Chapter 15

Diseases of Immune Dysregulation: STAT1 and STAT3 Gain of Function

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Introduction

Immune dysregulation occurs when the immune system cannot regulate normal control over inflammation, leading to severe inflammatory complications. Two of these diseases are called STAT1 Gain of Function (GOF) Disease and STAT3 Gain of Function (GOF) Disease. STAT stands for: signal transducer and activator of transcription. There are six STAT proteins. STATs are important proteins that enhance immune responses, particularly the production of interferon gamma, another protein that is crucial for defense against certain infections and for the control of inflammation. Mutations in STAT proteins can lead to:

- Loss of function of the protein where it does not function at all, or
- Gain of function of the protein where the protein functions too much and cannot be turned off.
- Gain of function of the STAT1 and STAT3 proteins cause diseases of immune dysregulation, autoimmunity, and increased risk of infections.

Definition

STAT1 and STAT3 GOF Diseases are genetic disorders in which immune cells are over activated. STAT1 and STAT3 are proteins found inside most immune cells that are activated after the immune cell itself is activated by other signaling proteins called cytokines, such as interferon gamma and IL-6, respectively. Once the cell is stimulated, the STAT protein activates and encourages other immune responses to help the cell to kill bacterial, viral, and fungal infections. Overactive STAT1 and STAT3 lead to dysfunction of both STAT1 and STAT3, and it places individuals at increased risk of infections and autoimmune disease.

Clinical Presentation

STAT1 GOF

Individuals with STAT1 GOF will present to a healthcare provider because of chronic or unusual infections or severe autoimmune disease that is not easily controlled with standard immune suppressing medications.

One of the most common manifestations in individuals with STAT1 GOF is chronic infections with a fungus that are mostly limited to mucosal surfaces, skin, and nails, also known as mucocutaneous candidiasis (CMC). This occurs in more than 90% of individuals. CMC is an infection of the mucus membranes of the mouth (called thrush), gastrointestinal tract, skin, and nails with *Candida* or other common skin fungus. Presentation of CMC is usually in childhood, with some as young as age of 1 at the time the infections start. CMC can often be difficult to treat, requiring oral anti-fungal medication, and likely will return when anti-fungal medications are stopped. More rarely, individuals with STAT1 GOF can be susceptible to severe invasive fungal infections. These infections include *Aspergilllus, Histoplasma, Coccidiomycosis*, and *Cryptococcus*. Pneumonia, an infection of the lungs, is the most common site of invasive fungal infection.

Bacterial infections with common community acquired bacterial organisms also occur in individuals with STAT1 GOF. The infections have a tendency to occur in the lungs as lower respiratory tract infections, bronchitis, or pneumonia. Bacterial infection of the eye, skin, and nail beds are also common. Individuals with STAT1 GOF are also susceptible to Mycobacterial infections. Mycobacterium is a class of bacteria that typically only infect individuals with immunodeficiency or those that are immune suppressed.

Viral infections are also a source of concern in these individuals. The most common viruses causing infection are Herpes family viruses such as herpes simplex virus, the cause of cold sores; varicella zoster virus, the virus that causes chickenpox and shingles; Epstein Barr virus (EBV), the cause of mononucleosis; human papilloma virus (HPV), the cause of warts; and cytomegalovirus (CMV), a virus that typically goes unnoticed by people with competent immune systems but causes severe disease in individuals with immune deficiency. These viruses can cause skin infection, pneumonia, or enter the blood stream where they cause widespread infection and dysfunction of different organ systems.

Most individuals develop some form of autoimmunity by the third decade of life. The autoimmunity that occurs in STAT1 GOF often affects the endocrine and hematologic systems. Hypothyroidism and early onset diabetes are common. Autoimmune hemolytic anemia and autoimmune thrombocytopenia (autoimmune destruction of red blood cells or platelets) can be life threatening and may require blood or platelet transfusions. A subset of individuals with STAT1 GOF have symptoms very similar to Immunodysregulation-Polyendocrinopathy-Enteropathy-X-linked (IPEX). (See IPEX Chapter.) These individuals will have early onset autoimmunity, such as diabetes mellitus and hypothyroidism as well. In addition, individuals with STAT1 GOF with similar symptoms to IPEX can have severe enteropathy. Enteropathy is destruction of the small and large intestine's absorptive surface. Individuals with enteropathy have substantial difficulty in absorbing nutrients and have very frequent diarrhea with weight loss and malnutrition. Because of poor nutrition, individuals will have growth failure.

Other clinical features include a susceptibility to the development of aneurysms in the brain. An aneurysm is an abnormal out-pouching of a blood vessel that causes the blood vessel wall to become weak. Small numbers of individuals have learning disabilities. Some individuals also demonstrate susceptibility to skin, gastrointestinal tract, and throat cancer.

The immune features in individuals with STAT1 GOF can be very variable. Individuals may have low lymphocyte counts and function including low T cell, B cell, and NK cells. Some individuals may also have hypogammaglobulinemia (low IgG, low IgA, or low IgM). Susceptibility to infections, particularly viruses and Mycobacterium, occurs when there are abnormal lymphocyte counts and/or function.

Clinical Presentation

STAT3 GOF

Individuals with STAT3 GOF most commonly present with severe early onset autoimmunity. Individuals often have more than one autoimmune disease and the symptoms of autoimmunity are severe and hard to control. The most common types of autoimmunity involve the endocrine (hormone) system, the hematologic system (blood cells and platelets), gastrointestinal tract, lungs, and liver. Thyroid disease is the most common autoimmune endocrine disorder, treated with thyroid replacement. Hematologic autoimmune disorders include autoimmune destruction of the blood cells and platelets that can be life threatening and require transfusions of blood or platelets. Enteropathy due to autoimmune destruction of the lining of the intestinal tract as chronic diarrhea can cause severe malabsorption of nutrients and failure to thrive. In addition, some individuals may have inflammation of the intestine or colon, termed colitis, that can also lead to poor weight gain, abdominal pain, chronic diarrhea, and blood in the stool. Autoimmune destruction of the liver or lung can lead to organ dysfunction or failure respectively. Other autoimmune disorders, including eczema, rheumatoid arthritis, and eye disease, can also occur.

