

type 3 Gaucher disease

information



Introduction	1
What is Gaucher disease?	2
What is type 3 Gaucher disease?	3
How common is type 3 Gaucher disease?	4
How is type 3 Gaucher disease diagnosed	5
Genotype - phenotype correlation	6
How is type 3 Gaucher disease inherited?	8
Non-neurological disease and its assessment	9
• Kyphosis	9
• Enlargement of abdominal lymph nodes	10
• Lung development	11
• Eye involvement	12
• Bone involvement	13
• Other assessments	13
Neurological involvement and its assessment	14
• Eye movements	14
• Squint	15
• Hearing	16
• Ataxia	17
• Seizures	17
• Intellectual function	18
• Behavioural problems	19
• Overall neurological pictures	20
Gaucher specific treatment	22
Clinical management	23
Impact on daily living	26
• Birth, early childhood	26
• Older children & adolescents	27
• Young adults	28
• Older adults	29
Impact on education	30
• Eye movements	30
• Hearing	31
• Intention tremor and co-ordination	32
• Special educational needs	33
Glossary	34

Welcome to the Gauchers Association information booklet on type 3 Gaucher disease. In 2016 The Gauchers Association undertook a survey amongst their members to understand what information they would like to see in an information booklet.

Following on from the analysis of this survey the information in this booklet, along with additional inserts is to help you understand type 3 Gaucher disease, such as, how is it inherited, how will it affect your life and its clinical management.

We hope you find it informative and useful, whether you have been living with Gaucher disease for many years, or you or a family member have just been diagnosed or you work within the Gaucher community.

If you have any unanswered medical questions please refer back to your Gaucher specialist or if you have any unmet non-medical needs contact the Gauchers Association's Patient & Family Support Service on 01453 549231.

Further information on Type 1 and 2 Gaucher disease is available on the Gauchers Association website at www.gaucher.org.uk



Emily

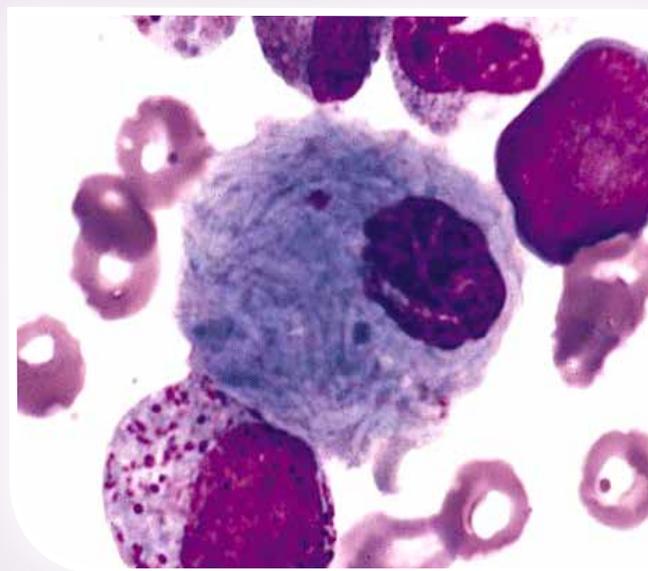
what is Gaucher disease?

Gaucher disease is a rare inherited (genetic), enzyme deficiency disorder. Symptoms range from mild to severe and can appear at any time, from infancy to old age. They may include anaemia (low haemoglobin), tiredness (fatigue), easy bruising and a tendency to bleed. An enlarged spleen and liver with a protruding stomach may also occur as well as bone pain, loss of bone strength and density with an increased risk of fractures.

People with Gaucher disease lack sufficient activity levels of an enzyme called glucocerebrosidase. This enzyme helps the body break down worn-out cells and as a result, a fatty substance called glucocerebroside accumulates usually in the spleen, liver, bone marrow, rarely in the lungs and in some types of Gaucher disease in the central nervous system.

The most common form of Gaucher Disease (type 1) affects 1 in 100,000 of the general population but 1 in 850 of Jewish (Ashkenazi) descent, although not all those who inherit the mutated genes for this disorder will show symptoms.

In the rare Neuronopathic (types 2 and 3) Gaucher Disease, neurological symptoms occur which include an eye movement disorder (oculomotor apraxia) and unsteadiness (ataxia). Patients can in some cases develop fits (seizures), loss of skills and learning difficulties. Children with type 2 Gaucher disease usually die within the first few years of life.

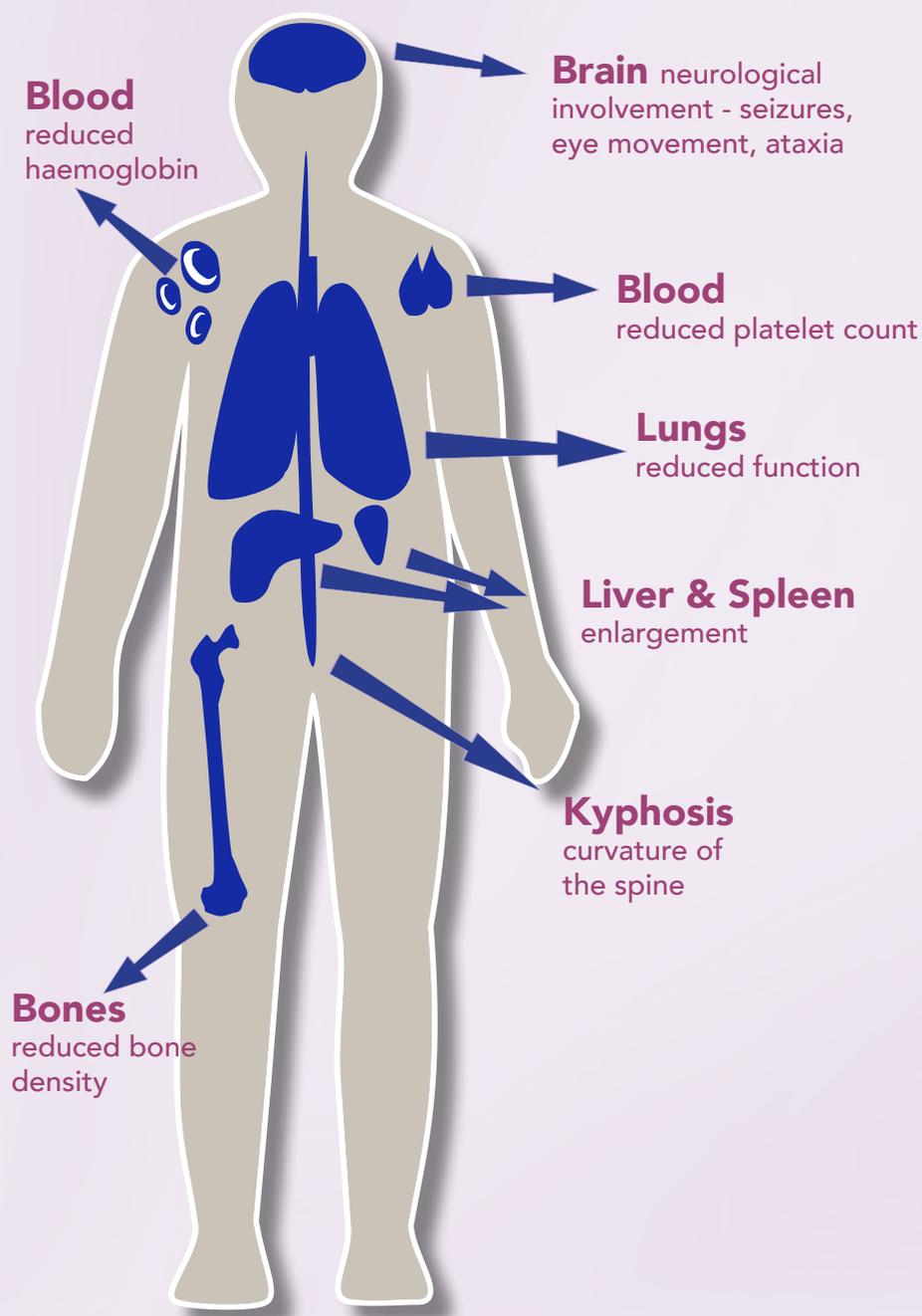


Gaucher cell

what is type 3 Gaucher disease?

Type 3 Gaucher disease, or chronic neuronopathic Gaucher disease, is an intermediate variant, between type 1 and 2. Affected patients have both visceral (the internal organs of the body, for example, the lungs, liver and spleen) and neurological (brain) involvement. However, the neurological involvement is much less severe than type 2.

Most patients have significant visceral disease which tends to respond well to treatment such as enzyme replacement therapy (ERT). For example the liver and spleen may return to normal size. However, not all aspects of the visceral disease respond well, and this results in varying degrees of chronic ill-health.



Neurological involvement, is present almost from birth and in most cases, remains very mild and stable for the majority of patients, with minimal progression, throughout life. However, for some patients it can be quite severe and progressive. Even in the "mild" group there are significant implications for day-to-day living, education, and independence.

The combination of chronic visceral and neurological involvement means that patients need careful monitoring. Equally important, as they grow to become young adults and become more independent, they need to become empowered to be able to access information themselves.

We have tried to cover many, if not all, of these issues in this booklet.

how common is type 3 Gaucher disease?

The overall incidence is less than 1:100,000 in the general population. However, the incidence varies considerably in different parts of the world. In the USA and Europe, type 3 Gaucher disease accounts for about 5% of the total Gaucher population. In countries such as China and Japan, it is more common; approximately a third of individuals affected by Gaucher disease have type 2 or 3. This is largely due to genetic differences (explained later). In the UK, approximately 10% of the Gaucher population have type 3 disease.

Geographical Distribution

Type 3 Gaucher disease is pan ethnic; that is to say, people of all ethnic groups are affected. However, in some countries, a *founder effect* is seen. A founder effect occurs when a small group in a population 'splinters' off from the original population and forms a new one. Examples of these are to be seen in the Norbottian region of northern Sweden, where all known patients are descended from just two families who settled there in the 16th century and have the L444P/L444P mutation. Also, a group of Arab patients reported from Israel in 1995, who have the D409H/D409H genotype.



Laurena



Zac & family

how is type 3 Gaucher disease diagnosed?

The process of diagnosing Gaucher disease is not always straightforward, often the patient initially visits their doctor for another problem. Although making a diagnosis of Gaucher disease is not difficult, some symptoms may resemble other diseases. The doctor may first perform other tests to eliminate more common disorders. For example, in cases where patients have low platelets, doctors may first test for leukaemia.

The diagnosis of Gaucher disease can be suspected clinically if there is;

- Enlargement of the liver and spleen, especially when accompanied by low blood counts.
- Persistent bone pain, accompanied by fractures, especially if there are acute attacks (known as crises). These are often mistaken for, and wrongly treated as, infection.
- Recurrent attacks of cough and wheeze, often mistaken for asthma and despite anti asthma medication, lung function may remain abnormal.

