Transient hypogammaglobulinemia of infancy and early childhood: outcome of 30 cases

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Transient hypogammaglobulinemia of infancy (THI) is characterized by an abnormal delay in the onset of immunoglobulin synthesis. In the present study, clinical and immunological data and outcome of 30 patients with THI are presented. Between 1995-2001, 464 patients with frequent upper and lower airway infections admitted to the Pediatric Immunology and Allergy outpatient clinic; 30 of them (aged between 6-46 months) were diagnosed as THI. Patients had periodic evaluations at 3-6 month intervals until their condition had improved clinically and immunoglobulins had normalized. In 21 patients immunoglobulin levels reached normal age-matched levels at a median age of 27 months. In nine patients (aged 25-57 months) immunoglobulin levels were still under 2SD for age and various IgG subclass deficiencies were detected in five of them. The results of the present study indicated that THI is not a rare disease. Long-term follow-up with detailed clinical and laboratory evaluations is needed in these patients.

Key words: transient hypogammaglobulinemia of infancy, outcome, hypogammaglobulinemia.

Transient hypogammaglobulinemia of infancy (THI) is characterized by prolongation and accentuation of the "physiologic" hypogammaglobulinemia that is normally observed during the first three to six months of life[1]. The incidence and cause of this entity are uncertain and little is known about its natural history and clinical course[2,3]. Although spontaneous recovery occurs usually between two to four years of age, the immunoglobulin abnormalities have not always been found to be transient and were not necessarily limited to the period of infancy[4]. For that reason the certain diagnosis can be made only retrospectively, when normal immunoglobulin levels have been achieved. Several authors have suggested designating this entity as transient hypogammaglobulinemia of early childhood[3,4].

In the present study, clinical and immunological data and outcome of 30 patients with transient hypogammaglobulinemia are presented and compared to the published data.

Material and Methods

The study population consisted of 30 patients of 464 referrals to Ankara University, Department of Pediatric Immunology & Allergy outpatient clinic between 1995-2001 with the complaints of frequent upper and/or lower airway infection and who were diagnosed as transient hypogammaglobulinemia of early childhood according to the following criteria[3-5].

1. Patients less than four years of age at presentation.
2. Serum level of one or more of the major immunoglobulin subclasses 2SD below the mean for age according to the reference values.
3. Normal production of isohemagglutinins.
4. No clinical or laboratory evidence of cellular immunodeficiency or other immunodeficiency states.

None of the patients had a family history of immunodeficiency. Patients had been examined at presentation and had periodic evaluations at three to six month intervals until their condition had improved clinically and immunoglobulins had normalized. Evaluation included assessment of overall health status and laboratory tests, including imunoglobulins, isohemagglutinin titers (Anti A, Anti B, N: ≥1-10), peripheral blood lymphocyte subsets and lymphoproliferative response to phytohemagglutinin (PHA).

Immunological studies were carried out in the Pediatric Immunology-Allergy Research Laboratory of Ankara University. Serum IgG, IgA and IgM levels were measured by nephelometry and compared to age-matched serum immunoglobulin reference ranges of Turkish children[6]. Peripheral blood (PB) lymphocyte subsets were determined by double staining and using CD3-FITC/CD16+56– PE, CD 3– FITC/CD4–PE, CD3–FITC/CD8–PE, CD19–FITC monoclonal antibodies (Immunotech, Marseille, France) and flow cytometry (Coulter-EPICS-XL-MCL), Isohemagglutinin titer was determined according to the standard methods. In vitro lymphoproliferative response to PHA was determined as decribed previously[7].

Results

The mean age for the patient population at first visit to our clinic was 22.5 months (range: 6-46 months), median: 23 months. Fifteen of 30 patients were ≥24 months of age (12 between 24-36 months, 3 between 36-45 months). The male/female ratio was 2:1. The initial indication for immunologic evaluation was recurrent upper respiratory tract infections (n:28), pneumonia (n:8), recurrent otitis media (n:8) and recurrent gastroenteritis (n:4). Eleven of 30 patients had a history of obstructive airway disease with infection and were diagnosed as asthma according to the Pediatric Asthma Consensus Group Reports[8] (median age 24 months, range: 17-45 months). Three of 11 patients were found to be atopic (positive specific IgE levels and/or positive skin prick test to common inhaler allergens). Three of 30 patients had a history of eczema and one of 30 was diagnosed as allergic rhinoconjunctivitis (Table I).

