Causes and Pathophysiology of nGD

Dr Ashok Vellodi FRCPCH, is Consultant Metabolic Paediatrician at Great Ormond Street Hospital, London one of the four national designated Gaucher centres in the England. Dr Vellodi looks after the majority of neuronopathic Gaucher disease children in the UK and is a member of the European Cerezyme Access Programme (ECAP) medical advisory board.

‘Why does nGD occur? In other words, why do some people with Gaucher disease develop the neuronopathic form and others not? We need to understand this first before we are able to develop suitable treatments.

‘As we know there are three subtypes of Gaucher disease: 1, 2 and 3. Historically Type 1 is known as non-neuronopathic and types 2 and 3 as the neuronopathic forms of the disease. We know that people with nGD have less residual enzyme than those with Type 1 Gaucher disease. In general the lower the residual enzyme the more severe the disease.

‘The source of the substrate, Glucosylceramide, may be important. Outside the nervous system it is derived from
blood cell membranes, while inside the brain it is derived from gangliosides which are only found in the brain. In all forms of the disease, there is insufficient enzyme to break down the glucosylceramide derived from blood cells, while in type 1 disease there is enough enzyme in the brain to break down glucosylceramide derived from gangliosides. However, in nGD the enzyme level in the brain is not enough, and glucosylceramide therefore accumulates in the brain.

The form of enzyme may be important. There are three different forms of beta-glucosidase, each with a different molecular weight. In Type 1 GD all three of these forms are present; however in types 2 and 3 one of the forms is missing. Nobody knows what this means but it may be important.

'It is important to understand that in the brain, the distribution of enzyme activity is uneven. This may explain why the disease does not affect all parts of the brain equally.

**Question:** Where does glucosylceramide accumulate in the neurones?

'If a lysosomal enzyme does not work properly or is missing, then the substrate will accumulate in the lysosome. But oddly in nGD there is no lysosomal accumulation of glucosylceramide in the neurons and very little in other cells. Why is this?

We know that glucosylceramide is the last step in the breakdown pathway of many metabolic processes. Therefore glucosylceramide is being produced in large quantities in the body. If little or no lysosomal accumulation is seen in nGD then it means that excess glucosylceramide must move out of the lysosome without being broken down. Therefore it must accumulate somewhere else.

**Neuronal Storage: how does this cause nGD?**

'Firstly we will look at the role of glucosylceramide. Is glucosylceramide toxic to the brain? When Professor Tony Futerman and colleagues at the Weitzman Institute in Israel studied hippocampal neurons from a rat (the hippocampus is a very active part of the brain and easy to study so it is widely studied) and incubated them with glucosylceramide, they discovered changes in the functional calcium stores. Calcium has a normal pathway in the nerve cells and has to be stored and be able to move in a normal fashion but if this is disturbed then neuronal death occurs. Interestingly when the enzyme glucocerebrosidase was added to the neurons neuronal death was reversed. This suggests that if we could get the enzyme into the nerve cells this mechanism might be reversed and cell death prevented.

'Now calcium channels in the brain are located in an area of the cell called the endoplasmic reticulum (ER). Therefore, in order for glucosylceramide to disturb these channels, it must accumulate in the ER (see above).

**The Role of Glucosylphosphinosine**

'Glucosylphosphinosine is a modified form of glucosylceramide. It has been shown that the brains of patients with nGD had much higher levels of glucosylphosphinosine than from type 1 Gaucher disease, it was the highest in type 2 Gaucher disease. It therefore seems to be related to the neurological problems that are seen in Gaucher disease. It is also known to upset calcium transport in the cell (as does glucosylceramide but by a different mechanism).

What is the Role of Inflammation

'It is thought that inflammation plays a major role in Gaucher disease. It tends to be more severe in types 2 and 3. It may not even need much storage to trigger inflammation. At the National Institute Health (NIH) a few years ago Dr Rick Proia developed a knock out mouse that was deficient in the enzyme. This mouse had massive inflammation in the tissues but no Gaucher cells. Until recently it was not clear whether this was seen in the brain as well. In 2006 Korean scientists showed that there was upregulation (a surge) of pro inflammatory cytokines (chemical messengers) in the brain of type II Gaucher mice; these triggered inflammation in the brain of the Gaucher mouse. How inflammation causes neuronal damage is not clear.

**Conclusion**

'The mechanisms by which Gaucher disease can cause apoptosis (programmed cell death) may therefore include glucosylphosphinosine, inflammation, or disturbances in intracellular calcium. So there may be more than one mechanism responsible. What is clear is that these are all secondary events; the primary event being storage resulting from enzyme deficiency. Once these secondary events are set in motion, other therapies may be necessary to control them, so it is important to try and understand them.'
Auditory Involvement and Learning in nGD

Pauline Campbell is a Lecturer in Audiology and Hearing Science at the Queen Margaret University College in Edinburgh. Pauline has been looking at the auditory involvement in patients with nGD for a number of years. Her talk focused on identifying the implications for patients and what can be done to support them on a daily basis. Pauline has been involved in recording the auditory brainstem responses by a sensitive test of brainstem involvement in nGD.

‘Sound comes in through the ear drum where there are three bones that help to mechanically ‘push’ the sounds through to the cochlea (inner ear). The cochlea is very important as it is here that the sounds are split into high and low pitch. These sounds are then sent to the auditory nerve. In clinic children will have a simple hearing test to see if the cells lining the cochlea are working. This test is called otoacoustic emissions. In the majority of cases the children can hear and respond to different tones.

‘Sound in the auditory brainstem pathway is measured using a test called the Auditory Brainstem Response (ABR). It is assessed by placing 3 small sensors on the head and a clicking sound is heard through headphones. Audiologists analyse the ABR by looking at the presence of a five point peak. In most nGD patient’s peaks I and II are seen, however peaks III, IV and V that measure the higher brainstem disappear or deteriorate over time in some patients. To get a five point peak the cells in the auditory nerve and brainstem need to fire (or respond) at the same time. If the cells are not firing synchronously this may tell us that there is a timing difficulty.’

To demonstrate this point Pauline asked the audience to number themselves off as number 1, 2 and 3. In the first exercise all numbers 1, 2 and 3 standing up in sequence and calling out their number. She then asked number 1s to sit down and repeated the exercise with just number 2s and 3s. Finally number 2s sat down and it just left number 3s to call out. This demonstrated how the timing of different sounds could upset the flow of information.

What is like in a classroom?
In another exercise to recreate the environment of a child with nGD Pauline asked the audience to put their fingers in their ears. She then divided the room in half and asked one group to talk among themselves. While this was happening she walked away from the microphone and continued talking. After a short period she asked the audience to remove their fingers from their ears and whether they had been able to hear what she had been saying? The response was that the audience could not hear and she explained that this is the experience of what a child with nGD hears in a classroom and demonstrated how difficult it may be for them to understand what is happening.

Pauline recited a poem by Hall and Mueller (1998) which describes what it is like to have auditory processing deficits.

“Words coming in seem foreign; I catch them as I can. Catch a few, hold them tight, watch the rest continue flight. Take a few, turn then ‘round’, fitting pieces until they sound.”

She highlighted that many nGD children of these children may have short term memory issues which is not surprising if they are unable to “catch” all of the words being said to them.

Evidence to support learning in the classroom
Pauline emphasised the need to collect the evidence on auditory processing deficits and have it published so that parents can use this to access support for their children in school and college.

There are some new tests that look at the brainstem response and try and identify why nGD children do not understand speech when there is background noise, or the child can not see the teachers face. These portable tests can be taken into the child’s home or school and carried out. These tests look at:

- How they use consonants and vowel sounds and is able to identify which part of the word may be absent and therefore cause the problem.
- The onset (start) and offset (finish) of sounds and how the brain recognises when these stages happen.
- Startle response to see if the brain can learn, i.e. to simulate a loud noise and then next time it happens to see if the brain has learnt to react to it in a less startled way.

Pauline talked briefly about neural plasticity and some environmental modifications that can help nGD children at school. Finally she also showed a list of websites which might be useful for parents to look at. These are programmes, auditory integration techniques and listening exercises that can be used to train the brain.

- FastForWord (Scientific Learning Corporation, 1997) http://www.scilearn.com/
- Phonomena (Isis Innovation, the technology transfer arm of Oxford University http://www.mindweavers.co.uk/)
Dr Catherine Devile is a neurologist at Great Ormond Street Hospital (GOSH), London. Catherine looks after all of the nGD children and young people seen at GOSH. Catherine spoke of the huge clinical variation in nGD and its heterogeneity and how manifestation can vary in patients.

