Autoimmunity in Primary Immunodeficiency

Chapter 28

The immune system is a complex set of organs, cells, proteins and other substances that function to prevent infection. Primary immunodeficiency diseases are characterized by abnormalities in specific components of the immune system that lead to an increased susceptibility to infection. Many times, abnormalities in the immune system that lead to primary immunodeficiency diseases also result in immune dysregulation, which is an immune response that is not properly controlled or restrained. This can lead to autoimmunity, one form of immune dysregulation in which the immune response is directed against normal parts of the body such as cells, tissues or organs (called auto-antigens). Put another way, it is when the immune system attacks the body in which it resides.

Definition of Autoimmunity in Primary Immunodeficiency

A normal immune system makes proteins known as antibodies that recognize and prevent foreign organisms (bacteria, viruses) from causing infection. One common type of autoimmunity is when the immune system makes antibodies against normal cells and/or tissues of the body which are known as "autoantibodies." Sometimes people with primary immunodeficiency diseases cannot make "good" antibodies to protect against infection but only make "bad" autoantibodies, which then cause autoimmune disease. Sometimes these antibodies themselves are harmless but suggest the presence of an autoimmune disease. In other autoimmune diseases, the cellular immune system may also react against a body's auto-antigens.

One of the ironies of this situation is that the treatment for autoimmune conditions is the use of immune suppression to shut down the inappropriate immune response that is causing the problem. Obviously, using immunosuppressive treatment in a patient already afflicted with immunodeficiency involves a complex balancing act to avoid unwanted infections and other serious side effects while still using sufficient immunosuppressive treatment to control the autoimmune process. It is recommended to use a team approach when using immunosuppressive treatment, joining the skills of the immunologist with those of a specialist in treating the organ system involved, be it gastroenterology, rheumatology, pulmonology, endocrinology, nephrology, dermatology or hematology.

Autoimmune complications have been reported in a wide range of primary immunodeficiency diseases. However, certain primary immunodeficiency diseases have autoimmune disease as their primary problem. These include Autoimmune Polyendocrinopathy; Candidiasis; Ectodermal Dysplasia (APECED or APS-1); Autoimmune Lymphoproliferative Syndrome (ALPS); and Immune dysregulation; Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome.

Certain other immune disorders are frequently associated with autoimmune complications. These include Common Variable Immune Deficiency (CVID), Wiskott-Aldrich Syndrome (WAS), IgA deficiency, Good Syndrome, Hyper IgM Syndrome, Idiopathic T-cell Lymphopenia (ICL) and Complement disorders. Most of these diseases are discussed in greater detail in other chapters. The focus of this chapter is to provide an overview of the types of immune dysregulation and autoimmunity that can occur in various primary immunodeficiency diseases.

Autoimmune Cytopenias

The development of autoantibodies that bind to and destroy blood cells is the most common autoimmune disease seen in primary immunodeficiency diseases. The blood cells affected are the red blood cells (RBCs), platelets and white blood cells (WBCs).

Red Blood Cells

The RBCs carry oxygen to the body's tissues. Oxygen is necessary for the body's tissues to perform their function. Anemia is the term used to describe a low number of RBCs. Autoantibodies against the RBCs can cause destruction of these cells and is called autoimmune hemolytic anemia (AIHA).

Symptoms associated with AIHA include fatigue, headache, dizziness, fainting and poor exercise tolerance. The person sometimes looks pale. In severe cases the individual can develop a yellow discoloration to the skin and eyes known as jaundice. The spleen may become enlarged as it traps the damaged red blood cells. The body tries to compensate for the decreased capacity to carry oxygen by working the lungs and heart harder.

Platelets

Injuries to the tissues can cause bleeding. Platelets help create blood clots to stop bleeding. A low number of platelets is called thrombocytopenia. When autoantibodies are formed against the platelets and cause thrombocytopenia, it is known as idiopathic thrombocytopenic purpura (ITP). ITP can cause abnormal bleeding. Patients frequently notice increased bruising, sometimes in unusual areas or without known trauma to the area. They may develop a pinpoint red rash caused by small hemorrhages called petechiae. They may notice nosebleeds that are more frequent and difficult to resolve. The gums may bleed easily. The urine may have an orange, pink or red color. Stools may appear black and tarry, which can indicate bleeding in the intestinal tract. Rarely, bleeding in the brain can cause altered mental status or death.

