Fcγ receptor polymorphisms in patients with transient hypogammaglobulinemia of infancy presenting with mild and severe infections

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Summary

Background: **Patients with transient hypogammaglobulinaemia of infancy (THI) may have mild infections or be asymptomatic. About 20% of THI patients have very severe and recurrent infections and receive intravenous immunoglobulins (IVIg) for replacement therapy and infection prophylaxis. It is still not clear why some THI patients are severely symptomatic; it has been suggested that there might be additional immunologic or environmental factors or other co-morbidities.**

Objective: **As an immunological factor, Fcγ receptor polymorphisms (H/H-131, H/R-131 and R/R-131 for FcγIIa; V/V-158, V/F-158 and F/F-158 for FcγRIIIa; NA1/NA1, NA1/NA2 and NA2/NA2 for FcγRIIIb) were analysed in THI patients who had very severe infections and need hospitalisation (treated with IVIg) (n:18) and in THI patients who were asymptomatic or had mild infections (treated with antibiotics or received no medication) (n:25).**

Results: **Genotypic distributions between two groups did not deviate significantly from the Hardy-Weinberg equilibrium expectations ($p > 0.05$) and odds ratios for "disease risk estimate" did not show any dominance for any genotype. Allele frequencies did not show any significant difference between the two groups ($p > 0.05$). The number of infections per year for each Fcγ receptor genotype was not significantly different between both groups.**

Conclusion: **There is no association between the heterogeneous clinical picture of THI patients and Fcγ receptor gene polymorphisms.** ***(Asian Pac J Allergy Immunol 2015;33:312-9)***

Keywords: *Fcγ receptor polymorphisms, transient hypogammaglobulinaemia of infancy, infection, IVIg*

Introduction

Transient hypogammaglobulinaemia of infancy (THI) is a heterogeneous and transient immunoglobulin production defect often extending into early childhood, which is defined as the depression of IgG serum levels to more than 2SD below the mean age-specific reference value in a child who otherwise lacks any known congenital immunodeficiency.[1,2] The prevalence of primary immunodeficiencies for Turkish patients is 30.5/100,000 (18.8/100,000 for Ege University records) in the ESID (European Society for Immune Deficiencies) database; two thirds of them are humoral immunodeficiencies.[3] THI is the most common disorder with a prevalence of 7.01/100,000 in registered patients.[3]

Maturation delay in the normal production of immunoglobulins resolves by 30-40 months of life [1,2] and rarely extends up to 5 years.[4] In the blood samples of these patients, initial serum IgG levels are lower than two standard deviations below the mean for age-specific reference values. Then, they begin to increase and are followed by normal values. The diagnosis of THI can be made retrospectively.[5,6] Most of the patients frequently have mild infections and/or are sometimes asymptomatic. About 20% of THI patients may have very severe infections and need hospitalisation because of these infections.[7] In addition, these infections damage the quality of life and prevent attendance at day-care centres. The Primary Immunodeficiency Committee classifies THI among primary humoral immunodeficiency and suggests that severely symptomatic THI children should be treated with intravenous immunoglobulin (IVIg) only after the failure of large spectrum antibiotic prophylaxis.[8,9]

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In paediatric immunology clinics, IVIg is preferred in about 10-20% of THI patients to stop the vicious circle of recurrent infections.[1,9] However, it is not still clear why some of the patients are severely symptomatic and others are not. It has been suggested that there might be additional immunologic or environmental factors or some other co-morbidities for those THI patients who need IVIg to prevent infections.

Fcγ receptors-expressed on haematopoietic cells, including macrophages, dendritic cells, and neutrophils, occur in different subtypes, some of which are activating and others are inhibitory. Fcγ receptors provide a link between cells of the innate and adaptive immune systems.[10] Several studies have shown that IVIg may influence the effect of Fc receptor-mediated activity of immune relevant cells by interacting with Fc regions.[10] It is generally thought that IVIg acts to block activating receptors, induce inhibitory factors and cause a down-regulation of the damaging activity of macrophages.[10]

On the other hand, it has been reported that the FcγRIIa gene polymorphism (R131R) may increase the risk and susceptibility for recurrent infectious diseases in children.[11] It might be speculated that some THI patients may have some FcγR gene polymorphisms increasing the severity of illness. Furthermore, clinical response and the success of IVIg therapy in THI patients may have an association with these polymorphisms.