**Spectrum of neurological features**

The neurological features in nGD include: horizontal gaze palsy, squint, disorder of muscle tone, movement and co-ordination, feeding and swallowing difficulties, reduced clarity of speech, learning difficulties and seizures.

**Abnormalities of Movement**

Abnormalities in movement are caused by different neurological pathways. Those movements seen in nGD include: Ataxia causing poor co-ordination of the voluntary muscles, issues with balance which may affect motor skills and cause a tremor at the end of a movement; Spasticity which cause increase muscle tone in the hamstrings and ankles and is noticeable when there is a quick movement or a change in direction of movement; Extra pyramidal affects the control and movement of voluntary movement and some involuntary movement causing a resting tremor and rigidity with increased resting muscle tone and finally; Bulbar Impairment which affects the muscles of the tongue, face, throat and swallowing causing muscle stiffness, lack of facial expression, chewing and swallowing problems and problems with the production of speech.

**Clinical Presentation**

All nGD patients present with horizontal gaze palsy which is the failure to move your eyes quickly from side to side and adjust them to fix on a target which can cause difficulties in a busy area such as a school playground. Eye movements are a very complicated area and we know that the main function of that comes from the brainstem. In all nGD patients there is the presence of horizontal gaze palsy and in some patients there may be vertical involvement affecting the movement of the eyes up and down.

‘Looking at the motor aspects of clinical presentation, the presence of gait ataxia which may or may not present with a tremor which may cause difficulties with fine motor skills are the most common found in nGD patients.

‘Learning may be affected in nGD with some cognitive impairment and a lower IQ, however the cognitive assessment is only one area of our assessment and it is important to recognise that there may be areas of strengths and weaknesses. It is therefore crucial to recognise any learning impairment to ensure that these children are able to get help and support at school and that this support is assessed on a regular basis.

‘Some children with nGD may develop seizures. Seizures are essentially an abnormal electrical discharge from brain neurons (cells). Epilepsy is a name for recurrent seizures. In nGD there are a number of different types of seizures, these are:

- Myoclonic seizures which are usually very small and very brief but can over time become more frequent and may build up to be more severe.
- Generalise seizures, more commonly known as Grand mal seizures, these affect the whole body causing stiffness of the arms and legs and the person will become unconscious.
- Partial seizures that cause a blank vacant facial expression, odd jerks and stiffness with partial unconsciousness.

‘It is important to try and be as accurate when identifying the type of seizure to ensure that the correct management and treatment are given.

**Functional Impact**

The neurological complications described in nGD can have an impact on day to day functions and they may also delay some aspects of development earlier on in life. However it is important to highlight that the challenges and stresses of tasks over time may seem like the disease may be getting worse, however the underlying disease may not be changing but the tasks are getting more challenging.

**Practical Management**

Our aim is always to maximise potential and function so by identifying the goals we can put interventions in place where necessary in the areas of physical and motor skills, feeding and nutrition and seizures.

**Summary**

There is a wide spectrum of neurological features and how these affect children functionally. It is essential to monitor and neurology and learning accurately as changes maybe slow and we need to be clear and accurate about disease progression. This will enable evaluation of potential responses to treatment and target management and support to the child and family.

**Future Developments**

Catherine described the development of a severity scoring system for the neurological aspects of nGD looking at all of the neurological features with the aim of having a systemic tool that can be used across centres.
A Personal Story

Laureonna is 23 years old and has Type III Gaucher disease, here is talks about the challenges that she has faced since her diagnosis in 1986;

‘My name is Laureonna some of you may know me or might have heard of me. I would like to share my story with you. ‘I was born in 1984 and in January 1986 doctors discovered I had Gaucher disease; my parents were told and they had no idea what it was. The doctors at Kings College explained that there was no cure and that my bones would deteriorate and I would be in a wheel chair by my early teens and dead by my late teens. ‘As we were leaving a doctor suggested we contact the Westminster Children’s hospital where we met a very nice doctor they called ‘The Professor’. He explained to my parents that all they could offer me was a bone marrow transplant (BMT) and that the risks were high but that this was my only option. There wasn’t any enzyme replacement therapy then. ‘In March 1986 all of my family were tested to see if they were a match for me but none of them were suitable donors, so we asked the Anthony Nolan Trust for help. They found one possible donor out of 40,000 people. ‘In August 1986 my spleen was very large and I was unable to walk so I had a splenectomy, this operation had to be done anyway so that I could have a BMT. ‘In September 1986 my Gaucher disease had accelerated and doctors told my parents that I must have a BMT. We went to the Anthony Nolan Trust and asked to use the donor they had identified as a possible match, even though with this random match the success rate was low. Preparing for my BMT ‘In 1986 I went into hospital to prepare for my BMT, they bathed me in a special soap and placed me in a small cubicle. This was to be my home for two months. I was given many drugs for my BMT, these made me loose my hair and stooped me from eating. ‘In January 1987 we found out that the BMT had failed and that we needed to find a better donor. A few months later in April ‘The Professor’ retired and new doctors arrived but still no donor. Throughout 1987 and then in 1988 new doctors came to the hospital but many of them left as the Government were closing down hospitals and Westminster Children’s Hospital was one of the hospitals they wanted to close. My second BMT ‘In 1989 we met a new doctor, he wanted to give me a second BMT and a new donor, a woman was found. My first donor had been a man and we hoped with the second donor being a women this may give me a better chance. In June 1989 I prepared for my second BMT, the operation took place but things didn’t go well. Nobody knew why I wasn’t getting better and I had to stay in hospital for five months. Coming Home ‘In January 1990 I went home but couldn’t go to school so I had to have home tuition. By September 1990 I was able to go to school for two or three days a week but all of the teachers knew that if anyone in the school had a bad infection I had to be sent home and have an injection. ‘During my primary school years the teachers understood that I had problems, that I was slow at doing things. When I was 11 years old the teachers said that I was not capable of going to secondary school, but I did go and I did struggle but I had a teaching assistant to help me. At the age of 14 I was preparing for my GCSE’s, again the teachers said I couldn’t do them, but I achieved six out of the seven I took. I am now at college and on a Saturday I work in a shop called ‘New Look’ for three hours. Life is Good ‘I know some of you think that you have been dealt a bum card in life but I have come here to tell you my story to show you that life isn’t that bad. You should all be happy to be alive and living life to the full despite everything. Even though I am epileptic now and take a lot of medicine, it really helps. ‘Before I go I would just like to thank someone who has helped me stand here today and tell you my story to show you that life isn’t that bad. You should all be happy to be alive and living life to the full despite everything. Even though I am epileptic now and take a lot of medicine, it really helps. ‘Before I go I would just like to thank someone who has helped me stand here today and tell you all about myself. Back in 1990 a young doctor did stay at Westminster Children’s hospital and helped me through my second BMT, even though the hospital was going to close. He never walked away, he found me a new hospital and looks after me today. You all should like me be glad that he looks after you all, I am of course talking about Dr Ashok Vellodi.’
A Fathers Story

Abdul Waheed is the father of nine year old Hajira who has Type III Gaucher disease, here Abdul talks about his precious daughter Hajira;

‘Today my daughter asked me what I was going to talk about, I said that I was going to talk about her. She said promise me that you won’t say anything sad, only the good things.

‘Hajira was born on 3 May 1998 at Queen’s Medical Centre, Nottingham, at a time of great stress to our family. She was a precious gift to our family. One of my sisters was in the late stages of Ovarian cancer, my father was struggling with leukaemia and my mother had for several years been living with renal failure.

‘Sadly the leaf of hope that had come into our life in the form of Hajira was diagnosed with neuronopathic Gaucher disease in November 1999. This was a very testing time for our family, the diagnosis was very difficult, and being so rare the doctors were clueless. Initially Hajira’s large abdomen was diagnosed as excess wind! Scans, tests and trips to Queen’s Medical centre and then to Manchester confirmed our worst fears. However it was during this time that the human compassion and support came as a sign from God not to lose hope. Friends and family rallied around us and gave us support at a time of uncertainty.

‘Friends organised charity events and fundraising activities including the ‘Gaucher Cricket Cup’. I remember the look of great delight in Hajira’s face as she sat at the controls of a train organised by a friend of mine who works for the Midland Mainline. Even the boxer Amer Khan came round to our house to see Hajira.

