Pediatric OMS Research Fund [Opsoclonus Myoclonus Syndrome]

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Dancing Eye Syndrome Support Trust

The REPORT from the Sixth International Workshop on Opsoclonus Myoclonus Syndrome

Clinical and Basic Science

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EUROIMMUN

BRAIN A JOURNAL OF NEUROLOGY

The Neuroblastoma Society fighting childhood cancer

Sparks For children's health

INTRODUCTION

Opsoclonus Myoclonus Syndrome, also known as Dancing Eye Syndrome is a rare condition affecting approximately 1 in 1 000 000 children in the UK every year. It is characterised by a number of features including opsoclonus (abnormal conjugate eye movements), tremor, ataxia and severe irritability. These symptoms vary in severity amongst affected children. However, distressing as these symptoms are ,it is the long -term neurodisability that is most devastating for these children and their families.

In at least 50% of cases the syndrome is associated with a neuroblastoma (a childhood cancer of the nerve cells).This figure is rising as methods of detection of these tumours improve. Other cases may be precipitated by a virus or another unidentified agent.

The Dancing Eye Syndrome Support Trust, which was set up initially by two sets of parents with affected children, has funded biannual scientific workshops since 2001 .The aim of these being to bring together a diverse group of International professionals including basic scientists and clinicians to try and stimulate research into OMS with a view to ultimately developing a successful treatment for this devastating disease.

This year we have been extremely grateful for the support in the UK from The Neuroblastoma Society, Sparks and Brain , from Euroimmun in Germany and The Pediatric OMS Fund in the US.

First session – Trials and best practice

Dr. Mike Pike , Paediatric neurologist in Oxford opened the workshop and the session with a general introduction that described the main clinical features of Opsoclonus-Myoclonus Syndrome (OMS) .The number of new cases per year in the UK is 1 in 1 000 000 children. Although, he explained, we do not yet know the cause of this condition or the best way of treating it we now have a set of diagnostic criteria for the condition-these were developed at a meeting prompted by the 2004 workshop.

We know that the clinical course can be extremely varied and there are many challenges ahead. However, since the start of the workshops back in 2001 there has been significant progress largely due to collaboration between doctors and scientists from many countries and different clinical and scientific backgrounds. We have: simple diagnostic criteria, a uniform approach to diagnosing a neuroblastoma, shared assessment of severity scores and systems in place for long term follow-up.

The major characteristics of the syndrome were best illustrated by the recently published results, given by **Dr. Carlos de Sousa** , Paediatric neurologist from London, of the largest retrospective study so far (Brunklaus et al. Pediatrics 2011, 128:e388-94). This looked back over **53 years** at **101 children** diagnosed with OMS and seen in London and Glasgow. The average age children were diagnosed was 18 months with 91% of children being less than 3 years old.

The children presented with **severe** symptoms in **82%** of cases, **moderate** symptoms in **14%** and **mild** in **4% .**

21% of children had a neuroblastoma detected but this figure rose to **45%** in more recent years with better scanning technology.

The first aim of the study was to look at the long term outcome in these children who were mostly treated by steroids (with IV Immunoglobulin for some) with an average time of 30 days from becoming ill to starting treatment.

Follow-up of these children revealed that **7% recovered spontaneously** after their first episode, **32% experienced several episodes** of symptoms and in **61%** their symptoms **fluctuated** over years.

Treatment led to a **good response** (including resolution of symptoms and normal learning ability) **in 35%** ,**moderate improvement in 60%** and **no change in 5%** of children. **51%** of children had **learning disabilities**, **46% behavioural problems** and **60% motor disabilities**.

A second aim of the study was to find out if there were any factors at the time of diagnosis which could be linked to later outcome. The more severe the symptoms of OMS were at

diagnosis and the younger the child the more likely that that child would have a poor outcome. Whether or not they had a neuroblastoma, whether there was a delay from diagnosis to treatment and their initial response to treatment did not affect the outcome for a particular child. The study also revealed the side effects from steroid treatment including increased blood pressure, poor growth, brittle bones and a delay in going through puberty.

Dr. Pedro de Alarcon from the University of Illinois , reported on the still on-going trial comparing 2 different treatments in children with OMS and a neuroblastoma. One group are being given cyclophosphamide and prednisone and the other cyclophosphamide, prednisone and Intravenous Immunoglobulin.The trial will soon close and the outcome for the 2 groups will be compared.