The most abundant immunoglobulin, IgG, mediates key effector functions through interaction with Fcγ receptors (FcγRI, FcγRII, FcγRIII) encoded by distinct genes, and differ in their distribution on different cell types, strength and capacity.[12,13] Polymorphisms in the human FcγR genes IIa, IIIa and IIIb further enhance the heterogeneity of these molecules.[13]

In this study, we aimed to identify the Fcγ receptor polymorphisms in THI patients with very severe infections who needed hospitalisation (treated with IVIg) and in THI patients who were asymptomatic or had mild infections (treated with antibiotics or received no medication) in order to understand whether there is an association between the heterogeneous clinical picture of THI patients and FcγR genes polymorphisms.

Methods

Study design and patient characteristics

The following criteria were used to diagnose THI patients in Ege University Faculty of Medicine, Department of Paediatric Immunology, Izmir, Turkey: 1- At admission, IgG serum levels below up two standard deviations (SD) of age-related normal values; 2- circulating B cells >2%; and 3- the exclusion of known causes of hypogammaglobulinaemia such as drugs, genetic disorders, chromosomal abnormalities, infectious diseases, neoplasia, systemic disorders and prematurity. Forty-three patients whose IgG reached age-related normal levels during follow-up were included in the study. In these patients, 18 of them received IVIg (IVIg group) and 25 patients received prophylactic antibiotics or did not receive any medication (non-IVIg group) before normalisation of their immunoglobulin levels.

THI patients with the following criteria had received IVIg therapy: 1- patients who had six times or more upper respiratory infections and/or otitis media, or two or more sinusitis, or one or more pneumonia in one year; 2- patients who used antibiotics more than six times a year; 3- patients who needed intramuscular or intravenous injection for the recovery of infections; and 4- patients who had severe infections such as meningitis or sepsis. Patients fulfilling these criteria had received 400-500 mg/kg IVIg with 4 week intervals and were all monitored for IgG-M-A levels just before IVIg replacement. Ethics Committee approval and informed written consent for participation was obtained in all cases.

Demographic data such as name, gender, date of birth, age at onset of symptoms, age at admission, age at diagnosis, family history, follow-up and IVIg therapy duration, as well as clinical data including frequency of infections, were also recorded.

Methods

The following laboratory methods were used for the evaluation of THI patients:

Whole blood count, *leucocyte counts, absolute neutrophil and lymphocyte counts* were analysed with a haemocounter, Cell-Dyn 3700, Abbott Diagnostics, USA. *Serum immunoglobulins (IgG, IgM, IgA)* were analysed quantitatively by Dade Behring BNII nephelometer, Siemens, Germany. *Percentages and absolute counts of lymphocyte subsets* (T, B, T helper, T cytotoxic, natural killer and active T cell) were investigated by flow cytometry, FACSCalibur, Becton Dickinson, USA. All cell subpopulations were acquired using Cell Quest-Pro software (BD Biosciences). Antibody responses to tetanus and *Haemophilus influenza* were analysed by commercial ELISA kits.

Fcγ receptor genotyping analyses

All patients were evaluated for Fcγ receptors polymorphisms as follows: H/H-131, H/R-131 and R/R-131 for *FcγIIa;* V/V-158, V/F-158 and F/F-158 for *FcγRIIIa*; NA1/NA1, NA1/NA2 and NA2/NA2 for *FcγRIIIb*.

DNA purification

Blood Mini Kits (Qiagen GmbH, Hilden, Germany) were used according to the manufacturer's instructions.

FcγIIa genotyping

FcγIIa genotyping was performed by using the method defined by Flesch et al. (14). A 25 μL PCR mixture containing 2.5 μL of 10x PCR buffer (Applied Biosystems, Foster City, CA, USA), 2 mM $MgCl_2$, 200 μM of each dNTP (Promega, Madison, USA) and 0.5 U AmpliTag DNA Polymerase (Applied Biosystems) were used. In addition, 0.5 μM of H131-specific sense primer (5'-ATCC-CAGAAATTCTCCCA-3') from the extracellular domain or 0.5 μM R131-specific sense primer (5'-ATCCCAGAAATTCTCCCG-3') was used. All oligonucleotides were synthesised by Qiagen Operon Co. and 0.5 μM common anti-sense primer from an area down-stream of the intron (5'-CAATTTTG CTGCTATGGGC-3'). The resulting fragment was 253-bp in length. As an internal PCR control, 0.125 μM human growth hormone (HGH)-1 forward primer (5'-CAGTGCCTTCCCAACCATT CCCTTA) and 0.125 μM HGH-II reverse primer (5'-ATCCACTCACGGATTTCTGTTGTGTTTC-3') were used, resulting in a 439-bp fragment.