The diagnosis can be confirmed by a simple blood test by measuring the amount of the enzyme glucocerebrosidase in white blood cells and checking for the mutation in the Gaucher gene by looking at the patient's DNA.

Enzyme levels do not distinguish type 3 from type 1.

While the diagnosis of type 3 can be suspected on the basis of the genotype, it can only be made clinically. The most specific clinical sign is the abnormal horizontal eye movement (described in the *neurological involvement and its assessment* section of this publication).

All other neurological signs, while suggestive, are non-specific.



genotype — phenotype correlation

Genes code for proteins and proteins help our body work in different ways. Some proteins are enzymes, like glucocerebrosidase which is needed to help the body process substances. Gaucher disease results when not enough of this protein is made and this is caused by a change in the gene which codes for it; called the GBA gene. These changes in a gene are often referred to as *mutations*. These changes can be passed on through generations and to develop Gaucher disease a patient needs to have inherited one altered gene from each parent; we call these altered genes alleles.

More than 350 mutations have been reported in the GBA gene (so there are more than 350 different alleles a patient may have for this gene). The combination of two alleles is what we call a genotype for a particular disease. Some genotypes are associated with distinct phenotypes. In this section, we will discuss the ones that are relevant to type 3 Gaucher disease.

All patients with Gaucher disease have mutations in their DNA that affect the production of the enzyme, glucocerebrosidase. The most common mutation in type 3 is L444P. When a copy of this mutation is inherited from both parents, the individual has the L444P/L444P genotype.

This is the most common *genotype*, accounting for about 70% of patients. The majority of patients with this genotype have a relatively mild neurological *phenotype*, but often have quite severe visceral disease, with marked enlargement of the liver and spleen appearing in the first year of life. There are, however, some exceptions and severe neurological disease occurs in a few individuals for reasons that are not fully understood.

Another common mutation seen throughout the world is the D409H. The mutations L444P/D409H and D409H/D409H together account for about 15% worldwide. The D409H/D409H genotype have mild neurological involvement. They have very little visceral disease, with one exception i.e. involvement of the heart valves and first part of the aorta (the large vessel arising from the heart) by calcium. The involvement of the aorta, in particular, results in a striking white appearance in an x-ray called "porcelain aorta". However this is not that common in the UK.

Certain genotypes have been found to be associated with *myoclonic epilepsy* e.g. N118S. (see section on *neurological involvement and its assessment*).

The *genotype* of an individual refers to their genetic identity. It is nearly always inherited. The *phenotype* of an individual refers to their actual physical makeup, for example the colour of their eyes or hair. There is often, though not always, a strong correlation between the two, and this is referred to as the *genotype-phenotype correlation*.

Gaucher disease results from mutations in the GBA gene that is responsible for the formation of the enzyme, glucocerebrosidase.



DNA strand

Modifier Genes

It is now widely accepted that there is considerable phenotypic variation amongst patients with the same genotype (this means that patients with the same genotype have different symptoms and severity of disease). One is the presence of *modifier genes*. A modifier gene is one that influences the effect of another gene. Some genes that might fit this role (candidate genes) have been suggested. *Epigenetic factors* may also be responsible; these are "non-DNA" processes that operate within a cell and affect the behavior of a gene, rather than its structure (as mutations do). Epigenetic factors can be affected by outside influences such as aging, environment etc. A lot of work still remains to be done in this important area.



Irma & Shriya



Zaid and his Dad

how is type 3 Gaucher disease inherited?

All forms of Gaucher disease are inherited in an autosomal recessive manner. Autosomal inheritance means that the gene is located on one of the autosomes (chromosome pairs 1 through 22) rather than the sex chromosomes X and Y, males and females are therefore equally affected. Recessive means that two copies of the gene are necessary to have the disease, one inherited from the mother, and one from the father.

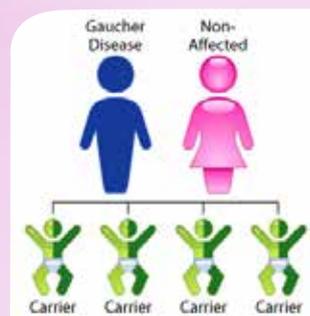
In the case of Gaucher disease, the gene for the production of the enzyme glucocerebrosidase is unable to function normally.

To develop Gaucher disease a person must have two copies of that abnormal gene (often referred to as a 'mutation'). A person with one normal and one mutated gene is a "carrier" of Gaucher disease and will not have the condition, but there is a 50% chance that they will pass the "Gaucher gene" onto their offspring. This is illustrated in the diagram below.

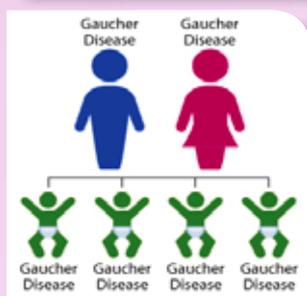
The possibilities of passing on the mutated Gaucher gene:



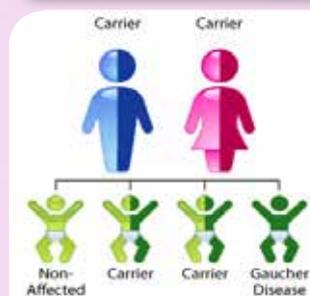
If both parents have normal genes for glucocerebrosidase, each child will inherit two normal genes, one from each parent, and will neither have Gaucher disease nor be a carrier.



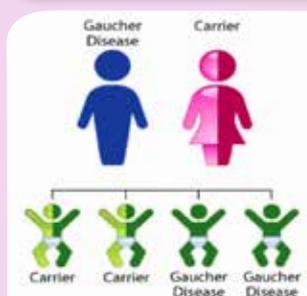
One parent has Gaucher disease and the other parent is not affected. All the children will inherit the Gaucher gene from the affected parent and become carriers, but none of the children will have Gaucher disease.



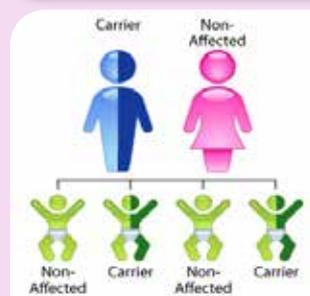
If both parents have Gaucher disease, all of their children will inherit two Gaucher genes and will have the disease as well.



Both parents are Gaucher carriers. Their children have a 50% chance of being a carrier and a 25% chance of having Gaucher disease and 25% of being neither.



One parent has Gaucher disease and the other parent is a carrier. Their children will have a 50% chance of having Gaucher disease and a 50% chance of being a carrier.



One parent is a Gaucher carrier (one mutated gene and one normal), and the other parent has two normal genes and is therefore not affected. Their children have a 50% chance of being a carrier but none of their children will have the disease.

Many of the mutations of the gene for Gaucher disease have been identified; therefore, carrier testing is possible in affected families.

If you are interested discuss this with your specialist centre.

Visceral (liver, spleen, lungs) involvement is seen in all patients with Gaucher disease to varying degrees. It tends to be more severe in type 3 than in type 1. It is therefore not surprising that the response of visceral disease to treatment in type 3 is less satisfactory. This occurs for two reasons:

- There is more *disease burden* to start with (impact of disease ie, severity)
- Certain organs and tissues do not seem to respond as well

The areas that this booklet will cover are

- Kyphosis, excessive curvature of the spine
- Enlargement of the abdominal lymph nodes (abdominal lymphadenopathy)
- Lung involvement
- Eye involvement
- Bone involvement

Kyphosis

Kyphosis is excessive curvature in any part of the spine. The curvature is from front to back, resulting in a bowing of the spine. Type 3 patients have a curve affecting the thoracic part of the spine (between the neck and the lower back). Kyphosis is seen in the vast majority of type 3 patients. The cause of the kyphosis is unclear. It is usually not present in infants and very young children, but commonly appears during childhood. A particularly striking feature is that the vertebral bones themselves appear to be normal. This difference is so striking that many people feel that it should be categorised as a neurological feature. In fact, it is included as a neurological feature in the Modified Severity Scoring Tool for type 3 (information on the scoring system is included in the section on Neurological Involvement). However, no specific neurological or muscle problems have been identified.

Kyphosis may not be obvious on clinical examination in the early stages, so it is extremely important to perform an x-ray of the spine. The x-ray should be taken from the side 'lateral position'. The thoracic spine has a normal curve. The angle of the curve is known as the angle of kyphosis, and it can be measured on an x-ray as shown in the diagram opposite.

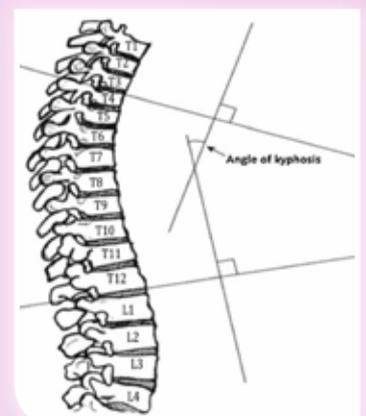
A radiologist will determine whether the angle is abnormally increased or not. In the general population, the angle gradually increases with age.

Once a kyphosis has been detected, x-rays should be taken once a year. The angle should be measured every time. In this way, an objective record over time is available; this is very useful for the doctors when it comes to making decisions about management.

Impact of kyphosis

If the kyphosis is very severe, it may impact on day-to-day living in several ways

- The person may not be able to look up or ahead properly, due to restricted movement; this can affect mobility and independence.
- The chest may not be able to expand properly; this can affect how the lungs work. If lung function is already affected by type 3 Gaucher disease (see *lung involvement* below) the overall effect on lung function can be quite significant.



Kyphosis

Assessment: Spine

All patients should have a baseline x-ray of the whole spine from front and side (referred to as anteroposterior (AP) and lateral). This should be repeated every 1-2 years. If kyphosis is detected, then a referral to a spinal specialist should be made.

Enlargement of the Abdominal Lymph Nodes

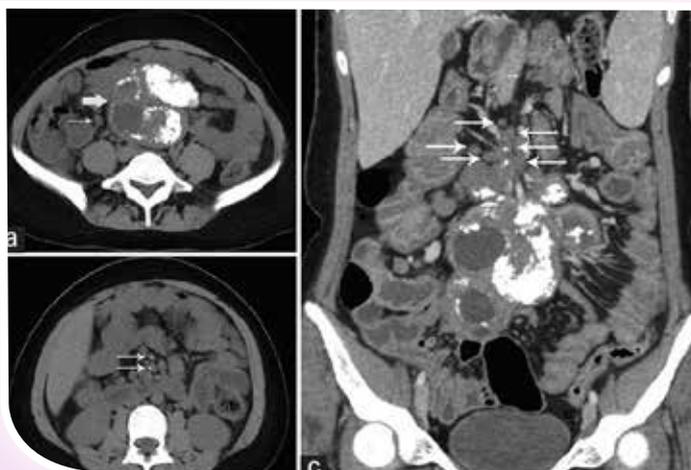
Abdominal lymphadenopathy (the term given to enlarged lymph nodes) is common in type 3 Gaucher disease. Any area of the abdomen may be involved, but the *mesenteric nodes* are the most commonly affected. These nodes are situated in the mesentery, a membranous fold attaching the bowel to the back of the abdominal cavity.

