

HYPOGAMMAGLOBULINEMIA OF INFANCY

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In their classic report from 1956, Gitlin and Janeway¹⁶ first coined the term *transient hypogammaglobulinemia of infancy* (THI). Although THI has been recognized for many years and despite significant progress in understanding the molecular basis and identifying the genes involved in the pathogenesis of many other forms of humoral immunodeficiencies (ID), little is known about this specific entity. This article summarizes previous studies and reports our long-term experience with THI.

ANTIBODY RESPONSES TO SPECIFIC ANTIGENS IN NEONATES AND INFANTS

Full-term neonates can produce specific antibodies to T-cell dependent protein antigens soon after birth.³⁴ In fact, even premature infants as young as 24 weeks' gestation and small for gestational age (SGA) infants appear to respond in a similar manner to protein vaccines.^{20, 34} These and several other studies^{2, 6, 11} suggested that the interval from birth to immunization is a more important factor than the gestational age itself. In sharp contrast to the adequate response to protein antigens shortly after birth, the response to polysaccharide T-cell independent antigens is severely blunted until approximately 18 to 24 months of age.^{1, 33} The same pattern has been observed in premature and SGA

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infants. This could be partially explained by the slow rise of IgG2 and IgG4 concentrations. IgG2, and to a lesser degree, IgG4, are the predominant antibodies produced after natural exposure to polysaccharide antigens.²⁷

IMMUNOGLOBULIN CONCENTRATIONS IN NEONATES AND INFANTS

The basic cellular elements of the immune system, including sIg-bearing B cells, are well-established by 15 weeks' gestation. Nevertheless, serum immunoglobulin concentrations remain very low (below 100 mg/dL) until 18 to 20 weeks of gestation. Most of the newborn's serum immunoglobulins are derived from the transfer of maternal IgG across the placenta during the third trimester of pregnancy.²¹ There may be a preferential active transport of IgG1 and IgG3 across the placenta because of a higher affinity of the Fc receptors on trophoblasts for these IgG subclasses.^{13, 25, 37} As a consequence, serum IgG levels at birth are equal or slightly higher than maternal serum IgG levels.²¹ Accordingly, premature infants have lower IgG concentrations. In fact, premature infants of 30 to 32 weeks' gestation have cord IgG concentrations of only approximately 400 mg/dL.¹⁸ SGA neonates may have somewhat lower IgG levels than full-term neonates, reflecting possible impaired placental transport.^{13, 31}

After birth the levels of maternally derived IgG decline rapidly and reach their lowest point of approximately 400 mg/dL at 3 to 6 months. At the same time, the infant's own production of IgG is not fully developed. This sequence of events is generally accepted as representing normal "physiologic" hypogammaglobulinemia. This phenomenon is more pronounced in premature infants, as they have proportionally lower IgG levels at birth and values reach an even lower nadir at 3 months of age. Ballow et al⁴ reported concentrations of 60 mg/dL and 100 mg/dL at 3 months of age in premature infants born at 25 to 28 and 29 to 30 weeks' gestation, respectively. Interestingly, most of these infants did not have a higher incidence of infections in spite of these very low IgG concentrations. By the age of 1 year, the total IgG concentration is approximately 60% of that of adults. There is also a different pattern of progression in the synthesis of the Ig subclasses after birth. IgG1 and IgG3 reach adult concentration earlier than IgG2 and IgG4, at 8 and 10 to 12 years of age, respectively.²⁷

IgA, IgM, IgD, and IgE are not placentally transferred under normal circumstances. In fact, the presence of elevated levels of IgM or IgA in cord blood suggests intrauterine infection.³ In normal infants, IgM concentration rises rapidly for the first month after birth, presumably in response to the massive antigenic stimulation of the new environment, and then more gradually up to 60% of adults' level by the age of 1 year. Serum IgA levels rise slower than IgM, up to values of only 20% of those of adults by 1 year of age and then continues to rise progressively throughout adolescence.⁴⁰