Table I. Clinical Features of Patients

	Number of patients	%
Upper respiratory infections	28/30	93
Pneumonia	8/30	26
Otitis	8/30	26
Gastrointestinal infections	4/30	13
Asthma	11/30	36
Other allergic diseases (Atopic dermatitis, allergic rhinitis)	4/30	13

All 30 patients at initial evaluation demonstrated low serum IgG levels, 13 (43%) patients had decreased IgA levels and six (20%) patients had low IgM levels. All patients had normal isohemagglutinin levels. Peripheral blood lymphocyte subset analysis revealed normal CD3, CD4, CD8, CD19 and CD16+56 numbers according to age range of healthy Turkish children in all 20 children studied. Lymphoblastic transformation response to PHA was found to be normal in all children studied (n:16) (Table II).

Patients were followed up five to 28 months (median 12 months). In 21 patients immunoglobulin levels reached normal age-matched levels at a median age of 27 months

Table II. Immunologic Features of Patients

	Number of patients	%
Low IgG at presentation	30/30	100
Low IgA at presentation	13/30	43
Low IgM at presentation	6/30	20
Low IgG, IgA and IgM at presentation	3/30	10
Low IgG and IgA at presentation	11/30	36
Low IgG and IgM at presentation	3/30	10
	X±SD	X±SD
	Relative size (%)	Absolute count ($x10^9$/L)
CD3+ (%)	64.8±5.9	2.39±0.69
CD4+ (%)	38.8±7.0	1.42±0.37
CD8+ (%)	22.7±4.4	0.85±0.33
CD19+ (%)	21.1±5.3	0.80±0.39
CD16+56+ (%)	12.8±4.2	0.47±0.26
	Mean	Range
Lymphoblastic transformation response to PHA (%)	75	64-85

PHA: phytohemagglutinin.

(range: 18-66 months). Recovery was achieved in 16 of 21 patients before 36 months. The oldest patients in the study who were 42, 45 and 46 months of age at diagnosis were followed up 6,11 and 20 months, respectively, and except for the second, the others attained normal immunoglobulin levels. In nine patients (median age 46 months, range: 25-57 months), who have been under follow-up for a median of 16 months (range: 11-27 months), immunoglobulin levels (IgG and IgA in 7 patients, IgG in 2 patints) were still under 2SD for age. To exclude possibility of isolated IgG subsclass deficiencies, IgG subclasses were measured by ELISA 6 (age range: 27-45 months) of these nine patients. Two IgG1 and IgG3; 1 IgG1; IgG2 and 1 IgG3 deficiencies were detected. Five of these six patients had low IgG and IgA levels at diagnosis. To determine predictive factors, we carried out statistical analyses of the differences between patients with full recovery (Group 1; n: 21) and patients with still low immunoglobulin levels (Group 2; n.9) using Mann-Whitney U test. There were no significant differences regarding the mean age and immunoglobulin levels at time of diagnosis. However, the age at which the recurrent infections started was significantly ($p<0.01$) higher in patients with still low immunoglobulin levels (Group 2) (Table III).

(IVIG) treatment (400 mg/kg/month) because of severe invasive infections and infections causing failure to thrive. The patients who needed IVIG replacement achieved full recovery at the age of 23 and 27 months, respectively.

Discussion

After birth, the levels of maternally derived IgG decline rapidly and reach their lowest point of approximately 400 mg/dl at 3-6 months. At the same time, the infant's own production of IgG is not fully developed. The sequence of events is generally accepted as representing normal physiologic hypogammaglobulinemia; prolongation of this condition is classically defined as "transient hypogammaglobulinemia of infancy"[1].

The precise frequency of this condition is uncertain. A number of researchers have reported THI as a very rare condition, while others have suggested that THI is not infrequently discovered in clinical practice[3-5,10-12] (Table IV). The disparity of incidence among various center reports can be explained by different study populations and lack of strict criteria for the diagnosis of this disorder. In studies in which immunoglobulin levels of patients were determined because of frequent infections, the number of patients diagnosed as THI was higher, as seen in our study[4,5,12].

