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IMMUNODEFICIENCY

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ABSTRACT

Severe combined immunodeficiency syndrome (SCID) is a rare genetic disorder characterized by defective or absent T cell and B cell function. Patients usually present in the first 6 months of life with sepsis, disseminated tuberculosis following BCG vaccine, candidiasis, pneumocystis carinii pneumonia, severe viral infections, chronic diarrhea, failure to thrive and malabsorption. Primary immunodeficiency disorder (PID) refers to a large heterogeneous group of disorders that result from defects in immune system development and function. PIDs are broadly classified as disorders of adaptive immunity T cell, B-cell or combined immunodeficiency or innate immunity phagocyte and complement disorders. Although the clinical manifestations of PIDs are highly variable, many disorders involve an increased susceptibility to infection. Early consultation with a clinical immunologist is essential, as timely diagnosis and treatment are imperative for preventing significant disease-associated morbidity. PIDs should be suspected in patients with recurrent sinus or ear infections or pneumonia within a 1 year failure to thrive, poor response to prolonged use of antibiotics; persistent thrush or skin abscesses; or a family history of PID. Patients with multiple autoimmune diseases should also be evaluated. Diagnostic testing often involves lymphocyte proliferation assays, flow cytometry, measurement of serum immunoglobulin (Ig) levels, assessment of serum specific antibody titers in response to vaccine antigens, neutrophil function assays, stimulation assays for cytokine responses, and complement studies. The treatment of PIDs is complex and generally requires both supportive and definitive strategies. Ig replacement therapy is the mainstay of therapy for B-cell disorders and is also an important supportive treatment for many patients with combined immunodeficiency disorders. The disorders affecting the activity of the T-cell arm of the adaptive system, such as severe combined immunodeficiency, require immune reconstitution as soon as possible. The treatment of innate immunodeficiency disorders varies depending on the type of defect but may involve antifungal and antibiotic prophylaxis, cytokine replacement, vaccinations and bone marrow transplantation. This article provides an overview of the major categories of PIDs and strategies for the appropriate diagnosis and management of these rare disorders.

Severe combined immunodeficiency (SCID) is a category of immunodeficiency that is uniformly fatal if left untreated. At least nine varieties exist whose genetic basis and the corresponding phenotype is known to date. Also, there are at least eight other forms that can be considered to be part of the same disease spectrum. We discuss a 9-month-old female who presented with Pneumocystis carinii pneumonia. She was diagnosed with X-linked SCID. This report discusses the presentation of such infants, as well as the multiple genetic abnormalities, diagnosis, and management of this rare but important disorder. Severe combined immunodeficiency (SCID) is a heterogeneous group of inherited defects involving the development of T- and B-lymphocytes. Physicians caring for infants in the first months of life need to know the normal ranges for absolute lymphocyte counts (ALCs) during that age. Any ALC <2500/μL is potentially pathogenic in early infancy and should be evaluated. With a 2-month history of an oral ulcer, intermittent fever, recurrent otitis, decreased appetite, weight loss, and a new respiratory illness with hypoxemia. She had been in in-home daycare since birth. The patient's primary care physician had seen her frequently and obtained blood counts, but her persistent lymphopenia had not been appreciated. The infant was ultimately diagnosed with $T^-B^-NK^+$ (lacking both B and T lymphocytes and having primarily natural killer [NK] cells), recombinase-activating gene 2 (RAG2)-deficient severe combined immunodeficiency (SCID). However, because she had already developed 2 difficult-to-treat viral infections parainfluenza 3 and adenovirus, she did not survive long enough to receive a bone marrow transplant. Newborn screening would not only have made the diagnosis at birth but would have led to measures to protect her from becoming infected before she could receive a transplant. Newborn screening would also reveal the true incidence of SCID and define the range of conditions characterized by severely impaired T-cell development. Until screening for SCID and other T-cell defects becomes available for all neonates (either

by quantifying T-cell receptor excision circles in Guthrie spots or using other tests that quantify T cells), all pediatricians should know the normal range for ALCs according to age. Recognition of the characteristic lymphopenia of SCID can facilitate early diagnosis.

INTRODUCTION

Immunodeficiency a failure or absence of elements of the immune system including lymphocytes, phagocytes and complement systems. These immunodeficiencies can be either primary such as Bruton's disease or secondary as the one caused by HIV infection. It is a state in which the immune system's ability to fight infectious disease and cancer is compromised or absent. Most cases of immunodeficiency are acquired secondary due to extrinsic factors that affect the patient's immune system.

In the clinical setting, the immunosuppression by some drugs, such as steroids, can be either an adverse effect or the intended purpose of the treatment. Examples of such use are in organ transplant surgery as an anti-rejection measure and in patients suffering from an overactive immune system, as in autoimmune diseases. Some people are born with intrinsic defects in their immune system or primary immunodeficiency. A person who has an immunodeficiency of any kind is said to be immunocompromised. An immunocompromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect everyone. Immunodeficiency also decreases cancer immunosurveillance, in which the immune system scans the body's cells and kills neoplastic ones. Severe combined immunodeficiency syndrome (SCID) is a rare genetic disorder incidence of 1 in 5, 00, 000 characterized by defective or absent T cell and B cell function. Children with SCID usually present in the first 6 months of life with sepsis, disseminated tuberculosis following BCG vaccine, candidiasis, Pneumocystis carinii pneumonia, severe viral infections, chronic diarrhea, failure to thrive and malabsorption. SCID is often fatal within the first year of life unless abone marrow transplant or hematopoietic stem cell transplant is done. SCID is classified into 2 major groups those without T cells and B cells (T-B-) and those with B cells (T-B+). T-B+ SCID is usually inherited as an X-linked recessive disorder but rarely can be an autosomal recessive due to Jak3 kinase deficiency. However, T-B-SCID occurs equally in boys and girls. Primary immunodeficiency disorder (PID) refers to a heterogeneous group of disorders characterized by poor or absent function in one or more components of the immune system which predisposes affected individuals to increased frequency and severity of infection, autoimmunity, and aberrant inflammation and malignancy. More than 250 different disorders have been genetically identified to date, with new disorders continually being recognized. Most PIDs result from inherited defects in immune system development and function; however, acquired forms have also been described, such as neutralizing anti-interferon-γ autoantibody-associated immunodeficiency (which has been noted in over 95% of patients with disseminated infections by non-tuberculous mycobacteria. It is important to note that PIDs are distinct from secondary immunodeficiencies that may result from other causes, such as viral or bacterial infections, malnutrition, immunoglobulin (Ig) loss, malignancy or treatment with drugs that induce immunosuppression. Except of immunoglobulin A (IgA) deficiency, the estimated overall prevalence of these disorders in the United States is approximately 1 in 1200 live births. IgA deficiency is the most common PID, occurring in approximately 1 in 300 to 1 in 500 persons. The clinical presentation of PIDs is highly variable; however, most disorders involve increased susceptibility to infection. Many PIDs present as "routine" infections often of the sinuses, ears, and lungs and, therefore, may go undetected in the primary-care setting. PIDs may present at any age, and the accurate and timely diagnosis of these disorders requires a high index of suspicion and specialized testing. Therefore, consultation with a clinical immunologist who is experienced in the evaluation and management of immunodeficiencies is essential, since early diagnosis and treatment are critical for preventing significant disease-associated morbidity and improving patient outcomes. This article provides an overview of the major categories of PIDs as well as strategies for the timely identification, diagnosis, and management of these disorders.

