Impaired specific antibody response and increased B-cell population in transient hypogammaglobulinemia of infancy

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Background: Transient hypogammaglobulinemia of infancy (THI) is a heterogeneous disorder with poorly understood pathophysiology.

Objectives: To better characterize THI and improve understanding of its pathophysiology.

Methods: Twenty-four children with hypogammaglobulinemia defined by an IgG level less than 2 SDs below the mean on 2 occasions, who did not have other immunologic diagnoses, were followed and retrospectively reviewed.

Results: The average z-score for IgG level at presentation was −2.4 (mean age, 12 months; median age, 8 months), with a mean level of 254 mg/dL. Thirteen of 24 patients had IgA levels less than 2 SDs below the mean, 5 had IgM levels less than 2 SDs below the mean, and 7 of 23 had elevated IgE levels. Eighteen were followed up until their IgG levels normalized (mean age, 27 months; median age, 23 months), with 12 of 18 normalizing by 24 months and the remainder by 59 months. There was a significant association between presenting IgG z-score and duration of disease ($P = .05$). Five of the 18 patients had absolute $CD19^+$ B-cell counts greater than the 95% percentile for age ($P < .001$), and the mean percentage and absolute $CD19^+$ B-cell count across all patients were greater than those of the age-matched controls ($P = .02$). Most patients had nonprotective titers to *Haemophilus influenzae* type b vaccine, and one third had nonprotective titers to tetanus vaccine. Twenty patients carried at least one atopic diagnosis, and 13 of those had recurrent wheezing.

Conclusions: THI is associated with a number of immunologic abnormalities beyond just hypogammaglobulinemia. These abnormalities include impaired specific antibody responses and increased proportions of $CD19^+$ B cells and may be suggestive of particular immunologic mechanisms that result in hypogammaglobulinemia.

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INTRODUCTION

In transient hypogammaglobulinemia of infancy (THI) the propensity for infection is presumably related to a low IgG level, and it is generally believed that specific antibody production remains intact. However, the observation of incidental hypogammaglobulinemia in healthy individuals does not support hypogammaglobulinemia as the sole cause of recurrent infection. Absent virus-specific antibodies, despite recurrent viral infection, have been described in THI.[1] Additional studies report the inability of some THI patients to sustain vaccine-specific antibody responses.[2] The increased frequency of infection seen in THI patients suggests that impairment of vaccine responses could be more consistent than currently recognized.

The physiologic nadir in serum IgG levels occurs normally at 6 months of age, when the infant's endogenous production of IgG just begins to exceed the rate of consumption of maternally transferred IgG. Persistence of hypogammaglobulinemia beyond infancy is a primary immunodeficiency described as THI. This appears to be a heterogeneous disorder, often extending beyond infancy and into early childhood.[3] It has been defined in a number of ways but most rigorously as the depression of an immunoglobulin class more than 2 SDs below the mean for age on at least 2 separate specimens that show a trend toward normalcy in a child who otherwise lacks known immunodeficiency.[4] The incidence of THI has been estimated at anywhere from 1.1 per 1,000[4] to 0.061 per 1,000 live births.[5] Affected children can be asymptomatic but are believed to have a propensity toward recurrent infections, most frequently including those of the upper respiratory tract.[6] This predisposition is presumably a feature of their low immunoglobulin levels. In addition, atopic comorbidities have been reported at an increased prevalence in certain series. Two reports have proposed a greater prevalence of atopy than would be expected in the general population,[5,7] but other authors have identified these diseases with a prevalence expected or less than that expected in otherwise healthy children.[6] Other comorbidities have not been definitively recorded.

A number of immunologic causes have been proposed for THI, including a qualitative and quantitative deficiency of $CD4^+$ T cells[8] and defective and aberrant cytokine production.[9,10] An enhanced production of tumor necrosis factor α, tumor necrosis factor β, and interleukin-10 has been observed in THI, whereas secretion of interleukin-4 and interleukin-6 was essentially the same as controls.[10] Despite these insights,

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the underlying basis for THI is poorly understood. It has been postulated that the population of children with THI represents a group of distinct immunologic defects that have a common clinical phenotype.[2] Given the paucity of proposed mechanisms for THI, we longitudinally monitored laboratory characteristics, clinical course, and duration of hypogammaglobulinemia in patients with THI to better characterize this disease and improve our understanding of its pathophysiology.

