Case Report

A Case Report and Review of Increased IgE in Patients with Transient Hypogammaglobulinemia of Infancy Who Received Immunoglobulins

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Abstract: Background: The coexistence of a high IgE level and transient hypogammaglobulinemia of infancy (THI) with atopic dermatitis (AD) is well known, but the coexistence with a marked serum IgE level ≥ 1000 IU/mL is a rare finding. Literature is scarce regarding IgE levels in patients with THI and AD after treatment with immunoglobulin (Ig). The present article is the first to describe a finding of marked IgE elevation (> 1000 IU/mL) after treatment with intravenous immunoglobulin (IVIG). This paper also reviews previous related reports and series. **Case presentation and review:** We reported on a female infant 8 months old, with THI and severe AD. She was treated with IVIG infusion after the failure of conventional therapy. Initially, serum levels of IgE were high, and serum levels of IgG were low. After 4 weeks of treatment with IVIG, the patient showed clinically improved AD in parallel with elevated IgG level but increased IgE level to a higher level. We also review previous results of IgE levels reported in cases with THI and AD before and after Ig therapy. The mean increment in IgE levels was 227.5 IU/mL (SD = 164.2). The review showed that the IgG is directly related to IgA and IgM in addition to IgE. Results also showed that IgA and IgM also have a direct relation with IgE. **Conclusions:** We reported a case of marked IgE level in a THI patient with AD after IVIG treatment. Also, there were increased levels of IgA and IgM. A similar finding was observed in other reviewed cases.

Keywords: immunoglobulin; atopic dermatitis; atopy; IVIG

1. Introduction

Transient Hypogammaglobulinemia of Infancy (THI) is a primary immunodeficiency caused by a transitory drop level of immunoglobulin G (IgG). It is characterized by a transient delay in reaching normal levels of IgG over 6 months of age.[i] [,ii] IgG is significantly low (less than 2 standard deviations). This most commonly is corrected by 24 months of age but may persist for a few more years. Typically, the IgG level is low (less than 400 mg/dl), and the IgA and IgM antibodies may also be lower.

Several causes of THI have been postulated. These include delayed maturation of B cell function, deficiencies of helper T cells, and a clinical heterozygous state of other more severe immunodeficiencies. It is also likely that some cases of THI may reflect normal children who fall below the lower end of a normal range, particularly as it has been shown that such children have a normal specific antibody response.[iii]

The clinical picture varies from asymptomatic cases to children presenting with recurrent respiratory and gastrointestinal infections, fever of unknown origin, and allergy. As in many disorders with immune dysregulation or immaturity, allergic diseases may be present including eczema. [iv] The frequency of THI is unknown. It has been described in most parts of the world and is believed to be significantly underdiagnosed. Among patients with transient hypogammaglobulinemia of infancy (THI) with recurrent infections 31% had high IgE levels and 24% had atopy.[v]

High frequencies of atopic disorders have also been described in primary immunodeficiency deficiencies .[5]

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There is evidence that immunoglobulin (Ig) therapy can ameliorate atopic symptoms in **atopic dermatitis (**AD), THI ,and primary immunodeficiency deficiencies [5]. Little is known about IgE levels after patients' IgG is normalized or patients are cured of THI although there is strong clinical evidence of a cure from atopy.

Herein we describe a case of marked IgE elevation despite normalization of IgG and improved atopic symptoms in an infant having THI and AD treated by IVIG. We also reviewed IgE levels among infants who had IVIG or had spontaneous recovery.

2. Cases presentation

Eight months aged female presented with skin lesions for a 5-month duration starting at three months of age. Her weight is 7.800 Kg. She had generalized inflamed skin including flexor and extensor surfaces.

The infant has a history of recurrent wheezy chest treated with bronchodilators and cough remedies, she has history of a simple UTI treated with a simple antibiotic. The family consulted the dermatology department for these skin lesions and give local remedies without response to treatment. She was sent for full gene sequencing to yield a normal Bruton tyrosine kinase (*BTK*) genotype hence the infant was labeled as just a case of AD.

She is a product of C/S twin delivery for a P3A3 mother, and; the other twin partner is a male 1.5 kg who succumbed after 2 hours due to severe respiratory embarrassment. She was admitted to NICU, responded to respiratory supportive measures and other supportive measures and kept for 12 days at NICU, and discharged in good condition.

Her sister is 8 years with a history of recurrent wheezy chest. There is no family history of recurrent or severe infections, or familial AD or PID with a negative evident family history of immunodeficiency, life-threatening infections, and atopy.

On presentation, she had frequent bowel motions and occasional vomiting for two days duration treated by oral rehydration therapy(ORS) and a probiotic sachet. She had generalized papular urticaria, no signs and symptoms of severe infection with normal vital signs, patient was sent for Igs assay which showed reduced levels of IgG. IgE was high. (Table 1). The infant was put on hydrolyzed milk formula and given 1st dose of IVIG was given at a dose of 400 mg/kg and followed for seven weeks period.

