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Clinical and immunological features of 55 adult patients with selective IgG4 subclass deficiencies

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Abstract

Aim: Despite intensive research on elevated IgG4 concentrations in serum, little is known about the importance of selective IgG4 subclass deficiency. We investigated the clinical and immunological characteristics of 55 patients with selective IgG4 subclass deficiency.

Materials and Methods: IgG subclass analyses performed in our hospital over 3 years were examined. The clinical features of patients with selective IgG4 subclass deficiency were reviewed, and the definitive diagnoses and the reasons for IgG subclass analysis were recorded.

Results: Of 1,675 IgG subclass analyses performed, 55 were indicative of selective IgG4 subclass deficiency. The final diagnoses associated with selective IgG4 subclass deficiency were variable. The most common clinical finding was recurrent infections (33 patients, 60%), and most had upper respiratory tract infections (18 patients, 54.5%). Allergic diseases were noted in 25 patients (45.4%) and were the second most common conditions. Allergic rhinitis was the most frequent allergic disease. Autoimmune diseases were noted in 18 patients (32.7%), Hashimoto thyroiditis being the most frequent.

Conclusion: This is the first study of adult selective IgG4 subclass deficiency at a single tertiary medical center in Turkey. In patients with IgG4 deficiency, while the primary concern is the presence of recurrent infections, consideration should also be given to allergic and autoimmune diseases.

Introduction

Four subclasses of human IgG were identified in 1964 using monoclonal IgG from multiple myeloma patients [1]. The selective IgG subclass deficiency is defined by normal levels of total IgG, IgA, and IgM and a significant reduction in the serum level of one or more IgG subclasses (< 2 SDs below the mean) [2]. IgG4 subclass deficiency in the serum was first described in 1981 in four patients with frequently recurrent upper respiratory tract infections [3]. It was later observed in other diseases, including asthma and pulmonary hemosiderosis [4]. In healthy individuals, IgG1 accounts for 65%, IgG2 for 25%, IgG3 for 4–8%, and IgG4 for 1–5% of total IgG [5]. The half-life of IgG4 is about 21 days [6].

In adults, the reference range for IgG4 is 0.051–1.240 g/L, with an upper limit of 0.85–1.36 g/L [7]. A high level is defined as >1.36 g/L [8]. A cut-off value of 0.05 g/L is utilized for adults to identify IgG4 deficiency [9]. Serum levels decrease with age and are lower in women than men [6]. As other IGs, IgG4 consists of two heavy and two light chains but differs in that noncovalent bonds link its two heavy chains. IgG4 heavy chains have two disulfide bonds in the hinge region. The IgG4 molecule exhibits low affinity for C1q and is incapable of activating the classical complement pathway [10]. Unlike other IgG immunoglobulins that play a role in the opsonization of microbes by phagocytes, IgG4 does not bind to Fcγ and C1q receptors due to its low affinity for target antigens [11]. IgG4 contributes to protection against allergic diseases by actively inhibiting mast cell degranulation. However, it suppresses antitumor responses via Fc-gamma receptor 1 blockage. Extended or recurrent exposure to antigens can elevate the serum levels of IgG4 [12].

The IgG4 level is higher in bronchoalveolar lavage fluid than in serum. Like IgA and IgE, IgG4 mediates immune

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defense of the lung by being present on mucosal surfaces [13]. While respiratory tract infections are the most prevalent indicators of selective IgG4 subclass deficiency, it can also manifest as diarrhea and recurrent giardiasis based on effects on other mucosal surfaces [14].

Elevated serum levels of IgG4 have been a focus of research. By contrast, selective IgG4 subclass deficiency has been neglected despite its close association with infectious and non-infectious inflammation. Most studies of IgG subclass deficiency have involved children, and few have evaluated the clinical and immunological features of IgG4-deficient adult patients.

Materials and Methods

Study design

The results of IgG subclass evaluations performed from January 1, 2020, to January 1, 2023, at the Adult Clinical Immunology and Allergy Department, Necmettin Erbakan University, Konya, Turkey, were analyzed. The study protocol received approval from the university's ethics committee (decision no. 2023/4121). Selective IgG4 subclass deficiency data were gathered from patient files and the hospital database. In total, 1,675 patients were enrolled and 1620 were excluded for the reasons shown in Figure 1. We identified 55 adult patients with selective IgG4 subclass deficiency, and a study has been completed on these patients. Patients were ≥18 years old at the time of diagnosis, had IgG4 values checked at least twice, and the IgG4 level was ≤0.05 g/L while maintaining normal levels of IgA, IgM, IgG, IgG1, IgG2, and IgG3.

