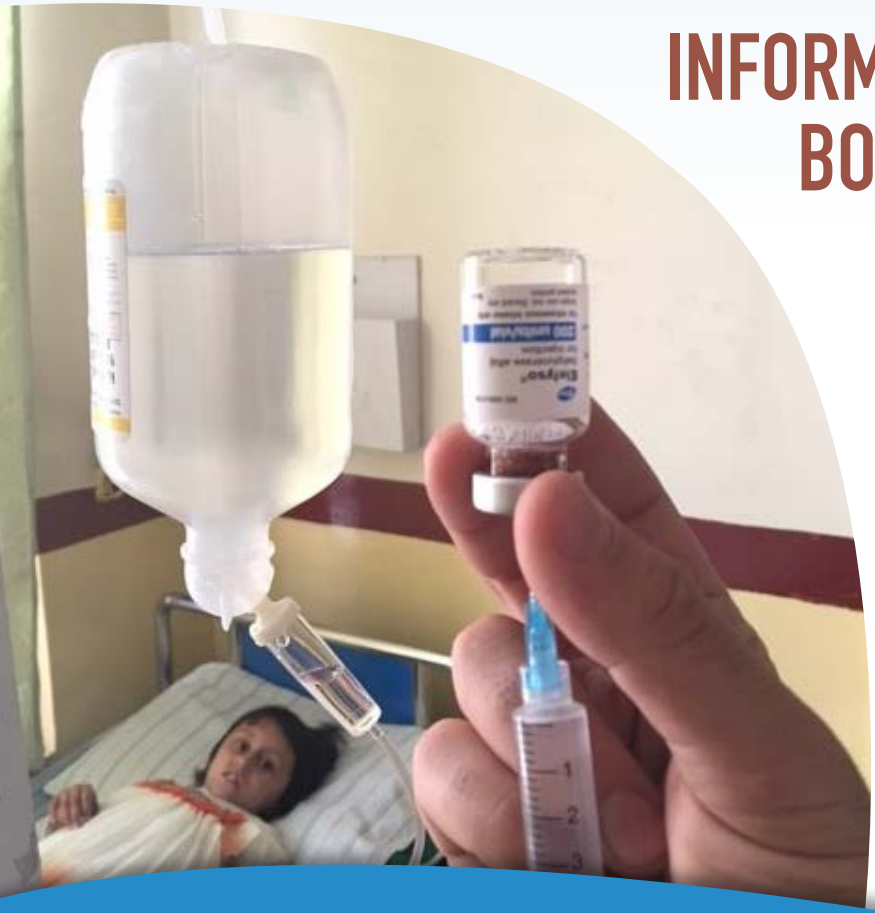
IGA INTERNATIONAL GAUCHER ALLIANCE
Driven by passion for patients

GAUCHER DISEASE

BASIC INFORMATION BOOKLET



Dr Rami Ballout (graduated from the American University of Beirut, Lebanon) speaking to a Gaucher patient

Front cover image: Gaucher patient from Afghanistan receiving treatment.

CONTENTS

INTRODUCTION

Welcome to the International Gaucher Alliance (IGA) information booklet on Gaucher disease Types 1, 2 and 3. We have developed this booklet as a source of information for patients and their carers and to answer questions on Gaucher disease, such as what it is? How is it inherited? How will it affect my life? What is the latest research?

Patients and carers can share this booklet with their doctor and other professionals who will benefit from learning more about Gaucher disease.

We hope that you find it informative and useful, whether you have been living with Gaucher disease for many years, or have just been diagnosed or your work involves people with Gaucher.

If you have any unanswered medical questions please refer to your doctor or if you have any unmet non-medical needs contact your national Gaucher patient support group or the IGA on:
admin@gaucheralliance.org

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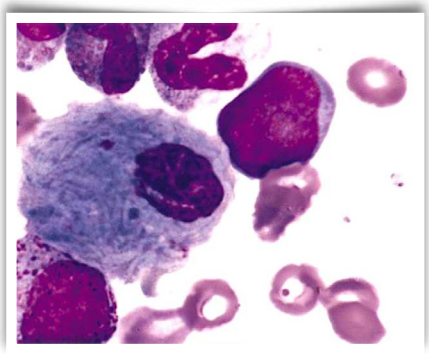
WHAT IS GAUCHER DISEASE?

