Transient hypogammaglobulinemia of infancy: predictive factors for late recovery

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This study evaluates the clinical/immunological features and outcomes of 91 patients with the diagnosis of transient hypogammaglobulinemia of infancy(THI). Mean age at diagnosis was 8.4±5.2 months. IgG levels normalized at 30.6±11.88 months. Sixty three patients (69.3%) resolved in their first 3 years of life and 28 patients (30.7%) thereafter. In the univariate analysis, presence of atopy, occurrence of recurrent infections (>6/year) and hospitalization, initial low IgA and IgM levels were found to be associated with the late recovery. Patients with longer breastfeeding duration recovered earlier. Recovery time for Ig levels was found to be longer in patients who received IVIG (n=55, 60.4%). This study confirmed that delayed resolution in THI is not rare. Frequent infections, initial low IgA and/or IgM levels and presence of atopy were found as associated factors for the late recovery. Breastfeeding should be encouraged and IVIG should be used in well selected patients.

Key words: clinical presentation, immunoglobulins, late recovery, transient hypogammaglobulinemia of infancy, outcome.

Transient hypogammaglobulinemia of infancy (THI) is characterized by reduced levels of one or more of the three major classes of immunoglobulins, mainly immunoglobulin (Ig) G. It may be considered as accentuation and prolongation of the physiologic hypogammaglobulinemia of infancy, which is seen during the first 3-6 months of life.[1] Several heterogenous mechanisms have been postulated, but underlying basis have not been definitely established yet. THI may lead to recurrent sinopulmonary infections or remain asymptomatic.[1,2] Severe or life threatening infections are rarely seen. It can be definitely diagnosed only after Ig levels return to the age-normal reference ranges. Spontaneous normalization of Ig levels is expected by the age of three.[3,4] However, it has been shown that resolution of the defect in Ig production can be delayed to later ages.[5,6,7] To know the predictive factors for recovery time of a child who falls within the catch-all diagnosis of THI would be valuable in follow up of these patients and reassurance of the parents. Van Wickle et al.[8], reported that presence of protective specific antibody titers, absence of other known immune deficiency, initial immunoglobulin levels and sex may predict time to normalization.

In this study, we presented clinical data and outcome of 91 patients with THI, with a specific focus on the risk factors associated with late recovery of Ig levels beyond the age of three.

Material and Methods

Study population

This study consisted of 91 patients who were diagnosed as THI in the Pediatric Infectious Diseases and Clinical Immunology outpatient clinic of Istanbul Medical Faculty between January 2010 and December 2014. Only those patients who caught up to normal Ig levels for age were included. Some of the study

patients were referred to our clinic because of previously detected low Ig levels in other clinics. Most of the patients presented to our outpatient clinic with the complaint of recurrent infections and later were identified as having THI. Finally, some other patients were detected to have hypogammaglobulinemia when they were admitted to our hospital due to a serious infection. Diagnosis of THI was made according to the following criteria[9]: (i) low serum IgG levels (<2SD below the mean for age) which may be accompanied by low IgA/IgM levels; (ii) exclusion of known etiologies of hypogammaglobulinemia like drugs, genetic disorders, chromosomal abnormalities, and systemic disorders, (iii) absence of clinical and laboratory characteristics of other known types of immune deficiency syndromes. Patients were followed up at 2-4 months interval for monitorization of Ig levels and recurrent infections. The patients who were sufferring from frequent infections or serious infections like pneumonia or meningitis were given intravenous immunoglobulin (IVIG) with a dose of 400-500 mg/kg. They were seen at least 6 weeks after and IVIG replacement was reassessed by serum Ig levels and clinical recovery findings. Some patients with frequent upper respiratory tract infections, who were not justifiable for IVIG replacement were followed by prophylactic antibiotics. Pneumococcal vaccine response was tested in patients who were ≥2 years old.