MATERIALS AND METHODS

Patients

This study was a retrospective review of 24 patients identified through the Children's Hospital Boston outpatient immunology program during a 4-year period who were followed up longitudinally. Those patients who were included in the study met the following criteria: (1) serum concentrations of IgG below 2 SDs for age on 2 or more independent consecutive specimens drawn at least 2 months apart, (2) analyses of subsequent serum samples showing a clear rise in these values to or toward normal, and (3) absence of any other immunologic diagnosis. These criteria are similar to and derived from previous studies.[1,2,8,10] They are more stringent than the criteria used in some reports,[3,4,6] however, because patients who had a normal IgG level but an IgA or IgM level that fell below 2 SDs for age were not included. Resolution of THI was defined by clinical improvement and 2 samples consistent with normalized age-specific IgG levels or rising levels demonstrating a clear trend toward normalization.

Children were referred for evaluation because of recurrent infection or the incidental discovery of hypogammaglobulinemia. Patients were evaluated clinically, and histories of atopic diseases, including asthma or wheezing, allergic rhinitis, urticaria, atopic dermatitis, and food allergies, were obtained. Food allergy was defined by a ImmunoCAP specific IgE value of greater than 0.35 kU/L to foods that correlated with histories of clinical allergy on exposure. Skin prick testing was conducted by 1 of 2 skin testing technicians. A positive response was regarded as surrounding erythema and wheal more than 3 mm greater than the negative control. In addition, developmental history and any other major medical histories were noted. During the period of observation for hypogammaglobulinemia, most patients received prophylactic antibiotics (19 of 24), with 4 of those patients subsequently receiving gammaglobulin infusions because of recurrent infection. One patient received gammaglobulin infusions without initial antibiotic prophylactic therapy because of very low IgG levels and severe infection. Analysis of patients was performed with the informed consent of parents and with the permission of the Children's Hospital Committee for Clinical Investigation.

Immunologic Studies

Serum concentrations of IgG, IgA, IgM, and IgE were measured by nephelometry, and reference ranges were from Behring Nephelometer product literature. Specific antibody responses to tetanus, *Haemophilus influenzae* type b (Hib), and pneumococcal conjugate vaccine (PCV7) were determined by measuring antibody titers against tetanus toxoid, Hib polyribosylribitol phosphate, and 6 pneumococcal polysaccharides, respectively. The initial specific antibody titers were performed at the time of evaluation irrespective of the number of vaccinations previously received. If titers were low, reimmunization was recommended. If adequately protective, titers were rechecked again at the time of normalization of serum IgG to ensure the presence of memory. Responses were compared with laboratory reference values for protective titers. Complete blood cell counts with differential analysis were obtained along with flow cytometric enumeration of $CD4^+$ T-cell, $CD8^+$ T-cell, and $CD19^+$ B-cell subsets to determine the relative percentage and absolute numbers of these cell populations. Results obtained were compared with published age-specific reference values.[11] All studies were performed in Clinical Laboratory Improvement Act–certified laboratories using standard techniques. Lymphocyte mitogen-induced proliferative capacity was evaluated using phytohemagglutinin, concanavalin A, and pokeweed mitogen. This information was not available in a fraction of patients, reflecting either inadequate blood sampling or the family's wishes to decline testing. Antigen-induced proliferative capacity was evaluated using tetanus antigen and diphtheria antigen when clinical concern for a potential cellular deficit was present. Assays were performed as described, and results obtained were compared with laboratory control ranges.[12]

Statistical Analysis

Using SPSS statistical software, version 8.0 (SPSS Inc, Chicago, IL), we compared the median lymphocyte subset distributions in patients with age-matched controls using the 2-sided *t* test. *t* tests were also conducted on IgG levels and individual covariates, such as presence or absence of atopic dermatitis, wheezing, food allergy, elevated IgE level, low IgA, low IgM, and lack of protective specific antibody titer. Regression analysis was conducted on $CD19^+$ B cells and IgG levels, $CD19^+$ B cells and duration of disease, and IgG levels and duration of disease.