White Blood Cells

There are many different types of WBCs. Neutrophils are WBCs that have a major role in responding to infections. A low number of neutrophils is called neutropenia. Autoimmune neutropenia (AIN) occurs when antibodies are produced against neutrophils.

The most significant symptom associated with AIN is fever, as this may indicate a serious infection. Other signs of infection such as cough, vomiting, diarrhea and rash may also be present. Serious infections can progress rapidly in people with AIN, and they may require evaluation in the emergency room or admission to the hospital. Antibiotic therapy is urgently needed in these cases. Patients with AIN may also have ulcers or sores develop in the mouth, esophagus or intestine. The gums may also become inflamed and red.

Diagnosis of Autoimmune Cytopenias

Autoimmune cytopenias are diagnosed with blood tests. Typically, a simple blood count is the blood test performed to establish the presence of a cytopenia. Additional blood tests can determine whether an autoantibody is present. A specialist such as a clinical immunologist, hematologist or oncologist typically evaluates patients for these disorders. Sometimes a bone marrow sample needs to be obtained to determine whether there is a problem with production of blood cells.

Treatment of Autoimmune Cytopenias

Autoimmune cytopenias may be temporary and require little to no treatment. If treated, the goal of therapy is to remove the autoantibodies and let the body replenish the blood cells. Several treatments have been used including intravenous immunoglobulin (IVIG), steroids, chemotherapy drugs and drugs such as anti-CD20, which is used to specifically deplete B-cells that produce antibodies. The therapy that is best for a

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particular patient is based on many factors. Autoimmune cytopenias often respond well to therapy. At times however, symptoms may recur or may require long-term treatment. Patients rarely require blood transfusions except in extreme circumstances. In all cases, patients with cytopenias require close follow-up by their specialist.

Most patients can be treated successfully and have no major restrictions on their daily activities. However patients with chronically low platelet counts may have to refrain from activities with a higher risk of injury such as contact sports.

Autoimmune Lung Disease

There are multiple causes of lung disease in patients with primary immunodeficiency diseases, including infection, malignancy and autoimmunity. Differentiating between these can be difficult. In most cases of lung disease, the autoimmunity is not due to formation of an antibody, but an abnormal accumulation of white blood cells in the lung tissues, causing inflammation and damage. Sometimes white blood cells accumulate in a specific part of the lung known as the interstitium. This is called interstitial lung disease and interferes with the ability of oxygen to be absorbed into the bloodstream.

Some patients with certain types of primary immunodeficiency diseases develop aggregates of immune cells called granulomas in the lung. Granulomas are sometimes formed in an attempt to contain an infection that cannot be resolved or because the immune cells are not being regulated properly, a situation that sometimes occurs in primary immunodeficiency diseases. Two primary immunodeficiency diseases that often have granulomas in the lung are Chronic Granulomatous Disease (CGD) and CVID. Patients with CVID sometimes develop both interstitial lung disease and granulomas in the lung. This disease is called Granulomatous Lymphocytic Interstitial Lung Disease (GLILD). Occasionally, patients with Ataxia-Telangiectasia and APECED also develop interstitial lung disease. At times, the inflammation caused by granulomas and/or the accumulation of white blood cells in the interstitium of the lung can be so severe and persistent that fibrosis, or scarring, develops in the lung.

Symptoms

In most cases, the symptoms of interstitial lung disease develop slowly over time. Patients with CGD will usually have a more acute onset as they have a persistent infection causing the lung inflammation. Patients may notice a decrease in their endurance with everyday activities. They may find themselves having to cut back on exercise such as biking or running. These changes are often attributed to other causes, which may delay the diagnosis of the lung disease itself. Patients often complain of a cough, which is usually non-productive. Enlargement and rounding of the toenails and fingernails can be seen and is termed clubbing. Clubbing is not specific to primary immunodeficiency diseases or to lung damage but is a clue that the lungs should be evaluated. In some cases, the lung damage can lead to a severe lowering of blood oxygen causing patients to have a bluish tint to their skin or mucous membranes known as cyanosis. Fever is not a typical finding, unless infection is also present. On the lung exam, a practitioner may hear abnormal breath sounds such as crackles, wheezes or a decrease in the amount

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of air moving in and out of the lung with breathing. Often these symptoms lead to the incorrect diagnosis of asthma or a lung infection by physicians not familiar with autoimmune lung diseases in primary immunodeficiency diseases.