Data collection

The medical records were reviewed to obtain demographic information, family history, clinical symptoms, allergies, autoimmune diseases, and malignant conversion of the patients. Warning sign responses recommended by the European Society of Immunodeficiency (ESID) for adult primary immunodeficiency diseases (PID) were obtained from the patient files and the hospital [15]. The reasons for evaluating IgG subclass were recorded. None of the patients used drugs known to cause a decrease in immunoglobulins selective. Patients with a diagnosis of systemic lupus eritematosus (SLE) and systemic sclerosis were receiving hydroxychloroquine. No asthma patients were using systemic steroids.

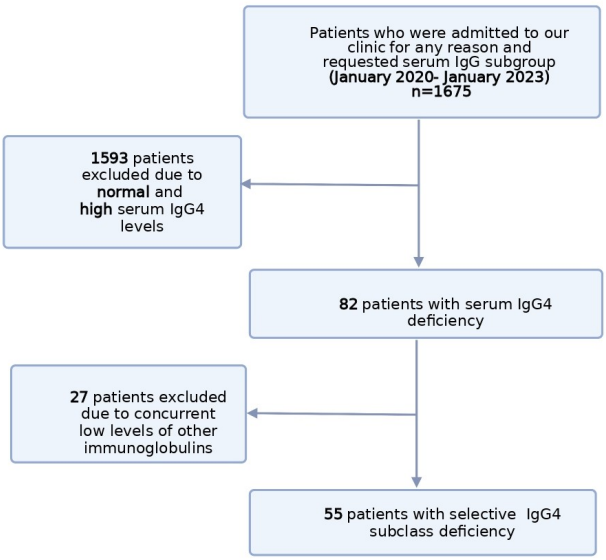

Figure 1. Flow chart of patient screening based on the inclusion and exclusion criteria.

Serum immunoglobulin measurements

Serum levels of immunoglobulin were determined using nephelometric methods (Siemens BNII System, Erlangen, Germany).

Flow cytometry

Peripheral blood lymphocyte subsets were assessed through flow cytometry, employing a panel that included $CD3^+$ (T cells), $CD3^+CD4^+$ (helper/inducer T cells), $CD3^+CD8^+$ (cytotoxic T cells), $CD19^+$ (B cells), and $CD3^-CD16^+CD56^+$ (NK cells) cells. The normal ranges of immunoglobulins (mg/dL) are as follows: IgM: 46–304, IgA: 70–400, IgG: 700–1600, IgG1: 405–1011, IgG2: 26–136 IgG3: 11–85, and IgG4: 5–201. The normal ranges of lymphocyte percentages (absolute numbers) are: $CD3^+$: 56–86 (830–3050), $CD3^+$ $CD4^+$: 32–63 (495–1475), $CD3^+$ $CD8^+$: 13–43 (185–1175), $CD19^+$ CD3– : 5–30 (120–670), and CD3–$CD16^+$ $CD56^+$: 4–26 (75–765).

Statistical analysis

The analyses conducted in this study were primarily descriptive. Data were analyzed using SPSS software, v. 22.0. Descriptive analyses provided the frequency data regarding count (n) and percentage (%). The normality of numerical data was examined using the Kolmogorov-Smirnov test. Data not conforming to normal distribution were presented using the median (interquartile range (IQR)) with a 95% confidence interval.

Results

In all, 1675 IgG subclass analyses were conducted. The median age of patients was 37 years (IQR, 27–48 years) and 1005 (60%) were female. Selective IgG4 subclass deficiency was found in 55 patients. Among the 55 patients, a notable female predominance was observed with a female-to-male ratio of 2.6:1, and the median age at diagnosis was

Table 1. Reasons for IgG subclass measurement among patients with selective IgG4 subclass deficiency (n = 55).

Reason	n (%)
Frequent infections or PID suspicion	25 (45.4%)
Urticaria or angioedema	10 (18.1%)
Rhinosinusitis	8 (14.5%)
Asthma or BHR	5 (9%)
Family history of PID	2 (3.6%)
Others	5 (9%)

Abbreviations: BHR, bronchial hyperresponsiveness; PID, primary immune deficiency.

Table 2. Clinical characteristics of patients with selective IgG4 subclass deficiency.

Sex (female: male)	2.6:1
Age (years)	32 (26–44) (95% CI=33.14-39.81)*
Repeated infections	33 (60%)
Allergic diseases	25 (45.4%)
Bronchial asthma	9 (16.4%)
Allergic rhinitis	17 (30.9%)
Urticaria	13 (23.6%)
Autoimmune diseases	18 (32.7%)
Hashimoto thyroiditis	7 (12.7%)
Coeliac disease	4 (7.3%)
Behçet's disease	2 (3.6%)
Ankylosing spondylitis	2 (3.6%)
FMF	2 (3.6%)
Systemic sclerosis	2 (3.6%)
SLE	2 (3.6%)
Crohn's disease	1 (1.8%)
Vitiligo	1 (1.8%)
Primary immunodeficiency	2 (3.6%)
Malignancy	4 (7.3%)
Hereditary angioedema	1 (1.8%)
Total patients (n)	55

* Data are medians (IQR) (95% CI).. Abbreviations: FMF, familial Mediterranean fever; SLE, systemic lupus erythematosus.