Support

‘The greatest support came from my brothers and sisters who looked after the rest of the family for our never ending trips to hospital in Manchester, London and Plymouth. However amazing support that we received and will treasure for the rest of our lives came from two complete strangers. The first was a pony tailed stranger wearing jeans, a t-shirt and sandals. This was Dr Ed Wraith who became Hajira’s Consultant at Manchester Children’s Hospital. He gave us his personal mobile number and told us we could call him at any time if we needed to talk.

‘The second person was our own Tanya Collin-Histed who simply offered help and one day appeared on our doorstep all the way from Watford. She spent the whole day with us reassuring us and providing information in Gaucher disease.

Our Brave Daughter

‘Despite a total of 186 infusions to date and various problems with administering Hajira’s enzyme replacement therapy, Hajira continues to be an inspiration to us, with her beaming smile and maturity beyond her years.

‘This has been evident in the last three years and has helped us to bear the loss of my father, my sister and recently my beloved mother. Hajira has been a precious gift from God, she reminds us of God’s creation, her resilience and the way she has coped with her condition has been a true inspiration.’
Dr David Begley is co-Director of the Blood Brain Barrier Research Group at Kings College London. In November 2004, David spoke at the first European nGD Family Conference in Leicester on the blood brain barrier (BBB). “I was working in a BBB laboratory was working on the transport of substances in and out of the brain across the BBB. That meeting in 2004 changed the direction of the work that goes on in my laboratory and since then I have started studying aspects of the BBB and its importance in lysosomal storage disorders including Gaucher disease. The nGD meeting in 2004 was therefore a critical meeting for me and for my work.”

Dr Begley introduced Dr Charlie Pontikis who is now working alongside him at Kings College, London and said;

‘The BBB was discovered by Paul Erlich who was working on infection and later developed the first treatments for Syphilis. It was in his laboratory that the first sign of the BBB appeared. Whilst he was working on sleeping sickness caused by parasitic Trypanosomes he noticed that when rats were injected with a blue dye their bodies went blue but their brains did not. At the time he thought that the dye had not stuck to the rat’s brain. One of his students Edwin Goldmann repeated Erlich’s experiment and got exactly the same result. He then injected the dye into the blood of the rats and observed that it didn’t get into the cerebral spinal fluid (CSF). At this point Goldmann went onto do a second experiment which was to inject the dye straight into the brain and observed that the brain went blue. He concluded that it wasn’t that the dye had not stuck to the brain in the first place it just did not leak out of the brain and back into the blood. As a result the BBB was discovered.

‘The BBB is a very effective barrier to many things in the blood including many medicines and drugs we take, including enzyme replacement therapy, and stops it getting into the brain.

‘Why does it do this?

1. The brain requires a very stable environment. The constitution of our blood varies, it goes up and down all the time, each time we eat, drink, and don’t drink. Nerve cells couldn’t work if this was the case, they have to have a stable background as they rely on generating nerve impulses in order to work, and they have to talk to each other by chemical transmissions.

2. The BBB protects the brain from nasty things in the blood which would damage the nerve cells. Many foods contain neurotoxins which would kill nerve cells. Each day we lose nerve cells. If the BBB was leaky then more nerve cells would be destroyed.

‘Because of the BBB there are a large number of diseases that effect mankind where treatment is currently unavailable, including the lysosomal storage disorders. Many lead drugs under development by pharmaceutical companies for central nervous system (CNS) diseases might do the job they are designed for but they don’t reach the brain in sufficient quantities, therefore they are dropped during development and never reach the market. Therefore we need to understand now how these drugs react with the BBB to be able to treat these diseases better.

Laboratory Studies

‘In Dr Fran Platt’s laboratory at Oxford experiments have been carried out on mouse models for Tay Sachs disease, Sandhoff disease and Gangliosidosis. Blue dye was injected into blood of the mice. In the normal mouse model and the Tay Sachs mouse no dye was observed in the brain, however in the Sandhoff and GM1 mice large amounts of dye were seen to leak into the brain. This would conclude that in Sandhoff disease and GM1 the tight junctions are damaged or that the cell membrane properties have been altered and therefore are not acting as a barrier.

‘In my laboratory at Kings College we are looking at Sanfillipo syndrome (MPS III A/B). These studies are looking to see if the BBB is damaged in MPS III A/B, how the damage occurs; does the damage contribute to the CNS pathology, can we do anything to cure or reduce the defects in the barrier; and do current treatments like Miglustat improve the barrier function? Apparatus has been developed over a period of one year to carry out these studies and will look at the mouse brain to see how much of the drug test substance gets into the mouse brain and which area of the brain, hindbrain, cerebellum, hemispheres, midbrain and olfactory lobs. These studies are being funded by the UK and Spanish MPS Societies.

‘The transport of Zavesca across the BBB is another area of work being carried out at Kings College. Evidence from Oxford shows that Zavesca penetrates the CSF however it is not yet know if it gets into brain tissue where it is needed. This is the first of the questions that need to be answered. If Zavesca does get into the brain tissue, to what extend and what is the mechanism by which it does? This current work is funded by Actelion Pharmaceuticals.’
In this presentation Dr Ashok Vellodi presented a number of possible methods for future treatment of nGD and the challenges facing researchers. He started with a discussion on Enzyme replacement therapy;

‘There is, as yet, no evidence that intravenously administered enzyme crosses the blood-brain barrier (BBB). However, there is some evidence from work done in animal models that it may result in reduction of storage in the brain. So far, this has been seen in mouse models of alpha-mannosidosis, metachromatic leukodystrophy and MPS VII. In the MLD mouse, the storage reduction was accompanied by improved neurological status. Of particular interest in the MPS VII mouse was that there was no effect on storage when the mice were given 4 mg/kg/week for 4 weeks, but after giving them 20 mg/kg/week for 3 weeks there was a reduction. Thus, there may be a threshold beyond which an effect is seen. It is important to realise that clearing of storage may not be uniform. For example, in the MPS VII mice there was no clearing in the cerebellum. Whether any clearing is seen in humans is not known.

Getting enzyme across the blood brain barrier
‘Several approaches have been found to achieve this in animal models:
- By packaging it so that it is carried across e.g. in liposomes. In particular, stealth liposomes have been found to escape capture by the lungs and enter the brain.
- By modifying the enzyme. Certain proteins can enter the brain easily. They do this by means of small areas called protein transduction domains (PTD). These can be transferred to other proteins enabling them to enter the brain as well. This approach has been successfully used in the mouse model of Parkinson disease.
- By direct administration

- a) Using a virus to carry the gene.
- b) Using cells that have been made to secrete the enzyme by a virus e.g. bone marrow cells
- c) Using neural progenitor cells
- d) Direct administration of enzyme into the CNS.

Of the methods listed above, the only one currently being trialled in patients is CNS gene therapy using a virus. Two trials are in progress, one in a lysosomal disorder, Batten’s disease, and the other in a non-lysosomal disorder, Canavan’s disease. Both are trials of safety rather than efficacy.

‘A single patient with type II Gaucher disease has undergone direct CNS infusion of enzyme. Again, this was a safety study only; the procedure was tolerated well.

Chaperone therapy
‘It is not possible to discuss the rationale of chaperone therapy in detail here. However, it is important to realise that different chaperones may be required for different Gaucher mutations. Most work has been done on the mutations responsible for type I GD. Effective chaperones (at least in the laboratory) have been for these mutations. However, very little progress has been made so far on the mutations responsible for type III GD. One reason for this seems to be that these mutations are located on a domain (area) of the enzyme that is not easy to access. Further research in this area is urgently needed, particularly since chaperones are small molecules that will probably cross the blood brain barrier.

RNA interference (RNAi)
‘This is a relatively new and very interesting area of research. It was first observed in 1990 when Jorgensen, who was working with petunias, wanted to create a petunia of an deeper shade of purple by introducing the “purple” gene. Instead, a white petunia was created. Clearly, the “purple” gene had been switched off or silenced. It immediately became obvious that this phenomenon could be used to study the function of a gene by switching it off and observing the effect. However, it was only recently that Mello and Fire showed how this happened, using a microscopic roundworm as a model. They called this RNA interference or RNAi. In fact, RNAi is an ancient human trait and probably a defence against viruses. In this sense it is unique. There is potential for clinical applications, for example, switching off viruses such as hepatitis B. However, it does not cross the blood brain barrier and therefore may face the same problems as ERT.

