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Clinical Features, Allergic Comorbidities, and Autoimmune Diseases in Children with Selective Immunoglobulin A Deficiency: A Five-Year Single-Center Study

Selektif İmmünoglobulin A Eksikliği Olan Çocuklarda Klinik Bulgular, Alerjik Komorbiditeler ve Otoimmün Hastalıklar: Beş Yıllık Tek Merkezli Çalışma

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Abstract: Selective immunoglobulin A deficiency (SIgAD) is the most common predominantly antibody deficiency and one of the most frequently encountered inborn errors of immunity. This study evaluated the demographic, clinical, and laboratory characteristics of children with SIgAD. Medical records of 15,815 children who underwent serum immunoglobulin A (IgA) measurement between May 2021 and May 2026 at a tertiary referral center were retrospectively reviewed. According to the European Society for Immunodeficiencies (ESID) diagnostic criteria, 47 children were included. The median age at diagnosis was 8 years (interquartile range [IQR], 6–12 years), and 53.2% were male. Recurrent infections were identified in 66.0% of patients, while allergic diseases and autoimmune diseases were present in 42.6% and 29.8%, respectively. Allergic rhinitis was the most common allergic disease, whereas celiac disease was the most frequent autoimmune disease. Among the 16 patients who underwent allergy testing, inhalant allergen sensitization was detected in 12 (75.0%), with pollen representing the predominant allergen. Serum IgG and IgM concentrations were normal in all patients, and lymphocyte subset analysis revealed no consistent abnormalities among the evaluated cases. These findings indicate that recurrent infections, allergic diseases, and autoimmune diseases are common manifestations in children with SIgAD. Comprehensive clinical assessment and long-term multidisciplinary follow-up remain important for the recognition and management of associated comorbidities in this tertiary-center cohort.

Keywords: immunoglobulins; immunology and allergy; autoimmunity; infections; pediatrics

Ethics Committee Approval: The study was approved by the Afyonkarahisar Health Sciences University Non-Interventional Clinical Research Ethics Committee (Approval No:2026/9-364 Date:08.05.2026).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Concept: SAB. Design: SAB. Data Collection and/or Processing: SAB, ATO, HK, AG, AS, NÖ, AHB, ŞŞ, AA, AYB, AAK. Analysis and/or Interpretation: SAB. Literature Search: SAB. Writing: SAB. Critical Review: ATO, HK, AG, AS, NÖ, AHB, ŞŞ, AA, AYB, AAK.

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Özet: Selektif immünoglobulin A eksikliği (SIgAD), en sık görülen baskın antikor eksikliği ve en sık karşılaşılan doğuştan bağışıklık sistemi bozukluklarından biridir. Klinik seyri oldukça heterojen olup tekrarlayan enfeksiyonlar, alerjik hastalıklar ve otoimmün hastalıkları içermektedir. Bu çalışmada SIgAD tanılı çocuk hastaların demografik, klinik ve laboratuvar özelliklerinin değerlendirilmesi amaçlandı. Mayıs 2021-Mayıs 2026 tarihleri arasında üçüncü basamak bir merkezde serum immünoglobulin A (IgA) düzeyi ölçülen 15.815 çocuk hastanın kayıtları retrospektif olarak incelendi. Hastalar Avrupa İmmün Yetmezlikler Derneği (ESID) tanı kriterlerine göre değerlendirildi ve tüm kriterleri karşılayan 47 hasta çalışmaya dahil edildi. Hastaların medyan tanı yaşı 8 yıl (çeyrekler arası aralık [IQR]: 6–12 yıl) olup %53,2'si erkekti. Tekrarlayan enfeksiyonlar hastaların %66,0'ında, alerjik hastalıklar %42,6'sında ve otoimmün hastalıklar %29,8'inde saptandı. En sık alerjik hastalık alerjik rinit, en sık otoimmün hastalık ise çölyak hastalığı idi. Alerjik duyarlanma açısından değerlendirilen hastaların %75,0'inde inhalan alerjen duyarlanması saptanmış olup en sık polen duyarlanması görüldü. Tüm hastalarda serum IgG ve IgM düzeyleri normal sınırlarda iken, lenfosit alt grup analizlerinde anlamlı bir anormallik izlenmedi. Bulgularımız, tekrarlayan enfeksiyonların yanı sıra alerjik hastalıklar ve otoimmün hastalıkların da çocukluk çağı SIgAD klinik spektrumunun önemli bileşenleri olduğunu göstermektedir. Bu nedenle SIgAD tanılı çocukların eşlik eden komorbiditeler açısından kapsamlı değerlendirilmesi ve uzun dönem multidisipliner izlenmesi önem taşımaktadır.

