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Introducing the diseases
Tay-Sachs & Sandhoff

A practical guide for parents and carers

Produced by
The CATS Foundation

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*Introducing the diseases
*Tay-Sachs & Sandhoff

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Tay-Sachs and Sandhoff disease cause a variety of symptoms.


CATS

Supporting each other

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One of our key objectives is to ensure we have a support network who can help each other out in the time of need.

Coping with a diagnosis of Tay-Sachs or Sandhoff is one of the most difficult things to deal with as a parent and as a family.

*Introduction
*The guide

Deborah
—
"Without the support of the CATS Foundation, however, we would not have been able to achieve many of the memorable trips that we have taken over the past years."

This guide has been developed with the help of parents and carers of individuals affected by Tay-Sachs and Sandhoff disease. It aims to provide information, reassurance and support to those caring for a loved one affected by the diseases.

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The Cure & Action for Tay-Sachs (CATS) Foundation recognizes the value and knowledge, skills and experience gained by families caring for someone affected by the diseases. We hope that the information included in the guide will assist those providing care.

*Daniel Lewi - Charity Director

01

*The CATS Foundation
*How we started

Patricia - charity co-founder
—
"When Amélie was diagnosed we could not believe there was no charity dedicated to providing support to families. The impact we have made since starting The CATS Foundation has been phenomenal and one piece of advice I have for new families is that you are not alone."

The Cure & Action for Tay-Sachs (CATS) Foundation was established in 2011 by Daniel and Patricia Lewi after their daughter was diagnosed with Tay-Sachs. At the time there was no UK based charity dedicated to providing support for families affected by Tay-Sachs and Sandhoff disease.

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The CATS Foundation's main focus is supporting families affected by the diseases whilst also raising awareness of Tay-Sachs and Sandhoff.

*The CATS Foundation can help

*The charity
*How we help

Raising awareness

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By raising the profile of the diseases it has helped us reach out to families who previously did not know about the charity.

Sharing information

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The charity shares all information relating to the research into a potential treatment for Tay-Sachs and Sandhoff disease.

The CATS Foundation was founded with the main aim to ensure that families do not feel alone after recieving a diagnosis of Tay-Sachs or Sandhoff disease. The charity provides a variety of services, including a support network, respite trips and vital equipment so that a person affected by either disease has a quality of life which is as high as possible. The CATS Foundation also provides funding to the research team who are investigating a potential treatment for Tay-Sachs and Sandhoff disease.

The main goal at The CATS Foundation is to ensure that all the families affected by the diseases are supported once a diagnosis has been made. Feeling isolated at such a time can have a dramatic effect on an individual and their family. At The CATS Foundation we have three main aims which we focus on:

- Raise awareness

  Holding events, visiting schools and undertaking community projects are some of the ways the charity raises awareness of Tay-Sachs and Sandhoff disease.

- Support families

  The CATS Foundation supports families by providing respite trips, equipment, a support network and access to information about the diseases.

- Support research

  The CATS Foundation supports the research into a potential treatment for Tay-Sachs and Sandhoff disease in the UK

With these aims we have been able to ensure that all of the children who we support have as high a quality of life as possible.

Nikki

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“Along the way I found a few other lifelines, the CATS Foundation definitely being one of them. They offered unwavering unconditional love and support from the moment I found them. They supplied Ruby with a specialist piece of equipment that I couldn’t afford.”

02

*The diseases
*An introduction

Katherine
—
“Receiving the diagnosis was a relief initially; finally we knew what we were dealing with, but it was followed by total despair. The diagnosis was as bad as it could be. Andy still refers to it as the worst day of his life. Even today we sometimes wonder if we have fully come to terms with it.”

The GM2 gangliosidoses are a group of related genetic disorders that result from a deficiency of the enzyme beta-hexosaminidase which catalyzes the biodegradation of fatty acid derivatives known as gangliosides. All of the GM2 gangliosidoses are rare diseases in the general population.