DEFINITION

THI has been classically defined as an accentuation and prolongation of the "physiologic" hypogammaglobulinemia of infancy normally observed during the first 3 to 6 months of life. Nevertheless, the criteria for the diagnosis are not well standardized. The World Health Organization (WHO) in 1992⁴¹ included both diminished IgG and IgA in defining criteria, whereas the latest published report²⁸ stated that "one or more classes of Ig may be very low—within an immunodeficient range." Most of the reports used low IgG levels as a mandatory inclusion criterion, whereas others have used other Ig isotypes, such as low IgA.²⁴ The fact that IgA levels reach only 20% of adult values at 1 year of age together with the high variability in the normal range of IgA⁴⁰ levels make it an unreliable determinant for diagnosis of THI. Although most of the published studies^{10, 12, 24, 36} require that the concentration of at least one class of Ig be more than two standard deviations (SD) below the mean for age-matched controls, others have used three SD for definition.³² In our practice we have used a definition based on IgG levels that fall at least two SD below the mean for aged-matched controls as an invariant criteria with or without diminished values of other immunoglobulin isotypes.

INCIDENCE

The precise frequency of THI remains undetermined. Tiller and Buckley³⁶ reported that only 11 cases of THI were identified among more than 10,000 patients whose sera were sent for Ig measurements, suggesting that THI is not a common entity. Dressler et al¹² supported this assumption by finding only five new cases in more than 8000 samples over a period of 11 years.

Walker et al³⁹ reported 15 patients with proven THI and another 25 patients with possible THI out of 2468 referrals over a 10-year period. This shows an incidence of 23 or 61 per 10⁶ live births, respectively.³⁹ An overview of a nationwide survey on primary immunodeficiency in Japan indicated that 18.5% of patients were diagnosed as having THI.¹⁷

From the 1632 infants and children who were referred to the immunology clinic at the Hospital for Sick Children, Toronto, Canada, between 1985 and 1995, 35 were diagnosed as having THI.¹⁰ These patients were referred to our clinic because of recurrent infections, and therefore, they may not represent the true frequency of this condition; however, because all referrals of cases with significant recurrent infections in our region are channeled to our clinic, it is reasonable to assume that we captured most symptomatic cases of THI.

The disparity of THI incidence among various centers can be best explained by the lack of strict criteria for the diagnosis of this disorder.

CAUSES

The cause of THI remains unknown in spite of numerous pathogenic mechanisms that have been proposed. Fudenberg and Fudenberg¹⁵ demonstrated that gamma globulin (Gm) antigenic determinants present on human fetal IgG molecules, but not in the mother, can induce the synthesis of maternal IgG anti-Gm antibodies during pregnancy. They concluded that such alloantibodies might cross the placenta and cause transient suppression of fetal immunoglobulin production. A prospective study on this issue, however, did not support this hypothesis.²⁶ Another theory was suggested by Soothill³⁵ after his finding of THI in relatives of patients with a variety of ID disorders. He suggested that THI is a manifestation of genetic heterozygosity for some other ID diseases. Although this remains a possibility, an example of such a trend has not been found so far. In 1981, Siegel et al³² proposed that a defect in helper-T-cell maturation could be the basis of THI. This conclusion was supported by a finding of normal B-cell number and function together with numerical and functional deficiency in CD4+ T helper cells. Moreover, they demonstrated that this defect was transient, as patients who had recovered from THI normalized CD4+ T-cell number and function. Unfortunately, this observation has not been supported by many other studies conducted since.^{10, 12, 23, 29}

More recent work suggested a role for cytokines in the pathogenesis of THI. Kowalczyk and coworkers²³ demonstrated an enhanced production of tumor necrosis factor (TNF)- α , TNF- β , and IL-10 in THI patients, whereas secretion of other cytokines, such as IL-1, IL-4, and IL-6, was essentially similar to controls. They also demonstrated that exogenously added TNF- α and TNF- β inhibited IgG and IgA secretion by pokeweed mitogen-stimulated mononuclear cells. Moreover, normalization of serum IgG levels in THI patients was associated with a decrease in TNF- α and TNF- β production, but IL-10 production remained unchanged. They concluded that TNF may be involved in the regulation of IgG and IgA production and the balance between TNF production (suppressing IgG synthesis) and IL-10 (inducing IgG switch) may be important for the normal development of IgG-secreting B cells. More studies are definitely needed to confirm or dispute this hypothesis.