Diagnosis of Pulmonary Complications

Radiology tests can be helpful in identifying lung problems. Chest X-rays are useful for diagnosing infections (pneumonia). However, a chest X-ray can sometimes be normal, even when there is still significant lung disease present. A chest CT scan can frequently pick up abnormalities not seen on a routine chest X-ray. In patients with CVID and GLILD, changes on the chest CT scan will often appear before the patient exhibits symptoms.

Breathing tests, called pulmonary function tests (PFTs), can indicate the degree of lung impairment. There are changes in PFTs that can be found in interstitial lung disease and other types of lung disease. However, patients often must lose a significant amount of lung function to demonstrate symptoms that prompt ordering of the PFTs.

In some cases, a lung biopsy is needed to make the correct diagnosis and define the correct treatment course. A lung biopsy is a surgical procedure usually done by making a small incision in the chest and inserting a small scope and instruments to obtain a piece of lung tissue. The biopsy is evaluated by a pathologist, a doctor who performs a variety of tests on the lung tissue including a microscopic examination. The tests performed by the pathologist can determine the specific type of lung disease that is present (for example, cancer, infection, interstitial lung disease, granuloma).

Treatment

Patients with malignancies are referred to an oncologist (cancer doctor) for continuing care. Patients with infections are treated with antibiotics. Inflammatory changes in the lung are usually treated with immunosuppressant drugs that suppress or alter the immune system. The most common medicine used is corticosteroids (like prednisone), which can be given by inhalation, orally or intravenously (IV). Steroids can be effective, but sometimes may not provide long-term improvement. Prolonged oral or IV steroid use is associated with significant side effects such as high blood pressure, high blood sugar, osteopenia (weak bones), hyperlipidemia (high cholesterol), and stress on the kidney and eyes. Other immune suppressive medicines such as cyclosporine and Sirolimus are sometimes helpful. Some types of lung disease respond to one type of immunosuppressant medication but not another. IVIG can sometimes improve the inflammation in the lungs in addition to other drugs.

Without treatment, interstitial lung disease can progress and cause permanent lung damage. Fibrosis (scarring), which is the end result of chronic untreated inflammation, cannot be reversed. It is very important that your doctor has the correct diagnosis of your specific lung disease and expertise in treating the specific disorder in order to insure the best outcome.

Autoimmune Skin Disease

Skin conditions due to autoimmunity or immune dysregulation are not unique to people with primary immunodeficiency diseases. Common skin conditions like eczema or psoriasis are seen in people with normal immune systems as well. Sometimes, skin disease is one of the earliest symptoms of a primary immunodeficiency disease and can lead to further clinical or laboratory evaluation to identify immune deficiency. In addition to skin disorders that are autoimmune or inflammatory in nature, other abnormal skin manifestations, such as dry, sparse hair, abnormally formed teeth and fingernails, and absent sweat glands, can be seen in certain primary immunodeficiency diseases but are not due to autoimmunity, and these will not be covered in detail here.

Eczema

Eczema, also known as atopic dermatitis, is generally a mild skin disease and is the most common skin disease in primary immunodeficiency diseases. Often referred to as "the itch that rashes," eczema typically begins as patches of dry, itchy skin which worsen and erupt into rash as they are scratched. It is not unusual for patients with primary immunodeficiency diseases who have other autoimmune manifestations to also have eczema. Some primary immunodeficiency diseases are, however, associated with more severe eczema. These include WAS, Hyper-IgE Syndrome (HIES), IPEX syndrome, and certain forms of Severe Combined Immune Deficiency (SCID). In these disorders, the eczema may be quite resistant to typical therapies.

Psoriasis

Psoriasis is another type of autoimmune skin disease that is more severe than eczema. Psoriasis plaques are typically red, raised, itchy and painful. They are characterized by the presence of a silvery scale on the surface of the plaques that often bleeds if it is removed. Plaques of psoriasis occur most frequently on the scalp or on the elbows or knees. It occurs most frequently in patients with CVID but can also be seen in IPEX and occasionally in other primary immunodeficiency diseases.

