Four Most Common Antibody Deficiencies in the First Year of Life

Infants are often diagnosed with these four antibody deficiencies, two of which can cause serious complications, however they resolve with time for most.

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PHYSIOLOGIC HYPOGAMMAGLOBULINEMIA, specific antibody deficiency (SAD), hypogammaglobulinemia of the newborn and transient hypogammaglobulinemia of infancy are the four most common antibody deficiencies infants experience in their first year of life. The infant in the clinical vignette (opposite page) had all four antibody deficiencies, two of which are present in every young child (physiologic hypogammaglobulinemia and SAD), while the other two (hypogammaglobulinemia of the newborn and transient hypogammaglobulinemia of infancy) are less common and more serious after 6 months of age.

All of these disorders predispose infants to infection, contributing to the high risk of death during their first year of life. The first month of life is the most critical with deaths due to profound prematurity; birth defects; maternal complications; placental, cord and membrane complications; and bacterial sepsis. The next five months of life are also hazardous because of congenital malformations, sudden infant death syndrome, unintentional injuries, circulatory disorders and homicide.[1]

These disorders will be detailed below, preceded by a brief summary of B cell and immunoglobulin development.

Fetal B Cells

B cells (CD19+), the basic cells of the immunoglobulin system, first appear in the liver, bone marrow and circulation at approximately the eighth week of gestation. Fetal B cells increase steadily all through gestation so, by term birth, the B cells represent 15 percent of peripheral blood lymphocytes and number approximately 400 cells/ul.[2] These intrauterine B cells do not develop into plasma cells for immunoglobulin production for the circulation or secretions, in part because of immaturity and in part because of lack of antigen stimulation within the sterile womb. Thus, these B cells are antigenically naive with a CD19+CD27-phenotype, unlike memory B cells that have a CD19+CD27+phenotype.

Transplacental IgG Immunoglobulin

The lack of fetal immunoglobulin production is compensated

by the placental transfer of maternal IgG immunoglobulin beginning about the 12th week of gestation. This transfer accelerates during late pregnancy so, by the time of term birth, the infant's IgG level is slightly higher than the maternal IgG level.[3] This transfer is accomplished by the FcRn, the neonatal FcReceptor.[4] The Fc stands for the tail of the Y-shaped IgG immunoglobulin molecule. This receptor is present on placental syncytotrophic cells at the maternal-fetal interface where it ingests maternal IgG and transfers it to the infant's circulation. This transfer is restricted to IgG; no other maternal immunoglobulin (IgA or IgM) is transferred (Figure).

Maternal IgG provides infants with protective antibodies to the microbes they have encountered either from infection or from immunization. This emphasizes the importance of immunization for prospective mothers before or during pregnancy (excluding live virus vaccines during pregnancy). Premature infants will receive less of these protective antibodies and thus are more susceptible to infection than are term infants.

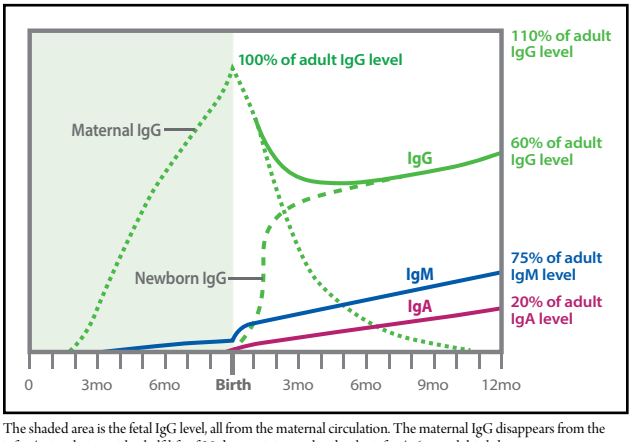
Immunoglobulin Levels in the First Year of Life

The maternal IgG transferred to her newborn has a half-life of 30 days so it disappears gradually from the infant's circulation over a six-month period. By that time, infants have started making their own IgG and IgM and are able to respond to vaccines and microbes. Newborns first make IgM, then IgG and finally IgA, so by 1 year of age, newborns have an IgM 75 percent of an adult's, an IgG 60 percent of an adult's and an IgA 35 percent of an adult's as shown in the Figure.[5]

I. Hypogammaglobulinemia of the Newborn

Prematurity is the most common cause of neonatal

Figure. Immunoglobulin (IgG, IgM, IgA) Levels in the Fetus and Infant in the First Year of Life



The shaded area is the fetal IgG level, all from the maternal circulation. The maternal IgG disappears from the infant's circulation with a half-life of 30 days, so it is very low by the infant's 6-month birthday.

A Clinical Vignette

Baby boy Asa was born prematurely at 31 weeks because of maternal bleeding. It was the 21-year-old mother's first pregnancy, and she was in good health with a normal IgG level of 1,090 mg/dl. Asa's immunoglobulins at birth were IgG 280 mg/dl, IgM 5 mg/dl and IgA less than 5mg/dl. A heel stick TREC test excluded severe combined immunodeficiency disease.