Enlarged nodes are probably present at the time of diagnosis, but their detection is difficult as they are hidden from view by the enlarged liver and spleen, and in children, examination may be very difficult due to the child being/becoming upset during examination. Therefore, they may be noticed for the first time after only a few months of treatment, when the liver and spleen have become smaller and (in the case of children) examination becomes easier.

The nodes may be discrete (separate from one another), or may join together to form a mass, though they may be separate. If the mass is large enough, it can be felt. Usually it is detected on routine ultrasound scans, to assess liver and spleen. However, unless the radiologist is asked specifically to look for the presence of lymphadenopathy, it may not be reported unless it appears unusual in size or location. It is therefore important for the doctor who is requesting the scan to specifically request examination for enlarged lymph nodes and think about using MRI as an additional imaging method if a child has symptoms which might be caused by lymphadenopathy. Most patients will have no symptoms or problems resulting from enlarged lymph nodes.

If lymphadenopathy is a problem it can be difficult to treat. For reasons that are not clear, the nodes do not respond to enzyme replacement therapy. They may stay the same size for years. In some patients, they increase in size. In the majority, this does not cause any problems, other than a feeling of heaviness or discomfort. In a small number, however, the following complications may arise:

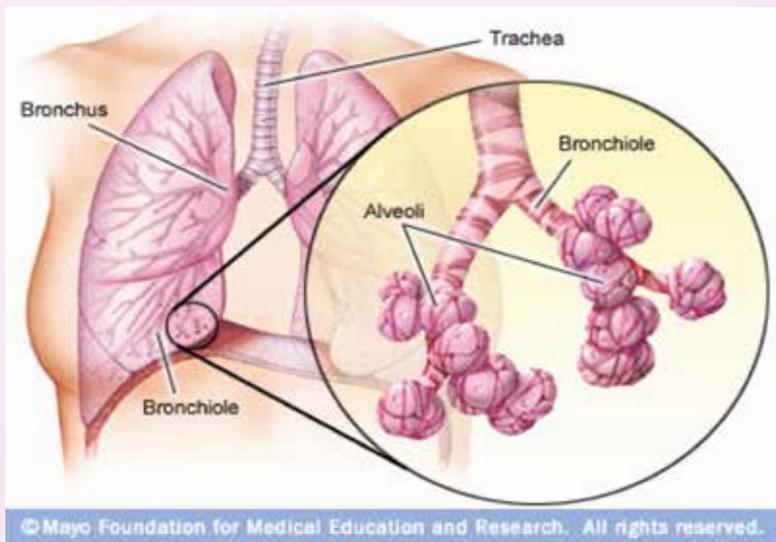
- Excessive loss of protein in the stools; this is known as protein-losing enteropathy
- Fat malabsorption (poor absorption of fat)
- Blood vessels flowing through the mass are compressed. The blood supply to some areas may be reduced, causing them to become critically compromised. Symptoms of poor blood flow may include pain in the abdomen.



Abdominal computed tomography (CT)

These complications are rare. They will have to be assessed individually as and when they arise; some success has been found with new approaches to treatment and your doctor can discuss this with you when more evidence is available.

Whilst the occurrence of lymph nodes associated with type 3 Gaucher disease is well described it is important to monitor for changes which might suggest the emergence of another pathology and which may merit further investigation such as a biopsy.



Lung Involvement

Gaucher lung disease typically affects the *alveoli*, the small air sacs at the end of the airways (illustrated on the left).

What is the role of the alveoli? The alveoli are where gas exchange takes place. Oxygen enters the blood and carbon dioxide is removed.

Whilst there is no specific clinical test that can confirm that lung signs and symptoms in someone with Gaucher disease are caused by the disease, it should be assumed that this is the case

unless proven otherwise. The assessment of Gaucher lung disease is by lung function. Standard lung function tests will not detect this. A special test known as *diffusion coefficient* needs to be performed. Unfortunately, it is not possible to do this in small children, as a minimum lung volume of about 1 litre is needed; this is achieved at approximately 6-7 years of age. Once the child reaches this age, diffusion coefficient should be added to the list of lung function tests to be performed.

Although there is no specific test for Gaucher lung disease, persistent changes on the chest x-ray which do not improve after acute symptom resolve, and/or changes on a CT of the chest, supported by the clinical history are usually fairly conclusive.

The most effective treatment is with corticosteroids. Inhaled steroids are usually commenced as soon as the diagnosis of lung involvement is made, and given regularly even in the absence of symptoms. A short course of oral steroids may be necessary if there are acute symptoms.

Symptoms in the lungs can be affected by the presence of kyphosis as the shape of the chest is changed by the shape of the spine, limiting how well the lungs can expand. Thinking about how the spine can be managed and even using simple physiotherapy techniques can be helpful in maintaining good lung volumes.

Patients who have lung involvement often take longer to recover from a general anaesthetic. Their oxygen levels remain a little low, and they may need to stay in recovery for longer. These symptoms can often be minimised by the use of a short course of oral prednisolone commenced a few days prior to a planned operation. In patients with significant lung disease, it may be too risky to undergo procedures requiring a full general anaesthetic; they should therefore be fully assessed by an anaesthetist prior to any procedures.

If there is lung involvement, a referral to a respiratory specialist is recommended.

If the patient is being treated with ERT, the frequency and severity of the acute lung symptoms should gradually reduce over a period of time and it is usually possible to eventually stop inhaled steroids. Care should be taken while stopping steroids, as lung function may remain abnormal even in the absence of symptoms.

Assessment: Lung function

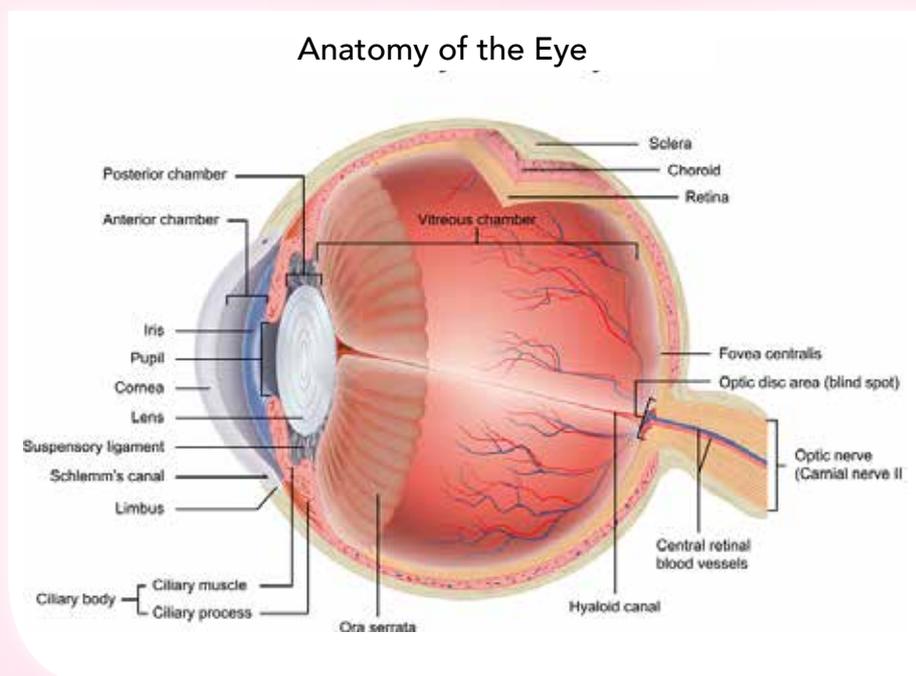
All patients should have chest x-rays and age-appropriate lung function tests at baseline (if possible), whether they are symptomatic or not. These should be repeated every year. A diffusion coefficient should be measured as soon as it is feasible to do so. The Gaucher specialist will decide if and when a referral to a respiratory specialist should be made.

Eye Involvement

Eye movement abnormalities in type 3 are due to neurological control and not the eyes directly. However, direct involvement of the eyes by Gaucher disease does occur. The following complications have been described:

Vitreous opacities (floaters)

These are small particles seen in the vitreous humour, referred to as the vitreous, a clear gel at the back of the eye, between the lens and the retina, as illustrated in the image below.



The vitreous is normally clear. However, sometimes small specks are seen. They are thought to be undissolved vitreous gel. Vitreous opacities are often asymptomatic. However, they cast shadows on the retina at the back of the eye and may appear as small dark objects floating across the field of vision. Symptomatic vitreous opacities (or SVO) are known as floaters.

In Gaucher disease, floaters seem to be more common than in the general population. Gaucher cells have been found in the vitreous, and often there is inflammation (known as vitritis). Whether this is responsible for the increased incidence is not clear.

In a small number of people, the vitreous can start to fill up with these floaters, and vision may be severely impaired. The vitreous becomes "sticky" and starts to pull away from the retina. Sometimes it may detach from the retina; this complication is known as *posterior vitreous detachment* or PVD. Occasionally the retina itself may separate from the layer underneath; this is known as *retinal detachment*.

In the image below, you will see the small white deposits, these are the vitreous opacities in a patient with type 3 Gaucher disease.



Vitreous opacities in a patient with type 3 Gaucher disease

Assessment: Eyes

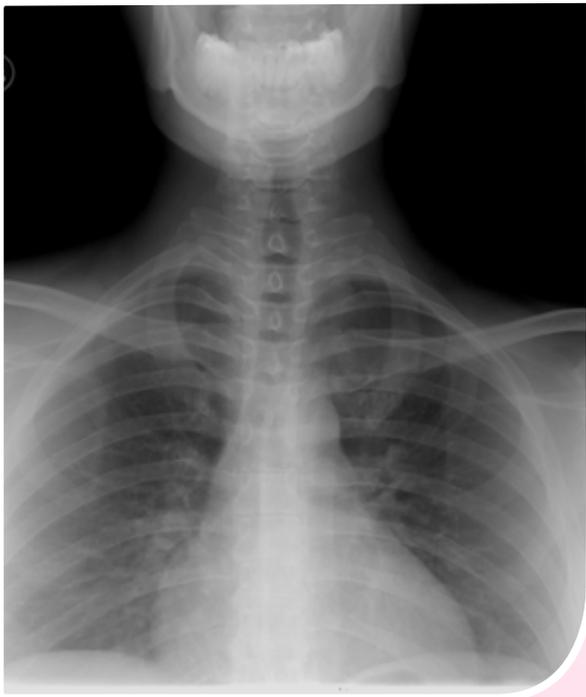
All patients should be referred to an ophthalmologist at or soon after diagnosis for a detailed examination, which should include measurement of the intraocular pressure. The specialist will decide, depending on the presence and severity of eye lesions, how frequently follow up is required.

