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APPROACH TO IMMUNODEFICIENCY

Developed by Dominique Ferrarelli and Dr. Sneha Suresh for PedsCases.com.
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Introduction:

The topic of this podcast is paediatric immunodeficiencies. Listening to this podcast should allow you to:

1. Delineate the various primary immunodeficiencies that affect children and understand their aetiologies.
2. Review the general clinical features of primary immunodeficiencies, including key findings to differentiate between them, and the diagnostic investigations performed for each.
3. Discuss the key considerations in the management of these patients.

Overview of the Immune System:

We can recall that our immune system is a complex organisation of cells, each with their own respective functions that collectively serve to protect the host from infection, malignancy, and autoimmunity. The components of the immune system can be divided functionally into innate or adaptive components, and the adaptive immune system can be further divided into cellular or humoral components.

- **Innate responses** are the first defence against infection. The cellular components of the innate system include NK cells and Macrophages. Other components of the innate system include toll-like receptors, mannose-binding protein, and the complement system.

- **Adaptive responses** develop more slowly, are highly specific, and improve with repeated exposure to an antigen. The cellular components of the adaptive system include: T cells (which can be identified by CD4 and CD8), while the humoral components include: B cells (which produce immunoglobulins and can be identified by CD19 and CD20).

Depending which type of immune system dysfunctions - adaptive or innate, and cellular or humoral - you can get a different spectrum of immunodeficiency.

Clinical Vignette

Let's begin with a case. A parent brings their two-year-old boy into your office for an assessment because of their concerns about the number of infections he has acquired since the age of 6 months. He has been diagnosed with six ear infections treated with antibiotics and has been hospitalised twice for pneumonia. Are you concerned? What do you suspect?

When to Suspect Immunodeficiency

If you are thinking it could be some type of immunodeficiency, you would be correct. First, we'll speak about primary immunodeficiencies more generally. The first thing to understand is when to even suspect immunodeficiency in a child. One of the important clinical signs is infections that are severe, persistent, unusual, or recurrent (mnemonic SPUR). **Severe** or **persistent infections** can involve two or more months of antibiotics with little effect, sepsis in the absence of a known risk, bacterial meningitis, or pneumonia with empyema. **Unusual infections** can include Pneumosyctic jiroveci Pneumonia (PJP) , gram negative pneumonia or sepsis, or be more subtle (such as difficult-to-treat candidiasis). **Recurrent infections** can mean six or more new infections in one-year, recurrent tissue or organ abscesses, two or more serious sinus infections in one year, or two or more pneumonias in one year. And there are various **other conditions** that could hint at immunodeficiency as well. These include failure to thrive, a family history of immunodeficiency or unexplained early deaths, lymphopenia in infancy, or complications from a live vaccine.

Another important feature of the immune system is to regulate itself and prevent autoimmunity. Therefore, severe, difficult-to-treat, or multi-system autoimmunity can also be a clinical clue for an underlying immunodeficiency.

It's important to note the onset of these clinical features is usually at **6 months**, since we know the mom provides antibodies for the baby's first few months of life. (Incidentally, combined immunodeficiencies can present earlier at 3 months, as maternal immunity is not enough to combat the more severe entities.) Diagnosis and treatment will vary according to which immunodeficiency, which we'll delve into now.

Disorders of B Cells

The first category of immunodeficiencies that we will discuss includes the ones affecting the humoral component of the adaptive system; in other words, the diseases affecting the B cells. This category consists of diseases that include: **X-linked Agammaglobulinemia**, **Common Variable Immunodeficiency, and IgA Deficiency**. In general, clinical findings will be sinopulmonary and systemic infections, enteric infections, and autoimmune diseases (immune thrombocytopenia, haemolytic anaemia, inflammatory bowel disease). Initial diagnostic tests will evaluate immunoglobulin levels (IgG, IgM, IgA), as well as antibody levels to vaccines the patient has received.

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Subsequent advanced tests can include B-cell enumeration, flow cytometry, or genetic testing for specific proteins (such as Bruton's tyrosine kinase - Btk).

We'll first discuss in more detail **X-linked (Bruton) Agammaglobulinemia**.