A thermal cycler (GeneAmp 9700, Applied Biosystems) was used to perform a hot-start PCR as follows: 5 min at 95°C, 10 cycles of 1 min at 95°C, 2 min at 57°C, and 1 min at 72°C; thereafter, to enhance sensitivity, we used 22 cycles of 1 min at 95°C, 2 min at 54°C, 1 min at 72°C and a final extension step of 5 min at 72°C. The PCR amplification products were separated on a 2% agarose gel and visualised by ethidium bromide staining.

FcγIIa genotyping

FcγIIIa genotyping was performed using the method of Van den Berg et al.[15] In this amplification refractory mutation system-PCR, the allele specific primers (KIM-G(V): 5'TCTCTGAAGACACATTT TACTCCCTAC-3' and KIM-1 (F): 5'-TCTCTGA AGACACATTTCTACTCCCTAA-3') amplified a 160-bp fragment with their anti-sense downstream primer A103 (5'-ATATTTACAGAATGGCACA GG-3'). The internal control primers were Ctrl-1 and Ctrl-2, amplifying a 270-bp product. Again, two PCR procedures were required to genotype a subject.

Reactions were performed with 175 ng of genomic DNA in a 25 μL reaction volume, containing 2.5 μL PCR Gold buffer, 62.5 nmol $MgCl_2$, 1.25 nmol each of the four dTNPs, 11.9 pmol KIM-G(V), 66.4 pmol KIM-G(F), 15.4 pmol A013, 1.1 pmol each of the two control primers and 0.5 U Ampli Tag Gold (Applied Biosystems).

PCR conditions were denaturation for 10 min at 95°C; 32 cycles of 95°C for 30 s, 57°C for 20 s, 72°C for 25 s and a final extension step at 72°C for 7 minutes.

FcγIIIb genotyping

FcγIIIb gene genotyping was performed using the method of Bux et al.[16] The NA1-specific primer (5'-CAGTGGTTTCACAATGTGAA-3') gave a 141-bp fragment, and the NA2-specific primer (5'-CAATGGTACAGCGTGCTT-3') amplified a 219-bp fragment. The reverse primer (5'-ATGG ACTTCTACCTGCAC-3') did not differentiate between the two allotypes. Because there was a substantial difference in length between the NA1-specific and NA2-specific reaction products, both alleles could be detected in the same reaction. The 25 μL reaction mixture used contained 100 ng of genomic DNA, 3.7 μL 10x PCR buffer (Applied Biosystems), 25 ng $MgCl_2$, 1 nM of each dNTP (Promega), 4 pmol of each of the control primers, 0.012 nmol of the NA1 and NA2 primers, 0.025 nmol of the reverse primer and 0.5U AmpliTaq DNA polymerase (Applied Biosystems). After denaturation for 3 min at 94°C, 30 PCR cycles consisting of 94°C for 1 min, 57°C for 2 min and 72°C for 1 min were run. After a final extension of 1 min at 72°C, samples were resolved in 2% agarose gels stained with ethidium bromide.

To validate the accuracy and reproducibility of the results obtained using the techniques described above, we randomly ran 20% of samples from both groups for each FcγIIa, FcγIIIa and FcγIIIb genotype using a direct DNA sequencing technique with the ABI PRISM 310 Genetic Analyser System (Applied Biosystems).

Statistical analysis

All clinical and laboratory data between the IVIg and non-IVIg groups were compared with each other. Statistical analyses were performed using SPSS Windows Version 17.0, SPSS Inc., Chicago,

Table 1. Demographical and laboratory data of patient groups (patients treated with or without IVIg)

