

Dancing Eye Support Trust

Report on the 4th DES workshop

Abingdon 31st January – 2nd February 2008

CLINICAL FEATURES AND TREATMENT OF DANCING EYE SYNDROME

Richard Stanton-Roberts welcomed participants to the 4th workshop and **Dr. M. Pike (Oxford UK)** made the introductions.

Professor W London (Florida USA) gave an update on the current position of the Childrens Oncology Group (COG) trial ANBLOOP3. So far 21 patients have been recruited of whom 10 have gone into the group treated with cyclophosphamide (25mg/kg) and prednisone (2mg/kg for 4 weeks and then gradually reduced). The remaining 11 have gone into the other arm of the study which comprises the same treatment plus additional Intravenous Immunoglobulin (IVIg 1mg/kg) at 4 weekly intervals for 6 months and three further doses at 2 monthly intervals.

So far no outcomes are available although it was commented that there have been **no** toxic side effects to patients in either treatment courses. Recently there has been reduction in the numbers of new cases being recruited into the trial which may prolong the time required to obtain a large enough study population.

Drs B Hero/G Schleiermacher (Köln Germany, Paris France) reported that progress is being made for the establishment of a European Trial, but because the trial will operate in a large number of different countries consent has to be obtained in each country dependent on the laws in that particular country. There are large national variations, with regulations in Germany being particularly strict.

Barbara Hero felt that a trial was perhaps **at least** 3 years away.

AIMS

- 1] Registration of patients
- 2] Collection of samples
- 3] Clinical trial

To register a patient for the trial the patient must meet 3 out of 4 of diagnostic criteria :

- Opsoclonus [eye movements]
- Ataxia and /or myoclonus [unsteadiness or muscle tremors]
- Behavioural changes[irritability] +/- sleeping difficulties
- Neuroblastoma

SAMPLES

- Blood
- CSF [fluid from around the spine]
- Special research samples

At diagnosis of OMS/DES various scans would be carried out: MRI of head

neuroblastoma : scans to identify a

To assess response to treatment standard scoring scales would be used.

5 items have been selected for scoring:

- 1] stance
- 2] gait
- 3] arm/hand function
- 4] opsoclonus
- 5] mood

Assessments of Age -appropriate cognitive development and behaviour would also be carried out at 1 YEAR and 2 YEARS after diagnosis and at age 5 and age 10 .

TREATMENT

An escalating treatment schedule would be implemented ie if no response to initial treatment then further drugs would be introduced.

- 1] Dexamethasone and Intravenous Immunoglobulin given every 4 wks for 1 year

If after 3 mths response poor [as determined by scoring scales] then

- 2] Cyclophosphamide would be added in.[chemotherapy drug but used in lower doses as a suppressant of the immune system]

[Cyclophosphamide is a good immunosuppressant , it has been used a lot in other conditions so doctors are familiar with it .Side effects would need to be balanced with outcome.]

3] ?? Rituximab

There are still a number of issues to be resolved eg How specific the cognitive testing would be and the language barriers to overcome

Progress has been disappointingly slow from a parents perspective which was commented upon at the workshop .It may be that initially the trial may start in those countries which have less strict bureaucracy than others so as not to delay the trial further.

E Tate (Illinois USA) was scheduled to present a pharmacokinetic study of rituximab in DES but was unable to attend due to ill health.

INFLAMMATION IN THE BRAIN

Professor H Perry (Southampton) reviewed the impact of generalised infections on the brain and concluded with the following hypothesis. OMS is usually associated with neuroblastoma and the development of antibodies that then attack specific structures in the brain. There is evidence of a genetic(inherited) susceptibility to this attack by these antibodies in those children who have specific genes. There is also an association with a family history of auto-immune disease. (eg Rheumatoid Arthritis,Coeliac Disease,Crohns Disease etc)It was postulated that infection may also play a part in the development of OMS and that there is evidence of relapse after minor infections.

F Aloisi (Rome Italy) talked about the relevance of finding lymph gland activity outwith the normal lymph glands in chronic diseases such as Multiple Sclerosis.

