



# To What Extent do Transient Hypogammaglobulinemia of the Infancy and Allergic Diseases Coexist?

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## ABSTRACT

**Objective:** To investigate the clinical features and follow-up results of the patients with transient hypogammaglobulinemia of infancy (THI) and to understand to what extent the condition coexists with allergic diseases.

**Materials and Methods:** Between January 2010 and February 2019, 172 patients who had been referred to Ankara University Faculty of Medicine's Pediatric Immunology and Allergy Outpatient Department for findings of atopic disease or for frequent infections with a suspicion of PID, who were diagnosed with THI, and followed-up for at least one year were included in this study. Their clinical and immunological features and follow-up results were evaluated retrospectively.

**Results:** Of the 172 patients, 59% were boys. Median time of symptom onset was 14 months (1-46 months), median time of admission was 20 months (6-30 months), and consanguineous marriages were seen in 20% of the families. The most common referral complaints were respiratory tract infections and non-wheezing allergic diseases with rates of 71.5% and 27%, respectively. Cellular immune system analyses were normal. During a median follow-up time of 36 months, 42% of the patients recovered, 25% (n=43) still had THI, 25% (n=43) had unclassified hypogammaglobulinemia (UCG), 4% (n=7) had partial IgA deficiency, and 4% (n=7) had partial IgM deficiency. Allergic diseases were seen in 46% of the patients. An asthma diagnosis was made in 35.4% of the patients, allergic rhinitis in 5% and atopic dermatitis in 12.7%. The skin prick test was positive in 15% of them.

**Conclusion:** THI mostly improves spontaneously in time. However, hypogammaglobulinemia can last until later years in life in a group of patients. Allergic diseases increase with the presence of THI. In patients who are admitted with allergic disease symptoms, underlying hypogammaglobulinemia should also be investigated.

**Keywords:** Transient hypogammaglobulinemia, infancy, allergic diseases

## INTRODUCTION

The level of IgG transferred from the mother to the newborn decreases rapidly after birth and reaches a nadir at 3-6 months of life. During this period, the baby starts its own IgG production and this period is called physiological hypogammaglobulinemia as it is insufficient. Transient hypogammaglobulinemia of infancy (THI) is the extension of this process. It has initially been described in 1956 (1). Nearly 50 years after its definition, it was included in the Primary Immunodeficiencies (PID) classification of the International Union of Immunological Societies (IUIS) (2).

It has a share of 24% among all hypogammaglobulinemias and usually improves spontaneously around 2-4 years of life. However, there is a subset of patients who are reported to have the disease until early childhood or as late as the third decade of life (2-4). This group is called unclassified hypogammaglobulinemia (UCH) (5). There is no test that can predict the patients who will improve and this is why the real diagnosis of THI can only be established retrospectively (6).

THI is a PID where Ig synthesis is impaired; it shows common phenotypical features with PID but its etiology has not been fully understood. Its incidence has been

reported as 0.06-1.1/1000 live births (7). Some of the infants with THI are asymptomatic whereas some have increased tendency for infections and especially for respiratory tract infections. Many PID patients are reported to have allergic diseases as well. Antibody deficiencies include common variable immunodeficiency (CVID), IgA deficiency, hyperimmunoglobulin M syndromes (HIGM) and THI (6-9). Here, we aimed to investigate the clinical and immunological features of patients being followed-up for THI and assess its association with atopic diseases.

## MATERIAL and METHODS

We included 172 patients who were followed-up at Ankara University Faculty of Medicine Pediatric Immunology and Allergy Department from January 2010 to February 2019 for at least one year with the diagnosis of THI. These patients were suspected to have PID because of the frequent infections they had; admissions to the hospital with the findings of atopic disease, and identification of hypogammaglobulinemia while being investigated for other reasons. The diagnosis of THI is established on the basis of the following criteria: a) having an IgG level of lower than 2SD on two measurements for infants older than three months of age, b) exclusion of other causes that might lead to hypoglobulinemia (PIDs, a family history of PID, chromosomal abnormalities, malignancies, secondary immunodeficiencies), c) having normal vaccine responses (anti-HBs and anti-Rubella-IgG) and normal isohemagglutinin titers, and d) having a normal cellular immune system, either clinically or immunologically. Patients who were diagnosed as THI and who continued to have low levels of IgG and/or low levels of two isotypes after four years (48 months) of age were regarded as unclassified hypogammaglobulinemia (UCH). The patients were followed-up for recurrent infections, atopic diseases and IgG levels at 3-6-month intervals.

