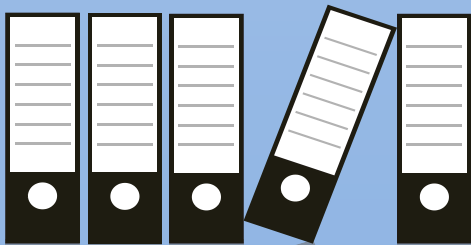


# LANGERHANS CELL HISTIOCYTOSIS

## LCH-ADULTS



## 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.

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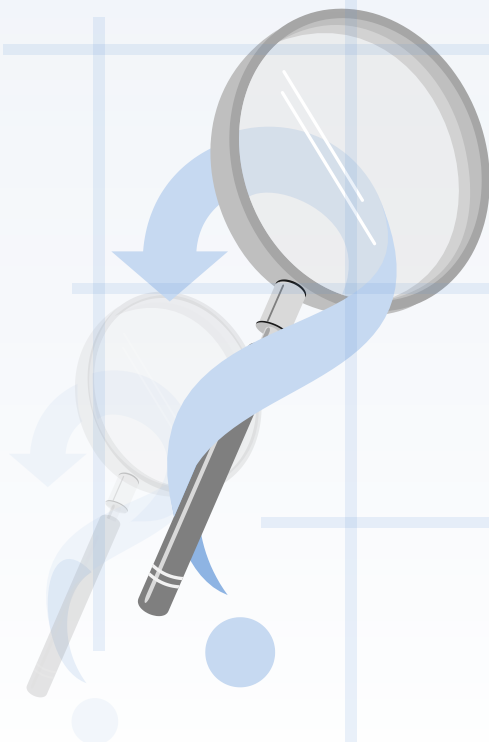
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## WHAT IS HISTIOCYTOSIS

### 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?

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.

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 can therefore be treated by cancer specialists (oncologists/ haematologists).

The vast majority of patients 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.

Although some forms of this disease were first described over a century ago, it has only been in recent years that LCH has received more attention, especially in adults.

It is estimated that LCH occurs in 1-2 adults per million people but no large scale studies on the incidence have been performed. It is important to remember that there are still many undiagnosed/misdiagnosed patients. The length of time from presenting symptoms to diagnosis can be years, which emphasizes the importance of finding a physician who is knowledgeable about this disease.

It is estimated that 63% of adults with LCH have lung-only disease, pulmonary Langerhans Cell Histiocytosis (PLCH), although it can also occur with other involvement, such as bone, skin or diabetes insipidus.

Although the cause is unknown, it is believed that 90-95% of adults with this disease are past or current smokers, suggesting that smoking is related. It has also been reported that children with LCH in organs other than the lungs who acquire the habit of cigarette smoking in adulthood may develop PLCH, sometimes years after the initial diagnosis.

There are no known environmental risk factors associated with LCH, with the exception of cigarette smoking in lung disease.

LCH can be systemic, and most often an oncologist/haematologist takes the main role in treating patients. However, since LCH can affect so many areas of the body, sometimes a team approach may be appropriate, and the oncologist may enlist the help of specialists such as surgeons, respiratory physicians (lung), dermatologists (skin), dentists or endocrinologists (diabetes/hormones) to give their input.

Most patients will survive the disease. Some will remain symptom free, while others may develop life-long problems. In some cases, especially those that are not treated and/or followed closely, the disease may become life threatening.

The patient's chances of survival and a good quality of life depend on the individual case, but research has suggested that the course is less favourable for elderly patients, those with multiple locations of disease and those who may have risk-organ (lungs, liver, spleen, bone marrow) involvement. Limited involvement can also become serious, depending on the particular sites involved, how quickly the disease continues to progress and the patient's response to treatment.

## FAQ - LCH IN ADULTS

### 1. What causes LCH in Adults?

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 so LCH is related to cancer but is not a fully developed malignant cancer. It is not contagious, nor is it believed to be inherited.

### 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. Follow-up care and What is considered to be remission?

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

Some 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 you have specific concerns about your condition and treatment, it's best to discuss them with your specialist medical team who know the situation in detail.

