Research Update on Neurological Aspects of Gaucher Disease

Dr Ashok Vellodi, Consultant Metabolic Paediatrician at Great Ormond Street Hospital, London gives an update on current research being undertaken and publications;

Delivery of treatment to the central nervous system.

'There have been important advances in the treatment of Lysosomal Storage Disorders (LSD's) involving the brain and several papers have been published, most of them involving some form of gene therapy. However, the drawback of these methods is they direct administration, usually in the form of an infusion delivered via a pump. Needless to say, there are considerable reservations about applying this to patients, not least of all because of the invasive nature of the methods used.

'Recently, at least two groups have reported ways of achieving this by intravenous infusion.

'The phenomenon of "gene silencing" was briefly alluded to in my talk at the NGD conference in Wembley earlier this year (see June 2007 edition of Gaucher News). The molecule used to achieve this is called siRNA (small interfering RNA). One of the disadvantages of this method is that siRNA does not cross the blood brain barrier. Writing in the July 7 issue of *Nature*, Kumar et al describe, for the first time, a way of making this crossing[1]. They achieved it by taking a small piece out of the rabies virus protein and attaching it to the siRNA. Intravenous injection of this complex into mice resulted in effective gene silencing in the brain. Importantly, no side-effects were seen even after repeated administration.

'At the Society for the Study of Inborn Errors of Metabolism (SSIEM), held in Hamburg on 4-7 September, Dr Beverley Davidson from Utah reported during the Plenary session the results of intravenous gene therapy in the mouse model of MPS VII (which is another LSD in which there is a deficiency of the enzyme beta-glucoronidase). Mice with this disease were injected with the gene attached to a special virus, AAV-4 (AAV stands for adeno-associated virus). This virus enters the endothelial cells of the blood vessels of the brain. They found increased enzyme activity in the brain.

In summary: While not directly related to GD, these are very interesting developments, as they demonstrate, for the first time, a way of getting enzyme into the brain without having to directly inject it. An important point to make, however, is that larger animals need to be treated using this method, as the mouse brain does not seem to react to foreign substances entering it, while that of larger animals does.

However, the drawback of these methods is that they involve direct administration, usually in the form of an infusion delivered via a pump.

'There were also some interesting posters displayed at the SSIEM related to Neuronopathic Gaucher disease.

Peripheral Neuropathy

'One of most interesting was a study of peripheral neuropathy in untreated type I patients. This was a large multinational prospective 2-year study involving 8 countries. A total of 103 patients with GD1 between the ages of 18-75 were recruited. Standard neurological examination and nerve conduction studies were performed. A total of 11 patients (10.7%) had both clinical as well as electrophysiological evidence of polyneuropathy at baseline. Thirty-six patients had electrophysiological abnormalities, though not all had clinical signs/symptoms. So there were patients with abnormal signs/symptoms with normal electrophysiology, and vice versa. The incidence of neuropathy was higher than in the normal population. Only four patients had a co-morbidity (such as B12 deficiency). The authors conclusion was that careful clinical examination and testing were warranted in all patients with GD1. This is an ongoing study and further data will be available at 1 and 2 years[2].

In summary: These findings are just as pertinent to GD3 as to GD1 and careful follow up for neuropathy in patients is warranted.

Lung Involvement in Type III Patient

'A 9 year old girl with type III, homozygous for the L444 mutation, whose sister had died of Gaucher lung disease, was investigated for lung disease. She had been well controlled on ERT for 4 years. Despite having no symptoms, broncoalveolar lavage (BAL- a process in which the lungs are washed out with saline) and lung biopsy showed the presence of Gaucher cells. This shows that microscopic evidence of lung disease may be present even in the absence of symptoms[3].

In summary: This is an interesting case report. It illustrates the fact that the lungs may not be as easily accessible to ERT as other areas. Nevertheless, it is not clear whether such invasive procedures should be undertaken in children, particularly (as in this case) when the authors do not explain how the findings altered the management.

Effect of Enzyme Replacement Therapy on Rare Cardiac Involvement

'An 11 year old boy from Spain who was homozygous for the D409H mutation. This combination usually results in cardiac disease which is often fatal. This child had been treated since the age of 2 months and had developed no signs of heart disease. The authors suggest that this might have resulted from early commencement of ERT[4].

In summary: This was an interesting case report, as it suggests that the cardiac involvement in these patients may be prevented or at least considerably reduced by early ERT. However, one needs to be cautious about this interpretation. A comparison with other cases in the literature would have helped to strengthen the case. Also, it is unclear how the oculomotor apraxia was measured. This is important since it was stated that it had improved over the past 2 years.

Parkinsonian Symptoms

'A 67 year old man reported from

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Portugal who developed unsteadiness and weakness at the age of 60. Closer examination revealed more neurological signs including absence of horizontal and vertical eye movements, spasticity, and Parkinsonian features. He was found to be homozygous for the N370S mutation. He had no haematological problems, and his bones were normal[5].

