Primary Immunodeficiency Disorders

**IgA DEFICIENCY: FACTS AND FALLACIES**

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**ABSTRACT**

Selective IgA deficiency (IgAD) is the most common primary genetic immune defect, with high prevalence in Western countries and relatively low prevalence in the East. The laboratory definition of IgAD is based on the measured serum component. However, the important manifestations of deficiency of IgA, the most prevalent of human antibodies, relate to the absence of secretory IgA, which covers a vast surface area of the human body. Diagnostic criteria by the International Union of Immunological Societies (IUIS) define IgAD as very low or absent levels of IgA (< 0.07 g/L) in a child older than 4 years of age. IgAD is asymptomatic in the majority but if symptoms do occur, these generally manifest with mild infections of the respiratory tract with encapsulated bacteria or intermittent diarrhoea with *G.lamblia*. Symptomatic patients should be investigated for deficient polysaccharide antibody responses, IgG subclass deficiency or allergies because of increased frequency of these conditions co-existing in these patients. IgAD also increases risk for autoimmunity and malignancies but surveillance guidelines are currently lacking. Treatment of IgAD includes reassurance of the asymptomatic patient, optimal control of allergies, prophylactic antibiotics and very rarely immunoglobulin replacement.

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**INTRODUCTION**

An estimated 6 million individuals worldwide are affected by Primary Immunodeficiency (PID), also called genetic immunodeficiencies. In Africa alone up to 900 000 people may be living with a PID, most of whom are not recognised. The overall prevalence is approximately 1:10,000 live births and this is increased in countries with high consanguinity or genetic isolation. Genetic defects of the immune system usually cause increased susceptibility to infections that are often severe, persistent, unusual, recurring (SPUR), debilitating and sometimes fatal. More recently also autoinflammatory and dysregulatory conditions have been included in the International Union of Immunological Societies (IUIS) classification.

Primary antibody deficiencies (PAD) are the most common of the genetic deficiencies of the immune system. Mutations of antibody related genes may result in impaired regulation of B-cell development and maintenance or in the immunoglobulin genes. Characteristic is the inability to produce sufficient functional antibodies for protection against harmful antigens, with onset of symptoms commonly in early childhood, although onset may also occur in adulthood. Typical symptoms of hypo-agammaglobulinaemia are those of respiratory infections such as sinusitis, bronchitis and pneumonia although skin infections, gastrointestinal complaints, arthritis and other may be seen also. Autoimmune manifestations and allergies may be features of antibody deficiencies too. Infections are classically caused by encapsulated bacteria, because these require anti-polysaccharide antibodies which do not require T-cell assistance for effective clearance of infection. But patients with antibody deficiencies may also show inability to maintain long-term antiviral immunity despite adequate T-cell control. This is exemplified by the dissemination of poliovirus from the gut and enteroviral encephalitis seen in patients with severe antibody deficiencies such as agammaglobulinaemia.

IgAD, the commonest of antibody deficiencies in the Western world, is thought to be present from birth, with the majority of affected people being clinically asymptomatic. True deficiency is defined as serum IgA levels equal to or below 0.07 g/L with normal IgM and IgG levels at age 4 years or older. It is important to be aware of different test methodologies and ranges of detectable levels, as some laboratories may not taper out to these low levels.

Symptom onset can already be in the first year of life but the physiologic lag in serum IgA production can delay the diagnosis until after age of two. Infections may later disappear with maturity or they may persist throughout life. Symptoms are more likely to occur in association with IgG...
subclass deficiency or specific polysaccharide antibody deficiency, and co-existing allergies. The presence of these other deficiencies can cause more severe disease and should therefore always be investigated in symptomatic IgAD. An association with several autoimmune diseases has been observed in IgAD and there is suggestive evidence for a shared genetic background.4

Secondary or acquired IgA deficiency is more likely to be transient with variable onset depending on exposure to the cause. It may be the result of viral infections, e.g. congenital rubella infection, EBV, parvovirus B19, or it may be related to exposure to drugs particularly Phenytoin, where the implicated mechanism is that of induction of suppressor T-cell activity specific for IgA.

This article is focused on the most common of genetic antibody deficiencies and the most common PID in the Western World, IgAD.