M.S. is a disease of unknown cause in which chronic inflammation within the brain leads to damage to nerve pathways. It has been suggested that the unknown causal agent ,possibly the Epstein Barr virus [which causes Glandular Fever] may lead to an abnormal response from the hosts immune system which then attacks its own

nerve cells. Collections of lymph gland cells have been found at postmortem in the brains of patients with M.S.

It is suggested that these collections of lymph gland cells can easily be reactivated leading to production of more antibodies that continue to attack the patient's own brain leading to chronic inflammation.

Perhaps in OMS/DES infection with some common virus leads to this immune process being initiated and then the patient's own immune system keeps the destructive process switched on. There is no evidence that the Glandular Fever virus is the causal agent as yet.

This **might** offer one explanation for the underlying process in OMS/DES patients. It is not however the whole story.

Dr M Pranzatelli (Illinois USA) was scheduled to review the cerebrospinal fluid and serum chemokines in DES but was unable to attend due to ill health.

ADVANCES IN IMMUNOLOGY,ANTIBODIES

Dr L Bataller (Valencia Spain) reviewed the clinical and pathological aspects of adult OMS in a series of 24 patients, 14 with underlying cancer and 10 with no underlying cause found. Of the latter 10, eight had a monophasic course (one episode of illness) and two a relapsing/remitting course. All seemed to recover with immunosuppressant therapy, however the tendency was for the condition to improve in any case so it is not clear how significant the effect of the immunosuppressants were. Of the 14 with cancer, those that were fit to undergo anti-tumour therapy as treatment for the underlying cancer showed improvement in the OMS. Those that were not fit however deteriorated and 5 died from brain inflammation(encephalopathy).

In the majority of cases no pathological changes were found in the brain although in several there was nerve cell loss in the cerebellum/brainstem with an increase in inflammatory cells. In 2 out of the 24 cases with antibodies these were found throughout the brain with the highest concentrations in the brainstem.

Dr V Pistoia (Genoa Italy) has looked at the blood and CSF [spinal fluid] of patients with OMS/DES **and** neuroblastoma. He has found that there is an increased number of antibodies that bind to the surface of cells in those patients with OMS and neuroblastoma but **not** in those **without** OMS. There are increased numbers of

these cells with increased severity of the disease and antibody numbers decrease with the duration of the disease .

He is trying to identify those specific antibodies, what causes their activation and what causes the development of lymph gland tissue in abnormal places.

V Fuehlhuber (Giessen Germany) following on from their report in the previous workshop gave an update of their work in identifying surface binding autoantibodies to cerebellar (hindbrain) nerve cells and concluded that whilst an OMS specific antibody had not been identified, antibodies binding to chemicals on the cell surface (alpha-enolase and retinal dehydrogenase) were found in 25% and 50% of OMS patients respectively.

BEHAVIOURAL PHENOTYPES(specific patterns of behaviour)

Dr T Umasunthar (London UK) reported on his study of 19 children with OMS recruited as volunteers from the DES Support Group. The study was devised to see if there is a particular Developmental and Psychiatric profile in children with OMS.

Both parents and teachers were asked to complete behavioural checklists. Most of the children were seen at their homes by Dr.Umasunthar.

Recognized assessment tools were used including ADHD/Hyperactivity and Autism questionnaires.

Results

Both parents and teachers gave a similar picture : OMS children tend to be

overactive

easily distractible

have a poor attention span

be impatient and impulsive

disobedient and prone to tantrums

have low self-esteem

be shy

show social naivety and social immaturity

attention-seeking

No psychotic phenomena were reported

On the ADHD scale 6 out of 8 children showed features consistent with ADHD/Hyperactivity.

The Sleep questionnaire identified problems during the acute initial phase of the illness and during relapses but not in the remission phase.

In the Autism questionnaire 3 out of 9 children had features of an autistic spectrum disorder.

Assessments looking at communication, activities of daily living, socialisation and motor skills graded OMS children on the mild learning difficulty to low average intellectual ability range. 70% had a mild disability.

Language skills again fell in the mild disability to normal range. Interestingly parents often **underestimated** their child's abilities in language.

Most parents commented that their children had high pain thresholds.

In summary : there were higher rates of ADHD, conduct disorder and autism than expected. However , this was a self-selected group of children and we don't know about the children who did not take part in the studies.

Dr K Humphreys (London UK) gave a work in progress report on 2 on-going studies.