Anahtar Kelimeler: immünglobulinler; immünoloji ve alerji; otoimmünite; enfeksiyonlar; pediatri

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1. Introduction

Selective immunoglobulin A deficiency (SIgAD) represents the most common predominantly antibody deficiency and one of the most frequently encountered inborn errors of immunity (IEI) worldwide (1–3). Although many affected individuals remain clinically silent, SIgAD has attracted increasing attention because of its association with recurrent infections, allergic diseases, autoimmune diseases, and other immune-mediated conditions. Consequently, SIgAD is no longer considered merely a laboratory abnormality but rather a clinically relevant immunological condition with a highly variable phenotype (3–5).

Immunoglobulin A (IgA) is the principal antibody found at mucosal surfaces and constitutes a critical component of host defense in the respiratory and gastrointestinal tracts (6). Through neutralization of pathogens, prevention of microbial adherence, and maintenance of mucosal homeostasis, IgA contributes substantially to immune protection. Deficiency of this immunoglobulin may compromise mucosal immune function and increase susceptibility to recurrent infections, particularly involving the upper and lower respiratory tract (6–8). However, clinical manifestations are not limited to infectious complications. Considerable interindividual variability exists, and some patients remain asymptomatic despite profoundly reduced serum IgA levels (3,7,8).

Beyond infectious susceptibility, allergic diseases are among the most frequently reported comorbidities in patients with SIgAD. Allergic rhinitis, asthma, atopic dermatitis, food allergy, and chronic urticaria have all been described at higher frequencies than expected in the general population (9–13). Several mechanisms have been proposed to explain this association, including impaired mucosal barrier integrity, enhanced allergen penetration, altered antigen presentation, and dysregulated immune tolerance (11–13). These mechanisms may contribute to the increased frequency of allergic diseases in children with SIgAD. Recent studies have suggested that allergic manifestations may represent a major component of the SIgAD phenotype and may significantly influence quality of life and healthcare utilization (9,10,12).

Autoimmune diseases constitute another important aspect of the SIgAD clinical spectrum. Celiac disease, type 1 diabetes mellitus, autoimmune thyroiditis, vitiligo, immune thrombocytopenia, and various rheumatologic diseases have repeatedly been reported in association with SIgAD (3,14–17). The coexistence of SIgAD and autoimmunity likely results from complex interactions involving genetic susceptibility, immune dysregulation, and impaired mechanisms of self-tolerance (15–17). Because autoimmune manifestations may appear years after the initial diagnosis, recognition of these associations is essential for long-term patient management.

According to the European Society for Immunodeficiencies (ESID), SIgAD is defined by serum IgA levels below 0.07 g/L in individuals older than four years of age, normal serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels, preserved vaccine-specific antibody responses, exclusion of secondary causes of hypogammaglobulinemia, and absence of evidence suggesting a T-cell defect (2). Furthermore, increased susceptibility to infections, autoimmune manifestations, or the presence of an affected family member supports the clinical diagnosis of SIgAD (2). These criteria provide a standardized framework for patient identification and facilitate comparisons between studies.

Despite increasing awareness of SIgAD, pediatric data from Türkiye remain limited, and the relative burden of infectious, allergic, and autoimmune manifestations has not been fully clarified. Furthermore, many available studies have focused primarily on recurrent infections, whereas allergic and autoimmune comorbidities have received less attention. Therefore, the present study aimed to investigate the demographic characteristics, clinical manifestations, allergic diseases, autoimmune diseases, family history, and laboratory findings of children with SIgAD diagnosed at a tertiary referral center and to provide a comprehensive overview of the pediatric SIgAD clinical spectrum.

2. Materials and Methods

2.1. Study Design and Participants

This retrospective cross-sectional study was conducted at the Department of Pediatrics, at a tertiary referral center in Türkiye. Medical records of pediatric patients aged 0–18 years who underwent serum IgA measurement between May 2021 and May 2026 were retrospectively reviewed.

A total of 15,815 patients with available serum IgA measurements were screened through the hospital

electronic database. Patients with serum IgA levels below 0.07 g/L were identified. Individuals younger than four years of age were excluded because selective immunoglobulin A deficiency (SIgAD) cannot be reliably diagnosed before this age due to physiological maturation of the immune system (2).