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The diseases are better known by their individual names and Tay-Sachs and Sandhoff disease are two of the GM2 gangliosidoses and are due to a fault on the same metabolic pathway.

*Both diseases are very rare

*GM2 gangliosidoses
*A group of diseases

Rare diseases

Both Tay-Sachs and Sandhoff are very rare diseases with a birth rate of around 1 in 320,000 a year in the UK.

Small but vital

The missing or reduced levels of enzymes which cause Tay-Sachs and Sandhoff disease are actually very small but they play a very important role in the body.

The GM2 gangliosidoses are a group of lysosomal lipid storage disorders caused by mutations in at least one of three recessive genes: HEXA, HEXB, and GM2A. Normal products of all three genes are required for normal catabolism of the GM2 ganglioside substrate. Deficient activity of these enzymes leads to accumulation of the substrate inside neuronal lysosomes, leading to cell death.

GM2 gangliosidoses is due to a reduction in beta-hexosaminidase which is a vital hydrolytic enzyme found in the lysosomes, whose role is to break down lipids. When beta-hexosaminidase is no longer functioning properly, the lipids accumulate in the nervous tissue of the brain and cause problems. Gangliosides are made and biodegraded rapidly in early life as the brain develops. Except in some rare, late-onset forms, the GM2 gangliosidoses are fatal.

The three disorders which make up the GM2 gangliosidoses are Tay-Sachs; Sandhoff; and GM2-gangliosidosis, AB variant. All three disorders might easily have been defined together as a single disease because they are associated with failure of the same metabolic pathway and have the same outcome.

Classification and naming for many genetic disorders reflects history, because most diseases were first observed and classified based on biochemistry and pathophysiology before genetic diagnosis was available.

However, the three GM2 gangliosidoses were discovered and named separately. Each represents a distinct molecular point of failure in a subunit that is required for activation of the enzyme.

Patricia

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"It is so rewarding to know that sharing our own experiences of looking after Amelie has helped other families look after their own children."

*Lysosomal storage disorders
*A name grouping diseases

Sally

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I was told over the phone that Hope had Tay Sachs and that she was high end of the disorder. Needless to say I was devastated, a broken middle aged woman and my family shared the grief”

There are over storage disorde both Tay-Sachs disease are. Th defective genes rare.

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*LSDs are very similar

80 lysosomal
ers (LSDs) of which
s and Sandhoff
ney are all due to
s and each are very

*Tay-Sachs
*An explanation

Tay-Sachs is a genetic disorder caused by a defect in the HEXA gene which produces the beta-hexosaminidase A enzyme. The enzyme is important as it breaks down harmful waste products in the brain and without it these build up and cause extensive damage to the brain's nerve cells. Physically, an individual diagnosed with Tay-Sachs will suffer a relentless deterioration of mental and physical abilities over a period of time.

Tay-Sachs sufferers have two basic problems: they do not have enough (or any) Hexosaminidase A (Hex-A) enzyme and they end up with too much GM2 waste. Hex-A is an enzyme that is created outside of a cell and absorbed into the cell.

When the enzyme is mutated the cell does not recognize it and a quality control mechanism within the cell will not allow the mutated enzyme to be absorbed. The Hex-A's primary job is to break down waste inside the lysosomal storage area and that is why Tay-Sachs is considered a Lysosomal Storage Disease (LSD).

The waste product is called GM2. It is basically a big complicated strand that is too big and long for a brain cell to deal with. The Hex-A breaks the GM2 down into little strands that can be used by the cell. When there is too-little Hex-A, the large GM2 strands begin to accumulate. As the waste accumulates the storage area begins to swell; it is the swelling that causes the cell to malfunction and eventually die. Hex-A and GM2 are created in brain cells and that is why Tay-Sachs is primarily a neurological condition.

"I researched every possible neurological condition until I found one that described Isabella perfectly. It was called Tay-Sachs Disease. I knew in my heart that this was the one, but tried to remain positive."

