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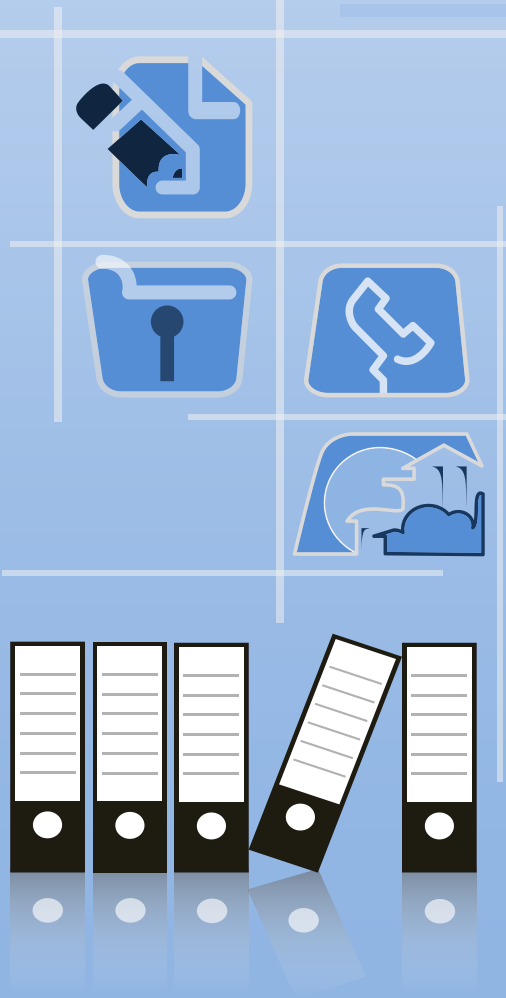
Haemophagocytic Lymphohistiocytosis

HLH – Adults & Young People



Histiocytosis UK

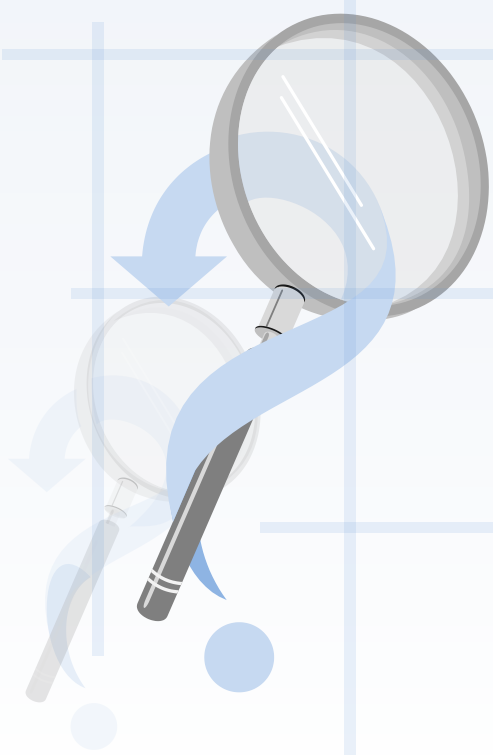
Introduction

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

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?

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.

Haemophagocytic Lymphohistiocytosis (HLH)
HLH for short.

Haemophagocytic Syndromes

Haemophagocytic Lymphohistiocytosis (HLH) is a rare disorder of the immune system primarily affecting young infants and children, although it can develop for the first time at any age. According to a large, population-based study published in Sweden, it was estimated to occur in 1.2 cases per million children, which corresponds to 1 in 50,000 births. However, this number must be considered minimal, as there are probably many patients today who are not diagnosed. For the autosomal-recessive forms of HLH (FHL), there is believed to be an equal number of male and female patients, but in addition, there are two known X-linked forms of FHL, affecting only males.

HLH involves over-production and activation of white blood cells called histiocytes and T cells, which normally combat infection. In contrast, often NK (natural killer) cell function is decreased. Decreased NK function is related to the consequence of genetic mutations which cause HLH. HLH is often referred to as either the “primary” form which is hereditary, or the “secondary” form associated with infections, viruses, autoimmune diseases, and malignancies (or cancers).

What is Haemophagocytic Lymphohistiocytosis (HLH)?

In the primary form, also known as Familial Haemophagocytic Lymphohistiocytosis (FHL or FHLH), defective genes are inherited from either both parents (autosomal recessive) or from the mother alone. In the latter case, the disease is called X-linked and only male children are affected. Since 1999, five genes have been identified which correspond with five subtypes of autosomal recessive HLH. The genes are PRF1 (perforin), MUNC13-4, STX11 (Syntaxin), STXBP2, and RAB27A. PRF1 encodes the protein (or toxin) normally involved in “killing” or eliminating abnormal immune cells. The proteins encoded by the other four genes facilitate the delivery of perforin to the cells which are to be killed.