RESULTS

Patient Characteristics and Immunoglobulin Levels

Retrospective review of patients who were followed up longitudinally through our outpatient immunology clinic revealed 24 patients who ultimately fulfilled criteria for a diagnosis of THI. Thirteen patients were male, 11 were female, and all were white. The reason for referral to our program was either serious or recurrent infection or the incidental discovery of low IgG levels. The mean age at which the patients were diagnosed as having hypogammaglobulinemia was 12 months (range, 1–38 months; median age, 8 months). The mean IgG level at presentation was 254 mg/dL (z-score = −2.4) (median level of 247 mg/dL). Although all patients fulfilled diagnostic criteria for THI, the mean age at which the IgG levels rose above 2 SDs below the mean for age was 27 months (median age, 23 months). Twelve patients' (50%) IgG levels rose above 2 SDs below the mean for age by 24 months; 6 patients (25%) achieved this level by 60

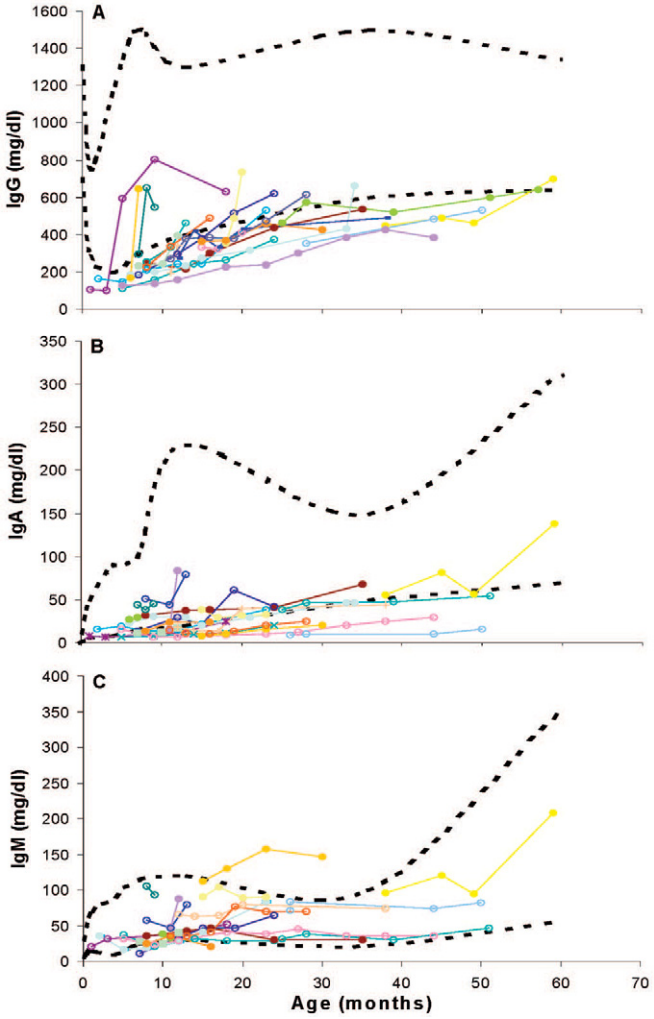

Figure 1. Longitudinal measurement of immunoglobulin levels in patients with transient hypogammaglobulinemia of infancy. Serum IgG (A), IgA (B), and IgM (C) levels were measured at presentation and thereafter at intervals dictated by the patient's clinical management. The values for each individual patient are depicted with either a unique color or an open or closed circle. The longitudinal values for an individual patent are connected with a solid line to highlight any trend. The 5th and 95th percentiles for age for each immunoglobulin are approximated by the dashed lines.

