



Dancing Eye Syndrome
Support Trust

Report on DES Workshop at Abingdon 17th-19th November 2005

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Abbreviations: Ab – antibody; DES - dancing eye syndrome, used synonymously with OMS – opsoclonus-myoclonus syndrome and with OMA – opsoclonus-myoclonus-ataxia syndrome; HLA - histocompatibility antigen; ivlg – intravenous immunoglobulin, LE – limbic encephalitis, NB-neuroblastoma; TCR - T cell receptor; VGKC - potassium channel.

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Clinical update

Mark Bourgeois (Chairman DESST) welcomed participants and outlined the purpose of the Abingdon workshops, and the interest in reviewing the progress in research since the first workshop in 2001.

Dr M Pike (Oxford, UK) focussed on the clinical aspects of DES for the benefit of those participants who did not have direct experience of the condition. Dr Pike has been the co-ordinator of the first prospective survey of DES in the UK, in association with the British Paediatric Neurology Association. In the 2 years since it started in May 2003, there has been an 89% response rate and 19 new cases were notified. Parents of 15 children agreed to further evaluation. Their average age at presentation was 17 mths (range 3-42 mths), and average duration of illness before diagnosis was 15d (range 1-60d). A neuroblastoma (NB) was identified by MRI in 4 children with DES, whereas other laboratory tests were unhelpful. In 7 children with DES in whom NB was not identified, there were symptoms of recent upper respiratory tract infection but not in those children with NB. Through liaison with reporting doctors, samples of blood and spinal fluid from several affected children were sent to Dr Beth Lang of the Neurosciences Group at the Institute of Molecular Medicine at Oxford for investigation for anti-neuronal antibodies (see later).

Professor A Pearson (Sutton,UK) presented a review of current thinking about NB and its management, and about DES from the standpoint of a cancer specialist. At least 33% of NBs regress spontaneously. About 2% of children with NB had DES, whilst NB is found in 80% of children with DES who are scanned by MRI. In these latter children, the NB usually responds to treatment better than in those without DES, whose more aggressive NBs often need more aggressive treatment. The International Society for Paediatric Oncology is organizing a prospective treatment trial in children with DES who both have and have not got demonstrable NB. There is a widespread feeling in the USA that, even in patients with no NB, the DES needs quite heavy immuno-suppressive treatment, eg with steroids plus cyclophosphamide, a powerful drug that also doubles-up as a chemotherapy agent. Instead of steroids, some prefer to use adrenocorticotrophic hormone (ACTH), the natural stimulator of steroid production by the adrenal glands, which does not “shut them down” in the way that high doses of steroid do.

Dr P de Alarcon (Memphis,USA) described a prospective trial of ivlg in the treatment of NB-associated DES. Six patients have been recruited so far. First they are all immuno-suppressed with steroids plus monthly cyclophosphamide. Half the patients randomly selected will be given ivlg for twelve months, and outcome then compared between the two groups respectively.

Dr B Hero (Cologne, Germany) – is chief co-ordinator of a prospective therapeutic trial in children with OMS – with or without NB - from Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Nordic countries, and UK. Diagnostic and prospective assessment criteria have been agreed, but it has been difficult to achieve agreement over the treatment regimen. Most European paediatric neurologists accept the use of cyclophosphamide in children with tumours: for those children without tumours, some are more reluctant, because of the drug's serious potential side-effects, and the consequent shift in balance between risks and benefits. The inevitable side-effects of steroids, especially in the long term, are also of concern. The proposed European regimen comprises increasing doses of medication, first with pulsed (ie short courses) dexamethasone, then ivlg followed by cyclophosphamide. Although broad agreement has been reached, the programme has not yet been funded

Management of DES

Dr B Wilken (Cassel, Germany) reported 2 children (one with NB) who were severely affected for 9 yrs and 4 yrs respectively in whom there was dramatic and long-term benefit after 7 pulses of dexamethasone (steroid) and cyclophosphamide .

Dr J Turk (London, UK) compared the consistent and distinctive behaviour problems in children and young adults with DES with other distinctive and specific behaviours associated with particular conditions such as Down's Syndrome and fragile X syndrome. This approach grappled with the dual problems of identifying the underlying biological mechanisms and also, especially, the challenging problems of management.