Bone Involvement

Bone problems are one of the most common manifestations in all types of Gaucher disease. It can result in pain, disability, and reduced quality of life. The stored fatty materials in the bone and bone marrow cause abnormalities in blood cell production and the balance of cells which build up (osteoblasts) and break down (osteoclasts) bone. This results in problems with remodelling of the skeleton, reduced bone mineral density and a tendency to abnormal growth of bone marrow cells including plasma cells that make antibodies. Other findings include *cortical bone thinning*, *fragility fractures*, *avascular necrosis* and *osteolytic lesions* which are areas where the bone has been 'eaten away' by bone cells. Secondary arthritis can occur in areas of bone damage.

Assessment: Bone involvement

Regular assessment of bone density, marrow infiltration, and the skeleton recommended. MRI is the gold standard for monitoring bone involvement. Plain X-ray may also be helpful where MRI is not available.



A DEXA scan is a test of the lumbar spine and left or right hips, are recommended to monitor bone density. Management of bone disease includes Gaucher-specific therapy i.e. Enzyme replacement therapy, calcium and vitamin D and management of pain and orthopaedic complications. In children, bone density is only measured at the lumbar spine.

A DEXA scan is a test that assesses whether you have normal bone density, low bone density (also referred to as osteopenia), or osteoporosis.

Other Assessments

Height and weight should be plotted on a growth chart at every visit; this is important to check that ERT is effective and to signal to clinicians where other problems might be developing e.g. abdominal lymphadenopathy (see page 10 for more information).

Speech and Language Therapy (SALT) - an assessment or referral may be made if there are difficulties with communication, eating, drinking or swallowing.



MRI Scanner

neurological involvement & its assessment

Neurological Features

The earliest involvement of the brain is seen in the *brainstem*. This is the region of the brain that connects it with the spinal cord, and consists of three parts, the midbrain, the pons and the medulla, as illustrated in the diagrams on the right.

Most of the nerves to the face and neck arise from the brainstem. Therefore, the earliest signs and symptoms relate to structures in these areas, including eye movement problems, squint, and hearing problems. Importantly, however, the centres for higher function (intelligence, etc.) are not located in the brainstem. Therefore, higher function is not affected for a long time in the majority of patients.

Eye Movements

In the vast majority of patients, the earliest evidence of neurological involvement is an abnormality of horizontal eye movements. The reason for this is that the centres that control eye movements are located in the brainstem, as illustrated in the diagram above.

First, let us consider what normally happens when an object passes in front of us and we wish to continue looking at it, or if we just wish to look from one place to another. We can do this in one of three ways. We can rotate our entire body keeping our eyes and head still, we can rotate just our head, or we can move just our eyes. It is the last one (moving our eyes) that is relevant in type 3.

There are different types of eye movements but the relevant ones to consider are *smooth pursuit and saccades*.

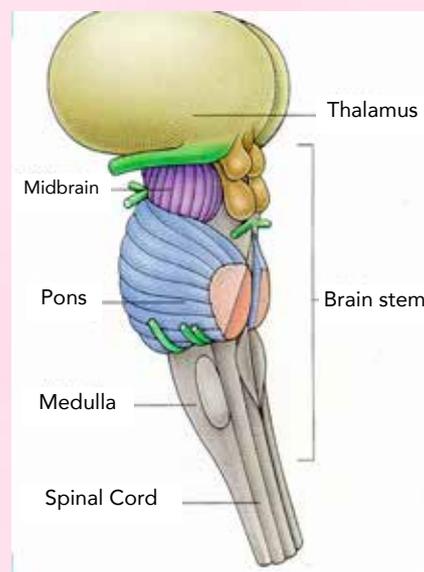
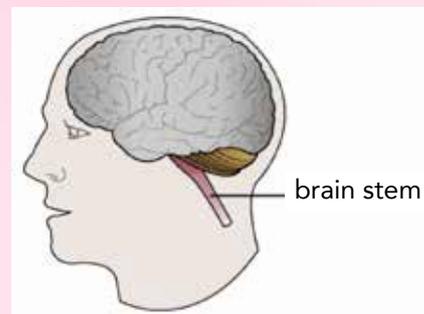
In smooth pursuit the eyes move smoothly instead of in "jerks". It is called pursuit because this type of eye movement is made when the eyes follow an object. To test smooth pursuit, the examiner asks the patient to look at their finger, then keeping their eyes fixed on the finger while the examiner's hand is moved in a straight line across the patients face.

Saccades are eye movements used to rapidly refixate from one object to another. The examiner can test saccades by holding the index fingers of both hands in front of the patient and asking the patient to look back and forth between the two fingers. The fingers are placed close to each other to start with and gradually moved apart.

Both smooth pursuit and saccades can be either horizontal (side to side) or vertical (up and down). In Gaucher disease, although vertical saccades are involved, it is the horizontal movements that are more relevant.

In type 3, smooth pursuit is often normal, at least in the early stages. As the condition progresses, the patient needs to blink and rapidly move the head (head thrusting) in order to keep following the examiner's finger.

By contrast, horizontal saccades are always abnormal. With the examiner's fingers placed close together, one may not notice any abnormality. However, as the examiner moves his fingers further



apart, the patient finds it more and more difficult to move their eyes from one finger to the other, until a point is reached when they are no longer able to do so without blinking their eyes and head thrusting

Since the diagnosis of type 3 is a clinical one, it is crucial that the correct procedure for testing saccades is followed. If only smooth pursuit is tested, the diagnosis may be missed.

As the condition progresses, smooth pursuit also becomes involved. Vertical saccades become affected as well (in fact they are usually abnormal initially, but this can only be detected using special equipment, and may therefore escape detection by the naked eye). In extreme cases, the patient may eventually lose their ability to move their eyes either horizontally or vertically; this tends to happen over time.

In very young children, or children who are unable to comply with testing as described above, it may be necessary to use special equipment.

Squint

Squint (medical name strabismus) is a condition where the eyes do not look in the same direction. While one eye looks forwards to focus on an object, the other eye turns either inwards, outwards, upwards or downwards.

Most squints occur in young children. A child with a squint may stop using the affected eye to see with. This can lead to a form of visual loss called amblyopia, which can become permanent unless the squint is treated early in childhood.

Whatever type of squint a child has, it may be described in different ways by the professionals looking after your child's eyes. The squint may be described depending on:

- When it can be seen - *constant*, if it is visible all the time and *intermittent* if it comes and goes.
- When it is first noticed - *infantile* if it develops within the first 6 months of life and *acquired* if it occurs later.
- How the eye turns - if the turn is inwards it is called a *convergent squint* or *esotropia*, if the turn is outwards it is called a *divergent squint* or *exotropia*, if the turn is upwards it is called a *hypertropia*, if the turn is downwards it is called a *hypotropia*.
- Whether particular muscles are involved - *incomitant* if the squint changes when looking in different directions and *concomitant* where the squint is the same when looking in every direction.

It is important to remember that in the general population, about 2-3% of children will develop a squint. However, it is more common in type 3 Gaucher disease than in the normal population. The squint that is seen in type 3 is usually a convergent squint (eyes turning in).

Assessment: Squint

There are a number of tests used to detect a squint. A detailed explanation of these tests is beyond the scope of this booklet, but the eye specialist will provide more information if and when testing is required.



Kavian

Hearing

Hearing itself can be normal. There are two problems related to hearing that need to be investigated even if hearing is normal.

- The hearing pathway from the ear to the brain may be affected. Testing for this is carried out by the *brainstem auditory evoked response* test (BAER). This BAER test is done to check that the pathway from the ear to the brain is functioning properly, by recording the responses to clicks or sounds delivered through headphones placed over the ears.

Why is this test important?

The test is important because it tells us that the brainstem is involved and this is only seen in types 2 and 3. It is therefore useful as a diagnostic test, especially in children in whom eye movement testing is difficult or impossible. As the condition progresses, the abnormality becomes more pronounced. Since one can almost predict that this will happen, and since there is no treatment that will result in improvement, the test really has little or no role in clinic beyond a diagnostic one.

- The patient may experience difficulty in suppressing background noise. Imagine that you are in a noisy room, with a lot of background chatter. The person next to you starts talking to you. For someone without type 3 Gaucher disease, the background noise is automatically suppressed so that one can hear what the person is saying. However, people with type 3 have difficulty in doing this. It is sometimes mistakenly referred to as cocktail party syndrome. It has important implications for education (see *impact on education* section for more detailed discussion).

They may have an *auditory processing disorder* (APD). Typically, the brain processes sound seamlessly and almost instantly. Most people can quickly interpret what they hear. This is known as auditory processing. Children with APD can have different sorts of problems:

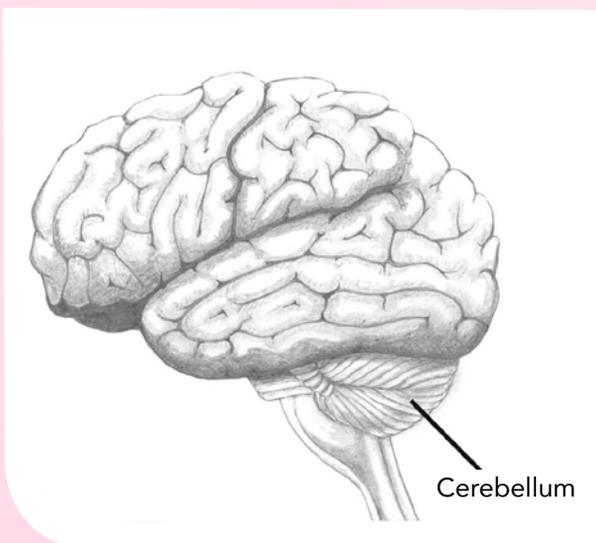
- **Auditory discrimination:** The ability to notice, compare and distinguish between distinct and separate sounds. The words seventy and seventeen may sound alike, for instance.
- **Auditory memory:** The ability to recall what you've heard, either immediately or when you need it later
- **Auditory sequencing:** The ability to understand and recall the order of sounds and words. A child might say or write "ephelant" instead of "elephant," or hear the number 357 but write 735.

It should be pointed out that APD is quite common. Figures vary but approximately 5% of general population are thought to have APD. It is unclear whether it is more common in type 3.

Ataxia

Ataxia refers to the difficulty in control of posture and movement/balance, resulting in poor coordination. Ataxia is a symptom, not a disease or a specific diagnosis. It can be due to many different causes. Cerebellar ataxia refers to ataxia due to pathology in the cerebellum, which is located at the back of the brain, as shown in the diagram.

People with this disorder have a broad-based gait, which means that their feet are wider apart when they walk, because of their unsteadiness and can be in danger of falling. In addition, they may experience problems in maintaining balance while sitting and standing.



A tremor of the hands may be seen. This increases as the person moves their hand towards an object with the intention of holding or touching it, hence it is called an *intention tremor*. The overall result is that the person can appear clumsy. They may have difficulty in walking or holding objects. As the condition progresses, independent walking can become more challenging and this may result in the patient needing a wheelchair for frequent or infrequent use, however this is not inevitable and the majority are able to walk independently.