The diagnosis of SIgAD was established according to the ESID diagnostic criteria, including serum IgA levels below 0.07 g/L, age greater than four years, normal serum IgG and IgM levels, preserved vaccine-specific antibody responses, exclusion of secondary causes of hypogammaglobulinemia, and absence of evidence suggesting a T-cell defect (2). In addition, patients were required to have increased susceptibility to infections, autoimmune manifestations, or an affected family member, as defined by the ESID working definitions (2). Low serum IgA levels were confirmed on at least two separate measurements in all included patients. Preserved vaccine-specific antibody responses were confirmed by documented protective anti-hepatitis B surface antibody (anti-HBs) and anti-tetanus IgG antibody levels retrieved from the electronic medical records.

Patients with malignancy, chemotherapy exposure, immunosuppressive treatment, secondary hypogammaglobulinemia, other inborn errors of immunity, incomplete laboratory data, or insufficient medical records were excluded. Following application of the inclusion and exclusion criteria, 47 patients fulfilling the ESID diagnostic criteria for SIgAD were included in the final analysis.

2.2. Data Collection

Demographic characteristics, including age at diagnosis, sex, anthropometric measurements, referral department, family history, clinical manifestations, laboratory findings, and accompanying diseases were extracted from electronic medical records.

Clinical manifestations were categorized as recurrent infections, allergic diseases, autoimmune diseases, or combinations thereof. Data regarding recurrent infections included recurrent upper respiratory tract infections, pneumonia, sinusitis, lymphadenitis, and gastroenteritis.

Diagnoses of allergic diseases, including allergic rhinitis, asthma, atopic dermatitis, food allergy, chronic urticaria, and drug allergy, as well as autoimmune diseases including celiac disease, type 1 diabetes mellitus, Hashimoto thyroiditis, vitiligo, and immune thrombocytopenia, were recorded from the hospital database.

Serum IgA, IgG, IgM, total immunoglobulin E (IgE) levels, and complete blood count parameters were available for all included patients and were extracted from electronic records. Lymphocyte subset analysis results, including CD3+ T lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, CD19+ B lymphocytes, and CD16/56+ natural killer (NK) cells, were recorded when available. Serum IgA, IgG, and IgM concentrations were measured in the hospital central laboratory using an immunoturbidimetric assay (Beckman Coulter AU5800, Beckman Coulter Inc., Brea, CA, USA). Immunoglobulin levels were interpreted according to age-adjusted reference ranges established for healthy Turkish children by Aksu et al (18).

Among patients with allergic diseases, allergy test results were available only for those whose allergy evaluation had been performed at our institution. Patients whose allergy evaluation had been performed at external centers were included based on their documented clinical diagnosis; however, their allergy test results were unavailable.

2.3. Definitions

Frequent infection was defined according to the warning signs proposed by the Jeffrey Modell Foundation, including recurrent otitis media, recurrent pneumonia, recurrent sinusitis, deep-seated infections, or other clinically significant recurrent infections requiring repeated medical evaluation or treatment (19). In addition, recurrent upper respiratory tract infection was defined as eight or more episodes per year, in accordance with commonly accepted pediatric definitions (20).

Diagnoses of allergic rhinitis, asthma, atopic dermatitis, food allergy, chronic urticaria, and drug allergy had been established by pediatric allergy and immunology specialists according to the relevant international guidelines and consensus documents, including the Allergic Rhinitis and its Impact on Asthma (ARIA), Global Initiative for Asthma (GINA), and European Academy of Allergy and Clinical Immunology (EAACI) guidelines, and were documented in the medical records (21–23). Allergen sensitization was defined as a positive skin prick test and/or serum allergen-specific IgE level ≥0.35 kUA/L.

Skin prick testing was performed using standardized commercial allergen extracts on the volar surface of the forearm. Histamine hydrochloride (10 mg/mL) and saline solution were used as positive and negative controls, respectively. A mean wheal diameter at least 3 mm greater than that of the negative control was considered positive (24).

Diagnoses of celiac disease, type 1 diabetes mellitus, Hashimoto thyroiditis, and immune thrombocytopenia had been established and followed by pediatric gastroenterology, pediatric endocrinology, pediatric hematology, and other relevant pediatric subspecialty clinics according to accepted diagnostic criteria and were confirmed through review of the electronic medical records. In children with SIgAD, the diagnosis of celiac disease was established according to the current European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines using IgG-based serological tests and, when indicated, histopathological confirmation by duodenal biopsy (25).

2.4. Ethics Approval

The study was approved by the Institutional Clinical Research Ethics Committee (Approval No:2026/9, Date: 08.05.2026). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Owing to the retrospective design of the study and the use of anonymized electronic medical records, the requirement for written informed consent was waived by the Ethics Committee.

