Transient Hypogammaglobulinemia of Infancy

Chapter 7

An unborn baby makes no IgG (antibody) and only slowly starts producing it after birth. However, starting at about the sixth month of pregnancy, the fetus starts to receive maternal IgG antibody through the placenta. This increases during the last trimester of pregnancy until at term birth the baby has a level of IgG, the main class of antibody in the circulation, equivalent to that of the mother.

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The baby does not get any maternal IgM, IgA or IgE as they do not cross the placenta, so if IgM is found it may suggest the baby has encountered an infection in utero. If the baby is born prematurely, the IgG level is lower than that of a term infant, in proportion to the degree of prematurity. The IgG from the mother protects the baby from many infections in the first months of life.

The newborn baby may get additional antibody via breast feeding, but this antibody does not get absorbed from the baby's gastrointestinal tract. However its presence in the baby's pharynx and intestinal tract protects the baby from diarrheal diseases, and to some extent from respiratory disease.

The transplacental IgG slowly disappears from the infant's circulation and is essentially all gone by about 6 months of age. The baby, however, starts to make its own IgG starting at birth and this increases gradually throughout the first months of life. Between 3 and 6 months all infants have low levels of IgG as a result of the maternal IgG falling and the infant's IgG just starting to be made. This low level is termed physiologic hypogammaglobulinemia of infancy and is usually not clinically significant. It is more pronounced in premature infants because the amount of IgG from the mother is decreased.

In addition to lower levels of IgG and other immunoglobulins, the newborn's immune system is immature and does not respond as well to vaccines or infections, so it is more vulnerable to many infectious diseases.

In some infants the period of hypogammaglobulinemia is more severe or prolonged beyond 6 months of age. This is termed transient hypogammaglobulinemia of infancy (THI) and is the subject of this chapter.

Definition of Transient Hypogammaglobulinemia of Infancy

THI is defined in infants over 6 months of age whose IgG is significantly lower (less than 2 standard deviations) than 97% of infants at the same age. This most commonly is corrected by 24 months of age but may persist for a few more years. Typically the IgG level is less than 400 mg/dl and IgA and IgM antibodies may also be lower. However the ability of these infants to make antibodies is frequently near normal and most of the patients are not unusually susceptible to infection.

The frequency of THI is unknown. It has been described in all parts of the world and is believed to be

(Definition of THI continued)

significantly underdiagnosed. There is a male predominance (2:1), and approximately 60% of patients are discovered by age 1 and the remaining 40% thereafter, often times not until age 5 or 6. In one survey of 17 immunodeficiency centers within the U.S., THI was found to represent about 2% of immunodeficient patients.

Most children with THI are diagnosed because they have recurrent infections. Others are diagnosed because another family member was diagnosed with immunodeficiency. Immune globulin levels are not routinely measured in normal infants so that the actual incidence of asymptomatic THI may be considerably higher.

Cause of Transient Hypogammaglobulinemia of Infancy

Proposed causes for THI include: (1) suppressive maternal antibodies (IgG) which cross the placenta and suppress fetal immunoglobulin production; (2) genetic variation in certain families with a propensity to immunodeficiency; 3) abnormal T-lymphocytes that fail to stimulate antibody production by B-cells; 4) unbalanced cytokine production; (5) abnormal or immature B-cells, not unlike patients with Common Variable Immune Deficiency (CVID).

Clinical Features of Transient Hypogammaglobulinemia of Infancy

The usual clinical features include upper respiratory tract infections (in about two-thirds of patients), lower respiratory tract infections (approximately a third of patients), allergic manifestations (one-half of patients) and gastrointestinal difficulties (in 10% of patients). Typically, children have a combination of these symptoms. Ear and sinus infections are most common. Nasal and throat infections as well as swollen glands are also seen. Bronchitis, bronchiolitis or pneumonia are less common. Occasionally, severe chickenpox, persistent thrush (candida on the mucous membranes of the mouth) and urinary tract infections are reported. Severe infections from live viral vaccines have not been reported. Severe life-threatening infections are rare but have included severe pneumonia, opportunistic infections caused by fungi or staphylococcus, gastrointestinal problems or bloodstream infections.

