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Original Article

Demographic Features, Clinical, and Laboratory Findings of Partial and Selective IgA Deficiency in Children

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ABSTRACT

Aim: Immunoglobulin A deficiency (IgAD), which is the most common primary antibody deficiency, can cause clinical problems due to significant infections and associated diseases, while some individuals with IgAD remain symptomless throughout their lives. This study evaluated the demographic features, clinical, and laboratory findings for those patients with selective and partial IgAD.

Materials and Methods: A retrospective study was conducted at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Clinical Immunology, and Allergy Outpatient Clinic. This study included 149 children, 122 diagnosed with selective and 27 diagnosed with partial IgAD.

Results: The median age at diagnosis was 6 years, and the majority of the patients (55.0%) were male. Nine patients transitioned from selective to partial IgAD, while four patients switched from partial to selective IgAD. The majority of patients experienced infections (56.3%) and allergies (47.7%). Autoimmune diseases were present in 14.1% of the study group; thyroiditis was the most common. Immunoglobulin G (IgG) subgroup deficiencies were detected in 20.2% of 84 patients who were examined. B-cell subpopulation analysis was carried out in 22 patients, revealing differentiation abnormalities in 18.1%. Two of these patients were siblings; one had low CD27+IgD-class-switched memory B-cells.

Conclusion: This study revealed that infections were the most common concern, but the frequencies of allergic manifestations and autoimmunity were also significant. While studies on B lymphocyte subgroup analysis continue to gain importance, the presence of patients with defects was observed in this study. Following an IgAD diagnosis, patients should undergo close immunological and clinical monitoring.

Keywords: IgA deficiency, immunodeficiency, autoimmunity, allergies, B lymphocyte

Introduction

Immunoglobulin A deficiency (IgAD) occurs due to a defect in immunoglobulin A (IgA) production, although other immunoglobulin isotypes can be produced by B-cells (1). It is the most common primary antibody deficiency (2,3). Although the pathogenesis has not been explained yet, defects of B-cells in terminal differentiation or transformation into IgA-producing plasma cells have been implicated (3,4). IgA-producing plasma cells in the peripheral circulation are reduced, and immature B-cells are increased (2,4). Furthermore, a decline in Iα germline transcription prior to class transformation has been identified as the underlying factor for selective IgAD. It is also proposed that partial IgAD arises due to the inhibition of B-cell development following class transition (5). Another perspective suggests that heightened depletion of B-cell subsets may be the underlying cause of the deficiency (4).

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The primary antibody of the mucosal immune system is secretory IgA, and if deficient, microorganisms, aeroallergens, and food-borne allergens easily penetrate the mucosal barrier and enter the body (3). Therefore, the common complaints are sinopulmonary, gastrointestinal system infections, allergies, and autoimmune disorders (6). Most individuals with impaired IgA production are asymptomatic (approximately two-thirds); these patients can be diagnosed via random immunoglobulin examinations, while the remaining one-third progress with clinical symptoms (7).

Selective and partial IgAD generally have a favorable prognosis, and it is possible for their immunoglobulin levels to rise during the course of their follow-up (2,8). However, chronic allergy complaints, autoimmune diseases, and accompanying immunological disorders closely relate to the course of this disease and the severity of infections. Assessing the different subgroups of B lymphocytes in the development of diseases has become increasingly important in recent years. Class-switched memory B lymphocytes have been demonstrated to be a crucial biomarker for clinical prognosis in patients (7).

The objective of our study was to analyze the demographic characteristics of those patients diagnosed with selective or partial IgAD. We aimed to identify their complaints upon admission, clinical findings, associated diseases, infections, complications, and any differences between the two groups by reviewing their laboratory data. This study aimed to present clinical experience of over 30 years and to enhance awareness regarding this disease.

Materials and Methods

A retrospective cohort study was conducted in the Cerrahpaşa Faculty of Medicine, Department of Pediatrics, Clinical Immunology and Allergy Outpatients' Clinic, İstanbul University-Cerrahpaşa, İstanbul, Turkey. Those patients diagnosed with IgAD between the ages of 0 and 18 during the prior 30 years, beginning in 1989, were assessed. Demographic characteristics, underlying medical conditions, clinical findings and laboratory characteristics, medical treatment, complications, and prognosis were collected from the medical records. Autoimmune diseases, allergies, other accompanying diseases, and previous infections were documented during the follow-up period.