PRIMARY IMMUNODEFICIENCY

B-cell Deficiencies

X- linked Agammaglobulinemia (Bruton's disease)

First described by Bruton X-linked disorder Found in male babies expressed around 5 to 6 months of age (maternal IgG disappears).

In boys, pre-B cells did not differentiate into mature B lymphocytes. There is a mutation in the gene that encodes for a tyrosine kinase protein. Low level of all immunoglobulins (IgG, IgA, IgM, IgD ,and IgE) is present. Infants with X-linked agammaglobulinemia suffer from recurrent bacterial infections: otitis media, bronchitis, septicemia, pneumonia, and arthritis, and Giardia lamblia causes intestinal malabsorption. Intermittent injections of large amounts of IgG keep the patient alive, but a patient may die at a younger age if infection with antibiotic-resistant bacteria occurs. Bone marrow transplantation is critical.

Selective Immunoglobulin IgA Deficiencies

IgA deficiency is more common than other deficiencies of immunoglobulins. These patients are more prone to recurrent sinus and lung infections. A malfunctioning in heavy-chain gene switching may cause this problem. Treatment should not include gammaglobulin preparations to prevent hypersensitivity reactions.

T-cell Immunodeficiencies.
Congenital thymic Aplasia DiGeorge Syndrome. Tetany is present. Fungal and viral infections are common. A transplant of the fetal thymus is needed to correct this deficiency. Chronic Mucocutaneous Candidiasis. Selective defect in the functioning of T-cells.
Patients with this disorder usually has a normal T-cell mediated immunity to microorganisms other than Candida. The B-cells function is normal. Disorders affect both genders, and it is inherited. Patient in addition to the above will have other disorders like parathyroid deficiencies. Antifungals are useful.

Hyper-IgM syndrome
This disorder is characterized by bacterial infections including pneumonia, meningitis, otitis, among others that start in early childhood.
High levels of IgM. Other immunoglobulins are defective. Lymphocytes are normal in numbers. The gene encoding the CD40 ligand on T lymphocytes is faulty. B and T lymphocyte cooperation in the immune response are compromised.
The failure to interact with CD40 results in an inability of the B cell to switch from the production of IgM to the other classes of antibodies. Immunoglobulin therapy is recommended.

Interleukin-12 receptor deficiency
Mycobacterial infections are frequent due to the lack of the interleukin-12 receptor. Treatment involves selective antimicrobials.

T-cell and B-cell Deficiencies
Severe combined immunodeficiency disease (SCID). There is a failure of early stem cells to differentiate into T and B lymphocytes.
The deficiency of the interleukin-2 receptor is the most prevalent. Other problems are due to defective genes encoding ZAP-70, Janus kinase 3 and the genes involved in the DNA recombination of immune cells receptors: RAG1 and RAG2.
Clinically characterized by a variety of infections, including those caused by opportunistic pathogens. Selective antibiotics, antivirals, and antifungals are available after the pathogen identification. Immunosuppressive therapy is not needed after allograft transplantation.

Wiskott-Aldrich syndrome
This syndrome is associated with normal T-cell numbers with reduced functions, which get progressively worse.
IgM concentrations are reduced, but IgG levels are normal. Both IgA and IgE levels are elevated. These patients have a defective WASP which is involved in actin filament assembly.

Immunodeficiency with ataxia-telangiectasia
This is a deficiency of T-cells associated with a lack of coordination of movement (ataxia) and dilation of small blood vessels of the facial area (telangiectasis). T-cells and their functions are diminished to various degrees. B-cell numbers and IgM concentrations are normal to low. IgG is often reduced, and IgA is considerably reduced. There is a high incidence of malignancy, especially leukemias, in these patients.

MHC deficiency (Bare leukocyte syndrome)
These subjects have had fewer CD4+ or CD8+ T lymphocytes that predispose these individuals to be prone to recurrent infections.
Antibody production is affected and predispose to bacteremia. Complement Deficiencies.

Hereditary angioedema
This disease has an autosomal dominant genetic pattern. Caused by C1 inhibitor deficiency. Clinically characterized by generalized edema including the one leading to acute suffocation. Therapy with oxymetholone and danazol can help correct the defect.

Recurrent infections
Frequent infections by extracellular bacteria may be caused by C3 deficiency. C5 deficiency predisposes to viral infections.
Patients with adeficiency of the membrane attack complex (MAC) are particularly susceptible to bacteremia caused by Neisseria species.

Autoimmune diseases
This is caused by C2 and C4 deficiencies and mimic systemic lupus erythematosus. Phagocyte Deficiencies.

Chronic granulomatous disease (CGD)
It is mostly an X-linked disorder. It is clinically characterized by a defective NADPH that interferes with the intracellular ability of neutrophils to kill engulfed bacteria species. NAPDH oxidase is required for the generation of peroxidase and superoxides that will kill the organisms. The intracellular survival of the organisms leads to the formation of a granuloma, an organized structure consisting of mononuclear cells. These granulomas can become large enough to obstruct the stomach, esophagus, or bladder.