As in many disorders with immune dysregulation or immaturity, allergic diseases may be present including asthma (25%), eczema (15%) and food allergy (12%). Gastrointestinal symptoms may include chronic diarrhea, persistent vomiting, food allergy and/or intolerance. Neutropenia (low white blood cells) is not uncommon.

Most infants with THI appear normal with none of the classic findings present in other primary immunodeficiency diseases, although the tonsils and lymph nodes may be small. The chest x-ray is usually normal, and the thymus is typically normal in size.

Diagnosis of Transient Hypogammaglobulinemia of Infancy

By definition, the IgG level is lower than two standard deviations below the mean for age. More than one-half of children with THI have IgG levels as low as 200 mg/dl. Levels less than 100 mg/dl and/or pan-hypogammaglobulinemia (very low IgM and IgA as well as IgG) may suggest a permanent immunodeficiency.

Most children with THI produce normal antibodies to vaccines including tetanus, diphtheria, conjugated Haemophilus influenzae, hepatitis A and B vaccines as well as to measles, mumps and rubella vaccines. In the U.S. most infants receive the conjugated pneumococcal vaccine (Prevnar 13) and will respond adequately. Tetanus antigen is a potent vaccine and lack of response suggests a more serious defect and should prompt a more comprehensive evaluation.

If the child lacks protective antibodies against a prior vaccine, a booster shot can be given and the antibody response checked four to six weeks later. If the antibody response is poor, repeat titers may be done in six months. If the young child continues to have frequent or severe infections, additional studies and referral/consultation with an immunologist might be required.

A complete blood count with differential may suggest a primary immunodeficiency. B- and T-cell enumeration is indicated if there is lymphopenia, persistent or severe fungal infections, failure to thrive, chronic diarrhea, and infections with opportunistic microorganisms or severe skin disease.

Chest or sinus X-ray or CT scans may be helpful in the child with chronic respiratory tract infection.

Treatment of Transient Hypogammaglobulinemia of Infancy

For asymptomatic infants and young children, no treatment is required. Clinical observation and supportive counseling may be all that is required. IgG levels should be repeated every four to six months.

For infants with recurrent or persistent infections, common sense measures such as reducing exposure to infections (e.g. choosing a smaller day care center, judicious restriction of exposure to other children) and prompt and appropriate treatment of respiratory infections is warranted. Inactivated (killed) vaccines (diphtheria, tetanus, pertussis, Haemophilus influenzae and pneumococcal vaccines, killed influenza vaccine, killed polio vaccine, inactivated Hepatitis A and B vaccines) should be given as scheduled.

Live viral vaccines (measles, mumps, rubella, Varicella, Rotavirus) should be postponed. *(See chapter titled "General Care.")* Occasionally, prophylactic antibiotic therapy during the respiratory infection season may be prescribed. Monitoring immunoglobulin levels and vaccine antibody levels are done at four to six month intervals.

Immunoglobulin (Ig) replacement therapy is not usually necessary except in rare instances when infections are severe and the child is not thriving. Ig administration will mask or even delay the recovery of these patients. If the child is doing well on Ig for several months, a trial off of Ig therapy is indicated. Generally in cases such as this, Ig treatment is discontinued in the spring or summer when respiratory infections are not as prevalent and the child is retested when the child has been off of Ig for four to five months.

Expectations for Patients with Transient Hypogammaglobulinemia of Infancy

Most children with THI develop age appropriate levels of IgG by age 3. Another 40% attain normal levels by age 5, but 10% may persist beyond this age. In those children with protracted hypogammaglobulinemia, some may develop normal IgG levels but have persistent selective antibody deficiency (impaired response to polysaccharide antigen). Some may have selective IgG subclass deficiency, have persistent infections and may require prolonged antibiotic therapy.

Some children, whose hypogammaglobulinemia persists beyond 5 years of age, may have adequate antibody responses and do not experience serious infections. Why this occurs, is subject to debate. Occasionally, some patients with THI develop serious infections, have persistently low IgG levels and functional antibody defects and may have a CVID-like disease that persists for several years or permanently.