	IVIg group median (IQR)	**non-IVIg group** median (IQR)	***p* value***
Age (months)	39 (29.2-53.5	43 (32.5-68)	0.307
Age at beginning symptoms (months)	2.75 (1.0-5.25)	6 (2-14.5)	0.085
Age at admission (months)	10 (5-14.5)	18 (15-25.5)	0.000
Follow up duration (months)	26 (20-369	20.5 (8-48.2)	0.467
IVIg treatment duration (months)	12 (6-16)	-	
Infection per year (n) (during follow-up)	9 (6-12)**	7 (5.5-8)	0.064
Frequency of infection			0.773
<6 times per year	%18.8***	%17.6	
6-12 times per year	%56.2***	%64.7	
>12 times per year	%25.0***	%17.6	
Leucocyte count (10^3/ μL)	11.1(7.87-12.9)	9.46 (8.49-12.3)	0.853
Absolute lymphocyte/ mm^3	5315 (4187-8641)	4650 (3920-6090)	0.479
Initial IgG (mg/dL)	314 (262.2-447.5)	520.5 (428.2-612.7)	0.000
Initial IgA (mg/dL)	14.1 (10.5-26)	24.4 (17-43.5)	0.013
Initial IgM (mg/dL)	60.6 (39.5-91.8)	68.5 (50.5-84.2)	0.542
$CD3^+$ T cells %	63 (58.8-70.5)	65 (59.6-68.5)	0.702
$CD3^+4^+$ T helper cells %	45 (38.4-47.9)	38.9 (35.2-46)	0.058
$CD3^+CD8^+$ T cytotoxic cells %	17 (13.9-23)	21.3 (16.5-25.6)	0.103
$CD19^+$ B cells %	25.7(18.7-29.4)	24.6 (18.1-27.3)	0.344
$CD3^-CD16^+CD56^+$ Natural killer cells %	7.6 (4.23-11.3)	7 (5.31-13.5)	0.828
$CD3^+$HLA DR^+ T cells %	5.9 (2.25-7.89)	5.66 (4.75-5.66)	0.333
Anti-tetanus antibody (IU/mL)	0.1 (0.09-0.17)	1.14 (0.23-4.09)	0.050
Anti-Hib antibody (IU/mL)	0.59 (0.43-0.49)	2.65 (0.80-6.34)	0.086

**p* value: Mann Whitney U test, SPSS.17.0 between median-IQR/interquartile range or % values

** During IVIg therapy in follow-up period, not before IVIg therapy

***Before IVIg therapy

IL and the Epi-info 3.3.2 program. A two-sided *p* value less than 0.05 was considered to indicate statistical significance. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated and deviation from the Hardy Weinberg expectancy was examined with the Chi-square test.

Results

Clinical and immunological data of 43 THI patients (n = 15, 35% female and n: 28, 65% male) between the ages of 12 and 112 months (mean 47.7±22.1) were evaluated. A total of 42% patients (n = 18) received IVIg treatment and twenty- five patients (58%) who were not treated with IVIg served as disease control group. Demographical and clinical data of two groups were listed in Table 1.

The onset of symptoms were earlier in IVIg group (p = 0.085) and there was a statistically significant difference for the median age at first admission to our clinic (10 and 18 months in IVIg and non-IVIg group, respectively) ($p < 0.001$). When receiving regular IVIg therapy, there was no statistically significant difference in terms of frequency of infections between two groups (p = 0.773), although infections were much more frequent and severe before these patients joined the IVIg group.

Initial immunoglobulin concentrations were significantly lower in the IVIg group than the non-IVIg group for IgG ($p < 0.001$) and IgA (p = 0.013) showing the severity of immune deficiency in those patients who were recruited into the IVIg therapy group. Lymphocyte subsets did not show any statistically significant difference between the two groups. Specific antibody response against tetanus (anti-tetanus IgG) and *Haemophilus influenzae* type B (anti- Hib IgG) were found to be very low and inadequate in the IVIg group (Table 1). This was further evidence for the need to receive IVIg therapy in IVIg group patients. Percentages of $CD19^+CD27^+$

Table 2. Fcγ receptor genotype frequency of THI patient groups who treated or untreated with IVIg

Genotype	IVIg group			non-IVIg group						
	observed		expected	observed		expected	*p*	X^2	OR**	OR (95% CI)
	n	%	n*	n	%	n*				
FcγRIIa										
HH	9	50	8.68	7	28	9.61	0.141	2.168	0.560	0.26 - 1.22
HR	7	38.9	7.64	17	68	11.78	0.058	3.596	1.749	0.92 - 3.31
RR	2	11.1	1.68	1	4	3.61	0.367	0.815	0.360	0.04 - 3.67
FcγRIIIa										
VV	7	38.9	7.35	4	16	6.76	0.090	2.880	0.410	0.14 - 1.19
VF	9	50	8.31	18	72	12.48	0.141	2.168	1.440	0.85 - 2.43
FF	2	11.1	2.35	3	12	5.76	0.929	0.008	1.080	0.20 - 5.82
FcγRIIIb										
NA1	6	33.3	5.56	8	32	8.41	0.927	0.008	0.960	0.40 - 2.29
NA1/NA2	8	44.4	8.89	13	52	12.18	0.625	0.239	1.170	0.62 - 2.22
NA2	4	22.2	3.56	4	16	4.41	0.605	0.268	0.720	0.21 - 2.50

