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The Four Most Common Pediatric Immunodeficiencies

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Abstract. Other than the physiologic hypogammaglobulinemia of infancy, 80% of the confirmed immunodeficiencies consist of four syndromes: transient hypogammaglobulinemia of infancy (THI), IgG subclass deficiency, partial antibody deficiency with impaired polysaccharide responsiveness (IPR), and selective IgA deficiency IgAD. None are life threatening, all can be readily managed, and many recover spontaneously. An exact incidence of these disorders is not known. A summary of immunodeficiency registries in four countries listed IgAD in 27.5% of the patients, IgG subclass deficiency in 4.8%, and THI in 2.3%. The 1999 US survey of primary immunodeficiencies conducted by the Immune Deficiency Foundation found that 17.5% of these patients had IgAD and 24% had IgG subclass deficiency, while THI and IPR were not listed. The Jeffrey Modell Foundation (2005) survey of their global centers in 2004 reported IgAD in 15.5%, subclass deficiencies in 8%, and THI in 2% of their patients.

1. Transient Hypogammaglobulinemia of Infancy

1.1. Definition and History

This disorder was first described in 1956 (Gitlin and Janeway 1956). It is classically considered a prolongation of physiologic hypogammaglobulinemia that occurs from age 3 to 6 months as a result of disappearance of maternal transplacental IgG and slow increase of the infants' own IgG levels (Roifman 2004; Dalal and Roifman 2006). Despite their low IgG levels, most infants are able to respond to vaccine antigens during the first 6 months of life.

Although some use low levels of either IgG, IgM, or IgA below 2 SD from the mean as diagnostic criteria, transient hypogammaglobulinemia of infancy (THI) is best defined as low levels of IgG with or without depression of IgA and/or IgM in an infant beyond 6 months of age in which other primary immunodeficiencies have been excluded. The condition can persist up to the age of 5 years (Roifman 2004; Dalal and Roifman 2006). This definition will include many infants who have no increased susceptibility to infection and have normal antibody responses to vaccine

antigens. Such infants rarely come to the attention of the immunologist. Thus, a clinically significant THI occurs in that subgroup of THI infants with frequent infections and/or poor antibody responses to one or more vaccine antigens.

1.2. Etiology

Various causes of this disorder have been proposed. An early study suggested that IgG genetic allotypes (Gm types) of the fetal IgG induced anti-Gm antibodies in the mother that crossed the placenta and suppressed fetal immunoglobulin production (Fudenberg and Fudenberg 1964). This was not confirmed in another study (Nathenson 1971). A genetic cause was suggested that THI represented heterozygosity for genetic hypogammaglobulinemia based on family studies (Nathenson 1971). Another suggested that a T-helper deficiency caused THI (Siegel et al. 1981). A final study suggested cytokine imbalance (Kowalczyk et al. 1997). Another cause is seen among infants, usually premature, who have had prolonged stays in the neonatal ICU for a variety of illnesses. Their IgG is often low because of stress, loss of plasma into the GI or respiratory tract, steroid use, and frequent blood draws. Finally, many of these children may simply be at the low end of the normal range for IgG and/or at the low end of the normal progression of immune maturation as reflected by IgG levels, thus have no immunodeficiency, and are like the asymptomatic patients with low CD4 cells who are designated as idiopathic CD4 lymphopenia.

1.3. Clinical Features

THI is more common in males, who usually are identified at an earlier age than females (Whelan et al. 2006). About 25% of the symptomatic patients are identified before the age of 6 months, another 50 % from ages 6 to 12 months, and the rest after age 12 months.

Two groups of THI patients are recognized. The first group of infants are asymptomatic who have immunoglobulins done routinely or because a family member has an immunodeficiency. Most of these infants remain asymptomatic, have normal responses to vaccine antigen, and grow out of their hypogammaglobulinemia after several years. The second group is infants identified because of recurrent or severe infection often starting in the first weeks of life. The majority of their infections are respiratory-otitis, sinusitis, and bronchitis. Other children have recurrent diarrhea, or prolonged oral candidacies.