CLINICAL MANIFESTATIONS

THI has been described in two distinct groups of infants based on the circumstances in which a diagnosis was obtained. The first group consisted of relatives of patients with other well-defined ID diseases. Most appear to be in good health with no history of recurrent infection, and diagnosis was reached only because they were screened for Ig concentrations. These patients normalized their Ig levels and clinically remained asymptomatic.^{35, 36} The significance of this finding remains unknown. In contrast, the second group consisted of infants whose Ig measurement was determined because of recurrent infections starting

early in life. The spectrum of severity and type of infections varied from otitis media and bronchitis to life-threatening invasive infections such as bacterial meningitis.⁴⁰ The initial indication for immunologic evaluation in our patients¹⁰ was recurrent upper respiratory infections, with or without ear infections, in 17 patients (49%). Of these, 8 patients (23%) also had at least one episode of pneumonia or sinusitis. Three patients (8%) presented with upper respiratory infection and recurrent gastroenteritis. Other indications included severe varicella (2), prolonged oral thrush (2), polioliike disease (1), and invasive infection (bacteremia with cellulitis and meningitis) (2).

In most series, including ours, atopic diseases have not been a prominent feature^{10, 36}, but Fineman et al¹⁴ described four infants with THI, increased IgE concentration, and food allergy. Recently, Walker et al³⁹ reported that 12 out of 15 patients with THI had symptoms of either atopic disease or food allergy/intolerance.

Another manifestation observed infrequently is hematologic abnormalities. Transient neutropenia has been observed in a few cases.³⁶ In our series, we reported two patients with transient neutropenia and thrombocytopenia, one patient with persistent neutropenia (absolute neutrophils less than $0.5 \times 10^9/L$), and one patient who developed acute lymphoblastic leukemia (ALL).¹⁰ It is tempting to speculate that the same immune dysregulation in this patient accounts for both THI and ALL, although it could be a coincidence.

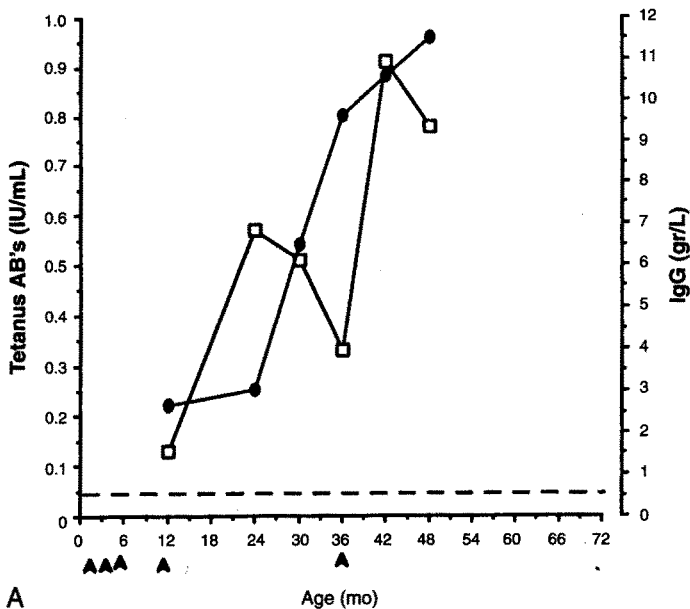
Most of the reported patients with THI had normal or near normal antibody responses to immunization with tetanus and diphtheria toxoids, sometimes well before Ig levels became normal. They also had isohemagglutinin values within normal range for age-matched controls.^{29, 36} Cano et al⁸ demonstrated that 11 of 12 THI patients studied before the age of 17 months had made no specific antibodies to a panel of respiratory viruses despite recurrent upper respiratory infections. Resolution of the THI was marked by the appearance of specific viral antibodies, even before the serum IgG increased to normal levels.⁸ Unfortunately, data regarding specific antibodies to immunizations or isohemagglutinins are missing in that report.

In our series,¹⁰ the ability to maintain protective levels of antibodies is as important as achieving the initial adequate response. Some of our patients showed an abnormal pattern in which they had substantial but unsustained response to reimmunization despite normalizing total Ig concentrations. This type of dysgammaglobulinemia can be easily missed unless multiple determinations are obtained over a period of years.