While great progress has been made through research in recent years to define these genes, there remains a considerable proportion of FHL patients with as yet unknown underlying gene defects.

Onset of disease occurs under the age of 1 year in an estimated 70% of cases. FHL is suspected if siblings are diagnosed with HLH or if symptoms recur when therapy has been stopped. In the autosomal recessive form of the disease, each full sibling of a child with FHL has a 25% chance of developing the disease, a 50% chance of carrying one copy of the defective gene (which is very rarely associated with any risk of disease), and a 25% chance of not being affected and not carrying the gene defect. In the X-linked form of the disease 50% of male children will carry the defective gene and may develop disease. Fifty % of female children also carry the defective gene and may transmit it to their children but do not develop disease because they inherit a normal copy of the gene from their father.

So-called “secondary HLH” is often diagnosed in older patients who have no family history of this disease. It may be associated with vaccinations, viral infections such as Epstein-Barr, cytomegalovirus (CMV) or other herpes viruses, as well as other underlying diseases, principally autoimmune disorders and cancers, as mentioned previously.

It is difficult to know whether a patient has primary or secondary HLH on the basis of symptoms, which may be very similar. Therefore, genetic testing is usually recommended in order to make the proper diagnosis, regardless of age.

As awareness and understanding of this disease have increased worldwide, the diagnosis and survival rates have improved significantly. However, HLH remains a rapidly progressive disease requiring effective immunosuppressive and anti-inflammatory therapy.

It is sometimes difficult to establish the diagnosis of Haemophagocytic Lymphohistiocytosis (HLH), and the combination of the physical symptoms and certain laboratory tests is required. (Note: The understanding of the pathology underlying HLH/FHL disease is evolving, and recommended “diagnostic” criteria are likely to be revised in the future.)

- Low or absent NK (natural killer) cell function.
- Prolonged fever.
- Blood cell abnormalities (low white cells, low red cells, low platelets).
- Enlarged spleen.
- Increased triglycerides (fat) or decreased fibrinogen (protein necessary for clotting) in the blood.
- Increased ferritin (protein that stores iron) in the blood.
- Abnormal bone marrow test with evidence of Haemophagocytosis (ingestion of red or white cells by histiocytes) but not malignancy or other cause.
- Abnormally high CD25 (also known as sIL2ra) in the blood indicating abnormally increased T-cell activation.

The test for low or absent natural killer cell (NK) function has been found useful in making a clinical diagnosis of HLH. This abnormality is found in many patients with FHL, as well as in many cases of secondary disease but rarely in the X-linked forms.

However, it is just one piece of information and should not be used to determine the diagnosis of HLH as primary or secondary. NK function cannot be determined before birth, and it may not be reliably studied until a child is at least 6 weeks of age. FHL is suspected if siblings have been diagnosed with HLH, if symptoms intensify during treatment for HLH, or if symptoms return after therapy has been stopped.

Since it is difficult to tell the difference between secondary HLH and FHL, any case of HLH should be considered for genetic testing to confirm the diagnosis. Since 1999, at least seven defective genes have been identified. Autosomal recessive: PRF1 (perforin), MUNC13-4, STX11 (Syntaxin), STXBP2, and RAB27A. X-linked: SH2D1A, BIRC4.

There are some FHL patients (approximately 30%) with no identified gene defect, so normal genetic test results do not necessarily rule out the diagnosis of FHL. Genetic testing is usually done on blood, although other kinds of tissue samples can be used. Once the genetic cause is known, the parents can quickly be tested to confirm that they are carriers for that specific genetic type of FHL. Other siblings can also be easily tested, even before birth, once the genetic cause of the disorder in the family is known. Even in the event of death, salvaged tissue can be tested to determine if siblings are at risk.

In 1994, as a result of an international cooperative effort, the first treatment protocol for patients with HLH/FHL was designed. This included a combination of chemotherapy, immunotherapy and steroids, as well as antibiotics and antiviral drugs, followed by a stem-cell transplant in patients with persistent or recurring HLH or those with FHL. The HLH-2004 protocol was based on the HLH-94 protocol with minor changes such as cyclosporin, an immunosuppressant drug, being started at the onset of therapy rather than week #8. This protocol has been widely accepted internationally and is used in numerous countries on all continents but should still be considered experimental.