Table 3. Infection status.

Upper respiratory infections	18 (54.5%)
Lower respiratory infections	8 (24.2%)
Urinary tract infections	5 (15.1%)
Gastroenteritis	3 (9%)
Furunculosis	3 (9%)
Subacute thyroiditis	1 (3%)
Herpes zoster	1 (3%)
Number of infected patients (n)	33

A patient may have more than one infection at the same time.

32 years (IQR, 26-44 years) (Table 2). The reasons for IgG subclass measurement are listed in Table 1. Frequent infections and suspicion of PID were the main reasons for IgG subclass measurement in 25 patients (45.4%).

The final diagnoses of patients presenting with selective IgG4 subclass deficiency are listed in Table 2. The most common clinical finding was recurrent infections (33 patients, 60%), and most had upper respiratory tract infections (18 patients, 54.5%) (Table 3). Allergic diseases were noted in 25 patients (45.4%) and were the second most common conditions. Allergic rhinitis was the most common allergic disease. Autoimmune diseases were noted in 18 patients (32.7%), Hashimoto thyroiditis being the most common. Other associated autoimmune diseases were celiac disease, ankylosing spondylitis, Behçet disease, familial Mediterranean fever (FMF), SLE, systemic sclerosis, Crohn disease, and vitiligo. Four patients (7.3%) had cancer (bladder carcinoma, bronchopulmonary carcinoma, breast carcinoma, and malignant mesenchymal tumor). Two patients (3.6%) were previously diagnosed with

Table 4. ESID warning signs in patients with selective IgG4 subclass deficiency (n = 55).

	n (%)	
	No	Yes
1: Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)?	22 (40%)	33 (60%)
2: Recurring infections or infections requiring prolonged antibiotic therapy?	45 (81.8%)	10 (18.2%)
3: Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, or cellulitis)?	55 (100%)	0 (0%)
4: Two or more radiologically proven pneumonia within 3 years?	47 (85.5%)	8 (14.5%)
5: Infection with unusual localization or unusual pathogen?	55 (100%)	0 (0%)
6: Primary immunodeficiency disease in the family?	50 (90.9%)	5 (9.1%)

Abbreviations: ESID, European Society of Immunodeficiency; PID, primary immunodeficiency disease.

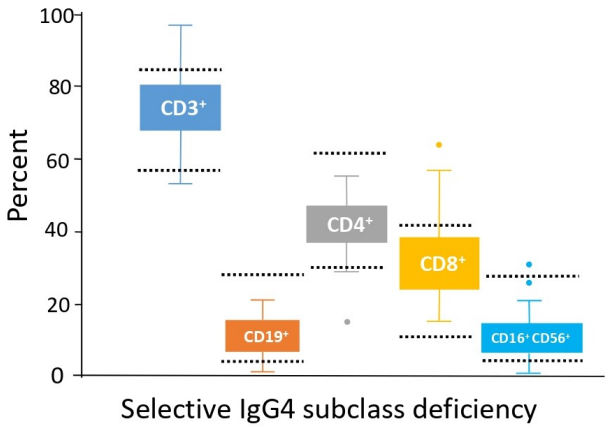

Figure 2. Upper and lower limits of normal for lymphocyte subsets (horizontal lines). $CD3^+$ T cells; $CD3^-CD19^+$ B cells; $CD3^+CD4^+$ helper T cells; $CD3^+CD8^+$ T cells; and $CD3^-CD16^+CD56^+$ natural killer (NK) cells.

primary immunodeficiency, and intravenous immunoglobulin (IVIG) therapy was initiated. One patient (1.8%) had hereditary angioedema (Table 2).

Patients were asked about the six ESID warning signs for adult PID. Thirty-three patients (60%) stated that they had four or more infections per year. See Table 4 for the

remaining data. None of the patients had a history of severe infection or infection with an unusual pathogen.

The lymphocyte subpopulations of 44 patients (80%) were examined. The proportions of T cells, B cells, helper/inducer T cells, cytotoxic T cells, and NK cells are shown in Figure 2. The percentages of lymphocyte subgroups in most patients were within the normal range. One patient had low numbers of helper/inducer T cells; genetic testing indicated GATA2 deficiency. Large numbers of cytotoxic T cells and NK cells were found in one and two patients, respectively.

Discussion

We report the clinical and immunological results of adult patients exhibiting selective IgG4 subclass deficiency. We found selective IgG4 subclass deficiency more dominant in females, consistent with other IgG subgroup deficiencies in the literature [16, 17].

