

## Chapter 13

# Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) Syndrome

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*Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome is an inherited immunodeficiency in which individuals develop severe, early-onset autoimmune disease because of a problem with how the immune system is controlled and regulated. Unlike most immunodeficiencies that are very susceptible to frequent or severe infections, infections are not a major problem for most individuals with IPEX. Rather, severe autoimmunity causes a poor quality of life and leads to early death in most individuals.*

### Overview

IPEX is an X-linked disorder (See Inheritance Chapter) in which affected boys develop severe autoimmunity that can target any organ. The gut, skin, and endocrine organs — particularly the pancreas and thyroid gland — are the most common targets. Usually, the autoimmunity begins early in life and can be very severe. It tends to worsen and spread as individuals age, leading to a poor quality of life and early death in virtually all cases. Treatment for IPEX is a combination of supportive care and immune suppression. Hematopoietic stem cell transplantation (HSCT), also referred to as bone marrow transplantation, is the only treatment where improvement is seen for this condition and should be considered early in most cases.

### Immunobiology

A variety of mechanisms are used by the immune system to restrain autoimmune reactions. One of the key mechanisms is generation of a group of T cells known as regulatory T cells, sometimes referred to by immunologists as Treg cells. These Tregs make up only a small portion of the total T cells in the human immune system, but they play a powerful role in controlling or restraining the actions of other immune cells. In fact, they might be considered to be like

a small police force that has the job of monitoring the responses of other immune cells to make sure that they don't react longer than necessary, respond too strongly, or inappropriately target other cells or organs of the host's body.

The problem in IPEX is that this small population of regulatory T cells is missing or not working effectively so the immune system is unrestrained in its responses. Essentially, the immune system can be activated normally but has no brakes. Once threats like infectious organisms have been attacked and cleared, the activated immune system will turn its assault on the host if it is not controlled by regulatory T cells using a variety of tools that they have for this purpose. One of the key proteins that is required for regulatory T cells to develop and function normally is called FOXP3. Mutations that damage or destroy the FOXP3 protein are the cause of IPEX.

Using animal models of IPEX, it has been determined that when Tregs are absent, the remaining T cells become highly activated and play a major role in driving the autoimmunity and inflammation that are characteristic of the disease. Since T cells have the ability to guide and direct the activities of other immune cells, these highly activated T cells attract other immune cells into the inflammatory process leading to an overwhelming, uncontrolled immune response.

## Clinical Presentation

Most individuals with IPEX develop autoimmune problems when they are very young, often when they are infants. There are four autoimmune disorders that are most common in individuals with IPEX. Most individuals have at least two of these:

**Enteropathy:** This is an autoimmune attack on the gastrointestinal tract that often presents with severe, watery diarrhea that makes it difficult for individuals to absorb nutrients. As a result, it is very common for individuals to have problems gaining weight and growing. Individuals often lose weight after the diarrhea starts. Occasionally, there may also be blood in the diarrhea although this is less common. More than one-third of individuals complain of food allergies that may cause worsening of the diarrhea or may lead to full-fledged allergic reactions with breathing problems, hives, and other complications.

**Rashes:** Inflammatory rashes of the skin are present in most individuals, with eczema being the most common. Other rashes may also occur including psoriasis, characterized by itchy, red, scaly patches of skin, or pemphigus, a rash in which inflamed blister-like patches develop on the skin.

**Diabetes:** Autoimmune diabetes, sometimes referred to as type 1 diabetes, leads to high blood sugar levels that develop because the cells in the pancreas that are supposed to be making insulin are under attack by the immune system so their capacity to produce insulin is destroyed. As a result, individuals may need to be treated with insulin shots to control their blood sugar levels.

**Thyroid disease:** Autoimmune attack of the thyroid gland leads to problems with normal production of thyroid hormone. In most cases this causes hypothyroidism or a decreased level of thyroid hormone production. As a result, individuals may feel cold, have low energy, etc. In some individuals the autoimmune attack may cause hyperthyroidism or increased thyroid hormone levels that can cause them to feel hot, overly energetic, lose weight, and have thinning hair.

In addition to these four autoimmune disorders, other autoimmune problems are also quite common in IPEX. Approximately half of individuals develop problems with destruction of blood cells by autoimmune attack leading to anemia (low red blood cell numbers), thrombocytopenia (low platelet numbers), or neutropenia (low neutrophil numbers). Autoimmune liver disease and autoimmune kidney

disease are also present in some individuals. IgE levels are highly elevated in virtually all individuals with IPEX, and this is often accompanied by allergies to foods or medications but severe asthma is not particularly common.

Milder forms of the disease have now been diagnosed in some older individuals (> 20 years old) who only have inflammatory bowel disease, severe allergies, eczema, or early-onset type 1 diabetes, and it is likely that other clinical presentations will become evident as more individuals are diagnosed by genetic testing.

## Diagnosis

IPEX is usually suspected in individuals that have the characteristic clinical findings of early-onset diarrhea, endocrine problems (particularly early-onset type 1 diabetes), and rash. A diagnosis of IPEX is confirmed by identification of a mutation in the FOXP3 gene sequencing. Almost all individuals have highly elevated levels of Immunoglobulin E (IgE), but this can be seen in other immune deficiencies or in some individuals with allergies, so is not diagnostic. Many individuals have a decreased number of regulatory T cells circulating in blood. Some individuals with IPEX have a normal or increased number of regulatory T cells. These cells however, do not function appropriately to suppress other immune cells. Since there is no reliable clinical test for assessing the function of regulatory T cells, the measurement of Treg numbers or function is inadequate as a diagnostic test for IPEX.

