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Primary Immunodeficiency disorders

1. Autoimmune Lymphoproliferative Syndrome (ALPS)

Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disorder of the immune system first described by NIH scientists in the mid-1990s that affects both children and adults. In ALPS, unusually high numbers of white blood cells called lymphocytes accumulate in the lymph nodes, liver, and spleen and can lead to enlargement of these organs. ALPS can also cause anemia (low level of red blood cells), thrombocytopenia (low level of platelets), and neutropenia (low level of neutrophils, the most common type of white blood cell in humans). These problems can increase the risk of infection and hemorrhage.

## **Causes**

Most cases of ALPS are caused by mutations in theFAS gene. FAS produces a receptor that, when activated, leads to programmed cell death, or apoptosis. This programmed death is an important part of the normal cell lifecycle. When cells do not receive the message that it is time for them to die, an abnormal buildup of cells can result. In the case of ALPS, mutations in FAS cause an abnormal buildup of white blood cells.

## **Symptoms & Diagnosis**

The major clinical symptoms of ALPS, including fatigue, nosebleeds, and infections, result from a proliferation of lymphocytes and autoimmune destruction of other blood cells. The diagnosis of ALPS is based on clinical findings, laboratory findings, and identification of genetic mutations.

## **Treatment**

There currently is no standard cure for ALPS. The disorder can be managed by treating low blood-cell counts and autoimmune diseases that occur in people with ALPS, as well as by monitoring for and treating the proliferation of immune cells, enlarged spleen, and lymphoma.

1. BENTA disease

BENTA disease is a rare genetic disorder of the immune system caused by mutations in the gene *CARD11*. BENTA stands for “B-cell expansion with NF-jB and T-cell anergy.” The disease is characterized by high levels of certain immune cells starting in infancy, an enlarged spleen, enlarged lymph nodes, immunodeficiency, and an increased risk of lymphoma, a type of cancer. Breaking down the name, BENTA, helps explain the syndrome.

• A ***B cell*** is a type of immune cell from the bone marrow.

• ***Expansion*** means that the number of B cells is greater than normal.

• ***NF-*j*B*** is a protein complex involved in gene expression, or the degree to which certain genes are turned on or off.

• A ***T cell*** is a type of immune cell that matures in the thymus, a small organ located in the upper chest under the breastbone.

• ***Anergy*** refers to a “less-than-normal” (T cell) immune reaction to foreign substances. BENTA disease is diagnosed based on clinical and laboratory findings as well as genetic testing.

**Clinical Symptoms**

People with BENTA disease have polyclonal B-cell lymphocytosis (elevated levels of certain types of B cells) that develops in infancy, splenomegaly (enlarged spleen), and lymphadenopathy (enlarged lymph nodes). These features, as well as laboratory findings characteristic of BENTA disease, likely contribute to the mild immunodeficiency seen in people with BENTA disease. People with BENTA disease are susceptible to recurrent sinus and lung infections, as well as infections with viruses such as molluscum contagiosum virus, Epstein-Barr virus, or BK virus.

**Treatment**

Currently, minimal treatment options are available for people with BENTA disease. Doctors closely monitor BENTA patients for infections and for signs of development of B-cell cancers. Splenectomy, or spleen removal, potentially could help reduce the B-cell burden in patients with BENTA disease. However, according to two published reports, B-cell counts increased dramatically in two patients who underwent the procedure. It remains to be determined whether immunosuppressive drugs, including B-cell-depleting drugs such as rituximab, are effective for treating BENTA disease.

1. Chronic Granulomatous Disease (CGD)

Chronic granulomatous disease (CGD) is a genetic disorder in which white blood cells called phagocytes are unable to kill certain types of bacteria and fungi. People with CGD are highly susceptible to frequent and sometimes life-threatening bacterial and fungal infections.

**Causes**

CGD is caused by defects in an enzyme, NADPH oxidase, that phagocytes need to kill certain bacteria and fungi. Mutations in one of five different genes can cause these defects.

**Symptoms & Diagnosis**

People with CGD are highly susceptible to infections caused by certain bacteria and fungi, such as Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Nocardia species, and Aspergillus species. These people may develop abscesses (boils) in their lungs, liver, spleen, bones, or skin; and masses of cells, called granulomas, that can obstruct the bowel or urinary tract. In some people, granulomas can cause an inflammatory bowel disease similar to Crohn’s Disease. In addition, heart or kidney problems, diabetes, and autoimmune disease may occur in people with CGD, but this varies depending on which gene is mutated.

CGD is diagnosed by special blood tests that show how well phagocytes produce hydrogen peroxide, an indicator that they are functioning properly.

**Treatment**

People with CGD take lifelong regimens of antibiotics and antifungals to prevent infections. Injections with interferon gamma, a protein that improves the activity of phagocytes, also may help reduce the number of severe infections. Abscesses need aggressive care that may include surgery. Granulomas may require steroid therapy. Some people with CGD have been treated successfully with bone marrow transplantation.

