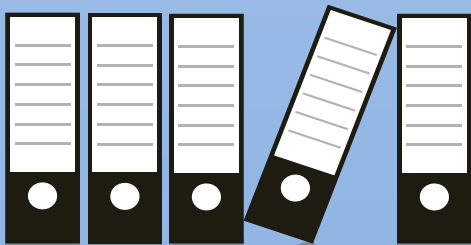


# LANGERHANS CELL HISTIOCYTOSIS LCH-CHILDREN



## Introduction

Despite the misery it causes, Histiocytosis is too rare a disease to have generated substantial research in medical circles. Unfortunately, for every child or adult fighting for his or her life, the pain and suffering are just as severe for children and adults afflicted with other better known disorders receiving funding.

For the children and adults battling these illnesses, there is now reason to hope. To ensure the research continues, we ask for your help, to complete the funding puzzle.

Our awareness and research programmes provide a beacon of hope for the many children and adults battling Histiocytosis, to ensure this research continues we ask you to pledge your support.

## Table of Contents

[WHAT IS HISTIOCYTOSIS](#)

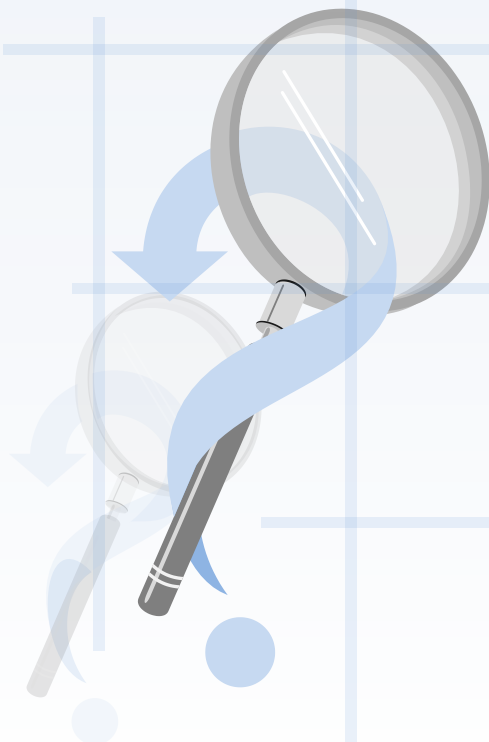
[WHO WE ARE](#)

[LANGERHANS CELL  
HISTIOCYTOSIS](#)

[WHAT IS LANGERHANS CELL  
HISTIOCYTOSIS \(LCH\)](#)

[FAQ](#)

[POSSIBLE SIDE EFFECTS](#)



## WHAT IS HISTIOCYTOSIS

### What is Histiocytosis?

Histiocytosis is an umbrella term applied to a group of rare diseases, characterised by increased numbers of white blood cells called histiocytes in the blood and tissues. In all forms of histiocytosis, these cells, which are part of the protective immune system, begin to attack the body, targeting many organs of the body including the bone marrow, liver, spleen, lungs, skin, bone and brain.

The prognosis for patients varies greatly depending on the form of histiocytosis.

**Please be advised that all the information you read in this document is not a replacement for the advice you will get from your consultant and their team.**



## WHO WE ARE

### Who we are?

Histiocytosis UK is a registered charity dedicated to promoting and funding scientific research into uncovering not only the causes of all histiocytic diseases, which include Langerhans Cell Histiocytosis and Haemophagocytic Lymphohistiocytosis, but also ensuring early diagnosis, effective treatment and a cure.

The Charity aims to support patients and their families by means of information and awareness as well as raise public and professional awareness of histiocytic disorders. Its team of Trustees include the UK's leading paediatric LCH and HLH specialists.



## LANGERHANS CELL HISTIOCYTOSIS - LCH

### Langerhans Cell Histiocytosis, LCH for short.

Histiocytes called Langerhans cells, which are normally found in the skin, may spread to many organs and damage them, so that symptoms vary depending on which organs are affected, but skin rashes, destruction of bone, breathing problems and damage to the brain are common.