### Data Collection

Symptoms at the time of admission, the time for the onset of symptoms, the age at admission, sex, parental consanguineous marriage, the types and frequency of infections, examination findings, and the presence of atopic disease, laboratory findings and follow-up results were obtained from the medical records of the patients. Complete blood count was performed and serum albumin, total protein, globulin, immunoglobulin, isohemagglutinin titers, antibody responses (anti-HBs and additionally anti-Rubella IgG for children older than

one year of age) were measured in all patients. Serum Ig G, A, M levels were measured with nephelometric methods (Dade behring marburg GmbH, Germany). Total IgE levels were measured with the ELISA method. All Ig measurements were evaluated according to age reference normal levels for Turkish children (10). The decision to perform peripheral blood lymphocyte subgroup, B cell subgroup, and lymphocyte activation response analyses was made based on the clinical findings of the patients and the results were evaluated according to age reference normal levels (11).

If the patient had more than eight upper respiratory tract infections (URTI) in a given year and/or four or more otitis episodes, two or more sinusitis episodes, two or more pneumonia episodes, recurrent skin and organ abscesses, persistent fungal infections of the skin and mucosa, and two or more severe infections (like sepsis, meningitis), these were regarded as recurrent infections.

For children between three months to two years of age, food panel (egg, wheat, peanut, hazelnut, milk, sesame, soya, fish, histamine, and negative controls) and for children above the age of two years, common inhalant allergen panel [*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria*, *Aspergillus*, *Cladosporium*, *Betulaceae*, *Grass mix*, *Tree mix*, *Artemisia*, *Oleaceae*, *Saliceae*, *Parietaria*, feather mixture (duck, goose, hen), cat hair, and dog hair] (ALK-USA) skin prick tests were performed. In patients not having a skin test, allergen specific IgE levels were measured by the enzyme allergosorbent test. Allergic diseases were classified as asthma, atopic dermatitis (AD), food allergy (FA), allergic rhinitis or rhinoconjunctivitis (AR, ARC). AD diagnosis was based on Hanifin and Rajka criteria, asthma diagnosis was based on GINA (Global Initiative for Asthma) criteria, and allergic rhinitis diagnosis was based on ARIA (Allergic rhinitis and its Impact on Asthma) criteria (12-14). It was recorded whether IgG and other isotypes returned to normal or not and when they returned to normal levels. Ongoing diseases during the last control visit (like recurrent infections, allergic diseases) were also recorded. Ankara University Faculty of Medicine Human Research Ethical Board approval was obtained for this study (Decision no: İ3-190-20).

### Statistical Analysis

Statistical analyses of the data were performed with the "Statistical Package for Social Sciences (SPSS Version 15.0,

Chicago, IL)” package program. Discrete variables were presented as numbers and percentages while continuous variables were given as minimum-maximum and median.

## RESULTS

### Patient Characteristics

Fifty nine percent (101/172) of the patients were boys and 41% (71/172) were girls. Median time for the onset of symptoms was 14 months (min-max: 1-46 months), mean time of admission was 20 months (min-max: 6-30 months), and the rate of parental consanguineous marriages was 20% (35/172). Among the complaints for admission, respiratory tract infections ranked first with 71.5% (123/172) while non-wheeze allergic diseases ranked second with 27% (29/172). The recurrent bronchiolitis/bronchopneumonia rate was 40% (n=70), frequent URTI 30.8% (n=53), AD 12.7% (n=22), FA 2.9% (n=5), moniliasis 3.4% (n=6), urticaria 1.1% (n=2), growth retardation 2.9% (n=5), perianal abscess 1.7% (n=3), recurrent urinary tract infections 1% (n=2), and extended diarrhea 1.7% (n=3). Three (1.7%) patients were asymptomatic but had been referred as they had been identified to have hypogammaglobulinemia coincidentally. Demographical data are presented on Table I.