4 weeks after receiving IVIG, the infant had improved in the IgG level, and AD symptoms. At the same time, there was a rising in the IgE level from 418 IU/ml (which already had an elevated baseline level) to 1014 IU/ml. 7 weeks after IVIG there was a decline in levels of IgG (but still within normal range) and IgE (but still in the high range) (table 1). IgA and IgM were in the normal ranges during initial, follow-up, and final tests but show a direct relation with IgE and IgM results (Table 1).

CBC on April 17,2022: WBC:13.7 x10-9 /l;LYM % : 36.2 ,MID% :4.7 and GRAN%: 59.1; RBC: 5.24; HGB: 13.4g/dl HCT:38.3%; PLT: 630 x 10-9/l.

Total serum protein and liver function enzymes were normal.

Table 1. Immunoglobulins assay before and after IVIG infusion for the case report.

Date	IgA	NV	IgG	NV	IgM	NV	IgE	NV
April 28 ,2022 Before IVIG infusion	30.6* Mg/100 ml	7-83 mg/dL	370* Mg/ dL	453-916 Mg/ dL	74.7* Mg/ dL	0-145 Mg/ dL	418** IU/ml	<10 IU/ml
May 28, 2022 1 month after IVIG infusion	95* Mg/100 ml		1042* Mg/ dL		56* Mg/ dL		1014** IU/ml	
June 11, 2022	34		805		46			
June 15,2022 7 weeks after IVIG infusion	31.8		635		26		888	

*By AGAPPE MISPA -i2 autoanalyzer ** Immuno-assay by Electrochemiluminescence (ECL) technology by the Roche cobas ***

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We also identified a previous report of three cases with THI and AD treated by Igs.

Table 2 summarizes IgE levels before and after normalization of IgG among cases treated by Igs including the present case. All cases showed an increment in IgE levels parallel with an increase in IgG levels. The mean IgE increment equals to 227.5 IU/mL (SD = 164.2).

Results also show an increased mean IgE level from 418.25 to 645.75 with a higher standard deviation of IgE final levels than initial levels.

It seems that IgA and IgM also have a direct relation with IgE (Table 3).

Table 2. Initial, final, mean, deviation from the mean and SD for IgE levels for the cases reviewed.

No	IgE (IU/mL		Ig	Last Ig dose	IgE Increment (IU/mL)
	Initial	final			
1*	160	340	im	At 23 mo of age, 3 mo after cessation of gammaglobulin therapy	180
2*	850	1000	im	At 21 mo of age, 2 mo after cessation of gammaglobulin therapy,	150
3*	245	355	im	At 24 mo of age, 2 mo after cessation of gamma globulin therapy	110
4 * *	418	888	IV	At 9 mo age , after 7 weeks of IVIG	470
Mean	418.25	645.75	-	-	227.5
SD	307.2	347.5			164.2

2,256.25+6,006.25+13,806.25+58,806.25

*Cases number 1,2,and 3 were described by Fineman SM et al. (Fineman, S. M., Rosen, F. S., & Geha, R. S. (1979). Transient hypogammaglobulinemia, elevated immunoglobulin E levels, and food allergy. Journal of Allergy and Clinical Immunology, 64(3), 216–222. https://doi.org/10.1016/0091-6749(79)90098-8)

**(Present case)

Table 3. Immunoglobulin levels for the reviewed cases.

Case number	Time (in relation to Ig therapy)	G	M	A	E
1	Before	180	18	20	160
	3 months after	720	110	85	340
2	Before	220	20	35	850
	2 months after	880	ND	ND	100
3	Before	180	16	26	245
	2 months after	550	ND	ND	355
4	Before	370	74.7	30.6	418
	4 wks after	1042	56	95	1014
	6 wks after	805	46	34	ND
	7 wks after	635	26	31.8	888

3. Discussion

We reported a markedly high IgE level exceeding 1,000 lU/ml in a case with THI and severe AD 4 weeks after being given IVIG (Tables 1&2). Such marked elevation is the 1st to be reported in the presence of normal IgG level after initiating treatment with IVIG.

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Fineman SM et al also reported a markedly high IgE (equal to 1000 IU/ ml) in a child after normalization of IgG but to a lesser extent compared to our current case (table 2).Elevation of IgE levels among patients with THI and AD were also reported in patients was achieved normal IgG levels without receiving Ig. Fineman *et al* described one such case in 1979. [vi] Yasuno T, *et al* in 2007 described 5 cases of infants with high initial IgE levels improved (in terms of normalization of IgG) at age 18-24 months without Ig therapy. IgE levels were increased in three cases, not changed in one case ,and decreased in one case .[vii]

Minowa *et al* in 2018 presented and reviewed 14 cases [4] to clarify the diagnostic features of underlying THI in cases without a history of infections. They found initial high IgE levels among 12, one with normal, and one had no described level. Among those with initial high IgE levels four cases presented with markedly high levels i.e. ≥1000 IU /ml.