Hair and Skin Pigmentation Changes

Multiple primary immunodeficiency diseases can have autoimmunity that affects the hair and skin pigment. Some patients develop alopecia, or patches of baldness as a result of autoantibodies against hair producing cells. Alopecia areata refers to round circular areas of hair loss. Some patients also develop vitiligo, or loss of the pigment in the skin. The affected area of skin will appear white in color. The contrast of the surrounding skin will determine how apparent the change is. The affected areas often change somewhat over time. Vitiligo and alopecia are most commonly associated with APECED, CVID, IPEX and T-cell disorders such as 22q11 deletion (Di George) syndrome although they can develop in a wide range of primary immunodeficiency diseases.

Diagnosis of Skin Diseases

Most of the time, a knowledgeable healthcare provider can diagnose skin disorders just by physical exam. If a rash is unusual, however, a skin biopsy is sometimes needed to determine what type of rash it is. Biopsies are typically taken from the area where the rash is most evident using a sharp "punch" that cuts and removes a small circular core of skin tissue that can be evaluated microscopically by a pathologist to determine what type of rash it is. This is typically a very minor procedure that can be done in the office with local numbing of the skin.

Treatment

While not typically life threatening, autoimmune and inflammatory disorders of the skin can lead to significant emotional consequences and in rare situations can lead to permanent disfigurement. Because the skin plays an important role as a barrier to bacteria and other organisms from the environment, severe rashes like eczema may serve as an entry point to the bloodstream for bacteria from the skin.

Mild skin conditions can be diagnosed and treated by a primary care provider or an Immunologist but more severe skin conditions often require diagnosis and

(Autoimmune Skin Disease continued)

treatment by a dermatologist. Treatment for most conditions typically begins with local application of moisturizing lotions and steroid ointments directly to the rash. If this is not sufficient to control the symptoms, ointments containing more potent steroids or other immunosuppressant medications can be applied. In rare cases, oral or IV immunosuppressant medications may be needed to treat severe disease.

Autoimmune Gastrointestinal Disease

Autoimmune gastrointestinal diseases are common among patients with primary immunodeficiency diseases, particularly patients with CVID, CGD, IPEX, X-linked Agammaglobulinemia (XLA), APECED, WAS, Omenn syndrome, NEMO deficiency and others. This is likely due to the fact that the intestines are constantly bathed in bacteria, bacterial products and food, which all have the potential to cause irritation of the intestinal lining (the mucosa). As a result, the immune system plays a particularly important role in maintaining the barrier function of the intestines and in protecting the body from invasion by the bacteria present in the bowel.

Mucosal Changes

Autoimmune or inflammatory diseases of the gastrointestinal tract can disrupt the mucous membranes that line the mouth, esophagus, stomach, and intestines. This can cause a variety of symptoms including: geographic tongue, an abnormal appearance of the tongue that can be mistaken for an oral yeast infection (thrush); gingivitis or inflammation of the gums; oral ulcers or canker sores; abdominal pain; diarrhea that may be watery or bloody; an urgency to stool after eating; and weight loss despite a reasonable diet. Similar symptoms can also be present in patients with primary immunodeficiency diseases who have bowel infections with organisms such as Giardia, Cryptosporidium or Clostridium difficile. Because both autoimmune and infectious complications can lead to serious problems in patients with primary immunodeficiency diseases, it is important that new gastrointestinal symptoms be evaluated *(see next page)* when they arise. In rare cases, ongoing gastrointestinal symptoms can be a sign of cancer in the bowel, which is more common in some types of primary immunodeficiency diseases than in the general population.

Liver Inflammation

The liver is part of the gastrointestinal system and plays many important roles in the normal function of the body. Among the most important are: the metabolism of nutrients absorbed from the intestines, the production of important blood proteins such as clotting factors, the metabolism of drugs and other toxic molecules present in the blood, and the removal of waste products from the blood and excretion of these into the bile. Autoimmune or inflammatory disease of the liver, which can occur in primary immunodeficiency diseases, can cause temporary or permanent damage that can disrupt one or more of the liver's important functions. This may lead to accumulation of fluid in the abdomen (ascites), elevated bilirubin in the blood leading to jaundice, blood clotting abnormalities, etc.