Definitions

The diagnosis of selective IgAD was confirmed over four years of age by an IgA level below 7 mg/dL with normal immunoglobulin M (IgM) and IgG levels, excluding other causes of hypogammaglobulinemia (2). Partial IgAD was defined as an IgA level above 7 mg/dL but below the expected 2 standard deviations (SD) for age (2).

The serum levels of IgG, IgA, IgM, and immunoglobulin E (IgE) in the patients were determined using the nephelometric method. These values were categorized as either low or high based on SD and age. IgG subgroup deficiency is defined in patients over seven years of age with at least one of the IgG subgroups below the 5th percentile. Immunoglobulin and IgG subgroups were analyzed with reference to the study by Aksu et al. (9).

Lymphocyte subgroups (CD45, CD4, CD8, CD19, CD20, CD16-56) were recorded, and those below 2 SD of normal levels for age were classified as low. These percentages and values were examined taking the research by Ikincioğulları et al. (10) as the reference. A flow cytometer was used to assess the results of B lymphocyte subgroups (CD19, CD19+CD27+, CD27-IgD+, CD27+IgD+, CD27+IgD-, CD27-IgD-, CD38highCD24high). These results were compared to the values of B lymphocyte subgroups determined by Duchamp et al. (11).

Ethics

Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa Clinical Research Ethics Committee approved this study (date: 15.12.2018, no: 29430533-90399).

Statistical Analysis

Statistical analysis of the research data was carried out with the SPSS v21 (IBM Corp., Armonk, NY, USA) package program. Descriptive data, frequencies, and percentages are given for categorical variables and compared by the Pearson chi-square test. Descriptive analyses are given using means and SD for normally distributed variables, and Student's t-test was used to compare two independent sample groups; since continuous variables did not meet the normal distribution conditions, they are given using median, minimum and maximum and evaluated using non-parametric tests (the Mann-Whitney U test). Statistical significance was accepted as $p<0.05$.

Results

There were a total of 149 patients in the study cohort, consisting of 122 selective IgAD and 27 partial IgAD. The majority of the patients, eighty-two, were male (55.0%). Nine patients (6.0%) were diagnosed with selective IgAD due to an IgA level below 7 mg/dL at admission. However, during follow-up, their IgA rose roses but still were 2 SD below their age expected levels, and so they subsequently

classified as partial IgAD. Despite being below 2 SD by age at diagnosis, four patients (2.6%) transitioned from partial IgAD to selective IgAD as a result of their IgA values decreasing below 7 mg/dL. Table I illustrates the demographic characteristics of the patients.

Two families (2.7%) had a history of primary immunodeficiency, and the rate of consanguineous marriage was found to be 11.4% of the study group. There were twins with selective IgAD and siblings with selective and partial IgAD. The median age of the patients at the onset of symptoms was 3 years, and the median age at hospital admission was 6 years (Table I). At the time of admission, the age divisions of the patients were as follows: 25.5% were between the ages of 0 up to 4 years, 39.6% were between the ages of 4 up to 8 years, 22.1% were between the ages of 8 up to 12 years, and 12.8% were 12 years of age or older. The mean follow-up period for our patients was 4.99±4.3 years. Some of our patients were monitored until the age of four, while others were monitored until the age of 22. Twenty-two patients (14.7%) had underlying diseases.

Table I. The demographic and clinical characteristics of the study population

Characteristics	**n (%)**
Selective IgA deficiency	122 (81.8)
Partial IgA deficiency	27 (18.1)
Male	82 (55.0)
Consanguineous marriage	17 (11.4)
Primer immune deficiency in family	4 (2.6)
Accompanying autoimmune diseases	21 (14.1)
-Autoimmune thyroiditis	9 (6.0)
-Juvenile idiopathic arthritis	2 (1.3)
-Celiac disease	2 (1.3)
-Type 1 diabetes	2 (1.3)
-Inflammatory bowel disease	2 (0.6)
-Systemic lupus erythematosus	2 (0.6)
-Vasculitis	1 (0.6)
-Vitiligo	1 (0.6)
-Myasthenia	1 (0.6)
-Psoriasis	1 (0.6)
-Mixed connective tissue disease	1 (0.6)
Other underlying diseases	22 (14.7)
Frequent infections	84 (57.3)
Allergies	71 (47.7)
Age at admission (median, min.-max.)	6 years (6 months-17 years)
Age at onset of symptoms (median)	3 years (6 months-16 years)