LCH occurs in children, often during infancy but also in adults. It is usually a chronic disease and may cause severe disabilities due to brain damage. The diagnosis is made by microscopic examination of a tissue specimen obtained by biopsy. The prognosis depends very much on the extent of disease and organs affected, which can be assessed by imaging studies. LCH is thought to be caused by alterations in the DNA of Langerhans cells.



## WHAT IS LCH?

### What is Langerhans Cell Histiocytosis (LCH)

Langerhans Cell Histiocytosis (LCH) is the most common of the histiocytic disorders and occurs when the body accumulates too many immature Langerhans cells, a subset of the larger family of cells known as histiocytes. Langerhans cells are a type of white blood cell that normally help the body fight infection. In LCH, too many Langerhans cells are produced and build up in certain parts of the body where they can form tumours or damage organs. Most data support the concept that LCH is a diverse disease characterized by a clonal growth of immature Langerhans cells, that in more than half the cases have a mutation called V600E of the BRAF gene and related mutations in some other cases. V600E is found in tumours such as melanoma and thyroid cancer.

There has been some controversy about whether LCH is a cancer, but it is classified as such, and sometimes requires treatment with chemotherapy is not a fully developed malignant cancer. It is not contagious, nor is it believed to be inherited.

About 50 children in the UK develop LCH each year. It can affect children of any age and is more common in boys than in girls.

LCH is an unusual condition. It has some characteristics of cancer but, unlike almost every other cancer, it may spontaneously resolve in some patients while being life-threatening in others. LCH is classified as a cancer and sometimes requires treatment with chemotherapy. LCH patients are therefore usually treated by children's cancer specialists (paediatric oncologists/ haematologists).

The vast majority of children will recover completely from LCH.

Histiocytosis was first described in the medical literature in the mid to late 1800s. Through the years, it has been known by various names, such as histiocytosis-X, eosinophilic granuloma, Abt-Letterer-Siwe disease, Hashimoto-Pritzger disease, and Hand-Schüller-Christian syndrome. In 1973, the name Langerhans Cell Histiocytosis (LCH) was introduced. This name was agreed upon to recognize the central role of the Langerhans cell.

**LCH is believed to occur in 1:200,000 children**, but any age group can be affected, from infancy through adulthood. In new born and very young infants, it occurs in 1-2 per million. It is, however, believed to be under-diagnosed, since some patients may have no symptoms, while others have symptoms that are mistaken for injury or other conditions. It occurs most often between the ages of 1-3 years and may appear as a single lesion or can affect many body systems, such as skin, bone, lymph glands, liver, lung, spleen, brain, pituitary gland and bone marrow.

Information has been collected in various studies which show that bone involvement occurs in approximately 78% of patients with LCH and often includes the skull (49%), hip/pelvic bone (23%), upper leg bone (17%) and ribs (8%). Skin LCH is seen in as many as 50% of patients. Lung lesions are seen in 20% to 40% of patients, while 30% of patients have lymph node involvement.

Symptoms depend on the location and severity of involvement. It is usually diagnosed with a tissue biopsy, in addition to other testing, such as x-rays and blood studies. A biopsy of an involved site is necessary to make a definitive diagnosis.

While some limited cases of histiocytosis may not require treatment, for patients with more extensive disease, chemotherapy may be necessary. Haematologists and oncologists, who treat cancer, also treat children with Langerhans cell histiocytosis.

Most patients with LCH will survive this disease. LCH in the skin, bones, lymph nodes or pituitary gland usually gets better with treatment and is called "low-risk." Some patients have involvement in the spleen, liver, bone marrow, lung and skeleton. This is called "high-risk disease" and may be more difficult to treat. Some patients may develop long-term side effects such as diabetes insipidus, stunted growth, loss of teeth, bone defects, hearing loss, or neurologic problems; while other patients remain without side effects. In a minority of cases, the disease can be life-threatening.

Certain factors affect the chance of recovery and options for treatment. These factors include the extent of the disease, whether "risk organs" (liver, spleen, lung, bone marrow) are involved, and how quickly the disease responds to initial treatment.