We recently identified seven infants with severe eczema with low levels of IgG (Lin, Roberts, and Stiehm, unpublished observations), possibly associated with protein loss through the skin. Positive skin or Radioallergosorbent tests (RAST) and elevated IgE levels are often seen in these patients. Hematological abnormalities are often present, such as mild neutropenia and less commonly thrombocytopenia. Tonsils and lymph nodes are present but may be small.

1.4. Laboratory Features

In addition to decreased levels of IgG, low levels of IgM and IgA are noted in over half of the patients (Whelan et al. 2006). There is no molecular test for THI. Antibody titers to tetanus, diphtheria, hepatitis A and B, *Hemophilus influenza,* and pneumococcal vaccine antigens are variable. About 15% of the patients have non-protective antibody titers to one or more of these antigens, most commonly 1 or more of the serotypes present in the conjugated pneumococcal vaccine. Under these circumstances, a booster immunization is recommended followed by repeat titers after one month. Lymphocyte subsets (CD3, CD4, and CD8 T cells), CD19 (B cells), and CD16/CD56 (NK cells) are usually normal. Very low numbers of B cells suggest X-linked agammaglobulinemia. As noted, allergy tests including IgE levels may be abnormal. Repeated respiratory infections may be associated with chronic sinusitis as identified by sinus film or limited CT scan.

1.5. Management and Prognosis

Infants in group 1 require no treatment. In symptomatic patients, a conservative approach is initially warranted, such as removing the infant from day care, prompt treatment of respiratory infections, and occasionally prophylactic antibiotic therapy. In the rare THI patient who has severe infections or very poor antibody responses to vaccine antigens, Intravenous immunoglobulin (IVIG) substitution at a dose of 400–500 mg/kg q3 or 4 weeks is used, usually for a 6–12 month period. IVIG is then stopped, and immunoglobulin levels and antibody responses are retested 3 months later.

By definition, all of these patients eventually recover. Most patients recover by age 2, but in some patients low IgG levels may persist until age 5. Patients with a combined IgG and IgA deficiency (IgGD and IgAD, respectively) may develop selective IgAD. Other patients will develop an IgG subclass deficiency, while others with poor antibody responses may normalize their IgG levels but have persistent impaired polysaccharide responsiveness (IPR). There was a striking difference in immune maturation, with females having persistently slower recovery (Whelan et al. 2006).

2. IgG Subclass Immunodeficiency

2.1. Definition and History

Schur et al. in 1970 first described IgG subclass deficiencies in three adult patients (Schur et al. 1970). Since then, numerous publications have identified subclass deficiencies in many patients, particularly children. Indeed, it is perhaps the most common immunodeficiency described, and certainly the one for which IVIG is most often used and misused.

The definition of an IgG subclass deficiency is the finding that one or more IgG subclasses are <2 SD below the mean for age with normal or near normal total IgG levels (Stiehm et al. 2004; Lemmon and Knutsen 2006). Up to 20% of the population will thus have an IgG subclass deficiency of one or more IgG subclasses. Since most

of these subjects are asymptomatic, the previously mentioned definition only defines a clinical laboratory finding, not a disease. A clinically significant IgG subclass immunodeficiency is associated with recurrent infection and a significant defect in antibody responsiveness. Many such patients present with recurrent respiratory infections. Others, often with more serious infections, may have a subclass deficiency in association with another primary immunodeficiency (e.g., selective IgAD and DiGeorge syndrome), or with a secondary immunodeficiency (e.g., HIV infection and cirrhosis), or with an autoimmune disease, for example, immune thrombocytopenia and lupus (Stiehm et al. 2004).

2.2. Etiology

The four IgG subclasses are defined by unique structures of the constant region of their heavy chains. They make up about 70%, 20%, 7%, and 3% of the total IgG levels. Each has unique structural, antigenic, and biologic characteristics (Stiehm et al. 2004). The most significant biologic difference is that IgG2 contains the preponderance of antibodies to polysaccharide antigens. Other differences include activation of the classical complement pathway by IgG1 and IgG3, a shorter half-life for IgG3, and less placental passage for IgG2. Other antibodies are not evenly distributed, and mostly in the IgG4 subclass.