months and 6 patients (25%) failed to achieve normalization by 5 years but had demonstrated longitudinally upward trending IgG levels (Fig 1A). Thirteen (54%) of 24 patients had IgA levels less than 2 SDs below the age-related mean, 5 (20%) of 24 had IgM levels less than 2 SDs below the mean, and 7 (30%) of 23 had IgE levels greater than 2 SDs above the mean for age. In general the IgM and IgA levels trended upward over time, with all patients having an IgM and all but 4 patients having an IgA that ultimately fell within the normal range for age (Fig 1B-C). None of the patients had complete IgA deficiency, but 1 patient clearly had persistently abnormally low IgA levels. A significant predictor of the duration of hypogammaglobulinemia was the IgG level at initial presentation. Although no cutoff levels were established that would correspond to disease duration, patients with lower presenting IgG z-scores remained hypogammaglobulinemic for longer periods ($P = .05$) (Fig 2). Aside from 1 patient who had a history of meningitis, none of the patients had at presentation or subsequently developed serious infections, including sepsis, osteomyelitis, or meningitis. Most patients had recurrent sinopulmonary infections, with 1 patient presenting with periorbital cellulitis. Nineteen (79%) of 24 patients received prophylactic antibiotics, with 4 (21%) of those patients subsequently receiving gammaglobulin infusions due to recurrent infection. One patient received gammaglobulin infusions without initial antibiotic prophylactic therapy due to very low IgG levels and severe infection. There was no association with likelihood of subsequently receiving gammaglobulin and lower presenting IgG levels. In total, 5 (21%) of the 24 patients received intravenous gammaglobulin infusions.

Comorbid Characteristics

A number of comorbidities were noted either at presentation or to have developed during the period of hypogammaglobulinemia. Most patients had some form of atopy, with rhinitis in 10 patients (42%), food allergy in 9 patients (38%), atopic dermatitis in 6 patients (25%), and urticaria in 4 patients (17%). A history of recurrent wheezing consistent with a diagnosis of asthma was common, occurring in 13 patients (54%). Six of 9 patients evaluated for the presence of food antigen specific IgE had detectable amounts to either egg or milk by ImmunoCap assay or percutaneous testing. This represents 67% of the subpopulation clinically suspected to have reactivity and 25% of the cohort overall. Because many patients were relatively young, aeroallergen skin prick testing was less consistently evaluated. Other recurrent patterns noted in greater than 10% of the population included 4 patients (17%) with some degree of developmental delay requiring at least early intervention services as recommended by their pediatrician or developmental pediatrician and 3 patients with congenital heart disease (13%), all of whom had

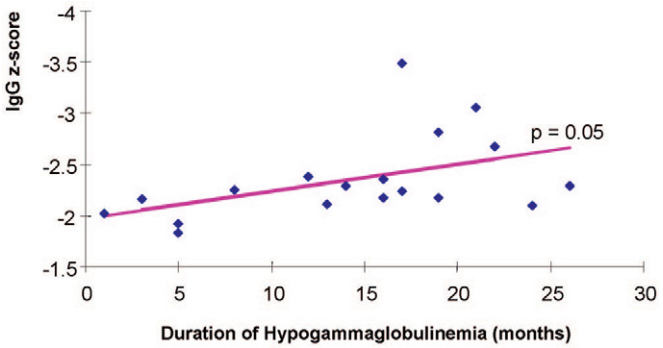

Figure 2. Correlation between IgG level at presentation of transient hypogammaglobulinemia of infancy and duration of hypogammaglobulinemia. For each patient, the z-score of the IgG level at presentation was plotted on the y-axis against the duration of hypogammaglobulinemia on the x-axis.