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 of an enzyme called glucocerebrosidase. This enzyme helps the body to 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.

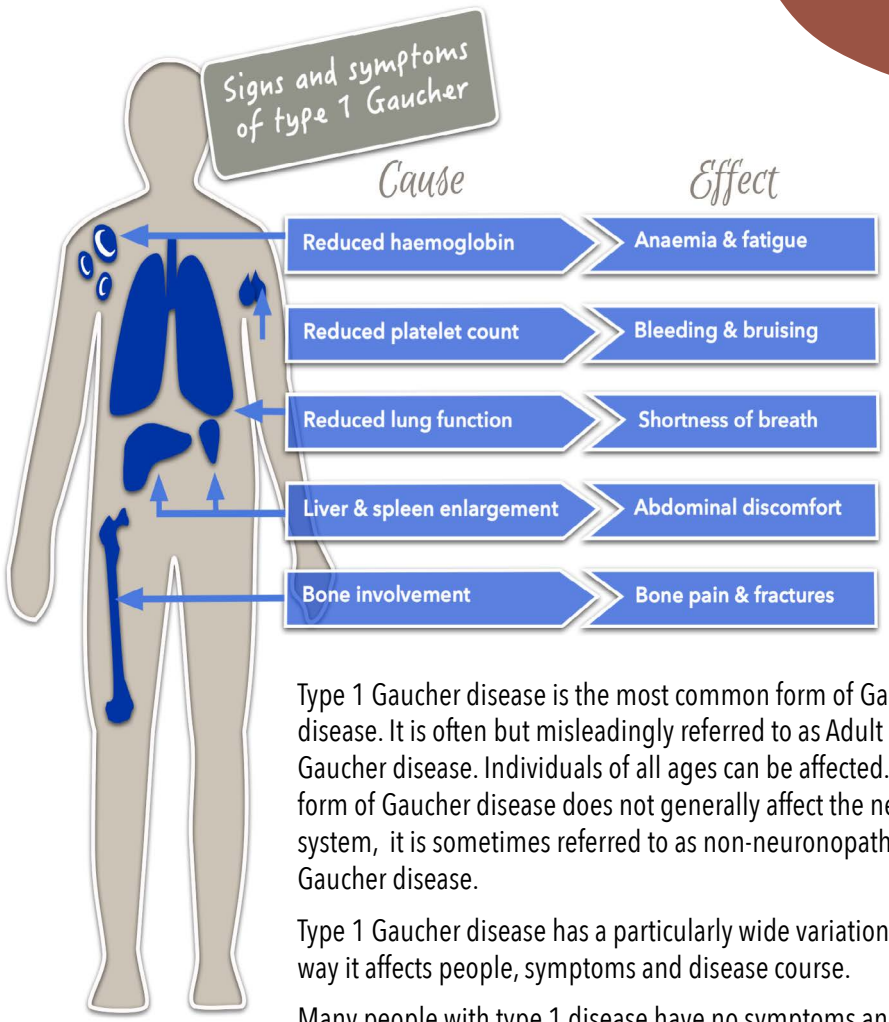
The most common form of Gaucher disease (type 1) affects 1 in 100,000 of the general population but 1 in 850 people of Jewish (Ashkenazi) descent. Not all those who inherit the mutated genes for this disorder will show symptoms.

In the rare Neuronopathic (types 2 and 3) Gaucher disease, neurological symptoms occur which include an eye movement disorder (oculomotor apraxia), unsteadiness (ataxia), fits (seizures), some impairment of thinking (cognitive) and the way the brain handles sounds (central auditory process disorder). Children with type 2 Gaucher disease usually die within the first few years of life.



Cells (usually macrophages) that contain excessive amounts of glucocerebroside, causing them to enlarge, are called Gaucher cells and are characteristic of Gaucher disease.

SIGNS & SYMPTOMS: TYPE 1



Type 1 Gaucher disease is the most common form of Gaucher disease. It is often but misleadingly referred to as Adult Gaucher disease. Individuals of all ages can be affected. This form of Gaucher disease does not generally affect the nervous system, it is sometimes referred to as non-neuronopathic Gaucher disease.