### Immunological Analysis

All patients had normal lymphocyte counts. Three patients had temporary neutropenia. There were 34 (19.7%) patients with only low levels of IgG, 51 (29.6%) with low levels of IgG and IgA, 26 (15.1%) with low levels

of IgG and IgM, and 61 (35.4%) with low levels of IgG, IgA and IgM. At the time of admission 145 patients had normal isohemagglutinin titers. Twenty-four babies, who were younger than 12 months, had repeated isoagglutinin titer measurements at follow-up visits after one month and these results were also normal. Three patients had the AB blood group. One hundred sixty five patients had sufficient levels of vaccine response. Seven patients with low anti-HBs response were given one dose of booster vaccine. When anti-HBs titers were measured afterwards, they had reached protective levels. The median eosinophil count was 200/mm<sup>3</sup> (min-max: 10-1170), median total IgE level was 9 kIU/L (min-max: 2-948) and six percent had skin test positivity.

Eighty-four patients had peripheral blood lymphocyte subgroup analyses and all had normal CD3+ T, CD3+CD4+ T, CD3+CD8+ T, CD19+B lymphocyte counts, CD3-CD16+56+ NK cell counts, and lymphocyte activation responses for their age. Six patients had low levels of B cell subgroups based on age references (four had low levels of *switched memory* B cells and two patients had low levels of both *switched memory and marginal zone* B cells). All patients had normal levels when measurements were repeated six months later. Immunological data are presented in Table II.

### Follow-up Results

In the median follow-up period of 36 months (min-max: 12 months-120 months), 42% (n=72) of the patients had normal levels of all Ig isotypes. Median time for

**Table I. Demographic features of the patients.**

	n	%
Gender	M: 101 F: 71	58.7 41.3
Consanguinity	35	20
The time for the onset of symptoms (mo) (min-max)	14 (1-46)	
The age of diagnosis (mo) (min-max)	20 (6-30)	
The median follow-up time (mo) (min-max)	36 (12-120)	
The age of recovery (mo) (min-max)	48 (10-118)	
The complaints on admission	n	%
• Rec. bronchiolitis/bronchopneumonia	70	40
• Upper respiratory tract infections	53	30.8
• Atopic dermatitis	22	12.7
• Food allergy	5	2.9

**Table II. Immunological features of the patients.**

At the time of diagnosis	n	%
Decreased IgG	34	19.7
Decreased IgG and IgA	51	29.6
Decreased IgG and IgM	26	15.1
Decreased IgG, IgA and IgM	61	35.4
At the end of the follow-up period	n	%
Normalized IgG, IgA and IgM	72	42
Transient hypogammaglobulinemia of infancy (continuing THI)	43	25
Unclassified hypogammaglobulinemia (UCH)	43	25
Partial IgA deficiency	7	4
IgM deficiency	7	4

improvement was identified as 48 months (min-max: 10-118 months). Of the remaining patients, 25% (n=43) had THI, 25% (n=43) had UCH where IgG and/or at least two isotype deficiencies continued, 4% (n=7) had partial IgA deficiency, and 4% (n=7) had partial IgM deficiency that continued.

Among the children with recurrent wheezing episodes and recurrent URTI, the rate of those diagnosed with asthma after five years of age was 35.4% (n=61). The rate for those diagnosed with allergic rhinitis (AR) was 5% (n=9). Seven patients with AR had asthma simultaneously. Of the 22 patients with AD, 17 patients continued to have symptoms at the end of the follow-up period. Throughout the follow-up period, there were allergic diseases (asthma, AD, FA, allergic rhinitis) in 46% (n=79) of the patients. The skin prick test results were positive in 15% of the patients with allergic disease. Forty five percent (n=31) of the patients who were older than five years and were followed up for an allergic disease had at least one isotype deficiency that persisted. Fifty-eight percent (n=97) of the patients received prophylactic antibiotic treatment for a median duration of 12 months (6-36 months). None of the patients received IVIG support. Other than two patients who were hospitalized in the intensive care unit for severe RSV pneumonia, none of the patients had severe infections such as sepsis or meningitis.

## DISCUSSION

THI is the lengthening of the physiological hypogammaglobulinemia without an impairment in specific antibody responses. Antibody deficiencies constitute more than 50% of all PID. In a study evaluating the data of 2076 participants registered in the ESID database from 18 countries and 46 centers, there was selective IgA deficiency in 25%, THI in 24% and common CVID in 23% of the cases as the three most common types (3). Yorulmaz et al. followed-up 1054 patients who presented to Meram University Faculty of Medicine's Pediatric Immunology-Allergy Outpatient Department for five years. Among these patients, 27.2% (n=287) were diagnosed as THI, which corresponded to seven percent of all the patients who presented to outpatient departments (15). Based on this data, it is possible to say that THI is a frequently seen PID. The rate of parental consanguinity was 20% in the current study, correlating with the Turkish data. There are studies stating that the incidence in the children is higher if there are other immunodeficiencies in the family

members, whereas other studies have demonstrated normal IgG levels in the parents and siblings of these children (7, 16, 17).