- **Pathology**

We know that B cells produce immunoglobulins, so any impairment affecting the development and differentiation of B cells, results in reduced levels of serum immunoglobulins - X-linked Agammaglobulinemia is just that. It's caused by mutations in the Bruton tyrosine kinase (BTK) gene on the X chromosome. If you recall, in the bone marrow, pro-B cells develop into pre-B cells that express a pre-BCR complex. BTK activates this complex, initiating the downstream signalling necessary for B cell maturation and release into the peripheral circulation. If you have a mutated BTK, this process becomes arrested at the pre-B cell stage, resulting in the failure of B cell release and immunoglobulin heavy chain rearrangement, abrogating the production of immunoglobulins.

- **Clinical Presentation**

So, while there are a normal number and function of T-cells, there is a paucity of B cells - less than 1% in peripheral blood. Therefore, this illness is characterized by severe hypogammaglobulinemia (in other words, no antibodies in the blood). Because you don't have any antibodies, there is increased susceptibility to infections with encapsulated bacteria (S. pneumoniae, H. influenzae, S. aureus) - so sinopulmonary infections will be common - and also chronic enteroviral infection may occur as well. However, the history should not only include any frequent, chronic, or recurrent infections, but also information about general health status, hospitalizations, surgeries, and vaccinations.

On physical exam, attention should be focused on the upper and lower respiratory, lymphatic, gastrointestinal, and integumentary systems. Auscultation may reveal prolonged expiration or inspiration, cough, and any increase in respiratory effort that may reflect underlying bronchiectasis from recurrent pneumonias. Lymphoid tissues are typically hypoplastic, with tonsils difficult to visualise, and cervical or inguinal lymph nodes non-palpable.

- **Diagnosis**

There are several different diagnostic tests that you can do. Quantitative immunoglobulin measurement will reveal profound decreases in all immunoglobulin isotypes (so no IgA, IgG, or IgM essentially). Flow cytometry will show that B cells are either absent or greatly diminished, but T cells are still present and cell-mediated functions are still preserved. Finally, mutation analysis can reveal a mutated BTK gene, which can confirm the diagnosis.

- **Treatment**

The treatment is simply to replace the immunoglobulins through: immunoglobulin replacement, IV or subcutaneous injections; prophylactic and therapeutic use of antibiotics to prevent bacterial infections; and counselling about the importance of receiving immunizations, except for those containing live bacteria/viruses.

Next, we'll discuss **Common Variable Immunodeficiency.** This is a heterogenous group of disorders, characterized, again, by hypogammaglobulinemia and a decreased response to vaccines.

- **Pathology**

Although some genetic defects have recently been elucidated, the genetic basis is still largely unknown. But CVID is caused by a variety of defects in B-cell function or in B-cell-T cell interaction. So, while the majority of patients still have a normal number of B cells, many of them have decreased isotype-switched memory B cells, which produce the immunoglobulin isotypes critical in antibody response recall. This appears to happen in the bone marrow with aberrant gene rearrangement, decreased V gene replacements, reduced diversity of naïve B cells, and impaired somatic hypermutation.

- **Clinical Presentation**

Again, with reduced amounts of immunoglobulin isotypes, you are more susceptible to infection. So, the clinical features can include respiratory infections (frequently caused by Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae), and gastrointestinal infections accompanied by chronic diarrhoea (often caused by G. lamblia and campylobacter jejuni). It can also include autoimmune disorders, such as rheumatoid arthritis, autoimmune thyroiditis, autoimmune thrombocytopenia and autoimmune haemolytic anaemia. Furthermore, there is also an increased risk of malignancy. The physical exam may be normal in these patients or may show the sequelae of their multiple complications.

- **Diagnosis**

Concerning diagnosis, the complete blood count will be normal, but the quantitative immunoglobulin measurement should typically show low IgG along with another low isotype (IgA and/or IgM). You can assess decreased antibody function by measuring titers generated in response to childhood immunizations. Finally, flow cytometry can be done to see if there are decreases of isotype switched memory B cells. In cases of gastrointestinal problems, pulmonary nodules, or dermatologic findings, biopsies and imaging can be done to look for malignancy or autoimmunity that can be associated with CVID.