Patients with this disease are very susceptible to opportunistic infections by certain bacteria and fungi especially, with Serratia and Burkholderia. Nitroblue tetrazolium (NBT) dye reduction test confirms the diagnosis of CGD and the dichlorofluorescein (DCF) test is also useful. Aggressive therapy with wide-spectrum antibiotics and antifungal agents is required.

Leukocyte adhesion deficiency syndrome
Characterized by pyogenic infections including pneumonia and otitis. It is an autosomal recessive disease, and the faulty gene encodes for an integrin. There are an impaired adhesion and defective phagocytosis of bacteria. Treatment involves the use of selective antibiotics. Secondary Immunodeficiency.

Use of Drugs (Steroids)
Administration of steroids has direct effects on immune cell traffic and functions. T cells are more affected than B cells.
Cytokine synthesis is inhibited.

Nutrient Deficiencies
They are associated with an impaired immune systems. Affects cell-mediated immunity, antibody production, phagocyte function, complement system, and cytokine synthesis. Aggravated by infections. Multiple enzymes with important roles require zinc, iron and other micronutrients.

Obesity
It may cause impaired immune responses. There are an altered NK function. Cytotoxicity is compromised and the ability of phagocytes to kill microorganisms. Acquired Immune Deficiency Syndrome (AIDS). Caused by human immunodeficiency virus (HIV), which is a retrovirus transmitted sexually, perinatally or blood products. Immune dysfunction results from the direct effects of HIV and impairment of CD4 T cells. HIV proteins may act as superantigens. There are decreased responses to antigens and mitogens. Interleukin-2 and other cytokines are decreased. Infected cells may be killed by HIV-1 specific CD8+ T cells. In HIV-1 infection neutralizing antibodies appear to be ineffective in controlling viral replication and infection.

Etiology
Primary immunodeficiency diseases result from intrinsic defects in immune cells including T cells, complement components, and phagocytes. Recurrent pneumonia caused by extracellular bacteria suggests antibody deficiency. On the other hand, recurrent fungal infection may be caused by a lack of T lymphocytes. Severe combined immunodeficiency disorders (SCID) are incompatible with life and affected children usually die within the first 2 years. SCID is more common in the male. It is caused by a gene defect on the X chromosome in more than 50% of cases. The defective gene encodes the gamma chain of the interleukin-2 (IL-2) receptor. This chain forms a molecular part of the receptors for IL-2, IL-4, IL-7, IL-11, IL-15, and IL-21. On the other hand, few cases of SCID are caused by defective genes that encode for adenosine deaminase or nucleoside phosphorylase. The deficiency of these enzymes causes ribonucleotide reductase inhibition leading to a defect in DNA synthesis and cell replication. Mutation in the genes encoding RAG1 or RAG2 cause an autosomal recessive form of SCID.

The DiGeorge anomaly arises from a defect in the third and fourth pharyngeal pouches that causes a developmental abnormality of the thymus. The T-cell defect is variable depending on the severity of the thymic lesion. These infants have partial monosomy of 22q11-pter or 10p.

In the bare leukocyte syndrome, there is a mutation in the gene that encodes for the MHC class II transactivator (CIITA) resulting in the absence of class-II MHC molecule on antigen-presenting cells including macrophages and dendritic cells. A mutation in the gene that encodes for transport-associated protein (TAP) results in the lack of class-I MHC molecule expression, which is manifested by a deficiency of CD8+ T lymphocytes. Secondary immunodeficiency may be caused by drugs including steroids, cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, ciclosporin, tacrolimus, and rapamycin, which affect the functions of both T and B lymphocytes. Viral infections can cause immunodeficiency. For example, HIV causes AIDS, which mainly affects CD4+T cells and down-regulates cellular immune responses that produce opportunistic infections and cancers, which are threatening to human health. Malnutrition is a cause of the secondary deficiency, for example, the protein-energy malnutrition affects cell-mediated immunity and phagocytosis, the ingestion of microorganisms is intact, but the ability of phagocytic cells to kill intracellular organisms is impaired. Nutritional deficiency can result from cancer, burns, chronic renal disease, multiple trauma, and chronic infections. Zinc and iron deficiencies have a variety of effects on immunity including a reduction in delayed cutaneous hypersensitivity. Vitamin supplementation (B6 and B12), selenium and copper are also important for a normal function of the immune system.

Epidemiology
A total of 152 patients with primary immunodeficiencies (PID) observed from 2001 to 2005. The prevalence was 11.25 per million children. The most frequent immunodeficiencies found were antibody deficiencies, 53.3%, followed by phagocytic disorders, 28.9%. Sweden carried out a study of the frequency of this problem during the period 1974 through 1979 and resulted in 201 reported cases. Antibody deficiencies were the most frequent (45.0%), followed by phagocytic disorders (22.0%) and combined T-cell and B-cell deficiencies (20.8%). In a Taiwan tertiary hospital from January 1985 to October 2004, 37 patients with primary immunodeficiencies were identified: the highest prevalence corresponded to antibody deficiency (46%), followed by defective phagocyte function (24%) and T-cell immunodeficiencies (19%). In South Africa a study was conducted on 168 patients diagnosed with PID from 1983 to 2009, antibody deficiencies predominated (51%). Similarly, in Singapore between 1990 and 2000, 39 patients with PID were identified, and antibody deficiency (41%) was the most prevalent. The prevalence of common variable immunodeficiency (CVID) varies widely worldwide. The most prevalent secondary immunodeficiency is the one caused by HIV and causes the acquired immunodeficiency syndrome, which prevalence varies worldwide. Approximately 37 million individuals were living with HIV at the end of 2016. There were 20.9 million people infected that were

receiving antiretroviral therapy (ART) by mid-2017. Seven out of 10 pregnant women living with HIV received antiretroviral treatment. A massive expansion of antiretroviral therapy (ART) has reduced the global number of people dying from HIV-related causes to about 1.1 million in 2015, 45% fewer than in 2005. Since 2003, annual AIDS-related deaths have decreased by 43%. In the world's most affected region, eastern and southern Africa, there were 10.3 million people on treatment, this number of people has doubled since 2010. Deaths due to opportunistic infections and other AIDS-related illnesses have decreased by 36% since 2010. The population at high risk of HIV/AIDS includes people in prisons and other closed settings, individuals who inject drugs, sex workers, transgender people, patients receiving blood transfusions or blood products, and infants born to HIV-infected mothers.