2.5. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test together with visual histogram inspection. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were expressed as number and percentage. Because of the descriptive nature of the study, analyses primarily focused on summary statistics. A two-sided p-value <0.05 was considered statistically significant.

3. Results

During the study period, 15,815 children aged 0–18 years underwent serum IgA measurement. Among these, 316 patients had serum IgA levels below 0.07 g/L. After excluding 174 patients younger than four years of age, 142 patients remained eligible for further evaluation. Subsequently, 95 patients were excluded because of secondary hypogammaglobulinemia, malignancy, immunosuppressive treatment, missing IgG or IgM data, incomplete medical records, other inborn errors of immunity, or the absence of recurrent infections, autoimmune disease, or a positive family history according to the ESID criteria. Consequently, 47 patients fulfilling the ESID diagnostic criteria for SIgAD were included in the final analysis (Figure 1).

The demographic and baseline clinical characteristics of the study population are summarized in Table 1. The median age at diagnosis was 8.0 years (IQR: 6.0–12.0 years), and 25 patients (53.2%) were male. Anthropometric evaluation demonstrated normal mean height, weight, and body mass index standard deviation scores. Recurrent infections were the most common clinical manifestation and were present in 31 patients (66.0%). Allergic diseases and autoimmune diseases were identified in 20 (42.6%) and 14 (29.8%) patients, respectively. A positive family history of SIgAD in a first- or second-degree relative was documented in three patients (6.4%). More than half of the patients were referred from the general pediatrics outpatient clinic, followed by the pediatric allergy and immunology and pediatric hematology clinics (Table 1).

Clinical manifestations and associated diseases are presented in Table 2. Allergic rhinitis was the most frequent allergic disease, affecting nearly one-third of the patients, followed by asthma. Drug allergy, atopic dermatitis, and chronic urticaria were observed less frequently. Among the 20 patients with allergic diseases, allergy test results were available for 16 patients whose allergy evaluation had been performed at our institution, whereas four patients had been diagnosed at external centers and their allergy test results were unavailable. Among these 16 patients, inhalant allergen sensitization was detected in 12 (75.0%). Pollen sensitization was the predominant sensitization pattern, followed by house dust mite, mold, and cat/dog sensitization. None of the five patients tested for food allergen sensitization had a positive result.

Recurrent upper respiratory tract infection represented the most common infectious manifestation, occurring in 24 patients (51.1%). Recurrent pneumonia and recurrent acute gastroenteritis were observed in 12.8% and 10.6% of patients, respectively, whereas recurrent lymphadenitis and recurrent sinusitis were uncommon. Only one patient required long-term antibiotic prophylaxis because of recurrent infections (Table 2).

Autoimmune diseases were identified in 14 patients (29.8%). Celiac disease was the most frequently encountered autoimmune disease, followed by type 1 diabetes mellitus. Hashimoto thyroiditis, vitiligo, and immune thrombocytopenia were observed in a smaller number of patients (Table 2).

Immunological and hematological findings are summarized in Table 3. Median serum IgA concentration was 0.9 mg/dL (IQR: 0.3–2.95 mg/dL), whereas serum IgG and IgM concentrations were within normal age-adjusted reference ranges in all patients. Median total IgE level was 41.0 IU/mL (IQR: 6.5–121.5 IU/mL). Complete blood count parameters, including white blood cell, lymphocyte, neutrophil, and eosinophil counts, were generally within normal reference ranges (Table 3).

Lymphocyte subset analysis was available for 16 patients (34.0%). Median CD3+, CD4+, CD8+, CD19+, and CD16/56+ lymphocyte counts and percentages are presented in Table 4. No consistent abnormalities in T-cell, B-cell, or natural killer cell populations were identified in the evaluated patients.

Exploratory subgroup analysis according to allergic disease status is presented in Table 5. Patients with allergic diseases had a significantly higher frequency of recurrent infections than those without allergic diseases (85.0% vs. 51.9%, *P*=0.029). No significant differences were observed regarding age at diagnosis, sex, the presence of autoimmune diseases, positive family history of SIgAD, serum immunoglobulin concentrations, total IgE levels, or absolute eosinophil counts (Table 5).

A similar subgroup analysis according to autoimmune disease status is summarized in Table 6. Patients with autoimmune diseases were diagnosed at an older age (median 9.5 vs. 7.0 years, *P*=0.032) and had a higher frequency of recurrent infections than those without autoimmune diseases (92.9% vs. 54.5%, *P*=0.018). No significant differences were found with respect to sex, allergic diseases, positive family history of SIgAD, serum immunoglobulin concentrations, total IgE levels, or absolute eosinophil counts (Table 6).

