Chapter 32

Autoimmunity in Primary Immunodeficiency

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The immune system is a complex set of organs, cells, proteins, and other substances. Primary immunodeficiency diseases (PI) are characterized by abnormalities in these substances that can lead to an increased susceptibility to infection. Many times, abnormalities in the immune system that lead to PI also cause immune dysregulation, which is an immune response that is not properly controlled or restrained. One form of immune dysregulation is called autoimmunity, in which the immune system is misdirected to attack normal parts of the body such as cells, tissues, or organs.

Definition

A normal immune system makes proteins known as antibodies. Antibodies recognize, prevent, and resolve infections in the body. Autoimmunity occurs when the immune system makes antibodies against itself—these are known as autoantibodies. Sometimes people with PI cannot make "good" antibodies to protect against infection but make "bad" autoantibodies, which then cause autoimmune disease.

Medicines that suppress the immune system (and therefore shut down the inappropriate immune response) are used to treat autoimmune conditions. Immune suppressive medications, however, may also suppress the "good" antibodies as well as the "bad" autoantibodies. Additionally, some immune suppressant medications can also decrease the number of types of white blood cells. These side effects of immune suppressive medications may result in an increased chance of developing a serious infection. Managing the good effects and the side effects of immune suppressant medications in an individual who has an underlying immune deficiency can be complex, as the goal is to avoid infections while still controlling the autoimmune disease. It is best to use a team approach when using immunosuppressive treatment, joining the skills of the immunologist with the appropriate specialist, which may include gastroenterology, rheumatology, pulmonology, endocrinology, nephrology, dermatology, and/or hematology.

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

Some others are frequently associated with autoimmune complications. Examples include Common Variable Immune Deficiency (CVID), Wiskott-Aldrich Syndrome (WAS), IgA deficiency, Good Syndrome, Hyper IgM Syndrome, Idiopathic T-cell Lymphopenia (ICL), and Complement Deficiencies.

Rather than great detail on the previously mentioned diagnoses, the focus here is to provide an overview of the types of immune dysregulation and autoimmunity that can occur in various types of PI.

Autoimmune Cytopenias

The development of autoantibodies that bind to and destroy blood cells is the most common autoimmune disease seen in PI. The blood cells affected include the red blood cells (RBCs), platelets, and white blood cells (WBCs). Cytopenia is the general term used to describe low numbers of blood cells.

Red Blood Cells

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

Symptoms associated with AIHA include fatigue, headache, dizziness, fainting, and a decrease in the ability to exercise. 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. Individuals 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 look like tar, 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.

One of the most important symptoms associated with AIN is fever, as this may indicate a serious infection. Other signs of infection such as coughing, 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. Individuals 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 complete blood count (CBC) is the blood test performed to establish the presence of a cytopenia. A CBC is a test that measures the number of red blood cells, different types of white blood cells, and platelets in the bloodstream. Additional blood tests can determine if an autoantibody is present. A specialist such as a clinical immunologist, hematologist, or oncologist typically evaluates individuals for these disorders. Sometimes a bone marrow sample needs to be obtained to determine if 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) replacement therapy, steroids, chemotherapy drugs, and other immune suppressive drugs. The therapy that is best for a 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. Individuals rarely require blood transfusions except in extreme circumstances. In all cases, individuals with cytopenias require close follow-up by their specialist.

Most individuals can be treated successfully and have no major restrictions on their daily activities. Individuals with platelet counts that remain low, however, 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 individuals with PI 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, which is the site where oxygen is taken up from the lung to the bloodstream. Too many white blood cells in the interstitium can cause a disease called interstitial lung disease, in which the ability of oxygen to be absorbed into the bloodstream is impaired.