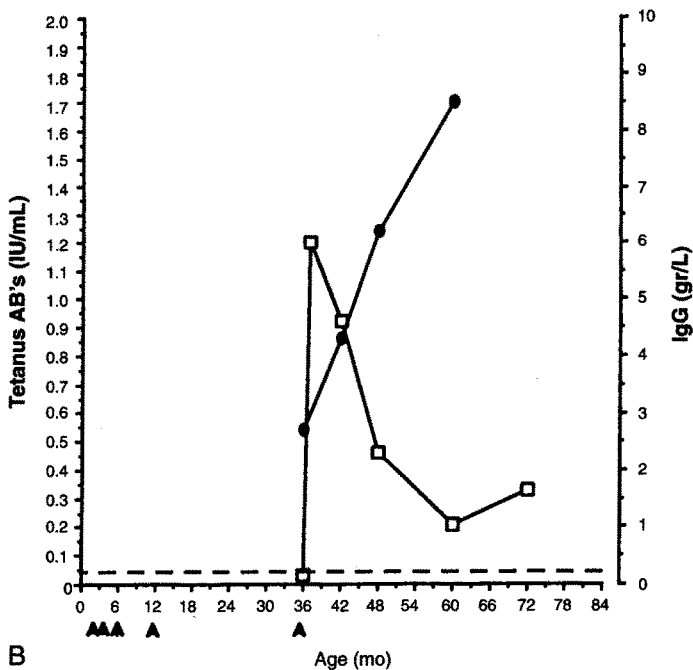
Lymphocyte subpopulations, as well as cellular immunity measured by proliferation assay in response to mitogens or specific antigen stimulation, were intact in most of the studies, including ours.

DIFFERENTIAL DIAGNOSIS

By definition, THI is a self-limited disorder. Unfortunately, this diagnosis cannot be made with confidence until after a full laboratory

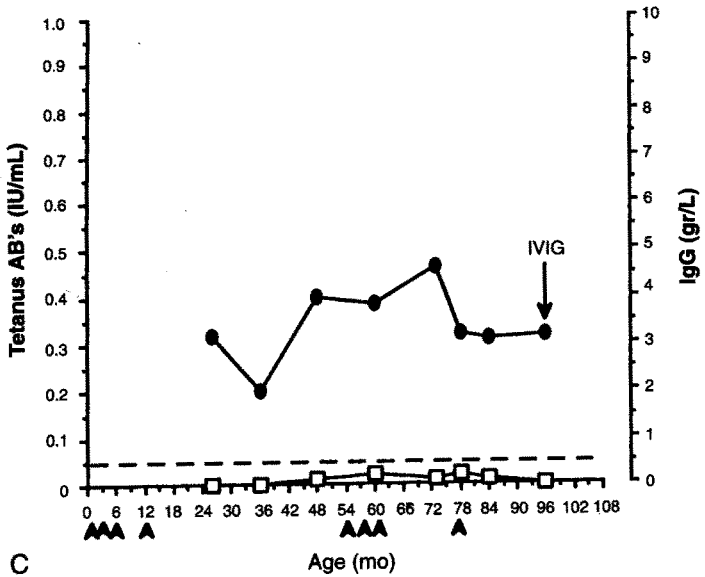


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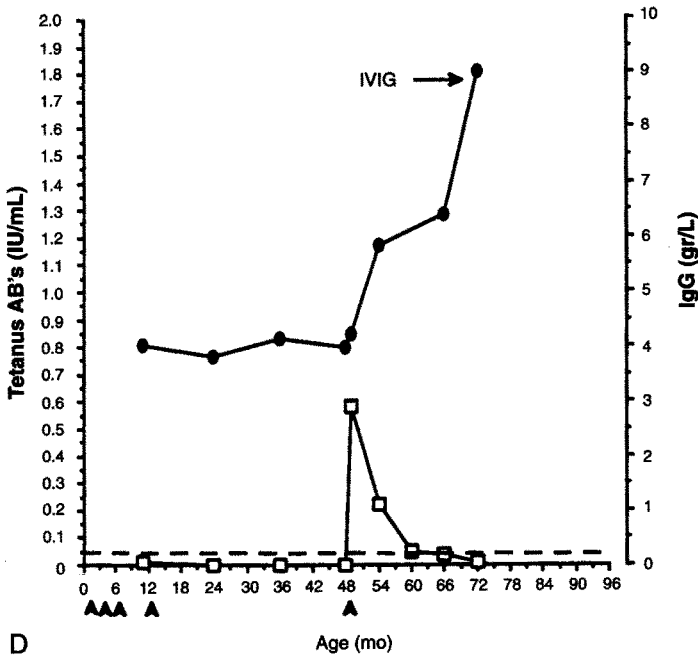


B

Figure 1. Time course of serum tetanus toxoid antibodies (*square*) and IgG levels (*circle*) in four patients demonstrating various patterns in the evolution of specific antibody and IgG levels. Arrowheads represent immunization with tetanus and diphtheria toxoid, poliovirus, and *Bordetella pertussis*. The area above the dashed line indicates normal levels of tetanus toxoid antibodies (≥ 0.05 IU/mL). A normal pattern is shown in which the ability to mount sustained specific antibody response precedes the normalization of total IgG levels (A) and parallels the normalization of serum IgG levels (B).