Table 1. Demographic and Clinical Characteristics of Patients with Selective Immunoglobulin A Deficiency

Variable	Value (N=47)
Age At Diagnosis, Years, Median (IQR)	8.0 (6.0–12.0)
Male Sex, N (%)	25 (53.2%)
Height SDS, Mean ± SD	−0.12 ± 1.24
Weight SDS, Mean ± SD	−0.12 ± 1.50
BMI SDS, Mean ± SD	−0.05 ± 1.34
Recurrent İnfections, N (%)	31 (66%)
Allergic Diseases, N (%)	20 (42.6%)
Autoimmune Diseases, N (%)	14 (29.8%)
Positive Family History Of Sıgad*, N (%)	3 (6.4%)
Referring Department, N (%)	
• Pediatric Allergy And İmmunology	16 (34%)
• General Pediatrics	24 (51.1%)
• Pediatric Hematology	7 (14.9%)

Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or number (percentage), as appropriate.
**Family history of selective immunoglobulin A deficiency in a first- or second-degree relative.*
Abbreviations: BMI, body mass index; IQR, interquartile range; SDS, standard deviation score; SIgAD, selective immunoglobulin A deficiency.

Table 2. Clinical Manifestations and Comorbidities in Patients with Selective Immunoglobulin A Deficiency

Variable	Value (n=47)
Allergic diseases	
Allergic rhinitis, n (%)	15 (31.9%)
Asthma, n (%)	5 (10.6%)
Atopic dermatitis, n (%)	2 (4.3%)
Chronic urticaria, n (%)	1 (2.1%)
Drug allergy, n (%)	3 (6.4%)
Inhalant allergen sensitization, n/N (%)	12/16 (75%)
Pollen	8/16 (50%)

House dust mite	4/16 (25%)
Molds	2/16 (12.5%)
Cat/dog	2/16 (12.5%)
Food allergen sensitization, n/N (%)	0/5 (0%)
Recurrent infections	
Recurrent upper respiratory tract infection, n (%)	24 (51.1%)
Recurrent pneumonia, n (%)	6 (12.8%)
Recurrent acute gastroenteritis, n(%)	5 (10.6%)
Recurrent lymphadenitis, n(%)	2 (4.3%)
Recurrent sinusitis, n (%)	1 (2.1%)
Autoimmune diseases	
Type 1 diabetes mellitus, n (%)	4 (8.5%)
Celiac disease, n (%)	7 (14.9%)
Hashimoto thyroiditis, n (%)	2 (4.3%)
Vitiligo, n (%)	2 (4.3%)
Immune thrombocytopenia, n (%)	1 (2.1%)
Antibiotic prophylaxis use, n(%)	1 (2.1%)

Data are presented as number (percentage).
Abbreviations: SIgAD, selective immunoglobulin A deficiency.

Table 3. Immunological and Hematological Findings

Variable	Value (n=47)
Immunoglobulin G (IgG), mg/dL, median (IQR)	1258 (1000–1426)
Immunoglobulin A (IgA), mg/dL, median (IQR)	0.9 (0.3–2.95)
Immunoglobulin M (IgM), mg/dL, median (IQR)	97.8 (85.0–109.5)
Total Immunoglobulin E (Total IgE), IU/mL, median (IQR)	41.0 (6.5–121.5)
White Blood Cell Count (WBC), $\times 10^3/\mu L$, median (IQR)	7.91 (6.72–9.50)
Lymphocyte Count, $\times 10^3/\mu L$, median (IQR)	2.66 (2.08–3.19)
Lymphocyte Percentage (%), mean ± SD	34.8 ± 10.9
Neutrophil Count, $\times 10^3/\mu L$, median (IQR)	4.23 (3.38–5.54)
Neutrophil Percentage (%), mean ± SD	54.6 ± 11.7
Eosinophil Count, $\times 10^3/\mu L$, median (IQR)	0.15 (0.10–0.25)
Eosinophil Percentage (%), median (IQR)	1.9 (1.2–3.6)

Data are presented as mean ± standard deviation (SD) for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables.
Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IgE, immunoglobulin E; IQR, interquartile range; SD, standard deviation; WBC, white blood cell count.