The etiology of THI has not been fully understood. Various causes have been reported including functional and numerical deficiencies of CD4+ T cells, resulting in B cells not being sufficiently stimulated/supported for proper antibody production, maternal IgG suppressing IgG production, and high levels of TNF- $\alpha$ , TNF- $\beta$  and IL-10 in these patients suppressing IgG and IgA production by B cells (18-20). In two different studies performed by another group in children, the THI Treg cell count was higher than in the control group and high levels of Treg in children with THI decreased with age and together with the disappearance of the suppressive effect the IgG levels were normalized (21). In a study by Artaç et al., CD19 complex and B cell subgroups were evaluated in children with THI and the mean fluorescence density of the CD19 molecule was low while CD21 and CD81 expressions were high. When we take into account that the CD19 complex regulates the processes after antigen stimulation, the changes seen in the CD19 complex during THI can be associated with the insufficiency in antibody production. Moreover, *switched memory B* cell and *marginal zone B* cell ratios were low compared to healthy controls (22). Çipe et al conducted a study in our department in 2011 evaluating 41 patients with THI. This study revealed that absolute B cell counts, *marginal zone B* and *switched memory B* cell counts were not different than the age reference normals of healthy controls. However, naive B cells (p=0.001) were higher in THI patients compared to age-matched healthy controls and activated B cells were significantly lower than the normal of the same age group (p=0.001) (23). On the other hand, there are studies reporting normal B cells in THI as well (8). Eroğlu et al. included 20 children with THI and 40 healthy controls in their study and reported similar age-related changes in B cell subgroups for both groups. During a median follow-up of 6.6 years, 13 patients with normalized IgG levels before four years of age were diagnosed with definitive THI. The memory subsets of these patients were lower but not significantly different than those of healthy controls. The remaining seven patients had persistent hypogammaglobulinemia after four years of age and had substantially lower memory B cells. Six years later, a re-evaluation of the patients' B-cell subsets revealed increased levels of memory B-cell ratios comparable to healthy controls despite slightly low

IgG levels (24). In our study, B cell percentages were in correlation with age references. Four patients had low levels of *switched* memory B cells and two patients had low levels of *switched* and *marginal zone* B cells. In their next follow-up visit, these levels were normal although the THI persisted. The common finding in all these studies is that *switched* memory B cells are mildly lower compared to healthy controls but this improves to a large extent in time in THI. In patients with UCH, there is a need for studies investigating the changes in the B cell subgroups.

THI patients generally recover spontaneously at 2-4 years of age, but many studies report patients who normalize later in childhood or even during adulthood (4, 8, 16). From 1995 to 2001, Doğu et al. had 464 patients admitted with frequent upper and lower respiratory tract infections. Of these patients, 30 were diagnosed with THI and they reported that 70% of their patients recovered at a median of 27 months (25). Amertunga et al. had 42 THI patients in their study; 37% of these recovered at four years of age; among the others, some patients continued to have hypogammaglobulinemia until the third decade of their lives (4). Karaca et al. evaluated 101 patients with THI in their study reporting a normalization of IgG at 30 months on average (26). In the study by Özen et al., 131 children were monitored for hypogammaglobulinemia. There were 33 patients with THI; 8 of these recovered at  $2.4 \pm 0.55$  (min-max: 1.5-3 years) years of age while the other 25 patients normalized at  $8.1 \pm 1.8$  years (min-max: 4.9-11.7 years) and this second group was described as *transient hypogammaglobulinemia of early childhood* (27). In the study by Karaman et al. the diagnosis of THI was retrospectively established in 193 patients and their 5-year follow-up results showed the time of recovery as  $30.6 \pm 10.5$  months (28). Keleş et al. analyzed 374 patients in their study (UCH: 303 and THI: 71); they found more than -2 SD decrease in one or more Ig levels with normal antibody response and normal lymphocyte subgroups. Mean recovery time for THI patients was  $68.87 \pm 36.5$  months and 95% of them recovered before 10 years of age. Meanwhile, they found the mean age at the time of diagnosis as  $52 \pm 42$  months for SHG patients (8). In the current study, the mean age for recovery was 48 months (min-max: 10-120 months). Differences in recovery times are seen in studies published from Turkey and other countries. This can be related to the differences in the diagnostic criteria and patient numbers as well as the nature of the disease itself, which can only be understood in time.