Table III. Comparison of Patients with Full Recovery (Group 1) to Those with Still Low Immunoglobulin Levels (Group 2)

	Age at diagnosis (months)	Age at start of symptoms (months)	IgG levels at diagnosis (mg/dl)	IgA levels at diagnosis (mg/dl)	IgM levels at diagnosis (mg/dl)	Follow-up (months)
Group 1 [n:21]						
Mean	20.8±10.4	6.7±3.0	484.7±97.8	38.6±22.1	88.3±40.6	11.9±6.4
Median	18	6				
Range	6-46	2-12	278-608	6-96	11.3-220	5-28
Group 2 [n:9]						
Mean	26.5±9.5	10.4±3.3	473.3±96.1	38.1±23.6	79.2±32.5	18.5±7.0
Mean	28	10				
Range	11-45	6-18	328-619	12-77	29-125	11-27
p	>0.05	P<0.01	p>0.05	p>0.05	p>0.05	

In most of the patients, frequency of infections decreased as they grew older and normal immunoglobulin levels were achieved. Eleven of 30 patients had received trimethoprim-sulphamethoxazole prophylaxis and two of 30 patients had received intravenous immunoglobulin

The cause of THI remains unknown in spite of numerous pathogenic mechanisms that have been proposed[1]. These include delayed maturation of B cell function[13], defect in T helper cell maturation[2], cytokine dysregulation[14] and a clinical heterozygous state of other more severe immunodeficiencies[15].

Table IV. Incidence of THI Reported in the Literature Together with the Present Study

	Investigated population	Number of reported cases	Study period
Tiller&Buckley, 1978[10]	10,000 blood samples	11	12 years
McGeady, 1987[4]	Patients with frequent infections	23	8 years
Dressler, 1989[3]	8,000 blood samples	5	11 years
Walker, 1994[11]	2,468 blood samples	40	10 years
Dalal, 1998[5]	Patients with frequent infections	35	10 years
Kılıç, 2000[12]	Patients with frequent infections	40	9 years
Doğu, 2002	464 patients with frequent infections	30	6 years

THI: transient hypogammaglobulinemia.

In the present study, none of the patients had a family history of immunodeficiency, and T cell number and functions were found to be normal in all studied patients. The spectrum of clinical features and range of postulated etiologies suggest that multiple factors may contribute. Further studies are needed to define immunopathogenesis of this disorder.

Clinical manifestations of THI vary from patients who are free of any symptoms to others with severe recurrent infections[3]. Another striking finding reported in some series was preponderance of atopy and allergic diseases[11]. In our study 14 of 30 patients had asthma or other allergic diseases.

Although THI has been long recognized, little was known about the long-term outcome of these patients until recent years. Prospective evaluation of these infants revealed that acquisition of normal immunoglobulin levels was often delayed beyond infancy, usually resolving at 30-40 months of age. Dalal et al[5]. followed 35 children with hypogammaglobulinemia for 10 years and showed that all except three patients had normal IgG levels within 6-100 months. In Kılıç et al'.s[12] study, 40 patients with THI were prospectively evaluated, and normalization of immunoglobulin levels in 33/40 patients was shown. In the present study 53% (n:16) of the patients had normal immunoglobulin levels before 36 months of age. In five cases (20%), recovery was achieved after 36 months (41-66 months). Nine cases who have been under follow-up for a median of 16 months still have low immunoglobulin levels. Comparison of the improved versus unimproved patients revealed the unexpected finding that the age at which the recurrent infections had started was significantly higher in the second group. In recent years, it has been widely considered that the clinical presentation of primary immunodeficiency diseases has not always been homogeneous. Heterogeneous presentations and courses have also appeared. This leads us to the supposition that there could be a transition to the other dysgammaglobulinemias in this group of patients. Peripheral blood (PB) lymphocyte subsets and proliferation assay in response to PHA were found to be normal in all of these patients. IgG subclasses were measured in six of these nine patients, and various deficiencies were detected. These findings underline the importance of long-term follow-up with detailed examination of serial clinical and laboratory parameters in these patients. Decreases in the levels of one or more of the immunoglobulins may sometimes represent the prodromal phase of dysgammaglobulinemias or other more severe immunodeficiencies such as partial IgA deficiency, IgG subclass deficiency or common variable immunodeficiency. Therefore, THI could be a diagnosis of exclusion that should be established in retrospect.

In general, symptomatic patients with repeated bacterial infections frequenctly benefit from antibiotic treatment. Rarely, temporary replacement therapy with IVIG is needed. In the present study two of 30 patients needed IVIG replacement; one for severe pneumonia requiring ventilation and the other for recurrent infections causing growth retardation. Both cases responded to IVIG treatment, which helped to decrease frequency and severity of infections, and both attained normal immunoglobulin levels before 36 months of age.

In conclusion, to better understand the clinical course, incidence and pathogenesis of THI, further studies are needed.

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