Table 4. Lymphocyte Subset Analysis

Variable	**Value (n=16)**
CD3+ T lymphocyte count, cells/μL, median (IQR)	1903.6 (1541.8–2265.5)
CD3+ T lymphocyte percentage (%), median (IQR)	73.6 (67.5–75.7)
CD4+ T lymphocyte count, cells/μL, median (IQR)	1013.5 (895.3–1352.3)
CD4+ T lymphocyte percentage (%), median (IQR)	40.7 (37.4–45.2)
CD8+ T lymphocyte count, cells/μL, median (IQR)	780.4 (680.3–923.8)
CD8+ T lymphocyte percentage (%), median (IQR)	29.6 (25.2–32.0)
CD19+ B lymphocyte count, cells/μL, median (IQR)	367.0 (333.2–541.0)
CD19+ B lymphocyte percentage (%), median (IQR)	13.8 (12.8–16.3)
CD16/56+ NK cell count, cells/μL, median (IQR)	283.5 (195.7–408.8)
CD16/56+ NK cell percentage (%), median (IQR)	9.6 (8.7–11.8)

Lymphocyte subset analysis was available in 16 patients. Data are presented as median (interquartile range [IQR]).
Abbreviations: CD, cluster of differentiation; NK, natural killer; IQR, interquartile range.

Table 5. Comparison of patients with and without allergic diseases

Variable	Allergic disease (+) (n=20)	Allergic disease (–) (n=27)	*p* value
Age at diagnosis, years, median (IQR)	7.0 (4.0–10.5)	9.0 (7.0–12.5)	0.095
Male sex, n (%)	13 (65.0)	12 (44.4)	0.238
Recurrent infections, n (%)	17 (85.0)	14 (51.9)	**0.029**
Autoimmune diseases, n (%)	3 (15.0)	11 (40.7)	0.105
Positive family history of SIgAD, n (%)	1 (5.0)	2 (7.4)	1.000
Serum IgG, mg/dL, median (IQR)	1156 (993.0–1479.2)	1260.0 (1035.0–1376.5)	0.872
Serum IgA, mg/dL, median (IQR)	1.8 (0.4–3.2)	0.8 (0.3–2.5)	0.406
Serum IgM, mg/dL, median (IQR)	100.2 (91.2–120.5)	93.0 (85.0–106.0)	0.189
Total IgE, IU/mL, median (IQR)	55.8 (11.4–129.8)	19.8 (1.4–78.8)	0.149
Absolute eosinophil count, $\times 10^3/\mu L$, median (IQR)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	0.568

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Statistically significant P values are shown in bold.

Table 6. Comparison of patients with and without autoimmune diseases

Variable	Autoimmune disease (+) (n=14)	Autoimmune disease (-) (n=33)	*p* value
Age at diagnosis, years, median (IQR)	9.5 (7.3–13.0)	7.0 (5.0–10.0)	**0.032**
Male sex, n (%)	7 (50.0)	18 (54.5)	1.000
Recurrent infections, n (%)	13 (92.9)	18 (54.5)	**0.018**
Allergic diseases, n (%)	3 (21.4)	17 (51.5)	0.105
Positive family history of SIgAD, n (%)	0 (0.0)	3 (9.1)	0.544
Serum IgG, mg/dL, median (IQR)	1135.5 (943.5–1290.0)	1293.0 (1006.0–1504.0)	0.055
Serum IgA, mg/dL, median (IQR)	1.2 (0.3–2.7)	0.9 (0.3–3.0)	0.898
Serum IgM, mg/dL, median (IQR)	104.5 (87.3–116.0)	94.0 (84.4–106.0)	0.306
Total IgE, IU/mL, median (IQR)	15.5 (1.6–47.7)	57.9 (9.6–135.0)	0.085
Absolute eosinophil count, $\times 10^3/\mu L$, median (IQR)	0.19 (0.14–0.26)	0.14 (0.09–0.25)	0.124

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Statistically significant P values are shown in bold.

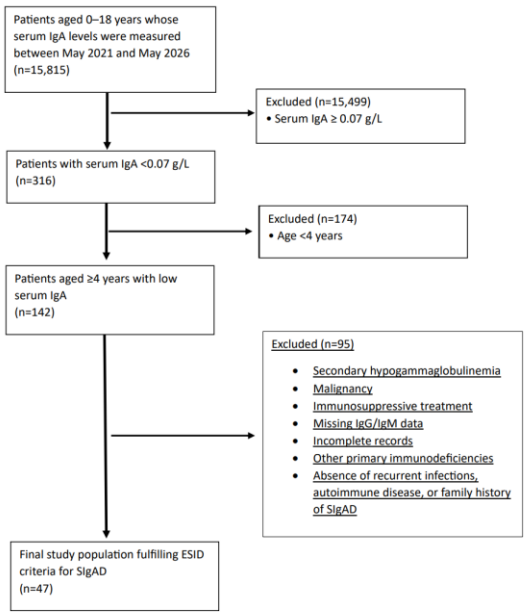


Figure 1. Flowchart of patient selection according to the ESID diagnostic criteria.