Type 1 Gaucher disease has a particularly wide variation in the way it affects people, symptoms and disease course.

Many people with type 1 disease have no symptoms and lead normal lives. In some cases, however, the disease may become life-threatening.

In general, the later in life first symptoms appear, the less likely it is that the disease will be severe.

It is thought that people with Gaucher disease may have a risk of developing other conditions later in life including Parkinson's disease and Multiple Myeloma (cancer of the white blood cells).

SIGNS & SYMPTOMS: TYPE 2

Type 2 Gaucher disease is a very rare, rapidly progressive form of Gaucher disease which affects the brain (central nervous system) as well as the spleen, liver, lungs and bones. It is characterised by severe neurological (brain) involvement in the first year of life. It is also called acute neuronopathic Gaucher disease.

Fewer than 1 in 100,000 newborn babies have type 2 disease and this form of the disease is not associated within any particular ethnic group.

Babies usually appear normal at birth but develop neurological and other symptoms by the age of 3-6 months. Type 2 is almost always apparent by 6 months of age. Many children die in infancy and survival beyond 2 years is rare. In some exceptional cases, the disease course may be prolonged over a number of years.

Early signs and symptoms include slow development, squint (strabismus), poor feeding and slow weight gain. In the subsequent months, developmental milestones may be lost (regression), there may be rigidity of the neck and limbs (hypertonia), back arching, abnormal head postering, and noisy breathing (stridor), swallowing problems and recurrent vomiting may become apparent. The abdomen may appear very swollen due to enlargement of the liver and spleen.

As the disease progresses, other difficulties such as throat (laryngeal) spasm, seizures, low blood counts, bleeding and a failure to shake off colds and other infections may complicate the course. The lungs may also be affected and the bones may show signs of disease.

In later stages of the disease the infant may show signs of pain and distress that may arise from spasms, seizures, choking, breathing difficulites, infections, bleeding and bone pain. It is very important to recognise and manage these symptoms with appropriate measures and pain relief in order to keep the child as comfortable as possible.

Sudden death may occur or in some cases the baby may eventually switch off, not reacting to parents or stimulus for a period before death. It is important for families to seek palliative care for their child to ensure the child is as comfortable as possible and to support those caring for the child.

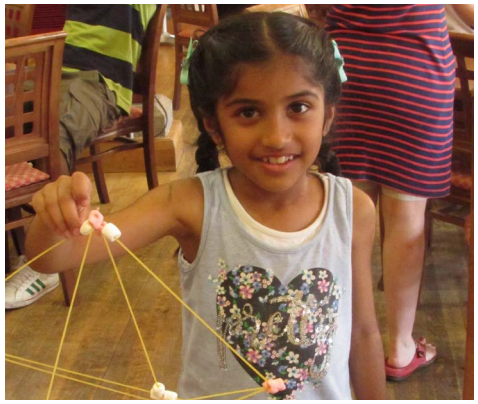
SIGNS & SYMPTOMS:

TYPE 3

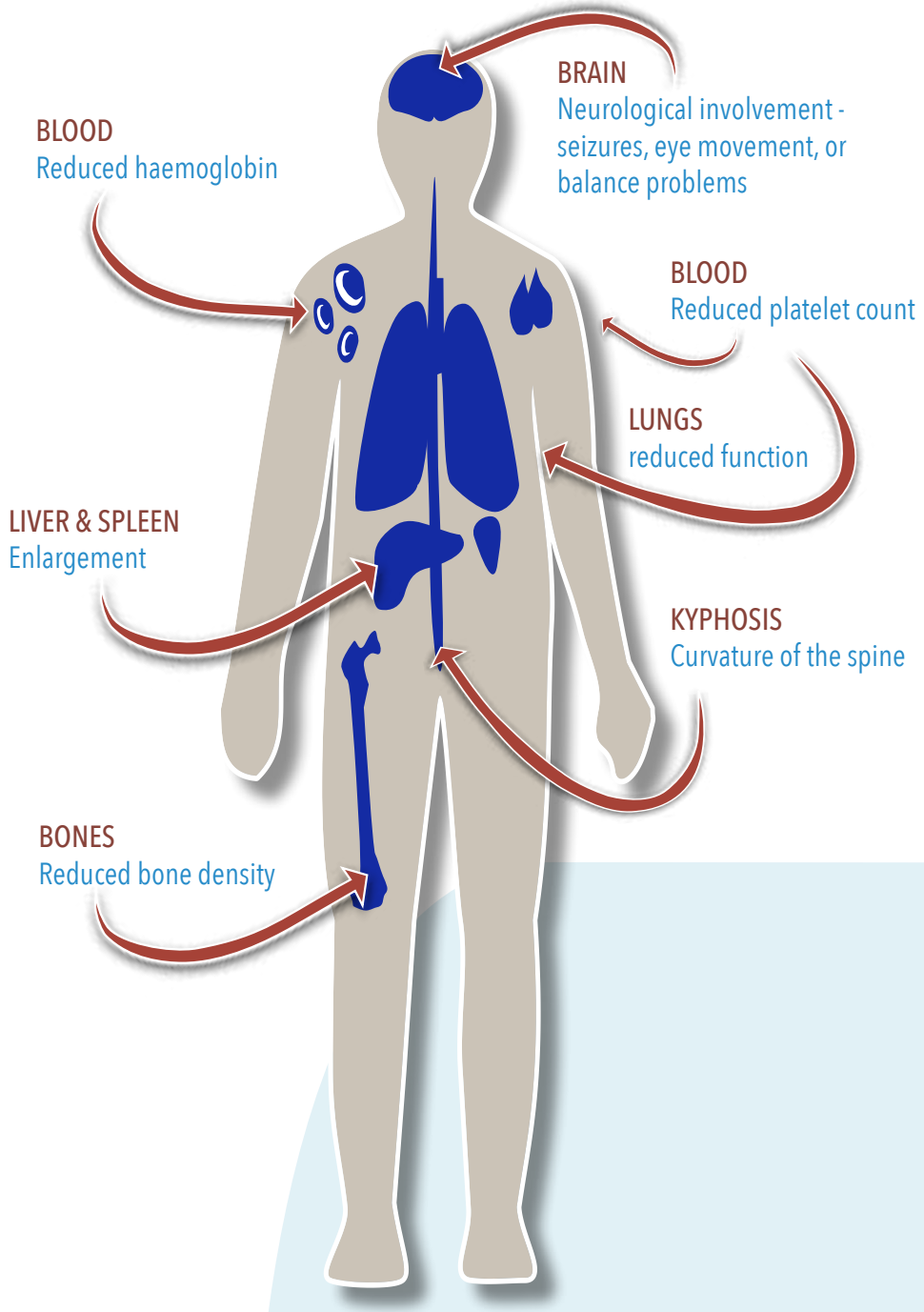
Type 3 Gaucher disease, or chronic neuronopathic Gaucher disease, is intermediate, between type 1 and type 2. Affected patients have both visceral (the internal organs of the body, for example, the lungs, liver and spleen) and neurological (brain) involvement. However, the neurological involvement is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



HOW IS GAUCHER DISEASE INHERITED?

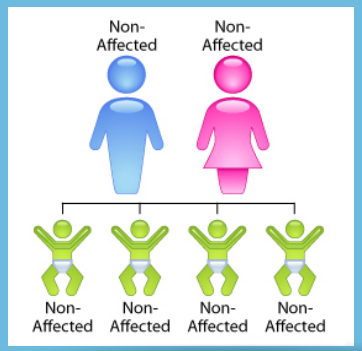
An individual inherits two copies of every gene; one from each parent. In the case of Gaucher disease, there is a mutation in the gene for the production of the enzyme glucocerebrosidase.

To get Gaucher disease a person must have two copies of the mutated gene. 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 mutated gene onto their offspring. The risks are for each pregnancy. Whilst this means that there is a 1:4 chance each of an affected or unaffected child and a 2/4 chance of a carrier, in fact, as each pregnancy is independent by chance all off spring may be affected or unaffected.