Dr. Gudrun Schleiermacher of the Institut Curie in Paris , gave news of the future European trial that will look at all children with OMS either with or without a neuroblastoma who will be treated in a stepwise fashion from steroids to cyclophosphamide to rituximab. The trial will involve 100 children from more than 8 different European countries over, hopefully, 3 years. The trial is ready to go except for a legal problem involving monitoring of the drugs used.

Dr.Barbara Hero from Cologne, Germany gave us information on children in Germany who received an escalation-type treatment, close to the proposed European Trial protocol. Of the 34 children, 12 received steroids only, 16 went on to be treated with cyclophosphamide and 6 went on to have rituximab.

Second session - Neuroblastoma

Dr John Maris of the University of Pennsylvania, USA explained that there have been no improvements in the cure rates of solid tumours (including neuroblastomas) since the 1990s. In order to improve survival greater amounts of chemotherapy have been tried which have resulted in more toxic side effects and increased longer term side effects. He suggested that we need to pinpoint treatment better. Dr. Maris described the use of specific genetic studies to examine whether any common genetic variants are associated with the presence of a NB and why some children get an aggressive form whilst other children get less aggressive tumours. In 99% of cases there is no family history of neuroblastoma (NB) and no single gene abnormality. One study compared 500 NB cases with 10,000 controls (children without neuroblastoma) and showed a significant association with a *certain genetic marker* which was found in larger amounts in the group of patients with the most aggressive forms of neuroblastoma.

Applying this to OMS he wondered whether through genetic studies we might discover genetic factors in specific children which could explain why there is a wide range of severity of symptoms and a difference in response to the various treatments. There is also the potential for more targeted treatments.

Dr. Gudrun Schleiermacher from the Institut Curie, Paris, France presented her work on the genetics of neuroblastoma tumours. The results showed that depending on the number of chromosomes and their makeup in a tumour that some children had a better outcome or survival than others.

Dr.Lizzia Raffaghello, from the G.Gaslini Institute in Genoa, described the different kinds of cells from the immune system found around a neuroblastoma tumour.These cells are responsible for a tumour growing and spreading. Finding a way to impair,destroy or modify these cells might improve outcome.

The final talk in the session was by **Dr Franz Blaes** from Gummersbach, Germany who spoke about B-cell activating factor (BAFF) in neuroblastomas. Previously Dr Blaes and his group had shown that BAFF was elevated in the CSF (fluid around the brain and spinal cord) of children with OMS.

Third session - Neuroimmunology and immunotherapy

The cause of OMS may be explained as follows- cells within our bodies' immune defence system produce substances called antibodies which then attack any invaders (eg viruses or bacteria) or foreign material (eg tumours) but in OMS these attack not only neuroblastoma cells but also cells in key areas of the brain . These antibodies damage brain cells leading to the symptoms associated with OMS. This session looked at the possible role of B-cells, which are the cells that produce antibodies, in OMS and the treatments for OMS that try to kill B-cells and antibodies.

Dr. Jessica Teeling of Southampton University provided an overview of how B-cells work. As B-cells change from younger to older cells they reveal different markers on their cell surfaces which can then be attacked by specific drugs called immunotherapy drugs.eg Rituximab and Ocrelizumab. Another treatment which attacks antibodies in a less specific manner is intravenous immunoglobulin (IVIg).

B-cells survival depends on a substance called BAFF (B-cell-activating –factor). Medications that can interfere with BAFF are undergoing laboratory trials at the moment. As we understand more about the biology of the B-cell so there are increasing opportunities for developing treatments.

Professor Josep Dalmau of the University of Barcelona described a study of adult patients with OMS to possibly provide clues as to how OMS might arise in children with neuroblastoma. Symptoms in adults can be very similar to those in children .

In adults the causes of OMS are divided into 2 main groups-those who have a malignant tumour (paraneoplastic cause) and those who develop OMS either following infection or who have no obvious underlying cause (idiopathic) . For example certain kinds of breast cancers, lung cancers and ovarian tumours may lead to OMS. Cell surface antibodies have been found in some cases and may help provide clues to the cause of OMS and also help in the development of treatments. Although there are similarities between adults and children with OMS there are also differences. Adult patients with tumours who do not undergo treatment for their cancer have a poor outcome in terms of survival and often effective treatment of the tumour can lead to disappearance of OMS symptoms in patients. The same is not true in children. Antibodies may not be the whole answer and more research is needed.

