



Dancing Eye Syndrome
Support Trust

Report on the first Workshop on Dancing Eye Syndrome Clinical and Basic Science Abingdon, UK, 22nd-24th February 2001

The First Workshop on Dancing Eye Syndrome, Clinical and Basic Science was held in Abingdon, UK. The meeting sponsored by the Dancing Eye Syndrome Support Trust brought together parents, clinical and basic scientists to discuss what is known about Dancing Eye Syndrome (DES), what is being done in the management and treatment of DES, and most importantly what needs to be done to further our understanding for improved treatment of this condition. This two day meeting involved presentations from parents, clinicians and basic scientists from Europe and the USA. This synopsis of the meeting draws together what is known about the syndrome as a clinical entity, what might be the underlying pathogenic mechanisms, and the implications for future research and therapy.

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The clinical picture

Dancing Eye Syndrome, also known as opsoclonus - myoclonus, opsoclonus ataxia, or myoclonic encephalopathy of Kinsbourne is a rare disease that primarily afflicts children but it is likely that the number of cases will increase as awareness of the disease and correct clinical diagnosis improves. Descriptions of the clinical picture (de Sousa, Kinsbourne, Mitchell, Pike) were remarkably similar in the UK and USA and covered many decades of experience. The onset of the disease is between 10 months and three years of age, mostly occurring around the 2nd year of age in children with no preceding history of neurological disease. The onset of the disease is sub-acute, usually over a period of a few days, or weeks, and characterised by a jerky ataxia, shivering movements, and bursts of multi-directional conjugate eye movements along both horizontal and vertical axes. As described by both clinicians, and parents alike (Fraser Ross, Sandra Greenberg), the children are severely distressed and this is expressed in intense irritability, very disturbed patterns of sleep and a desperate need to be held, almost constantly.

The factors that might precipitate the illness in otherwise perfectly healthy 2 year old children were a subject of much discussion. In UK studies (de Sousa, Pike) perhaps as many as 50% of children, while in the USA more than 90% were found to have a neuroblastoma (Mitchell). In all cases where it was present the neuroblastoma was small and was surgically removed. There was debate as to whether small apparently rather benign tumours may have escaped detection in the children reported not to have neuroblastoma. Outcome from the point-of-view of the neuroblastoma seems to be almost invariably good; this has no bearing however on the outcome of the DES. The second factor associated with the illness was recent or ongoing infection. As many as 50% had had a recent viral infection, but of course children at this age commonly suffer from minor infections. The possible significance of neuroblastoma was further discussed (see below).

Apart from the clinical features described above there is remarkably little useful information available to the clinician to help understand the nature of the disease. In those children where more detailed clinical examination has been possible, investigations of the brain by routine magnetic resonance imaging (MRI) or computer topography (CT) provide little evidence of abnormalities or overt damage. Similarly analysis of the electrical activity of the brain by recording from the scalp (EEG - electroencephalography) has not proven useful, and neither has analysis of the cerebrospinal fluid (CSF) which bathes the ventricles and surface of the brain.

With so little clear evidence as to the cause of the illness that presents in these children the choice of therapeutic interventions is by no means straightforward. However, all the clinicians agreed that at least in the short term treatment with steroids was useful in controlling the symptoms. Prednisolone was found to be effective in this regard as was ACTH (de Sousa, Mitchell, Pike). The use of high doses of steroids is not without its side-effects and thus reducing the dose to the minimum required to control the symptoms is desirable. Of much interest was that a systemic infection (e.g. influenza) could often lead to a relapse and worsening of the symptoms. The responsiveness of the illness to steroid treatment and the onset of relapse associated with an infection point to significant involvement of the immune system in the disease. The finding that intravenous immunoglobulins (IgG) can also help to alleviate the acute symptoms also supports the idea that the immune system is involved in the disease. More aggressive immunosuppression has been used in a small number of children and this also reduced the acute symptoms.