Some individuals with certain types of PI develop clusters of immune cells in the lung, called granulomas. 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 PI. Two types of PI that often have granulomas in the lung are Chronic Granulomatous Disease (CGD) and CVID. Individuals with CVID sometimes develop both interstitial lung disease and granulomas in the lung. This disease is called Granulomatous Lymphocytic Interstitial Lung Disease (GLILD). Recent studies show GLILD can also occur in other rare forms of PI that are similar to CVID. Occasionally, individuals with Ataxia-Telangiectasia and APECED will develop a different type of interstitial lung disease, which can also decrease the ability of the lung to absorb oxygen. Without proper treatment, the inflammation caused by interstitial lung disease can be so severe that it will cause scarring (fibrosis) of the lung and permanently impair the ability of the lung to absorb oxygen.

Symptoms of Autoimmune Lung Disease

In most cases, the symptoms of interstitial lung disease develop slowly over time. Individuals with CGD can develop symptoms more quickly due to an infection causing lung inflammation. Individuals may notice a decrease in their endurance with every day 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. Individuals often complain of a cough, which is usually non-productive. Enlargement and rounding of the toenails and fingernails, termed clubbing, is not specific to PI or to lung damage, but they are a clue that the lungs should be evaluated. In some cases, the lung damage can lead to a severe lowering of blood oxygen causing individuals to have a bluish tint to their skin or mucous membranes. This is 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 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 PI.

Diagnosis of Autoimmune Lung Disease

Chest X-rays are useful for diagnosing infections (pneumonia). A chest X-ray can sometimes be normal, however, even when there is still significant lung disease present. A chest CT scan is a much better test to detect lung abnormalities even when the chest X-ray is normal. In individuals with CVID and GLILD, changes on the chest CT scan will often appear before the patient has symptoms.

Breathing tests, called pulmonary function tests (PFTs), can demonstrate how well the lungs are working. Changes in PFTs can be found in interstitial lung disease and other types of lung disease. However, individuals often must lose a significant amount of lung function to show symptoms that lead to 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 lung 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, such as cancer, infection, interstitial lung disease, granuloma.

Treatment of Autoimmune Lung Disease

Individuals with cancer are referred to an oncologist (cancer doctor) for continuing care. Individuals with infections are treated with antibiotics. Inflammatory changes in the lung are usually treated with drugs that suppress or alter the immune system. The

most common medicine used is corticosteroids (like prednisone), which can be given through an inhaler, by mouth, or intravenously (IV). Steroids can be effective but may not provide long-term improvement. Steroids can cause side effects such as high blood pressure, high blood sugar, osteopenia (weak bones), hyperlipidemia (high cholesterol), and stress on the kidney and eyes if used for a long period of time. 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, in addition to other drugs, can sometimes improve the inflammation in the lungs.

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

Autoimmune Skin Disease

Skin conditions due to autoimmunity or immune dysregulation can be seen in individuals who have PI. Common skin conditions like eczema or psoriasis are also seen in people with normal immune systems as well. Sometimes, skin disease is one of the earliest symptoms of a PI and can lead to further testing to identify an immune deficiency. In addition to skin disorders that are autoimmune or inflammatory in nature, other abnormal skin symptoms, such as dry, sparse hair; abnormally formed teeth and fingernails; and absent sweat glands, can be seen in certain types of PI but are not due to autoimmunity. 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 PI. Often referred to as "the itch that rashes," eczema typically begins as patches of dry, itchy skin that worsen and erupt into rash as they are scratched. It is not unusual for individuals with PI who have other autoimmune manifestations to also have eczema. Some types of PI are, however, associated with more severe eczema. Examples include WAS, Hyper-IgE Syndrome (HIES), IPEX syndrome, and certain forms of Severe Combined Immunodeficiency (SCID). In these disorders, the eczema may be difficult to treat with the usual therapies.

Psoriasis

Psoriasis is another type of autoimmune skin disease that may be confused with eczema. The typical rash in psoriasis are called plaques and may appear as red, raised, itchy, and painful. These lesions have 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. Psoriasis can occur in a number of types of PI.

Hair and Skin Pigmentation Changes

Multiple types of PI can have autoimmunity that affects the hair and skin coloring (pigment). Some individuals 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 individuals 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 genetic disorders such as 22q11 deletion (Di-George) syndrome, although they can develop in a wide range of PI.