Since each subclass is encoded by a different heavy chain segment, gene deletions may be responsible for some subclass deficiencies, particularly those associated with a complete absence of a subclass (Lefranc et al.1983; Migone et al. 1984). Other abnormalities may include transcriptional defects or genetic association with certain genetic IgG allotypes (Gm types). The most common subclass deficiencies among patients presenting with recurrent infections are IgG4 deficiency (40%), IgG2 deficiency (28%), IgG3 deficiency (17%), and IgG1 deficiency (14%). Isolated IgG1 deficiency is rare. Combinations of one subclass deficiency with another IgG subclass or an IgAD are common, notably IgG2 and IgG4, IgG4 and IgA, IgG3 and IgA, IgG2 and IgG4 and IgA, and IgG2 and IgA combinations in that order of frequency (Stiehm et al. 2004).

2.3. Clinical Features

Subclass deficiencies are heterogeneous and rarely familial. IgG4 subclass deficiency may occur in as many as 20% of both adults and children, depending on the sensitivity of the assay and thus is of rare clinical significance. In adults, IgG3 deficiency is the second most common deficiency, and females are more likely to be affected. Adults with IgG subclass deficiency generally have more severe infections, and some of them may be developing common variable immunodeficiency (CVID).

In children, males make up 75% of the cases, and IgG2 is the second most common deficiency. Children under the age of 6 years may be recovering from transient hypogamma-globulinemia, so it is difficult to diagnose an IgGD deficiency in children before age 4.

Selective IgG1 may be associated with more severe infections and is more common in adults. Selective IgG2 deficiency is the most common subclass disorder

associated with recurrent infection and may be accompanied by IgA and/or IgG4 deficiencies. Many of these patients have IPR as discussed in Impaired Polysaccharide Responsiveness. IgG2 deficiency may resolve with time. Most symptomatic IgG3- deficient subjects have an associated deficiency of another class. Familial IgG3 deficiency has been recorded. As noted, isolated IgG4 is common and not usually of clinical significance. However, recurrent pneumonia has been described, suggesting that it is a marker for these illnesses rather than the cause of them.

2.4. Laboratory Features

IgG subclass determinations are indicated for patients with documented antibody defects, in patients with IgA deficiencies, and in patients in which early CVID is suspected. Levels must be compared with age-matched controls, especially in the first 2 years of age. For children aged 4–10 years, an IgG1 level less than 250 mg/dl, an IgG2 level less than 50 mg/dl, an IgG3 level less than 15 mg/dl, and an IgG4 level less than 1 mg/dl are abnormal. For subjects older than age 10, an IgG1 level less than 300 mg/dl, an IgG2 level less than 75 mg/dl, an IgG3 level less than 25, and an IgG4 level less than 1 mg/dl are abnormal.

A clinically significant IgG subclass deficiency must be established by measuring the antibody response to a vaccine antigen, particularly pneumococcal polysaccharide vaccine. A deficient response is defined as non-protective titers to a majority of the 12 serotypes tested or failure to exhibit a twofold rise in titer to serotypes for which there were non-protective titers. Tests for cellular immunity, complement activity, and phagocytic function should be done as necessary.

2.5. Management and Prognosis

Many patients do well with prompt medical management of each infectious episode, and the use of antibiotics early in the course of respiratory exacerbation is of value. Some patients with recurrent infections or chronic infections do well on prophylactic antibiotics. Vaccines should be kept current unless there is complete absence of antibody responses. A failure of prolonged antibiotics, severe symptoms, and persistent radiographic abnormalities may occasionally require IVIG therapy (Buckley 2002). The presence of a subclass deficiency alone is not an indication for IVIG. Nevertheless, it is a common practice to give IVIG under such circumstances, which is a costly misuse of a scarce and potentially harmful form of therapy and labels the patients as chronically ill and uninsurable. Its use in young children has the potential of inhibiting normal immune maturation.