Conclusions
‘There are several promising areas of research, some more advanced than others. It is likely that no one therapy on its own is going to be effective; combination therapy may be the way forward.’
Gauchers Disease: Studies, Treatments and Costs
Preparing for the Future

Agenda:

9.30  Registration and Coffee
10.00 Conference - Introduction by Jeremy Manuel OBE
10.15 Future Trials and Therapies *
     Prof. Ari Zimran, Shaare Zedek Medical Center, Jerusalem
11.15 Coffee
11.30 Bone Collaboration Project *
     Prof. Timothy Cox and Dr. Patrick Deegan, Addenbrooke’s Hospital, Cambridge
12.00 Growing old with Gaucher Disease *
     Dr. Atul Mehta, Consultant Haematologist, Royal Free Hospital, London
12.30 Questions and Answers
12.45 Alan Gordon Memorial Award Presentation
     Presented by Robert Gordon
1.00 Lunch
2.00 Annual General Meeting
     Session Chaired by Don Tendell
2.15 Doctor – Patient – Partnerships, how the past can address the future *
     Prof. Timothy Cox, University of Cambridge School of Clinical Medicine and
     Addenbrooke’s Hospital, Cambridge
3.15 ‘Efficiency versus Equity: Should society fund orphan treatments?’
     Hanna Hyry, University of Cambridge.
3.30 Specialist Commissioning for Gaucher disease and other LSDs *
     Dr. Edmond Jessop, Medical Director, National Specialist Commissioning Advisory Group,
     Department of Health.
3.50 Tea
4.10 Personal Experiences: Chaired by Tanya Collin-Histed
     Introduced by Dr. Ashok Vellodi, Consultant, Great Ormond Street Hospital.
4.15 Jo Bardoe Mother of Mia Bardoe) – Living with Type 3 Gauchers disease *
4.25 Daniel Brown – Living with Type 1 Gauchers disease *
4.35 Panel - Questions and Answers
4.55 Raffle Draw
5.00 End of Conference

(The talks marked with an * are reported on the following pages)
Future Trials and Therapies

Thanking the UK Gauchers Association for its support and friendship over the years, Prof Ari Zimran explained how a fellowship grant from the Helen Manuel foundation more than 15 years ago had steered his career into Gaucher disease.

‘For a decade there had been one single treatment made by one company. After the amazing success of Cerezyme and then Cerezyme for Gaucher disease, the benefits of ERT have revolutionized the natural history of Gaucher disease and, when given before skeletal complications become manifest, patients are able to enjoy a good quality of life. The success of ERT in Gaucher disease has lead the way to the development of enzyme treatments for other lysosomal storage diseases like Fabry, MPS, Pompe and more new treatments are under development for other rare diseases.

‘Despite it success there are still some unresolved issues regarding ERT dosage, maintenance, tissue distribution, combination with other drugs, and access to the central nervous system that need to be addressed.

Development of a “second generation” Cerezyme is problematic because of the excellent safety and efficacy profiles of Cerezyme and the real difficulty in demonstrating clinically significant advantages over this very good product. For other companies trying to develop new enzymatic preparations, a major challenge is to recruit naïve (patients who have not received treatment before) patients for clinical trials.

‘Currently there are five clinical trials for type I Gaucher disease. Three of these trials involve new infusible enzyme replacement therapies and two are oral small molecule therapies.

New Enzyme Replacement Therapies

‘Two new infusible enzyme therapies are: Gene activated human glucocerebrosidase (GA-GCB) produced by Shire Human Genetic Therapeutics (SHGT, USA), and the plant cell expressed recombinant human glucocerebrosidase (prGCD) produced by Protalix Biotherapeutics (Israel).

GA-GCB

‘The GA-GCB produced by SHGT is identical to the natural enzyme, and is produced from a human cell line. This technology has proven to be effective in two other products by this company that have already been licensed: Replagal for Fabry disease and Dynepo (erythropoietin) for chronic anaemia in patients with end-stage renal failure or malignancies.

‘Phases I and II of the clinical trials of GA-GCB have been reported in the June 2006 and December 2006 editions of the UK Gaucher’s Newsletter, and the extension of the Phase II trial in naïve patients is on-going in our centre. Phase III studies in naïve patients and in a switch-over protocol are now underway in a number of centres. The TKT 032 study will be a multi-centre, dose-ranging study for naïve patients from age two years and older. TKT 034 will be a multi-centre, switch-over study (where patients will switch from Cerezyme to GA-GCB at their current dose), again including children. See page 18 of the Gauchers News for a further report on these studies.

prGCD

‘This unique biotechnology platform uses carrot cells as the cell line to produce human proteins. This technology is safe and cost efficient. Unlike the bioreactors for other enzyme replacement therapies, Protalix technology uses disposable parts and therefore it should prove to be easy to scale up production as necessary.

‘Scientists from the Weitzman Institute (Israel), led by Prof Tony Futerman have crystallised the enzyme product and have shown that the 3-D structure overlaps almost perfectly with the 3-D structure of Cerezyme, indicating that they are bio-identical. Following a successful Phase I study in six healthy volunteers, the FDA has waived the need for a Phase II trial. Protalix has submitted their Phase III design to the FDA and hopes to begin recruitment this year.

Substrate Reduction Therapy

‘ERT does not answer all the clinical needs of all patients with Gaucher disease, i.e. pre-existing lesions, access to the brain, and (in some patients) access to the lungs. Therefore, there is still a need for therapy based on an alternative modality to enzyme therapies.

‘Clinical trials were conducted in Type I Gaucher disease using the substrate reduction therapy miglustat (Zavesca; Oxford GlycoSciences, UK, currently Actelion Corp, Swutzerland). Miglustat works by partially inhibiting the enzyme glucosylceramide synthetase, thus reducing the amount of storage accumulating in the lysosome. Some patients developed significant side effects such as diarrhoea. Miglustat has been approved for patients with Type I Gaucher disease who are not deemed suitable for ERT.

‘One of the benefits of SRT is that it crosses the blood brain barrier. A clinical trial in Type III Gaucher disease however failed to benefit patients and therefore there is still a need for new products that can traverse the blood-brain barrier and benefit neurologically affected patients.

GENZ 112638

‘Genzyme Therapeutics has developed a small molecule therapy, GENZ 112638. Unlike miglustat which is a sugar analogue of the enzyme, GENZ 112638 is a ceramide analogue. Preclinical data seem to indicate that GENZ 112638 is dissimilar clinically to miglustat: it does not cause comparable side effects, but also probably does not cross the blood-brain barrier and hence may not be effective for the neuronopathic forms of Gaucher disease. Phase I studies were completed in more than 100 healthy volunteers given 600-fold dosage of GENZ 112638 relative to the expected therapeutic dosage for Gaucher disease. Phase II clinical trial in naïve patients is ongoing in several centres.'
A Different Concept

Pharmacological chaperones known as EET (enzyme enhancement therapy) are small molecules. An oral therapy for Gaucher disease is being developed by Amicus Therapeutics using this approach (see previous report in the June 2006 and December 2006 edition of the Gauchers News).

‘For many years it was believed that Gaucher disease was the result of the inability of the mutated enzymes to effectively break down the stored glucocerebrosides (the substrate) in the lysosome. Recently it has become evident that there is an additional mechanical problem engendered by the mutated enzyme because of its inability to fold properly, and hence to get from where it is being made (in another sub-cellular compartment called the ER = endoplasmic reticulum) into the lysosome. The pharmacological chaperons can selectively bind to the mutated enzyme in the ER, stabilize it and restores its ability to traffic to the lysosome and increase the degradation of the substrate.

‘A Phase I trial using Amicus’ oral Gaucher chaperone AT2101 has been completed in healthy volunteers, and currently patients are being recruited to Phase II trials in several centers in the USA. See page 15 of the Gauchers News for an up to date report on these studies.

Clinical Trials

‘Patients are now faced with a plethora of new treatments for Gaucher disease, how does the patient decide whether or not to participate in a clinical trial?

‘If a patient is symptomatic and needs therapy, the first thing to consider and discuss with his physician is whether to take the commercially available drug (Cerezyme) which should be the first choice or to participate in a clinical trial. In type 1 Gaucher disease the option to join a clinical trial may also be altruistic, to help develop a new therapy or to encourage competition which is good for patients, doctors and scientists. Once the decision is made to opt for a clinical trial, the second step is to decide which drug would be appropriate.