Dr. Mark Gorman, Paediatric neurologist, Boston Children's Hospital reviewed the present treatment and highlighted some of the lessons that have been learned. As yet there is no evidence to indicate that delay in diagnosis and hence treatment of OMS has a poorer outcome although studies in other autoimmune conditions have shown a better outcome with earlier treatment. Most physicians who care for children with OMS think that early intervention is critical. There are many unanswered questions around this and larger studies are needed to answer these.

A further difficult aspect of immunosuppressive treatment is how long should treatment be continued and at what dose. A common experience is that reducing medication can lead to relapses of OMS symptoms. It is not known what causes these relapses but they have even occurred many years after the disease started but usually with symptoms less severe than the initial symptoms. Furthermore, although it is thought that the disease 'burns itself out ' with passing years and/or age it is not clear how common relapses are in adults who had OMS as children: the monitoring and recording of these relapses has not been done. This is clearly a gap in our understanding of the disease that needs to be filled. The growing list of new drugs that might be of value in the treatment of OMS offers new opportunities for early treatment and the treatment of relapses.

Fourth session – Neuropsychology and behavioural therapies.

The first presentation was by **Cathy Taylor**, Principal Speech and Language Therapist/Systemic Family Therapist Queen Mary's Hospital, Roehampton. She had interviewed a small group of OMS patients, including children, a young adult and a parent . Interviews focussed on language, communication, social interaction and emotional impact. Individual findings were presented and general themes explored. All of the children had speech difficulties when the OMS first started and many were left with residual problems in the long-term.

Emotional impact on the child and their family was very significant and related to early distressing symptoms and loss of skills eg walking, talking in the acute phase, communication and physical problems, the uncertain course of the condition, appointments, procedures, the treatments and side-effects, and fewer social experiences.

Parents described the difficulties of judging whether their child's symptoms are due to the disease, its treatment or – especially in relation to behaviour – are a normal and age-appropriate response to a distressing situation. The uncertainty of the disease course and the effect on siblings who received less parental attention added to the emotional distress.

Priorities from parents and older patients were transparency from professionals, Dancing Eye Syndrome Support Trust support, multi-disciplinary team approach and speed of access when needed.

Dr Keir Jones, South London Trainee in Child and Adolescent Psychiatry , gave a presentation on the mental health aspects of OMS. He talked about symptoms both early on in the disease and the longer-term problems. Irritability, mood swings, hyperactivity, anxiety, social withdrawal, depression, obsessional traits and sleep disturbances are various symptoms.

Behavioural approaches used to help with these problems included input from speech and language therapy, occupational therapy, educational psychology and support groups.For specific problems drug treatment was reviewed including use of antidepressants and melatonin. Clearly each child should be considered individually before deciding whether and which mediation(s)to consider.

Dr John Wilson, Emeritus consultant paediatric neurologist at Great Ormond Street Hospital, posed the question as to whether children may be inconsolable during the acute phase of their illness because they are in pain and would painkillers be of help? At a previous workshop an adult with OMS described painful headaches during his illness.

Dido Green, Reader in Rehabilitation at Oxford Brookes University, explored the potential role of sensory and perceptual difficulties as possibly explaining some of the symptoms of OMS which have appeared up until now to be mainly a movement or behavioural problem. Examples of problems include an over or under reaction to different material textures, a hug or to pain. As a result the child may try to avoid that particular sensation and appear anxious. A questionnaire survey for parents and children is being planned.

Dr Andrew Sheridan, Clinical Neuropsychologist at the Oxford University Hospitals NHS Trust, spoke on the neuropsychological assessment findings in a small OMS group and then on the role of neuropsychological advice especially in relation to educational provision. The assessments were summarised and showed that the majority of children had below average scores but not in the learning difficulties range. Specific difficulties which may have an additional impact in the educational setting were identified in a number of children and included speech difficulties, attentional difficulties, coordination difficulties, social interaction problems. There were reading, writing and maths attainment issues in at least half the group even if IQ scores were within the normal range.