## Inheritance

The FOXP3 gene is on the X-chromosome, and inheritance of IPEX occurs in an X-linked recessive pattern. Females that carry a mutation of FOXP3 on one chromosome do not exhibit symptoms of IPEX because they have a second X-chromosome that has a normal copy of the FOXP3 gene that compensates for any problems. Boys of carrier mothers have a 50% chance of being born with IPEX since they inherit one X-chromosome from their mother. If they receive the X-chromosome that has a mutation in the FOXP3 gene, they develop IPEX because the Y chromosome received from their father does not have a copy of the FOXP3 gene on it.

## Treatment

Because of the severe autoimmunity in IPEX, initial treatment typically involves a combination of supportive care and aggressive immune suppression. Supportive care needs vary among individuals depending on their major clinical symptoms.

**Supportive care:** Most individuals with IPEX have had at least some degree of nutritional compromise due to chronic diarrhea and malabsorption, often leading to significant weight loss and poor growth so nutritional support is very important. Some individuals can improve by receiving supplemental oral feeding using elemental formulas made up of basic nutrients. Often these need to be given by nasogastric tube (NG-tube) or gastrostomy tube (G-tube) so they can be delivered at a slow, steady rate throughout the day. In some individuals, even this slow, gentle approach of delivering nutrients to the bowel leads to worsening of the diarrhea. In these individuals, a central venous catheter is placed, and nutrition is delivered intravenously in the form of Total Parenteral Nutrition (TPN). Little or no food is given into the bowel. This allows the individual to receive much needed nutrition without making the diarrhea worse.

The severity of skin disease in IPEX varies widely with some individuals having only mild eczema and other individuals having severe psoriasis-like rashes that are associated with skin fissuring and ulceration. Aggressive treatment of the skin using a combination of moisturizers, steroid ointments, ointments containing other immunosuppressants, like tacrolimus, and wet wraps can help to control skin disease. Often referral to dermatology, and in severe cases, consultation with wound care specialists is very helpful.

All individuals with IPEX need to be screened for diabetes and thyroid disease. Individuals diagnosed with diabetes or hypothyroidism should be evaluated by an endocrinologist and treated with insulin and/or thyroid hormone as appropriate. Individuals who have autoimmune disease causing anemia or low platelet counts may require transfusions with red blood cells or platelets. Supportive treatments to counteract the effects of autoimmunity on other organs should also be provided as needed.

**Immune suppression:** As described above, previous research in the animal model of IPEX has determined that T cells play a major role in driving the immune attack that is characteristic of the disease. Initial immunosuppressive treatments

therefore focus on decreasing the activity of T cells with drugs like tacrolimus, cyclosporine, or rapamycin. Steroids like prednisone are often used initially when individuals have very active disease but as they improve, the steroids can often be discontinued and individuals can be maintained on tacrolimus, cyclosporine or rapamycin alone. In individuals who have autoantibodies that target specific organs and make the autoimmunity worse, treatment with rituximab or similar drugs that deplete the B cells can be helpful. Since anything that activates the immune system like vaccination or severe infection may cause disease symptoms and autoimmunity to worsen, individuals who have not been vaccinated may be started on intravenous or subcutaneous immunoglobulin replacement (See Immunoglobulin Replacement Therapy Chapter) to try to prevent infections and avoid the need for further vaccination. Often, individuals require progressively increasing immune suppression over time, which leads to a need for other treatments such as Hematopoietic Stem Cell Transplantation (HSCT).

**Hematopoietic stem cell transplantation:** The only transformative treatment for IPEX at the present time is HSCT, also referred to as bone marrow transplantation. There are a variety of approaches used to perform the transplants in individuals with IPEX, and the approach used often varies by transplant center. Often, HSCT in IPEX is complicated because individuals are ill and pre-existing organ damage caused by autoimmunity or side effects of medications can increase the risk of transplant. Aggressive supportive care to stabilize individuals and improve their clinical status prior to initiating transplant is critical. Overall survival after transplant has been reported to be 60-85% in most studies. Gene therapy and gene editing approaches to treat IPEX are under development and may be available in the future but neither are clinically available at the present time.

## Expectations

Historically, individuals with the most severe forms of IPEX died within the first two years of life from complications associated with autoimmunity. With increased recognition of the disease by pediatricians and pediatric subspecialists along with initiation of appropriate supportive care and immune suppression, most individuals with severe disease can be stabilized until they can undergo HSCT. Individuals with milder forms of IPEX can survive much longer even without ideal management. That said, most individuals with milder forms of

the disease still have multiple and severe clinical complications. As a result, it is unusual for individuals to survive beyond 30 years of age without a HSCT. HSCT can potentially treat the clinical problems associated with the disease except for diabetes or thyroid disease. If these develop prior to transplant, it is usually the result of significant damage to the pancreas or thyroid gland. This damage is typically permanent and does not recover after transplant. This suggests that evaluation for early transplant after the diagnosis is made is an important consideration. The earliest transplants for IPEX were done more than 20 years ago, and those individuals who have had successful transplants have continued to do well although some individuals have had transplant-related complications or recurrence of some autoimmune problems.