1. Common Variable Immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is a primary immune deficiency disease characterized by low levels of protective antibodies and an increased risk of infections. Although the disease usually is diagnosed in adults, it also can occur in children. CVID also is known as hypogammaglobulinemia, adult-onset agammaglobulinemia, late-onset hypogammaglobulinemia, and acquired agammaglobulinemia.

NIAID supports research to determine genetic causes of CVID that may lead to therapeutic approaches to address the disease. Researchers also are exploring how antibody-based drugs may lessen the severity of the condition.

**Causes**

CVID is caused by a variety of different genetic abnormalities that result in a defect in the capability of immune cells to produce normal amounts of all types of antibodies. Only a few of these defects have been identified, and the cause of most cases of CVID is unknown. Many people with CVID carry a DNA variation called a polymorphism in a gene known as TACI. However, while this genetic abnormality confers increased risk of developing CVID, it alone is not capable of causing CVID.

CVID is also linked to IgA deficiency, a related condition in which only the level of the antibody immunoglobulin A (IgA) is low, while levels of other antibody types are usually normal or near normal. IgA deficiency typically occurs alone, but in some cases it may precede the development of CVID or occur in family members of CVID patients.

**Symptoms & Diagnosis**

People with CVID may experience frequent bacterial and viral infections of the upper airway, sinuses, and lungs. Acute lung infections can cause pneumonia, and long-term lung infections may cause a chronic form of bronchitis known as bronchiectasis, which is characterized by thickened airway walls colonized by bacteria.

People with CVID also may have diarrhea, problems absorbing food nutrients, reduced liver function, and impaired blood flow to the liver. Autoimmune problems that cause reduced levels of blood cells or platelets also may occur. People with CVID may develop an enlarged spleen and swollen glands or lymph nodes, as well as painful swollen joints in the knee, ankle, elbow, or wrist. In addition, people with CVID may have an increased risk of developing some cancers.

Doctors can diagnose CVID by weighing factors including infection history, digestive symptoms, lab tests showing very low immunoglobulin levels, and low antibody responses to immunization.

**Treatment**

CVID is treated with intravenous immunoglobulin infusions or subcutaneous (under the skin) immunoglobulin injection to partially restore immunoglobulin levels. The immunoglobulin given by either method provides antibodies from the blood of healthy donors. The frequent bacterial infections experienced by people with CVID are treated with antibiotics. Other problems caused by CVID may require additional, tailored treatments.

1. Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome is a rare genetic disorder of the immune system that primarily affects boys. It is characterized by abnormal immune function and a reduced ability to form blood clots. Wiskott-Aldrich syndrome is caused by mutations in the *WAS* gene, which provides instructions for production of a protein called WASp. This protein plays an essential role in relaying signals from the surface of the blood cell to the cell’s actin cytoskeleton, the network of fibers that make up the cell’s structural framework. Immune cells that lack the WASp protein have a decreased ability to respond to their environment, fight invaders, and form functional platelets.

**Clinical Symptoms**

Wiskott-Aldrich syndrome typically is characterized by three major features:

• Low number of platelets and small platelet size, which can lead to an increased tendency to bleed • Recurrent bacterial, viral, and fungal infections • Eczema (an inflammatory skin disease)

In addition, some patients with Wiskott-Aldrich syndrome have autoimmune diseases, such as autoimmune hemolytic anemia (destruction of one’s own red blood cells) orvasculitis (destruction and inflammation of blood vessels). Additionally, a minority of people with Wiskott-Aldrich syndrome develop lymphoma or leukemia. Occasionally these cancers occur in young children, but they are more likely to develop as people age.

**Treatment**

Once a diagnosis is made, treatment for Wiskott-Aldrich syndrome is based on a person’s clinical condition. Possible treatment options for some people with Wiskott-Aldrich syndrome include immunoglobulin (antibody) infusions, platelet transfusions, topical creams for eczema, and steroids or similar medications to control autoimmunity. Because of their abnormal immune function, people with Wiskott-Aldrich syndrome may be advised to avoid live-virus vaccines. In severe cases, bone marrow transplantation or gene therapy may be considered.

Secondary Immunodeficiency Disorder

1. Acquired immunodeficiency syndrome (AIDS)

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging your immune system, HIV interferes with your body's ability to fight infection and disease.

HIV is a sexually transmitted infection (STI). It can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth or breast-feeding. Without medication, it may take years before HIV weakens the immune system to the point of having AIDS.

When AIDS occurs, the immune system has been severely damaged. It will be more likely to develop opportunistic infections or opportunistic cancers — diseases that wouldn't usually cause illness in a person with a healthy immune system.

**Signs and symptoms**

The signs and symptoms of some of these infections may include; Sweats, Chills, Recurring fever, Chronic diarrhea, Swollen lymph glands, Persistent white spots or unusual lesions on your tongue or in your mouth, Persistent, unexplained fatigue, Weakness, Weight loss, Skin rashes or bumps

## **Causes**

HIV is caused by a virus. It can spread through sexual contact or blood, or from mother to child during pregnancy, childbirth or breast-feeding.

### **How does HIV become AIDS?**

HIV destroys CD4 T cells — white blood cells that play a large role in helping your body fight disease. The fewer CD4 T cells you have, the weaker your immune system becomes.