- **Treatment**

Finally, the management of CVID involves immunoglobulin replacement, either IV or subcutaneous, and aggressive management of infections with antibiotics. Chronic diarrhoea management includes nutritional support. Autoimmune manifestations often require immunosuppressive therapy.

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Next, we'll discuss **IgA Deficiency**.

- **Pathology**

As the name implies, this is characterized by low serum IgA concentrations, but usually normal levels of other immunoglobulin isotypes. However, IgA deficiency may be associated with other defects in many patients - 50% with IgA deficiency have IgG def, and 20-30% have IgG_2 or $_4$ subclass deficiencies. A genetic basis, including chromosomal abnormalities, cytogenetic defects, and mutations in JAK3, RAG1, RAG2, TACI, CXCR4, STAT1, is sometimes present; however, the precise cause is usually unclear. The main problem appears to be in immunoglobulin class switching, wherein the IgA-bearing B lymphocytes cannot differentiate terminally into IgA-secreting plasma cells.

- **Clinical Presentation**

As a result of reduced IgA, you cannot fight off mucosal offenses. So, while most patients remain asymptomatic, the clinical features can include respiratory infections (such as sinusitis, pneumonia, and otitis media), GI manifestations (such as chronic diarrhoea and infection with Giardia lamblia), autoimmune and rheumatic diseases (such as systemic lupus erythematosus, juvenile rheumatoid arthritis, and celiac disease), and atopic diseases (such as allergic rhinitis, eczema, urticaria, and asthma).

- **Diagnosis**

Apart from noticing the enhanced susceptibility to infections, especially respiratory ones, it is definitively diagnosed by quantitative measurement of serum immunoglobulins, which reveals the deficiency of IgA only (<8-3 g/L). Diagnosis is usually made at older than 4 years of age.

- **Treatment**

There is no treatment for this, as IgA cannot be replaced – IV-administered immunoglobulins is not usually indicated because it contains almost all IgG, which is not deficient in these patients. Therefore, all you can do is identify and manage infections. Patients with IgA deficiency can still mount an antibody reaction to IgA, and therefore should receive any blood products without IgA.

Combination Disorders

The second category that we'll discuss are combination immunodeficiencies. This means that they can affect two different arms of the adaptive immune system: cellular and humoral, or in other words, both the lymphocytes, B cells and T cells. Since there are 300 disorders that can be considered as such, this category will focus on the following: **DiGeorge syndrome**, **Wiskott-Aldrich syndrome**, **Ataxia telangiectasia**, and **Severe Combined Immunodeficiency**. In general, clinical features will include recurrent, and severe, viral, fungal and opportunistic infections. Initial diagnostic tests can include: TRECs newborn screening and total lymphocyte counts. Advanced

diagnostic tests can include: T-cell enumeration (CD3, CD4, CD8); and in vitro T-cell proliferation to mitogens, antigens, or allogenic cells.

First, we'll discuss **DiGeorge Syndrome.**

- **Pathology**

This is a congenital immunodeficiency syndrome broadly classified in the group of 22q11.2 deletion syndromes, since it is the result of a submicroscopic deletion on chromosome 22, more specifically on the long arm (q) at the 11.2 locus. Most of the mutations are de novo.

- **Presentation**

An important gene at this locus is the TBX1 gene, which is believed to be involved in the development of the heart, thymus, and parathyroid glands. Therefore, though the clinical presentation can vary, the most common findings include cardiac anomalies, a hypoplastic thymus, and an absence of parathyroid hormone (which results in hypocalcaemia, and clinically can present as tetany and seizures). Nonetheless, 22q11.2 encodes over 90 genes, so this syndrome can be characterised by other features as well, including abnormal facies (wide-spaced eyes, low-set ears, small face), cleft palate, and infections with fungi or pneumocystis pneumonia.

- **Diagnosis**

The diagnosis is clinical, but microdeletions can be detected by fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), single nucleotide polymorphism (SNP) array, comparative genomic hybridization (CGH) array, or quantitative polymerase chain reaction (qPCR). Given how diverse the presentation of this disease is, other system-specific tests may also warrant consideration.

- **Treatment**

The treatment is prophylaxis with TMP-SMX, and immunizations, boosters, and intravenous immunoglobulins, depending on the patient's laboratory values and clinical presentation. Symptom-specific management can also be considered, such as giving calcium and vitamin D supplementation for hypocalcaemia. In more severe immunodeficiency, intravenous immunoglobulins can be given until thymic transplant can occur.