In summary: Patients who have the N370S mutation are thought to have no neurological involvement, so this finding is very surprising. Importantly, full sequencing appears to have been carried out. Further assessment and reporting of this patient is very important.

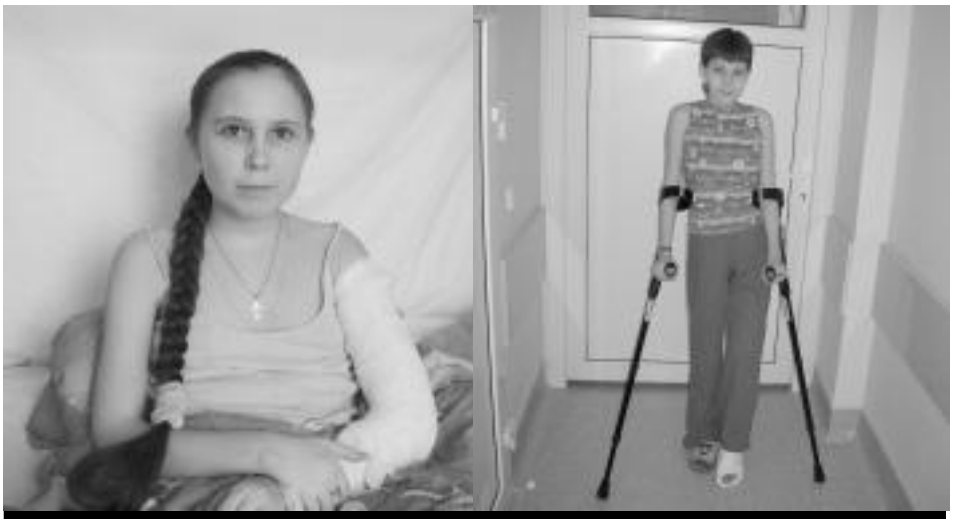
Brains 4 Brain Initiative

'In the last edition of the Gauchers News (July 2007), Brains for Brains (B4B) a new European Initiative was reported. The B4B group have submitted a grant application to the European Union. The title was "Restorative Approaches for Therapy of Paediatric Neurodegenerative Diseases". This bid illustrates very well the close collaboration between the members of the group which consist of doctors, scientists and patient organisations. The outcome is expected in the early part of 2008.'

References

1. Kumar P, McBride JL, Jung KE et al. Transvascular delivery of small interfering RNA to the central nervous system. Nature 2007 Jul 5;448(7149): 39-43.
2. Hollak CEM, Biegstraaten M, Van Schaik IM et al. Prevalance of polyneuropathy in adult type I Gaucher disease (GD1); A multinational, prospective observational study. SSIEM 2007, Poster 427
3. Djordjevic M, Minic P, Djuricic S et al. Pulmonary involvement in patient with Gaucher disease type III after 4 years of enzyme replacement therapy. SSIEM 2007, Poster 476.
4. Del Toro M, Dominguez C, Chabas A, Roig M. Ten year follow up of an homozygous D409H Gaucher patient under enzyme replacement therapy. SSIEM 2007, Poster 475.
5. Macario MC, Lacerda L, Pires P et al. Very old Gaucher type 3. SSIEM 2007, Poster 428.

Russia Gets ERT into Ministry of Health Programme



Young Russian Gaucher patients who have suffered severe bone crisis prior to begining ERT

Marina Terekhova, President of the Russian Gauchers Association writes:

'This year has been very successful for the Association. We have managed to work with the Ministry of Health to get Gauchers disease and Cerezyme into a State programme which recognises expensive treatments for Russian people.

'On the 31st of October 2007 seven organisations (including the Russian Gauchers Association) dealing with the diseases recognised in this programme were invited to the Ministry of Health to participate in a meeting. At the meeting the State announced the amount of money available for the provision of treatments for next year.

'In the past patients with Gaucher disease had to register as disabled with the State to access treatment and for personal reasons many patients did not register as disabled and therefore could not access treatment. The new Ministry of Health programme will mean that every patient with Gaucher disease will receive Cerezyme without a disability status.

'By the end of 2007 there will be 86 gaucher patients receiving Cerezyme and in 2008 we plan to increase this to 140 patients.

'We are very proud of what has been achieved for Gaucher patients in Russia.'

NGF tribute to Susan Lewis

'Tanya Collin-Histed receives a tribute to Susan Lewis from Rhonda Buyers of the National Gaucher Foundation (NGF) at their recent patient conference in Atlanta in October 2007'

The plaque reads 'Susan Lewis: In Celebration of your life and the lives you've touched. Your passion and caring for others is your legacy to this world. Your light will shine forever.' National Gaucher Foundation