The clinical findings of THI patients are heterogeneous. Recurrent infections and atopic diseases are the most important clinical findings (4, 6, 16, 17, 29-32). Mucosal damage and inflammation caused by the infections stemming from hypogammaglobulinemia facilitates allergen transfer, and the disappearance of the protective relationship that secretory immunoglobulin A has established with immunomodulatory molecules and receptors results in the development of allergic diseases (33). THI patients also had atopic diseases that could be due to allergen-induced gastrointestinal inflammation possibly contributing to gastrointestinal loss of IgG (31). Altun et al. conducted a study in our department from 2013 to 2016, evaluating 238 patients followed-up with immunoglobulin isotype deficiency, and reported the allergic disease rate as 67% (34).

In a study by Dorsey and Orange on 24 THI patients, 42% had AR, 38% had FA, 25% had AD, and 17% had urticaria (6). In a study by Whelan et al., there were 49 patients who had decreased levels of at least one immunoglobulin isotype before the age of two; of these patients, 77.6% had recurrent otitis, 61.2% had experienced minimum one episode of wheezing, and 26.5% had skin test positivity (29). In a study performed at our department in 1995-2001, 30 THI patients were evaluated: 93% had URTI, 26% pneumonia, and 49% had atopic diseases (25). There are other studies reporting similar rates of allergic diseases for THI patients as in the general population (31). In the study by Yorulmaz et al. evaluating 287 patients; 54.35% had URTI, 50.5% had lower respiratory tract infections (LRTI) and 23.3% had atopic diseases (15). Keleş et al. covered both THI and UCH groups, reporting main complaints at admission as LRTI (THI 50%, UCH 53%), URTI (THI 42%, UCH 39%), and asthma (THI 52%, UCH 55%) for both groups (8). Similarly, complaints at admission in our study were recurrent bronchiolitis-bronchopneumonia 40%, frequent URTI 30.8%, and non-wheezing allergic diseases 27%.

Özen et al. reported the results of a study recruiting 131 hypergammaglobulinemic patients, identifying asthma in 62.6% of the patients and atopy in 19.8% (27). In another study on babies with THI, 54% of those experiencing recurrent wheezing episodes developed asthma (6). Karaca et al. reported atopy in 16.8% of their THI patients (26). In a study conducted in Adana, the prevalence of atopic diseases in childhood was reported as follows: asthma 12.6%, AR 13.6%, and AD 8.3% (35). In our study, among

patients admitted with respiratory tract infections, the percentage of patients diagnosed as asthma during follow-up was 35.4% (61/172). Forty one percent (30/72) of the patients with improved hypogammaglobulinemia had asthma; this percentage was 59% for UCH patients. In the current study, the frequency of allergic diseases was similar to those of other studies. The different rates in various studies could be due to having diverse study populations and also different groups predominating the patient group at certain centers. On the other hand, when children are referred with atopic diseases, the coexistence of hypogammaglobulinemia should be considered and these patients should be investigated. In severe asthma patients having frequent attacks, hypogammaglobulinemia has been shown to be one of the underlying causes (36). Children with THI have been reported to have atopic dermatitis in certain studies and this condition was associated with an inadequate response to skin pathogens (37). In the current study, we observed severe and infected AD lesions in five patients. Patients having normal immunological tests could be controlled with systemic antibiotics and local treatments.

There were no severe bacterial infections in any of our patients. In a large group of THI patients with recurrent infections, prophylactic antibiotics can provide sufficient protection. Nearly 10% of THI patients are reported to be hospitalized and treated for severe infections and they might need to receive IVIG (38, 39). In our series, we did not need to administer IVIG to our patients.

THI mostly improves spontaneously after four years of age together with the maturation of the immune system. However, in a group of patients, hypogammaglobulinemia can continue until the later years of life. Larger series should be reported with longer and regular follow-up results to better understand the course of this group. Patients with THI and UCH should also be evaluated for allergic diseases.

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