Assessment: Ataxia and Dystonic movements/posturing

A scoring system has been developed for neurological assessment by Dr Elin Davies (Journal of Inherited Metabolic Disease: October 2011, Volume 34, issue 5). It is known as the modified Severity Scoring Tool (mSST). It has 13 components. Each is scored according to severity and a total score is calculated. This is a useful objective way of monitoring the neurological status over a period of time. Any qualified person can administer it. Importantly, the results are reliable between different observers. That is to say, the score will be the same regardless of who administers the test. It is recommended that mSST scoring be carried out at least once a year as part of the annual assessment.

Seizures (Fits)

The likelihood of seizures occurring is difficult to predict in a given individual but they are more common in people who have more severe neurological involvement, although mildly affected patients can have seizures as well. Different types of seizures can be seen and some people may have more than one type of seizure.

Myoclonic seizures are clusters of rapid jerky movements, that can affect the face, limbs and muscles of the trunk, they can indicate more severe neurological involvement. They tend to occur in people with certain genotypes (see information on *genotype-phenotype correlation*).

Symptoms of seizures will be managed by a neurologist, who will recommend medications called anticonvulsants.

Involuntary Movements

As the name suggests, involuntary movements are movements over which we have no control. There are several types of involuntary movements; only the ones relevant to type 3 Gaucher disease will be discussed here.

Dystonia

This is the term used to describe uncontrollable and sometimes painful spasms caused by incorrect signals from the brain. This causes muscles to spasm and pull the body incorrectly. This forces the body into twisting, repetitive movements or abnormal posture. If persistent and severe, they may result in pain and will have to be treated with specific medications on the advice of a neurologist.

Intention Tremor

This has already been discussed under Ataxia (see above).

Myoclonus

The term myoclonus refers to short, jerky movements occurring singly. They can be seen in the general population, and are particularly common when falling asleep (hypnagogic myoclonus). They can be quite troublesome, for example if they occur when holding a cup or a spoon. However, they are quite different from myoclonic seizures (see above).



Mia

Assessment: Investigation of Seizures

If seizures occur, their investigation and management should be overseen by neurologists. There may be more than one neurologist involved, both at the tertiary (Gaucher centre) centre and at the local hospital. This is because:

- Changes in medication may need to be made from time to time
- Occasionally hospital admission is required for seizure management; this would nearly always be to the local hospital

Intellectual Function

Although specific problems with intellectual function may be seen during the school years (see *impact on education* section), by and large it is fairly well preserved during childhood. Intellectual disability becomes more apparent in late adolescence and early adult life as young people are challenged more academically. They don't necessarily lose intelligence or skills but the difference between them and their peers becomes more apparent, and they may not meet their previously anticipated potential predicted in early childhood.

This is by no means a consistent pattern; there is a very wide spectrum. Overall, a degree of developmental delay is seen in about 50% of children at the time of diagnosis. When doctors and psychologists measure "development" they look at all aspects of development; physical abilities, hearing, vision and thinking ability. The delayed development in Gaucher disease is usually dominated by physical delay in things like walking and this catches up to normal rates when ERT is started. Some children, particularly if they have seizures at an early age or other significant neurological symptoms will also have delayed intellectual development, their ability to learn and understand things will be slower than their peers.

Problems with executive function are very common in type 3 Gaucher disease. Executive function refers to skills that we all use to organise information that we receive and act on it. Depending on age, you may notice 'problems' or 'difficulties' with the following:

- **Impulse control**
- **Emotional control**
- **Flexible thinking (adjusting to the unexpected)**
- **Working memory (ability to hold information for processing and guidance of decision making and behaviour)**
- **Self-evaluation**
- **Planning and prioritizing**
- **Task initiation (being able to start a task)**
- **Organisation**

Assessment: Intellectual Function

It is not necessary to carry out detailed testing of intellectual function at every visit. However, a general description of your child's progress and behaviour, including school performance, should always be discussed. In young children, the doctor will ask about developmental milestones. These are skills such as taking a first step, smiling for the first time, and waving "bye bye". It is a good idea to discuss these at every visit, as any deviation from normal may suggest an underlying problem for which there may be a helpful intervention available.

For older children, there are specific assessment tools. They do not need to be administered unless there are concerns, either at home or at school. It is quite useful to administer them at key stages (e.g. entry to primary school, transition from primary to secondary school, leaving secondary school) as information gained can be useful for the family as well as the educational authorities, and can help determine the individual special educational needs for the child.

Tests of intellectual ability (also known as cognitive function) are usually administered by a qualified psychologist. In the educational setting this would be an educational psychologist, while in the hospital it would be a clinical psychologist. A general age-appropriate assessment of function, is usually performed first. These consist of a series of tests assessing different aspects of intelligence. This gives the psychologist a general overview of the child's level of functioning. If this flags up concerns in specific areas, for example reading or understanding, more specific tests can be carried out to examine these areas further. At the end of the assessments, if there are any concerns, the psychologist will suggest ways and means of addressing these.

As mentioned earlier, people with type 3 Gaucher disease may have specific problems in intellectual function during childhood. They may not be very obvious, but it is very important that they are identified as early as possible, so that appropriate support measures can be implemented (see *impact on education* section).

Testing of intellectual function is also referred to as *cognitive testing*. It is tiring and time-consuming, difficult to explain the tests and can be difficult to explain the results. Any measures often take a long time to achieve results, and may not be apparent to the child. It is important to incentivise them, for example, by doing the tests at key stages in education, it can be explained that we are trying to find the best school for them, and make sure they get help if necessary.

Behavioural Problems

The availability of enzyme replacement therapy (ERT) has significantly improved the life expectancy of patients. As a result, problems that had not been reported in the past are becoming "unmasked".

There has been an increasing awareness in the last few years of behavioural problems in older children and young adults. It is well known that people with chronic illness, even when it does not involve the brain, tend to have more behavioural/psychological problems than the general population. So, it isn't surprising that this is even more evident when the brain is involved.

Some of the problems that have been observed are:

- Depression
- Anxiety
- Low mood
- Manic episodes
- Oppositional defiant disorder
- Impulsivity
- Depression
- Negative and disruptive behaviour

A small number of children may exhibit extremely disturbed behaviour, such as severe attention deficit disorder. Referrals can be made to Mental Health Services and psychology.

In addition, many parents show levels of distress warranting professional attention and should discuss this with their general practitioner (GP).



Assessment: Behaviour

This may be needed if parents or school have concerns about the child's behaviour. Problems such as attention deficit disorder may be identified during general testing, and further assessment performed as necessary by the psychologist. However, more serious problems such as aggression or tendency to self-harm may require referral to a psychiatrist.

Overall Neurological Picture

Now that we have discussed the various neurological problems that can be seen in type 3, let us look at the common neurological presentations (also known as phenotypes). For convenience, we will also discuss the genotype-phenotype correlation (see page 8 for information on genotype – phenotype correlation).

The most common presentation is seen in children who present in early childhood, usually in the first year. The most common genotype is L444P/L444P. Abnormal horizontal saccades are often the only sign of neurological involvement for many years. Gradually, other signs such as ataxia and auditory problems appear. Intellectual function is usually well preserved throughout the early years. Gradually, the specific intellectual difficulties referred to above appear. Seizures may appear during childhood, but often don't usually appear till adult life and many patients will remain seizure free.

A small number of children with this genotype may have severe behavioural and neurological problems from the outset. The reasons for this are not clear. It is known that there are modifier genes that may alter the clinical picture.

People who have more complex genotypes tend to have more severe neurological problems from the outset. The eye movements may be noticeably abnormal, seizures may appear very early, and there may be severe learning disabilities.

Myoclonic epilepsy is seen more often in people with certain genotypes.

Although there is now a lot more information available about type 3, than when ERT first became available, ERT has not been around for long enough to know what to expect over the course of a lifetime.

Assessment: Neurological Involvement

When discussing neurological assessment, it is important to bear a few things in mind.

- The assessment of neurological involvement in routine clinical practice is different from that which is carried out as part of a research study or clinical trial. In a clinic, the focus is on function and how this impacts on day-to-day activities
- The type of assessments will need to be geared to the age of the patient and the extent to which they comply with examination. Sometimes, at diagnosis and for some time thereafter, only a limited examination may be possible, especially in young children who may be very irritable
- It is recommended to see a neurologist on a regular basis. In fact, it is a good idea to have a neurologist as part of the medical team

Neurological Examination

A full, age-appropriate neurological examination should be performed at every visit to the specialist Gaucher clinic. This should be a standard neurological examination with particular attention paid to the following:

Eye movements

The method used to assess eye movements depends on the age of the child.

- In very young children, observation of the child while being rotated rapidly in the parent's arms.
- In older, more compliant children, and adults, saccades can be looked for in the clinic

Whatever technique is used, it is very important, as mentioned above, to observe saccades (see page 14) and not smooth pursuit. Eye movements should be checked at each visit, to see if smooth pursuit and vertical saccades become abnormal, as this can impact on day to day function. An examination by a neurologist is recommended every 2-3 years.

Role of CT/MRI Scans

Computed tomography, more commonly known as a CT scan, is a diagnostic medical test that, like traditional x-rays, produces multiple images or pictures of the inside of the body.

It differs from a standard X-ray as it produces pictures of cross-sections of the brain or spine. It also provides greater detail than traditional x-rays, particularly of soft tissues and blood vessels.

MRI (magnetic resonance imaging) scanning uses magnetic fields and radio waves to create pictures of tissues, organs and other structures within the body, which can then be viewed on a computer. This means that, unlike some other modes of medical imaging, there is no exposure to X-rays or any other damaging forms of radiation.

The main differences between the two are relevant to type 3 is that an MRI scan provides much more detail of the brain structure than a CT scan and does not involve any radiation. MRI scanning in young children often requires the use of general anaesthesia, whereas a CT scan can often be performed without one.

The MRI brain scan may show abnormalities, but these tend to be non-specific and appear to have little correlation to intellectual functioning or seizures. An MRI may be performed at initial presentation. Regular scans are probably unnecessary and should only be done if a patient has new neurological symptoms which are not typical of type 3 Gaucher disease, to look for alternative and treatable causes.

Below is a list of the suggested schedule of assessments.

At initial presentation:

- Full neurological examination including modified Severity Scoring Tool (mSST)
- Eye movements assessments
- Hearing (standard hearing tests and BAER)
- MRI scan of brain - not always

Follow up:

- Neurological examination and mSST at each visit
- Eye movements at each visit
- Hearing once a year or more often if there are concerns



Gaucher specific treatment

The management of the visceral disease of type 3 Gaucher disease can be considered under two headings; Gaucher specific treatment and clinical management. These two topics are discussed in the next two chapters.