Pathophysiology

Immune cells include B and T lymphocytes. B-cells transform in plasma cells that produce large amounts of antibodies. These antibodies or immunoglobulins fight extracellular microorganisms. That explains why in B-cells deficiencies including X-linked agammaglobulinemia there is ahigh susceptibility to pneumonia, otitis and other infections caused by extracellular bacteria. SCID can be caused by RAG-1/2 deficiency and characterized by defective VDJ recombination due to a defect of recombinase activating gene RAG1 or RAG2. May present with Omenn syndrome. T-cells differentiate into helper, cytotoxic or suppressor T cells. Helper T cells stimulate antibody production. In T-cell deficiencies including DiGeorge syndrome, the antibody production may be compromised to an extent. T-cells fight intracellular microorganisms including fungi, viruses and also tumors, which infect or proliferate in individuals with HIV/AIDS, SCID, hyper-IgM syndrome and other T-cell deficiencies. The innate immune response is the first line of defense against infections. It comprises of the phagocytic cells, complement system proteins and a large number of cytokines and their receptors. Innate immunity plays a key role in helping B and T lymphocytes to accomplish their fundamental functions. Deficiencies of the innate immunity characterized by susceptibility to infections by rare and opportunistic pathogens, failure to thrive, and certain inflammatory or autoimmune disorders, for example, C4 deficiency is linked to the occurrence of lupus-like syndromes.

Most immunodeficiencies are congenital and have an X-linked or autosomal recessive inheritance pattern. For example immunodeficiency with ataxia-telangiectasia is an autosomal recessive disease caused by mutations in the genes that encode DNA repair enzymes. The defects arise from breakage in chromosome 14 at the site of TCR and Ig-heavy chain genes.

Histopathology

A curious case of immunodeficiency is the hyper-IgM syndrome that results in a medical problem where individuals are IgG and IgA deficient but secrete a large amount of IgM. The gallbladder in these patients shows a submucosa that is filled with cells with pink-staining cytoplasm and eccentric nuclei. These cells synthesize and secrete IgM. In SCID in the microscopical examination, numerous Giardia lamblia parasites can be seen swarming over the mucosa of the jejunum. In the thymic stroma, there is not the presence of lymphoid cells, and no Hassall's corpuscles are seen. The gland has a fetal appearance. In AIDS, small bowel biopsies from patients with diarrhea caused by cryptosporidia show intermediate forms of cryptosporidia, which are small pink dots on the surface of the mucosa. Pneumonia caused by P. jiroveci is the most frequent opportunistic infection seen in AIDS, and the diagnosis is made histologically. P. jiroveci stain brown to black with the Gomori methenamine silver stain and with Giemsa or Dif-Quik stain on cytologic smears, the dot-like intracystic bodies are seen. Cytomegalovirus (CMV) is frequently a disseminated opportunistic infection seen with AIDS. It causes pneumonia and other problems. The presence of large cytomegalic cells that have enlarged nuclei that contain a violaceous intranuclear inclusion surrounded by a clear halo distinguish CMV. Sometimes, basophilic stippling is present in the cytoplasm. Lymphoid atrophy is a prominent morphological feature of malnutrition. Histologically, the lobular architecture is ill-defined, there is a loss of corticomedullary demarcation, and there are fewer lymphoid cells. Hassall's corpuscles are enlarged and degenerate; some may be calcified. Atrophy is observed in the thymus-dependent periarteriolar areas of the spleen and the paracortical section

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Diagnosis

Blood tests, skin tests, a biopsy, sometimes genetic testing. Doctors must first suspect that an immunodeficiency exists. Then they do tests to identify the specific immune system abnormality. Doctors suspect immunodeficiency when one or more of the following occur: A person has many recurrent infections (typically sinusitis, bronchitis, middle ear infections, or pneumonia). Infections are severe or unusual. Severe infection is caused by an organism that normally does not cause severe infection (such as Pneumocystis, fungi, or cytomegalovirus). Recurring infections do not respond to treatment. Family members also have frequent and severe recurring infections. Blood tests, including a complete blood count (CBC), are done. CBC can detect abnormalities in blood cells that are characteristic of specific immunodeficiency disorders. A blood sample is taken and analyzed to determine the total number of white blood cells and the percentages of each main type of white blood cell. The white blood cells are examined under a microscope for abnormalities. Doctors also determine immunoglobulin levels and the levels of certain specific antibodies produced after the person is given vaccines. If any results are abnormal, additional tests are usually done. Skin tests may be done if the immunodeficiency is thought to be due to a T-cell abnormality. The skin test resembles the tuberculin skin test, which is used to screen for tuberculosis. Small amounts of proteins from common infectious organisms such as yeast are injected under the skin. If a reaction (redness, warmth, and swelling) occurs within 48 hours, the T cells are functioning normally. No reaction could suggest a T-cell abnormality. To confirm a T-cell abnormality, doctors do additional blood tests to determine the number of T cells and to evaluate T-cell function. A biopsy may be done to help doctors identify which specific immunodeficiency disorder is causing the symptoms. For the biopsy, doctors take a sample of tissue from the lymph nodes and bone marrow. The sample is tested to determine whether certain immune cells are present. Genetic testing may be done if doctors suspect a problem with the immune system. The gene mutation or mutations that cause many immunodeficiency disorders have been identified. Thus, genetic testing can sometimes help identify specific immunodeficiency disorder. Screening Genetic testing, usually blood tests may also be done in people whose families are known to carry a gene for a hereditary immunodeficiency disorder. These people may wish to be tested to learn whether they carry the gene for the disorder and what their chances of having an affected child are. Talking with a genetic counselor before testing is helpful. General measures and certain vaccines to prevent infections.

Antibiotics and antivirals when needed

Sometimes immune globulin, Sometimes stems cell transplantation, Treatment of immunodeficiency disorders usually involves preventing infections, treating infections when they occur, and replacing parts of the immune system that are missing when possible. With appropriate treatment, many people with an immunodeficiency disorder have a normal life span. However, some require intensive and frequent treatments throughout life. Others, such as those with severe combined immunodeficiency, die during infancy unless they are given a stem cell transplant.