Possible sites of brain injury

Whatever the cause(s) of DES it is important to know which parts of the brain are affected by the disease and also whether the damage to the brain is a single injury or an ongoing

progressive process. It is not easy to establish, in a disease that affects the developing brain, whether injury to the brain has prevented the normal development of the brain and thus prevented the appearance or acquisition of a particular motor or cognitive skill, or whether the illness is ongoing and continuously affecting these skills. Evidence from children examined 2-11 years after diagnosis suggests that the disease may affect not only motor and cognitive skills but also that the older children appeared more impaired. This would imply that the disease is progressive even when the symptoms are apparently controlled by steroids (Mitchell).

The ataxic disturbance of limb and trunk movements are entirely consistent with damage to the cerebellum, although precisely which circuits or cells remains to be defined. The abnormal eye movements that are so characteristic of the illness and give it its name, DES, point to direct damage of the neuronal circuitry that controls eye movements. This circuitry is well understood in the normal brain and detailed examination of the abnormal eye movements could give a clear idea of where to look for damage to particular neurons (Harris).

The wild, intermittent and arrhythmic horizontal and vertical saccades that occur back to back, is a pattern rarely found in other neurological conditions. There are groups of neurons in the brain stem that control the horizontal and vertical movements of the eyes so that the two eyes move together (conjugate eye movements) to let us fix our gaze on a particular object. The nerve cells in these centres are in under the control of another group of neurons, in the paramedian pontine reticular formation (PPR), the so-called "pause neurons". One hypothesis is that damage to some pause neurons, or inputs to them could account for the abnormal eye movements. It is important to note that the damage to these circuits cannot be complete otherwise the symptomatic relief brought about by drug treatment, or spontaneous remission could not take place.

Other components of the illness must also have neurological substrates, the irritability, the disturbed sleep and the cognitive impairment. At the present time it is wholly unclear whether these components reflect secondary consequences of the disturbed motor co-ordination and eye movements, or whether they reflect damage to specific pathways. It is possible that the irritability and desire to be held arise because the child's balance and visual world are so unstable. Similarly these problems could contribute to the learning difficulties and cognitive impairment seen in the children.

Summary - Clinical picture

The clinical picture of Dancing Eye Syndrome, also known as opsoclonus-myoclonus, opsoclonus ataxia, myoclonic encephalopathy of Kinsbourne is characterised by:

- *Disturbed motor control of limbs, trunk and head, with some features of cerebellar damage.*
- *Abnormal horizontal and vertical conjugate, arrhythmic saccades indicative of damage to the neural centres controlling eye movements.*
- *Severe irritability, disturbed sleep patterns and a need to be held.*

- *The symptoms are usually of acute onset at about 2 years of age with no previous neurological history.*

- *The symptoms are often responsive to steroids, or immunoglobulin in the short term, but may fluctuate or relapse subsequently, often precipitated by minor inter-current illness..*
- *The effects of treatment on long-term outcome are uncertain but motor and cognitive defects usually persist, and may get worse with age.*
- *The illness is associated with the presence of a neuroblastoma probably in half the cases, although surgical removal of the tumour does not affect the outcome.*

Underlying Mechanisms of Disease

Genetics

There is no family history of neurological disease associated with DES suggesting that the disease is sporadic in nature. However, this does not mean that there are no genes that predispose particular individuals to DES. This is a subject for possible research.

Initiating events.

A striking feature of DES is the narrow age range over which the disease appears with the majority appearing at close to 2 years of age. There is a clear association with the presence of a neuroblastoma in most cases reported in the USA (Mitchell) and an increasing percentage of cases in the UK (de Sousa, Pike). If the neuroblastoma is associated with the initiation of the disease it is certainly not necessary for the maintenance or progression of the disease, since removal of the tumour has no apparent effect on disease progression. In those children where no tumour was found there was usually no later appearance of a tumour suggesting that if it existed in the first place it regressed spontaneously. The neuroblastoma does appear to have initiated an immunological reaction since histological analysis of the tumour shows evidence of a T-cell infiltrate. The extent to which the tumours are identical or even similar in phenotype was unclear. It is important to establish this since the particular form of the neuroblastoma may help to explain the onset of the disease at two years of age.