Specific treatment for Gaucher disease

Only two specific forms of treatment are clinically used for type 3 - enzyme replacement therapy (ERT - middle illustration) and substrate reduction therapy (SRT - bottom illustration)

Enzyme Replacement Therapy (ERT)

See insert on Homecare for more information. ERT is a bi weekly intravenous injection. The recommended starting dose of ERT in type 3 is 60 units/kg every two weeks. Each patient's dose will be decided by their specialist consultant.

ERT is very effective in treating visceral disease. The specific assessments needed for type 3 are discussed in the section *non-neurological disease and its assessment*. As discussed, certain organs appear to be more resistant to ERT. These are discussed under *clinical management*.

There is no evidence that ERT crosses the barrier between the body and the brain and therefore there is no expectation that the neurological symptoms will get better with ERT, even at high doses. Therefore, the dose of ERT should be determined solely by the extent and severity of visceral disease.

Substrate Reduction Therapy (SRT)

SRT is an oral therapy taken daily. There may be a role for SRT in the management of specific problems; the Gaucher specialist will discuss this with individual patients as and when the need arises.



In Gaucher disease, it is as if there are too many leaves to be dealt with by one rake, so a leaf pile accumulates.



Enzyme Therapy (ERT)

With ERT, it is as if more rakes are made available, so you are able to get rid of the leaves.



Substrate Reduction Therapy (SRT)

With SRT, it is as if fewer leaves fall from the tree, so the rake available is adequate to get rid of the leaves.

Possible Research and Clinical Trials

Information on research and clinical trials for type 3 Gaucher disease can be found on the Gauchers Association website at:

www.gaucher.org.uk

More information can be found in the inserts to this booklet.

As discussed previously in the introduction and in the section *non-neurological disease and its assessment*, the non-neurological disease responds very well to ERT on the whole. However, some of the visceral problems do not respond well to ERT, and so particular attention needs to be made to them. These are:

- Lungs
- Abdominal lymph nodes
- Kyphosis
- Eyes

The management of these are suggestions only, as every patient should be individually assessed and management planned accordingly. Furthermore, management recommendations may change in the light of new findings.

It is important to cross reference this information with the section on non neurological disease and its assessment.

Lungs

Although Substrate Reduction Therapy (SRT - see page 24 for further details) is not licensed for use in type 3, in the clinical trial of the SRT Zavesca in type 3, the lung function improved in several patients. It is possible, therefore that SRT may have a beneficial effect on the respiratory problems. Should they not respond to a combination of ERT and steroids, SRT may be worth considering. The Gaucher specialist will decide this.

Abdominal Lymph Nodes

If malabsorption becomes an issue, the patient may need to be managed by dietary modification or, rarely, parenteral nutrition (giving nutrition intravenously). Management can be very difficult, and is complicated by the fact that enzyme replacement therapy does not seem to help. Referral to a gastroenterologist may be necessary.

There has been a recent case report of protein losing enteropathy in a patient who was already on ERT and substrate reduction therapy responding to the addition of oral budesonide (a steroid preparation).

Removal of part or all of the mass is technically very difficult, as it usually has blood vessels running through it.

Kyphosis

The management of kyphosis depends on the severity, flexibility and the age of the person. In the early stages, the curve is mild and the spine more flexible. Referral to a spinal specialist should be made at an early stage. In most cases a "wait and watch" policy is all that is required. If the angle of the curve increases, then at some point intervention may be needed. Bracing is usually the first line of management if the curvature is not too severe, the spine is flexible and there is at least a year of growth left. Two decisions need to be made; which type of brace to use, and for how many hours a day it should be worn. Different types of braces are available; the specialist will decide which type is best. Young children may not tolerate the brace very well, especially in hot weather.

The spinal specialist will decide how often monitoring is required. In general, it is once every year. During puberty, it may be necessary to monitor more frequently. Puberty is associated with a growth spurt, and the curvature may increase during this period.

Surgery may be required if the curvature increases despite bracing. It is needed only very infrequently. The timing of surgery, and the type of operation required, will be decided by the spinal specialist, and are outside the scope of this booklet. One point to remember, however, is that bone density is often reduced in Gaucher disease. If the vertebral bone density is very low, it may be sensible to treat this before surgery is performed. Whether or not surgery should be deferred, and for how long, is a decision that should be made jointly between the Gaucher specialist, the spinal specialist and the patient.

It should be pointed out that *scoliosis* (sideways curvature of the spine) may also develop. Therefore, x-rays of the spine should always be done from both the front and the side. Scoliosis in the absence of kyphosis is very rare in type 3. The management of scoliosis is outside the scope of this booklet, but the spinal specialist will be able to advise on its management.

Eyes

All newly diagnosed patients should have a baseline eye examination. This should include a detailed examination of its various compartments. It is important that this be performed by a hospital eye specialist; an optician assessment is not enough.



Vitreous opacities

In most people, symptomatic vitreous opacities (SVO) or floaters are harmless and do not interfere with daily activity. However, in excess they can interfere with vision. This can affect their ability to read books or the board in an educational setting and has implications for education.

In an earlier chapter, we discussed the complications of posterior vitreous detachment (PVD) and retinal detachment. PVD can cause symptoms such as floaters, little flashes of light, or a cobweb effect across your vision. Some people get all three symptoms and others may only get one or two. Some people get a lot of each of these symptoms and others hardly any. Importantly, these same symptoms might mean there is a more serious problem, such as a retinal tear, which needs urgent attention. You will not be able to tell the difference between floaters and flashes caused by PVD or retinal detachment. The only way you can tell is to have your eyes examined by an ophthalmologist or optometrist. If you suddenly experience any of the following symptoms, make sure you have your eyes examined as soon as possible - preferably on the same day or within 24 hours:

- A sudden appearance of floaters or an increase in their size and number
- Flashes of light and/or a change/increase in the flashing lights
- Blurring of vision
- A dark "curtain" moving up, down or across your vision, as this may mean that the retina has already partially detached

Removal of the vitreous (an operation known as vitrectomy) is sometimes required. Infection is a known complication of this surgery. For this reason, it should not be undertaken lightly, as patients with floaters usually have good visual acuity.

Occasionally the opacities block the circulation of fluid in the aqueous humour, a clear fluid seen at the front of the eye (this is necessary to preserve healthy function in the eye). The fluid accumulates and the pressure increases, resulting in glaucoma (damage to the optic nerve).

These complications may develop despite enzyme replacement therapy and additional treatment may be required. For these reasons, it is recommended that all patients with type 3 be referred to an eye specialist at an early stage and regularly monitored.

Anaesthesia

The administration of general anaesthesia to patients with type 3 can carry a certain degree of risk. The vast majority of patients will not have any problems. However, it is important to understand what the risks are and the precautions that can be taken.

Quite often ventilation is accomplished by placing a mask over the nose and mouth. However, sometimes it is necessary to insert a tube into the airway through the glottis (the space between the vocal cords). This is known as *intubation*. The size of tube used will depend on the age and size of the patient.

Once the operation or procedure is over, a certain amount of time will be needed for recovery while the patient takes over the work of breathing themselves.

So, the issues to consider are

- Ease of intubation
- Ease of ventilation
- Ease of recovery

Intubation

This is usually not a problem. However, if the patient has *stridor* while awake it indicates a narrow glottis. Such patients may be difficult to intubate and a smaller tube than usual may be required. It is sensible to have a few smaller size tubes ready in case. In particularly severe cases, it may be sensible to perform a tracheostomy beforehand.

Ventilation

The lungs may be rather stiff and difficult to ventilate. This may result from several factors, either alone or in combination:

- Gaucher lung disease
- Kyphosis
- Abdominal distension resulting from enlargement of the liver and spleen

Recovery

This may take longer than anticipated, with oxygen needing to be administered for longer than is usually necessary.

These last two issues (i.e. difficult in ventilation and prolonged recovery) can be addressed to some extent by taking the following steps:

- Perform lung function tests pre-operatively if there are symptoms of lung involvement or significant kyphosis. Results should be reviewed by the anaesthetist
- If there are symptoms such as recurrent attacks of coughing and wheezing, consider a short course of steroids, to be commenced 2-3 days earlier and continuing for a couple of days afterwards



It is best to consider the impact on daily living at different ages. A few points should be emphasised at the outset:

- These descriptions apply to the majority of patients (about 70%) who will have the L444P/L444P genotype. Others tend to have more variable neurological problems
- The majority of patients are now being treated with ERT, and this will modify the picture considerably

Birth - early childhood

Pregnancy and delivery are usually quite normal. During the first year, rapid enlargement of the liver and spleen may become evident. This can result in breathing difficulty as a result of the abdomen pushing upwards on the chest. The abdominal distension may also interfere with feeding.

The majority of children with type 3 have lung disease. Repeated episodes of cough and wheezing are common. Respiratory symptoms such as cough and wheezing often appear at this stage. As described in the section *non-neurological disease and its assessment*, it is important to consider the possibility of Gaucher disease as the cause, while remembering these are common symptoms in otherwise well young children too.

The enlargement of the liver and spleen means that the diagnosis of Gaucher disease will often have been made within a few months of first appearance. However, neurological disease is sometimes not obvious at this stage as it is very difficult to detect the abnormal eye movements.

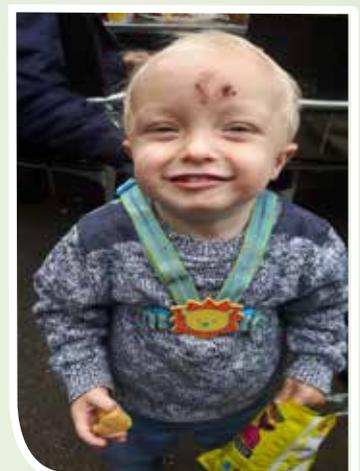
If ERT is available it will have been started after diagnosis, and the abdominal distension will gradually reduce. Feeding will improve, the child will become less irritable, they will have more energy and their growth often improves. For some patients choking can be a problem and this can be the first sign of neurological involvement, where this occurs certain foods should be avoided and a referral to a speech and language therapist (SALT) may be made

By this time, neurological problems/symptoms start appearing; they will appear in approximately 50% of patients before the age of 2 years. The majority have problems with horizontal gaze. The most common manifestations are inability to look to the left or right without moving their head, abnormally slow smooth pursuit and convergent squint (see section on neurological involvement and assessments). Some patients will also have difficulty in looking up or down.

If DNA testing is available, it will often have been done at diagnosis, and the genotype will be known. This will help the doctors to provide a more accurate long-term outlook. It should be borne in mind that such predictions can only be approximate; every patient is unique.

The neurological involvement in early childhood is very variable; some of the things which can occur can affect learning and so it is important to be vigilant. Hearing impairment is common and can significantly effect both a child's learning in the classroom and their social development outside the classroom.

Young children sometimes find the playground and PE lessons difficult. Children are unable to look around quickly, they may struggle to hear clearly in noisy environments, they may have mild balance problems and



Masen

their movements are not as coordinated as other children. This can result in a quite disorientating experience; efforts should be made to support children to relieve anxiety in these situations and not exclude them. Sometimes these difficulties manifest as withdrawal from participation and in some children, it may result in behavioural problems.

