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Let's talk

Histio UK Connect – Let's Talk
an inclusive online discussion platform for each of the different Histiocytic disorders.
Find your Histio Champion Community at **www.HistioUKConnect.org**

About Histio UK

Histiocytosis UK is a registered Charity in England & Wales Number: 1158789. We are a national organisation supporting research and projects into Histiocytic Disorders. We support parents and patients, individuals and families affected by all histiocytic disorders these include:

Haemophagocytic lymphohistiocytosis (HLH)

Langerhans Cell Histiocytosis (LCH)

Juvenile xanthogranuloma (JXG)

Rosai-Dorfman Disease (RDD)

Erdheim-Chester Disease (ECD)

Diabetes insipidus (DI)

Our website at **www.histiouk.org** provides useful information on this range of conditions and topics, it explains the work we do, our research and our information support programs.

If we can be of any assistance, please contact us at histio@histiouk.org

Histio UK is reliant on voluntary donations. To make a donation, please go to: www.histiouk.org and follow the donate button.

If you are a Health Professional and would like more information on or would like to join our HLH Across Speciality Collaboration, Histiocytosis Registry or our Specialist Advisory Group please email **histio@histiouk.org.**

Registered in England and Wales Number 1158789

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No-one should die of Histiocytosis

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Information on

DIABETES INSIPIDUS DI

ERDHEIM CHESTER DISEASE ECD

JUVENILE XANTHOGRANULOMA JXG

ROSAI DORFMAN DISEASE RDD

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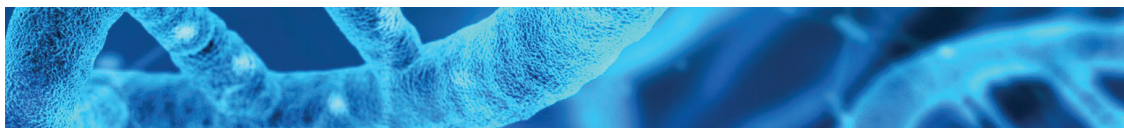

Introduction

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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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 LCH and HLH specialists.

Histiocytosis UK Registered in England & Wales Charity Number 1158789
Email: Histio@HistioUK.org www.histiouk.org

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.

Diabetes insipidus DI

Diabetes insipidus (DI) is a rare disorder that can occur as a consequence of histiocytosis involving the pituitary gland. It should not be confused with the more common diabetes mellitus, also known as sugar diabetes, which results from too much sugar in the blood. Although both disorders have similar symptoms, in every other way including the cause and treatment, they are completely unrelated diseases. The rate of occurrence for DI is not known, because there has been no organized method to count the number of patients.

Diabetes insipidus is a result of damage to the pituitary gland, a small gland at the base of the brain which stores and releases a hormone called ADH (antidiuretic hormone), also known as vasopressin. This hormone normally causes the kidneys to control the amount of water released as urine from the body. When the pituitary is damaged, the kidneys lose too much water (increased urination), which then leads to increased thirst.

The connection between histiocytosis and diabetes insipidus was first reported in the late 1800s. Since then, DI has been recognized as a characteristic feature of LCH. It is known to also occur in other histiocytic disorders, such as Rosai Dorfman and JXG.

It is believed that approximately between 5% and 50% of LCH patients develop DI depending on the extent of disease. The risk of developing DI in patients with multi-system LCH is 4 to 6 times more than those with single-system disease. Patients with skull, facial, and/or eye bone lesions are at much higher risk of developing DI. This risk is increased further if LCH remains active for a longer period or if it recurs.

Diabetes insipidus is recognized by a great increase in the amount of urine passed (often several gallons per day) and an increased thirst. Any patient with known LCH with an increase in drinking habits or passing large amounts of urine should be tested for DI.

Diabetes insipidus is diagnosed with a water deprivation test, which measures changes in body weight, blood values, urine output, and urine composition when fluids are withheld over a several-hour period. It is very important that this test be supervised by a knowledgeable physician in a medical setting. An x-ray test called an MRI scan is sometimes performed to see if there is change in the brain and pituitary area, but this test alone cannot diagnose DI.