Relevant and useful advice to help children with this range of difficulties in the educational setting include, for those with attentional problems – short periods of teaching, minimising distractions, regular breaks, individual repetition of material; for children with hand-writing difficulties – OT support, moulded pencil/pen grips, key-board access, help to learn touch-typing skills. General attention required for all children in relation to exam arrangements and extra time.

Fifth session – Cerebellum and function

The cerebellum is a part of the brain historically thought to play a role in the coordination of movement only. This session focused on the normal and abnormal structure and function of this part of the brain . The cerebellum is very likely a major target of the autoimmune attack (where the body's immune system starts attacking its own cells) in OMS. Over time, there has been growing, but not universal, belief that it also plays roles in learning abilities and behaviour. Two neuroscientists who study the cerebellum presented their views.

Dr. Narender Ramnani of Royal Holloway University of London presented evidence to support two major nerve pathways or circuits involving the cerebellum. One pathway is mainly involved in control of our body movements and the other pathway in learning and behaviour. Functional MRI studies (the brain is scanned whilst the person is performing an

action or carrying out a learning/thinking activity) support this view. Related to OMS, a problem of the first pathway probably leads to the movement symptoms, such as ataxia (poor balance and unsteadiness). Problems of the second pathway may lead to some of the learning difficulties and behavioural symptoms of the disorder.

Professor Mitch Glickstein of University College London discussed the role of the cerebellum in modifying rapid eye movements to targets (called "saccades"). Damage to this system may cause opsoclonus. He suggested that the cerebellum does not play a major role in learning and behaviour.

Professor Christopher Kennard, neurologist and neuroscientist at the University of Oxford further discussed the neuroanatomy (parts of the brain)of eye movements. There is a complicated nerve pathway amongst brain cells in both the cerebellum and the brainstem . These cells have the equivalent of bridges or gates on their surfaces which control what substances can enter the cell. He suggested that a malfunction of this pathway probably causes opsoclonus. He speculated that autoimmune mechanisms which target these bridges or gates could produce opsoclonus and that there may be medications which could help to control this symptom.

Professor Vincent des Portes, a paediatric neurologist at the University of Lyon, France who specializes in children who are born with abnormalities of the cerebellum, described three major groups of cerebellar medical conditions. He explained that there is significant variation in the learning ability outcomes of patients within these groups, with a spectrum from normal function to severe intellectual disabilities. This suggests that other factors are involved-for example genetic factors . In OMS, there is also a spectrum of intellectual outcomes and factors other than the OMS itself may be responsible for the variable outcomes. Professor des Portes's presentation supported the view that the cerebellum is involved in learning ability and behaviour.

Sixth session – Personal Experience of OMS

Professor Jeremy Turk read a very moving transcript from an adult, now in her 20s,who had OMS as a child and has now relapsed after many years. As the doctors treating her have little or no experience in OMS this has left her feeling very alone and scared.

This generated a large amount of discussion between delegates and the following points were made-

1) It is imperative to provide adult neurologists with easily accessible information and support from other doctors.
2) It is essential to follow-up children with OMS into adulthood to discover the full natural history of this condition.
3) The formation of a registry or database to aid long term follow-up and research
4) The idea of setting up national reference centres where both patients and clinicians could access information and support.

Seventh session – Perspective on research funding and OMS

Dr. Katrina Gwinn from the National Institute of Neurological disorders and Stroke in the US gave a very informative presentation on how to access help for funding research into OMS. She also explained that organisations such as the Office of Rare Diseases, for which both neuroblastoma and OMS qualify, provide a lot of helpful information on securing funding although not offering funding themselves.

Eighth session – Towards a final consensus statement

Dr. Mark Gorman raised the very important question-" Should there be a consensus statement created for OMS? " This is essentially a statement showing what we know about OMS, its diagnosis, the best treatment options, the outcome measures and how to aid research. It gives information CURRENTLY about OMS and thus has to be updated regularly. It would raise the profile of OMS and help parents and clinicians. He has volunteered along with support to draft one.

Professor Hugh Perry from Southampton University provided a very positive **summing up** of the workshop and has also suggested the formation of an Advocacy group which would promote and support all those affected by OMS.

This multidisciplinary workshop has reinforced the working bonds that have formed amongst the current and past attendees and the huge willingness to progress on all fronts to improve knowledge and find solutions to this rare and devastating disease.

Morag Macleod – DESST Chairperson