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A Case Report and Review of Increased IgE in Patients with Transient Hypogammaglobulinemia of Infancy and Atopic Dermatitis after Normalization of IgG

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Case Report

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ABSTRACT

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). We reported a female infant 8 months old, with THI and severe AD. She was treated with intravenous immunoglobulin (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, patient profile showed normalization of IGE and higher elevation in IgG level. The present article is the first to describe a finding of marked IgE elevation (> 1000 IU/mL) after treatment with IVIG. Furthermore, our finding is supported by our review of increased IgE levels in patients with THI and AD who received IG therapy. According to our review different trend of IgE levels in patients who achieved spontaneous normalization of IgG was found.

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ABBREVIATIONS

AD: Atopic dermatitis
BTK : Bruton tyrosine kinase
IVIG: Intravenous immunoglobulin
Ig: immunoglobulin

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 [1,2]. 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 [3].

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 [4]. 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 THI certain patients have high IgE levels and atopy [5]. High frequencies of atopic disorders have also been described in primary immunodeficiency deficiencies. Atopic dermatitis either non-IgE mediated intrinsic AD which represents just 20% of the AD cases or extrinsic AD (IgE-mediated). Furthermore, patients with IgE-mediated mechanisms may also present, concomitantly, anon-IgE mediated hypersensitivity mechanism [6].

There is evidence that Ig therapy can ameliorate atopic symptoms in atopic dermatitis (AD), THI, and primary immunodeficiency deficiencies. Little is known about the trend of IgE levels after IgG is normalized in patients with both THI and AD, whether this normalization is achieved by Ig therapy or spontaneously.

Herein, we described 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 Ig therapy or had spontaneous recovery. Literature is scarce regarding IgE levels in patients with THI and (AD) after Ig therapy. Furthermore, the coexistence of a high IgE level and THI with AD is well known, but the elevation of serum IgE level ≥ 1000 IU/mL after normalization with Ig therapy is a rare finding. The present article is the first to report such finding after treatment with Ig therapy. This paper also reviewes literature on IgE levels after spontaneous normalization and after IG therapy.

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 therapy with hydrating topical agents with no response to treatment. She was sent for Bruton tyrosine kinase (BTK), full gene sequence test which test for more than 600 mutations in BTK gene by polymerase chain reaction (PCR) followed by DNA sequence analysis. It yielded a normal *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. The stool examination was negative for pus cells and parasites. Stool culture for microbial agents was negative. She had a generalized papular urticaria, no signs and symptoms of severe infection with normal vital signs, patient was sent for serum Ig 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 at a dose of 400 mg/kg and followed for six months.

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 level of IgG (but was still within normal range) and IgE (which was still in the high level) (Table 1). IgA and IgM were in the normal ranges during initial, follow-up, and final tests.

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%;and PLT: 630 x 10-9/l.

Total serum protein and liver function enzymes were normal.

3. DISCUSSION

We reported a markedly high IgE level equal to 1,014 lU/ml in a case with THI and severe AD four weeks after receiving IVIG (Table 1). Such marked elevation is the 1st to be reported after normalization of IgG level with IVIG.

Elevation of IgE levels concomitant to Ig therapy have also been described previously in a three casee series by Fineman SM *et al.* after normalization of IgG with intramuscular Ig injection in 1979 (Table 2) [7]. One of these cases showed a marked high IgE (equal to 1000 IU/ ml) which is slightly lower than our reported cas in a child at 20 months of his age. Fineman SM et al. case series findings support our finding.

IgE levels among patients with THI and AD who achieve spontaneous normalization of IgE looks to have a different trend. The final IgE levels were either lower, higher; or equivocal. The reported higher levels of IgE were to a lesser extent compared to patients who achieved normal IgG levels after receiving Ig therapy. Fineman et al. [7] described one case with higher final IgE level in 1979. Yasuno T, et al. [8] in 2007 described 5 cases of infants with high initial IgE levels (range 41-681), they were improved (in terms of normalization of IgG) at age 18-24 months spontaneously without Ig therapy. IgE levels were mildly increased in one case, no clear trend in 3 cases, and decreased IgE in one case. Sumikawa also described two cases of final lower IgE after spontaneous normalization of IgG [9].

All reviewed cases in Table 2 and our case had a high initial IgE levels except a case presented by Minowa *T* et al. [4] in 2018.

Breslin ME et al. [10] reported six cases with high IgE levels in the range of 309-12,760 treated by Igs. Although these case series described a clinical improvement to IVIG , IgE levels were not included within the outcome parameters.