Most patients do well on conservative therapy outlined above, but treatment may be prolonged and in some lifelong. Children under 10 may recover from a subclass deficiency spontaneously, particularly if there is not a complete absence of a subclass. By contrast, symptomatic adults may progress to CVID.

3. Impaired Polysaccharide Responsiveness

3.1. Definition and History

IPR is characterized by recurrent bacterial respiratory infection, an absent or subnormal response to a majority of polysaccharide antigens, normal or elevated immunoglobulins and IgG subclasses, and intact antibody responses to protein antigens in subjects over age 2 (Stiehm et al. 2004; Sorensen and Paris 2006).

As early as 1968, patients were described who had normal immunoglobulin levels, but had profound deficiencies of antibodies to both protein and polysaccharide antigens (Blecher et al. 1968; Saxon et al. 1980). This entity, *antibody deficiency with normal immunoglobulins*, should not be confused with IPR since such patients are considerably more susceptible to infections and more akin to CVID in their prognosis.

IPR was identified in the late 1980s following the introduction of unconjugated *H. influenza* type B polysaccharide vaccines (Granoff et al. 1986b). This large collaborative study identified children greater than 2 years of age that had a poor response to this vaccine despite normal responses to other vaccines. Subsequent studies indicated that sometimes this deficiency was familial and occurred more frequently among certain ethnic groups such as Apache Native Americans and Alaskan Eskimos (Stiehm et al. 2004). Adults with IPR were first described in 1987 (Ambrosino et al. 1987). Since unconjugated *H. influenza* vaccine has been replaced by a protein-conjugated vaccine that is immunogenic in infants, IPR is usually identified by a deficient response to the pneumococcal polysaccharide vaccine (Pneumovax) in children greater than 2 years of age and adults. Sorenson and Paris have identified this disorder as the most common immunodeficiency among children presenting with increased susceptibility to infection (Sorensen and Paris 2006).

3.2. Etiology

IPR is a heterogeneous illness with several postulated causes. In younger children aged 2–6, it may be an exaggeration of the physiologic non-responsiveness to polysaccharide vaccines of infants less than 2 years of age; these children recover spontaneously with time. Some of these youngsters have had THI with poor antibody responses. Most polysaccharide antibodies are in the IgG2 subclass, so that selective IgG2 subclass deficiency with or without selective IgAD must be sought. IPR may be part of another primary immunodeficiency such as Wiskott–Aldrich syndrome, DiGeorge syndrome, and mucocutaneous candidiasis, secondary deficiencies associated with aging, HIV disease, immunosuppressive drugs, genetic syndromes, chronic lung disease, and absence or deficiency of the spleen (Stiehm et al. 2004). IPR may be genetic in some families and linked to certain Gm and Km IgG allotypes (Granoff 1986a). A defect in the B cell repertoire, similar to certain mice strains, has been postulated (Ambrosino et al. 1987) and Ambrosino et al. have suggested a splenic defect in the marginal zone where dendritic cells interact with B cells. One adult IPR male with few circulating B cells had a BTK mutation associated with X-linked agammaglobulinemia (Wood et al. 2001).

3.3. Clinical Features

IPR is more common in males and may be more common in certain ethnic groups. Most of the patients are children aged 2–7, and most of these patients recover completely from their illness. Clinically, IPR patients resemble patients with IgG subclass and selective IgA deficiencies. They usually have recurrent bacterial respiratory infections such as sinusitis, otitis, and bronchitis: less common are systemic infections including pneumonia, sepsis, or meningitis. Many patients have asthma or wheezing with infections, often because of chronic sinusitis. Many have had ear tubes placed, tonsillectomy, a history of decreased hearing, and multiple courses of antibiotics. The physical examination often suggests chronic respiratory allergy, with circles under the eyes, pallor, gaping mouth, post-nasal drip, purulent nasal discharge, and moderate cervical adenopathy.