Preventing infections

Strategies for preventing and treating infections depend on the type of immunodeficiency disorder. For example, people who have an immunodeficiency disorder due to a deficiency of antibodies are at risk of bacterial infections. The following can help reduce the risk: Being treated periodically with immune globulin (antibodies obtained from the blood of people with a normal immune system) given intravenously or under the skin, practicing good personal hygiene (including conscientious dental care eating undercooked food not drinking water that may be contaminated. Avoiding contact with people who have infections Vaccines are given if the specific immunodeficiency disorder does not affect antibody production. Vaccines are given to stimulate the body to produce antibodies that recognize and attack specific bacteria or viruses. If the person's immune system cannot make antibodies, giving a vaccine does not result in the production of antibodies and can even result in illness. For example, if a disorder does not affect the production of antibodies, people with that disorder are given the influenza vaccine once a year. Doctors may also give this vaccine to the person's immediate family members and to people who have close contact with the person. Generally, vaccines that contain live but weakened organisms (viruses or bacteria) are not given to people who have a B- or T-cell abnormality because these vaccines may cause an infection in such people. These vaccines include rotavirus vaccines, measles-mumps-rubella vaccine, and chickenpox (varicella) vaccine, one type of varicella-zoster (shingles) vaccine, bacille Calmette-Guérin (BCG) vaccine, influenza vaccine given as a nasal spray, and oral poliovirus vaccine. The oral poliovirus vaccine is no longer used in the United States but is used in some other parts of the world.

Treating infections

Antibiotics are given as soon as a fever or another sign of infection develops and often before surgical and dental procedures, which may introduce bacteria into the bloodstream. If a disorder (such as severe combined immunodeficiency) increases the risk of developing serious infections or particular infections, people may be given antibiotics to prevent these infections.

Antiviral drugs are given at the first sign of infection if people have an immunodeficiency disorder that increases the risk of viral infections (such as immunodeficiency due to a T-cell abnormality). These drugs include oseltamivir or zanamivir for influenza and acyclovir for herpes or chickenpox. Replacing missing parts of the immune system. Immune globulin can effectively replace missing antibodies (immunoglobulins) in people with an immunodeficiency that affects antibody production by B cells. Immune globulin may be injected into a vein (intravenously) once a month or under the skin (subcutaneously) once a week or once a month. Subcutaneous immune globulin can be given at home, often by the person with the disorder.

Stem cell transplantation can correct some immunodeficiency disorders, particularly severe combined immunodeficiency. Stem cells may be obtained from bone marrow or blood (including umbilical cord blood). Stem cell transplantation, which is available at some major medical centers, is usually reserved for severe disorders. Transplantation of thymus tissue is sometimes helpful. Gene therapy, along with transplantation, is an intervention with the potential to cure genetic disease. In gene therapy, a normal gene is inserted into someone's cells to correct a genetic abnormality causing a disorder. Gene therapy has been used successfully in various primary immunodeficiency disorders such as severe combined immunodeficiency, chronic granulomatous disease, adenosine deaminase deficiency, and others. Although there are various limitations and obstacles with the procedure, gene therapy provides promise for potential cures in the future.

Evaluation

The immunological investigation of a patient with immunodeficiency includes the assessment of immunoglobulins including isohemagglutinins and antibody activity, B and T-lymphocyte counts, lymphocyte stimulation assays, quantification of components of the complement system and phagocytic activity.

Quantitative Serum Immunoglobulins
IgG, IgM, IgA, IgE.
IgG Sub-Classes
IgG1, IgG2, IgG3, IgG4.
Antibody Activity
IgG antibodies (post-immunization)
Tetanus toxoid, Diphtheria toxoid, Pneumococcal polysaccharide, Polio
IgG antibodies (post-exposure)
Rubella, Measles, Varicella zoster
Detection of isohemagglutinins (IgM)
Anti-type A blood, Anti-type B blood
Other assays
Test for heterophile antibody, Anti-streptolysin O titer
Immunodiagnosis of infectious diseases (HIV, hepatitis B, and C, HTLV and dengue)
Serum protein electrophoresis
Blood lymphocyte subpopulations
Total lymphocyte count
T lymphocytes (CD3, CD4, and CD8)
B lymphocytes (CD19 and CD20)
CD4/CD8 ratio
Lymphocyte stimulation assays
Phorbol ester and ionophore
Phytohemagglutinin
Antiserum to CD3
Phagocytic function
Nitroblue tetrazolium (NBT) test (before and after stimulation with endotoxin)
Unstimulated
Stimulated
Neutrophil mobility
In medium alone
In the presence of chemoattractant
Complement System Evaluation
Measurement of individuals components by immunoprecipitation tests, ELISA, or Western blotting
C3 serum levels
C4 serum levels
Factor B serum levels
C1 inhibitor serum levels
Hemolytic assays
CH50
CH100
AH50
Complement system functional studies
Classical pathway assay (using IgM on a microtiter plate)
Alternative pathway assay (using LPS on a microtiter plate)
Mannose pathway assay (using mannose on a microtiter plate)
Measurement of complement-activating agents
Circulating immune complexes
Cold agglutinins
Assays for complement-binding
C1q autoantibody ELISA
C1 inhibitor autoantibody ELISA
Others complement assays
LPS activation assay
Specific properdin test
C1 inhibitor activity test
Autoimmunity Studies
Anti-nuclear antibodies (ANA)

Detection of specific auto-immune antibodies for systemic disorders (anti-ds DNA, rheumatoid factor, anti-histones, anti-Smith, anti-(SS-A) and anti-(SS-B)
Detection of anti-RBC, antiplatelet, and anti-neutrophil
Testing for organ-specific auto-immune antibodies

Microbiological studies
Blood (bacterial culture, HIV by PCR, HTLV testing), Urine (testing for cytomegalovirus, sepsis, and proteinuria).