Table 1. Specific Antibody Titers at Diagnosis and Resolution

	Titer, median (range)	No. (%) of patients with protective titers*
Diagnosis		
Tetanus	0.195 (0.02–0.68) IU/mL	12/18 (67)
Hib	421.5 (110–5,063) ng/mL	3/18 (17)
Pneumococcal 14†	9.438 (0.843–37.119) μg/mL	14/15 (93)
Pneumococcal 19F†	5.865 (0.625–81.25) μg/mL	13/15 (87)
Pneumococcal 23F†	3.281 (0.625–26.081) μg/mL	13/15 (87)
Pneumococcal 6B†	1.838 (0.625–50.581) μg/mL	9/15 (60)
Pneumococcal 3	0.875 (0.312–7.088) μg/mL	4/15 (27)
Pneumococcal 7F	0.688 (0.625–7.069) μg/mL	4/15 (27)
Resolution		
Tetanus	0.870 (0.13–7.00) IU/mL	17/18 (94)
Hib	4,880 (355–9,000) ng/mL	14/18 (78)
Pneumococcal 14†	19.562 (2.225–211) μg/mL	15/15 (100)
Pneumococcal 19F†	8.869 (0.625–81.25) μg/mL	14/15 (93)
Pneumococcal 23F†	17.169 (0.793–134.313) μg/mL	13/15 (87)
Pneumococcal 6B†	12.062 (0.962–81.25) μg/mL	12/15 (80)
Pneumococcal 3	1.763 (0.625–92.062) μg/mL	9/15 (60)
Pneumococcal 7F	1.066 (0.625–31.313) μg/mL	6/15 (40)

Abbreviation: Hib, *Haemophilus influenzae* type b.

* Protective titers defined as tetanus more than 0.15 IU/mL, Hib more than 1,000 ng/mL, and pneumococcal vaccine of 1.3 μg/mL or more. Tetanus titer represents specific antibody against tetanus toxoid, and Hib titer is defined as specific antibody against the polyribosyl phosphate of *Haemophilus influenzae*.

† Serotype found in pneumococcal conjugate vaccine.

negative fluorescence in situ hybridization for microdeletion of chromosome 22q11.

Humoral Immunity

Table 1 represents patients who underwent 2-, 4-, and 6-month recommended primary immunization series. Twelve (66%) of 18 patients had a protective level of tetanus-specific antibody at presentation, which increased to 17 (94%) at resolution following further immunization (patients with nonprotective titers were therapeutically reimmunized out of sequence with the normal pediatric immunization schedule). The 1 patient without protective tetanus titers at resolution developed protective polyribosylribitol phosphate polysaccharide levels at resolution. Three (17%) of 18 had a protective Hib-specific antibody at presentation, increasing to 14 (78%) at resolution after reimmunization. Six pneumococcal serotypes were screened (4 of 6 serotypes screened are found in PCV7), and the median number of protective serotypes against which patients had protection (titer of $\geq$1.3 μg/mL) was 4 at presentation and increased to 5 at resolution (Table 1). At presentation all patients had protective levels of antibody directed against at least 1 pneumococcal serotype. Patients who received primary PCV7 series and booster and had protective titers in less than 2 PCV7 serotypes of the 4 serotypes measured received the 23-valent pneumococcal vaccine. PCV7 was given to patients younger than 2 years and those who did not complete the PCV7 series and booster. Three (20%) of 15 patients had protective tetanus, Hib, and at least 1 pneumococcal serotype. This number increased to 13 (87%) of 15 at resolution. All patients with protective Hib titers also had protective tetanus titers.

Cellular Immunity

Lymphocyte subset evaluations were performed in 75% of the patients at presentation, who ranged in age from 1 to 38 months (Fig 3). The total numbers of lymphocytes and $CD4^+$ and $CD8^+$ T-cell populations were not significantly different from age-matched controls. Five (28%) of 18 patients, however, had absolute $CD19^+$ B-cell counts greater than 95% for age. In this light, the mean $\pm$ SD percentage (29 $\pm$ 8) and absolute counts (1,891 $\pm$ 1,210) of $CD19^+$ B cells was greater than expected for age-matched controls ($P < .001$ and $P = .02$, respectively). Some patients had repeat lymphocyte enumeration studies that revealed persistently elevated $CD19^+$ B-cell counts closer to the time of resolution. B-cell populations were not studied in follow-up after resolution; thus, we are unable to determine how long the elevations persist. There was no significant correlation between $CD19^+$ B cells and IgG z-score at presentation. Lymphocyte mitogen-induced proliferative capacity to phytohemagglutinin, concanavalin A, and pokeweed mitogen was within laboratory control ranges for the 7 of 24 patients who were studied. Similarly, lymphocyte antigen-induced proliferative capacity to tetanus and diphtheria antigen was within laboratory control ranges for the 6 patients studied (data not shown).