Final Comments

‘Ethical considerations in clinical trials for rare disease with expensive drugs need to be highlighted. These considerations are many and multi-faceted. Of immediate importance are those that relate to recruitment and enrolment of patients. Is there justification to run placebo-controlled trials with symptomatic patients rather than give standard therapy; alternatively, should relatively mild patients only be recruited, albeit exposing them to the rigours of a clinical trial?

‘In some cases there may be some conflict with patient advocacy groups who may receive grants from pharmaceutical companies to support their work (unlike the UK Gaucher’s Association which does not). Finally, other aspects that may require further investigation are non-disclosure of trial results, per-patient investigators’ fees, off-label use, and direct to consumer marketing.’

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‘Age at first bone crisis ranged widely although there was a cluster around 11, 12, 13 years of age before and during puberty which is not surprising and fits in with clinical suspicion that something happens to the bones around this time.

‘Splenectomy was identified as a risk factor in this group of patients as there was a clear relationship with patients who had had a splenectomy. The debate is whether a splenectomy is a cause of avascular necrosis or just a marker of severity. Splenectomised patients reported that their bone crisis had occurred after they had had their spleen removed.’

**Clinical Prediction of AVN**

‘The Zimran severity score Index was associated with AVN however this is not surprising as AVN is a part of the definition of the severity score index. Other factors included the age of presentation and diagnosis, the earlier the disease occurs the more likely the patients was to have AVN. Unrelated factors included gender, the presence of osteoporosis or Erlenmeyer flask deformity.

**Biochemical Risk Markers**

‘The biomarkers PARC (CCL18) and chitotriosidase were found to be highly related to the risk of AVN. A number of other markers are under investigation including the molecule MIP-1B to predict the effectiveness of ERT in preventing AVN. Early indications are that it does not predict whether a patient responds to ERT in relation to AVN. Further studies on all 100 patients will be carried out.

**Consequence of AVN is Joint Surgery.**

‘Out of the 100 patients in the study 78 had had no surgery, four had their left hip replaced, three their right hip replaced and eight had both hips replaced.

**Osteoporosis**

‘This is a reduction in calcium composition of the bone and causes fragility of the bone. Osteoporosis is a factor in Gaucher disease however it is hard to measure in everybody. The conventional way to measure it is by bone mineral density. Within the study there is no data on bone mineral density but there is data on fractures.

‘The bone undergoes constant break down and repair, a process called osteoclast breaks down the bone and osteoblast repairs it. Within this study the plan is to examine the markers of osteoclast and osteoblast activity to see if there is any relationship with fractures.

**Erlenmeyer Flask Deformity**

‘Erlenmeyer flask deformity is a common finding in Gaucher disease. The normal shape of the end of the femur is like the shape of an Angel’s trumpet with a flared end, whereas patients with Erlenmeyer flask deformity have a triangular shape at the lower end of the femur. Bones grow from the ends, in your teenage years length is added to the bone by the end plate and as bones get longer they get wider and the bone is laid out in a triangular fashion. Due to the remodelling of the bone the osteoclasts (break down bone) migrate in and reshape the bone to form a trumpet shape. In the Erlenmeyer flask deformity this process is somehow interrupted and does not happen and so the bone form is a history of the size of the bone plate as it grew. An x-ray of a patient at the age of 24 years who began ERT at the age of 11 years illustrated the possible change from Erlenmeyer flask to trumpet at the start of treatment which could illustrate that ERT may restore the remodelling of bone.

**Mobility and Quality of Life**

‘Participants in the study were asked how well they moved and if they required assistance, 67 had no difficulty in walking, 22 walked with a limp, 7 used one stick, 1 used two sticks and 2 were in a wheelchair.

‘An extensive quality of life was carried out; participants were asked to pick a number between 0 and 100 to indicate their health related quality of life. The average score was 75% which is normal range, a quarter scored less than 60 and a quarter scored more than 90.

**Summary**

‘This presentation of some of the early data has given some of the descriptions of aspects of Gaucher bone problems, a look at some of the data in the bone project and an early indication of the effect of ERT on bone structure. The bone project will officially finish in the autumn this year and a full report on all the data and findings will be presented to the Gauchers Association and its members after that.’
Dr Atul Mehta leads the Gaucher Centre at the Royal Free Hospital in London, one of the four national designated Gaucher centres in the England. Dr Mehta is a Consultant Haematologist. He began his talk by congratulating the Gauchers Association on its 15th Anniversary.

‘My talk today will introduce the patients cared for at the Royal Free Hospital, Hampstead London, see where they are in their progress, what they have achieved and how their condition has responded to treatment. I will also hope to give an overview of what Gaucher patients in the developed world can expect with the treatment available today. There are challenges ahead, I will try to identify what they might be and look at strategies to meet and defeat them.

‘In total 73 Gaucher patients are seen at the Royal Free Hospital in London in the Lysosomal Storage Disorder unit. 28 of these are of Ashkenazi origin and the age of diagnosis ranges from 2 – 90 years. 20 of these are homozygous for the N370S mutation. The make up of this group reflects the ethnic diversity of modern day London which includes people from Europe, Eastern Europe and Sri Lanka.

‘Gaucher disease is an accumulation disease and this point is important when considering how to monitor individual’s progress on treatment. ‘Goals of Therapy’ developed by an International Expert Group are used to monitor and analyse the progress of the patients at the Royal Free hospital. These parameters are things that one can measure to see responses in patients to treatment and include; Bone disease, growth, anaemia and tiredness, estimated transfusions needs, bleeding and bruising, liver and spleen size, lung function, quality of life and biomarkers.

Response to Treatment

‘One patient still receives Cerease due to an allergic reaction to Cerezyme, 64 patients are currently taking Cerezyme, nine have been on Zavesca (all of these were previously on Cerezyme) and 18 have undergone a Splenectomy.

‘Data from this cohort of patients showed that treatment has led to a reduction overall in bone diseases in these patients, it has not totally eliminated bone disease but has lessened the progress of osteonecrosis, although it has not eliminated it.

‘A significant improvement in haemoglobin levels were seen, in most of the patients the need for blood transfusions was eliminated, there was a reduced tendency to bleeding in all patients, the feeling of tiredness had improved in all patients and there was an improvement in platelet count when baseline was low. Response to treatment in these areas had overall improved.

‘A reduction in liver and spleen size was seen in all patients and the effects on the lung function were seen in response to treatment except in one patient.

‘The goal was to restore or improve physical function for performing normal activities; all but four patients reported an improvement.

‘Using biomarkers enables the systematic progress of patients to be measured. In total four biomarkers were measured; Chitotriosidase; Acid Phosphatase and Serum angiotensin converting enzyme. All show a positive response to treatment.

Summary

‘The Goals of Therapy for Gaucher disease are usually met – particularly with regard to blood counts, liver and spleen size and bone pain.

‘Bone disease and quality of life is difficult to measure in patients. The data confirmed that the longer patients had been on treatment and the earlier onset of treatment was associated with better outcomes.

‘Patients who had undergone a Splenectomy in general had a more severe disease.

Future Challenges

‘Within the cohort of patients at the Royal Free, one patient had Parkinson’s disease and a number had paraproteinaemia.

‘Paraproteinaemia is an abnormal protein which is a marker of an abnormal immune system.

Parkinson’s Disease

‘There have been recent observations of Parkinson’s disease or parkinsonism in the Gaucher population. In a recent study by Aharon-Peretz et al, Neurology 2005 it showed 148 Ashkenazi with idiopathic Parkinson’s disease. They were screened for the Gaucher gene mutation, 50 (27%) were Gaucher carriers and four were homozygous for the N370S mutation.

Paraprotein/Myeloma*

‘Myeloma is a form of blood cancer and in the UK 6,000 new patients are diagnosed with Myeloma each year. The incidence is 1: 10,000 and figures indicate that there is a 5-10 fold increase in people who have Gaucher disease of developing Myeloma. 1% of the Gaucher patients seen at the Royal Free have Myeloma; however with patients living longer this number could increase.

Summary

‘Gaucher disease is a multi-system disease. Using the ‘Goals of Therapy’ on the cohort of patients at the Royal Free Hospital, current treatment for Gaucher disease is effective in treating the majority of symptoms. The remaining challenges are the delivery of ERT to the bone, the central nervous system and the relationships between other conditions such as; Parkinson’s disease and Myeloma.’