Data Collection and Study Design

Medical records of the patients were reviewed and data about the following criteria were recorded: age at symptom onset, age at diagnosis, presence of paternal consanguinity, localization and frequency of infections, serial measurements of serum IgG, IgA and IgM at admission and during follow up, lymphocyte subset analysis at admission, presence of atopy which was determined by specific IgE and/or skin prick tests, medications (IVIG and/or prophylactic antibody, if given), total duration of follow up and recovery time of hypogammaglobulinemia. Patients were divided into two groups as those who regained normal Ig levels within 36 months of age (early recovery group) and those who regained normal Ig levels after 36 months of age (late recovery group). In order to define predictive factors for the late recovery of Ig levels in THI, these two groups were compared regarding relevant clinical and laboratory parameters.

Laboratory studies

Serum Ig and IgG subgroup analyses were performed by nephelometrical method using commercially available kits (Date Behring Marburg Gmbh, Germany) and compared with age-related normal values.[10] Absolute numbers and percentages of lymphocyte subsets (CD3+ as total T cells, CD3+/CD4+ as helper T cells, CD3+/CD8+ as cytotoxic T cells, CD19+ and CD20+ as B cells, CD3+CD16/56+ as natural killer cells) were measured by four-color flow cytometry (BD Facs Calibur, BD Calibur, BD Biosciences, San Jose, California, USA). Patients' results were compared with age-related normal values.[11] Antibody response to pneumococcal vaccination was tested. For this purpose, 23-valent pneumococcal polysaccharide vaccine was used and IgG antibodies against pneumococcal capsular polysaccharide present in serum were measured before and 4 weeks after the vaccination (Binding site VaccZyme anti-PCP IgG EIA-kit, USA). Less than 2-fold increase in specific IgG response was considered an impaired antibody response to polysaccharide antigens.

The study protocol was approved by the Ethics Committee of Istanbul Medical Faculty.

Statistical Method

Statistical analysis of data was performed with statistical package for social science (SPSS) for Windows version 21.0 (SPSS 21.0, SPSS Inc. USA). Variables between groups were compared by using "Fisher chi-square" and "independent sample t-tests". P values < 0.05 were accepted as statistical significance limit. The significant predictors of late recovery with a p value of ≤ 0.05 in univariate analysis were fitted to perform logistic regression analysis model to identify independent risk factors associated with late recovery of Ig levels in THI.

Results

Clinical and laboratory features of the patients with THI

Clinical features of 91 patients were shown in Table I. Parental consanguinity was present in 17 patients (18.7%). All study patients had

Table I. Clinical Features of 91 Infants with THI

Variables	
Gender, n (%)	
Male	55 (60.4%)
Female	36 (39.6%)
Age at symptom onset, months	
Mean±SD	4.2±1.3
Median (range)	6 (2-14)
Age at diagnosis, months	
Mean±SD	8.4±5.2
Median (range)	7 (2-24)
Duration of time for recovery, months	
Mean±SD	22.15±9.62
Median (range)	20 (18-60)
Age at recovery, months	
Mean±SD	30.16±1.18
Median (range)	25 (12-56)
Clinical presentations, n (%)	
Asymptomatic	28 (30.8)
Recurrent upper respiratory infections	29 (31.9)
Lower respiratory tract infections	10 (1.1)
Recurrent wheezing	18 (19.8)
Gastrointestinal system infections	3 (3.2)
Urinary system infection	2 (2.2)
Central nervous system infections	1 (1.1)
Atopic manifestations*, n (%)	35 (38.4%)
Atopy (positive SPT or specific IgE)	25 (27.5%)
High IgE level, n (%)	8 (8.7)
IVIG replacement therapy, n (%)	55 (60.4%)
Antibiotic prophylaxis, n (%)	11 (12.1%)
IVIG+antibiotic prophylaxis, n (%)	5 (5.5%)

*including bronchial hyperreactivity and atopic dermatitis

low IgG levels at presentation. In addition to low IgG titers, low serum IgA and IgM levels were also determined (Table II). Thirty two patients (80%) had achieved normal IgA levels for age at the time of IgG recovery. All patients with low IgM levels caught up to norms in the follow up. Lymphocyte subset analysis determined that total lymphocyte, T cell, B cell and natural killer cell counts of all patients were within the normal ranges for age. Mean values for absolute counts of lymphocyte subgroups were depicted in Table III.