***James**

*Sandhoff
*An explanation

Sandhoff disease is a lysosomal genetic, lipid storage disorder caused by the inherited deficiency to create functional beta-hexosaminidases A (Hex-A) and beta-hexosaminidases B (Hex-B).

Mutations in the HEXB gene causes Sandhoff disease. The gene provides instructions for making a protein crucial to the enzymes Hex-A and Hex-B which function in nerve cells to break down fatty substances, complex sugars, and molecules that are linked to sugars.

In particular, Hex-A breaks down a fatty compound called GM2 ganglioside. Mutations in the HEXB gene disrupt the activity of these enzymes, preventing the breakdown of GM2 and other molecules.

As a result, progressive damage caused by the resulting buildup of GM2 leads to the destruction of nerve cells, causing the signs and symptoms associated with Sandhoff disease.

Sandhoff disease symptoms are clinically very similar to Tay-Sachs. The classic infantile form of the disease has the most severe symptoms and is incredibly hard to diagnose at an early age.

Adult and juvenile forms of Sandhoff disease are more rare then the infantile form and in these cases individuals suffer cognitive problems and a loss of muscle coordination that eventually destroys their ability to walk.

As in Tay-Sachs, younger suffers of Sandhoff have a limited life expectancy as the disease progresses.

“We knew something was different with Ruby from about eight months. She was seen by pediatricians and was labelled as having Global Development Delay.”

***Alison**

03

*What causes the diseases
*An introduction to genetics

Daniel
—
"One of the most difficult things about learning your child has a disease like Tay-Sachs is actually understanding why they have it and if there is anything you could have done to prevent it."

Tay-Sachs and Sandhoff disease are acquired through autosomal recessive inheritance. This means that both parents of an affected individual have to be carriers of the faulty gene (mutation) which causes the disease.

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A mutation is a change or fault on a normal gene which means that it does not perform the function that it should do and parents seldom know that they are carriers of the gene that cause disease.

*Both parents must be carriers

*Inheritance
*The genetics

Tay-Sachs carriers

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1 in 300,000 people in the UK are carriers of the gene which causes Tay-Sachs.

Small but vital

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1 in 320,00 people in the UK are carriers of the gene which causes Sandhoff disease.

Autosomes are the non-sex-related chromosomes. The term autosomal recessive inheritance means that the effects of possessing a single copy of a disease-causing gene are hidden. With a recessive condition, a person may be a carrier of a disease gene, but may have no noticeable effect on their everyday health.

A positive diagnosis of Tay-Sachs or Sandhoff in an individual means that each parent is a carrier of a disease-causing mutation on the specific gene which causes the disease. The individuals may inherit identical mutations from each parent and this would be referred to as a homozygous. The homozygous condition may arise through intermarriage although this may not be obvious over many generations. In other instances, the parental mutations may be different; this would be referred to as heterozygous.

On the next page is an example of autosomal recessive inheritance with the potential offspring from two heterozygote parents. If you are born to parents who both carry an autosomal recessive change (mutation), you have a 1 in 4 (25%) chance of getting the malfunctioning genes from both parents and developing the disease. You have a 50% (1 in 2) chance of inheriting one abnormal gene. This would make you a carrier.

In other words, if four children are born to a couple who both carry the gene (but do not have signs of disease), the statistical expectation is as follows:

- One child is born with two normal genes (normal)
- Two children are born with one normal and one abnormal gene (carriers, without disease)
- One child is born with two abnormal genes (at risk for the disease)