Dr Mehta ended his presentation by thanking his team at the Royal Free Hospital.

*See page 7 of the Gauchers News for a report on the Myeloma study being undertaken at the Royal Free Hospital.
Doctor-Patient-Partnerships, how the past can address the future

Prof Timothy Cox of the Department of Medicine, University of Cambridge at Addenbrooke’s Hospital, one of the four national designated Gaucher centres in the England expresses the importance of collaboration in his talk ‘Doctor-Patient-Partnerships, how the past can address the future’;

‘When we talk about partnerships in the field of lysosomal diseases, it is important to appreciate the many different partnerships and complexity that exists. Each partner plays an integral part of an enormous socio-economic whole.

‘In the first instance, it is hard to make distinctions between doctors and scientists since many biological scientists know a lot about medicine and modern doctors know quite a little about science (some, a great deal!). Therefore the partnership is Doctor – scientist – patient partnerships. Then there are nurses, support staff, personal assistants to the professionals who all contribute and therefore the partnership arrangement is healthcare personnel – scientists – patient partnerships.

‘Finally there is the pharmaceutical industry that has been needed to make many things happen in rare disorders; for without them, all our lives would be very different and somewhat retarded. Therefore our real arrangement is healthcare personnel – scientist – patient partnerships: in effect, a large multicellular organism.

Successful Partnerships over Time

‘The Gauchers Association through partnership working has played a key and often initiating role in many different areas of development in the Gaucher field, from arguing for universal healthcare provision to raising awareness and disseminating up-to-date information. The successes of the Association, over just 15 years of its life, have been extraordinary.

Access to Treatment

‘Access to treatment for Gaucher patients locally in the UK and abroad has been achieved for all patients. This is due very largely to the Gauchers Association and many doctors- including some enlightened public health doctors in difficult positions- who worked tirelessly for individual patients in the UK. In the early days this was achieved by lobbying healthcare trusts individually. Not been content with that, the Association looked to patients outside the UK: it is well-known that over the past five years the Association have been instrumental, through their work in the European Gaucher Alliance (EGA), to make the case in partnership with Genzyme Therapeutics for humanitarian treatment for Gaucher patients in Eastern Europe and elsewhere.

Comprehensive Healthcare System

‘It has been 10 years since the development of a comprehensive healthcare system for Gaucher patients in England was established through the designation of the first four national centres for adults and children with Gaucher disease. This group of Specialist Centres, funded through the National Specialist Commissing Advisory Group (NSCAG) of the Department of Health. We are very pleased that these centres have now been expanded to take on the entire family of lysosomal storage disorders and include two new members in Birmingham and at the National Hospital for Nervous diseases.

Treatment Guidelines

‘The establishment of treatment guidelines published by the European Working Group on Gaucher disease (EWGGD) for miglustat in Type 1 Gaucher disease and the guidelines for the management of neuronalopathic Gaucher disease reflect the larger Gaucher community. Each publication had representation from members of the UK Gauchers Association and the EGA who are full co-authors.

‘The development of National guidelines produced by NSCAG through the national centres for Lysosomal Storage Disorders including Gaucher disease, providing agreed protocols for treatment and clinical management; the management structures of the Centres ensures that the highest standards of international practice are maintained, and that safety issues related to clinical governance are given due weight.

Political Journeys

‘There have been numerous political journeys by the Association and its partners over the years; these have largely arisen from the high cost of the treatment for patients with Gaucher disease and other lysosomal storage disorders. Two local issues merit special mention here:-

‘In 2004, The National Institute of Clinical Excellence (NICE) where asked by the Department of Health to undertake a feasibility study to review whether its procedures were appropriate for the assessment of high-cost treatments for rare disorders. NICE chose as their model the experience of Gaucher disease and the Gaucher Association were invited to play a role in this process – thus enabling the patient’s experience to be taken into consideration.

‘After designation of the Gaucher service in 1997 by NSCAG there was a threat of de-designation and through important political discussions with all its partners, the Association was successful in ensuring the continuation of this service in England.

Independent Research

‘The Association has not just encouraged us but provided meaningful support through their significant contribution to research, through a number of research grants all funded independently by its members. The Association supported early studies on enzyme targeting by Dr Pram Mistry, who has gone on to be a distinguished Gaucher expert and physician-scientist, now in the United States. Other projects include the collaborative bone study involving the original four national centres and the development of a Gaucher-specific gene expression library carried out by Mary Teresa Moran with studenthip support from the Association; in collaboration with Prof Hans Aerts from this research

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identified the marker PARC/CCL18 which is now in active development for treatment monitoring internationally and is a fine partner of Hans’s earlier discovery - chitotriosidase.

Knowledge & Information

‘Independent research is the source of knowledge – and clearly the promotion of understanding is important to the Association’s members; it enables them to see where they are and where they are going. Research also is the pathway to better treatment and health.

‘The Association publishes a twice yearly newsletter, with a circulation of 1400 copies world wide, this extensive newsletter contains unbiased information on clinical trials, current research, patient stories, fundraising activities, conference write-ups and current affair updates for members, their families and the wider Gaucher community.

‘In 1997 Prof Ari Zimran edited a book on Gaucher disease. The Association recognised this significant event and celebrated its publication at a reception at the House of Commons with the then Secretary of State for Health, the Rt. Hon. Frank Dobson MP. In 2006 a new book on Gaucher disease appeared, this time edited by the Secretary of State for Health, the Rt. Hon Frank Dobson MP. In 2006 a new book on Gaucher disease appeared, this time edited by Prof Ari Zimran and Prof Tony Futerman. This book represents a world partnership with authors from industry, scientists, physicians and representatives from patient organisations – naturally, including Susan Lewis, Jeremy Manuel OBE and Tanya Colin-Histed. The Association held a reception and launch for this new book in London at the offices of SJ Berwin LLP in November 2006 in partnership with the Weitzman Institute.

ECAP

‘In the UK, most, if not all Gaucher patients are in effect looked after by NSCAG. However many patients worldwide do not have access to dedicated healthcare. At the recent meeting to celebrate the 20th Anniversary of the Dutch Gaucher Association, members of the EGA approached Henri Temeer from Genzyme Therapeutics one morning at breakfast and explained to him their concerns about the Gaucher patients in Eastern Europe who did not have access to treatment and were very ill. Henri Temeer made a promise to look into this. He kept his word and after several meetings with the EGA the European Cerezyme Access Programme (ECAP) was born. The mission of the programme was to treat patients seriously affected by Gaucher disease in eastern Europe and the Balkan countries, where reimbursement is currently inadequate to meet the demand for access to treatment. At the time of writing, well over 100 patients in 13 countries receive Cerezyme through ECAP. Treatment through ECAP will only be given in the presence of an appropriate healthcare infrastructure for administering treatment and disease monitoring by responsible physicians- and so the benefit has been of catalytic importance for the expert care of patients with this disease in the former Eastern block.

Roles of the partnerships for the future

- Supporting cases of urgent need
- Providing independent information and improving access to care
- Education and engagement of healthcare professionals
- Negotiating with the pharmaceutical industry
- Political advocacy at all levels
- Being united in work and purpose
- Contributing with industry to the design and conduct of clinical trials

‘All of the partners involved seek the same goal to provide treatment for all patients, to ensure better relief of illness through effective and safe medicines - and to face the challenge of hitherto unmet needs. All parties seek the same goal but for each party the outcome is different. For healthcare professionals and industry the outcomes are not greatly dissimilar; but for patients and their families, the outcome is the difference between health and the misery of illness.

The Need for Research

‘There is a continuing need for research: Anne Begg MP, who was elected in wheelchair with the late complications of severe Gaucher disease said she couldn’t have done what she has done in her career as a teacher and now successful politician- without Ceredase and then Cerezyme. Anne was able to move from her rewarding success as a teacher to become a politician (she was elected in 1997), but perhaps if she had been able to receive definitive treatment earlier, she would be without the need of a wheel chair now.

‘Bone disease and the neurological manifestations of Gaucher disease, present formidable challenges for adults and children, as well – tragically- as a few babies. The field requires us all to think critically and imaginatively about these aspects of the very special and ultra-orphan disorder that is Gaucher disease; for without strong and indissoluble partnerships, we cannot hope to solve them.

