Lysosomal Diseases and the Brain

Following the success of the first Lysosomal Diseases and the Brain Conference in 2004, in Washington, USA the Children's Gaucher Fund, in partnership with NIH (National Institutes of Health), organised a two day conference to listen to presentations on cutting edge research on Lysosomal Diseases that affect the brain. Tanya Collin-Histed reports:

'The founders of the Children's Research Fund, ***Gregory and Deborah Macres*** started the Fund after their son Gregory sadly died in 1997 at the age of four years old following complications after a bone marrow transplant. They decided to honour his memory by raising the profile of, and raising research funds for, Types 2 and 3 Gaucher disease in order to help other families throughout the world.

Pathological Mechanisms

'**Prof Tony Futerman** of the Weizmann Institute, Rehovot, Israel opened the conference by talking about the *Pathological Mechanisms* (altered or caused by disease) in *sphingolipid* (a group of lipids, e.g. glucocerebroside) disorders. The challenge is to understand what happens in the cells of patients with lysosomal diseases. For example, in Gaucher disease we know that the altered protein (enzyme) is the primary event which results in the accumulation of glucocerebroside. However, the question remains; how does this cause nerve cell damage in the neuronopathic forms of GD. Prof Futerman's team has carried out pioneering research into intracellular calcium and have found that this is disturbed in certain storage disorders, such as Sandhoff disease, Gaucher disease and Niemann-Pick disease type A. Interestingly, the disturbances are not the same for all these diseases.

Impact of Systemic Inflammation

'Prof. Hugh Perry is the Director of the Southampton Neuroscience Group (SoNG) that brings together clinical and basic scientists investigating aspects of the major diseases of the nervous system.

'Dr Perry's talk 'The Impact of systemic inflammation on chronic neurodegenerative disease' focused on the possible pathways and mechanisms by which peripheral inflammation may impact on ongoing inflammation in the brain.

'We have all at one time or another experienced feeling ill or sick during an infection. The reason for this is that our immune system produces cytokines (chemical messengers) and it is these molecules that communicate with the brain to generate a fever and the spectrum of behavioural changes known as "sickness behaviour".

'In chronic neurodegenerative disease of the central nervous system (CNS) there is a highly atypical (not the usual or normal type) inflammatory response. This inflammatory response is characterised by the presence of large numbers of activated microglia (macrophages) in a perivascular (around the blood vessels) location in the brain

'The role of the activated microglia in disease pathogenesis has been investigated in diverse animal models, including models of Alzheimer's disease, lysosomal storage diseases and prion disease. In studies of the murine (mouse) prion disease the activated microglia appear to play a relatively minor role since deletion of cytokine genes or treatment with anti-inflammatory drugs has little impact on disease progression. However, the microglia appear to be "primed" by ongoing neuronal degeneration. If a systemic infection was mimicked, the mice exhibit exaggerated sickness behaviour and a switch in cytokine synthesis in the brain. This switch in cytokine profile is likely to reflect a switch in microglia phenotype (outward appearance). Associated with this cytokine switch was an acute increase in the number of neurons undergoing apoptosis (cell death).

'Perhaps the most interesting part of Dr Perry's talk was a small study his team had recently carried out in senile dementia. They studied a group of elderly patients over a defined period to see whether having more infections predisposed to dementia. They found that patients having more than three infections a year were more likely to get dementia.

'These data suggest that systemic inflammation generated by infection or injury may impact on diseased brain to increase the rate of neuronal degeneration in chronic neurodegenerative disease, including perhaps lysosomal storage diseases.

Knockout Mouse

'Dr Lorne Clarke (Univ. of British Columbia, Canada) spoke about the work his team have been doing with a conditional knockout mouse model for Gaucher disease. A conditional "knockout "model is one in which the gene of interest is inactivated only in specific tissues. The team have produced a mouse with decreased glucocerebrosidase activity in the liver and spleen and have significant pathology by 26 weeks of age with obvious Gaucher cells in the spleen. This work represents the first conditional mouse model with Gaucher disease and will allow the team to investigate the pathophysiology of Gaucher disease and the testing of novel therapeutic approaches.

Gene Expression Profiling

'Dr Sung-Chul Jung (Ewha Woman's University, South Korea) spoke on "Gene expression profiling and neuronal survival in the brain of a mouse model of Gaucher disease". Although neuronal death has been reported in the neuronopathic forms of this disease, the mechanisms responsible have not been identified. The group studied the effects of neurotrophic factors during development in a mouse model of Gaucher disease. The expression of brain-derived factors such as nerve growth factor was reduced in the cerebral cortex, brainstem, and cerebellum of Gaucher mice, compared with that in wild-type mice.

Parkinsonism

'There was a lively after-dinner debate led by **Ellen Sidransky**, (Chief, Molecular Neurogenetics, NIH) and **Matt Farrer** (Mayo Clinic) on "Gaucher Disease & Parkinsonism – Is There a Connection?"