4. Discussion

Selective immunoglobulin A deficiency (SIgAD) exhibits remarkable clinical heterogeneity, and its presentation extends far beyond recurrent infections alone. Increasing evidence indicates that allergic diseases, autoimmune diseases, and immune dysregulation represent integral components of the SIgAD phenotype, particularly during childhood (3,9,14–17). In the present study, we systematically screened 15,815 children who underwent serum immunoglobulin A measurement over a five-year period and identified 47 patients who fulfilled the complete ESID diagnostic criteria for SIgAD. This rigorous selection process resulted in a well-defined pediatric cohort and reduced the likelihood of diagnostic misclassification. Importantly, this cohort represents children who underwent serum IgA testing based on clinical indications at a tertiary referral center rather than a population-based screening cohort, and the findings should therefore be interpreted within this clinical context. Our findings demonstrated that recurrent infections remained the most common clinical manifestation; however, allergic diseases and autoimmune diseases were also frequently documented, highlighting the broad clinical spectrum of pediatric SIgAD. Taken together, these findings underscore the importance of comprehensive clinical assessment of children with SIgAD beyond recurrent infections alone.

Infectious complications remain the hallmark clinical manifestation of SIgAD and represent the leading cause of referral to immunology clinics. In the present study, recurrent infections were observed in approximately two-thirds of the patients, with recurrent upper respiratory tract infections being the predominant presentation. This finding is consistent with previous pediatric cohorts in which respiratory tract infections constituted the most frequent clinical manifestation of SIgAD (9,13,26,27). Although the Jeffrey Modell warning signs primarily emphasize recurrent otitis media, pneumonia, sinusitis, and severe bacterial infections, recurrent upper respiratory tract infections often represent the earliest and most common reason for medical evaluation in children with antibody deficiencies (19,26). The absence of secretory IgA compromises the first-line mucosal defense of the respiratory tract, facilitating microbial adherence, colonization, and recurrent infections (6–8,26). Interestingly, nearly one-third of our patients did not have recurrent infections despite fulfilling the ESID diagnostic criteria, consistent with previous reports (3,9,26).

Beyond susceptibility to infections, our findings emphasize that allergic diseases constitute a major component of the pediatric SIgAD phenotype. Allergic diseases were identified in 42.6% of the patients, with allergic rhinitis representing the most frequent manifestation, followed by asthma. These findings are in agreement with previous studies reporting allergic disease frequencies ranging from approximately 25% to over 60% in pediatric SIgAD cohorts, depending on study design and diagnostic criteria (9–13,27,28). In the recent Turkish pediatric study by Ulaş et al., allergic rhinitis and asthma were likewise the predominant allergic comorbidities among children with SIgAD (9), whereas Lougaris et al. reported comparable frequencies in a large Italian pediatric cohort (10). The relationship between SIgAD and allergic disease is thought to result from impaired mucosal barrier function, increased allergen penetration, altered antigen presentation, and dysregulated immune tolerance (11,12,28). Together, these mechanisms may facilitate allergic sensitization and chronic airway inflammation**.** Supporting this hypothesis, inhalant allergen sensitization was detected in three-quarters of the patients who underwent allergy evaluation in our study, with pollen representing the predominant sensitizing allergen. Similar sensitization patterns have been consistently reported in both Turkish and European pediatric populations (9,11). Collectively, these findings reinforce the concept that allergic manifestations should be regarded as an integral component of SIgAD rather than merely coincidental comorbidities, highlighting the importance of comprehensive allergy assessment during both diagnosis and long-term follow-up of affected children.

The exploratory subgroup analyses performed in the present study provided additional clinically relevant observations. Children with allergic diseases had a significantly higher frequency of recurrent infections than those without allergic diseases. This finding may reflect the coexistence of impaired mucosal immunity and allergic airway inflammation, both of which may contribute to recurrent respiratory symptoms and increased healthcare utilization (9–11,28). Similarly, patients with autoimmune diseases tended to be diagnosed at an older age and more frequently experienced recurrent infections than those without autoimmune diseases. Although these findings should be interpreted cautiously because of the limited sample size and the exploratory nature of the analyses, they further support careful evaluation

of children with SIgAD beyond recurrent infections alone.