## FAQ - LCH IN CHILDREN

### LCH in Children

#### 1. What causes LCH?

In more than half of LCH patients, the LCH cells have a mutation called V600E in a gene called BRAF. This mutation is found in tumours such as melanoma and thyroid cancer. In some other LCH patients, related mutations are found. These findings indicate that LCH is related to, but probably not a fully developed, cancer.

#### 2. Is there a cure for LCH?

While some patients go into remission and may live normal lives with or without treatment, we usually don't use the term "cure" with this disease. No specific amount of time without active disease has yet been established for adults to determine when a patient is considered to be cured.

#### 3. What is considered to be remission?

Complete remission means that there is no evidence of disease, whereas partial remission means that most of the signs and symptoms of LCH are gone, but some still remain. Doctors use the term response and "non-active" to describe patients who are free of symptoms and signs of LCH. Usually a cure is linked to being in remission for a certain period of time. There is no established period of "non-active" disease before LCH is considered cured, but the chance for recurrence is low after five years from end of treatment.

#### 4. Where did LCH get its name?

In 1868, the German pathologist Paul Langerhans discovered a type of white blood cell which eventually came to bear his name. The various manifestations of LCH were previously known by a number of different names (histiocytosis-X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian syndrome, etc.). In 1983, it was suggested that this disorder be named "Langerhans cell histiocytosis," to recognize the key role of the Langerhans cell in all of the different manifestations.

#### 5. Is LCH fatal?

It can be. A small percentage of patients, most often those with multisystem risk-organ involvement that is unresponsive to treatment, may not survive.

#### 6. What are the different therapies/treatments commonly used to treat LCH?

Treatment is based upon the organ(s) involved, extent of disease and age of the patient. In some cases, no treatment is necessary. Others may respond to surgical removal, steroids, or anti-inflammatory drugs (NSAIDs). Low-dose radiation is helpful in some situations, but should be carefully used in children. There are patients who require chemotherapy such as vinblastine, vincristine, etoposide (VP-16), methotrexate, cytosine-arabioside (Ara-C), and/or 6-MP. In patients with severe disease that does not respond to initial treatment, stronger chemotherapy combinations may be used. Ultraviolet light (PUVA) may be helpful for limited skin disease. In very rare instances, a transplant of the liver, lung, or bone marrow may be necessary.

#### 7. Can an infant be tested at birth for LCH?

A biopsy of the affected tissue, rather than a blood test, is required for diagnosis and would therefore not be appropriate as a routine test unless this disease is suspected.

#### 8. Is LCH hereditary?

Although there are rare families (less than 2% of all cases) documented with more than one member diagnosed with LCH, at this point, there is no clear evidence that this disease is inherited.

#### 9. Signs, Symptoms & can LCH spread?

The symptoms of LCH will depend on which part of the body is affected and whether the disease is affecting more than one part of the body. The lymph glands may be enlarged, and the child may be irritable and have a poor appetite.

Pain in the bone and/or swelling and lumps on the skull can occur if LCH is affecting the bone. A skin rash such as cradle cap or nappy rash may occur if the skin is affected. A discharge from the ear or hearing problems can occur if the ear is affected. The child may have breathing difficulties if LCH affects the lungs or chest. Tummy problems such as diarrhoea and liver problems including jaundice can occur if LCH affects the gut or liver.

In 10–20% of patients with multi-system disease, the pituitary gland at the base of the brain is affected, causing hormonal problems.

This can lead to the child passing larger amounts of urine and being very thirsty. This is called diabetes insipidus, which is different from sugar diabetes and can be well-controlled with specific medicines. Occasionally, other pituitary hormones may be affected, causing poor growth or delayed puberty, which can also be treated. The exact mechanism that causes lesions to appear in other locations in the body is not yet known. However, some researchers believe that abnormal LCH cells travel through the blood like tumor cells and "seed" in different locations, creating new lesions.

#### 10. Is there a blood test to diagnose LCH?

LCH is diagnosed with a biopsy of the affected tissue. Blood tests may be done to help determine the extent and/or severity of involvement, but blood tests are not diagnostic of the disease.