Dr R Forsyth (Newcastle on Tyne, UK) explored recent developments in the treatment of acute physical injury of the brain, particularly during rehabilitation by promoting restoration of functioning connections between surviving neurones and neural networks. He speculated on relevance of this work to immune-mediated brain damage as in that suspected in DES.

Dr J Fawcett (Cambridge, UK) described successes with embryonic brain cell transplantation in Parkinson's disease, where neuronal loss is well-localised. One promising area of recent research is into exploiting the neural stem cells that persist into adult life in special areas of the brain. Another is into encouraging nerve connections to re-form, even when they have been "set in aspic" in normal development, or blocked by scar tissue after brain damage.

Dr A Klein (Zurich, Switzerland) reported on the long-term follow-up of 10 children with DES. Unsteadiness improved in all and was not relevant in every day life but behavioural and learning problems were common.

Advances in Immunology I – Antibodies (Abs)

Antibodies are proteins that circulate in the blood and are tailor-made to latch on to particular infectious germs in an attempt to destroy them. Occasionally, patients mistakenly make Abs that instead attack their own cells/ tissues and cause autoimmune diseases. It is important to recognise these autoimmune diseases, because they are more treatable, for example by immunosuppression, than many neurological diseases which are incurable.

Professor A Vincent (Oxford, UK) reviewed the role of antibodies in damaging brain cells. Some bind to cell surfaces and clearly cause disease: others recognise nuclear proteins, and are probably just by-products of attack by other immune cells, although these Abs may still be very useful markers for diagnosing particular diseases. The generation of antibodies can be provoked by tumours (eg of lung, breast or ovary). Particularly vulnerable targets include receptors for the chemical signals between nerves, and the ion channels that control how these signals are conducted, such as voltage-gated calcium and potassium channels (VGCC and VGKC). Disorders caused by these Abs are sometimes known as channelopathies.

Antibodies against VGKC are found in some patients with:

Acquired neuromyotonia
Morvan's syndrome
Limbic encephalitis
Some epilepsies and other seizure-related disorders.

Limbic encephalitis(LE), provides an interesting model for DES research although it mostly affects adults. Some but not all cases are associated with cancer. Some patients have high levels of Abs against VGKC that also bind to brain tissues. Most importantly, LE is an example of a condition where even recent memory loss and/or seizures may improve dramatically after treatment with plasma exchange, ivlg and/or corticosteroid treatment.

Dr B Lang (Oxford, UK) reviewed the evidence for the presence of antibodies in OMS. In adults with OMS mean age is 66 yrs in those with a neoplasm but 40 yrs in those without. Anti-neuronal Abs are present in 81% of a cohort of OMS children with NB but in only 25% of children with NB alone. However, in the recent UK National survey (Pike & Pang see above) candidate antibodies against excitatory receptors/ion channels in the brain have not as yet been identified.

Dr F Blaes (Giessen, Germany) reported his studies on antibodies in sera of children with OMS. 11(9 with NB)/14 had antibodies which bind to living cultured cerebellar granule neurones derived from rat brain, supporting the notion that in OMS there is an autoimmune process against a neuronal surface protein. Surface binding to neuroblastoma cells by antibody (IgG) from children with OMS was higher than that found with antibody from patients with NB alone or controls. These results suggest that patients with OMS raise a specific anti-NB response not seen in NB-patients without neurological dysfunction

Advances in Immunobiology II – Cells

Certain white blood cells, T lymphocytes, are the major players controlling and directing the immune system; when they recognise a foreign microbe, graft etc. they instruct other cells to destroy it, and they can also help other 'B cells' to make antibodies. Both T and B cells are an extremely diverse mixture of different clones. They have antibody-like surface receptors tailor-made to recognise one particular target. Most T cell receptors (TCR, whether $\alpha\beta$ or $\gamma\delta$) recognise these targets only when they are served-up on the tissue-type 'HLA' molecules on infected cells. (It is these HLA types that have to be matched for grafting kidneys etc.).

