IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

WHIM SYNDROME

ABBREVIATIONS

G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte–macrophage colony-stimulating factor
HPV	Human papillomavirus
IG	Immunoglobulin
IgG	Immunoglobulin G
PID	Primary immunodeficiencies
WBC	White blood cell
WHIM	Warts, Hypogammaglobulinaemia, Infections and Myelokathexis

WHIM syndrome (1st edition).

IPOPI wishes to thank Prof Raffaele Badolato, a paediatric immunologist at the University of Brescia, Italy, for his kind support in the preparation of this booklet.

IPOPI wishes to thank the patient and family who shared their pictures to illustrate this leaflet.

Published by IPOPI: IPOPI.org

INTRODUCTION

This booklet explains what WHIM syndrome is, how it is diagnosed, what treatment options are available and ways to manage the disease.

WHIM syndrome is an extremely rare genetic primary immunodeficiency. Primary immunodeficiencies (PIDs) are rare diseases that occur when certain parts of the immune system are either missing or not functioning properly. The immune system protects the body from infections, allergies and other conditions, so when the immune system is not working properly persons with PIDs are more likely to get these conditions.

WHIM syndrome is characterised by **W**arts, **H**ypogammaglobulinaemia, **I**nfections and **M**yelokathexis; it is also characteristed by leukopenia, by neutropenia and lymphocytopenia, but this is not included in the acronym. The most frequent manifestation of WHIM is neutropenia, while the other symptoms are not necessarily present. As a result of the immune deficiency, individuals with WHIM syndrome have low white blood cell (WBC) counts and thus are more susceptible to potentially life-threatening bacterial infections and viral infections, notably human papillomaviruses (HPVs), the viruses that cause skin and genital warts and may lead to cancer.

The following sections explain how WHIM syndrome is diagnosed, what the symptoms are and the long-term effects of the condition, what treatment options are available and ways to manage the disease.

WHAT IS WHIM SYNDROME?

PIDs are rare diseases that occur when certain parts of the immune system are either missing or not functioning properly. WHIM is characterised by **W**arts, **H**ypogammaglobulinaemia, **I**nfections and **M**yelokathexis; it is also characterized by leukopenia, neutropenia and lymphopenia, but this is not included in the acronym). WHIM syndrome is an extremely rare disorder and its exact prevalence or incidence in the general population is unknown, although an incidence has been estimated at about 0.2 per million live births. Only approximately 100 cases have been reported in medical literature; it affects both males and females equally and onset usually occurs in infancy or early childhood.

The genetic mutation that causes WHIM is inherited as an autosomal dominant trait, which means only a single copy of an abnormal gene is necessary for the disease to appear, and it can be inherited from either parent. WHIM can also be the result of a new mutation in the affected individual. The risk of passing the abnormal gene from an affected parent to child is 50% for each pregnancy regardless of the sex of the child.

Individuals with WHIM syndrome have low numbers of WBCs (neutropenia, leukopenia), which are the primary defense against a large array of infections. Hence, persons with WHIM syndrome are more susceptible to bacterial infections, which can be mild or severe and often occur repeatedly, usually respond quickly to antibiotic therapy. Viral infections, notably HPVs, which are viruses that causes skin and genital warts (and can lead to cancer) are also common in WHIM patients.

The symptoms of WHIM syndrome can vary considerably between individuals; some may only have mild symptoms while others may develop potentially life-threatening complications, which usually affect the respiratory tract or pose WHIM patients at risk of developing malignancies. Because of the small number of identified cases, the lack of large clinical studies, and the possibility of other genes influencing the disease outcome, it is challenging for healthcare providers to have an accurate picture of associated symptoms and disease prognosis.

HOW IS WHIM SYNDROME DIAGNOSED?

CLINICAL PRESENTATION OF WHIM SYNDROME

Typically, symptoms are first apparent in early childhood (in the first decade of life). Not all features are present in all individuals; the main feature is that individuals with WHIM syndrome experience repeated bacterial infections that can be mild or severe, but usually respond quickly to antibiotic therapy.

Warts. Persons with WHIM syndrome may develop warts due to infection with HPV. Warts usually develop during the teenage years but can be seen in early childhood. Warts may be widespread across the body and affect particularly the hands, feet, face and trunk; warts often recur despite treatment. Mucosal, oral, and genital warts may also develop and are associated with an increased risk of cancer. Warts often recur after surgery or other conventional therapy. Regular monitoring to promptly detect and surgically remove any HPV lesions that appear pre-malignant or malignant is recommended.

Hypogammaglobulinaemia. Individuals with WHIM syndrome often have low levels of a specific type of WBC called B lymphocytes (also known as B cells). These cells are responsible for the production of antibodies that are needed to fight off bacterial and viral infections. As a result, these individuals often have low levels of or lack antibodies, a condition known as ***hypogammaglobulinaemia***. The lack of sufficient antibodies leaves individuals susceptible to infection by specific types of bacteria or, to a lesser extent, certain viruses. Some affected individuals may also have low levels of other WBCs such as T cells or natural killer cells, or even all WBCs, such a condition is called panleukopenia or pancytopenia. Not all persons have all of these features.

Infections. Repeated bacterial infections are extremely common and can include middle ear infections (otitis media), infections of the skin and underlying tissue (cellulitis, impetigo, folliculitis and abscess), chest (bacterial pneumonia) and nose (sinusitis); less common are infections of the joints (septic arthritis), dental cavities, gums (periodontitis), bone (osteomyelitis), urinary tract and meninges in the brain (meningitis). These infections usually respond quickly to antibiotic therapy. However, chronic infections can cause additional symptoms; for example, individuals who experience repeated ear infections may go on to experience hearing loss; repeated dental infections can lead to tooth loss; and repeated episodes of pneumonia may eventually lead to bronchiectasis, which can lead to repeated lung infections and potentially serious complications such as chronic lung failure.

