the Steering committee should refine the OMS SG Charter document taking account of these discussions and return a final draft for approval within a month. This was universally supported.

SESSION 8

Rapporteur: Mark Gorman

The summing up session was extremely upbeat and full of energy. The presentations and discussions in this workshop had covered a large number of very important issues including :

- the reporting of the 1st trial results
- the safety of rituximab
- the evidence suggesting that OMS is not a progressive disease
- the role of the cerebellum identified by advances in scanning technology and mouse model research
- raised pregnancy in OMS sufferers as a new issue
- the increasing role for fMRI scanning
- agreement has been reached on the formation of a registry, development of a consensus statement and a charter for OMS

Peter Beverly reiterated the progress that has been made over the 14 years since the 1st workshop and how fantastic it is to see International collaboration working.

However, we are only at the beginning, we need to spread the word about OMS round the world to recruit more patients for trials and to gather more information that will help lead to a consensus on terminology and definitions.

Highlighted in particular from this workshop is the need to define what constitutes a relapse of the condition and how to treat it.

The presentations suggest that this is a persistent disease that continues into adulthood and as such more expertise and knowledge is required by a wider field of medical and non-medical professionals. The process of transition and follow up from paediatric to adult services is vital.

The work continues.