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 the type of rash. Biopsies are typically taken from the area where the rash is most evident using a sharp punch that cuts and removes a small circular piece of skin tissue. A pathologist will look at the specimen under a microscope to determine the type of rash. This is typically a very minor procedure that can be done in the office with local numbing of the skin.

Treatment of Skin Diseases

While not typically life threatening, autoimmune and inflammatory disorders of the skin can lead to significant emotional distress and in rare situations can lead to permanent changes in appearance.

Severe rashes, like eczema, may serve as an entry point for bacteria and other organisms to enter the bloodstream due to the breakdown in the skin barrier.

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 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, stronger steroid creams or other immunosuppressant medications can be applied. In rare cases, immunosuppressant medications may be needed to treat severe disease.

Autoimmune Gastrointestinal Disease

Autoimmune gastrointestinal diseases refer to problems in the mouth, esophagus, stomach, intestines, and liver. These are common among individuals with PI, particularly individuals 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 exposed to bacteria, other organisms, and food, which all have the potential to cause irritation in the stomach and intestines. The immune system plays an important role in protecting the body from invasion by the bacteria present in the bowel.

Mucosal Changes

Autoimmune or inflammatory diseases of the gastrointestinal tract can break down 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 individuals with PI who have bowel infections with organisms such as Giardia, Cryptosporidium, rotovirus, norovirus, or Clostridium difficile. Because both autoimmune and infectious complications can lead to serious problems in individuals with PI, it is important that new gastrointestinal symptoms be evaluated when they occur. In rare cases, persistent gastrointestinal symptoms can be a sign of cancer in the bowel, which is more common in some types of PI 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 roles of the liver are:

- Breakdown of nutrients absorbed from the intestines
- Production of important blood proteins, such as clotting factors
- Processing of certain medications
- Removal of waste products from the blood
- Excretion of these into the bile

Autoimmune or inflammatory disease of the liver, which can occur in PI, can cause temporary or permanent damage that can alter 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 types of PI 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. Certain infections, such as Hepatitis (A, B, or C), Cytomegalovirus (CMV), and Epstein Barr virus (EBV) can also cause severe liver inflammation and damage. Symptoms of infection and autoimmunity can be similar, so individuals should always be tested for these specific infections as treatment of infection and autoimmunity will be different.

Diagnosis of Gastrointestinal Disease

The diagnosis of gastrointestinal disorders in PI often requires a combination of approaches. Individuals will undergo a physical exam, laboratory tests on blood and stool, and radiology tests. Physical exam findings may include oral or anal ulcers, abdominal tenderness, fluid in the abdomen (ascites), enlargement or tenderness of the liver, cracks or fissures around the anus, weight loss, and poor growth for children.

Laboratory tests include a complete blood count and an examination of the stool to determine whether the individual may be losing blood through the stomach or intestines. Lab tests will measure inflammation with a 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 evaluate for a bowel infection, testing of the stool is performed to identify bacteria or viruses. Samples of stool are also stained and evaluated under the microscope for the presence of specific parasites or other 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 diagnosis of either bowel or liver inflammation is to obtain a piece of tissue that can be evaluated under the microscope by a pathologist. For certain conditions, the physician may want to pass a scope into the esophagus, stomach, and intestines to directly see those areas. They may also perform biopsies and other tests in the liver. This is done by obtaining a small piece of liver tissue with a biopsy needle inserted through the skin and into the liver. 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 individuals with PI. The treatment plan has to balance the risks of the treatment against the risks of the disease. It may be helpful to work with a nutritionist to provide advice about an appropriate diet and vitamins. In some cases, including the bowel disease associated with CVID or CGD, steroids are often the first line of therapy, and in many cases, they may be sufficient to control symptoms. In contrast, the severe bowel disease associated with IPEX syndrome or Omenn syndrome typically requires stronger immunosuppressive medications. For individuals with PI who have significant gastrointestinal symptoms, it is essential to have a gastroenterologist involved to assist with diagnostic testing and 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 job of the kidney is to remove waste products and control fluid balance. The most common form of autoimmune kidney disease in PI is called glomerulonephritis, which is inflammation and destruction of the glomerulus units. This leads to decreased kidney function which can worsen over time if not treated. Glomerulonephritis is often seen in individuals with complement deficiencies, particularly complement components C1, C2, C3, or C4. Autoimmune kidney disease can also be seen less commonly in other PI including CVID and APECED.

