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Van Rensburg
Newsletter

Inborn errors of immunity

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Inborn errors of immunity (IEI), also known as primary immunodeficiencies, are a diverse group of genetic disorders that impair the immune system, resulting in inability to defend the body against certain infections, and sometimes the clinical outcomes are associated with autoimmunity or malignancy. These conditions occur because of defects in various components of the immune system, including immune cells, cytokines, receptors, and signalling pathways.

A. Classification of IEI

The International Union of Immunological societies (IUIS) classifies IEI depending on which part of the immune system is affected.[1]

1. **Combined Immunodeficiencies:** Involve defects in both the cellular and humoral components of the immune system. Examples include severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and ataxia-telangiectasia.
2. **Antibody Deficiencies:** Primarily affect the production of antibodies, leading to an increased susceptibility to bacterial and viral infections. Common examples include X-linked agammaglobulinemia, and common variable immunodeficiency (CVID).
3. **T-cell Deficiencies:** Characterised by impaired development or function of T cells, which is crucial for cell-mediated immunity. Examples include DiGeorge syndrome, chronic mucocutaneous candidiasis, and hyper-IgM syndrome.
4. **Complement Deficiencies:** (See **Section C** below) These defects involve abnormalities in the complement system, a group of proteins that play a crucial role in the immune response. Deficiencies in complement proteins can lead to increased susceptibility to bacterial infections and autoimmune diseases.
5. **Phagocyte Deficiencies:** Phagocytes, such as neutrophils and macrophages, are important immune cells responsible for engulfing and destroying pathogens. Defects in phagocyte function result in conditions like chronic granulomatous disease and leukocyte adhesion deficiency.
6. **Innate Immunity Disorders:** These conditions affect the innate immune system, impairing the initial recognition and response to pathogens. Disorders in this category include defects in Toll-like receptors (TLRs), natural killer (NK) cells, and interferon pathways.

B. Approach to Diagnosis

The diagnosis of IEI requires a comprehensive approach combining clinical examination and evaluation, laboratory investigations and genetic testing. The diagnostic approach will vary depending on the clinical presentation, age of onset, and suspected immunodeficiency.

The following steps are typically involved in the diagnostic process:

1. Clinical Evaluation

A detailed medical history and physical examination are essential to identify signs and symptoms suggestive of an immunodeficiency. Common clinical features include failure to thrive, autoimmune manifestations, a family history of immunodeficiency, recurrent or severe infections and poor response to treatment.

Infections may be unusual and may include organisms generally associated with secondary T-cell immunodeficiency including *Pneumocystis jirovecii* and *Mycobacterium avium intracellulare*. Patients with selective IgA deficiency are susceptible to *Giardia lamblia* diarrhoea, patients with hyper IgE syndromes are susceptible to recurrent and severe staphylococcal infections, and patients with agammaglobinaemia to recurrent enterovirus infections that can lead to chronic meningoencephalitis.

2. Screening Laboratory Evaluations*

a. Full Blood Count (FBC) plus platelets and differential, C-reactive protein (CRP): to evaluate the total number and distribution of blood and immune cells and the presence of inflammation.
b. Viral and TB testing: to exclude HIV infection and secondary immunodeficiency, EBV and CMV, and TB tests.
c. Immunoglobulin Levels: IgG, IgA, IgE and IgM can help identify either increased or decreased levels of specific antibodies.
d. Specific Antibody Responses to vaccination: testing responses to protein (conjugate) vaccines like diphtheria and tetanus toxoid and responses to polysaccharide pneumococcal vaccines provide insights into B-cell function.[2] Baseline levels need to be measured at the initial assessment, followed by repeat testing 4 – 8 weeks after vaccination with the relevant vaccine. Responses to specific pneumococcal serotypes may also be measured.
e. Flow Cytometry: Assesses the different immune cell populations, including T cells, B cells, and NK cells. Evaluation of surface markers and intracellular proteins can help identify abnormalities in cell subsets or signalling pathways.
f. Complement Levels and Activity: Measurement of complement levels and function can identify deficiencies in the complement system. Deficiencies in complement components can lead to an increased susceptibility to recurrent infections especially with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Neisseria meningitidis*, autoimmune diseases, and excessive inflammatory responses.
g. Additional investigations, including cytokine profiles, lymph node or tissue biopsies, and imaging studies may be performed based on the suspected immunodeficiency.