Asa did well in the nursery on two weeks of tube feedings and supplemental oxygen. At 8 weeks, he started his routine childhood vaccines, except for the live oral rotavirus vaccine that is not given in the newborn nursery because of possible spread to other newborns. He was discharged at 10 weeks of age with a weight of 2,200 grams. His IgG level was 240 mg/dl, thus he was diagnosed with hypogammaglobulinemia of the newborn.

Asa did well at home with weekly visits by a visiting nurse and monthly checks by his pediatrician. His vaccines were continued, including oral rotavirus vaccine, and he was started on monthly Synagis for respiratory syncytial virus prophylaxis since it was the winter months. At 4 months of age, his IgG was 280 mg /dl, his IgM was 28 mg/dl and his IgA was less than 5mg/dl. He was then diagnosed with physiologic hypogammaglobulinemia of infancy, aggravated by his low IgG level at birth.

He did well at home and by 8 months of age, he weighed 7 kg and had only one febrile illness with rhinorrhea (thin nasal mucus discharge) and a cough that lasted a week. His IgG level was 320 mg/dl, his IgM level was 40 mg/dl and his IgA level was 8 mg/dl. He had low but protective antibodies to tetanus and diphtheria and several pneumococcal serotypes. He was then diagnosed with transient hypogammaglobulinemia of infancy.

At 11 months of age, Asa developed bilateral otitis media (earache affecting both ears) resistant to ampicillin. A myringotomy (a tiny surgical incision in the eardrum to relieve pressure caused by excessive buildup of fluid from the middle ear) with culture revealed a pneumococcus serotype 14N not present in the conjugated pneumococcal vaccine (Prevnar 13) but present in the 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23). For this reason, Asa was given the latter vaccine and his titers were checked before being vaccinated and one month after vaccination. This disclosed protective titers to eight of the Prevnar serotypes but only two of the unique serotypes in Pneumovax (not present in Prevnar). His IgG had normalized at 450 mg/dl, and he was then diagnosed with specific antibody deficiency (also known as impaired polysaccharide responsiveness), which is common at this age, that persisted until age 3 years.

hypogammaglobulinemia (an IgG level less than 400 mg/dl during the first two months of life). Hypogammaglobulinemia is generally present in infants born before 32 weeks of gestation and/or weighing less than 1,500 grams. Ballow et al.[6] reported the mean IgG level of prematures born at 25 weeks to 28 weeks of gestational age was 251 mg/dl (range 114-552 mg/dl), and the mean IgG level of infants born from 29 weeks to 32 weeks gestation was 368 mg/dl (range 186-298 mg/dl). Despite their immaturity and in the absence of other illnesses, these newborns are able to respond to routine childhood vaccines by 8 weeks of age. But, they are kept in isolation until ready for discharge at 38 weeks and weighing 2,100 grams if they are otherwise well.

Hydrops fetalis due to maternal-fetal Rh incompatibility was a common cause of neonatal hypogammaglobulinemia before its prevention with Rh immunoglobulin.[7] These critically ill infants have generalized edema (swelling caused by excess fluid trapped in the body's tissues) associated with severe anemia (a lack of healthy red blood cells) due to lysis (destruction) of their Rh positive red cells by transplacental maternal Rh antibodies. The anemia results in heart failure with loss of plasma proteins, including IgG, into the soft tissues and serous cavities. Placental edema may also decrease maternal-fetal IgG transfer.[8]

Less-common causes of hydrops include severe anemia due to congenital hemoglobulinopathies, maternal infections, particularly parvovirus, congenital heart disease with heart failure and several other genetic disorders.[9] All require circulatory support, correction of the anemia and replacement of serum albumin and immunoglobulin.

Maternal hypogammaglobulinemia will result in newborn hypogammaglobulinemia, dependent on the maternal IgG level and the newborn gestational age. The most common cause is maternal rituximab therapy,[10] a monoclonal antibody to CD20 on B cells, which causes a marked decrease in B cells, plasma cells and IgG levels. Rituximab is used in several diseases associated with harmful autoimmune antibodies such as immune thrombocytopenic purpura or autoimmune hemolytic anemia. It also renders mothers hypogammaglobulinemic with less IgG transferred to their infants. If rituximab is given during late pregnancy, it may depress B cells in infants.[11] Other immune-suppressive drugs may also decrease maternal IgG levels, but not usually to the degree as rituximab therapy.

Additional causes of maternal hypogammaglobulinemia include untreated immunodeficiencies such as common variable immunodeficiency, parvovirus infection, hemodialysis (procedure to remove fluid and waste products from the blood and to correct electrolyte imbalances) or immunoglobulin loss into the GI tract, urine or serosal spaces such as the pleura (chylothorax) or peritoneum (chylous ascites).