Ig: Immunoglobulin, min.-max.: Minimum-maximum

The most common complaint at admission was frequent infections (n=84, 56.3%), defined as eight or more infection episodes yearly. Patients predominantly suffered from frequent upper respiratory tract infections (n=135, 90.6%), followed by 56 (37.6%) with frequent fever, 45 (30.2%) with lower respiratory tract infections (LRTIs), 24 (16.1%) with otitis, 43 (28.9%) with sinusitis, 24 (16.1%) with urinary tract infections, and 19 (12.8%) with gastroenteritis. Eleven (7.4%) patients had been hospitalized due to infectious diseases. Bronchiectasis developed in 2 (1.3%) of the patients, no other underlying immunodeficiencies were detected in either of them and it was thought to have developed following a severe LRTI. When the selective and partial IgAD groups were compared in terms of previous infections, the rate of frequent sinusitis was significantly higher in the selective IgAD group (32.7% vs. 11.1%, p=0.02). It was determined that ten patients (6.7%) used prophylactic antibiotics during their follow-up.

Allergy

Allergy was seen in 71 (47.7%) patients with IgAD; 49 (32.8%) had one allergic complaint, and 22 (14.7%) had multiple. Asthma was the most common allergic manifestation in 52 patients (34.8%) followed by allergic rhinitis diagnosed in 25 (16.8%), allergic skin rash in 16 (10.7%), and food allergy in 6 (4.0%). There was no significant difference in the prevalence of allergic illnesses between the selective and partial IgAD groups (p=0.36). Among those patients exhibiting hypersensitivity (n=71), 69.0% reported using medication. Specifically, 38 (53.5%) used leukotriene receptor antagonists, 22 (30.9%) used inhaler steroids, 24 (33.8%) used bronchodilators, 13 (18.3%) used antihistaminic drugs, and 14 (19.7%) used nasal steroids.

Autoimmune Diseases

Autoimmune diseases were present in 21 (14.1%) of all patients, with autoimmune thyroiditis being the most prevalent (n=9, 6%) (Table I). Three patients were diagnosed with more than one autoimmune disease. During the diagnostic procedures for autoimmune diseases, nine patients (6.0%) were diagnosed with IgAD. The appropriate diagnosis, treatment, and follow-up processes for autoimmune diseases were carried out by the relevant

departments. There was no significant difference between selective and partial IgAD for accompanying autoimmune diseases (p=0.46).

Immunoglobulins and Subgroups

The median value of IgG was significantly higher in the selective IgAD group (p=0.01). There was no significant difference between the median IgM values (p=0.77) (Table II). It was observed that the IgM level was elevated in 15 patients (10.0%) at the time of first admission.

IgG Subgroup Deficiency

IgG subgroups were studied in 84 patients, and low values were detected in 17 (20.2%) of them. Eight patients (9.5%) had low IgG4 values, four (4.7%) had low IgG3 values, two (2.3%) had low IgG2 and IgG4 values, one (1.2%) had low IgG1 values, one (1.2%) had low IgG3 and IgG4 values, and one (1.2%) had low IgG1 and IgG4 values. All of these patients were in the selective IgAD group. There was no significant difference in absolute values of the IgG subgroups between the patient groups (Table II).

Lymphocyte Subgroups

There was no significant difference between the patient groups for lymphocyte subgroup percentages. It was observed that the CD4/CD8 ratio was reversed in 12 patients (8.0%). In comparison to the reference values, the percentages of lymphocyte subgroups were within the normal range (Table III).

B lymphocyte Subgroups

Four patients (18.1%) exhibited B-cell differentiation defects when compared with the reference values during the examination of 22 patients. There was no significant difference between the patient groups for the mean percentages measured in 22 patients (Table IV).