3. Confirmatory Laboratory Testing

a. Functional Assays: Functional assays assess the ability of immune cells to perform their respective functions. Examples include lymphocyte proliferation assays, evaluation of neutrophil oxidative burst in chronic granulomatous disease, and NK cell cytotoxicity assays.
b. Genetic Testing: Genetic testing plays a pivotal role in confirming the diagnosis of inborn errors of immunity. Various techniques, such as Sanger sequencing, next-generation sequencing (NGS), and whole-exome sequencing (WES), can identify specific gene mutations or variants associated with immunodeficiencies.

C. Complement Deficiencies

The complement system plays a crucial role in host defence against bacteria, viruses, parasites and fungi. It is composed of a complex network of proteins that work together to recognise and eliminate foreign invaders, promote inflammation, and facilitate the clearance of immune complexes and cellular debris (See **Diagram 1**).

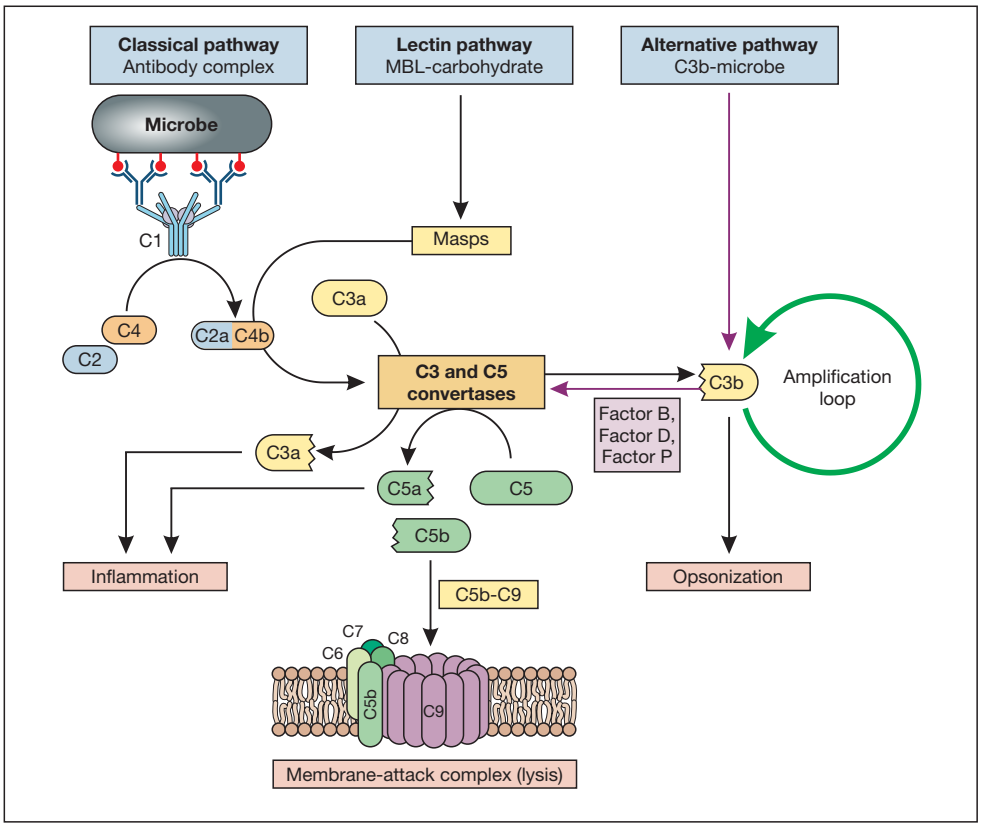
Clinical Presentation of Complement Deficiencies