PATHOGENESIS
The genetic defect and presumed pathogenesis is unknown but it is thought that IgAD may represent B cell failure or that there may be epigenetic causes. The mechanisms inducing the deficiency, while unclear, may possibly still be due to break of tolerance to IgA – as many as 30% of IgAD have measurable IgG or IgE antibodies against IgA or a defect in Ig switching process (APRIL) or activation (BAFF). A failure of B cell differentiation into IgA producing plasma cells may be related to a defect in T helper cells, Ag presenting cells or it may be intrinsic to the B cell.

Ex vivo synthesis of IgA can be induced by interleukin 21 with speculation that the cause may be due to epigenetic dysregulation rather than B cell defect.5

IgA has been described as the housekeeper molecule in maintaining gut immunity.6 Through anti-inflammatory actions of secretory IgA, the integrity of gut mucosa is maintained by limiting tissue damage due to various interactions at the gut surface with a variety of antigens. This process is complex through inhibition of neutrophil phagocytosis, chemotaxis and bactericidal activity, interference with IgM- and IgG-mediated complement activation.3 A deficiency of IgA therefore, not surprisingly also reflects with increased prevalence of autoimmune disease in the host and it is possible that IgAD and autoimmune diseases, with shared genetic predisposition, are clinically revealed through environmental triggers.8 (Table II)

PREVALENCE OF sIgAD
IgAD occurs sporadically, although familial inheritance has been described with autosomal-recessive or autosomal-dominant pattern – of variable or incomplete expression. The deficiency is also found more commonly in those with family members diagnosed with common variable immunodeficiency (CVID).

While the finding of IgA deficiency may be commonly reported in Western Europe, at a prevalence of 1:155 in Spain, it is not commonly observed in Eastern countries such as Japan 1:18550. The overall prevalence in Whites is estimated at 1: 600.7

Secondary IgAD is observed with drugs such as sulfasalazine, hydantoin, cyclosporine, gold, fenclofenac, sodium valproate, and captopril. As many as 20-40% of patients treated with phenytoin may develop IgA deficiency. This however is a reversible condition.

CHARACTERISTICS OF IgA
IgA measured in serum is the monomeric plasma cell derived form, and it indirectly reflects the most prominent form of IgA, the dimeric secretory IgA (S-IgA1 and S-IgA2) in external secretions.

Secretory IgA (sIgA) is the major antibody in luminal secretions of respiratory and GI tract, produced in epithelial cells of the mucosa which covers a surface area of approximately 1.5 tennis courts, but present also in breast milk, mucus and tears.

sIgA has a T piece protein and, unlike serum IgA produced by plasma cells, the secretory piece is made in epithelial cells and is added to IgA passing into secretions – this assists IgA transport across mucosa and protects from proteolytic digestion (Figure 1). Mucosal secretion of IgA reaches adult levels earlier than serum levels at 1 month to 2 years. Active transport is facilitated by the Ig receptor expressed on epithelial cells and slgA protects the host
by inhibiting microbial adherence, neutralisation of virus enzymes and toxins, but also through inhibition of IgM and IgG complement activation.3

DIAGNOSIS
IgAD is classified by the IUIS with the predominantly antibody related deficiencies.2 Here it is listed either as isolated selective IgA deficiency, in combination with IgG subclass deficiency, or as part of transient hypogammaglobulinaemia of infancy. Although the diagnosis is entertained as early as age 1 year, by consensus panel, the definition of IgAD is determined as serum IgA levels of < 7 mg/dl (< 0.07 g/L) in a patient > 4 years old. Any levels reported below reference range, but higher than 0.07 g/L, should be termed a light deficiency and this probably signifies even less frequent clinical relevance. The diagnosis of IgAD is commonly accidental as part of screening for allergies or autoimmunity. For the diagnosis of IgAD other causes of hypogammaglobulinaemia must be excluded and IgG antibody response to vaccination must be normal. An increase in production of IgA with aging must be remembered and values have to be compared with age-appropriate values and with awareness of age-matched norms, as serum IgA is the last isotype to reach adult levels. Adult serum values of IgA may only be reached in puberty and IgA is frequently the first isotype to decrease in PID. IgA-deficient mothers fail to secrete IgA in colostrum and even though compensatory IgM may be measured, the neonate is not optimally protected against intestinal pathogens through transient lack of passive immunity. This corrects with maturation of the infant.