How the inheritance works

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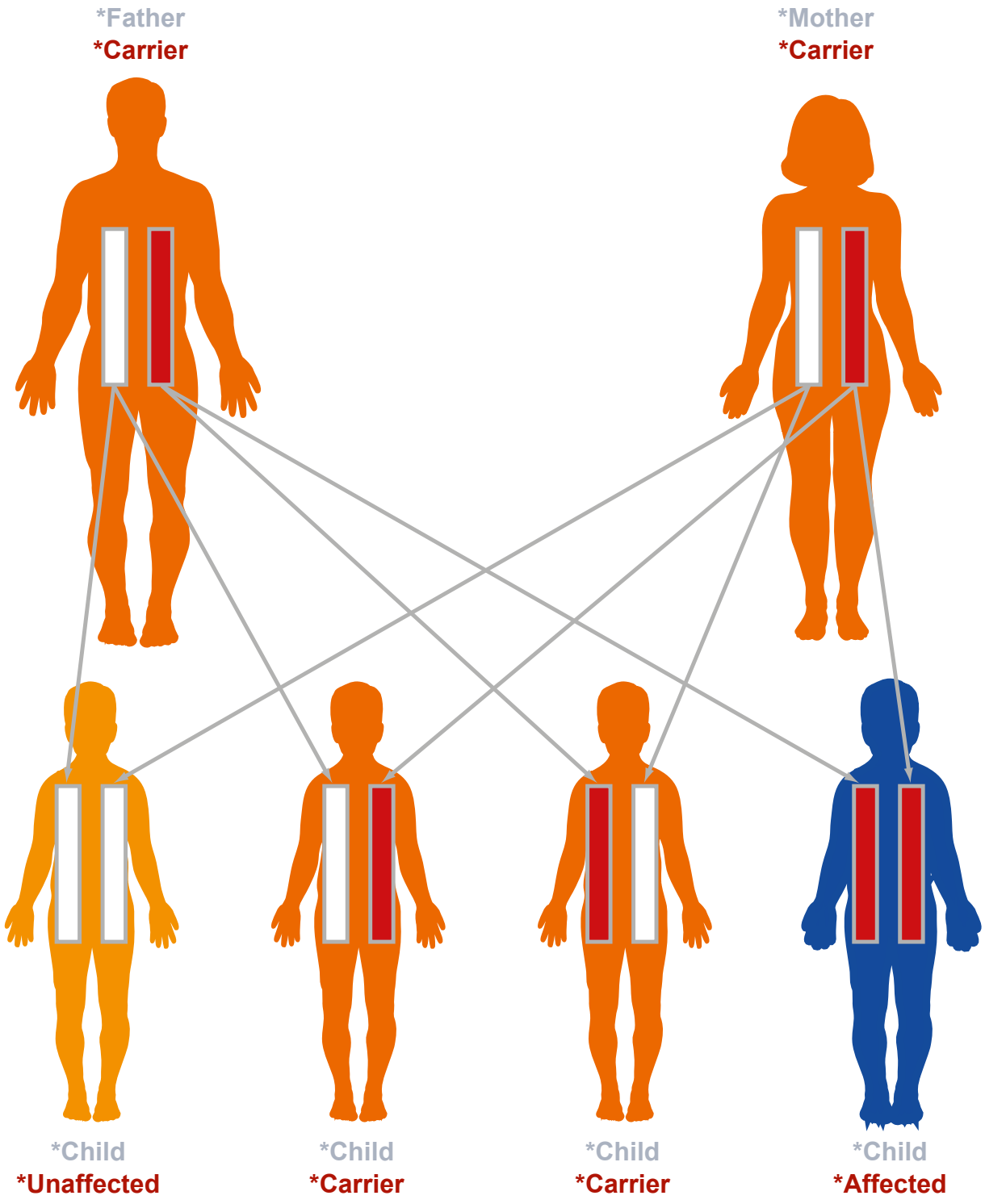
Autosomal recessive inheritance means that there is a 1 in 4 chance that a child may be born with a condition that both parents are carriers of.



04

*Diagnosis and symptoms
*What the diseases do

Sally
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"My initial reaction to Olivia's diagnosis was shock and thinking why hadn't this been tested for. Behind closed doors I had my private moments of upset."