In two patients, the total number of memory B-cells was decreased, while the number of naive B-cells was increased. The number of class-switched memory B-cells was decreased in one of these patients, while the number of non-class-switched B-cells was decreased in the other. A third patient exhibited a decrease in non-class switched memory B-cells, while a fourth patient exhibited an increase in naive B-cells. The characteristics of these patients are detailed in Table V.

Table II. IgG, IgM, and IgG subgroup absolute values of selective and partial IgA deficiency patients

	Selective IgA deficiency (median, min.-max., mg/dL)	Partial IgA deficiency (median, min.-max., mg/dL)	p value
IgG	1,420 (149-2,930)	1,080 (464-3,549)	**0.017***
IgM	116 (41-846)	110 (51-228)	0.771
IgG1*	1,035 (364-2,190)	834 (593-2,190)	0.296
IgG2*	307 (37-934)	227 (97-1,130)	0.377
IgG3*	45.4 (0.5-139)	45.6 (17-101)	0.980
IgG4*	31 (8.2-368)	35.2 (8.2-301)	0.352

*: IgG1, IgG2, IgG3, and IgG4 were determined in 84 patients, Ig: Immunoglobulin, min.-max.: Minimum-maximum

Table III. Lymphocyte subgroup percentages of selective and partial IgA deficiency patients*

	Selective IgA deficiency (median, min.-max., %)	Partial IgA deficiency (median, min.-max., %)	p value
CD45	97.4 (81.0-100)	98.1 (56.0-100)	0.569
CD3	70.0 (57.3-82.0)	68.9 (52.0-88.0)	0.754
CD4	40.0 (17.2-69.0)	40.0 (31.3-69.0)	0.588
CD8	30.7 (18.0-50.0)	26.6 (6.0-38.0)	0.310
CD19	15.1 (6.4-25.0)	19.0 (7.4-85.0)	0.156
CD20	18.0 (3.0-29.0)	17.1 (11.4-35.0)	0.440
CD16-56	9.9 (4.0-21.2)	9.5 (4.0-32.4)	0.694

*: Lymphocyte subgroups were determined in 65 patients, Ig: Immunoglobulin, min.-max.: Minimum-maximum

Table IV. B Lymphocyte subgroup percentages of selective and partial IgA deficiency patients*

	Selective IgA deficiency (n=17)	Partial IgA deficiency (n=5)	p
CD19 + B-cells	13.3±3.7	15.2±4.1	0.401
CD19 + CD27 + B memory cells	21.0±10.8	24.7±11.5	0.359
CD27- IGD+ naive B-cells	73.1±12.5	67.6±12.9	0.283
CD27+IGD+ non-class switched B memory	9.9±6.3	9.1±3.5	0.940
CD27+IGD- class-switched B memory	11.2±6.7	14.9±7.4	0.359
CD38 high CD24 high transitional B-cells	2.5±1.8	2.5±1.2	0.649

*: B- Lymphocyte subgroups were determined in 22 patients, Ig: Immunoglobulin

Table V. Characteristics of patients with B-cell subgroup anomalies

Patient no	Subgroup features	Patient characteristics
1	Memory B-cells decreased Naive B-cells increased Class-switched memory B-cells decreased	Partial IgA deficiency, selective IgA deficiency in her sister Allergic rhinitis and asthma IgM and IgE increased CD4/CD8 ratio reversed
2	Memory B-cells decreased Naive B-cells increased Non-class switched memory B-cells decreased	Selective IgA deficiency IVIG therapy for transient hypogammaglobulinemia IgG3 and IgG4 deficiency CD4/CD8 ratio reversed Diarrhea attacks, persistent sinopulmonary infections, and otitis media
3	Non-class switched memory B-cells decreased	Selective IgA deficiency Persistent sinopulmonary infections and otitis media
4	Naive B-cells increased	Selective IgA deficiency Persistent sinopulmonary infections and asthma