*Hardy- Weinberg expectancy

**Odds ratios (OR) with 95% confidence intervals (CI) (risk estimate) were calculated and deviation from the Hardy Weinberg expectancy was examined with the chi- square test. (SPSS.17.0)

memory B cells did not differ in IVIg and non-IVIg groups (median-IQR percentages of $CD19^+CD27^+$ memory B cells were 2.4 (1.80-3.16) and 3.4 (2.14-4.42) in the IVIg and non-IVIg groups, respectively, $p = 0.355$).

Genotype distributions of FcγRIIa, FcγRIIIa and FcγRIIIb for each group are presented in Table 2.

In the IVIg group, patients presented a genotype distribution as follows: 50% H131H homozygote (n = 9), 38.9% H131R heterozygote (n = 7), and 11.1% R131R homozygote genotype (n = 2) for FcγRIIa; 38.9% V158V homozygote (n = 7), 50% V158F heterozygote (n = 9), and 11.1% F158F homozygote (n = 2) genotype for FcγRIIIa; and 33.3% NA1 (n = 6), 44.4% NA1/NA2 heterozygote (n = 8) and 22.2% NA2 (n = 4) genotype for FcγRIIIb.

In the non-IVIg group, patients presented 28% H131H homozygote (n = 7), 68% H131R heterozygote (n = 17), and 4% R131R homozygote genotype (n = 1) for FcγRIIa; 16% V158V homozygote (n = 4), 72% V158F heterozygote (n: 18), and 12% F158F homozygote (n = 3) genotype for FcγRIIIa; and 32% NA1 (n = 8), 52% NA1/NA2 heterozygote (n = 13) and 16% NA2 (n = 4) genotype distribution for FcγRIIIb.

Genotypic distributions between two groups did not deviate significantly from the Hardy-Weinberg equilibrium expectations ($p > 0.05$) (Table 2). Odds ratios for "disease risk estimate" did not show dominance for any genotype in either group.

When we compared lymphocyte subsets according to genotype distribution, in the IVIg group, the initial CD19% was significantly lower in patients with the R131R genotype ($p = 0.026$). Genotypes H131H ($p = 0.009$) and H131R ($p = 0.001$) were more commonly present in male patients than in females and consanguinity was seen in patients with V158F genotype ($p = 0.023$), in the IVIg group.

Allele frequencies for both groups are summarised in Table 3. Odds ratios that were calculated for the mutated allele in relation to the normal allele did not show any significant difference between two groups ($p > 0.05$). In other words, none of these alleles had an effect on disease development. The number of infections per year (at admission) for each Fcγ receptor genotype also did not show any significant difference between IVIg and non-IVIg groups (Table 4).

Discussion

THI is characterised by a maturation delay in the normal production of immunoglobulin and resolves by three to five years old.[1,10]

In the report of Walker et al.,[17] the mean age of symptoms of THI patients was 10 months (range 2-24). The beginning of symptoms was earlier in the IVIg group (median 2.75 months) compared to other THI patients who did not receive IVIg (median 6 months). This was a supporting finding showing the

Table 3. Comparison of Fcγ receptor allotypes in IVIg and non-IVIg groups

allotype	IVIg group (n)	non-IVIg group (n)	p	OR	OR (95% CI)
H131	25	31	0.480	0.72	0.26 - 1.96
R131	11	19			
V158	23	26	0.270	0.61	0.23 - 1.61
F158	13	24			
NA1	20	29	0.820	0.82	0.43 - 2.87
NA2	16	21			

p: Mantel-Haenszel chi- square test

severity of infections and the importance of beginning IVIg therapy.

Antibiotic prophylaxis or follow-up without medication is often preferred by physicians, but some authors have proposed that a lack of specific antibodies should be used as a decision point when treating THI patients with IVIg.[17,18] Duse et al.[9] suggested that IVIg should be used in severely symptomatic children in order to stop the vicious circle of recurrent infections. The data obtained from patient records before including them into the study showed that infections were much more frequent and severe in the IVIg patient group (Table 1). Another important finding was the significantly lower levels of IgG, IgA and anti-tetanus IgG antibody levels in THI patients who were recruited into the IVIg group using only clinical findings.