Dr M Pranzatelli (Springfield, Illinois, USA) reported an unusual mix of T and B cells in spinal fluid from patients with DES. Although the total cell numbers were normal, the proportions of certain subsets of T and B cells were increased, whether or not the patient had NB or chemotherapy for NB; they seemed to correlate with both disease activity and severity. Proportions of B cells (antibody-producing) remained low for many months after treatment with an antibody against them (Rituximab®; anti-CD20), coinciding with clinical improvement in each case. Again, heavy immunosuppression seemed to be important; there were encouraging clinical responses to ACTH alone and to ACTH plus ivlg, but with less effect on B cell proportions. Removal of NB *per se* is insufficient for clinical improvement of DES symptoms.

Dr V Pistoia (Genoa, Italy) reviewed the microscopic findings in NB tumours, particularly in DES-associated cases which contain collections of B cells, implying that these may be reacting against some local target(s). His team can also identify molecules (chemokines) there that might be attracting B cells into the tumours - and probably also the numerous T cells (with $\alpha\beta$ or $\gamma\delta$ TCR). Although the significance of these observations in relation to the development of neurological manifestations is unclear, they may well be relevant.

Dr C Bien (Bonn, Germany) reviewed latest thinking on Rasmussen's encephalitis, a remorselessly progressive neurological illness that presents in later childhood, and is characterised by slowly progressive destruction of one cerebral hemisphere. More or less continuous focal fits are resistant to standard anticonvulsant drugs. On microscopy, there are inflammatory as well as destructive changes in the brain, with many CD8⁺ T cells. Until now the only treatment for the intractable epilepsy has been surgical removal of the affected half of the brain. One recently-developed and promising treatment for early cases is with high dose steroids and ivlg. Bien now also sees encouraging reductions in paralysis and brain atrophy (but not, alas, in fit frequency) after giving tacrolimus (FK 506), an immuno-suppressant used to stop rejection of organ transplants.

Dr B Hero (Cologne, Germany) reported her findings on HLA distribution in DES, research in which members of DESST have collaborated. (HLA refers to the tissue cell equivalents of blood groups, but which are much more numerous) Dr Hero found that HLA antigen DR.B1*01 was more frequent in children with OMS (+/- NB) than in children NB without OMS and in the general population (10%). This HLA antigen is strongly associated with rheumatoid arthritis, a relatively well-understood autoimmune disease.

Miscellaneous

Morag Macleod, a paediatrician and parent gave a very moving personal description of the impact of OMS and NB on her and her family. It provided a poignant, vivid and highly relevant insight for all participants in the workshop.

In the ensuing discussion the need to disseminate information about DES and the particular needs of affected children to medical and educational professionals, to the public and to family and friends was emphasised. Reappraisal of these needs should continue after school entry.

There was differing opinion about advice on immunisation, but, it was agreed that only killed vaccine should be given and that, in respect of influenza, to promote herd immunity other members of the family should be vaccinated, but not the affected child.

Dr P Campbell and Professor C Harris (Plymouth, UK) reported preliminary findings of an audiological study supported by DESST. The results of a questionnaire suggest that 70% children with DES have, or have had, intolerance of sound (hyperacusis), with 54% still frightened by certain sounds despite improvement in other symptoms and signs. A More objective assessment of one man aged 22 years showed abnormal sound processing in the brain; further studies should show how widespread this is in other subjects, and test the predicted involvement of the cerebellar vermis.

Studies of ocular movement in others showed abnormalities of volitional eye movement persisting even in some people whose DES was thought to be in remission.

Both audiological and oculomotor studies are enlarging our understanding of the distribution of neurological dysfunction.

Dr Y Morad (Zrifin, Israel) showed video of a premature infant with extremely rapid, but transient, vertical jerking of the eyes.

Updates and the future

Professor A Hayday (London, UK) explored understanding of the respective roles of B cells and T cells. Their receptors must be (or have been) diverse enough to meet the daily challenges posed by any infections now, as well as by the varied living conditions of our ancestors over the last 400 million years. Some particular TCRs are highly conserved in evolution, and presumably must be remarkably efficient to have persisted so broadly in different species. These conserved TCRs are over-represented in a set of T cells termed gamma-delta T cells.