Study 1. In this study OMS patients are recruited and undergo a variety of neuropsychological tests to try and determine whether there is a characteristic profile for OMS. So far 15 participants have been recruited, 6 males and 9 females. The group comprise 1 adult, 2 adolescents and 12 children. In 9 the OMS was caused by a tumour, in 4 it was infection and in 2 no cause was found. Preliminary results show an average IQ of 71 with 7 being learning disabled and 2 borderline. Verbal skills were better and working memory skills worse than expected for the given IQ. Overall strengths were social awareness and common sense. Weaknesses were attention span and working capacity. When fully analysed it is hoped this will result in a cognitive profile for OMS thereby allowing appropriate therapy targeting specific areas of deficit.

Study 2. In the second part of the study it is proposed to compare and contrast the OMS behavioural and cognitive findings with those of other syndromes to establish

whether techniques used in the treatment of these syndromes may be helpful in OMS.

Dr E Degrandis (Genova Italy) reported on a study of 14 children with OMS diagnosed between 1/1/83 and 31/12/06. She wanted to look at any psychological and radiological consequences of the condition.

Clinically, 50% of the children had a chronic course, 36% had a chronic relapsing course and 14% had a monophasic [one episode] course. Of these children 71% had neurological [affecting the nervous system] consequences.

These were :

speech difficulties [57%]

opsoclonus and eye abnormalities [50%]

tremor [43%]

ataxia(poor balance) [36%]

myoclonus(muscle spasms) [36%]

cognitive deficit [62% had an IQ less than 85]

attention deficit [77%]

MRI brain scans were normal in 64% but abnormal in 36% showing cerebellar atrophy [shrunken hind brain]

The conclusions drawn from this study [14 patients] were :

1] The importance of **prompt diagnosis**

2] That in a high percentage of children OMS causes longterm consequences which do not seem to be adequately prevented by current immunosuppressant treatment.

3] There is a need to establish standardised treatment plans and cooperative studies.

Dr P Campbell (Edinburgh UK) gave a presentation on her study looking at the differences in Auditory Brainstem Responses (ABR) between normal children and those with DES. The ABR is a way of assessing the brainstem's response to different sounds including speech. These responses mature at the age of 2 which is

much earlier than cortical (higher brain) responses which don't mature till the age of 30! Therefore a problem in brainstem development could result in a damaged input to the still developing higher brain functions which may cause significant difficulties in the interpretation and development of speech.

In her study Dr Campbell performed a comprehensive audiological (hearing) assessment of 10 children with DES, with an age range of 5-17years, four of whom were boys. She found significant differences between this group and normal children particularly in tests using speech.

Having discovered this difference is there anything that can be done to correct it?

There is now increasing evidence that the brainstem can be "retrained" in the way it handles sounds by top down effects. (ie stimulating the higher brain can lead to changes in the brainstem) and that recognised audiology programmes (Earobics, Fast for word) could be helpful although further study is required.

NEURODEVELOPMENT(BRAIN DEVELOPMENT)

V.Suhalter (New York, USA) presented a talk entitled **Language Development,causes of delay and possible areas of research for children with DES/OMS.**

Language development is at its most intensive during the first 3 years of life during which time most children with OMS present. For competent use of language children need ability in both linguistic skills [receptive and expressive language] and extralinguistic skills [attention, memory, motor control, problem-solving abilities, inhibitory control].

Presumptions about children with OMS are:

- 1) That the neurological consequences of OMS appear to disrupt the natural course of language development.
- 2) The emotional and motor consequences of OMS would be expected to interfere with the development of necessary linguistic and extralinguistic competencies.

Studies have shown that comprehension of speech is usually adequate but children with OMS are poorer at the meaning and understanding of the social function of language. They can also have substantial expressive language deficits. Pronunciation can be difficult and conversations are often one-sided, laboured and

difficult to follow. It is also important to consider the impact of motor and cognitive delay as well as the emotional problems of frustration, anxiety etc which make it even harder for children with OMS to learn effective communication skills.

However, most parents report that language development does increase with time and significant improvements occur.

Do children with OMS show a consistent pattern of language problems?

Studies are needed , possibly comparing OMS affected children with children who have suffered a brain injury, in order to find out more about the underlying causes of the language deficits seen in OMS. This might enable provision of appropriate early intervention.