The role of infectious agents in the initiation of the disease is a vexed problem. Children at two years of age are exposed to a wide spectrum of pathogens many of which are common for example Varicella (chicken pox), Epstein Barr Virus, Herpes viruses and so forth. It is possible that the disease is initiated as a result of an interaction between the immune response to the neuroblastoma and an infection.

Pathogenic mechanisms

At the present time it is not known what causes DES. However, on the basis of the available clinical evidence a number of hypotheses have been generated and these are under investigation. The main themes are presented below.

Antibodies.

The presence of a neuroblastoma, the apparent lack of an overt inflammatory reaction or tissue destruction in the brain and the fact that the disease responds to immunomodulatory therapy has parallels with other antibody mediated diseases of the central and peripheral nervous system, the paraneoplastic diseases. Paraneoplastic diseases are rare diseases associated with diverse cancers of non-neuronal tissues (Vecht). A localised tumour in a non-neuronal tissue, breast or lung for example, induces an immune response and the generation of antibodies directed against a protein on the tumour cell. These antibodies circulate in the blood, enter the brain and may then bind to nerve cells in particular brain structures. The

binding of the antibody may then lead to dysfunction of the nerve cell or even its frank degeneration. Paraneoplastic disorders are found in less than 1% of cancer patients. Examples of the diverse nature of paraneoplastic disease include cerebellar ataxia associated with breast cancer or lymphoma, or opsoclonus-myoclonus associated with breast cancer. In some instances the target antigens for the antibodies have been identified in biochemical preparations of brain tissue and the distribution of brain cells that express the antigen has been mapped by examining the binding of the antibodies to brain tissue sections. It is not altogether clear how or whether in many of these instances, the antibodies cause degeneration of the nerve cells.

In contrast in the peripheral nervous system there are very good examples of diseases where antibodies produce dysfunction of the nervous system (Lang, Vincent). The archetypal disease in this regard is myasthenia gravis, in which the patient's immune system generates antibodies against the acetylcholine receptor on the muscle fibre, thus rendering chemical transmission from motor nerves to the muscle much less effective. In addition to antibodies binding to the acetylcholine receptor it has been demonstrated that in Lambert Eaton myasthenic syndrome there are antibodies generated against the voltage gated calcium channels and in neuromyotonia against the voltage gated potassium channels.

Although there are the examples where antibodies against neural components are associated with cancers, there are also examples where an infection may trigger an immune response against neural tissue. Guillain-Barre' Syndrome is commonly associated with an enteric infection with a particular strain of *Campylobacter jejuni*. An example where peripheral infection may trigger the generation of antibodies that produce central nervous system dysfunction was described (Dale). Group A beta-haemolytic *Streptococcus* is a common throat infection in children that may in very rare circumstances lead to Sydenham's chorea, a syndrome of tics or dystonic movements in which these motor abnormalities may be associated with psychological dysfunction, revealed as obsessive compulsive disorder. In serum samples taken from children suffering from an acute neurological disease 10-14 days after a *Streptococcus* infection antibodies were present that stained a very limited number of proteins on a Western Blot of brain tissue, while few control samples stained the same bands. From these and others studies, it seems likely that the antibodies generated following the *Streptococcus* infection enter the brain and bind to neurons in the basal ganglia, and possibly other regions of the brain, leading to neuronal dysfunction.

It is clear that both cancers and infections may lead to immunological reactions that result in neurological disease. The most compelling evidence that antibodies are causal in disease, rather than a secondary effect of the disease, has been established in relatively few instances. In myasthenia gravis the disease can be ameliorated by plasma exchange, which of course removes the pathogenic antibodies, at least transiently. In addition injection of the antibodies into mice give rise to a disease that is like myasthenia gravis in man. Studies *in vitro* also demonstrate binding of the antibodies to the receptor and interference with transmission of signals from nerve to muscle. Ideally in all diseases where antibodies are believed to be the cause of neurological disease it would be desirable to meet these strict criteria.

Antibodies in DES.

An important component of the workshop was that it enabled scientists who had studied serum samples from children with DES to meet for the first time and exchange the details of their research (Connolly, Lang, Pranzatelli). As one might expect these serum samples are difficult to obtain and only available in small quantities.