Behaviour is reported in some patients to be problematic and there are children with type 3 Gaucher disease and autistic spectrum disorders. At the moment, not enough research has been done to determine whether these difficulties are a result of neuronopathic Gaucher disease or not, however we do know that all chronic diseases in children and all neurological diseases in children tend to increase the likelihood of both behavioural and intellectual disorders. As discussed later, assessments should be made by an appropriately trained psychologist where there are concerns.

Older children and adolescents

Children presenting after the age of 5-7 years tend to have less severe visceral disease than, those presenting earlier. Those diagnosed earlier will have been on ERT for some time, and therefore visceral disease will have considerably improved. However, the respiratory signs tend to persist, even in children who have been treated with ERT from an early age. Abdominal lymphadenopathy (see section on *non-neurological disease and its assessment*) also often becomes apparent during this period, usually on a routine scan.

The neurological signs and symptoms are largely similar to those seen in younger children. In the majority of children, there will have been very little, if any, progression. However, since they are more mobile, ataxia (difficulty with balance) may be seen. Patients presenting earlier often have more severe neurological problems, such as myoclonus, dystonia and seizures.

Most children have started school by this time (see *impact on education* section for more information).

As they get older, children will start to become more independent. Eating and drinking usually remain unaffected, although there are some suggestions from talking to patients that they modify their diet early in childhood to compensate for any difficulties with coordination, which makes the complex process of swallowing hard. Swallowing may become problematic in some; this is called dysphagia. It may take longer to finish a meal, and occasional choking may be seen. If this is an issue, a referral to a speech and language therapist should be made.



Naheed, Saphia, Sara, Irma, Radhika, Nadia & Maddie

Intention tremor and coordination make dexterous movements (detailed and coordinated movements) difficult and can cause difficulty in holding a cup or utensils, dressing and undressing. Myoclonus can affect this as well. Many patients report that they may be holding a cup when they suddenly lose control of their hand, which then jerks, causing them to spill the contents.

The horizontal eye movement abnormality affects the ability to look quickly from side to side. As children get older, they learn to compensate for this by blinking to unlock their eyes, followed by a head movement developing head thrusting. This is never enough to fully compensate. Mobility is affected, because the child has to walk more slowly in order to ensure that they are aware of their surroundings. Crossing roads safely can be a huge challenge, due to the difficulty in following the movement of traffic with their eyes.

The respiratory signs and symptoms can persist even if ERT has been commenced early, and a referral should be made to a respiratory consultant.

Spinal curvature can become problematic at this age, as it is a period of rapid growth, and so there is a risk of rapid progression (see section on kyphosis in *non-neurological disease and its assessment*).

Fatigue is common and can be quite problematic. The cause of fatigue is not clear, however when you consider the amount of continuous stress the body is under to function and overcome all of the issues mentioned above, fatigue becomes more understandable. In some cases, it is related to the timing of ERT infusion. It is usually worse at the end of the day, especially a school day. Even the smallest tasks take a long time to complete.

Children can experience a varying proportion of all these symptoms, which can present a different challenge for each patient as these symptoms respond variably to ERT.

By this time, the young person is likely to be aware that they have a medical problem. They may have been told the diagnosis, or at least given an explanation for their symptoms and need to attend hospital regularly for tests and appointments. Depending on the degree of disability, especially neurodisability, they may have begun to sense that they are *different* from other children in their age group. They are at risk of becoming socially isolated. This social isolation made particularly difficult by two things. Firstly, the majority of them have well-preserved intelligence, which means that they can understand what is happening and have a certain amount of insight. Secondly, their outward appearance is quite normal, which means that their peers think that they are pretending to be different and may subject them to bullying.

As type 3 Gaucher disease is a chronic lifelong condition, the child may struggle to come to terms with the diagnosis and an element of uncertainty about the future. This can affect the whole family including any siblings.

Learning ability is often affected and this obviously has implications for education. For further information see the section on *impact on education*.

The behavioural problems discussed earlier may have started to appear.

Young Adults

The majority of young adults with type 3 will have been on ERT for some years, so their visceral disease tends to be well controlled. The two main issues are neurodisability, the advancement of neurological problems and independent living.

Many young adults with type 3 will finish compulsory education and go onto college, some will go to university and are able to live independently. The more severe the neurological involvement, the more difficult it is to achieve this degree of independence. Examples of this are:

- Physical disability is usually accompanied by learning disabilities. Executive function, a term used to describe the ability to think, act, and solve problems, is often affected, making it difficult to perform everyday tasks
- Intention tremor affects handling of utensils, writing, counting money and other tasks involving fine motor movements of the hands
- Mobility is affected by the combination of horizontal saccade initiation failure and ataxia
- Driving will almost certainly be a challenge because of the abnormal horizontal saccades, which affect the ability to look from side to side





Karl

of having functions and responsibilities; taking a journey on public transport for example for some patients will be incredibly challenging. The noise and busy environment of a train station can be daunting, for all the reasons mentioned earlier. Additional, executive skills are often impaired, which makes planning and navigating a journey difficult. As a result, expectations of young adults need to be realistic and support given to make such tasks as manageable as possible.

Older Adults

There is very little information available about older people, as enzyme replacement therapy has really only been available since the early 1990's. Prior to that, life expectancy was significantly shorter than it is now.

Most of the available information on this group of patients comes from historical records and papers written in the 1980's. Therefore, the majority had not been treated with ERT. Features that are seen in many, though not all, include

- Complete absence of eye movements, vertical as well as horizontal
- Seizures
- Cognitive impairment
- Severe bone disease including fractures
- Marked spinal curvature; scoliosis as well as kyphosis
- Hearing impairment
- Heart and lung disease

Many older patients have adapted to their disease over time, and function, with some difficulties, with their own children and jobs. They demonstrate to us that despite their shorter duration on treatment, the difficulties of daily living associated with this condition are not wholly impairing.



Type 3 Gaucher disease has important implications for all stages of education; primary, secondary, and further education.

There is a lot of information available about the provision of education for children and young adults with special educational needs and disability (SEN), and the processes that are in place to ensure that they receive the help they need (see SEN leaflet for more information). This section focuses on the specific issues seen in type 3, and how they affect the learning process. For each issue, the impact will be discussed, followed by suggestions of what support may help.



Eye movements

The difficulty in looking quickly from left to right, and in some children, up and down, is referred to as saccade initiation failure, and is described in detail in *neurological involvement and its assessment*.

Impact

- Difficulty in reading as it involves moving the eyes from side to side. This results in a slower reading speed.
- Hard to constantly look up from book to white board/ teacher and down again
- Difficulty in using computers, having to look up and down from keyboard to screen
- Difficult in moving around between classrooms and between classes, especially in secondary school
- Fatigue - the effort required to complete tasks is much greater than in children that do not have type 3 Gaucher disease
- Vulnerable in crowded places such as playground
- When dexterity is an issue - recording information is difficult

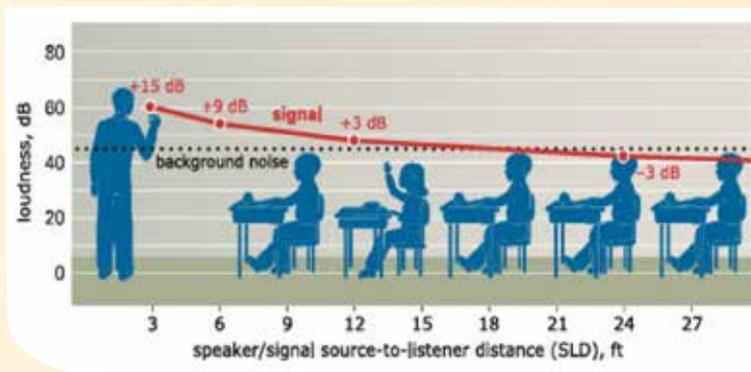
Suggested Support Measures

- The Teacher/ Teaching Assistant to ensure that everything that is written on the board is being written down or if possible have pre-prepared sheets of the lessons that can be next to the student to remove the need to keep looking up and down
- Allow the student to leave the classroom a few minutes early to go to the next class, to avoid the rush. In the event that this will result in information being missed, Teacher/Assistant to ensure that any information is written down i.e. homework
- Use a tablet or iPad rather than computer
- Use a sloping writing desk
- Take mini breaks to rest if necessary
- Use enlarged print on pre prepared sheets
- Sit near the front of the class in a central position



Difficulty in suppressing background noise

In any classroom, there is always some background noise from different sources; outside traffic, ventilation etc. So, the teacher's voice (signal) has to be audible above this background noise (noise). The louder the background noise, and the greater the distance they are from the teacher, the more difficult it is for a student to hear what the teacher is saying. The effect of distance from the teacher can be a significant factor; it is estimated that sound is lost, as shown in the illustration.



As can be seen from the diagram, by the time the signal of the teacher's voice reaches the back of the classroom, it falls below the level of the background noise, which means that a student sitting there will not be able to hear what the teacher is saying.

As can be seen from the diagram, by the time the signal of the teacher's voice reaches the back of the classroom, it falls below the level of the background noise, which means that a student sitting there will not be able to hear what the teacher is saying.

Impact

Most people will be able to suppress the background noise, so that they can hear the speaker. A child with type 3 is unable to do this, and would not be able to hear the teacher.

Suggested Support Measures

- Sit near front of class
- Voice amplification system (assistive technology). The teacher wears a microphone and the child wears a headset or small earpiece

Auditory Processing Disorder

Impact

- Finds it hard to follow spoken directions, especially multi-step instructions
- Asks speakers to repeat what they've said, or saying, "huh?" or "what?"
- Be easily distracted, especially by background noise or sudden loud noises
- Have trouble with reading and spelling, which require the ability to process and interpret sounds
- Struggle with oral (spoken) maths problems
- Find it hard to follow conversations
- Have poor musical ability
- Find it hard to learn songs or nursery rhymes
- Have trouble remembering details of what was read or heard

Suggested Support Measures

- As above. In addition, teacher's words to be relayed or transcribed by assistant
- Teacher/Assistant to ensure that the student has understood all instructions by asking them to repeat them
- Teacher/Assistant to give extra time to the student to complete tasks in the classroom and in tests
- Use of a dictaphone so the student can re-listen to what has been said

Intention Tremor and Co-ordination

Impact

- Difficulty writing
- Writing takes longer time
- Using keyboard difficult
- Multi-tasking can be very challenging
- Copying from a board or book can take longer and be a challenge

Suggested Support Measures

- Provide extra time for completing written work including during examinations
- Use tablet or iPad rather than computer
- Use assistive technology such as a dictaphone or software that uses voice recognition (such as Dragon) to reduce the need to physically write
- A scribe can be useful, especially in exams

The two biggest challenges facing these children, young people and their families is that, firstly, their outward appearance is so normal, and secondly, that many of the complications that they develop do not tick conventional boxes. For example, although the saccade abnormality (eye movement problem) can be very challenging, it is not recognised as a visual impairment. A visual impairment is usually defined and used when a child has reduced vision and may, as a result, be partially sighted or blind. Similarly, the auditory processing problems described earlier are not recognised as hearing loss. Since resource allocation is nearly always dependent on criteria being fulfilled, parents often face an uphill struggle to ensure that their child receives appropriate help.