Next, we'll discuss **Wiskott-Aldrich syndrome**.

- **Pathology**

This is caused by the mutation of a gene encoding Wiskott-Aldrich syndrome protein (WASp), on the short arm of the X chromosome, normally important in T-cell receptor signalling and cytoskeletal organisation. It is characterised by this triad of combined immunodeficiency, eczema, and congenital thrombocytopenia with small platelets.

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- **Presentation**

So clinically, immunodeficiency presents as susceptibility to infections with encapsulated organisms, such as H. influenzae and S. pneumoniae, as well as failure to thrive. Eczema is present in about 50% of patients in the first year and can predispose to skin infections. And thrombocytopenia may present as early as the first days of life with petechiae and prolonged bleeding. Some symptoms can be life-threatening, such as oral, gastrointestinal, or intracranial haemorrhage.

- **Diagnosis**

It is a diagnostic consideration in any male patient who presents with petechiae, bruises, and congenital or early-onset thrombocytopenia associated with small platelet size. A deleterious mutation in the WAS gene confirms this diagnosis; however, there are several diagnostic tests that can be done as well. Complete blood count will reveal thrombocytopenia and small platelets. Measuring immunoglobulin levels will show decreased IgM. Antibody response to polysaccharide antigens will be diminished. And finally, cellular immune function will be defective and anergy present. Patients have near-normal numbers of T cells, but they respond poorly to antigens and do not develop antigen-specific cytotoxic T cells.

- **Treatment**

HLA-matched bone marrow transplantation is the therapy of choice here. Intravenous immunoglobulins are administered for hypogammaglobulinemia. Furthermore, splenectomy can cure the thrombocytopenia in the majority of patients, improving their quality of life and simplifying the medical management; however, prophylactic antibiotics or intravenous immunoglobulins must be administered regularly after splenectomy. Gene therapy is a potential future cure.

Next, we'll discuss **Ataxia telangiectasia**.

- **Pathology**

This is an autosomal recessive disorder that results from a mutation of the ATM gene, located on chromosome 11q22-23, and normally involved in cell cycle control, DNA repair, and cellular responses to external triggers.

- **Presentation**

It's characterised by combined immunodeficiency, cerebellar ataxia, oculocutaneous telangiectasias, and a predisposition to malignancy. So clinically you'll see chronic sinopulmonary infections; a severe progressive cerebellar ataxia that results in a need for wheelchair assistance by early adolescence in most patients; telangiectasias that appear on the bulbar conjunctiva between 2 and 5 years of age, and later on exposed skin and areas of trauma; a high risk of malignancy, particularly lymphoma and carcinoma, as a result of those defects in DNA repair; and also some other clinical features such as café-au-lait spots, vitiligo, premature grey hair, and multiple endocrine abnormalities (growth retardation, hypothyroidism and hypogonadism).

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- **Diagnosis**

The diagnosis is made by measuring serum immunoglobulins, which reveals IgG and IgA deficiency. Additionally, evaluation of T-cell function may reveal skin test anergy and diminished T-cell proliferation to mitogens.

- **Treatment**

The only management for this disease is to treat the neurologic complications and aggressively treat infections, and to monitor for malignancies. These patients should avoid ionizing radiation, which exacerbates DNA breakage and repair, and increases the risk of malignancy.

Finally, we'll discuss **Severe Combined Immunodeficiency, or SCID.**

- **Pathology**

This is a group of inherited disorders characterized by profoundly defective T-cell and B-cell function. Essentially, you have no immune system. Multiple genetic abnormalities have been implicated, but there are potentially more. Some mutations causing SCID include those affecting cytokine signalling and signal transduction (IL2-Rγ, SCID-X1, JAK-3, CD45, IL7-R, CD3), and DNA rearrangement or recombination (RAG-1, RAG-2, DNA ligase IV). Autosomal recessive SCID is caused by a variety of genetic defects involving T-cell ontogeny or function, adenosine deaminase deficiency being a principal one.