Serum samples from children with DES were used to stain human brain tissue sections. The antibodies bound to the cytoplasm and nucleus of brain stem neurones and also to the cell

bodies of the Purkinje cells of the cerebellum (Lang). However, not all antibodies give the same staining patterns and only 8/10 bound to neuroblastoma cells grown *in vitro*. Attempts to find proteins that are equally recognised by antibodies in all of the serum samples have not been successful. Some of the serum samples contained antibodies that could inhibit the proliferation of neuroblastoma cell line *in vitro*. In a series of samples collected in the USA from 9 children with DES (Connolly) no common patterns of antibody binding to proteins of a particular molecular weight have emerged. Some of the neuronal components recognised by the antibodies had a molecular weight compatible with binding to neurofilament or histones. These antibodies are not uncommon in serum samples from patients with neurological disease suggesting that the antibodies are generated as a consequence of neuronal damage rather than being causal or pathogenic. It is important to note that although the experiments are conceptually straightforward they are not without their technical difficulties particularly when working with small volumes of precious samples.

It remains a puzzle as to how antibodies, which are relatively large molecules (150kDa), cross the endothelial cells of the blood-brain barrier although there is plenty of evidence that some do enter brain tissue albeit at low levels. One possibility is that in paraneoplastic diseases of the central nervous system there is some common component of the antibodies, their glycosylation patterns for example, that endows them with some special dispensation to enter the brain parenchyma.

Cell mediated immunity.

Cells of the immune system may also cause neurological disease. The archetypal autoimmune disease of the central nervous system is multiple sclerosis (Perry, Wraith). In this disease T-cells and macrophages from the blood invade the brain at focal sites, predominantly along the fibre tracts. At these sites the invading cells damage the blood-brain barrier, the myelin sheaths of the nerve fibres and the nerve fibres themselves. It is not known what initiates multiple sclerosis but it is rare in children. Not only does MS have a later onset but it also has a very different clinical picture from DES. However, there are important lessons from multiple sclerosis since this is an area where there are many new developments in therapeutics for neuroinflammatory disease.

The most common form of MS is a disease with periods of remission and relapse, the relapses being associated with activation of the inflammatory lesions within the brain. Many of the relapses in the MS patient are associated with an infection, commonly an upper respiratory tract infection. There are interesting parallels with relapses in children with DES. Activated T-cells may cross the blood-brain barrier no matter what antigens they are directed against, and thus it seems likely that the peripheral infection non-specifically further activates the immune system.

At the present time there is no evidence that DES involves a cell mediated immune response, but it may be a much more subtle cellular inflammation than that seen in MS. Research into the immune component of the paraneoplastic diseases has for many years focussed on the role of antibodies despite the fact that there was little strong evidence that the antibodies caused direct cellular damage. In recent years it has been shown that the antigens against which the antibodies are directed may also be targets for cytotoxic T-lymphocytes (CTLs). These CTLs have been identified in both the blood and brain tissue of patients with paraneoplastic disease. The possibility that DES involves a CTL mediated assault on the brain should be kept in mind.

Treatments in neuroimmune disease

There is now considerable clinical experience in the management of MS and as our understanding of the regulation of immune mechanisms has increased so have the possibilities for therapeutic intervention. Although it is not known what initiates MS, the immune effector mechanisms are well documented and an array of different approaches to limiting the immune response in the brain are now being used both in experimental models and clinical trials (Wraith). It is hard to overstate how important experimental models of MS have been in understanding the fundamental mechanisms and developing therapeutic strategies.

At one end of the therapeutic spectrum there are immunosuppressive therapies with little specificity. The use of such drugs AZA, and cyclophosphamide have a global immunosuppressive effect and of course these drugs have potentially serious side effects. The use of molecules that modulate cytokines that control immune responses is proving to be of benefit in MS (β -interferon) and in another autoimmune disease such as arthritis (inhibition of tumour necrosis factor). In experimental models of MS, where the antigen against which the immune system directs its unwanted attention is known, it has been possible to devise therapeutic strategies that target this antigen specifically. It is however, crucially important to identify the key antigens in the process. Steps are being taken to apply this knowledge to therapeutic intervention in man. Of particular note is that this targeted approach can be used to intervene when disease has already been established for some time.