Diabetes insipidus is usually a permanent, lifelong condition and cannot be cured. However, the symptoms of constant thirst and urination can be well controlled with treatment with DDAVP, a synthetic kind of vasopressin, and normal, symptom-free quality of life can be restored.

FAQ

1. What is the difference in diabetes insipidus and diabetes mellitus?
Two different types of hormones are involved: diabetes insipidus due to impaired production by the pituitary gland of a hormone called antidiuretic hormone and may occur as a consequence of histiocytosis. Diabetes mellitus, on the other hand, results from too much sugar in the blood, due to impaired insulin production by the pancreas. Although both disorders have similar symptoms of increased thirst and urination, in every other way including the cause and treatment, they are completely unrelated diseases.

2. 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 multi-system LCH.

3. Why is it important that the testing for DI be done in a clinic/hospital?
The water-deprivation test is a complicated procedure that requires highly trained medical professionals to perform specialized measurements. The body's water balance must be carefully monitored during the procedure to prevent rapid and dangerous dehydration.

4. How is a water deprivation test done?
This test includes timed measurements (some done every hour and others done every other hour) of blood pressure, pulse, weight, urine, and blood. Fluid is withheld during testing. The test may take up to 8 hours to complete, but it may be stopped sooner, depending on lab results. Further information and instructions will be provided by your physician.

5. Can diabetes insipidus be reversed?
Once DI has been diagnosed, the chance of reversal is uncommon. However, it has been reported in some cases where treatment was started within a few days of symptom onset.

6. Can diabetes insipidus occur before the diagnosis of LCH?
DI can be the first presenting symptom, although one half of these patients develop LCH lesions within 1 year after the onset of diabetes insipidus.

7. Can diabetes insipidus due to LCH occur when there is no known involvement anywhere else?
Yes. It is believed that this occurs in less than 10% of patients. The diagnosis is made from biopsy of the tumour in the pituitary stalk.

8. Can diabetes insipidus in LCH be prevented?
There is evidence that a rapid start of chemotherapy after onset of multi-system LCH may prevent DI.

Erdheim Chester disease ECD

Erdheim Chester disease is a rare form of non-Langerhans Cell Histiocytosis. It involves the excessive production of histiocytes, which are a type of white blood cell. These cells, which normally help fight infection and injury, then gather in different organs and tissues and can result in a variety of symptoms, including organ failure.

Erdheim Chester is a disease that most often becomes apparent in middle age, with an average age at onset of 53 years. It can affect men and women. The rate of occurrence is not known, although it is believed to be under-diagnosed and/or mis-diagnosed. At the present time, it is not categorized as a cancer, immune disorder, or infection. It is not believed to be contagious or hereditary. The cause is not known although some cases have the BRAF V600E mutation also found in LCH and cancers such as melanoma and thyroid cancer.

The first two cases of ECD were reported by scientists Jakob Erdheim and William Chester in 1930. In 1972, Dr Ronald Jaffe reported a third case and coined the name Erdheim Chester disease (ECD).

This disease mostly affects long bones (arms and legs), but it can occur in the tissues behind the eyeballs, kidney, skin, brain, lung, heart, pituitary gland, and a part of the posterior abdominal wall called the retro peritoneum. Erdheim Chester is sometimes mistaken for Langerhans Cell Histiocytosis. However, a biopsy of the affected tissue differs in a number of ways from LCH and can establish a definite diagnosis. The cells in ECD stain for the same proteins as Juvenile Xanthogranuloma (JXG) but the clinical presentation and age is different. The symptoms and course of the disease depend on the location and extent of the involvement of the internal organs (i.e. the disease outside the bones).

Because this is a very rare disease, no large studies have been performed, and no treatment plan has been established that is widely accepted. However, various treatments have been used with limited success. These include steroids, immunotherapy (treatment to restore the ability of the immune system such as interferon), chemotherapy to control the over-production of cells, the use of high-energy rays (radiation therapy), and/or surgery. Some patients with the BRAF V600E have been treated with Vemurafenib, which targets this mutation. While these treatments may control the symptoms and growth of the disease, there is no known “cure.”