Dr Justin Williams (Aberdeen) discussed the structural and functional imaging approaches to neurodevelopment. Since this involves studying young children who are susceptible to radiation, scanning techniques such as Computed Tomography (CT) and Positron Emission Tomography (PET) are not suitable. Instead neuro – imaging largely relies on Magnetic Resonance Imaging (MRI). MRI can give information not only about how structures look, but also their size (volume based morphometry), what they contain (MRI spectroscopy) and how they work (functional MRI).

Another approach is to look at typical movements (for example picking up objects, catching a ball) and very accurately measure how these movements are carried out. This is known as kinematics. A portable lap-top (C-Kat) has been developed that can give very accurate measurements of certain movements and a database of these movements in healthy children is being built up. It will then be possible to compare these movements in other children (such as those with DES) to see how they differ from other children. This information will help in trying to understand which part of the brain is affected and possibly direct specific treatment programmes.

Dr. Wendy Mitchell (Los Angeles , USA) gave the workshop an update on her study comparing brain scans[MRI] of children suffering from OMS and normal controls. **All** had normal MRI scans.

She then carried out MR spectroscopy scans[specialised scans] which showed some differences but the significance of these differences is unknown. The whole brain was initially looked at and then the middle part of the cerebellum [hindbrain] called the vermis was scanned. Here there appeared to be a significant difference in both the white matter[communications between nerve cells] and the grey

matter[nerve cells] but the significance in clinical terms is not known. Functional MRI scans of adults shows that activation of the inferior vermis is associated with word and language processing.

More research is needed into differences in function of affected parts of the brain which will not be detectable using standard scans.

UPDATES AND THE FUTURE

Richard Andrews (Doncaster) gave a moving account of his experience of DES as an adult.

He had been undergoing treatment for a Giant Cell Tumour of his hand (fortunately now resolved) and this was initially thought to be the trigger ,although subsequently a virus was thought to be responsible for stimulating his episode of dancing eyes.

He initially noticed a dull persistent left sided headache with episodic severe sharp pains, unresponsive to painkillers which lasted for several days. He then became “jumpy” and “nervous” and started feeling shaky and unbalanced. This then progressed to difficulty walking and holding things. He then noticed his eyes shaking at which point he went to his local Accident and Emergency Department.

After a long period as an in-patient and a battery of tests (MRI, CT, Lumbar puncture etc) the diagnosis was eventually made and he was referred to Dr Gibson,a neurologist in Sheffield ,by which time he felt “Like he was living in a horror film”. He was unable to read, watch TV or get up without falling. He was tired, depressed and irritable with difficulty sleeping.

He was started on high dose methyl prednisolone which quickly improved things and the dose was gradually reduced over the next 2 months which did result in a slight deterioration in the symptoms although they did gradually improve without treatment over the next few months.

Richard now feels back to his normal health although it took a year for his hand writing to return to normal and for him to stop feeling unstable and irritable.

He made the following comments about his treatment:

1. Blacked out pin-hole glasses seemed to help his eye-shaking allowing him to read/watch TV
2. An exercise programme seemed to help with strength/balance
3. He would have liked more control over his own steroid dose ie. so that he could have increased it if he felt his symptoms deteriorating.

A Family in Therapy **Stefan and Marion D. (Germany)** told us the story of their daughter Anne who developed OMS associated with a neuroblastoma when she was less than a year old.

Despite the emotional distress, they gave us a picture of the journey that they, like other parents, struggle along. After treatment with steroids, immunoglobulin and chemotherapy Anne's OMS became quiescent and the family then had to deal with the problems it left in its wake.

Both Stefan and Marion have always felt that occupational therapy had a very important role to play. In particular they feel that both specialist **and** parents' involvement is crucial. They followed the behavioural concept of 'Parents as Therapists' put forward by Fritz Jansen. This programme focuses on parents' behaviour and trains them to train the child. From the onset of her disease, Anne developed certain autistic traits, like a strong resistance, avoidance of eye contact and body contact, lack of empathy, unresponsiveness to reward or punishment, etc. – even though she was a very sweet and charming child.