Secondary HLH may resolve spontaneously or after treatment of the underlying disease, without the use of chemotherapy. Therefore, treatment should be guided in part by the severity of the condition, as well as the cause of the disease.

FHL, however, when not treated, is usually rapidly fatal with an average historical survival of about 2 months. The treatment included in the HLH-2004 research protocol is intended to achieve stability of the disease symptoms so that a patient can then receive a stem-cell transplant, which is necessary for a cure.

In recent years, some transplant centers have adopted the use of reduced intensity conditioning (or “RIC”) to prepare for the stem cell transplant. This approach offers the possibility of better survival with stem cell transplant than the intensive chemotherapy protocols previously used.

As research continues, the outcome for patients with HLH/FHL has improved greatly in recent years. Approximately two-thirds of children with HLH who undergo transplantation can expect to be cured of their disease. However, there are a number of complications that can occur during the process of transplant, including severe inflammatory reactions, anemia, and graft-versus-host disease.

Long-term follow-up of survivors of transplants for HLH/FHL indicates that most children return to a normal or near-normal quality of life. The results of transplantation are generally better when the procedure is performed at a major pediatric transplant center where the doctors are familiar with this disease. Early and accurate diagnosis is essential. However, there is still a high rate of death, indicating that education of the medical community regarding prompt diagnosis and management of the diseases is required.

FAQ - HLH

1. What causes HLH?
HLH can either be acquired (secondary HLH) or inherited (FHL). Both forms of the disease can be triggered by infections, although it is not known why this happens. Secondary HLH may be triggered by vaccinations, viral infections such as Epstein-Barr, CMV (cytomegalovirus) or other herpes viruses, or other underlying diseases such as autoimmunity or cancer. In FHL, defective genes are inherited from one or both parents. Some other rare inherited immunodeficiencies may also be associated with HLH. The underlying immune defect and/or triggering events result in an abnormal immune response with activation of certain types of white blood cells (lymphocytes and macrophages) and the release of inflammatory proteins which then cause disease.

2. Is there a cure for HLH?
HLH patients with an underlying genetic defect can only be cured when the defective immune system is replaced by a healthy one which is what happens with a hematopoietic stem cell transplant. Secondary HLH cases can usually be cured by treating the underlying disease and sometimes additional immunosuppressive/immunomodulatory therapy.

3. What are the different therapies/treatments commonly used to treat HLH?
Some cases of secondary HLH can resolve spontaneously or after treatment of the underlying disease. Other cases are treated with a combination of chemotherapy (VP-16, methotrexate), immunotherapy (ATG, cyclosporin), and steroids. Any triggering infection has to be treated with appropriate antimicrobial drugs. Patients with persistent or recurring HLH or those with FHL additionally require a hematopoietic stem-cell transplant for recovery.

4. Why is routine newborn screening not available?
Although HLH may occur more frequently than some of the diseases routinely tested for, genetic testing for this disease is very complicated and very expensive.

5. How do I know if my child has primary HLH (inherited/FHL) or secondary HLH?
The clinical symptoms and laboratory findings do not differ in genetic or acquired HLH. Specific immunologic testing can raise the suspicion of genetic disease. In families with more than one affected child or in cases with disease reactivations there is a high probability of genetic disease. However, the identification of a genetic defect is necessary to prove it. Genetic testing is therefore recommended, regardless of age. Depending on the ethnic background up to 30% of patients with FHL have no identified gene defect, so negative test results do not necessarily rule out FHL.

6. How can I find out if my child's siblings have HLH?
In autosomal recessive forms of the disease, each sibling of a child with FHL has a 25% chance of being affected. In related genetic disorders, including X-linked lymphoproliferative disease, each male child has a 50% chance of being affected. If a genetic defect is known in your family, genetic testing (before or after onset of symptoms) is available to identify siblings who may also be affected.

7. How can I find out if future children are at risk for developing HLH?
If a genetic defect has been identified in your family, prenatal diagnosis is possible by performing either amniocentesis or chorionic villus sampling (CVS) to test if the fetus is affected.

8. What is MAS (macrophage activation syndrome)?
Macrophage activation syndrome is a severe, life-threatening illness caused by the excessive production of types of white blood cells called T cells and macrophages. MAS has strong similarities with familial Haemophagocytic Lymphohistiocytosis (FHL) and virus-associated Haemophagocytic Lymphohistiocytosis (HLH). The exact relationship between MAS and HLH is yet to be determined, although some researchers believe that MAS is a secondary HLH disorder. The term is typically used for the HLH-like syndrome that can occur in patients with systemic onset juvenile arthritis.

9. 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.