Erdheim Chester can be life-threatening with complications such as heart failure, severe damage to the lungs, and kidney failure. However, with treatment, there are patients who are able to live a near-normal life.

FAQ

1. What causes Erdheim Chester Disease (ECD)?
Erdheim Chester disease involves the excessive production of histiocytes, which are a type of white blood cell.

Most, if not all, cases of ECD have mutations (changes in the DNA) in kinases, which are molecules involved in transmitting signals from outside the cell to the nucleus. Similar mutations are found in cancers such as melanoma or thyroid cancer. However, ECD does not behave like a typical malignant tumour. It is not inherited or contagious.

Some cases have the BRAF V600E mutation also found in LCH and cancers such as melanoma and thyroid cancer.

2. Is there a cure for Erdheim Chester Disease?
The best treatments available today may control and sometimes shrink the tumours associated with the disease. However, we usually do not use the term “cure” for this disease, since no specific amount of time without active disease has been established to determine that a patient is cured.

3. What are the different therapies/treatments commonly used to treat Erdheim Chester Disease?
To date, there is no universally accepted treatment for Erdheim Chester. Various treatments, however, have been used with variable success. These include steroids, interferon, radiation, surgery, and chemotherapy such as vinblastine, vincristine, Cytoxan (cyclophosphamide), Adriamycin (doxorubicin), and 2CdA (cladribine).

Other drugs have also been used including Vemurafenib, which targets the kinase mutation, BRAF V600E, which is found in many ECD and Langerhans Cell Histiocytosis patients. Vemurafenib has shown promising results in patients when other therapies have failed.

4. Can an infant be tested at birth for ECD?
No, a biopsy of the affected tissue, rather than a blood test, is required for diagnosis and unless the patient has a lesion this could not be performed.

What are the possible side effects of interferon?

1. More common signs/symptoms include:
a. Flu-like symptoms (fever, chills, headache, dizziness, fatigue, muscle aches, nausea, vomiting, diarrhoea)
b. Irritability/depression
c. Decreased appetite
d. Irregular heart rate
e. Decreased blood counts (red cells, white cells, and clotting cells)
f. Liver abnormalities

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

2. 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

Juvenile xanthogranuloma JXG

Juvenile xanthogranuloma, also known as JXG, is a rare, non-Langerhans Cell Histiocytosis that is usually benign and self-limiting. It occurs most often in the skin of the head, neck, and trunk but can also occur in the arms, legs, feet, and buttocks. JXG can affect the eye, most commonly in young children with multiple skin lesions. Less commonly JXG may involve locations such as the lung, liver, adrenal gland, appendix, bones, bone marrow, pituitary gland, central nervous system, kidney, heart, small and large intestines and spleen.

JXG involves the over-production of a kind of histiocyte called a dendritic cell (not a macrophage). These cells then accumulate and lead to various symptoms, depending on location. The cause of this disease is not known.

This disease may have been first reported by Rudolf Virchow in 1871 and again in 1905 by H.G. Adamson. In 1954, it was named Juvenile xanthogranuloma to reflect the appearance of the cells under a microscope.

JXG mainly affects infants and small children with an average age of 2 years, although it can also occur in adults of all ages. Usually it presents as a single skin lesion, which varies in size, but children less than 6 months of age are more likely to have multiple lesions. It occurs at birth in about 10% of patients and more males are affected than females. When JXG occurs in adults, it tends to be more complicated and is not known to spontaneously improve. The total number of patients with JXG is not known, but it may be higher than reported since this disease is sometimes mis-diagnosed or may spontaneously improve in children.

Skin lesions are self-limiting and rarely require treatment in most patients. Those with large abdominal masses, liver, bone marrow, or central nervous system involvement may do well with treatment such as chemotherapy similar to that used for Langerhans Cell Histiocytosis. Because this disease is so rare, no large studies have been performed, and there is no established, proven treatment for the more complicated cases.