It is therefore absolutely critical that families, specialist centres with the support of the Gauchers Association work closely with educational authorities. There are three key stages:

- Starting primary school
- Transitioning from primary to secondary school
- Transitioning to further education

Key professionals (e.g. school teachers, SENCO (Special Educational Needs Coordinator at the school), Educational Psychologists, teachers for the deaf and visually impaired, SALT and Occupational Health Therapist) should be identified at these key stages and provided relevant information about the condition. Ideally, the specialist centres and Gauchers Association should have face to face meetings with these key professionals. The child should be central to this process and the parents involved at every stage. Please see the 'education leaflet' for the most up-to-date information on this process.

Further Education

The transition from secondary school to further education is particularly challenging for many reasons:

- It comes at a stage when many aspects of the young person's life are changing - the move to adult health services (including, for some, adult mental health services), the increasing desire for independence, and emotional needs
- The young person is more aware that their peers achieving goals that they are finding challenging or are unable to attain



- The role of the parents / carers changes as the young person becomes more independent in their own decision-making especially around their condition
- Medical complications may have progressed, and new symptoms may have appeared

Finally, the strong, coherent support systems that are in place for children and their families are replaced by adult agencies which are unfamiliar to the family, and often unprepared for the specific issues that these young adults have.

Young adults with type 3 need a lot of support to ensure that they get the help that they need. This can be challenging for the same reasons as children in primary and secondary education, i.e. they don't "tick the right boxes".

Within this booklet is a separate 'Educational' leaflet that provides up to date information on where to find useful resources and up to date policies.

Special Educational Needs (SEN)

Children with type 3 Gaucher disease may need more support than others to reach their full learning potential. Many will attend mainstream schools and some will need a more specialist provision. The information given here mainly relates to England. In the rest of the UK it is slightly different - in Scotland it is called Additional Support for Learning and in Wales and Northern Ireland it is called a Statement of Special Educational Needs. Please check with your local authority for more detailed information.

Before starting school speak to the SENCO (special educational needs coordinator), show them this booklet - especially the *impact on education* section and how it can affect learning.

Initially support might be provided through the school budget with a School Action/School Action Plus (local authorities call these different names, such as My Plan/My Plan Plus - please check on your local council website in their education/ SEN section).

If this plan isn't enough, the next step is to request an 'Education, Health and Care needs assessment' - since 2014 this has taken over 'statementing'. The local authority must carry this out if they believe your child's SEN may require more help than a mainstream educational setting can normally provide. The process can be started by a parent, a young person (if they are over 16 years old) or school / college. They will need to see evidence that the child needs more support for their SEN than a mainstream setting can normally provide. The local authority must tell you in writing within 6 weeks whether or not they will assess your child.

Once they have agreed to assess they will gather all the information from the parent / child, school/college, other services involved (e.g. Educational Psychologist, specialist teachers, health and social care services). The local authority will then decide whether to issue an Education, Health and Care Plan. The final plan must be issued within 20 weeks from initial application.

If you would like support through this process please contact our Patient and Family Support Worker, who can guide you through this.

Anaemia: a condition defined by reduced haemoglobin in the blood. This reduces the amount of oxygen delivered to the body and which can make a person feel tired and look pale

Ataxia: difficulty in control of posture and movement/balance, resulting in poor coordination

Autosomal: any chromosome (each person has 22 pairs in their body) that is not a sex chromosome (this is X and Y)

Avascular necrosis: is the death of bone tissue due to a lack of blood supply, that can lead to tiny breaks in the bone and the bone's eventual collapse

Biomarker: something in the body that can be measured to indicate the presence of a particular disease, a particular biological process or a response to therapy

Bone crisis: an episode of severe pain in the bone, which is accompanied by local swelling, redness, tenderness and increased temperature at the site of pain

Bone marrow: the soft substance found at the core of bones, especially the long bones of the arms and legs, breastbone, spine, ribs, skull, and pelvic bones. Bone marrow contains the stem cells that make blood cells (red blood cells, white blood cells and platelets)

Bone mineral density (BMD): a measurement of mineral levels in the bones. A measure of BMD can show how strong bones are

Bone pain: non-specific pain in the bones

Brainstem: is the stem like part of the base of the brain that is connected to the spinal cord. The brain stem controls the flow of messages between the brain and the rest of the body, and it also controls basic body functions such as breathing, swallowing, heart rate, blood pressure, consciousness, and whether one is awake or sleepy

Carrier (relating to inheritance of disease): a person who has one faulty gene (for example, a faulty gene for glucocerebrosidase) and one healthy gene

Cell: the basic independently replicating structural and functional unit of all known living organisms

Cerebellum: is the part of the brain that that is responsible for human movement, co-ordination, motor control and sensory perception

Chromosome: a thread like structure of DNA (see below) and associated proteins containing many genes (see below)

Cortical bone thinning: thinning of the denser part of the bone, the cortical bone is found in the long bones such as the arms and legs

Diagnosis: the process of determining the presence of a particular disease or condition

Diffusion capacity: a test that measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries

DNA: an abbreviation for 'deoxyribonucleic acid' - the material that carries all the inherited information that defines the growth and development of an individual

Dystonia: refers to uncontrollable and sometimes painful spasms caused by incorrect signals from the brain

Enzyme: a substance (a protein) that causes specific biochemical reactions in the body to occur. The names of enzymes usually end in 'ase', for example, glucocerebrosidase.

Epigenetics: where there is a change in the way a gene works that is not due to a fault in the gene but from other factors i.e. age, lifestyle

ERT: abbreviation for enzyme replacement therapy, a treatment where healthy enzyme is introduced into the body to supplement the activity of a deficient enzyme

Executive function: the skills used to organise information that we receive and act on it

Fatigue: is a term used to describe an overall feeling of tiredness or lack of energy

Founder effect: when a new colony is started by a few members of the original population, and this "splinter group" has a very high frequency of a particular gene

Fragility fractures: is a type of pathologic fracture that occurs as result of normal activities, such as a fall from standing height or less

Gastroenterologist: a doctor who treats problems related to the digestive system

Gaucher cell: cells (usually macrophages) that contain excessive amounts of glucocerebrosidase, causing them to enlarge. Gaucher cells are characteristic of Gaucher disease

Gaucher disease: a rare lysosomal storage disorder that is characterised by a deficiency of the enzyme glucocerebrosidase and which leads to the accumulation of glucocerebrosidase in cells, particularly macrophages

Gene: a unit of DNA that codes for a certain inheritable characteristic

Genetic: what you inherited from your parents

Genotype: refers to a person's unique genetic identity

Gene therapy: an investigational therapy approach that is aimed at correcting genetic disorders by introducing healthy genes into cells of the body

Glaucoma: refers to an eye condition which may result in damage to the optic nerve and may cause visual reduction and in extreme circumstances visual loss

Glottis: the space between the vocal cords

Glucocerebrosidase: the enzyme that breaks down glucocerebroside, and which is deficient in Gaucher disease

Glucocerebroside: a fatty substance (a lipid) composed of a ceramide and glucose that accumulates in the tissues of patients with Gaucher disease

Haemoglobin: the iron containing protein in red blood cells. Haemoglobin gives red blood cells their colour. Its function is to bind (pick up) oxygen from the air in the lungs and to deliver it to cells in the body

Immune system: the system of organs, tissues and cells (such as the spleen, thymus, appendix, lymph glands, tonsils and white blood cells) that work together to protect the body from unwanted particles and substances such as bacteria, viruses, toxins, parasites, fungi

Infusion (relating to enzyme infusion): the introduction of enzyme replacement therapy into a person's blood stream through a vein

Intellectual ability: the skills required to think critically, see connections between disciplines and problem solve in new or changing situations. Memory, creative problem solving and vocabulary also contribute to the level of an individual's intellectual ability

Intellectual function: also called intelligence—refers to general mental capacity, such as learning, reasoning, problem solving, and so on

Intraocular pressure: fluid pressure inside the eye

Intubation: is when a flexible plastic tube is placed down the throat to maintain an open airway

Kyphosis: an excessive curvature in any part of the spine

Lysosomal storage disorder / LSD: A group of rare diseases characterised by deficiencies in the activity of specific lysosomal enzymes

Malabsorption: the inability of the small intestine to absorb enough nutrients

Mesenteric nodes: refers to a specific group of nodes (mass of tissue) in the abdomen

Myoclonus: this refers to involuntary short, jerky movements

Neurologist: a medical doctor who specializes in treating diseases of the nervous system

Neuronopathic/neuropathic/neuropathy: a disease process characterised by damage to nerves

Oculomotor apraxia: abnormality of horizontal or vertical eye movements

Ophthalmologist: a doctor who specializes in eye and vision care

Orthopaedic: relating to the prevention or correction of bone injuries

Osteoporosis: a bone condition where the bones have low bone mineral density, become weaker and more likely to break

Pan ethnic: people of all ethnic groups are affected

Phenotype: refers to a person's actual physical characteristics i.e. height, eye colour

Protein losing enteropathy: this occurs when there is an excessive loss of proteins from the body

Recessive: this means two copies of a gene are necessary to have the disease

Retinal detachment: this occurs when the thin lining at the back of your eye called the retina begins to pull away from the blood vessels that supply it with oxygen and nutrients

Saccades: the eye movements used to rapidly refixate from one object to another

Seizures: this occurs when there is a change in the brain's electrical activity and symptoms can occur such a violent shaking of the body and a loss of control. There are different types of seizures

Scoliosis: is a sideways curvature of the spine, or backbone

Smooth pursuit: the eye movement that allow the eyes to closely follow a moving object

Spleen: an organ situated to the left of the stomach below the diaphragm. It acts to break down and recycle old blood cells and filter unwanted substances from the blood

Stridor: is a high-pitched, wheezing sound caused by disrupted airflow

Substrate reduction therapy: a therapy that inhibits the production of a substrate (for example, glucocerebroside in Gaucher disease) to help stop the substrate from accumulating in cells

Thoracic spine: is the upper back, middle back, or mid-back

Tracheostomy: is an opening created at the front of the neck so a tube can be inserted into the windpipe (trachea) to help you breathe

Tremor: is an uncontrollable movement that affects a part of the body, for example the hand

Visceral: internal organs of the body i.e. liver, spleen, liver, heart, and lungs

Working memory: is the ability to hold information for processing and guidance of decision making and behavior



Family conference children's activities



Workshop with young adults with type 3 Gaucher disease



Family of Gaucher patient with healthcare professionals



Family conference organising committee



Hayley with Mum and Dad



Charity no. 1095657