CONCLUSIONS

We describe a series of 24 patients with a diagnosis of THI. In particular, all patients had serum IgG concentrations less than 2 SDs below the mean for age on 2 occasions and had no other clear pattern of immunologic abnormality. The mean age of diagnosis was 12 months, with resolution at 27

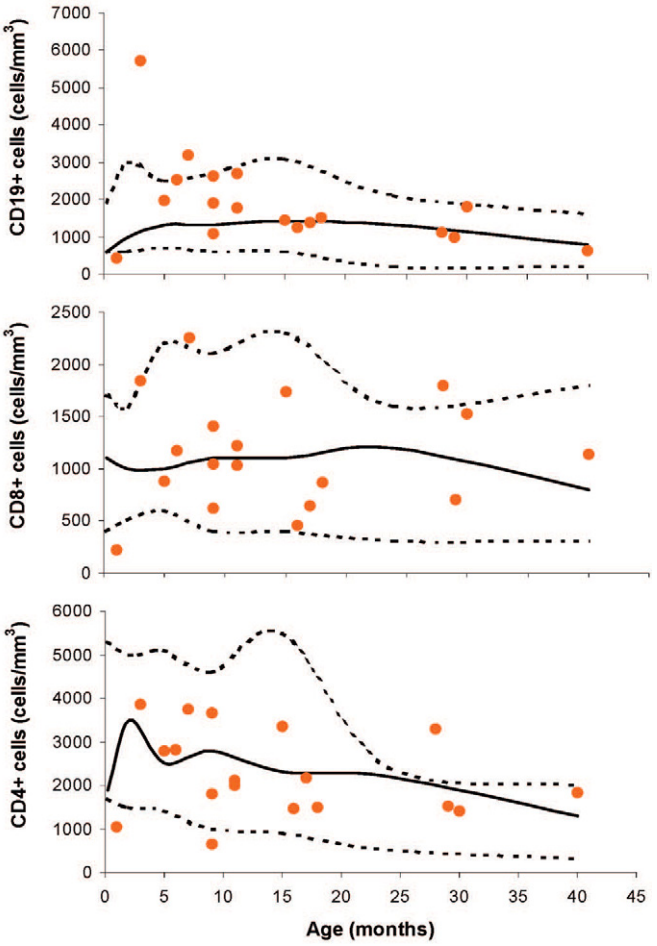

Figure 3. Absolute lymphocyte populations in patients with transient hypogammaglobulinemia of infancy at presentation. The absolute numbers of $CD19^+$ B cells (top), $CD8^+$ T cells (middle), and $CD4^+$ T cells (bottom) at presentation were plotted on the y-axis against the patient's age on the x-axis. Each point represents the presenting value from an individual patient. The solid line approximates the age-specific mean value and the dashed lines approximate the 5th and 95th percentiles. Only the $CD19^+$ B-cell counts in aggregate were significantly different from the age-specific mean ($P = .02$).

months. Half of the patients resolved by 24 months, one quarter by 60 months, and one quarter past 60 months. The duration of this disease indicates that it affects patients beyond infancy and into early childhood. A significant correlation was seen with duration of disease and IgG z-score values, such that longer duration was associated with lower presenting IgG z-scores ($P = .05$).

Deficiency in more than 1 immunoglobulin isotype is a common finding in THI.[2,3,5] Most patients in this cohort had other immunoglobulin levels less than 2 SDs below the mean, with more than half presenting with low IgA levels and roughly one fifth presenting with low IgM levels. This finding strengthens the earlier studies and thus suggests that THI does not represent an aberration of class switching from IgM to IgG and IgA.