Indissoluble partnerships

‘As we celebrate the achievements of the Gauchers Association in the UK, we must pay deep tribute to the true altruism of its magnificent founders and to the immense efforts of its members to improve the lot, not only of their immediate kith and kin, but through the external work of the charity, of the lives of fellow sufferers worldwide.

‘It is invidious to mention names, but I feel that I must commend the work of your Chairman, Jeremy Manuel and your erstwhile Executive Secretary, now Honorary Life President, Susan Lewis, who sadly is too unwell to join today’s proceedings. Jeremy does not have Gaucher disease but he did have the foresight to use earlier bequests in the memory of his late mother through The Helen Manuel Foundation to join with a group of wonderful people well known to us all, to establish the Association as a charity. The results are evident for you all to see and the record of independence maintained without any direct support from industry is a tribute to much hard work. There will be other opportunities to speak to this subject but all of you will wish to pay special tribute to the superhuman efforts and skill of Susan who, with her husband David, has done so much to make the Association what it is and to bring its principles of care to the international level.

‘All this was done without any financial reward over many years; but the word charity, means much more than kindness. Its classical linguistic derivation tells us rightly, that it is all about Love - in this case, practical love for fellow human beings suffering the isolation and pain that accompany challenging illnesses such as Gaucher disease, which are so very rare.

‘To conclude any discussion about Partnerships, the subject allocated to this talk, we must return to the hierarchy of human virtues beyond the one, charitas, above. I used to think that loyalty was the greatest human virtue; it is certainly a strong one, as the partnerships established by the Gauchers Association show. On reflection however, I have to agree with Winston Churchill, who put courage first - for all the other virtues depend upon it. The members of the Association have this virtue also in abundance: courage enables them to face their own illness head on and to further their work across many countries and cultures; of course, it is this very quality that inspires their loyal partnerships - and our admiration.’

Editors note: Sadly Susan died three months after this presentation.

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Dr Edmund Jessop is Medical Adviser for the National Specialised Commissioning Advisory Group (NSCAG). The NHS in Scotland, Wales and Northern Ireland are run by their own administrations: Dr Jessop’s presentation looks at England.

‘Commissioning means planning (what should be provided and where it should be provided), funding and monitoring health services.

‘Over the past five years there has been a strong policy from consecutive health ministers that commissioning decisions should be made at a local level. There has been a fundamental shift in policy to devolve spending power down to PCTs (Primary Care Trusts) over the last year. These decisions would probably be best made by the local doctors e.g. GP funding, practice based commissioning.

‘This approach allows the hospital to determine their own way of running things free from central government. This is the drive encouraging local hospital to become Foundation Trusts which are not answerable directly to Strategic Health Authorities and is the right way to get the decisions about the shape of the NHS made by the right people in the right place.

These arrangements are for common conditions such as heart attacks and stroke and for operations such as hip replacements or cataracts surgery.

Specialised Services

‘It has been recognised by the Department of Health for about 20 years that these arrangements are not strong in the case of rare diseases or specialised services. A lone GP will not know where the best place would be to have liver transplant, a heart transplant or get treatment for a condition seen by the average GP once every 200 years! The drive to have local commissioning and local decision making has been counter balanced by an argument to say that we also need national commissioning arrangements. This is the role of NSCAG.

‘NSCAG has an annual budget of about £250 million to directly fund NHS hospital treatment for a specified list of rare disorders or specialised services. In total there are currently 30 conditions/services in England covered by NSCAG. In the case of Gaucher disease, this is covered under the umbrella of lysosomal storage disorders.

Characteristics of Services

‘Services supported by NSCAG designation are rare disorders where the treatment is managed by an expert team, usually with a multi-team approach. No more than two to five centres in the whole of England would provide the service and the cost per patient would typically be £100,000 plus.

Benefits of NSCAG Designation

‘NSCAG designation means that there is a uniform national standard of care throughout England, enabling a patient to avoid any hassle accessing treatment or support as the service is free to PCTs therefore there is no administration barrier. Local clinicians feel a duty to refer the patient to the national centre. NSCAG services are also tightly monitored for quality of care through the national standards.

Health Technology Assessment Unit (HTA)

‘The HTA are the research arm of NSCAG and are currently undertaking a longitudinal study into Lysosomal Storage Disorders and Enzyme Replacement Therapy. This study is independent of any Pharmaceutical Company and therapy and will include all LSDs where there are currently therapies licensed but will also include those conditions where therapies are not yet available. Patient Associations in the UK for Gaucher disease, MPS, Pompe, Batten’s, Niemann-Pick and Climb are all involved in this study.’

Ms Hanna Hyry from the University of Cambridge repeated the talk she gave at the EWGGD workshop in July 2006 on the debate of efficacy versus equity in dealing with the questions: Should Society Fund Orphan Treatments? A summary of her talk was printed in the December 2006 Gauchers News on page 5.
Living with Type III Gaucher Disease

Jo Bardoe is the mother of six year old Mia who has Type 3 Gaucher disease, Jo’s presentation describes Mia’s determination and gives a taste of what it is like for the family living with Gaucher’s disease.

‘Mia was diagnosed in December 2000 just after her 1st birthday. She choked frequently from the age of nine months but the first thing we picked up was her eye movements. She has quite classic neurological symptoms. Although she no longer has choking problems – she has no horizontal saccades, so she can’t make horizontal movements with her eyes. She is ataxic, has impaired gross and fine motor skills and auditory processing issues. It took us a long time to get over the shock and of course as a parent you’re always coming to terms with the impact Gaucher disease has on your child. She’s been having Cerezyme now for six years and has just completed three years on the Zavesca trial, which sadly did not work.

Schooling
‘Mia is just 7yrs old and attends our local village primary school. She has a full statement of educational needs. This is because she has poor balance, problems walking, gripping and controlling a pencil which affects her writing and drawing. She needs more time to understand instructions and new concepts especially in mathematics. She also has issues with spatial awareness.

‘Mia requires specialist equipment at school including a sloping desk to help steady her hand as she has a tremor, and a saddle seat to aid her posture as she appears to have developed a postural kyphosis (curvature of the spine). Her learning support assistant sits beside Mia, reinforcing instructions in her maths lesson and also assisting her in P.E. She is very well cared for in her school and it is imperative that she has 1 to 1 support in terms of safety and understanding the curriculum.

The Indian National Anthem
‘I would like to share with you a recent event which happens to be an extremely proud moment for Christian and I.

‘Three days prior ago we were at Great Ormond Street Hospital attending a clinic appointment. This was a special day in itself. It would be the last time we sat in Dr Vellodi’s clinic discussing “the trial”. Zavesca had failed to provide us and the other families with the positive results we so desperately yearned. The trial had been an extremely stressful experience for Mia and us as a family especially in the early days. We were under no illusions that Zavesca would be the answers to Mia’s problems and we could only pray for a positive result. We have always known Mia is severely affected. There would have to be an alternative or something to complement Cerezyme.

‘It was also, sadly the last time we would be privileged with Elin’s company. She’d been a great support to us all. Kind, caring, supportive and professional. Only Elin I’m sure with her gentle, unthreatening and persuasive manner could cajole Dr Vellodi into a one off performance of the Indian national anthem that afternoon. He sung it so beautifully in Bengali. All for Mia’s benefit, as a thank you for taking part in the trial. For those of you who may seem perplexed singing the national anthem was a method we used to persuade Mia to take her tablet in the early days! I can assure you that not only is Dr Vellodi an exceptional doctor he has the voice of an angel.

‘It had been a long day and as usual Mia had taken it in her stride. “Tell Elin and Dr Vellodi what’s happening on Sunday”, Christian asked encouragingly. “I’m going to be in Aladdin” she whispered shyly.

Aladdin
‘She’d been attending Petersfield Youth Theatre work shops for six weeks. I’d been dropping Mia and her friend Georgia off on a Thursday afternoon.

‘I’m not sure if it was more of an achievement for me. I was extremely anxious about leaving her. I’d explained her situation to staff running the workshops and they were very positive but it wasn’t school and therefore unfamiliar ground. She didn’t have the one to one help she had at school although there was a chaperone assigned to the youngest group and I was reassured she would help Mia out when required.

‘There were to be be to two performances of Aladdin that Sunday at Petersfield Festival Hall. She’d also just completed 2 consecutive performances of ‘Holy Joe’ the Christmas school play so it had been pretty full on. Mia had said that she enjoyed the work shops but was not happy about going on stage. It had been a feat for Mia just attending the workshops. So we made a deal. I told her she could get someone to call me on performance day and I’d pick her up during rehearsals if she didn’t feel she could do the show – hardly ideal but they’d make an exception as she is special.