**11. Is it true that LCH is mostly a childhood disease?**

Not necessarily. Although we do know the incidence of childhood LCH, there is not enough data to determine how many adults are affected by this disease but because it is considered a childhood disease it is under diagnosed in adults.

**12. With the diagnosis and treatment of LCH, is my child more likely to develop cancer?**

Although this occurs rarely, LCH is associated with cancer more often than would be expected by chance. This can occur before, during, or after the diagnosis of LCH. Some cancers following the LCH diagnosis might be related to the treatments given. When cancer occurs before LCH, the histiocytosis might represent a “reaction” to the cancer itself.

**13. What are permanent consequences of LCH?**

Permanent consequences are also known as late effects of LCH, although they can occur early on. They are believed to be mostly related to the disease rather than treatment and include:

- a. Diabetes Insipidus
- b. Stunted growth
- c. Bone abnormalities
- d. Hearing loss
- e. Neurological problems, including poor coordination, unsteadiness, difficulty with handwriting, abnormal eye movements, problems with speech, learning disabilities/decreased school performance, memory loss, and behavior difficulties.
- f. Loss of teeth.
- g. Loss of spinal height
- h. Delayed puberty
- i. Bulging eyes.
- j. Scarring of lungs
- k. Scarring of liver/cirrhosis
- l. Secondary cancers

**14. What are the chances my child will develop permanent consequences?**

One or more permanent consequences are reported in an estimated 50% of all LCH patients, making long-term follow-up a necessity. Severity and type depends on the affected organs, number of lesions, and the treatment administered. Read more about permanent consequences of LCH.

**15. What is Neuro degeneration?**

Neuro degeneration is progressive loss of brain function. It occurs as a permanent consequence in some cases of LCH.

**16. Can neuro degeneration be prevented/reversed/treated?**

It is not currently known whether neuro degeneration can be prevented. It is believed that neuro degeneration cannot be reversed, and there is controversy whether patients with neuro degeneration can be successfully treated. There have been some promising results with Ara-C but more extensive scientific studies are required.

**17. What is “PLCH?”**

PLCH (pulmonary Langerhans Cell Histiocytosis) is LCH of the lung. It affects mostly adults who smoke and often occurs without other LCH involvement.

**18. What kind of doctor should we use?**

A pediatric oncologist most often provides primary treatment and coordinates a team of health professionals, which may include, but are not limited to, the primary care physician, pediatric surgeon, radiologist, pediatric nurses, and social workers.

**19. What should I look for in a doctor?**

LCH is most often followed and treated by an oncologist, who specializes in cancer-type illnesses. The level of experience with LCH can vary widely among physicians. If he/she is not knowledgeable about this disease, a willingness to learn more and consult with the experts can go a long way. Other qualities to look for are accessibility and good communication skills with you, as well as other physicians.

**20. Will my child grow normally?**

Most children with LCH do grow normally; it is believed that growth hormone deficiency affects approximately 10% of children with this disease.



## FAQ - LCH IN CHILDREN

### **21. What is the treatment for stunted growth related to LCH?**

If stunted growth is due to growth hormone deficiency, which occurs in approximately 10% of LCH patients, it can be treated with daily injections of growth hormone under the supervision of an endocrinologist. The treatment is usually prescribed as long as the child is growing.

### **22. Is growth hormone treatment safe?**

Growth hormone replacement appears to be safe and effective in LCH patients and is not associated with an increased risk of disease reactivation.

### **23. Are immunizations safe?**

This is a controversial topic. Most researchers believe that children should wait 3-6 months after chemotherapy and/or steroids to take regular vaccinations, especially live-virus vaccinations such as influenza, MMR, and polio. There is no proof that vaccinations trigger LCH. It is important to consult with your physician regarding your child's particular case.

### **24. What type of LCH involvement puts my child at higher risk for developing Diabetes Insipidus?**

CNS risk lesions have been identified as lesions affecting the facial bones or the front or side(s) of the skull. These include the temporal (around the temples), sphenoidal (behind the sinuses), ethmoidal (between the eyes), zygomatic (cheekbone), and orbital (eye socket) bone with tumor extension into the brain. Involvement of these bones increases the risk of developing Diabetes Insipidus, which is the hallmark of CNS disease.