C



D

Figure 1 (Continued). An abnormal pattern in which the patient failed to make specific antibodies after reimmunization and remained hypogammaglobulinemic (C). An abnormal pattern in which the patient had substantial but unsustained response to reimmunization with a slow rise in total IgG to normal levels (D). IVIG = intravenous immunoglobulin; ABs = antibodies.

and clinical recovery. Therefore, during this period, every effort should be made to differentiate THI from other primary IDs that could present in a similar manner such as X-linked agammaglobulinemia (XLA) or common variable immunodeficiency (CVID). Typically, XLA can be easily differentiated from THI. The former is characterized by severe deficiency of all Ig isotypes, inability to produce antibodies, absence of normal peripheral lymphoid tissues, absence or a very low number of circulating B lymphocytes, and severe pyogenic infections starting in the first to second year of life.^{7, 19} Since the discovery that XLA is caused by mutations in *BTK*,³⁸ there have been increasing reports of patients who have atypical clinical and laboratory features that make the distinction between THI and XLA difficult to ascertain,²² underscoring the need for molecular screening of all patients with hypogammaglobulinemia for possible mutations in *BTK*.

CVID, the most frequent type of hypogammaglobulinemia, is usually diagnosed in the second to third decade of life. Typically these patients are unable to produce protective levels of specific antibodies with variable immunoglobulin concentrations, with most having some impairment in cellular immunity.^{7, 19} In contrast, almost invariably, THI patients showed intact humoral and cellular immune function and normal antibody response.

In conclusion, THI is a diagnosis of exclusion that should be established in retrospect only after a long-term follow-up with thorough investigation of serial clinical and laboratory parameters.

OUTCOME

Although THI has been long recognized, little was known about the long-term outcome of these patients until our recent study.¹⁰

Previous studies predicted spontaneous clinical recovery by 9 to 15 months of age, and a rise to normal immunoglobulin levels by 2 to 4 years age^{30, 40}; however, by studying a limited number of patients, a few reports have shown that low IgA levels may persist beyond infancy up to the age of 5 years.^{5, 24, 36}

In a prospective study,¹⁰ we followed the evolution of hypogammaglobulinemia since infancy. Specific antibody titers and clinical manifestations were recorded in 35 patients for 10 years. In all patients, the indication for immune evaluation was recurrent infections. The results clearly distinguish three different patterns of evolution. The first and most common pattern includes patients who experienced fewer infections as they grew older, and eventually had normal total serum immunoglobulin levels, IgG subclass distribution, and specific antibody production. Some of these patients initially had low levels of specific antibodies but responded normally to reimmunization and were able to sustain these values. This process may span a decade and may include a transient phase whereby IgG subclasses may gradually normalize (group I, *n* = 29, Fig. 1A and 1B).

The second group consisted of patients who continued to suffer repeated infections and whose IgG levels remained low and who were unable to mount significant antibody titers despite reimmunization. These patients subsequently required permanent IVIG replacement therapy. Such patients can be classified as CVID in spite of the unusual presentation early in infancy (group II, $n = 3$, Fig. 1C).

The third pattern included patients who normalized their serum IgG levels but continued to experience significant infections. Upon reimmunization, they had a satisfactory but short-lived (declined within 1 year) response, despite having "normal" IgG levels. This group of patients therefore can be classified as dysgammaglobulinemia (group III, $n = 3$, Fig. 1D).

Although it is impossible to predict at presentation the pattern patients will follow, invasive infections and low antibody levels at presentation appear to significantly predict ultimate permanent antibody deficiency.¹⁰

TREATMENT

Symptomatic patients with repeated bacterial infections frequently benefit from prophylactic antibiotic treatment. Rarely temporary replacement therapy with IVIG is administered.^{8, 10, 40}

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