Table 1. Immunoglobulins assays before and after IVIG infusion

Date/NV	IgA mg/dl*	IgG mg/dl *	IgM mg/dl *	IgE IU/ml **
NV	7-83	453-916	28-145	<10IU/ml
April 28 ,2022 Before IVIG infusion	30.6	370	74.7	418
April 28 ,2022	IVIG infusion			
May 28, 2022	95	1042	56	1014
June 11, 2022	34	805	46	-
June 15,2022	31.8	635	26	888
August 17, 2022	52	408	27	708
September 10, 2022	16	635	75	902
October 8, 2022	65	643	72	901

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

Table 2. Case reports and series of transient hypogammaglobulinemia of infancy with corresponding immunoglobulin levels

Series	Reference	Time of immunoglobulin assay	Age (M)	gender	IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)	IgE (IU/ml)
Series had normalization of their IgG with im immunoglobulin therapy								
1	Fineman SM et al. [7]	Initial	9	F	180	18	20	160
		Last	23		720	110	85	340▲
2		Initial	10	M	220	20	35	850
		Last	21		880	ND	ND	1000▲
3		Initial	11	M	180	16	26	245
		Last	24		550	NA	NA	355▲
Series had normalization of their IgG with intravenous immunoglobulin								
4	Breslin ME [10]	Initial	3	M	87	27	9	2246
		Last	6		889			?
5		Initial	2	F	197	77	25	309
		Last	5		534			?
6		Initial	4	F	115	38	<25	2135
		Last	6		607			?
7		Initial	3	M	164	74	31	856
		Last	5		810			?
8		Initial	1	M	70	21	14	11,492
		Last	7		900			?
9		Initial	3	M	225	<20	29	12,760
		Last	11		677			?
Series with im immunoglobulin therapy had normalization of their IgG spontaneously								
1	Minowa T et al. [4]	Initial	4	M	100	N	N	<20
		final			373	-	-	-
2	Yasuno T et al. [8]	Initial	4	?	85	63	10	41 high
		final			Normalized	-	-	About 40 ↔
3	Yasuno T et al. [8]	Initial	4	?	101	41	8	44 high
		final			Normalized	-	-	About 105 ▲
4	Yasuno T et al. [8]	Initial	4	?	145	34	11	681 high
		final			Normalized	-		About 110 ▼
5	Yasuno T et al. [8]	Initial	4	?	152	39	11	71 (high(
		final			Normalized	-	-	About 70

Series	Reference	Time of immunoglobulin assay	Age (M)	gender	IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)	IgE (IU/ml)
6	Yasuno T et al. [8]	Initial	4	?	176	51	7	22 borderline
		final			Normalized	-	-	About 20↔
7	Sumikawa Y [9]	At 5 months age	6	F	50 low	51	21	218 high
		final			667	104	43	190▼
8	Sumikawa Y [9]	Initial	8	M	227	78	5 low	188 high
		final			569	159	26	99▼
9	Fineman SM et al. [7]	Initial	12	M	260	32	30	190
		Last	20		680	NA	NA	370▲

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 [11].

Most children with THI are diagnosed because they have recurrent infections. 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 THI in a topic infant 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 [12], this makes dermatologists asking for Bruton tyrosine kinase genotype. IgG levels in the first few months may reflect (in part) trans-placental passage; and physiological hypogammaglobulinemia. IgG levels reached the expected value around six months of age which represents the infant own production. In our case here, the absence of a history of severe infections, normal genetic test; and decreased IgG level confirmed the diagnosis of THI.

In our review improved AD symptoms were observed in almost all cases after normalization of IgG despite elevated IgE levels. Five out of six cases presented Breslin et al. [10] showed improvement in AD symptoms after normalization of IgG levels by IVIG infusion. Walker et al. [3] 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. This study did not describe whether these patients received any form of Ig or not.

Keles et al. [5] reviewed the medical records of 71 children (27 females, 44 males) with THI from 2001 to 2007. 21 out of 71 patients (30.9%) had high IgE levels. The mean final IgE level among these 71 children whose IgG was normalized was equal to 88 IU/l. Again, it is not included in this study whether these patients received Ig therapy or not.

Mechanisms that regulate IgE production may involve B-cell activation by binding to the Fc receptor through its Fc portion. In vitro studies have shown that IVIG can decrease T-cell secretion of TH2 cytokines [12,14].

Clinical studies have shown that Ig therapy can decrease serum IgE levels in patients with allergies without evidence of IgG or IgA deficiency [15]. It was suggested that high-dose IVIG may provide circulating antibodies that bind to IgE and remove them from the circulation. Jee et al. [16] described a high total serum IgE concentration during IVIG therapy for AD declined during IVIG treatment and were higher at the 3-month post-treatment visit [16].

In isolated increased IgE conditions, clinical studies have shown that Ig therapy can decrease serum IgE levels, and Ig therapy was suggested for the treatment in hyperimmunoglobulin E syndromes [17]. Again a different trend seems to operate among these patients compared to THI with AD patients who receive Ig therapy as Ig therapy leads to increase IgE levels although ameliorate AD symptoms.

4. CONCLUSIONS

Higher IgE levels were observed after Ig therapy in almost all cases. Spontaneous normalization of IgG is not usually accompanied by increase of IgE. Among cases showed an increase in IgE levels , we did not observe a very high increase in IgE levels like with cases treated by Ig.

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 to higher levels when normalization is achieved by Ig therapy compared to spontaneous normalization.

CONSENT

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying information.

ETHICS APPROVAL

The study was done under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments and comparable ethical standards.

AVAILABILITY OF DATA AND MATERIAL

Further data and material are available on request.

DISCLAIMER

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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