Clinical features depend on the specific complement components affected, and may include[3]:

1. **Increased Susceptibility to Infections:** Recurrent or severe infections, particularly with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.* Infections may involve the respiratory tract, bloodstream, or other sites.
2. **Autoimmune Diseases:** Early component complement deficiencies (C1q, C2, or C4) are associated with an increased risk of autoimmune diseases, such as systemic lupus erythematosus (SLE).
3. **Angioedema:** Hereditary angioedema (HAE) is a disorder characterised by recurrent episodes of localised swelling, typically involving the skin and mucous membranes. Deficiencies in C1 inhibitor, a regulatory protein of the complement system, is associated with HAE.
4. **Glomerulonephritis:** Deficiencies in C3 or factors involved in the alternative pathway, can predispose individuals to develop glomerulonephritis, which may present with haematuria, proteinuria, hypertension, and impaired kidney function.
5. **Increased Risk of Meningococcal Infections:** Deficiencies in late complement components (C5 – C9) increase the susceptibility to recurrent or severe infections caused by *Neisseria meningitidis,* including meningococcal meningitis and sepsis.
6. **Photosensitivity and Cutaneous Manifestations:** Deficiency of complement factor D is associated with increased photosensitivity, skin lesions, and dermatological manifestations.
7. **Increased Risk of Systemic Inflammatory Response Syndrome (SIRS):** Some complement deficiencies can result in uncontrolled and excessive activation of the complement system, leading to systemic inflammation and complement-mediated tissue damage. This can present as a systemic inflammatory response syndrome, with symptoms including fever, organ dysfunction, and coagulopathy.

8. **Complement has also been associated with haemolytic and thrombotic clinical entities[4],** including autoimmune haemolytic anaemia, disseminated intravascular coagulation (DIC), paroxysmal nocturnal haematuria (PNH) with haemolytic uremic syndrome (HUS) and pregnancy-related haemolysis with microangiopathic blood smear, elevated liver enzymes and low platelets (HELLP) syndrome.

Diagram 1. Complement Pathways



*** MASP = mannan-binding lectin-associated protease**

Laboratory Diagnosis of Complement Deficiencies*

Laboratory tests for diagnosing complement deficiencies involve the quantification of individual complement proteins or the assessment of their functional activity.

1. **Total Complement Activity (Ch50)**: This test measures the overall functional activity of the classical pathway of the complement system. A decreased CH50 result may indicate a deficiency in one or more components of the classical pathway.
2. **Alternative Pathway Haemolytic Assay (AH50):** This test measures the functional activity of the alternative pathway of the complement system. A reduced AP50 result suggests a deficiency in one or more components of the alternative pathway.
3. **Mannan Binding Lectin (MBL):** This test measures the functioning of the Lectin pathway.
4. **Component-Specific Assays:** These tests involve quantifying individual complement components to identify deficiencies. Measurements of C1q, C2, C3, C4, C5, C6, C7, C8, and C9 can be done, and decreased levels of a specific complement component indicate a deficiency.
5. **Functional C1q Assay:** This test assesses the functional activity of C1q, the first component of the classical pathway. It measures the ability of C1q to bind to immune complexes, which is essential for initiating the classical pathway. Reduced functional activity of C1q indicates a deficiency.
6. **Terminal Pathway Assays:** These assays evaluate the activity of the terminal complement components (C5 – C9). They can include tests for the quantification of soluble C5b-9 (also known as the membrane attack complex), or assessment of the ability of complement to form the membrane attack complex on target cells.

False-positive or false-negative results can occur due to various factors, including acute-phase reactions, recent infections, or medications. Repeat testing, along with a comprehensive clinical evaluation, is necessary to confirm the diagnosis of a complement deficiency.

** Note: Tests available at Lancet Laboratories*

References

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