# The crossroad between autoimmunity and immunodeficiency

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Autoimmune disease and immunodeficiency represent two ends of a spectrum of immune dysfunction. These are characterised by uncontrolled immune activation and pathogenic immune responses against self-antigen, or inability to mount protective immune responses against foreign antigens, respectively. Genetic analysis has unravelled the complex processes involved in immune cell development, immune regulation and signal transduction that are similar between autoimmunity and immunodeficiency. These are manifested by specific gene alterations that underlie inherited immunodeficiency syndromes with an autoimmune phenotype[1].

Primary Immunodeficiency Disorders (PIDs), also known as inborn errors of immunity are a heterogenous group of genetic disorders of the immune system characterised by impaired and/or uncontrolled immune responses. Individually, PIDs are rare, but collectively they represent a significant burden of disease[2,3]. Six million people world-wide may be living with a PID, with only 27,000 – 60,000 (0.45 – 1%) registered in national registries[2]. PIDs are underdiagnosed and underreported in sub-Saharan Africa due to lack of awareness. It is however estimated that as many as 902,631 individuals in Africa may be living with a PID[2].

PIDs frequently manifest in early childhood, but can also manifest for the first time in adulthood. The major presentation is with severe or recurrent infections. In the developed world, early diagnosis of PIDs has improved the lifespan of patients, due to timely intervention and prevention of infectious complications. These patients eventually develop non-infectious complications with up to 26% developing autoimmune or inflammatory symptoms[4].

PID-related autoimmune diseases have been described in deficiencies of both the innate and adaptive immune systems (phagocytes, complement, B cells and T cells). They may occur across the age spectrum, either as the presenting symptom of PID, or after establishment of the diagnosis. Antibody deficiencies account for the largest proportion of PIDs, with selective IgA deficiency being the most frequent type in children and adults. Selective IgA deficiency has a strong association with autoimmunity, with documentation of autoimmune disease in up to 36% of patients[5]. A decreased IgA level is often an incidental finding as the patients undergo evaluation for coeliac disease, which is the most frequent presentation[6].

Autoimmune manifestations are also frequent among patients with Common Variable Immunodeficiency (CVID). This is the most commonly diagnosed PID after selective IgA deficiency, and accounts for more than 50% of symptomatic PIDs[7], with an estimated prevalence of 1:10,000 to 1:50,000 in North America and Europe[8]. It is a heterogenous group of disorders characterized by defective B lymphocyte differentiation, hypogammaglobulinaemia, and defective antibody production. CVID is frequently diagnosed between the second and fourth decades, with clinical characteristics ranging from recurrent infections of the respiratory tract to autoimmune diseases, inflammatory diseases and lymphoproliferative disorders. Autoimmune manifestations occur in 20 – 30% of patients with CVID and may be evident at first presentation[9]. Despite the very low serum immunoglobulins and impaired specific antibody response to foreign antigens, autoantibodies and auto-reactive B cells can be paradoxically detected in these patients.

New classes of PIDs have been identified whose underlying defects are in the regulatory mechanisms of the immune system, as opposed to effector mechanisms. Patients with disorders of immune dysregulation typically present with autoimmune disease rather than recurrent infections. The mechanisms of autoimmunity in this subset of PIDs, include defects in complement and phagocytes that lead to ineffective clearance of immune complexes and apoptotic cells; defects in regulatory T cells that limit their suppressive activity; and defects that alter signaling through the T or B cell antigen receptor, leading to overactivation of these cells[10].

The most common autoimmune manifestations observed in patients with PIDs are autoimmune cytopaenias[10,11]. Immune Thrombocytopaenic Purpura (ITP) occurs most frequently, followed by autoimmune haemolytic anaemia and autoimmune neutropaenia. In up to 60% of CVID patients, the cytopaenia may precede the detection of hypogammaglobulinaemia[12]. Organ specific autoimmune or inflammatory complications commonly involve the lungs and gastrointestinal tracts, and it may be difficult to differentiate between infection and autoimmune disease in these organs. The skin, joints, endocrine, and connective tissue may also be affected, with development of vitiligo, juvenile idiopathic arthritis, rheumatoid arthritis, thyroiditis, Systemic Lupus Erythematosus (SLE), anti-phospholipid syndrome, Sjogren's syndrome, and vasculitis[9-11,13]. Deficiency of the early components of the complement system is strongly associated with early onset SLE, which is thought to arise due to defective elimination of immune complexes. SLE is identified in 93% of patients with C1q deficiency, with a lower association in those with C4 and C2 deficiencies[14].

Paediatricians, physicians and rheumatologists should be aware that autoimmunity and immunodeficiency may not always be mutually exclusive, and that significant autoimmune disease is common among patients with PID. Accurate diagnosis is essential for care that reduces disease-associated complications and optimizes quality of life. PID should be suspected in patients presenting with autoimmune or idiopathic cytopaenias, while those with an established diagnosis of PIDs such as CVID should undergo frequent screening for autoimmune disease. The existence of the two clinical phenotypes provides diagnostic and therapeutic challenges; for example, it may be difficult to interpret low or borderline positive levels of serum autoantibody levels in patients with underlying hypogammaglobulinaemia; and treatment of autoimmune manifestations with standard immunosuppressive therapy may be complicated by the inherent risk of infection. Multidisciplinary collaboration between the rheumatology and immunology specialties is prudent to optimal management of these patients.

**References**


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