CVID and CGD are among the primary immunodeficiency diseases most commonly associated with autoimmune or inflammatory liver disease but this has also been observed in APECED, IPEX, X-linked Hyper IgM syndrome, and others. Since infections by certain viruses, including Hepatitis (A, B, or C), Cytomegalovirus (CMV), Epstein Barr virus (EBV), and others, can also cause severe liver inflammation and

(Autoimmune Gastrointestinal Disease continued)

damage, these are typically excluded as the cause of disease before autoimmunity can be confirmed.

Diagnosis of Gastrointestinal Disease

The diagnosis of gastrointestinal disorders in primary immunodeficiency diseases often requires a combination of approaches that include a physical exam, laboratory tests on blood and stool, radiology tests, and endoscopy with biopsies of the intestinal mucosa. Common physical exam findings include oral or anal ulcers, abdominal tenderness, fluid in the abdomen (ascites), enlargement or tenderness of the liver, cracks or fissures around the anus, etc.

Laboratory tests that are often recommended on the blood include a complete blood count to determine whether the patient may be losing blood in the inflamed bowel, measures of inflammation including C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), albumin and pre-albumin levels as a rough measure of nutritional status, and AST, ALT, and Bilirubin levels as a measure of liver irritation. To exclude the possibility of a bowel infection, stool is often collected and cultured to identify bacteria or viruses. Samples of stool are also stained and evaluated under the microscope for the presence of specific bacteria or parasitic organisms.

Radiologic tests that may be helpful include an abdominal X-ray, abdominal and liver ultrasounds, and a CT scan of the abdomen after contrast material has been swallowed. Sometimes the only way to make a definitive diagnosis of either bowel or liver inflammation is to obtain a fragment of tissue that can be evaluated under the microscope by a pathologist. In the bowel, this is done by passing an endoscope into the bowel to both look at the mucosa and to obtain small pinch biopsies of mucosal tissue from the inside surface of the intestine. In the liver, this is done by obtaining a small piece of liver tissue with a biopsy needle inserted into the liver through the skin. Both of these procedures are typically done by a gastroenterologist, a doctor who specializes in the treatment of intestinal disorders.

Treatment

In general, immunosuppressant medications are used to treat autoimmune or inflammatory disorders of the bowel in most patients with primary immunodeficiency diseases. This process is very individualized requiring flexible treatment plans to balance the severity and risks of the autoimmune process with the severity and risks of the immune deficiency and immunosuppressive therapy. In some cases, including the bowel disease associated with CVID or CGD, steroids are often the first line of therapy, and in many cases, may be sufficient to control symptoms. In contrast, the severe bowel disease associated with IPEX syndrome or Omenn syndrome typically requires more aggressive immunosuppression with stronger medications. For patients with primary immunodeficiency diseases who have significant gastrointestinal symptoms, it is essential to have a gastroenterologist involved to assist with diagnostic testing and with directing treatment.

Autoimmune Kidney Disease

The kidney is made up of a large number of tiny filtration units. Each unit is called a glomerulus. The most common form of autoimmune kidney disease in primary immunodeficiency diseases is called glomerulonephritis; inflammation and destruction of the glomeruli caused either by direct attack or by deposition of immune complexes (aggregates containing autoantibodies and the proteins they are bound to). Destruction of the glomeruli leads to progressive loss of filtering capacity and decreased kidney function.

(Autoimmune Kidney Disease continued)

Glomerulonephritis is a common feature of patients with complement deficiencies, particularly those affecting complement components C1, C2, C3, or C4. Autoimmune kidney disease can also be seen less commonly in other primary immunodeficiency diseases including CVID and APECED.

Symptoms

In many cases, the first sign of autoimmune kidney disease is elevated blood pressure. This is often accompanied by the appearance of blood or protein in the urine. In the setting of active glomerulonephritis, blood in the urine may not appear pink, but instead is more likely to cause the urine to have a color closer to that of tea or cola. Blood and protein are easily detected in the urine using readily available test strips that are frequently called urine "dipsticks." If there is substantial protein loss in the urine, it can lead to fluid retention and swelling (edema) of the legs and feet.