Fifty five patients (60.4%) received IVIG replacement (Table I) with a mean of 1.23±0.54 (range:1-3) times and with a median duration of 1 month (range:1-18 months). It was given to 36 patients with recurrent infections, 15 patients with recurrent wheezing and 4 asymptomatic infants with serum IgG levels <3SD below the mean for age. IVIG therapy decreased infectious episodes in 81% of patients (30 out of 36 patients) with recurrent infections. It caused improvement in 66.6% of patients with recurrent wheezing (10 out of 15 patients).

Patients were followed up for a mean of 21.60±9.09 months. IgG levels reached the norms for age at a mean of 22.15±9.62 months (Table I). There was no difference between asymptomatic and symptomatic patients regarding the duration of IgG recovery (20.21±5.75 months vs 22.22±10.21 months, p=0.33). On the other hand, recovery time was found to be longer in patients who recieved IVIG therapy compared to patients who did not (23.61±10.20 months vs 18.52±6.0 months, p=0.008).

Predictive factors for late recovery from THI:

Sixty three patients (69.3%) recovered from

Table II. Evaluation of Initial Serum Ig Levels of the Patients

	Total n=91 (%)	Early recovery group[1] (n=63)	Late recovery group[2] (n=28)	p
Isolated low IgG	45 (49.5)	41 (65.1)	4 (14.3)	< 0.001
Low IgG-IgA	32 (35.2)	17 (27.0)	15 (53.6)	0.014
Low IgG-IgM	32 (35.2)	27 (3.2)	5 (17.9)	0.015
Low IgG-IgA-IgM	7 (7.7)	3 (4.8)	4 (14.3)	0.11
Low IgA	40 (43.9)	22 (34.9)	18 (64.3)	0.009
Low IgM	14 (15.4)	5 (7.9)	9 (32.1)	0.003

[1] The patients who regained normal Ig levels within 36 months of age. [2] The patients who regained normal Ig levels after 36 months of age.

hypogammaglobulinemia within 36 months of age (early recovery group) and 28 (30.7%) patients recovered after 36 months of age (late recovery group). These two groups were compared regarding clinical and laboratory features (Tables II-IV). Univariate analysis of the clinical features of early and late recovery groups were presented in Table IV. Older age at symptom onset, atopy, shorter duration of breastfeeding, higher frequency of infectios episodes/year and need for hospitalization were more frequent in the late recovery group.

Table II shows the comparative evaluation of initial serum Ig levels of the two groups. Accompanying low IgA and IgM levels at presentation were more frequently found in the late recovery group (p=0.009 and p=0.003 respectively, Table II). In Table III, initial mean levels of major Ig classes and mean absolute counts of lymphocyte subgroups were presented. Although the patients in the late recovery group had significantly lower absolute counts of lymphocytes and some lymphocyte subgroups, all of them were within the age-related normal ranges. A normal pneumococcal vaccine response was obtained in all patients who were ≥2 years old.

Logistic regression analysis was performed for clinically relevant variables with a p value of <0.05. Presence of recurrent infections with

Table III. Initial Mean Levels of Major Ig Classes and Mean Absolute Counts of Lymphocyte Subgroups of the Patients

	Total n=91	Early recovery group[1] (n=63)	Late recovery group[2] (n=28)	p
IgG, mg/dl				
2-5 months	217.96±54.70	220±10.4	192±32.8	0.39
6-8 moths	229.40±60.23	230±14.1	225±33.7	0.87
9-12 months	242.52±47.47	239±15.9	247±11.1	0.71
13-24 months	257.0±66.68	301±33.8	235±69.1	0.044
IgA, mg/dl	22.41±14.90	24.33±16.03	18.10±11.04	0.066
IgM, mg/dl	45.76±23.76	58.64±24.15	40.04±21.38	0.001
Lymphocyte, absolute number/mm^3	5027±2072	5430±2176	4122±1485	0.005
Lymphocyte subgroups, absolute number/mm^3				
CD3+ Tcells	3590±1483	3870±1500	2634±961	0.010
CD19+ B cells	1214±648	1286±670	848±367	0.081
CD3+CD4+ T helper cells	2598±1217	2808±1202	1522±570	0.005
CD3+CD8+ T cytotoxic cells	936±448	1010±425	556±383	0.007
CD3+CD16+56+ natural killer cells	613±382	660±463	371±247	0.23

[1] The patients who regained normal Ig levels within 36 months of age. [2] The patients who regained normal Ig levels after 36 months of age

more than 6 episodes per year (p=0.019, OR (95% CI): 4.70 (1.28-17.27)) and initial low IgA levels (p=0.015, OR (95% CI): 3.91 (1.31-11.71)) were found to be independent risk factors for the late recovery of IgG.