You can have an HIV infection, with few or no symptoms, for years before it turns into AIDS. AIDS is diagnosed when the CD4 T cell count falls below 200 or you have an AIDS-defining complication, such as a serious infection or cancer.

## **Risk factors**

Anyone of any age, race, sex or sexual orientation can be infected with HIV/AIDS. However, you're at greatest risk of HIV/AIDS if you; **have unprotected sex, have an STI and use IV drugs.**

**Complications**

HIV infection weakens your immune system, making you much more likely to develop many infections and certain types of cancers.

###  Infections common to HIV/AIDS - **Pneumocystis pneumonia (PCP), Candidiasis (thrush), Tuberculosis (TB), Cytomegalovirus, Cryptococcal meningitis and Toxoplasmosis.**

 Cancers common to HIV/AIDS-**Lymphoma, Kaposi's sarcoma.**

## **Prevention**

There's no vaccine to prevent HIV infection and no cure for AIDS. But you can protect yourself and others from infection.

To help prevent the spread of HIV:

* **Use treatment as prevention (TasP).** If you're living with HIV, taking HIV medication can keep your partner from becoming infected with the virus. If you make sure your viral load stays undetectable — a blood test doesn't show any virus — you won't transmit the virus to anyone else. Using TasP means taking your medication exactly as prescribed and getting regular checkups.
* **Use post-exposure prophylaxis (PEP) if you've been exposed to HIV.** If you think you've been exposed through sex, needles or in the workplace, contact your doctor or go to the emergency department. Taking PEP as soon as possible within the first 72 hours can greatly reduce your risk of becoming infected with HIV. You will need to take medication for 28 days.
* **Consider preexposure prophylaxis (PrEP).** The combination drugs emtricitabine plus tenofovir (Truvada) and emtricitabine plus tenofovir alafenamide (Descovy) can reduce the risk of sexually transmitted HIV infection in people at very high risk. PrEP can reduce your risk of getting HIV from sex by more than 90% and from injection drug use by more than 70%, according to the Centers for Disease Control and Prevention. Descovy hasn't been studied in people who have receptive vaginal sex.
* **Tell your sexual partners if you have HIV.**
* **If you're pregnant, get medical care right away.**
* **Use a new condom every time you have sex.**
1. Uremia

Uremia occurs when the kidneys become damaged. The toxins, or bodily waste, that the kidneys normally send out in the urine end up in your bloodstream instead. These toxins are known as creatinine and urea. Uremia is a serious condition and, if untreated, can be life-threatening. Uremia is a major symptom of renal failure. Uremia is also a sign of the last stages of chronic kidney disease. **Symptoms of uremia**

At the beginning of chronic kidney disease, you may not notice any symptoms. However, by the time uremia has started, your kidneys are very damaged. Uremia may cause you to have some of the following symptoms; extreme tiredness or fatigue, cramping in your legs, little or no appetite, headache, nausea, vomiting, trouble concentrating.

## **Causes of uremia**

Uremia is caused by extreme and usually irreversible damage to your kidneys. This is usually from chronic kidney disease. The kidneys are no longer able to filter the waste from your body and send it out through your urine. Instead, that waste gets into your bloodstream, causing a potentially life-threatening condition.

Causes of chronic kidney disease may include: -high blood pressure, polycystic kidney disease, diabetes (both type 1 and 2), inflammation of the filtering units in the kidneys called glomeruli

inflammation of the kidney’s tubules and the structures around them, enlarges prostrate, some types of cancer, kidney stones that block the urinary tract for a prolonged period of time, kidney infections that recur.

## **Treatment options**

By the time you have developed uremia, your kidneys are extremely damaged. Dialysis is the main treatment option for uremia. Dialysis is when the removal of wastes, extra fluids, and toxins from your bloodstream is handled artificially instead of by your kidneys. There are two types of dialysis. These types are:

* **Hemodialysis:** A machine is used to remove the waste from your blood.
* **Peritoneal dialysis:** A catheter (small tube) is inserted into your abdomen. A dialysis fluid fills your abdomen. This fluid absorbs the waste and extra fluid. Eventually, the fluid will remove the wastes from your body when it drains out.

A kidney transplant is another treatment option if you reach end-stage renal failure. A kidney transplant is when a healthy kidney is taken from a living or deceased donor and placed into your body. You’ll be put on antirejection medication long-term to prevent your body from rejecting the donor kidney.

## **How can it be prevented?**

The best way to try to prevent uremia if you are in end-stage renal failure is to have regular dialysis treatments. This will keep the waste filtered out of your blood. You should also avoid eating anything high in sodium, phosphorus, and potassium. Eating a healthy diet otherwise and exercising, if approved by your doctor, can help in the prevention of uremia.

Since uremia is caused by severe kidney disease and kidney failure, you can try to prevent uremia by taking steps to prevent kidney disease when possible. Some ways to prevent kidney disease include:

* controlling diabetes
* maintaining a healthy blood pressure
* taking steps to maintain cardiovascular health
* not smoking
* maintaining a healthy diet and exercise plan to avoid obesity