Marion described her awful distress that Anne resisted emotional and physical contact. They felt so helpless and out of despair that they turned to the KIT programme –a holding therapy. It was invasive, extremely stressful but in the end was successful. The programme involved twice or three times a week holding tight a resisting, crying child until she eventually soothed and gave in. This could take between 20 minutes and 1 hour. After 3 months the autistic traits subsided. Anne became much more open to learning and most importantly, she became responsive to affection, rewards and success.

Now Anne is in her 2nd year at mainstream school. She is still very shy and has social anxieties, but her relations to the family members and to close friends are good, and she enjoys learning. Now it is her mother who is undergoing therapy in the form of psychoanalysis to deal with the pressure of 'trying to fix it' for Anne.

Marion and Stefan gave us a brave and honest story .

Dr R.Vermeulen (Belgium) gave a impassioned talk on 'What the parents want'. He voiced many concerns about delay in diagnosis, lack of knowledge of treatments etc. He has suggested producing a universal information pack both in paper and electronic form to give to parents and to be accessible to clinicians . A meeting took place after the workshop to discuss how to take this further.

Professor Jeremy Turk (London) was planning to talk on the developmental ,emotional, behavioural ,educational and social support needs of individuals with DES/OMS and their families but as we were running out of time he felt the subsequent speakers should continue. However , he did pass on his lecture notes ,a brief summary appears below.

A child with developmental and intellectual disabilities is an individual at risk, a family with such a child is a family at risk. These risks are numerous from disharmony and family breakup to mental health problems , financial difficulties, social isolation etc.

He posed the question 'Does early identification of such problems with early initiation of interventions and supports improve outcome? '

We as parents know that empathic support and practical help is valuable and essential.

Professor Marcel Tardieu (Paris) presented his work on herpes encephalitis in children. Herpes simplex (HSV1) is a relatively common mild viral infection (causes cold sores)which rarely can progress to an encephalitis (inflammation of the brain) which is much more serious. Why does this more serious progression occur? The theory was that there is a genetic predisposition to a reduced immunity to HSV1 in the Central Nervous System (CNS). In a review of 85 children going back 20 years, 51 had blood samples taken and this did indeed reveal the presence of a genetic difference in the children that had encephalitis as opposed to simple HSV infection. The relevance for DES is that perhaps there is an as yet unproved genetic predisposition to developing the condition as a consequence of an external trigger such as neuroblastoma or infection.

Dr. Marcel Kinsbourne (USA) gave an overview starting with the important statement that 'you have to look back in order to look forward'

How far have we come since the 1st workshop in 2001?

We now have an appreciation of the longer term problems children with OMS face. Children with OMS don't have global learning difficulties but perhaps there is a subset of skills at risk which may affect the quality of learning which may then result in the variability of symptoms and response to treatment. On IQ tests children may come out with overall low scores although they may only have poor scores on certain tested areas and normal scores in other areas . This is important in advising teachers and therapists to focus on using the child's normal abilities in certain tasks

to help in those tasks in which the child has particular difficulties, rather than assuming the child to be generally poor in all areas.

OMS children seem to have problems in learning specific to the cerebellum[hind brain].The cerebellum does not initiate learning but acts more in refining/ quality control/precision of learning.

Understanding **is** helpful even if you cannot **do** anything to change things.

Professor P Beverley (UK) rounded off the meeting with a few observations-

The hypothesis is that OMS results from an original insult which disturbs the regulation of the immune cells resident in the brain, and this disturbance in regulation persists. These immune cells then respond abnormally to any further immune stimulus (inflammation) whether it arises in the periphery or the brain.

The consequences of this hypothesis are as follows/

1. It allows testable predictions.
2. It has implications for management in both the acute and chronic stages of OMS/DES

In the acute stage if the process is diagnosed and treated early enough is it possible to stop the chronic changes developing?

In the chronic stage treatment needs to target the response to the inflammation and also the cause of the inflammation.

It was also pointed out that attention now seems to be focussing on the B cells rather than T cells (types of white blood cells) as being key players in the development of OMS and further research into their actions/involvement is required.

There is also now more attention being paid to the pattern of disabilities suffered by OMS patients. Is there a characteristic pattern which can then be addressed with specific therapy/teaching techniques hopefully improving the outcome?

All these questions need to be answered. This will require on-going trials with communication and collaboration between specialists in many different countries.