3.4. Laboratory Features

IPR patients by definition have normal IgG, IgM, and IgA levels and IgG subclass levels, as well as normal responses to protein antigens such as tetanus, diphtheria, and *H. influenza* type B-conjugated vaccines. Thus, the diagnosis rests on their antibody response to pneumococcal polysaccharide vaccine. Pre-immunization titers are recommended followed by retesting 1 month following vaccination. A normal response is development of protective titers (>1.3 μg/ml) to a majority of the subtypes tested. Sorenson and Paris (2006) suggested that a normal response for children under 6 consists of a majority of responses to be protective and for older individuals at least 70% of the serotypes should be protective. Three types of responses are noted. In the severe form, there is essentially no response to any or just one or two of the serotypes, and then the titers are low but protective. In the mild/moderate form, there is some but less than expected responses. Some of these patients, as well as some patients with an adequate response initially proceed to the third form associated with poor immunologic memory. These patients, upon retesting in 6–12 months, have lost some or most of their previously protective titers and continue to have recurrent infections.

All of these patients should be tested for T cell, phagocyte, and complement deficiencies. In young children, repeat antibody testing is recommended at yearly intervals, because spontaneous recovery often ensues. Symptomatic adults should be followed periodically to look for progression to CVID.

3.5. Treatment and Prognosis

Many of these patients do well with prompt and vigorous treatment of each respiratory infection. Ancillary treatment with inhaled steroids, bronchodilators, and decongestants are often of value. Vaccines, particularly influenza vaccine, should be updated. We often give these patients two doses of the pediatric-conjugated pneumococcal vaccine to boost their immunity to the serotypes in this vaccine. If these measures are ineffective, a course of prophylactic antibiotics is tried, usually for at least 6 months. If there is persistent infection, a trial of IVIG should be

considered in full therapeutic doses. Only an occasional patient requires such therapy, but a good response has been documented in some series (Herrod 1993).

Children with partial responses usually recover with time. Patients with the severe form of disease usually have lifelong problems. Some of these patients may develop IgG subclass deficiency or CVID.

4. Selective IgAD Deficiency

4.1. Definition and History

Selective IgAD is defined as the absence or very low levels (<7 mg/dl) of serum IgA with normal levels of total IgG and IgM and no other major immune defects. This definition excludes young infants since they have low levels of IgA physiologically and do not obtain adult levels until 3 years of age. IgAD is the most common primary immunodeficiency, and in many individuals, it is unassociated with any illness including an increased susceptibility to infection. IgAD was first described in ataxia-telangiectasia, then in patients with frequent infections (West et al. 1962) and in normal subjects (Rockey et al. 1964). Low or absent IgA is a variable component of many other primary immunodeficiencies, notably all forms of agammaglobulinemia, ataxia-telangiectasia, mucocutaneous candidiasis (Kalfa et al. 2003) and IgG2 subclass deficiency (Oxelius et al. 1981). The frequency of IgAD varies in different ethnic groups, and is as high as 1:142 in Arabs (al-Attas and Rahi 1998) and as low as 1:15,000 in Japanese (Kanoh et al. 1986). Among Europeans and Americans, the frequency is about 1:500 (Hostoffer 2006).

4.2. Etiology

IgA is the second most abundant immunoglobulin synthesized; it appears not only in the serum but also in the secretions, including colostrums and breast milk. Much of the serum and all of the secretory IgA are synthesized in plasma cells of glandular tissues. Locally produced monomer IgA combines with an epithelial cell-synthesized secretory component and a joining chain and is secreted as a dimer (secretory IgA) into the lumen of the gland. Serum IgA does not get into the secretions; most of the serum IgA is synthesized locally and enters the blood stream in the monomeric form.

Selective IgAD deficiency is occasionally familial (Koistinen 1976), and in some families, there is a shared propensity of relatives of IgAD patients to have CVID. Genetic defects of a tumor necrosis factor receptor family member termed Transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI) have been identified in a few patients with IgAD and CVID, possibly causing defects in isotype switching (Castigli et al. 2005). There is an association of IgAD deficiency with certain HLA types, suggesting a linkage to the major histocompatibility complex (Lakhanpal et al. 1988). Genetic defects involving deletions of chromosome 14 and abnormalities of chromosome 18 and chromosome 4 are also associated with IgAD (Hostoffer 2006).