Diagnosis of Kidney Complications

When kidney disease is suspected, common blood tests are helpful to determine just how dysfunctional the kidneys may have become. Evaluation of the urine for the presence of blood, protein, inflammatory cells and electrolytes is also typically very informative. In many cases, a kidney biopsy is needed to make the correct diagnosis and define the correct treatment course. A kidney biopsy is usually done by inserting a biopsy needle through the skin and into the kidney to obtain a small core of tissue, which is usually sufficient to make the diagnosis. The biopsy is evaluated by a pathologist, who performs a variety of tests on the kidney tissue including a microscopic examination.

Treatment

Patients with autoimmune kidney disease are often referred to a nephrologist (kidney doctor) for evaluation and management of the kidney problems. Blood pressure medications are typically prescribed to manage the elevated blood pressure, and immunosuppressants are used to control the autoimmune process.

Autoimmune Endocrine Disease

The major endocrine organs include the pituitary gland in the brain, the thyroid and parathyroid glands, the pancreas, the adrenal glands and the gonads (testicles or ovaries). The endocrine organs secrete important hormones that play essential roles in maintaining basic bodily functions. Autoimmunity directed against endocrine organs can therefore cause significant health problems. Patients who have endocrine autoimmunity are often referred to an endocrine specialist (endocrinologist) for evaluation and management.

Thyroiditis

The thyroid gland secretes thyroid hormone, which plays an important role in maintaining the metabolic rate of the body. Patients with hypothyroidism (abnormally low thyroid hormone levels) typically gain weight, have a slow heart rate, feel cold and fatigued, are constipated and have coarse hair and stiffening in the skin. In contrast, patients with hyperthyroidism (abnormally high thyroid hormone levels) typically lose weight, have a rapid heart rate, feel hot and energetic, and have thin hair. Autoantibodies directed against the thyroid can cause either hypothyroidism or hyperthyroidism. Autoimmune thyroid disease is the most common autoimmune disease among the general population with an incidence of approximately 1 in 200. In certain primary immunodeficiency diseases, including CVID and IPEX syndrome, the incidence is even higher.

(Autoimmune Endocrine Disease continued)

Diagnosis of thyroid autoimmunity is typically made by a series of blood tests. Hypothyroidism is treated by taking supplements of thyroid hormone. Hyperthyroidism often has to be treated by decreasing the thyroid's ability to make thyroid hormone. This may require surgical removal of part of the thyroid or radiation or other drugs. This is always done under the direction of an endocrinologist.

Diabetes

Diabetes (abnormally elevated blood sugar levels) results from either not being able to produce enough insulin (Type I diabetes) or as a result of the cells of the body becoming resistant to the effects of insulin (Type II diabetes). Type I diabetes (T1D) is the form caused by autoimmune attack on the islet cells in the pancreas that produce insulin. Once islet cells are destroyed, they do not recover. When the number of Islet cells producing insulin drops below a particular threshold, patients develop diabetes. T1D is very common in some primary immunodeficiency diseases, such as IPEX syndrome where it occurs in approximately 70% of patients. Incidence is also higher in other primary immunodeficiency diseases, including CVID, APECED syndrome and others.

T1D is typically diagnosed by screening for the presence of glucose (sugar) in the urine and by measuring blood glucose levels. If these do not decrease as expected after eating or if they are high even when a patient is fasting, then diabetes may have developed. Identification of autoantibodies directed toward proteins in the pancreas (anti-islet cell antibodies) can help confirm that the process is autoimmune.

Treatment of T1D typically involves the administration of insulin either via shots or via an insulin pump. Even though T1D is autoimmune mediated, it is not yet clear whether the use of potent immunosuppressive drugs early in the course of disease will change the need for insulin treatment or not, but there are a number of therapeutic trials have been designed to address this question.

Other Autoimmune Endocrine Disorders

Insufficient parathyroid function leading to problems with regulation of calcium levels is a feature of DiGeorge syndrome and CHARGE syndrome, but in these cases the defect is caused by abnormal development of the glands, not by autoimmunity. Parathyroid autoimmunity does, however, occur as one of the main features of APECED syndrome, often in association with autoimmunity to adrenal glands and gonads.