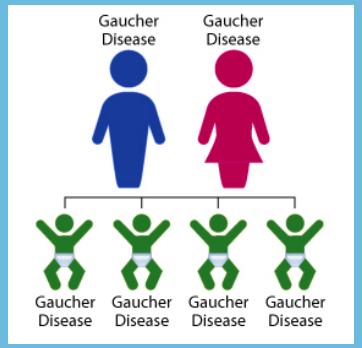
The possibilities of passing on the mutated Gaucher gene:

Many different mutations of the gene for glucocerebrosidase have been identified. The type of mutation is connected to the severity of Gaucher disease. Carrier testing is possible in affected families. If you are interested discuss this with your treating doctor.

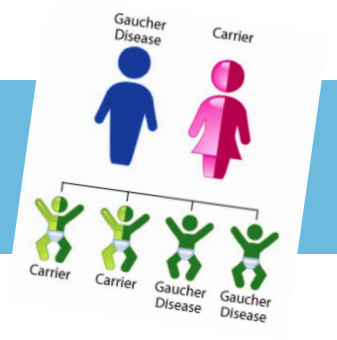
If both parents have normal genes for glucocerebrosidase, each child will inherit two normal genes, one from each parent, and will neither have Gaucher disease nor be a carrier.



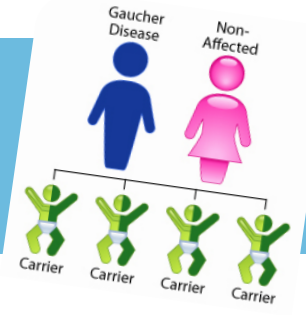
If both parents have Gaucher disease, all of their children will inherit two Gaucher genes and will have the Gaucher disease as well.



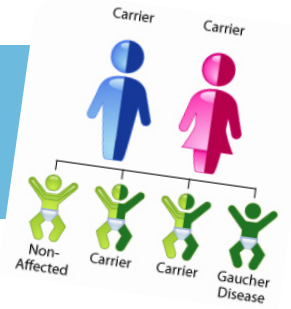
One parent has Gaucher disease and the other parent is a carrier. Their children will have a 50% chance of having Gaucher disease and a 50% chance of being a carrier.



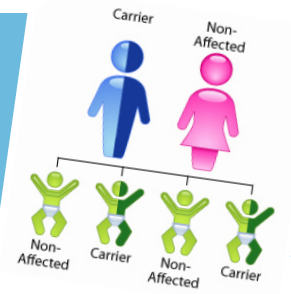
One parent has Gaucher disease and the other parent is not affected. All the children will inherit the mutated gene from the affected parent and become carriers, but none of the children will have Gaucher disease.



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 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 Gaucher disease.



HOW IS GAUCHER DISEASE DIAGNOSED?

The process of diagnosing many diseases, and especially Gaucher disease, is not always straightforward.

Often, the patient initially visits their doctor for another problem such as the flu, for non-specific pain, or for a routine check-up. 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 platelet counts, doctors may first test for leukaemia. If a patient complains of joint pain, the doctor may first suspect arthritis. Sometimes specialists at a genetics unit, a haematologist or a metabolic physician, may be helpful in distinguishing the symptoms of Gaucher disease from other diseases with similar symptoms.

Gaucher disease can be diagnosed by a simple blood test – by measuring the amount of enzyme in your blood and checking for mutations in the glucocrebrosidase gene.

Other tests used to make the diagnosis can include biopsy of bone marrow or liver and may be helpful if there are multiple potential causes for a person's symptoms. Sometimes testing for Gaucher disease can be recommended if members of the family are known to have the Gaucher disease.

Gaucher disease might be suspected in a person who has an unexplained enlargement of the spleen, tendency toward bleeding, bone or joint pains or spontaneous fractures.

A PAEDIATRICIAN might make the diagnosis in a child complaining of abdominal discomfort or of frequent nosebleeds.

A HAEMATOLOGIST might make the diagnosis in a person with low blood or platelet counts.

AN ORTHOPAEDIC DOCTOR might diagnose Gaucher disease in the course of treating someone suffering with frequent unexplained fractures.