'Dr Sidransky presented the data in support of the association between Parkinsonism and mutations in glucocerebrosidase (GBA). Parkinsonian manifestations have been described in some patients with Gaucher disease and in heterozygote carriers.

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European Task Force for Neuronopathic Gauchers Disease

During the European Working Group on Gaucher Disease Workshop in Cambridge on 18 – 22 July 2006, Dr Ashok Vellodi, Metabolic Consultant from Great Ormond Street Hospital presented an update on the EWGGD Task Force guidelines for the management of NGD that were published in 2000. Dr Vellodi reports:

'It was felt that the NGD guidelines needed revision. Accordingly, the Task Force met initially in London in July 2005 and reviewed long term follow up data on patients from four centres based in Sweden, Poland, Germany and the UK. However, there were difficulties with the analysis, largely related to inter-centre differences in practice. It was felt that data quality could be considerably enhanced by a systematic collection of data, albeit retrospectively, from patient records in each country. It was decided that one person (**Elin Haf-Davies**, a nurse from Great Ormond Street Hospital) should visit all the centres for this purpose. The centres involved were based in hospitals in Lumea, Sweden; Warsaw, Poland; Mainz, Germany; and London, United Kingdom. Forty-five patients were seen in clinic between November 2005 and February 2006, and the notes of a further 10 patients reviewed, making 55 in all. The study was confined to Type III patients. The majority were homozygous for L444P/L444P.

'The main purpose of the review was to ascertain the neurological outcome in patients with Type III treated with ERT at/on a dose of 120 units/kg/2 weeks. The highest doses were given to the youngest children. Such an age group might include a mixture of mild and severe patients; with different genotypes hence the outcomes might be mixed. Only a small number of children had been treated at this dose for more than 5 years and for whom good follow up data were available. Some of these children seemed to be quite stable neurologically. However, most of these children were still quite young and, given that neurological complications usually set in much later it was difficult to infer that the stability had resulted from high-dose ERT.

'The majority of adult patients (most of them from Sweden) seemed to have remained quite stable on lower doses of ERT. The majority of these were commenced on ERT as adults. Survival into adulthood may in itself reflect mild underlying disease. In fact most of the adults were L444P/L444P homozygote; this tends to be associated with milder disease.

'These data is now being prepared for publication and revision of the guidelines.

'The Task Force would like to thank the Gauchers Association for the travel grant to support Elin Haf-Davies to visit the four centres.'

Lysosomal Diseases and the Brain: continued from page 14. The term "Parkinsonism" refers to neurologic disorders that have many different causes, but share the classic manifestations of Parkinson's disease, such as tremor, stiffness and a shuffle walk.

'To further explore this association, the GBA gene was sequenced in 75 autopsied brain samples. Postmortem diagnosis identified 35 cases with diffuse Lewy body dementia (DLB), 29 with Parkinson's disease (PD), and 12 with multiple system atrophy (MSA). Of the 75 subjects, 9 (12%) were heterozygous for GBA mutations (23% of DLB subjects and 4% of PD),

'Dr Farrer, an expert on Parkinson's disease, felt that the evidence was not very strong and more work needed to be done in this area.

'Research into possible links between Gaucher disease and Parkinson disease is continuing at several centres. Some are looking at the frequency of Gaucher mutations in groups of Parkinson patients from different ethnic backgrounds. Others are studying the ways in which alterations in the GBA protein could affect cells in the brain and contribute to the changes seen in parkinsonism. Researchers hope that understanding how defects in glucocerebrosidase might affect the symptoms of Parkinson disease will lead to the development of more effective treatments or both disorders.

Advances in Treatment

'Dr Beverley Davidson (University of Iowa) spoke on "Advances in treating the CNS deficits of lysosomal storage diseases". Particularly interesting was the work that her group had done using AAV-4 virus to get the gene product (in this case a lysosomal enzyme) into the endothelial (the cells lining the inside of the blood vessels) cells of the brain. From there the enzyme spread to other areas of the brain. This was achieved by intravenous injection, which is a significant breakthrough; most previous attempts had involved direct intracerebral injection.

Chaperone Therapy

'Dr Jeffrey Kelly (Scripps Research Institute, California) spoke about "Therapeutic strategies against gain and loss of function misfolding diseases". This included the exciting new area of chaperone therapy. Dr Kelly explained that chaperone therapy, while certainly offering promise, seemed to be more effective against certain genetic mutations than others. However, the reasons for these differences were becoming clearer and hopefully one day it would be possible to overcome them.

Further Talks

'This report highlights only a handful of the presentations at the Conference. Various presentations at the meeting were in Sacramento was videoed by GOLD (Global Organisation Lysosomal Diseases). If you would like to access the video to see and hear the presentations to more of the talks please visit www.goldinfo.org and select the 'Education and Information' which will lead to many of the talks.