- **Presentation**

The clinical features of SCID are increased susceptibility to infection within the first few months of life, and with common pathogens or opportunistic organisms, such as Candida albicans and Pneumocystis jirovecii; chronic diarrhoea; and failure to thrive. There is also a very large range of physical findings.

- **Diagnosis**

There are many things you can see on diagnosis, but principally: persistent lymphopenia (<1500 lymphocytes/mL), decreased numbers of T-cells on flow cytometry, severe hypogammaglobulinemia on quantitative measurement of serum immunoglobulins, decreased white blood cell count, and severely depressed T-cell responses to mitogens and antigens. In addition, many countries have instituted new-born screening for SCID, and as such, these babies can be diagnosed early. It is important to note that new-born screening for SCID does not pick up all forms of SCID, so an infant may still have SCID even though their new-born screen is negative.

- **Treatment**

A SCID diagnosis is considered a medical emergency. Patients can have a good outcome if they are diagnosed early, infections are prevented, and they move to curative therapy with transplant or gene therapy early. To manage SCID, you should contact immunology and bone marrow transplant physicians early, and institute isolation measures, prophylactic antibiotics, and provide supportive psychosocial support care. In

some instances, breastfeeding may need to be stopped, especially if the mother is positive for a virus known as CMV. Monthly intravenous immunoglobulin replacement can also be administered. All these therapies, however, are only temporary solutions until curative treatment is undertaken (i.e. bone marrow transplant or gene therapy, if available).

Disorders of Granulocytes

The third category of immunodeficiencies that we'll discuss are the ones affecting the cellular component of the innate system: in other words, the diseases affecting granulocytes. This category includes: Chronic Granulomatous disease (CGD), Chediak-Higashi syndrome (CH), and Lymphocyte Adhesion Defects (LAD). In general, clinical features will include recurrent skin infections - cutaneous infections, abscesses, poor wound healing, and lymphadenitis (staphylococci, enteric bacteria, fungi, mycobacteria). Initial diagnostic tests include WBC/neutrophil count and morphology assessment, while more advanced tests are the neutrophil oxidative burst index, chemotactic assay, and phagocytic assay.

We'll first discuss **Chronic Granulomatous disease**, a predominantly X-linked disorder. It's characterized by defective neutrophil oxidative metabolism, resulting from defects in the NADPH oxidase system. Defective oxidative metabolism results in impaired intracellular killing of catalase-positive bacteria and some fungal pathogens. Therefore, the clinical features are increased susceptibility to infections involving the lungs, lymph nodes, liver, spleen, bones, and skin; the major pathogens being S. aureus, Pseudomonas aeruginosa, Salmonella species, Klebsiella pneumoniae, Serratia marcescens, Escherichia coli, C. albicans, and Aspergillus species. Abscess formation is also characteristic. On diagnosis, the dihydrorhodamine flow cytometry test demonstrates defective neutrophil oxidative burst. For management, there are three prophylactic options. Interferon-gamma can be given, Trimethoprim-sulfamethoxazole reduces the incidence of serious infections, and itraconazole reduces the incidence of Aspergillus infections. Abscesses usually require surgical drainage and antibiotics. Bone marrow transplantation is curative, and gene therapy is a potential future cure.

Next, we'll discuss two disorders of adherence and motility, beginning with **Chediak-Higashi syndrome,** which is characterized by oculocutaneous albinism, easy bruising, and variable neutropenia and thrombocytopenia. Abnormal function of NK cells results from mutation in the lysosomal trafficking regulator gene, so recurrent pyogenic infections, mainly from S. aureus, is common. The presence of large lysosomal granules, in white blood cells and bone marrow, are diagnostic. **Lymphocyte adhesion defect** is a defect of cellular adhesion molecules, clinically characterized by delayed umbilical cord separation, leucocytosis (with elevated neutrophil counts), as well as recurrent necrotic infections of skin, mucous membranes, and GI tract.

Disorders of Complement

The last category of immunodeficiencies that we'll discuss are the diseases involving absence or dysfunction of complement proteins. These disorders are genetically determined - most are autosomal recessive, and the clinical features are variable, depending on the biologic function of the components that are deficient.