Immunoglobulin loss in infants' circulation may also result in neonatal hypogammaglobulinemia. This loss can occur into the urine in congenital nephrosis (kidney disease),[12] into the bowel in early onset protein-losing enteropathy (abnormality of the intestinal tract)[13] or into serosal spaces such as the pleura or peritoneum. Immunoglobulin loss can also result with extensive blood loss due to hemorrhage, surgery (particularly cardiopulmonary bypass surgery),[14] frequent blood sampling or the twin-twin transfusion syndrome[15] (one twin bleeds into the other, causing anemia and hypogammaglobulinemia in the donor twin).

Management of these disorders is first directed at the underlying cause of the disease. Immune globulin (IG) therapy may be considered if there is refractory infection not responding to antibiotics. Sometimes IG is used to reduce hemolysis.

II. Physiologic Hypogammaglobulinemia of Infancy

All infants have a significant decrease in their IgG levels between 2 months and 6 months of age as maternal IgG levels disappear and the infants' own IgG synthesis is not yet well-established. This is markedly severe and prolonged if babies are born prematurely as noted above.[6] The presence of systemic infection or inflammatory diseases may accelerate IgG catabolism (the part of the metabolism responsible for breaking complex molecules down into smaller molecules) with resulting aggravation of the already low IgG levels. Blood or protein loss due to any reason will also aggravate the hypogammaglobulinemia. Despite these low levels and in the absence of systemic disease, routine immunizations should be continued. IG therapy is not indicated simply based on low IgG levels.[16]

The first six months of life is the period of highest infant mortality, as noted above.[1] Hypogammaglobulinemia may contribute to infants' demise, particularly in infections, sudden infant death syndrome and the pneumonia that accompanies many of these disorders.

III. Transient Hypogammaglobulinemia of Infancy (THI)

THI occurs in infants older than 6 months of age who have an IgG less than two standard deviations below the mean for age with or without low levels of IgM and IgA.[17,18] I prefer the simple definition of an IgG less than 400 mg/dl with measurable levels of IgA and IgM immunoglobulins, thus excluding selective IgA or IgM deficiency. Antibody titers are usually present but at reduced titers.[19]

THI is among the most common antibody deficiencies in

several immunodeficiency registries that include children, with its incidence similar to selective IgA deficiency and SAD. Two-thirds of infants with THI are boys. THI usually resolves by 5 years of age but may persist up to 10 years of age and beyond. Thus, one authority suggests it should be termed transient hypogammaglobulinemia of childhood.[20] A definitive diagnosis cannot be made until patients recover. The cause is not known, and it is not associated with known genotypes.

In infants with THI, immunoglobulin levels should be measured every 6 months to 12 months to follow progression of the disease. Antibody titers to protein vaccine antigens are usually protective but often slightly depressed. Most children have a concomitant SAD that may be prolonged (see below). A complete absence of an antibody response suggests a primary antibody deficiency. And, while B cell and T cell numbers are normal, B cells show a naive phenotype.

Many of these children remain well, but others have frequent respiratory infections, asthma, food intolerance or eczema. These children should be given their childhood vaccines. Continuous antibiotics and intravenous IG use is reserved for refractory and/or recurrent infections, with most infants experiencing only mild infections.

IV. Specific Antibody Deficiency (SAD)

SAD is defined as an inadequate response to polysaccharide antigens but normal responses to protein antigens, normal levels of immunoglobulin and no other immunodeficiency syndrome.[21] SAD is present in most infants after their IgG normalizes at about 6 months of age, and it persists in most infants until 24 months of age and often longer.

SAD is usually diagnosed by an inadequate response to the 23- valent pneumococcal polysaccharide vaccine. Adults should develop protective titers to 70 percent of the polysaccharide serotypes, while children under 6 years should respond to 50 percent of them.[21]

In children, SAD is associated with frequent respiratory infections, including sinusitis and chronic otitis (ear infection). It is also the most common antibody disease in adults, usually manifested by chronic rhinosinusitis. Up to 40 percent of patients with these symptoms have SAD, as do 10 percent of adult controls.[22] Patients over age 60 years are more likely to have SAD. And, although SAD in children often disappears after several months, the diagnosis in adults usually persists for a lifetime.

The cause of SAD is not known and probably multifactorial. It is a common secondary immunodeficiency in many chronic conditions such as hematologic malignancies, immunosuppressive therapy and older adults. Treatment includes antibiotics and occasionally IG therapy in refractory or persistent infection.

The Need for Long-Term Follow-Up and Vaccines

Two of the four common antibody deficiencies, THI and SAD, are experienced by all infants but are usually asymptomatic with a good prognosis. Neonatal hypogammaglobulinemia is common in premature infants but also associated with serious conditions. THI is often associated with frequent respiratory infections and allergies. Long-term follow-up of these illnesses is imperative, since most infants recover with time. Rarely are these antibody deficiencies precursors for adult disease. Vaccines are used both as therapy and diagnosis. Vaccines for pregnant mothers, infants and their families are important parts of optimal management, and they may prevent the need for antibiotics and illness in infants and their family members. ■

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