Gaucher disease would be particularly suspected in people with family members who are known to have the disease.

ROUTE TO A GAUCHER CENTRE:

IS THERE A CURE?

There is currently no cure for Gaucher disease, but different therapies are available which can help to treat many of the major symptoms. With treatment, people with type 1 Gaucher may lead full lives and may be able to carry out many of their normal daily activities.

Some people with type 1 Gaucher disease have no clinical symptoms and do not need treatment.

For Gaucher patients that do require treatment, the options are:

ENZYME REPLACEMENT THERAPY (ERT)

People with Gaucher disease are deficient in the enzyme glucocerebrosidase, the recommended treatment is enzyme replacement therapy; which has to be infused directly into a vein at regular intervals throughout the individual's life.

As such, enzyme replacement therapy (ERT) is an effective therapy, rather than a cure. There are three licensed enzyme replacement therapies available for doctors to prescribe to treat type 1 Gaucher disease and the visceral disease of type 3 Gaucher disease:

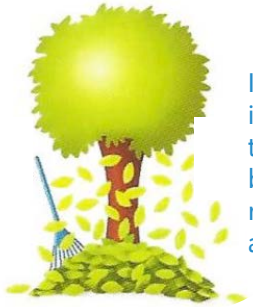
- Cerezyme© (imiglucerase) developed by Sanofi Genzyme;
- VPRIV© (velaglucerase alfa) developed by Takeda; and
- Elelyso© (taliglucersae alfa) developed by Protalix Biotherapeutics and marketed by Pfizer.

**Elelyso is not licensed for use by the European Medicines Agency (EMA) and therefore is not available in the European Union.*

SUBSTRATE REDUCTION THERAPY (SRT)

This treatment reduces the amount of fatty substances made in our cells and therefore helps to reduce their build up. SRT is an oral therapy, with two products licenced: Zavesca© (miglustat) manufactured by Actelion; and Cerdelga© (eliglustat) manufactured by Sanofi Genzyme.

These products are not suitable for everybody and your specialist doctor will advise if they are right for you.



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

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

Enzyme Therapy (ERT)

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

Substrate Reduction Therapy (SRT)

Imagine that the substance glucocerebroside is represented as leaves, and that the enzyme that breaks down this substance, glucocerebrosidase, is represented as rakes.

SPECIFIC THERAPIES:

BISPHOSPHONATE

For patients with Gaucher disease who have low bone density and fractures, the bisphosphonate group of drugs (e.g. oral alendronate or IV zoledranate) are often prescribed to help combat osteoporosis and bone disease.

BONE PAIN

If you experience bone pain, talk to your doctor about pain management it may be helpful if you keep a pain diary. If it is necessary for you to undergo orthopaedic surgery it is essential that this is planned in conjunction with your specialist centre.

SPLENECTOMISED PATIENTS

For those people who have had their spleen removed long term antibiotic therapy and up to date vaccinations are essential.

CURRENT CLINICAL TRIAL INFORMATION:

We want to empower you and anyone else affected by Gaucher disease, this requires that you have adequate information. With this in mind we want to strive to provide everyone with information in a format they can easily access – as we are aware of the challenges that can surround clinical trials. Our goal then, with regards to you and clinical trials, is to promote informed decision-making: this way you always fully comprehend what is going on every step of the way.

You can find information regarding current trials on ClinicalTrials.gov. This includes clinical sites, inclusion criteria, protocols etc. For your own convenience trial numbers are listed below alongside the relevant company name(s), simply input these numbers in the search bar on the **ClincialTrials.gov** website to learn more about each respective trial. Company websites can be accessed by clicking the company name, and a summary of current Clinical Trials is shown below against each Pharmaceutical Company.

If you have any further queries regarding clinical trials please don't hesitate to get in touch, by either email at: admin@gaucheralliance.org, or by telephone on: 00 44 1453 796402

DIFFERENT MODALITIES OF CLINICAL TRIALS

Gene Therapy

Gene therapy can be defined as the introduction of genetic material to cells of patients for therapeutic benefit. In simple terms, it involves providing a healthy functional copy of a gene to the patient's cells to compensate for a defective copy that causes the disease. Ideally this treatment would only need to be administered once in the lifetime of the patient. Even though the concept underlying gene therapy is straightforward, delivering genes into cells of a living organism is a very challenging process. Therefore, an essential component of gene therapy studies is the development of vectors that can efficiently deliver genetic material into cells.