Six of these reviewed cases were treated by Igs which represents the Breslin ME *et al* case series.[viii] Final IgE levels were not included within the outcome parameters in this study. [4,8]

Although these case series described this clinical improvement to IVIG, IgE levels were not included within the outcome parameters as mentioned

While THI is usually associated with AD or high IgE levels ,high IgE levels with no evidence of THI are observed in approximately 80% of patients with typical AD.[ix]

Currently, most children with THI are diagnosed because they have recurrent infections. Others are diagnosed because another family member was diagnosed with immunodeficiency. As far as THI might be associated with AD, routine measures of Igs should be performed routinely in every case of AD. The significance and advantage of diagnosis of a topic infant to have THI is to prevent life-threatening infections.

In line with the theoretical framework of allergy in the setting of agammaglobulinemic, it is striking that the occurrence of AD in these patients[x] ,this makes dermatologists asking for Bruton tyrosine kinase genotype as far as IgG measurement is not helpful in the first few months due to trans-placental passage , physiological hypogammaglobulinemia, and the IgG levels reached the expected value around 6 months of age which represents the infant's production. [2] In our case here, the absence of a history of infections and normal genetic test allowed the incorrect diagnosis of typical AD because the underlying THI was overlooked initially.

In our review improved AD symptoms were observed in almost all cases after normalization of IgG despite elevated IgE levels. Breslin *et al* described 6 patients with initial high IgE levels have been responding to IVIG infusion therapy by normalization of IgG levels and improvement in AD symptoms in 5 patients. [8] Walker *et al* described two children with THI and high IgE levels which increased during follow-up to even higher levels: one had markedly increased level to 1080 IU/ml.[3] This study did not describe whether these patients received any form of Ig or not.

Keles *et al* reviewed the medical recordsof children with THI from 2001 to2007. Results showed a high mean final IgE level among those whose IgG was normalized (88 IU/l and the standard deviation was 154). The frequency of high IgE was related to the age of recovery as it increased with age ($p < 0.0001$).[5] Among those with low Ig levels, the mean IgE level was 77 U/l.[5] Interestingly, although the mean IgE level in the low IgG group is lower than the level in patients whose IgG level is normalized. Again, it is not included in this study whether these patients receive Igs.

Clinical studies have shown that Ig therapy can decrease serum IgE levels in patients with allergies without evidence of IgG or IgA deficiency.[xi]It was suggested that high-dose IVIG may provide circulating antibodies that bind to IgE and remove them from the circulation. [11] The mechanism by which IVIG may attenuate the allergic response is still undetermined, clinical studies have shown that Ig therapy can decrease serum IgE levels , while in vitro studies have shown that IVIG can decrease T-cell secretion of TH2

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cytokines.[xii] [xiii] Furthermore, Ig therapy was suggested for the treatment in hyperimmunoglobulin E syndromes.[xiv]

Mechanisms that regulate IgE production may involve B-cell activation by binding to the Fc receptor through its Fc portion. [11]These Fc receptors found on B cells have a low binding affinity, they can bind only to high concentrations of IgG. [11]Production of the T cell-helper factor was suggested to be deficient in THI and AD despite normal numbers of circulating T cells. Low suppressor T-cell was suggested to underlie the elevated IgE levels in the hyperimmunoglobulin E syndromes.[xv]

It seems that in hyperimmunoglobulin E syndromes the IgG levels have an inverse relation with IgE levels so Ig therapy decreases IgE. On the other hand, IgG levels in THI have a direct relation with IgE levels so therapy with Igs therapy leads to increased IgE levels. In our review, the IgG seems to have a direct relation to IgA and IgM (Table 3). This relation is supported by Keles *et al* study which reported similar findings. Whether there is a causative relation between Igs or these findings reflect an underlying common immune abnormality leading to evident direct relations of Igs needs a further investigation. IgG reciprocal relation to IgE as explained above makes such investigations more difficult. IgM has been already shown that have a direct relation with Ig E and A in Keles *et al* study as well as our review (table 3), while in hyper Ig M syndrome there is low or absent levels of serum IgG, IgA, IgE and increased levels of serum IgM[xvi]. This makes IgM next to IgG having a paradoxical behavior too. This indicates the need to explore the pathogenesis of elevated IgE levels in these patients.

4. Conclusions

Given the small sample size and the nature of this review of uncontrolled case series, it is not possible to generalize these findings at this time. However, these findings initially indicate that while restoring normal IgG levels IgE levels have been increased.

Abbreviations

AD: Atopic dermatitis

BTK : Bruton tyrosine kinase

IVIG: Intravenous immunoglobulin

Ig: immunoglobulin

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