IgA deficiency, if symptomatic, must be investigated for one or more of the 4 IgG subclass deficiencies (most commonly IgG2 which rises more slowly to adult levels, IgG4 is least significant) and for specific polysaccharide antibody deficiency (SAD). This is relevant as IgAD has a tendency to occur in combination with these other 2 most prevalent primary antibody deficiencies of childhood. In both these other deficiencies the B cell numbers (CD19) and total serum IgG levels are also normal. Specific antibody deficiency is determined by impaired ability to produce antibodies to specific antigens on vaccine challenge, typically to Streptococcus Pneumoniae. However, only serotypes present in the vaccine can be tested for. The genetic defect for this is also unknown.

Autoimmune diseases should be investigated as indicated by their specific symptoms and findings because of the strong associations reported with several autoimmune conditions and it has even been suggested that IgAD in itself is an autoimmune disease.8 (Table II)

THE INITIAL DIFFERENTIAL DIAGNOSIS OF IgAD MAY INCLUDE THE FOLLOWING:
• Transient Hypogammaglobulinaemia of infancy;
• Common Variable Immunodeficiency;

TABLE II: IgAD AND ASSOCIATION WITH AUTOIMMUNE DISEASES*

| 1. IgAD 1:60 in Graves Disease (2011) with increased thyrotropin-receptor-autoantibodies (TRAb). |
| 3. IgAD 1:27-1:261 in Type 1 Diabetes (2011)). |
| 6. IgAD is overrepresented in 22q11 deletion syndrome and chromosome 18 abnormality – syndromes with increased autoimmune disease. |

• X-linked Immunodeficiency with Hyper IgM;
• Agammaglobulinaemia.

MANAGEMENT
• General guidelines include awareness for and treatment of concomitant atopy, autoimmunity and associated GIT manifestations. Aggressive, early use of antibiotics is required for recurrent respiratory tract infections, such as sinusitis, asthma, and bronchitis. Prophylactic use either seasonal or continuously is not well studied but can be considered especially when there is associated specific antibody deficiency (SAD) or allergy. Recommendations for prophylactic antibiotics are available for the more severe immunodeficiencies.9,10
• Vaccination may have a place preceding winter especially with Influenza vaccine and with Pneumococcal vaccine.11 Revaccination may be indicated in selected patients: Sorensen et al. (1998) showed that a significant percentage of children with specific antibody deficiency develop protective antibody levels to the conjugated pneumococcal vaccine (Prevnar) with subsequent decreased infections.
• Immunoglobulin (Ig) replacement or not? Ig replacement would very rarely be indicated in the treatment of IgAD, unless there are associated deficiencies. The most valid indication of antibody related immunodeficiency is the child’s ability to make specific antibody against polysaccharide antigens in determining the need for therapeutic intervention. Even if the patient cannot produce specific antibodies, the decision to treat with intravenous immunoglobulin (IVIg) is controversial. With significant symptoms a trial of IVIg at 400-600 mg/kg monthly for 6 months can be considered in setting of combined IgG subclass/specific antibody deficiency and only if this is well documented. IgG and IgE antibodies to IgA have been reported to cause severe transfusion reactions in IgA-deficient patients but only few reports describe true anaphylaxis in patients with selective IgA deficiency and common variable immunodeficiency (CVID) who developed antibodies after treatment with Ig.

PROGNOSIS
There is conflicting data on compensatory increase in IgM production and secretary IgM in mucosal lumen in IgAD and
normal levels of secretory IgA, in the presence of low serum IgA, may also explain the majority lacking clinical symptoms. The low switched-memory-B cell subgroup (IgM+CD21-B cells) exhibits more severe clinical features such as pneumonia, autoimmune disease, and bronchiectasis. This test may aid in the prognosis and management of IgAD in future.

With the advent of easier access to genetic mutation analysis, patients with increased disease susceptibility to CVID (Common Variable Immunodeficiency) and symptomatic IgAD may be identified and alerted to especially for possible progression to CVID.12

CONCLUSION
IgAD is an asymptomatic laboratory finding in the great majority of patients. If an excess of infections accompanies the low IgA, the aggravating conditions of allergies, specific antibody deficiency and rarely IgG subclass deficiency should be investigated. Secondary causes are temporary and should be excluded at the start.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

REFERENCES