Myelokathexis. This is a congenital disorder of WBCs that causes severe, chronic leukopenia (a reduction of circulating WBCs) and neutropenia (a reduction of neutrophils). Although neutrophil production occurs normally in the bone marrow of individuals with WHIM syndrome, when these WBCs reach maturity they are not released into the bloodstream but instead are trapped in the bone marrow – a condition is called ***myelokathexis***. This explains why patients with WHIM syndrome often have too many WBCs present in the bone marrow (hypercellularity) and low levels of circulating neutrophils in the blood (neutropenia). However, this can be overcome during periods of severe infection or stress.

Less common clinical characteristics include tetralogy of Fallot (a congenital defect that affects normal blood flow through the heart) and cerebellar abnormalities (usually affecting movement and coordination).

CLINICAL DIAGNOSTIC CRITERIA

A diagnosis of WHIM syndrome is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation, evaluation of neutrophil and lymphocyte counts, IgG level and genetic testing of the *CXCR4* gene. Individuals with a history of recurrent bacterial infections, neutropenia, and recalcitrant warts should be tested for WHIM syndrome.

A complete blood count will show neutropenia in uninfected patients, a variable degree of lymphopenia, and normal to low haemoglobin and platelet levels. Initial work-ups can also reveal hypogammaglobulinaemia or poor response to vaccinations.

If WHIM syndrome is suspected based on initial tests, the surgical removal and microscopic examination of bone marrow tissue (aspiration or bone marrow biopsy if needed) may be performed. If this biopsy confirms myelokathexis, this is strongly suggestive of WHIM syndrome.

GENES ASSOCIATED WITH WHIM SYNDROME

In recent years, genetic testing has allowed the genes associated with many PIDs to be identified. WHIM syndrome is caused by gain-of-function mutations in the *CXCR4* chemokine receptor gene, which makes the CXCR4 protein hyperfunctional. This is thought to prevent the release of mature neutrophils from bone marrow, although more research is necessary to determine the complex, underlying mechanisms that cause WHIM syndrome.

Some individuals with the characteristic symptoms of WHIM syndrome do not have a detectable mutation in the *CXCR4* gene, suggesting that the disorder may also have other genetic causes. That said, in most individuals molecular genetic testing can now confirm the diagnosis of WHIM syndrome. Because other PID can mimick WHIM syndrome, clinicial evaluation of each case by an immunologist specialised in WHIM may be required.

WHIM syndrome is an autosomal dominant genetic condition, which means that affected individuals have a single abnormal copy of the gene. The abnormal gene can be inherited from either parent as mentioned above or can be the result of a new mutation (sporadic or de novo gene change) in the affected individual. In the latter case, the gene mutation has occurred at the time of the formation of the egg or sperm for that child only, and no other family member will be found to be affected. For individuals carrying the mutated gene, the risk of passing it from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females. The disorder is usually not inherited from or “carried” by a healthy parent.

WHAT TREATMENT IS SUGGESTED FOR WHIM SYNDROME?

The treatment of WHIM syndrome is directed toward the symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists, potentially including a paediatrician (when the patient is a child), immunologist, haematologist, dermatologist and other healthcare professionals, to systematically and comprehensively create a treatment plan.

Prompt diagnosis and early aggressive treatment of infections is important to reduce long-term damage. Treatment may include injection of granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF), both of which stimulate the production and maturation of neutrophils and help reduce the risk of infection.

Monthly infusions with immunoglobulins (IGs) manufactured from human plasma, the fluid portion of the blood, can also be used to treat individuals with WHIM syndrome. With IG therapy the hypogammaglobulinaemia is treated and can help reduce the frequency of recurrent infections. IG therapy can be given subcutaneously or intravenously.

The preventative (prophylactic) use of antibiotics has not been studied in WHIM syndrome, but has proven effective in other PIDs.

Vaccinations against HPV should be strongly considered in individuals with WHIM syndrome given the severity of HPV infections in these persons. As antigen-specific antibodies induced after vaccination may wane, PID patients should rely on their PID specialist who may suggest to repeat the vaccination in few years intervals based on clinical evaluation and immunological work-ups.

Specific treatment of warts, such as topical application of the immune response modifier imiquimod, may also be considered.

Investigational therapies for WHIM syndrome include: bone marrow transplantation in which blood stem cells from another person (called an allogenic donor) may be effective, but there are no studies specifically evaluating this in WHIM syndrome; inhibitors of CXCR4 activity, such as plerixafor (which is approved for mobilisation of haematopoietic stem cells in patients with lymphoma or multiple myeloma), or mavorixafor, an oral therapy, which has been shown to help neutrophils and other WBCs move from the bone marrow into the bloodstream.

LIVING WITH WHIM SYNDROME

WHIM-affected individuals may live well into adulthood. Early vaccination against HPV is recommended as it may be able to prevent certain HPV infections and reduce HPV-related cancer potentially associated with WHIM syndrome.

HPV-associated warts frequently recur after surgery or other conventional therapies. Affected individuals should be regularly monitored to promptly detect and surgically remove any HPV lesions that appear pre-malignant or malignant.

Genetic counseling is recommended for affected individuals and their families. Psychosocial support for the entire family is also essential.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

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Supporting families affected by primary and secondary immunodeficiency

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

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www.immunodeficiencyuk.org
hello@immunodeficiencyuk.org
0800 987 8986