Nasopharyngeal swab (testing for Rhinovirus)
Stool (testing for viral, bacterial or parasitic infection)
Sputum (bacterial culture and pneumocystis PCR)
Cerebrospinal fluid (culture, chemistry, and histopathology)

Coagulation tests
Factor V assay, Fibrinogen level, Prothrombin time, Thrombin time, bleeding time.

Other investigations of immunodeficiency disorders
Complete blood cell count, Tuberculin test, Bone marrow biopsy, Histopathologic studies, Liver function test, and Blood chemistry.
Tumoral markers, Levels of cytokines, Chest x-ray, Diagnostic ultrasound, CT scan Fluorescent in situ hybridization (FISH).
DNA testing (for most congenital disorders).

Management
Immunoglobulin Therapy X- linked agammaglobulinemia, Transient hypogammaglobulinemia of infancy
Variable common immunodeficiency
Selective immunoglobulin deficiencies, except for IgA
Hyper-IgM syndrome
Lupus-like syndromes
Use of Transfer Factor (Dialyzable Leukocyte Extract)
Interstitial pneumonia is acquired immunodeficient states, recurrent viral infections in immunodeficiency syndromes
Chronic mucocutaneous candidiasis, Primary tuberculosis with immunodeficiency
Wiskott-Aldrich syndrome, Severe combined immunodeficiency disease, chronic active hepatitis
Coccidioidomycosis, Behcet disease, Aphthous stomatitis, Familial keratoacanthoma, Malignancy.
Use of Antibiotics
Primary and secondary antibody deficiencies
Hyper-IgM syndrome
Chronic mucocutaneous candidiasis
Interleukin-12 receptor deficiency
Severe combined immunodeficiency diseases
MHC deficiency
Complement system deficiencies
Chronic granulomatous disease
Leukocyte adhesion deficiency syndrome
HIV/AIDS
Nutrient deficiencies (zinc and iron)
Use of Antifungal Drugs
DiGeorge syndrome
Chronic mucocutaneous candidiasis
Severe combined deficiency diseases
Chronic granulomatous disease
Use of immunosuppressors
Obesity
HIV/AIDS
Malignancy
Use of Antiviral Drugs
DiGeorge syndrome
HIV/AIDS
Severe combined deficiency diseases
C5 deficiency
CMV in transplant recipients
Recurrent viral infections in immunodeficiency syndromes
Use of Immunosuppressors
The systemic lupus erythematosus (SLE)
Wiskott-Aldrich syndrome
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
Autoimmune lymphoproliferative syndrome
Idiopathic CD4+ lymphocytopenia
Complement system deficiencies
Malignancy
Transplantation
Bone marrow transplant
RAG-1/RAG-2 SCID
ADA-SCID
Artemis SCID
Wiskott-Aldrich syndrome
X-linked agammaglobulinemia Acute leukemia
Thymus transplant
DiGeorge syndrome
Use of Cytokines in the Immunotherapy of Advanced Malignancies
Interleukin-2
Interleukin-7
Interleukin-12
Interleukin-18
Interleukin-21
Use of Nutritional Supplements (Vitamins A, C, E and B6, Iron, Zinc, Selenium, and Copper)
Primary immunodeficiency with malnutrition
Lymphoma
Malignancies in general
Graft-versus-host reaction
Diseases with impaired cell-mediated immunity
Recurrent and chronic bacterial infections
SCID
HIV/AIDS
Burns
Phase III Clinical Trials of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib
Relapsed or refractory chronic lymphocytic leukemia
Small lymphocytic lymphoma
Relapsed or refractory Mantle cell lymphoma
Newly diagnosed non-germinal center B-cell subtype of diffuse large B-cell lymphoma

Use of Interferon Gamma
Chronic granulomatous disease
Bladder carcinoma
Melanoma
Chagas disease
Cryptococcal meningitis

Differential Diagnosis
These disorders are characterized by bacterial infections including pneumonia, meningitis, otitis, diarrhea, urinary sepsis, septicemia, osteomyelitis, cellulitis, conjunctivitis, hepatitis, gastroenteritis and in some Giardia lamblia causes intestinal malabsorption. They start in early childhood and include X-linked agammaglobulinemia, IgG selective deficiencies, transient hypogammaglobulinemia of infancy, common variable immunodeficiency, hyper-IgM syndrome and certain types of SCID.
They can are ruled out as follow: X-linked agammaglobulinemia is seen in male babies around 5-6 months of age when maternal IgG disappears. There is a low level of all immunoglobulins (IgG, IgA, IgM, IgD, and IgE) and DNA studies show Bruton's tyrosine kinase (BTK) mutations that cause B lymphocyte precursors in the bone marrow fail to develop into mature B lymphocytes. This mutation is a distinctive trait of this immunodeficiency, and therefore other immunodeficiencies can be ruled out.

Transient hypogammaglobulinemia of infancy is caused by a physiological immaturity of the immune system and manifests similarly to X-linked agammaglobulinemia, but recurrent bacterial infections stop once the infants start producing their immunoglobulins.

IgG selective deficiencies predispose to bacterial recurrent infections but they can be ruled out by the demonstration of absence or low serum levels of one or more IgG subclasses. This problem is corrected by the administration of gammaglobulins or intravenous immunoglobulins.

Common variable immunodeficiency is a cause of recurrent bacterial infections or more rarely viral infections, but it is ruled out because the infections start later in life and mostly after childhood. All causes of antibody deficiency most be rule out before considering the diagnosis of this problem.
Hyper-IgM syndrome is characterized by the presence of recurrent bacterial infections as those that appear in X-linked agammaglobulinemia but the cause of this illness is a mutation in the gene encoding for CD40 on T lymphocytes that causes a failure in T and B lymphocyte cooperation, which is important for B cell switching from IgM to other classes of immunoglobulins. A genetic study diagnoses this immunodeficiency.
Severe combined immunodeficiency diseases (SCID) are mostly characterized by the presence of recurrent bacterial infections, but they are ruled out because they are other manifestations such as malignancies and recurrent viral, fungal, parasitic and opportunistic infections.