Selective IgG4 subclass deficiency most commonly presents with recurrent infections. In a previous study, the prevalence of selective IgG4 subclass deficiency in children with recurrent infections was significantly higher compared to those without recurrent infections (7.3% versus 0.3%). Additionally, 10% of patients encountered severe respiratory infections necessitating hospitalization [18]. Selective or combined IgG4 deficiency is more prevalent in children compared to other IgG isotypes [19]. Recurrent infections have been associated in patients with bronchiectasis and chronic rhinosinusitis associated with selective IgG4 subclass deficiency [20, 21]. Selective IgG4 subclass deficiency is also associated with rare infections. In a case report, there was an acute spinal epidural abscess progressing rapidly to paraplegia in a previously healthy child. The swift progression of such an infection in a young child was an unusual circumstance. The immunologic evaluation of the child revealed only a low IgG4 level [22].

In this study, the most common reason for IgG subgroup analysis was suspicion of recurrent infection or PID. The patients most frequently had upper respiratory tract infections. Other common infections were pneumonia, urinary tract infection, gastroenteritis, furunculosis, and herpes zoster (shingles).

IgG4 has a protective effect during recovery from infectious diseases [23]. IgG4 deficiency is implicated in host immune dysfunction, leading to recurrent infections and an increased vulnerability to rare pathogens [18]. Immunoglobulin replacement therapy shows curative potential for selective IgG4-associated infection. IVIG increased the levels of IgG1, 2, and 3 but not 4 [24]. In this study, IVIG treatment was started in two patients with frequent hospitalizations, who did not benefit from prophylactic therapies. One patient was diagnosed with GATA-2 deficiency and had normal values of other IGs. Although the symptoms significantly improved after IVIG treatment, the IgG4 levels did not recover.

The ESID has developed a questionnaire for the early detection of PID. The questions are straightforward, and the questionnaire can be utilized for diagnosing diseases in developing countries [25]. In our study, while 'frequent infections' were cited as the reason for admission in 25 patients (45.4%), 33 (60%) affirmed a history of frequent infections in response to the initial ESID question. Therefore, ESID questions should also be asked in patients with allergies and autoimmune diseases.

In serum IgG4 deficiency, hypersensitivity reactions cannot be adequately suppressed, and immune tolerance cannot develop. The balance between IgG4 and IgE plays a crucial role in determining the development of allergies or immune tolerance when exposed to allergens. Maintaining an adequate IgG4 level is essential for tempering exaggerated IgE-mediated immune responses [26]. Because of these conditions, the prevalence of allergic manifestations is increased in patients with selective IgG4 subclass deficiency. Allergic and atopic manifestations were present in the records of 25 patients (45.4%). An important finding was that selective IgG4 subclass deficiency is the second most prevalent characteristic linked to allergic diseases. This aligns with reports of IgG subclass deficiency observed in individuals with bronchial asthma [27, 28].

Serum levels of IgG4 are associated with most autoimmune diseases. Type 1 autoimmune pancreatitis was the first disorder recognized to be associated with IgG4 [29]. IgG4 has the capability to inhibit complement activation mediated by IgG1 and IgG3, preventing their binding to antigens and consequently impeding the development of autoimmune diseases [30]. In a study, patients with IgG subclass deficiency were examined, and selective IgG4 subclass deficiency was identified in approximately one-fourth of these patients. In most of these individuals, autoimmune diseases were detected [27]. In another study, among 363 patients with autoimmune diseases, the IgG4 level was lower in patients with systemic sclerosis and primary Sjögren syndrome [31]. Indeed, 32.7% of the patients in our study had autoimmune diseases. Hashimoto thyroiditis (seven patients) was the most common.

Most individuals with IgG subclass deficiency display a normal distribution of T cells, T-cell subsets, B cells, and NK cells [16, 32]. In our study, T cell and NK cell abnormalities were observed only in isolated cases; the other lymphocyte subsets were normally distributed. The retrospective design of this study and the reliance on patient records introduced several limitations. One of these limitations is that we did not evaluate specific antibody responses due to limited test availability. Additionally, our analysis was restricted to patients attending our allergy clinic, potentially limiting the generalizability of findings to the broader population.

Conclusion

In conclusion, although most adult patients with selective IgG4 subclass deficiency are asymptomatic, the main clinical presentations are infectious complications, particularly respiratory tract infections. Additionally, selective IgG4 subclass deficiency should be considered in patients with allergies and autoimmune diseases. Clinically symptomatic patients should have their immunological function evaluated, and IVIG therapy should be initiated if necessary.

Ethical approval

Necmettin Erbakan University Faculty of Medicine, non-drug and non-medical device research ethics committee approved the study protocol (decision no. 2023/4121, date: 06/01/2023).

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