A major feature of individuals with STAT3 GOF is the presence of lymphoproliferative disease. In lymphoproliferative disease, immune cells in lymph organs grow at an abnormal rate. Lymphoid organs include the spleen, liver, and lymph nodes and when this growth occurs, these organs will expand causing abnormally large lymph nodes, liver, and/or spleen. Lymphoproliferation, which is growth of lymphocytes in increased quantities, can ultimately impact the function of the affected organ, and it can prevent the lymph cells from responding appropriately when there is infection.

Acute short stature is another common feature in individuals with STAT3 GOF. The height of individuals is often substantially lower than the expected normal for age, and this persists to adulthood. Individuals often are treated with growth hormone replacement, but this is controversial as to whether there is any benefit.

Immune abnormalities also are very variable in individuals with STAT3 GOF. Low T cell and B cell quantities can occur as can hypogammaglobulinemia (low IgG). It is often hard to differentiate if the

immune abnormalities are secondary to treatment of the autoimmune features. Infections can occur in STAT3 GOF, but the autoimmune features are the more common presentation. Infections, including bacterial, viral, mycobacterial, and fungal, can be severe, invasive, and life threatening. Prophylaxis against infections is often used especially if a substantial number of immune suppressing medications are used for treatment of autoimmunity.

Diagnosis

The definitive diagnosis for both STAT1 and STAT3 GOF Diseases currently consists of genetic testing and confirmation with functional tests. Thus far, the functional tests are only available on a research basis. However, it is critically important to perform a comprehensive immune evaluation to understand how the disease has affected the immune system.

Inheritance

Mutations in STAT1 and STAT3 that cause gain of function are inherited in an autosomal dominant manner. With autosomal dominant inheritance, one parent is affected. However, STAT1 and STAT3 GOF mutations can also occur spontaneously in individuals in which a parent is not affected.

Treatment

Treatment of individuals with STAT1 GOF and STAT3 GOF Diseases concentrates on suppressing the immune system to treat autoimmunity, treating infection, and preventing further infection. Treatment of the autoimmunity is challenging. If there is hypothyroidism or diabetes, hormone replacement with thyroid hormone or insulin is indicated. Treatment of other autoimmune features, including autoimmune anemia or thrombocytopenia (low platelet count), often is treated with corticosteroids or other immune suppressing medications. In some cases, the autoimmune features fail standard therapy and require the addition of several immunosuppressing agents. In these cases, risk of infection increases as these medications suppress the immune system.

Treatment of CMC in STAT1 GOF often requires oral or IV anti-fungal medications, and individuals should remain on anti-fungal prophylaxis to prevent CMC. Depending on the effects of immunologic evaluation – whether there is low lymphocyte counts or function and whether there is hypogammaglobulinemia will dictate whether an individual may need to receive prophylaxis against bacterial, fungal, or viral infections. Some individuals receive immunoglobulin (Ig) replacement therapy when there is low IgG.

The biology that leads to STAT1 and STAT3 activation has afforded the opportunity to use specific therapeutic agents that interfere with the mechanism of disease at the cell level. In STAT3 GOF, there is a strong signature with the inflammatory cytokine IL-6. IL-6 is a cytokine that is associated with the development of specific autoimmune diseases, particularly rheumatoid arthritis. Blockage of IL-6 with medications such as tocilizumab has been effective in a small number of STAT3 GOF individuals that have autoimmunity. Both STAT1 and STAT3 are activated in the cell after activation of specific proteins called janus kinases. Two medications are available that block janus kinase induced activation of STAT proteins: tofacitinib and ruxolitinib. These janus kinase inhibitors have been used off-label (in a non-FDA approved treatment regimen) in a small number of individuals and have been extremely successful at improving or resolving autoimmunity and in treating CMC. Tocilizumab, ruxolitinib, and tofacitinib are all FDA approved medications for treatment of other diseases and are not approved for use in STAT1 or STAT3 GOF. Therefore, these medications should be used cautiously, only when other methods of treatment have failed and used in consultation with an immunologist or rheumatologist. Clinical trials to understand how best to use these medications in individuals with STAT1 and STAT3 GOF are forthcoming.

Lastly, hematopoietic stem cell transplantation (HSCT) has been used successfully as a form of treatment in a small number of individuals with STAT1 and STAT3 GOF. In all cases, the transplantation was performed as a lifesaving procedure. Overall survival was disappointing at 40% and 56% in STAT1 and STAT3 GOF respectfully. Determining the optimal transplant strategy needs further study before HSCT is more widely and routinely used.

Expectations

Individuals with both diseases must take caution with infection exposures. Inflammation from infection can trigger or worsen inflammatory and autoimmune manifestations especially those in the lung and intestines. Individuals with STAT1 GOF are especially susceptible to fungal disease and viral disease with herpes family viruses. Individuals with STAT3

GOF are susceptible to progressive autoimmune disease. With early diagnosis and treatment of infections and autoimmunity with targeted therapy, individuals can have stable disease. For the more severe presentations, HSCT can be considered after a thoughtful discussion between the family and the immunology provider in order to weigh the risks and benefits on an individual basis. Genetic counseling is important for individuals and their families.