Tay-Sachs and Sandhoff disease are extremely rare diseases which each have a variable onset and progression over a course of years. In the past they were frequently misdiagnosed or in some cases, even undetected.

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In order to diagnose the diseases there are a variety of diagnostic tools which are used. Each of these help the doctors to understand the diseases and their progression in an individual.

*Diagnosis can take some time

*Diagnosis
*How the diagnosis is made

A complex process

Diagnosing Tay-Sachs and Sandhoff disease involves a variety of complex testing procedures.

Different tests

Some individuals willl undergo a varity of different tests before a diagnosis can be made. It is very common for everyone to have a different diagnosis experience.

The initial testing for Tay-Sachs involves an enzyme assay to measure the hexosaminidase in serum, fibroblasts or leukocytes. Enzyme assays are laboratory methods for measuring enzymatic activity and they are vital for the study of enzyme kinetics and enzyme inhibition. Total hexosaminidase enzyme activity is decreased in individuals with Tay-Sachs as is the percentage of hexosaminidase A. After confirmation of decreased enzyme activity in an individual the next step is to gain confirmation by molecular analysis.

Most patients with infantile Tay–Sachs have a “cherry red” macula in the retina (also known as a cherry red spot), easily observable by a physician using an ophthalmoscope. In fact, this is commonly the first sign that the individual may be affected by a lysosomal storage disease before any investigation into enzyme levels has been undertaken. This red spot is a retinal area that appears red because of gangliosides in the surrounding retinal ganglion cells. The choroidal circulation is showing through “red” in this foveal region where all retinal ganglion cells are pushed aside to increase visual acuity. Thus, this cherry-red spot is the only normal part of the retina; it shows up in contrast to the rest of the retina. Microscopic analysis of the retinal neurons shows they are distended from excess ganglioside storage. Unlike many other lysosomal storage diseases such as Neimann-Pick, Gaucher and Sandhoff there is no enlargement of the liver or spleen in those individuals affected by Tay-Sachs.

Sandhoff disease can be detected through a variety of procedures, which include performing a biopsy removing a sample of tissue from the liver, genetic testing, molecular analysis of cells and tissues (to determine the presence of a genetic metabolic disorder) and an enzyme assay.


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*Signs and symptoms
*Different variants

Different variants

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Although the variants are different they all result in the same outcome. The main difference is that the effects of the disease can be slower.

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*Three different forms

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babies and small
ille which affects
and teenagers; and
ch affects adults
iduals.

*Different variants
*Three forms

“From that day we decided to make Isabella’s life the happiest it could ever be, filling each day with love, laughter and adventure. A promise we have kept to date.”

<u>*Cassandra</u>

The earliest presenting form of the diseases in children is called infantile Tay-Sachs or Sandhoff disease and is the result of a lack or severely reduced level of the Hexosaminidase A (Hex-A) enzyme in Tay-Sachs and both Hex-A and Hexosaminidase B (Hex-B) in Sandhoff.

Infantile Tay-Sachs / Sandhoff

The signs of the infantile form of the diseases in a child usually appear after they are 6 months old. Up until this point the child appear to be developing normally but this development then begins to slow. Other physical signs at this age include a prominent startle reflex to loud noises and also a gradual reduction in vision.

A child with the classical form of Tay-Sachs or Sandhoff disease gradually regress and begin losing skills one by one, such as the ability to roll over, sit or reach out. Other symptoms include loss of coordination, progressive inability to swallow and difficulty breathing.

As the diseases progress most children experience recurrent seizures by age 2 and eventually lose muscle function,sight and hearing. Sadly, they become non-responsive to their environment.

Juvenile Tay-Sachs / Sandhoff

The Juvenile forms of the diseases are rarer than the infantile forms and are usually initially seen in children between the ages of 2 – 10 years of age.

Early symptoms of Juvenile Tay-Sachs and Sandhoff disease include lack of coordination or clumsiness and muscle weakness such as struggling with stairs. A child may also exhibit slurred speech, swallowing difficulties and

muscle cramps which develop as the diseases progress.