Autoimmune diseases represented another important component of the clinical spectrum in our cohort and were identified in nearly one-third of the patients. Celiac disease emerged as the most common autoimmune disease, followed by type 1 diabetes mellitus. These findings are consistent with previous reports demonstrating a substantially increased prevalence of autoimmune diseases among individuals with SIgAD compared with the general population (14–17). The association between SIgAD and autoimmunity is thought to be multifactorial and involves shared genetic susceptibility, impaired mucosal immune regulation, chronic antigenic stimulation, and defects in immune tolerance mechanisms (15–17). Among autoimmune diseases, celiac disease has been particularly linked to SIgAD because both conditions share common human leukocyte antigen (HLA) haplotypes, especially HLA-DQ2 and HLA-DQ8, which may contribute to their frequent coexistence (14,29). Similarly, type 1 diabetes mellitus and autoimmune thyroid diseases have repeatedly been reported at increased frequencies in both pediatric and adult SIgAD cohorts (16,17). Taken together, our findings further support the recommendation that patients with SIgAD should undergo careful evaluation and long-term surveillance for autoimmune manifestations, even in the absence of overt symptoms at the time of diagnosis.

Laboratory evaluation demonstrated profoundly reduced serum IgA concentrations with preserved serum IgG and IgM levels in all included patients, consistent with the ESID diagnostic criteria. In addition, no patient demonstrated clinical or laboratory findings suggestive of an alternative inborn error of immunity. Total serum IgE concentrations showed considerable interindividual variability in our cohort, with elevated levels observed in a subset of patients. This finding is consistent with previous reports indicating that increased IgE levels may accompany SIgAD, particularly in patients with coexisting allergic diseases (9,26,30). However, elevated IgE is not considered a characteristic laboratory feature of SIgAD and has limited diagnostic value when interpreted independently**.** Lymphocyte subset analysis, available in a subset of patients, revealed no consistent abnormalities in T-cell, B-cell, or natural killer cell populations. Similar observations have been reported in previous pediatric SIgAD cohorts, where routine lymphocyte subset measurements were frequently within normal limits despite the presence of clinically significant immune dysregulation (1,10,26,30). These findings highlight an important characteristic of SIgAD: conventional immunological investigations may remain largely unremarkable apart from low serum IgA levels, whereas clinically relevant manifestations such as recurrent infections, allergic diseases, and autoimmune diseases may still develop. Therefore, comprehensive clinical assessment remains essential for identifying patients who require long-term monitoring and multidisciplinary follow-up.

The major strength of this study is the systematic screening of 15,815 children over a five-year period and the inclusion of only those fulfilling the complete ESID diagnostic criteria for SIgAD. This approach resulted in a well-defined and homogeneous study population**.** In addition, infectious manifestations, allergic diseases, autoimmune diseases, and laboratory findings were evaluated simultaneously, providing a comprehensive overview of the clinical spectrum of pediatric SIgAD. However, several limitations should be acknowledged. This was a retrospective, single-center study, and the absence of a control group limits comparisons with the general pediatric population. The retrospective design may have resulted in incomplete clinical data for some patients, and a number of patients with low serum IgA levels were excluded because repeated confirmation of IgA deficiency was unavailable or because they did not fulfill the ESID clinical criteria. Furthermore, because this study was conducted at a tertiary referral center, the study population may not be representative of the general pediatric population, thereby limiting the generalizability of our findings. Finally, lymphocyte subset analyses and allergy evaluations were not available for all patients because these investigations were performed according to clinical indications and some patients had undergone allergy evaluation at external centers.

5. Conclusion

Selective immunoglobulin A deficiency is a clinically heterogeneous inborn error of immunity extending beyond recurrent infections alone. In this selected tertiary referral-center cohort, recurrent infections remained the predominant clinical manifestation; however, allergic diseases and autoimmune diseases were also frequently documented, with allergic rhinitis and celiac disease representing the most frequent comorbid conditions. These findings suggest that children with SIgAD evaluated in tertiary care may benefit from assessment not only for infectious complications but also for allergic and autoimmune diseases at the time of diagnosis and throughout follow-up. Early

recognition of this broad clinical spectrum may facilitate timely referral, multidisciplinary management, and improved long-term outcomes. Future prospective multicenter studies with larger patient populations are warranted to better define the natural history of pediatric SIgAD and to identify factors associated with disease progression and long-term prognosis.

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