Discussion

Transient hypogammaglobulinemia of infancy is a clinical entity that we encounter more frequently, as the physicians' and the parents' awareness of primary immune deficiencies increase. In this study, clinical and immunological features of 91 patients with a diagnosis of THI were evaluated. Furthermore, outcome of the patients were investigated with the aim of defining predictive factors for delay in achievement of normal Ig levels beyond the age of three. In 30.7% of our cohort, normalization of IgG occurred after the age of 3. Logistic regression analysis determined initial IgA levels that is <2SD below the mean for age

Table IV. Univariate Analysis of Clinical Variables of Early and Late Recovery Groups.

Demographic and clinical features	Early recovery group[1] (n=63)	Late recovery group[2] (n=28)	p
Gender, male n (%)	36 (34.5)	19 (65.5)	0.33
IgG recovery time, months			
Mean±SD	23.14±4.60	45.96±6.91	0.001
Median (min-max)	24 (18-36)	44 (38-60)	
Age of symptom onset, months			
Mean±SD	4.24±1.30	7.25±2.71	0.001
Median (min-max)	4 (2-6)	7 (3-14)	
Age at diagnosis, months			
Mean±SD	6.81±3.86	12.21±6.01	<0.001
Median (min-max)	6 (2-18)	12 (2-23)	
Duration of breastfeeding, months			
Mean±SD	12.84±4.21	10.71±4.31	0.03
Clinical presentataion, n (%)			
Asymptomatic	23 (36.5)	5 (17.9)	0.075
Recurrent upper respiratory tract inf.	11 (17.5)	18 (64.3)	< 0.001
Lower respiratory tract infection	3 (10.7)	7 (11.1)	0.89
Recurrent wheezing	8 (12.7)	10 (35.7)	0.011
Gastrointestinal system infection	2 (3.2)	1 (3.6)	0.92
Urinary system infection	1 (1.6)	1 (3.6)	0.79
Central nervous system infection	1 (1.6)	0	0.50
Number of infectious episodes, n(%)			
< 6 / year	24 (38.1)	2 (7.1)	0.003
6-12 / year	11 (17.5)	18 (64.3)	<0.001
History of hospitalization, n (%)	20 (31.7)	16 (57.1)	0.022
Atopic manifestations, n (%)			
Atopic dermatitis	13 (20.6)	4 (14.3)	0.47
Bronchial hyperreactivity	8 (7.9)	10 (35.7)	0.011
Presence of atopy (positive SPT or specific IgE), n (%)	13 (20.6)	12 (42.9)	0.028
IVIG replacement therapy, n (%)	37 (58.7)	18 (64.3)	0.61
Number of IVIG requirements			
Mean±SD	1.50±0.78	1.10±0.31	0.011
Median, min-max	1 1-2	1, 1-3	

[1] The patients who regained normal Ig levels within 36 months of age. [2] The patients who regained normal Ig levels after 36 months of age.
IVIG: intravenous immunoglobulin, SPT: skin prick test.

and history of recurrent infections more than 6 episodes/year as independent risk factors for the late recovery.

Although the upper age for normal Ig production is defined as 36 months, there are many studies indicating delayed recovery of Ig levels extending to the age of 10.[6,7,12-14] Ozen et al.[14] reported that only 24% of their cohort achieved normal Ig levels by the age of 3. In accordance with our findings, they also found that prevalance of asthma was higher and elevated IgE levels were more common in patients with delayed THI.[14] Similarly, in another study, higher prevalance of atopic diseases were reported in patients whose Ig levels normalized after 3 years of age.[7] They did not find any difference in the frequencies of respiratory infections between the early and late recovery groups.[7] However, our data indicated the occurrence of frequent infections as a predicting factor for the late recovery. Moreover, Ozen et al.[14] determined that symptoms started at an older age in patients with delayed THI, which is consistent with our findings.