Summary - Underlying mechanisms of disease.

- *There is no evidence to suggest a genetic basis to the disease.*
- *There is an association with neuroblastoma but the possible role of an infectious agent cannot be ruled out.*
- *The pathogenic mechanisms are poorly understood but the association with neuroblastoma, the response to immunomodulatory drugs (steroids) and the association of relapses with infections, all implicate the immune system.*
- *Antibodies against systemic tumours or infectious agents are implicated in rare but nonetheless well documented diseases of the CNS and PNS. Antibodies may enter the brain and cause neurological dysfunction.*
- *Analysis of serum samples from children with DES have shown that there are antibodies present that bind proteins present in both neuroblastoma and brain tissue. But there is as yet, no identified protein common to all the samples examined.*
- *There is no evidence that cell mediated immunity is involved in DES but recent evidence implicates cytotoxic T-lymphocytes in paraneoplastic disease.*
- *Studies in immune diseases of the CNS, such as multiple sclerosis and relevant experimental models, offer new directions for therapeutic intervention with increasing specific and potentially fewer side effects.*

Implications

A major gap in our clinical knowledge is a lack of understanding of the sites of the CNS which are implicated in the disease and whether the disease is progressive.

Although MRI studies have not shown specific brain lesions in children with DES new advances in magnetic resonance imaging and spectroscopy (MRI and MRS) have significantly enhanced the power of these techniques to detect abnormalities of brain structure and biochemistry (Gadian). A priority in DES must be to identify which regions of the brain are affected and whether the disease is progressive. The use of MRI volumetric analysis of the brain could play a major role in achieving this aim. Another important area where there have been major advances is in the neuropsychological assessment of children with neurological disease (Varga-Khadem). It would be valuable to use these tools to monitor the cognitive development of children with DES.

At the present time a major thrust of the research must be to discover the underlying pathogenic mechanisms and ways of treating the condition. Current research is focussed on the possible role of an immune mediated assault by antibodies and it will be critical to find out whether there is a single or a limited number of antigens which may serve as the site of attack by either antibodies or CTL's.

It is important not to lose sight of other possible pathological mechanisms. An hypothesis was presented (Dulac) that DES may reflect a disease in which the normal development of cerebellar neuronal circuitry was affected by some unknown agent and this then produced abnormal neuronal connectivity and excitability akin to childhood epilepsy. The apparent efficiency of ACTH in reducing the symptoms would be consistent with the role of ACTH in reducing cerebral blood flow and thus neuronal excitability. It is important to recognise that our understanding of the pathological mechanisms producing the clinical picture of DES cannot rule out either this hypothesis or the direct involvement of the immune system.

What is needed?

In the final session Peter Beverley posed the important questions: What do the patients (parents and children) need? What do the clinicians need? What do the research workers need?

Without doubt all of those groups need more information about DES but in particular the parents, the children and future sufferers of DES. DES is a rare disease and thus for a correct diagnosis to be made as quickly as possible it is very important that clinicians are aware of DES and that mechanisms exist for referral to clinicians with expertise in DES. It is also important that parents feel able to be informed about DES and kept up to date with progress in the diagnosis, management and treatment of the condition. The DES Support Trust and its international affiliates will be able to provide some of this through their web page.

The clinicians who deal with a rare disease need information and to share experiences. Although this can be done through scientific journals it is recognised that the nuances of a rare and complex disease can be best shared in face to face meetings. This Workshop provided a valuable example as to how this can be achieved and the benefits from meeting together.

The clinicians need better treatments for their patients and while this will come from empirical and shared experience it is research that will lead in new directions. The research scientist not only needs to know about the nature of the disease but to carry out research they need material, resources and good ideas. The needs for progress in research would include blood samples, the ability to carry out MRI or MRS studies on appropriate patients, the ability to carry out more detailed neurological and neuropsychological tests. The resources to carry out

research include money for research staff and the reagents and equipment they use. Last but not least the researcher needs good ideas to be creative and find a route into unravelling the disease process that leads to Dancing Eyes Syndrome.