Certain drugs, notably penicillamine, gold, fenclofenac, and valporate, may cause depression of serum IgA levels, which sometimes are permanent. Congenital rubella and Epstein–Barr virus infections have been implicated in a few cases of acquired IgAD.

4.3. Clinical Features

Up to 90% of IgAD patients are asymptomatic. Indeed a few patients, particularly children under age 5, with low but measurable IgA levels outgrow the illness; this is most unusual in adults and in patients without detectable IgA (Blum et al. 1982).

Most symptomatic IgAD patients have frequent respiratory infections similar to patients with IgG subclass deficiencies or IPR. Many of these patients have a concomitant IgG2 deficiency and/or IPR. The most common infections are otitis, sinusitis, or bronchitis. A few develop recurrent pneumonia, obstructive lung disease, or bronchiectasis or other chronic lung diseases.

Atopic patients have a high incidence of IgAD. This includes patients with asthma, rhinitis, hives, and eczema. A search for chronic sinusitis should be done in those with IgAD and asthma. Food intolerance, particularly milk allergy, is common in infants with IgAD; some of these patients have high titers of milk antibodies. Other causes of gastrointestinal symptoms in patient with IgAD include celiac disease, inflammatory bowel disease, nodular lymphoid hyperplasia, hepatitis, and others. Autoimmune disease is common among IgAD patients, notably rheumatoid arthritis, lupus erythematosus, and thyroiditis. At least 16 other autoimmune disorders have been identified in patients with IgAD, involving all organ systems such as the skin, central nervous system (mental retardation), and the hematopoietic system, (immune thrombocytopenic purpura and autoimmune hemolytic anemia). One theory is that absence of IgA in the serum permits cross-reactive antigens to enter the circulation and initiate autoimmune reactions. A very rare IgAD patient may have an anaphylactic reaction to a blood product containing IgA. Such patients have developed anti-IgA antibodies to a previous infusion and recognize IgA as a neo-antigen. Thus, blood products should be avoided in IgAD patients, and they should wear a Medic Alert badge to this effect. If IVIG is needed, a product low in IgA should be used, with caution and pre-medication (Cunningham-Rundles 2004).

4.4. Laboratory Features

Immunoglobulin and IgG subclass levels are the primary diagnostic tests. If IgAD is present, its absence should be confirmed by repeat sampling. Next, antibody titers to vaccine antigens should be done to determine whether there is a concomitant functional antibody deficiency. Assays for cellular immunity, phagocyte function, and complement ment are usually normal. The presence of autoimmune antibodies such as antinuclear antibodies (ANA) and antithyroid antibodies are common. Allergy tests are often positive. Milk antibodies and celiac antibodies should be done if there is evidence of food intolerance or malabsorption. Anti-IgA antibodies can be assessed but do not correlate well with intolerance to IVIG.

4.5. Treatment and Prognosis

Treatment of infections consists of prolonged or even prophylactic antibiotics. Vaccination status should be kept updated. A Medic-Alert badge is recommended for some patients to warn about administration of IVIG or blood products. A rare patient with refractory infection may require IVIG.

Prognosis is largely dependent on the presence of antibody deficiency, allergy, or autoimmune disease. IgAD is usually lifelong but not associated with life-threatening infections. Rare instances of spontaneous recovery have been recorded, particularly in young patients with measurable IgA. If the patient has been on a medication known to cause IgAD, its discontinuance may lead to recovery.

5. Conclusions

The four most common immunodeficiencies in pediatric patients are THI, IgG subclass deficiency, IPR, and selective IgAD. All four illnesses are characterized by recurrent bacterial respiratory infections such as purulent rhinitis, sinusitis, otitis, and bronchitis. Except for some IgA-deficient patients, the molecular basis for these illnesses is not known, and indeed each syndrome is heterogeneous, with multiple causes. The chronic respiratory infections present are rarely life threatening but often require prolonged antibiotics. Only a few of these cases require the use of IVIG, and the outlook for long life is excellent.

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