### **25. What are the chances my child will develop diabetes insipidus?**

DI occurs in as many as 25% of all patients and as many as 50% of patients with multisystem LCH.

### **26. What are risk organs?**

Risk organs include bone marrow, spleen, and liver and are more difficult to treat than other sites of involvement with LCH.

### **27. Follow-up care and What happens if my child has a recurrence or does not respond to treatment?**

It is important to know that the vast majority of children will recover completely from LCH.

Some children however, are left with persistent/recurring problems and for a very small number of patients with multi-system LCH, it can be a life-threatening condition. After successfully completing treatment, patients will have follow-up clinic appointments. LCH sometimes comes back ('reactivates') and may need treatment again. If this happens, treatments for LCH that have worked for them before may be effective again. The same or different treatment may then be required. Patients are also monitored for possible permanent consequences of the disease (e.g. a low production of certain hormones, hearing problems) and may need treatment for these conditions.

If disease recurs after treatment, repeat of the same chemotherapy is often used but will depend on which organs are involved and the length of time since previous treatment. If LCH recurs immediately after therapy or does not improve with therapy, alternative treatment such as 2CdA, Ara-C, vincristine, methotrexate, or bisphosphonates may be used. Rare cases of risk-organ disease that is progressive and not responsive to treatment may require a RIC stem-cell transplant.

### **28. What is reduced-intensity conditioning (RIC)?**

Reduced-intensity conditioning is a less toxic pre-transplant therapy with the goal of suppressing the patient's immune system enough so that it will accept donor stem cells while reducing the side effects of high dose chemotherapy. The RIC may be used in some HLH patients, as well as some LCH patients with severe, resistant disease.

### Possible Side Effects of Treatment

#### What are the side effects of vinblastine?

Side effects include:

- a. Low blood counts (with higher risk of infection). Mild nausea/vomiting/constipation
- b. Easily sunburned
- c. Skin irritation at site of injection
- d. Thin or brittle hair
- e. Fatigue
- f. Bone pain
- g. Hoarseness
- h. Seizures
- i. Shortness of breath
- j. Nerve damage (especially in adults) with tingling, numbness and/or pain of the hands and feet

#### What are the side effects of prednisone?

Side effects include:

- a. Increase in blood sugar
- b. Increase in appetite
- c. Heartburn
- d. Bloating/fluid retention/weight gain
- e. Difficulty sleeping
- f. Mood/behavior/personality changes
- g. Higher risk of infection
- h. Slow wound healing
- i. Muscle weakness
- j. Loss of bone calcium
- k. Increased hair growth

More unusual side effects may include:

- a. Problems with vision/eye pain
- b. Seizures
- c. Confusion

#### What are the side effects of methotrexate?

Side effects include:

- a. Mouth sores/swollen, tender gums
- b. Nausea/vomiting/diarrhea/decreased appetite
- c. Low blood counts
- d. Dizziness/drowsiness
- e. Headache

More unusual side effects may include:

- a. Blurred vision or loss of vision
- b. Seizures
- c. Confusion
- d. Weakness/difficulty moving one or both sides of the body
- e. Loss of consciousness
- f. Lung damage
- g. Allergic reactions

## POSSIBLE SIDE EFFECTS

### **What are the possible side effects of 6-MP (mercaptopurine)?**

More common signs/symptoms include:

- a. Low blood counts (red cells, white cells, and clotting cells)
- b. Nausea/vomiting/decreased appetite
- c. Headache
- d. Weakness/fatigue/achiness
- e. Rash/darkening of the skin

### **What are the possible side effects of 2-CdA (cladribine/leustatin)?**

More common signs/symptoms include:

- a. Flu-like symptoms (Fever, chills, headache, fatigue, nausea/vomiting)
- b. Decreased appetite
- c. Constipation
- d. Low blood counts (red cells, white cells, and clotting cells)
- e. Skin rash/redness/itching