Collectively, several novel conclusions can be derived from our group of patients. First, the mean $CD19^+$ B-cell percentages and absolute numbers were significantly higher in patients than age-matched controls. The $CD8^+$ T-cell and $CD4^+$ T-cell percentages and absolute numbers, in contrast, were similar to age-matched controls. Although other reports of THI of infancy have described low $CD4^+$ T-cell populations, we did not find evidence of quantitative T-cell abnormalities in this study.[8] The elevation in $CD19^+$ B cells, however, may provide some insight regarding the pathophysiology of this disease. The elevation of these cells in the circulation could reflect an alteration in the balance between tissues and fluid compartments as a result of changes in homing or recirculation. Another proposed explanation is that there is a lack of an adequate IgG level to provide negative feedback inhibition for $CD19^+$ B-cell proliferation, perhaps through a B-cell inhibitory IgG receptor such as CD32. However, this expansion could also result from an inherent B-cell defect that affects these types of regulatory systems, which may be particularly prominent in childhood. Therefore, future study in this disease might be directed at evaluating B-cell phenotype, apoptosis, and IgG production per B cell. Alternatively an aberrant signal provided from the $CD4^+$ T cells to the B cells, as previously demonstrated,[8] may result in their atypical expansion.

Second, we have identified an unusual pattern of impaired specific antibody responses in our patients. Although previous reports describe intact specific antibody production,[3,4,13] a single study has described absent specific viral antibody production.[1] One group that evaluated 32 patients, however, found that low tetanus antibodies at presentation were associated with increased morbidity.[2] We found more pervasively impaired specific antibody production in our population of patients during the period of hypogammaglobulinemia. At the time of diagnosis, 18 of the 24 patients had undergone full primary immunization series, with 4 patients having received boosters, yet only 67% had protective tetanus titer present. Tetanus titer after full primary immunizations has been described as adequately protective in greater than 85% of healthy patients up until a booster is received.[14,15] Resolution of THI, however, appears to be associated with evidence of protective tetanus titer (94% of patients), demonstrating that any defect in specific antibody production was only temporary. Importantly, the initial responses to Hib and PCV7 were even less robust than that to tetanus and highlight the relatively impaired antibody response against protein antigens in children with THI during the hypogammaglobulinemic period. Although at least some specific antibody was found uniformly in our patients, the gaps in vaccine-specific antibodies were surprising and might explain the susceptibility to bacterial infection found in patients with THI.[1,3,4,6] This feature might suggest the utility of prophylactic therapies such as antibiotics or even immunoglobulin replacement in selected patients. We have used this finding to justify the use of prophylactic antibiotics in our patients. Furthermore, these gaps in the vaccine-specific antibody repertoire raise the question of whether repeated immunization may be useful in

generating protective antibody titers in patients with THI to improve their defense against vaccine preventable infections, most notably those caused by pneumococcus. Ultimately, the transient defect in protein-specific antibody responses is likely to provide insight into the immunological mechanism underlying this condition.

Finally we have confirmed and extended the associations made between THI and other disorders. A large number of patients in our series had a diagnosis of atopic disease. Although this might represent some selection bias, this conclusion is supported by other authors.[1,4–6] We found the prevalence of asthma to be 10-fold greater (54%) in this disease cohort than the general population.[16] Additional comorbid conditions not previously described include increased prevalence (17%) of a diagnosis of developmental delay of varied degree, as well as 13% with congenital heart disease.

In conclusion, we believe that THI represents a distinct immunologic entity that may result from an intrinsic defect that affects B-cell regulation. Future study focused on B-cell development and function is likely to be fruitful. Most importantly, our data suggest that although children with THI largely achieve immunologic normalcy, they have specific deficits that may benefit from therapeutic intervention and thus should not be ignored. Finally, the associated comorbidities in this population warrant consideration of early monitoring, because they hold the potential to improve both the short- and long-term prognosis for patients with THI.

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