Performance Day
‘It was 5 o’clock on 10 December, the day before Mia’s 7th Birthday. Christian, myself, Skye (Mia younger sister) and one of her little friends took our seats in the rear stalls.

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‘I had not received a call so our assumption was that Mia was up for it and decided to ‘perform’. I felt really nervous as I looked out at the huge imposing stage.

The performance began, It was big, tuneful, colorful and professional. Mia had told me she was to be one of the jewels in the show. I imagined her standing in the wings anticipating her entrance onto the stage before an audience of 250 or so people and I thought back to June when she had had to endure 5 days in hospital. This had been as a result of some dreadful virus which pretty much knocked her out. Running a very high temperature, unable to speak, eat or walk, making the most frightening noises as she struggled to breathe. Doctors and nurses battled to get her body temperature to anything near normal. I remembered then being amazed the way she recovered five days after she was discharged as she joined the school sponsored walk, completing approximately two miles of the hike along the South Downs where we live. Her courage and determination are one of her many admirable qualities.

All Going Well

‘30 minutes into the show ....Enter the jewels..... my stomach lurched and I let out an audible gasp. .....there she was following her fellow jewels as they skipped onto the stage. Skip?! Mia of course wasn’t able to skip but she managed to launch one foot in front of the other at speed. Right foot, left foot, right again – I saw space between foot and floor. God she was running ......alone, no adult beside her– could she keep it up, would she trip and fall? I could hardly breathe. She was the youngest and by far the tiniest in the show. She looked like a petite fragile china doll, vulnerable, fine featured and beautiful. Shiny in her all black sequin coated tunic and tights. Her black and gold hat accentuated her little head thrusts as she glanced left and then right to check her position on the stage.

‘I could see every movement she made as a girl twice her height took her hands and they made an arch between them. They released their hands and Mia followed the carefully choreographed moves to the best of her physical ability. Turning and twisting, shuffling her feet trying to keep in time with the music. Her body more rigid than the other 20 jewels, movements less smooth, jerky and arms and legs stiff. I wondered if anyone else would notice? Then she missed a clockwise 360 rotation. Would it throw her? Recovery, composure and a side step to the right. Her friend Georgia, kind, thoughtful and accepting, extending her hand in order to guide Mia swiftly across the stage. It was paceier than I’d expected. I wondered what I had subjected her too. I had not witnessed her achieve anything at this level before and I questioned whether she was up to it? Had I become one of those pushy over ambitious mothers, desperate to witness her daughter on stage at any cost?

‘I squeezed my interlocked hands even tighter in my lap as I watched her find her place in the newly formed circle, maneuvering herself into a kneeling position hands in a prayer pose, head bent forward. Then hands at her side body swaying from left to right. She had to get up from here in time with the other jewels– tricky, how would she cope? Before I had time to work out the logistics for her they were up and off to the other side of the stage. She must be tiring, how were her legs bearing up? She could stumble at anytime, and there was a lot to remember. She was then guided across stage again by Georgia who compromised her natural pace in order to accommodate her friend they disappeared into the safety of the wings.

‘At last I could exhale and relax ridding myself of my neurosis just for a few minutes before the little jewels appeared for the finale with the rest of the ensemble. I watched Mia lift her head up beautiful face illuminated by the lights a small bow and little head thrust to the left. A gesture with her hand to the orchestra, applause and curtain.

A Proud Moment

‘She’s done it, survived, better than that, this was a truly exceptional achievement for Mia. I reached up and wiped the tears from my face. As I glanced at Christian, I realised he had clearly struggled more than I had during this impressive performance. Like me overcome with a pride and admiration we’d not experienced before now.

Being a Parent

‘I have learnt an awful lot about myself since Mia was a) born and b) diagnosed. I had not realized how stubborn, determined and sometimes obsessive I could be, I’ve pitied my poor family at times. I am always on the look out for new therapies any thing that could help in any way possible. I never discounted alternative complimentary medicines or therapies and I believe they have their place. She’d seen a cranial sacral healer for a while, cranial osteopaths, visited a herbalist and a kinesiologist (movement therapist). As a parent you will try anything to improve a situation one is so helpless to change.’
Living with Type I Gaucher Disease

Dan Brown lives in Hertfordshire with his wife and son. In his talk he tells us about his relatively recent journey with Gaucher disease;

'I was born in 1977 and in September 2003, age 26, I found out I had Gaucher disease. So it came as a bit of a surprise.

'For a few months I had been having some strange stomach pains and felt bloated a lot of the time. My wife was not too sympathetic and kept telling me I was eating too much! I saw my GP a couple of times but she did not think there was anything wrong with me. I once went to A&E but they told me that I was probably a bit constipated! However, I still felt that all was not exactly as it should be. After a weekend where the pain was markedly worse I decided I had to go back to my GP and it was at this point that I truly believe fate played its part in leading to my diagnosis.

'My GP was on holiday so I saw a locum instead (the first fateful event). His initial reaction was there was nothing serious wrong with me but he told me that if I was genuinely concerned I could go to see him at his private clinic in Harley Street, he could carry out some tests and it would give me some peace of mind.

From Harley Street to the Royal Free

'So the next day I went off to Harley Street. The doctor did a few blood tests and an ultrasound of my stomach and I went for a coffee to wait for the results expecting a telephone call to say that everything was ok. I waited for an hour or so and then my mobile rang and the doctor said that I should go back to his office as he had some results for me. The tests showed that I had some abnormalities in my liver and a large spleen. At this point I started to worry. He told me that he couldn’t be sure what was wrong but that we would get to the bottom of it very quickly and he referred me to a friend of his - Professor Hoffbrand, a haematologist at The Royal Free Hospital (the second fateful event).

A Diagnosis

'A week or so of worrying later I went off to the Royal Free. After some more blood tests Professor Hoffbrand told me that he would like to carry out a liver biopsy and at this point my family and I were all quite concerned. I unfortunately then had to wait another few days before the results came back and then went to see Professor Hoffbrand again. He sat me down and told me that he thought I had Gaucher disease and then laughed that I had come to the right place! He briefly explained that whilst Gaucher was a serious disease it could be treated and managed and that in fact on the 3rd floor of the hospital there was a Gaucher clinic - one of the few in the country. So I went downstairs with him and there he introduced me to Dr Atul Mehta.

What is Gaucher Disease

'I will never forget my first conversation with Dr Mehta. He explained to me what Gaucher disease was in very simple terms and to this day it is the explanation I use when described it to someone who has never heard of it before. This was his explanation:

“When you move house there is always loads and loads of stuff you have collected over the years and you don’t know what to do with it. So when you move house you put it all in the loft. After you have been in the house a few more years you have collected a bit more stuff so you start putting it in the second spare bedroom and when that is full you start using the first spare bedroom. Eventually all you’ve got left is your bedroom and your lounge and no space for anything else. Well that is almost what is going on inside your body. It is producing all this rubbish and doesn’t know where to put it so it puts it in the spleen, which is like your loft, as you don’t really need it. When this is full it looks for somewhere else and so on until it puts it somewhere where it will do some damage.”

Treatment

‘He then explained to me that until relatively recently there was no treatment for Gaucher and patients and their doctors were left to manage the symptoms rather than the cause. However Type 1 patients like myself could now be treated with enzyme replacement therapy and there was no reason why in due course my symptoms could not be reversed.

‘A short while later I had my first infusion of Cerezyme at the Royal Free and then had weekly visits from Healthcare at Home. My wife was trained to administer the IV and after just over a year of therapy my symptoms had indeed reversed.

‘In the space of a few weeks in 2003 I had gone from being petrified that my health was at serious risk to being told that I have a rare disease but that I should be able to lead a normal life. It was a bit of a rollercoaster for a while.

Living with Gaucher Disease

‘Whilst Gaucher disease cannot be taken lightly I feel privileged that, as a Type 1 sufferer, I am lucky enough to have been diagnosed at a time when many years of research and hard work have resulted in a successful treatment which is publicly funded and which allows me to lead a normal life. Now in 2007 my body is back to normal, I am 30 years old, married and have a six month old baby. I work hard as a lawyer in the city, play football, and have an active social life.

‘I am living, living with Gaucher disease. I would like to say a special thank you to Dr Mehta and his team at the Royal Free Hospital for all their support.’

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