Fc receptors for IgG form an essential bridge between the humoral branch and the effector cells of the immune system.[19] The two genetically determined structurally different allotypes of human FcγRIIa, the products of the FcγRIIa-R131 and FcγRIIa-H131 alleles, have functionally different reactivities with human IgG2.[19] In humans, FcγRIIa- R131 allotype does so only poorly.[19] Furthermore, binding studies using Ig fusion proteins of FcγRIIa (CD32A) alleles showed that the R allele has significantly lower binding not only to human IgG2, but also to IgG1 and IgG3 subtypes.[20]

Fcγ receptor polymorphisms are considered to be heritable risk factors for autoimmune and infectious diseases and support for a relevant role of these polymorphisms has been obtained in previous studies. Results from association studies are sometimes contradictory, possibly due to differences in the inclusion criteria, sample size, ethnicity and definitions of disease severity. The FcγRIIa-R131R genotype was found to be enriched among bacteriaemic pneumonia patients, suggesting that this polymorphism increases host susceptibility to pneumonia.[21] Similar to this study, decreased frequencies of FcγRIIa-H131H genotypes among Dutch children with recurrent upper airway infections by *S. pneumonia* have been reported.[22] In a previous study, the FcγRIIa-R131R genotype in children with recurrent febrile infections (25%) was significantly higher than that in the healthy controls (4.2%) (p = 0.001).[11] In addition, the R131R allele was higher in the study group, whereas H131 was higher in the control group, which suggests that the existence of the R131 allele alone increases the risk of infectious diseases.[11]

The clinical findings of THI patients are very heterogeneous, with some of them presenting recurrent, severe and early beginning infections (IVIg group in this study) and others being asymptomatic or rarely presenting mild infections (non-IVIg group). There might be an additional immunological factor such as Fcγ receptor polymorphisms causing severe and recurrent infections. We searched out the Fcγ receptor polymorphisms in both groups of THI patients. Genotypic distributions between two groups did not deviate significantly from the Hardy-Weinberg equilibrium expectations (p >0.05) and odds ratios for "disease risk estimate" did not show dominance for any genotype in both groups. In addition, different Fcγ receptor genotypes had a similar number of infections in the IVIg and non-IVIg group (Table 4). There are no other studies in the literature investigating the Fcγ receptor polymorphisms in THI patients, so we could not discuss our data with literature findings. In the IVIg group, "lower numbers of $CD19^+$ B cells" in the "R131R genotype" may have some importance for explaining clinical findings, because both of these immunological factors have correlations with an increased incidence of infection.

Binstadt et al.[12] tried to speculate on how Fcγ receptor polymorphisms might influence response to

Table 4. Comparison of number of infections per year in IVIg and non-IVIg groups for each FcγR genotypes.

genotype	infection per year (mean+SD)		*p*
	IVIg group*	non-IVIg group	
H131H	10.5±3.59	7.0±6.24	0.293
H131R	9.14±2.96	10.2±6.74	1.000
R131R	5.50±0.70	7.0±0.0	0.221
V158V	8.71±3.09	9.33±2.51	0.816
V158F	9.14±3.62	9.83±7.87	0.826
F158F	12.0±4.24	8.67±1.52	0.374
NA1	11.0±2.44	8±5.25	0.446
NA1/NA2	9.18±3.48	11.1±7.50	0.928
NA2	5.0±1.41	6.50±0.70	0.221

IVIg therapy in some autoimmune diseases (immune thrombocytopenic purpura, systemic lupus erythematosus, multiple sclerosis, etc.) for which clinically significant Fcγ receptor polymorphisms have been described. The authors could not find any evidence that Fcγ receptor polymorphisms might impact the efficacy of IVIg therapy for these diseases.[12] Recently, two reports have documented the involvement of the FcγRIIIa polymorphism in the therapeutic response of immune thrombocytopenic purpura and non-Hodgkin's lymphoma.[13] These two studies contrast with the current study, since in addition to genotypes, allele frequencies did not show any significant difference between IVIg and non-IVIg groups. There was no clear correlation explaining the severity of THI patients with Fcγ receptor polymorphisms, so we did not search for the efficacy of IVIg therapy in different patients with different Fcγ receptor polymorphisms.

In conclusion, there is no association between the heterogeneous clinical picture of THI patients and Fcγ receptor gene polymorphisms. In other words, different genotypes or alleles of Fcγ receptor genes do not explain why some THI patients are severely symptomatic.

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