Children with Juvenile Tay-Sachs and Sandhoff slowly decline, losing their ability to walk, eat on their own and communicate. Children are prone to respiratory infections and often experience recurrent bouts of pneumonia while many have seizures.

Juvenile Tay-Sachs and Sandhoff have a broad range of severity. In most cases, the earlier the first signs are observed, the more quickly the disease will progress. For example, a child who shows their first symptoms at age two will decline faster than a child with first symptoms at age five.

Adult onset Tay-Sachs / Sandhoff

Late Onset Tay-Sachs (LOTS), also known as Adult Onset is a very rare form of Tay-Sachs and Sandhoff disease which usually occurs in individuals in their 20s and early 30s.

Adult onset is frequently misdiagnosed, and is usually non-fatal. It is characterized by unsteadiness of gait and progressive neurological deterioration. The symptoms of LOTS, which present in early adulthood include speech and swallowing difficulties, unsteadiness of gait, spasticity, cognitive decline, and psychiatric illness.

As it is very difficult to identify, when an individual is finally given the diagnosis they often look back to their childhood and notice symptoms which were not obvious at the time. A common early sign is not being athletic and/or speech difficulties or a stutter as a child or teenager.

One early indicator which can lead to a LOTS diagnosis is a mental health problem, although this will just be the beginning of a long road to the final diagnosis. About 40% of affected adults experience mental health symptoms such as bi-polar or psychotic episodes.

Like all forms of Tay-Sachs and Sandhoff there is a loss of skills, although in LOTS this takes much longer than a child with the infantile forms of the diseases. Over a prolonged period of time adults with LOTS slowly decline and require more mobility assistance. Although many experience speech and swallowing difficulties only a few will eventually require a feeding tube.

As LOTS is very hard to diagnose, individuals can go many years before finding out they suffer from it. It is very common for LOTS to be misdiagnosed as Multiple Sclerosis, ALS or Friedreich ataxia.

Adults affected by the LOTS form of Tay-Sachs do not exhibit the tell-tale cherry red spot. This can make the road to diagnosis long and challenging. Unfortunately many healthcare providers are not aware of the rare adult forms of these diseases and dismiss the initial diagnosis due to the age of the patient.

There is currently no cure or treatment for Tay–Sachs disease. Even with the best care, children with infantile Tay–Sachs disease die by the age of four. Patients receive supportive care to ease the symptoms or extend life and improvements in life-extending care have somewhat lengthened the survival of children with Tay–Sachs and Sandhoff disease. In Late-onset Tay-Sachs and Sandhoff, medication can sometimes control psychiatric symptoms and seizures to make the individual more comfortable.

James

—

“Meeting other families has had such a positive impact on us as parents. We are able to share our experiences with people who know what we are going through.”

Eva

—

"We were told we would never meet another familiy affectd by Tay-Sachs. The doctors were so wrong and this has helped us look after Haylie."

*Acknowledgements
*Final words

Daniel - charity director
—
"The guides produced by The CATS Foundation will enable families to have access to all the informaiton they need when a diagnosis is made."

This booklet forms part of a resource pack published by The CATS Foundation. It is intended to be read in conjunction with the other parts of the pack.

If you do not have the other documents or would like further information please contact us.

Caroline Harding
CEO of Genetic Disorders UK
—
"We are delighted to be helping CATS Foundation who support children with Tay-Sachs and Sandhoff disease. Our grant programme is open to all UK support groups and registered charities who work to improve the lives of children and families affected by genetic disorders. In 2014, 25 charities will benefit from the funds raised by the public on Jeans for Genes Day."

The CATS Foundation would like to acknowledge the contribution made to this guide by parents, carers and medical professionals.

The CATS Foundation would also like to thank Genetic Disorders UK who provided a grant via the Jeans for Genes grant programe to enable the production and printing of the guides.

Funded by a grant from
Genetic Disorders UK

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