Symptoms of Autoimmune Kidney Disease

In many cases, the first sign of autoimmune kidney disease is elevated blood pressure. The affected individual may have blood or protein in the urine. With glomerulonephritis, blood in the urine may not appear pink, but instead it 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 test strips that are frequently called urine dipsticks. If there is a large amount of 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 if the kidneys are not working properly. Evaluation of the urine for the presence of blood, protein, inflammatory cells, and electrolytes is also typically performed. 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 piece of tissue, which is then evaluated by a pathologist, who performs a variety of tests on the kidney tissue, including a viewing under the microscope.

Treatment of Autoimmune Kidney Disease

Individuals 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 endocrine organs secrete hormones that play important roles in maintaining basic body functions. 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). Autoantibodies against endocrine organs can cause significant health problems. Individuals who have endocrine autoimmunity are often referred to an endocrine specialist (endocrinologist) for evaluation and management.

Thyroiditis

The thyroid gland secretes thyroid hormones, which play an important role in maintaining the metabolic rate of the body. Individuals 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, individuals 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. In certain types of PI, including CVID and IPEX syndrome, the incidence is even higher.

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, radiation treatment to the thyroid gland, or use of other drugs. This is always done under the direction of an endocrinologist.

Diabetes

Diabetes (abnormally elevated blood sugar levels) can be caused by not making enough insulin (Type 1), or the body's cells cannot use the insulin properly (Type 2). Type 1 diabetes (T1D) is caused by autoantibodies against 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 to a low level, individuals develop diabetes. T1D is very common in some PI such as IPEX syndrome where it occurs in approximately 70% of individuals. Incidence is also higher in other PI, including IPEX, CVID, APECED syndrome, and others.

T1D is typically diagnosed by checking the urine for the presence of glucose (sugar) and checking the blood for elevated 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 against the islet cells can help confirm that the process is autoimmune.

Treatment of T1D typically involves giving insulin either via shots or an insulin pump. Even though T1D is autoimmune mediated, it is not yet clear whether the use of immunosuppressive drugs early in the course of disease will change the need for insulin treatment or not.

Other Autoimmune Endocrine Disorders

The parathyroid gland controls calcium levels in the body. Autoimmunity against this gland is rare, but can be seen in APECED syndrome. The parathyroid gland can be underdeveloped in some syndromes such as DiGeorge or CHARGE syndrome.

Diagnosis of Endocrine Complications

As mentioned previously, 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 very important hormones that are supposed to be made by the 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 problem 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 individuals with PI, but some types of PI 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 individuals with XLA develop arthritis at some point, although it is often usually mild and temporary. In contrast, individuals with CVID can develop 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 PI.

Symptoms of Autoimmune Musculoskeletal Disease

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 worse after not moving the joint, for example in the morning after sleep or after resting, and often improves somewhat with activity. When the arthritis is active and flaring, individuals 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. Individuals 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 helpful in making a 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 of Autoimmune Musculoskeletal Disease

Treatment of arthritis often 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 person with PI 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 for Autoimmunity in Primary Immunodeficiency Diseases

Significant autoimmune or inflammatory disease is common among individuals with PI. Early recognition and treatment of these symptoms is critical for optimizing quality of life and decreasing complications associated with PI. This requires that individuals and their healthcare 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 PI, requires close cooperation between the individual with PI (and/or their caregiver) and the various specialists involved in their care. Treatment may require frequent dosage adjustments or changes in overall approach to reach the desired balance.

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