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. 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.

### 5. 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 patient 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 may occur if the skin is affected. A discharge from the ear or hearing problems can occur if the ear is affected. The patient 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 patient 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.

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.

### 6. 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.

### 7. 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.

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

Treatment is based upon the organ(s) involved, extension of disease, and in some cases, 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.

## FAQ - LCH IN ADULTS

### 9. How is LCH diagnosed?

LCH is diagnosed by 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.

A variety of tests and investigations may be needed to diagnose LCH. Tests are likely to include the removal of a sample of cells from an affected part of the body (a biopsy). This is usually done in an operation under a general anaesthetic. The cells are then examined under a microscope. X-rays are taken of the bones, the skull and the lungs. Blood and urine tests will also be done. Additional scans and tests may be required depending on which parts of the body is affected. These tests help the doctors decide whether the disease is a single-system or multi system type.

When you are having the tests, you may need to stay in hospital. Any tests and investigations that you need will be explained to you.

### 10. With the diagnosis and treatment of LCH, am I 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.

### 11. With a history of LCH, can I become pregnant?

Drugs used as part of the usual LCH treatment are not associated with infertility. These include vinblastine, vincristine, 2-CdA, methotrexate, Ara-C, and etoposide (VP-16). LCH can, however, affect the endocrine system, and complications can result in infertility. This is especially true if hormone loss is not diagnosed in time and if no hormone replacement is given. However, in some cases, hormone replacement therapy may restore fertility.

### 12. 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

### 13. What causes chronic pain in adults with LCH?

Some pain and cramping can be a side effect of treatment, such as vinblastine and steroids. Pain may also be directly related to active disease. In cases of more chronic pain, some researchers suspect that cytokines, which are a type of messenger, stimulate white blood cells to release inflammatory molecules that produce pain.

### 14. What healthcare workers should I see to help with pain management?

The primary oncologist/physician can treat and manage chronic pain in many cases. However, if the pain does not respond to the usual therapy and/or if the pain compromises quality of life, referral to a pain clinic may be necessary. Clinics differ in their approach and what they offer, but most include a team of health care providers with a variety of ways to manage pain and restore quality of life.

### 15. What should I look for in a doctor?

Many adults with LCH have been seen by a number of specialists, depending on their symptoms. It will be important to find a doctor knowledgeable about adult LCH who is willing to serve as the primary "hub" and coordinate input from the specialists. Ideally, this physician would be an oncologist who specializes in cancer-like illnesses and is qualified to provide systemic treatment. Accessibility and good communication skills with you, as well as other physicians, are important.

### 16. 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.

### 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.



## FAQ - LCH IN ADULTS

### **18. Why is cigarette smoking dangerous for me?**

It is believed that there is a strong link between cigarette smoking and pulmonary LCH. An estimated 90-95% of pulmonary-only LCH patients currently smoke or have smoked. Although the exact mechanism is not understood, it is believed that smoking can cause an accumulation of Langerhans cells in the lungs.

### **19. Can adults with a history of LCH donate blood or bone marrow?**

Although there is no data to prove a risk, adults with a history of LCH are advised against donating blood or platelets. They should also not be organ donors.

### **20. What is neuro-degeneration?**

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

### **21. 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.

### **22. What is chemo brain?**

Chemo brain is a term used for mild brain impairment that may occur during treatment. It can include symptoms such as difficulty concentrating, feeling disorganized, trouble with multi-tasking, memory lapses, slower thinking, word-finding difficulty, etc. For most patients, it lasts a short time.



### Possible Side Effects

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

Side effects include:

- a. Low blood counts (with higher risk of infection)
- b. Mild nausea/vomiting/constipation
- c. Easily sunburned 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
- d. Muscle twitching

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

a. Side effects include:

- b. Mouth sores/swollen, tender gums
- c. Nausea/vomiting/diarrhea/decreased appetite
- d. Low blood counts
- e. Dizziness/drowsiness
- f. 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 Weakness/fatigue/achiness
- d. 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