- Deficiency of C1 esterase inhibitor causes hereditary angioedema, and if it affects the airway, it can be fatal. The bowel wall may also swell, leading to severe abdominal pain.
- Deficiencies of the early components of the classic pathway (C1q, C2, and C4) are associated with autoimmune diseases.
- Deficiencies of the late components of the classic pathway (C5, C6, C8) are associated with increased susceptibility to meningococcal and gonococcal infections.

Diagnosis can be both quantitative and qualitative. Specific assays measure levels of specific components. The CH50 is the total haemolytic component. A normal total serum haemolytic complement indicates that all components of the classic complement pathway are present and functional. Other diagnostic tests include alternative pathway assay (AH50), mannose-binding lectin level, and individual complement component assay. Management involves treatment of bacterial infections and autoimmune diseases, and therapy with fibrinolysis inhibitors and attenuated androgens (such as danazol) for hereditary angioedema.

Return to the Case

Remember from the clinical scenario that this young boy was brought in because of a history of pneumonia and recurring infections. Severe, unusual, or recurrent infections are indications of potential immunodeficiency, so you obtain a more detailed history, asking about general health status, prior hospitalizations or surgeries, and vaccinations.

You then begin your physical examination, noticing that this boy's height and weight are in the 5th percentile, another indication of underlying immunodeficiency. You pay attention to the sites of recurrent infections in the patient's history to assess for any resultant complications. These sites could include: respiratory, lymphatic, gastrointestinal, or the integumentary systems. His ear infections prompt you look for scarring of the tympanic membranes and hearing loss; however, this is unremarkable. The last thing you evaluate is lymphoid tissue, during which you notice absent tonsils. This indicates agammaglobulinemia or SCID, while increased lymphoid tissue suggests CVID or CGD.

Given that he has recurring sinopulmonary infections and absent tonsils, you are suspecting a disorder involving B cells; however, to elucidate which specific disorder, you decide to perform various diagnostic tests. Since we know B cells affect production

of immunoglobulins, we order a quantitative screen. This reveals absent immunoglobulins, which suggests X-linked Agammaglobulinemia. If there were reduced amounts of immunoglobulins, you would have suspected CVID, and if there were decreased levels of IgA, you would have suspected IgA deficiency. Flow cytometry can validate the poor B cell count, and mutation analysis can reveal a mutated BTK gene, confirming the diagnosis of X-linked Agammaglobulinemia.

Because B cell disorders affect immunoglobulin production, the treatment approach is to replace immunoglobulins. Knowing the immunoglobulin count is low should prompt you to be vigilant in early identification and treatment of infections, and in providing counselling to your patient about the importance of receiving immunizations, except for those containing live bacteria/viruses.

Conclusion

In conclusion:

- We delineated various primary immunodeficiencies that affect children, categorising them according to the respective branches of the immune system that is dysfunctional.

- We reviewed indications of immunodeficiency, mainly severe or persistent infections, unusual infections, or recurrent infections. Furthermore, we discussed distinguishing clinical features of each primary immunodeficiency. Of particular note, associating: sinopulmonary or enteric infections with B cell involvement; viral, fungal, or opportunistic infections with T cell involvement; and cutaneous infection, abscesses, or poor wound healing with granulocyte involvement.

- We also reviewed a number of laboratory tests done to investigate immune function. With disorders affecting B cells, and therefore immunoglobulin production, initial tests involve evaluating immunoglobulin levels, while more advanced tests can involve B-cell enumeration, flow cytometry, or genetic testing. With disorders affecting T cells, tests can include lymphocyte counts, T-cell enumeration, and T-lymphocyte functional analyses. And with disorders affecting phagocyte function, initial diagnostic tests include neutrophil cell count and morphology, while more advanced tests include the neutrophil oxidative burst index, chemotactic assay, and phagocytic assay.

- Finally, we discussed the management approach in these patients, which differs according to the diagnosis and specific laboratory or clinical findings. In general, antibiotic prophylaxis can prevent recurrent infections, and any presenting infections should be promptly treated. More severe lymphocyte infections and certain disorders of neutrophil function may require stem cell transplantation, while milder antibody deficiencies may benefit from certain vaccinations. Monthly

immunoglobulin replacement therapy is also indicated in severe antibody deficiency diseases and SCID.

Thank you for listening, hopefully you can now apply your immunology knowledge to important clinical presentations of immunodeficiency.

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