Avrobio and Prevail have active gene therapy trials in Gaucher disease, however their approaches are different, more information can be found.

Avrobio: https://www.avrobio.com/technology

Prevail: https://www.prevailtherapeutics.com/programs/#pr001

Heat Shock Protein Therapy

This approach is focused on the cell-protective properties of the heat-shock response, a natural defence mechanism in all our cells. The heat-shock response protects cells from an accumulation of misfolded proteins or other waste products, which would otherwise lead to toxicity and disease. The heat-shock response is generated through the production of heat-shock proteins, which act as the cells' lifeguards. Current clinical trials are being undertaken by Orphazyme's drug Arimoclomol: https://www.orphazyme.com/about-arimoclomol/

SRT for Neuronopathic Gaucher disease

Sanofi Genzyme are currently in clinical trials with an SRT called Venglustat for type 3 Gaucher disease. Venglustat is an oral inhibitor of the enzyme called glucosylceramide synthase (GCS).

Venglustat is being investigated as a potential oral substrate reduction therapy for GD3. Preclinical studies indicate the novel oral treatment is a glucosylceramide synthase inhibitor that reduces the synthesis of glucosylceramide. Preliminary results in phase II clinical trials show potential activity against progression of neurological manifestations of GD3.

SRT for Paediatrics

Sanofi Genzyme are currently in clinical trials with the SRT Eliglustat (Cerdelga © licensed for adults with GD1).

For an update on clinical trials currently being undertaken in patients with Gaucher disease, see the IGA website at: www.gaucheralliance.org for up to date information.

LIVING WITH GAUCHER:

EMOTIONAL WELLBEING

People with Gaucher disease, their spouses, and friends may face a wide variety of emotional and social challenges in addition to the physical limitations or complications posed directly by the disease.

Which issues have to be dealt with, and to what degree will depend directly on the severity of the disease in each individual.

People with Gaucher disease may find that over time they experience some, none, or many of the following challenges:

- **Feelings of isolation**
- **Lack of knowledge of the disease,** both for those affected by the disease and their local healthcare professionals
- **Delayed diagnosis;** as a rare disease it can be a significant amount of time before a diagnosis is made
- **Anxiety** about relationships and having a family
- **Uncertainty about disease progress;** symptoms and their severity may vary widely and may occur at any time. Some people remain symptom-free for many years, while others may begin having symptoms very early in life. This can sometimes make it difficult in making short and long term plans.
- **Anxiety & depression;** being affected by a chronic disease can lead to anxiety and depression. If this affects you discuss with your healthcare team who can help you to access services available
- Accepting the diagnosis; long term denial can be dangerous particularly if this prevents or delays medical help.

However, these difficulties sometimes add to the development of exceptional inner strength that many people with chronic illnesses often possess, enabling them to live full and active lives.

If you are affected by any of these symptoms getting help is important. This could be psychology, counselling, or mental health services. The IGA can put Gaucher patients in contact with other Gaucher patients.

INTERNATIONAL GAUCHER ALLIANCE

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The IGA is a patient led international organisation that has become the 'go to' global voice for over 85% of the worldwide Gaucher community and has built its reputation through listening to and delivering outcomes that have impacted on patients and their carers' lives. If you need to find your local patient group, link to one of our 50+ member associations for local support, advice and news https://gaucheralliance.org/gb/members_directory

OUR VISION:

A world where all Gaucher patients have access to the treatment and care they need and there is a possibility of a cure

OUR MISSION:

- to **empower** its members
- to **advocate** on behalf of Gaucher patients
- to **ensure** that the Gaucher research agenda is **focused on patients' unmet needs**
- to **take collective action** to address challenges Gaucher patients worldwide face in accessing early diagnosis and optimal treatment and care.

OUR VALUES:

We are:

- patient focused
- trustworthy
- collaborative
- visionary
- passionate

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Driven by passion for patients

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