Prognosis
B-cells deficiencies have a better prognosis if they can be treated with intravenous immunoglobulins (every few weeks) and subcutaneous infusion that is needed once or twice a week. T-cells deficiencies such as DiGeorge syndrome has a poor prognosis, but if thymus transplantation is successfully done, a better prognosis occurs. SCID has the poorest prognosis unless bone marrow transplantation is successfully performed. Immunodeficiency with some congenital disabilities can be treated with surgery and can attain a better prognosis by the concomitant administrations of immunotherapy (for example, the use of immunomodulators). In general, for improving the quality of life of patients with primary immunodeficiencies a long-term treatment with antimicrobials, antiviral and antifungal drugs are needed. Most primary immunodeficiencies are rare and require personalized management, especially if gene mutations or a missing enzyme cause them. Currently, the use of gene therapy and stem cell transplantation offer a promising outcome that can be reflected in a better prognosis.

In secondary immunodeficiency such as HIV/AIDS a long-term treatment with anti-retroviral is required, as well as prophylaxis for fungal infections. If patients are malnourished, healthcare professionals must implement a balanced diet high in proteins, and they must administer vitamins, minerals, and other nutrients. In drug-related immunodeficiencies, the prognosis is reserved, especially in those patients with auto-immune disorders, inflammatory diseases, and organ transplants. The prognosis of patients with malignancies varies and depends on the type of cancer, evolution, staging and grading, and the response to treatment modalities including chemotherapy, radiotherapy, and even the use of natural products.

Complications
Life-threatening overwhelming infections caused by bacteria, viruses, fungi, and parasites.

Opportunistic malignancy, Septic shock, Anaphylactic shock, Bleeding disorders, Cardiac failure, Acute and chronic renal failure, Respiratory insufficiency, Multi-organ failure, Obstetric problems such as intrauterine growth retardation and fetal demise, Systemic lupus erythematosus or other systemic rheumatic disorders, Endocrinopathy, Congenital disabilities, Metabolic disturbances, Neurological complications including seizures and coma, Acidosis/alkalosis, Premature death.

Case presentation
S.R. Abu Agwaa month9 old female child weight 6kg admitted to hospital to PICU, a decrease of the level of consciousness, difficulty of breathing, wheezing in the

chest severe cough, Fatigue fever since 2 ago days, a revealed the past case history of grunting and dyspnea. Very severe chest wall indrawing and hypoxemia spo2 peripheral capillary oxygen saturation 80%. On examination HR190 bpm, RR60bpm, Temp40.8C high fever, BP 85/50mmhg.she was clinically baby dyspnea, irritable. Diagnosis with severe pneumonia and, physical assessment skin moist, pale, integrity healthy nails color bluish, texture smooth, head and face symmetrical, eye symmetrical, white sclera.no drug allergy. Ears symmetrical auricles, nose and, nasal sinuses, patent nostrils, good ability to smell, mouth throat and tongue moist, pink, teeth regular spaced, tongue pink, throat enlarged tonsils, neck full range of motion, carotid pulsation120beat/minute symmetrical, thorax and lung respiratory rate 60breath/minute, on inspection symmetrical chest, cough use accessory muscles, on percussion resonance, on auscultation abnormal breath sounds rhonchi, wheezes, crepitation, heart and blood vessels, apical pulse 130beat/minute regular, strong, BP90/50mmhg, peripheral pulse dorsal is pedis right and left normal, posterior tibial RT, LF normal, radial RT, LF normal, central line RT femoral, abdomen soft and relaxed, motor response obeys commands, sensory response identify fine touch, speech clear.

Abdomen Inspection Palpation -smooth to touch -no lesion -no swelling -warm to touch -round and symmetrical -abdomen rises with inspiration in synchrony with chest -smooth to touch -no lesion -no swelling -warm to touch -round and symmetrical -abdomen rises with inspiration in synchrony with a chest. Lower Extremities Inspection -bilaterally symmetrical and equal -right foot has complete fingers -skin color is as same as the other parts of the body -bilaterally symmetrical and equal -right foot has complete fingers -skin color is as same as the other parts of the body Posterior Lower Inspection and normal skin color, The child's immunization was incomplete.

On admission on Examination auscultation, crepitation was present in both lung fields right upper zone and left upper zone and rhonchi were present on upper and middles side of left lung field, she was admitted in PICU, crepitation both lower lobe for which he received symptoms treatment, comprising bed rest and paracetamol suppository 150mg as needed, moreover, he biological assessment was done that confirmed the clinical diagnosis pneumonia. After he presented progressive deterioration of the general condition and the onset of severe abdominal pain, chest u/s there is infiltration in the lower lobe in both sided; pneumonia lower lobe baby was intubated and connected to mechanical ventilation. She was born at full term with a birth weight of 1.8 kg. She was four in birth order and both elder sisters were asymptomatic. She had received BCG and 3 doses for OPV and DPT. On examination, his weight was 5.7 kg and length was 68 cm she had a respiratory rate of 66 minutes with bilateral coarse crepitations was normal. Milk scan for gastro esophageal there was no rash and systemic examination reflux showed no reflux. Sweat chloride was meq/L (normal range = 0-30 meq/L). X-ray17 chest showed right upper zone consolidation and thymus was not seen. High-resolution CT scan of the chest showed focal areas of fibrosis and patchy consolidation. Arterial blood gas and patchy consolidation. Arterial blood gas showed hypoxia (PO2 = 60 mm of Hg, Oxygen saturation = 92%) with normal ph. Bronchoalveolar
Lavage culture and smear were negative for bacterial, mycobacterial and fungal infection. Hemogram showed a total.

Leucocyte count of 20,400 cells/cumm with an absolute lymphocyte count of 936 cells/cumm HIV ELISA was negative. Given of suspected and investigations confirmed TB.lymphopenia, recurrent pneumonia, and failure + K- SCID. She was treated with IV amkacin and trimethoprim prim sulphamethoxazole (20 mg/kg/d of trimethoprim) along with chest physiotherapy for 21 days and discharged on trimethoprim-sulphamethoxazole prophylaxis.