Professor Hayday described fascinating experiments using genetically modified mice. They suggest that one important normal function of the $\gamma\delta$ -T cells, once activated, is to restrain the $\alpha\beta$ -T cells; if that goes wrong, it seems to worsen some autoimmune diseases (eg multiple sclerosis) in experimental animals. Could something similar happen in DES? [Interesting that upper respiratory tract infections frequently serve to trigger relapse in DES –JW].

Dr W Mitchell (Los Angeles, USA) presented first, preliminary data on magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) from 8 OMS patients and their 7 siblings. Although most imaging including MRS was normal, there was a hint of subtle but probably significant evidence from volumetric analysis of neuronal loss in the cerebellar vermis, which could account for ocular and auditory problems as well as unsteadiness. She also presented results of serial testing of learning skill which suggest that there was more improvement than could be accounted for by a maturation effect on a static condition. The children who never relapsed showed the greatest improvement.

Summing –up

Dr J Pritchard (Edinburgh, UK) and Professor P Beverley (Jenner Institute, UK) summarised the achievements since the first DES workshop in 2001 and outlined further objectives.

Achievements

- Using whole body MRI, NBs are found in ~ 80% of children with DES in USA (W.Mitchell), but in UK the proportion is ~ 25%. This raises questions about both referral bias and investigation protocols.
- The UK national survey has shown 0.2 new cases of DES/million population/year, a higher than expected proportion of atypical cases including some with rapid spontaneous recovery and a diverse approach to investigation for NB. (M.Pike, K.Pang).
- The idea of clinical homogeneity of DES is now in doubt: monophasic and self-limiting, severe but therapeutically responsive, and severe and relapsing forms are now identified.
- The autoimmune hypothesis of causation is strengthened. Although the autoantigen has not been identified, recent antibody-binding studies have provided useful leads (F.Blaes)
- Association with HLA- DRB1*1 demonstrated.(B.Hero)

- Altered B- and T-cell profiles in cerebrospinal fluid (M.Pranzatelli)
- Upsurge in international communication between scientists/clinicians and, through the internet with parents, world-wide.

To be done

- To agree clinical criteria on an international basis:
 - Diagnostic Criteria (probably as defined in Matthay et al. Cancer Letters 228 (2005), 275-282)
 - Staging/severity criteria (probably as per current US COG trial)
 - Response criteria (probably as per current US COG trial)
 - Risk factors
- To determine the underlying biology of the severe irritability seen in OMS children. It has been pointed out by Jeremy Turk that irritability is probably not just a consequence of nausea and disorientation but due to an underlying physical problem. Therefore we should seek
 - Better management of the child's irritability.
 - Better understanding of the problems encountered by parents and strategies should be developed for management of these problems.
- The "antibody hypothesis" has turned out to be more difficult to establish than initially envisioned. However Franz Blaes' study of antibody binding to the surface of neuroblastomas needs to be extended.
- If Wendy Mitchell's findings, which are in a preliminary form, are confirmed and the deficit seen in OMS children is situated in a small area of the brain (cerebellar vermis), could repair techniques outlined by J. Fawcett be used? It is vital to know whether or not there is neuronal loss, because that may set limits to how much recovery we can expect.
- To promote the standing of neuroimmunology as a discipline and take the lessons learnt from the work on DES to advance the studies on other rare neurological disorders.

WHAT WE WANT

- OMS Parent Support Package, which will be co-ordinated by Robert Vermeulen, (parent and doctor - Janssen-Cilag, Belgium)
- Predictive tests and biomarkers to indicate the possible outcome of OMS.
- International Trials. The dichotomy in the trial design between Europe and the US was highlighted by Peter Beverley. It was suggested that the design of the European Trial was not robust enough to allow us to learn very much about treatment, and it was not designed in a way that would allow us to compare the results obtained with historical controls. This was re-iterated by several of the European parents present, who said that they would not have been willing to join the trial as it is currently designed, placing more confidence in the US trial which aims to “hit hard from the start”. Peter Beverley asked the European trial co-ordinators to think “long and hard” about the design and to treat the disease as “a neurological emergency”.
- Publicity and Publications. We need to inform clinicians about OMS, so there is no delay in appropriate treatment and to promote understanding of OMS to the public and especially to professionals in the education system.