Diagnosis of Endocrine Complications

As discussed above, diagnosis of endocrine complications revolves around identifying abnormal levels of specific hormones in the blood or in measuring abnormal electrolyte or glucose levels in the blood. The identification of specific autoantibodies in the blood is helpful in confirming that the process is autoimmune in nature.

Treatment

In general, most autoimmune endocrine disease leads to a deficiency of critically important hormones that are supposed to be made by the targeted endocrine organs. Treatment typically involves administering replacement hormone to try and achieve normal levels. In the case of the thyroid, autoimmunity can also cause increased function, which requires removal or destruction of at least part of the gland to correct the problem.

Autoimmune Musculoskeletal Disease

Arthritis (inflammation of the joints) is a common malady in the general population. Arthritis can either occur as a result of wear-and-tear on the joints (osteoarthritis) or as a result of autoimmune attack of the joints (as in rheumatoid arthritis). There is no evidence that the incidence of osteoarthritis is higher in patients with primary immunodeficiency diseases but some primary immunodeficiency diseases are associated with a higher incidence of certain autoimmune arthritis syndromes.

For example, both DiGeorge syndrome and Selective IgA Deficiency have been associated with an increased risk for developing Juvenile Idiopathic Arthritis (JIA), a type of arthritis that affects children. Approximately 20% of patients with XLA develop arthritis at some point, although it is often not terribly inflammatory and frequently resolves when immunoglobulin replacement therapy (IVIG or SCIG) is optimized. In contrast, patients with CVID can develop severe rheumatoid arthritis or psoriatic arthritis (a type of arthritis that often accompanies psoriasis – see previous Autoimmune Skin Disease section). These can cause significant pain and limitation of daily activities and can lead to permanent damage to the joint.

Unlike arthritis, myositis (inflammation of the muscles) is relatively uncommon in primary immunodeficiency diseases with one exception, which is a dermatomyositis syndrome that occurs in patients with XLA who become infected with a particular type of bacteria called Helicobacter. In these cases, the inflammation is not treated with immunosuppressant medications but instead with antibiotics to treat the bacterial infection.

Symptoms

Typical signs and symptoms of arthritis include pain and stiffness of the joints, joint swelling, and sometimes warmth or redness over the joints that have arthritis. The stiffness is often worst after not moving the joint, like in the morning after sleep or after resting, and often improves somewhat with activity. When the arthritis is active and flaring, patients may also have fevers, feel fatigued, and may have decreased appetite.

Diagnosis of Musculoskeletal Complications

A physical exam by an experienced healthcare provider is extremely helpful in diagnosing arthritis. Patients are often referred to an arthritis specialist (rheumatologist) for evaluation.

Blood tests can help to determine whether there is ongoing inflammation. Measurement of specific autoantibodies in the blood can also be helpful for making a diagnosis. Radiology tests including X-rays, CT scans and MRI scans of inflamed joints can be helpful in determining if there is ongoing inflammation and whether the joint has signs of damage from the arthritis. Sometimes, obtaining a sample of the fluid from inside the joint for testing can be extremely informative in making a firm diagnosis and ruling out infection in the joint. This is typically done by withdrawing the fluid from the joint with a needle and syringe.

Treatment

Treatment of arthritis typically requires the use of immunosuppressants. Steroids like prednisone are among the most commonly used. These can be given by mouth, injected into the blood through an IV or injected directly into the inflamed joints. They are often very effective for a time but may not provide a long-term effect. To improve the chances for control of the arthritis, other non-steroid drugs are often added. Since giving immunosuppressant medicines to a patient with primary immunodeficiency diseases may suppress their immune system even more, making them more susceptible to certain types of infections, these treatments often need to be coordinated between an immunologist and a rheumatologist.

Expectations

Significant autoimmune or inflammatory disease is common among patients with primary immunodeficiency diseases. Early recognition and treatment of these symptoms is critical for optimizing quality of life and decreasing complications associated with primary immunodeficiency diseases. This requires that patients and their care providers be aware of signs and symptoms that may suggest an autoimmune disease and that appropriate diagnostic testing and treatment be initiated in a timely fashion. Maintaining a balance between the immunosuppression used to control the autoimmune process while avoiding compounding the defects of the underlying primary immunodeficiency requires close cooperation between the patient and the various specialists involved in their care. Treatment may require frequent dosage adjustments or changes in overall approach to reach the desired balance.