DISCUSSION

Most patients with SCID have thymic hypoplasia and small poorly developed lymph nodes and tonsils as was seen in our patients. The clinical presentation may differ. One of our patients presented with repeated diarrhea whereas the other two had respiratory symptoms. Patients with SCID usually succumb to recurrent viral bacterial or fungal infections in infancy as was seen in the first patient. Patients with graft versus host disease (GVHD) due to engrafted maternal T cells may present with erythematous maculopapular rash and hepatosplenomegaly which was not seen in any of our patients. Diagnosis can be established by the enumeration of lymphocyte subsets and immunoglobulins. Most patients with SCID have persistent lymphopenia (<1500 lymphocytes/cumm), CD3+ T lymphocytes count of less than 500 cells/cumm and hypogammaglobulinemia as was seen in 2 of our patients. Serum IgA and IgM levels range from an absent to normal to high for age. Despite the presence of detectable serum immunoglobulins in some patients, antigen specific antibody production is absent diagnosis of SCID is a medical emergency. A high degree of suspicion is essential to suspect SCID. The immediate concern is to bring any current infection under control and to ensure adequate nutrition Intravenous immunoglobulin may be used to bolster the immune response. Prevention of infections is a major step in managing patients with SCID. Prophylactic antibiotics especially trimethoprim-sulphamethoxazole to prevent pneumocystis' carinii pneumonia may be useful. Children with SCID should not receive live virus vaccines such as oral polio, measles vaccine, chickenpox vaccine and BCG vaccine as such vaccines can cause serious illness or even death. Curative therapy is bone marrow transplant. Severe combined immunodeficiency (SCID) is characterized by abnormal T and B cell

function from birth. It is the severest of all congenital immunodeficiencies and unless immunologic reconstitution is achieved through bone marrow transplantation or enzyme replacement, death usually occurs by 2 years of age. Several types of SCID have been identified and clinically classified as T-B+ or T-B- SCID depending on the affection of B cells. T cells and subsets are low to absent in all types. X linked SCID is the commonest form of SCID and patients present as T-B+ NK- SCID (decreased T cells, normal B cell quantity, and low Non-Killer cells) as was seen in our patient. Males are affected. Affected infants present with frequent episodes of diarrhea, pneumonia, sepsis and cutaneous infections within the first few months of life. Failure to thrive after infections is common. Viral infections such as Varicella, Measles, Parainfluenzae, CMV, Epstein Barr Virus and fungal infections such as Candida, Pneumocystis Carinii (PCP) are common. Our patient had a candidal urinary tract infection. BCG vaccine can lead to disseminated TB. Infants cannot reject foreign tissue and hence are at risk for graft-versus-host disease from maternal immunocompetent T cells or T cells in non-irradiated blood transfusion or allogenic bone marrow transplant. Thymus tissue is hypoplastic and hypoplasia of adenoids, tonsils and peripheral lymph nodes is seen as was seen in our patient. Investigations reveal profound lymphopenia with diminished serum immunoglobulins and no antibody formation following the investigation. Antibody levels may initially be normal due to passively transferred maternal antibodies. Analysis of lymphocyte subpopulation helps to identify the type of SCID. Treatment consists of abone marrow transplant. Primary immunodeficiencies are rare but can be extremely serious, and a PID diagnosis is life-changing for both the young child affected and their families. Current therapies provide some management of the condition but patients may remain susceptible to severe, recurrent infections. Novel therapies such as gene therapy represent an opportunity to fix the faulty gene responsible and allow these children the chance to have a normal life. Gene therapy is currently offered for a small number of immunodeficiency conditions, but with further research, it is hoped that the therapy can be offered to more patients in the coming years. The technique involves replacing a mutated copy of the gene with a healthy copy in stem cells isolated from the patient, which are then transfused back into the body – a process known as autologous stem cell transplantation. Results from a recent trial of this technique in a SCID disorder show 100% survival rates at 7 years post-treatment, xvi compared with 85% survival in patients receiving a stem cell transplant from a healthy sibling. However, a major limitation of this technique is that the vector carrying the healthy copy of the gene is inserted randomly, sometimes close to genes that have the potential to cause cancer. Therefore, in some cases the process of inserting the healthy gene can increase the activity of cancer-linked genes, leading to tumour formation.

The use of gene therapy in conjunction with new genome-editing technology, CRISPR, would allow the specific insertion of the healthy gene into sites in the genome that are known to be located far away from cancer-linked genes, reducing the risk of tumour formation. The first UK license for CRISPR use in editing genes in human embryos was granted in 2016, and CRISPR-edited cells to treat lung cancer were administered in the world's first human trials for the technique by a Chinese group in late 2016. This technology is still in the early stages of development and continued research is vital in to translate the technology into the clinic for PID gene therapy as soon as possible. Secondary immunodeficiencies are more common and some of the primary causes of them are global health issues. While immunological research will not solve SID issues related to malnutrition, further research into HIV/AIDS prevention and treatment is essential to reducing the impact of this devastating disorder, particularly in the developing world. Antiretroviral therapy has been very successful in reducing mortality from HIV/AIDS but relies on the patient taking an oral dose every day. There are myriad reasons why access to reliable supplies of anti-retroviral therapy may not be possible in the developing world, and HIV patients in the developed world are not immune from forgetting to take their daily dose. Non-compliance in teenagers and young adults is particularly high, with around 40-50% of adolescents and young adults not adhering to the therapy regimen in Europe and the USA. Research into long-acting antiretroviral therapy represents an exciting opportunity to tackle these issues and reduce the global burden of HIV related secondary immunodeficiency.

CONCLUSION

With rapidly improving genetic technology, the field of PIDs is expanding exponentially. As next-generation sequencing continues to discover new defects, there is a growing need to improve the functional immunological assays that uncover the underlying pathophysiology and molecular mechanisms. Gene therapy, newer biological agents, and possibly RNA interference (iRNA) therapies are on the horizon and promise to dramatically improve outcomes for individuals with PIDs and their families. For many SID disorders treatment of the primary condition will lead to the resolution of the immunodeficiency. This is of limited use in chronic conditions such as organ transplantation or HIV where the emphasis is on managing the condition to minimize immunodeficiency. With advances in medical science, the prognosis for these patients is now much improved. There is evidence to suggest that more patients with HIV now die from toxicity associated with the anti-retroviral therapy than the disease itself and that managing this is the next big challenge. Comorbidities, such as secondary infections, are a major cause for concern and account for a high proportion of deaths in SID patients. As with PIDs, high community vaccine rates and herd immunity are vital to prevent transmission of common diseases to

immunocompromised individuals, who cannot be vaccinated.

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