All major classes of Igs may show decreased levels in THI. Low IgA levels which accompany low IgG are frequently encountered.[14-16] In this study, it was found in 43.9% of patients and found to be a predictive factor for delay in the recovery of Igs. High incidence of initial low IgA (66%) was found by Ertac et al.[16], however, no delayed resolution of hypogamaglobulinemia was recorded in their cohort. In the previously mentioned study, Ozen et al.[14] reported that in their heterogenous cohort of hypogammaglobulinemia, markedly and persistently decreased IgA levels pointed towards more permanent immunodeficiency disorders like IgA deficiency or common variable immune deficinecy. Partial IgA deficiency was still persisting in 20% of our patients at the time when IgG levels normalized. Moreover, low IgM levels at admission was significantly more frequent in our late recovery group. All of them returned to the age related normal levels during follow up. In another study, a higher incidence of low IgM levels (61%) were determined at admission and 33% of measurements was still low at the time of IgG recovery.[16] Ozen et al.[14] also indicated in their study that lower levels of IgM were associated with persistent hypogammaglobulinemia, requirement for IVIG and more severe infections in all diagnostic groups. Based on all of these findings, we can conclude that among patients presenting with hypogammaglobulinemia who falls within the differential diagnosis of THI, those who have accompanying low IgM and/or IgA levels may be candidates for delayed resolution and should be handled as such.

A relatively high incidence of asymptomatic patients with THI was encountered in our patients. Majority of them were the patients referred from other physicians who detected their hypogammaglobulinemia during the evaluation of various symptoms such as lack of apetite, poor weight gain and non-specific rash. We think that increasing awareness of primary immune deficiencies both among physicians and the community lead to excessive laboratory examinations of immunologic parameters. They did not suffer from recurrent or serious infections during their follow up as well and achieved normal Ig levels within the expected time period.

In this cohort, a relatively high incidence of IVIG administration was determined compared to other studies.[2,15,17] IVIG therapy is not considered to be a preferred therapy in the follow up of THI. Physicians often prefer antibiotic prophylaxis or follow up without medication. However some authors suggest that IVIG is more effective than antibiotics in treating viral infections via its antiviral antibody contents. Therefore, another approach that was also accepted by our center was use of IVIG replacement therapy in the patients who suffered from severe or high frequency of infections. The frequency of overall infections decreased more frequently in patients who received IVIG than in patients who did not. This finding was also supported by similarly designed studies.[17,18] Furthermore, we observed that atopic symptoms especially bronchial hyperreactivity improved more commonly in IVIG recipients. However, there are concerns about IVIG therapy, regarding risk of interference with and delay in endogenous specific antibody production.[19] In a study, patients who received IVIG and patients who did not, reached normal IgG levels at similar ages.[17] In another study, it was found that all children produced a normal amount of specific IgG in response to vaccination carried out 5

months after the end of IVIG infusions.[18] In our cohort, recovery time for Ig levels was longer in the patients who received at least one dose of IVIG replacement. On the other hand, all patients with late recovery including those who received IVIG was found to have normal response to polysaccharide antigens. Thus, there are conflicting results on this issue. However, it may be suggested that indication for IVIG use in these patients should be restricted to the patients who are severely affected by infections and/or shown to have impaired immunological response to specific antigens.

In this study, we described clinical features, follow up and outcome of a large cohort of children with THI, who are increasingly encountered in our daily practice. Since they present with hypogammaglobulinemia and diagnosis of THI can certainly be made only after IgG levels normalize, clinical and laboratory features that will predict the duration and outcome of this clinical entity will help physicians in the follow up. Our findings indicate that if the patient has frequent infections, initial low IgA and/or IgM levels and atopy, she/he is more likely to have a delayed course of resolution. These patients should be attentively investigated and followed up in terms of evolution to other primary immunodeficiencies. Extending breastfeeding duration should be encouraged in these patients. Indication for IVIG replacement therapy should be restricted to those patients with severe or high frequency of infections.

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