FAQ ...continues on next page

1. What causes Juvenile xanthogranuloma (JXG)?
JXG involves the over-production of a kind of histiocyte called a dendritic cell. What triggers these cells to accumulate is not known but mutations (alterations to the DNA) in kinases have been detected in a proportion of cases. Kinases are molecules involved in transmitting signals from outside the cell to the nucleus. They are found in cancers such as melanoma or thyroid cancer but JXG does not behave like a typical malignant cancer.

2. Is there a cure for JXG?
We usually do not use the term “cure” with this disease, although most patients with only skin or soft tissue JXG have spontaneous remission over time without treatment. Children with liver, bone marrow, CNS involvement and masses in the abdominal cavity usually survive with chemotherapy treatment. There is no established period of inactive disease before JXG is considered cured.

FAQ ...continued

3. What are the different therapies/treatments commonly used to treat JXG?
Patients with a single lesion or just a few lesions, as well as children with skin-only JXG often require no therapy. Surgical removal may be required if the mass is causing organ dysfunction. A small percentage of patients with rapidly growing disease may require treatment with chemotherapy or low-dose radiation, however there is no agreed standard. Steroids have been used to treat eye lesions and in some cases low dose radiation has been effective in preventing visual loss.

4. Can an infant be tested at birth for JXG?
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.

Rosai Dorfman Disease RDD

Sinus Histiocytosis with Massive Lymphadenopathy (SHML)

Rosai Dorfman Disease (RD), also known as sinus Histiocytosis with massive lymphadenopathy (SHML), is a rare histiocytic disorder which involves the over-production of a type of white blood cell called non-Langerhans Cell sinus histiocytes. These cells then accumulate, most often in the lymph nodes but sometimes in other areas of the body and can lead to organ damage. The reason for over production of these cells is not known, although many possibilities have been considered, including viral, bacterial, infection, environmental and genetic causes.

In 1969, two pathologists, Juan Rosai and Ronald Dorfman, reported a distinct histiocytic disorder in several patients with massive enlargement of the lymph nodes, as well as other symptoms. They named this condition sinus histiocytosis with massive lymphadenopathy, and the disease has since come to be known as Rosai Dorfman disease.

The true number of RD cases is not known, although it does occur worldwide and seems to affect equal numbers of males and females. It is most commonly seen in the first 10 years of life, but it also occurs in adult patients.

Because this disease is so rare, no large studies have been performed, and there is no established, widely accepted treatment. However, RD is usually not life-threatening, and many patients do not require treatment.

FAQ

1. What causes Rosai Dorfman Disease?
Rosai Dorfman involves over-production of a type of white blood cell called a non-Langerhans Cell sinus histiocyte. A proportion of cases have mutations in kinases. These are molecules involved in transmitting signals from outside the cell to the nucleus. Similar mutations are seen in some forms of cancer. However, Rosai Dorfman does not behave like a malignant cancer and may resolve without treatment.

2. Is there a cure for Rosai Dorfman Disease?
While many patients go into remission and live normal lives with or without treatment, we usually do not use the term “cure.” There is no established period of inactive disease before RDD is considered cured.

3. What are the different therapies/treatments commonly used to treat Rosai Dorfman Disease?
Many Rosai Dorfman patients do not require treatment. Some patients with severe or persistent disease may need treatment with surgery, steroids, and/or chemotherapy. Rarely, radiation therapy is used.

4. Can an infant be tested at birth for Rosai Dorfman Disease?
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.

5. What causes chronic pain in adults with Rosai Dorfman Disease?
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.

What are the side effects of vinblastine?

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

What are the side effects of prednisone?

2. 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/behaviour/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?

3. Side effects include:
a. Mouth sores/swollen, tender gums
b. Nausea/vomiting/diarrhoea/decreased appetite
c. Low blood counts
d. Dizziness/drowsiness
e. Headache

4. 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

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

1. 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