Ig: Immunoglobulin, IVIG: Intravenous immunoglobulin

Discussion

Immunoglobulin A deficiencies have been examined from different perspectives via clinical findings, accompanying diseases, and immunological laboratory values, however, the pathogenesis of IgAD has not yet been significantly resolved. Our study observed that some patients diagnosed with partial IgAD could switch to selective IgAD, while others in the selective group could switch to partial deficiency. Moschese et al. (12) also observed that there were transitions between groups, as in our study, and they also reported that normalization of IgA levels was significantly more common in partial IgAD than in selective IgAD. Plebani et al. (13) observed that serum IgA can rise to normal levels in partial deficiencies but did not reach the normal range in severe deficiencies. A substantial number of patients demonstrated reversals in a comprehensive study conducted in Sweden, despite the fact that a diagnosis of IgAD was made after the age of 4 years (14). It is important to monitor these transitions and the potential for reversals in the risk assessment and follow-up of these patients.

Karaca et al. (15) studied the families of patients with common variable immunodeficiency (CVID) and IgAD in Turkey and observed that 33.6% of the cases were familial, 19.1% had low immunoglobulin levels, and the familial cases were more severe. Two familial cases were identified in the course of our research. The fact that two of our patients were siblings and both were diagnosed with IgAD suggests that individuals in a family with frequent infections should be screened for immunodeficiencies. The most significant risk factor for the development of IgAD and CVID is a positive family history and it is recommended that the families of IgAD and CVID patients undergo routine screening (15).

This study observed that the patients' complaints could begin over a wide age range, and most applied to a physician before 4 years of age. The period between the onset of symptoms and their application was approximately 3 years. This interval shows that awareness is not enough for both families and physicians. During the follow-up, the majority of their complaints consisted of infections. LRTIs and hospitalization rates reflect the clinical severity of these patients. There is a statistical difference in the frequency of sinusitis, although there were more cases of LRTI, bronchiectasis, and hospitalization in the selective IgAD without a significant statistical difference but with a

clinical significance. Moschese et al. (12) reported infections of the respiratory/gastrointestinal tract were the most common clinical manifestations in both selective IgAD (53%), and partial IgAD (64%). Our results demonstrate that both selective and partial IgAD patients were mostly struggling with recurrent infections, as previously reported. Additionally, selective IgAD patients exhibited slightly elevated infection rates.

Hypersensitivity was present in 47.7% of our patients, and most of them used medication (69.0%). Aytekin et al. (1) found that allergies (43.2%) were the second most common complaint following infections in patients with IgAD. Cinicola et al. (16) found the prevalence of allergy in the pediatric IgA deficiency cohort was 34%, while Shkalim et al. (17) found that 31.7% of patients with IgAD had allergic disorders, with asthma being the most prevalent, followed by allergic rhinitis, which aligns with our own findings. Abo Ali et al. (18) also revealed that the percentage of IgAD in asthmatic patients was 56%. This highlights the high frequency of allergy in IgAD patients and the necessity of vigilant monitoring of these individuals for allergic manifestations during both the diagnosis and follow-up phases.

IgAD and IgG subgroup deficiency can be seen together, causing more severe infections (8). Within this study, a total of 17 out of 84 patients with selective IGAD and IgG subgroup deficiency, representing 20.2% of the sample, reported recurring infection symptoms along with the presence of autoimmune disorders and allergies. Karaca et al. (19) observed in the IgG subgroup deficient pediatric patients that IgG3 deficiency was the most common, while they had recurrent infections, and that 30-40% recovered after six years of age. The fact that all of the patients with complete IgG subclass deficiency belonged to the selective IgAD patient group and that, as previously mentioned, the rates of serious infections were found to be higher in the selective IgAD group highlights the need for close monitoring of the selective IgAD group as they are considered to be at higher risk.

Autoimmunity has been the subject of extensive research and discussion in patients with IgAD in recent years. The association between IgAD and autoimmunity may be explained by the relationship between IgAD and abnormal T-cell regulation, particularly in regulatory T-cells and reduced switching memory B-cells (20). Autoimmunity was present in 14.1% of the participants in our investigation. Depending on the country, the study center, and the number of patients involved, the reported rates varied both in Turkey and in global studies. Abolhassani et al. (20) determined that the autoimmunity rate was 29.8% in their study. In their review, Vosughimotlagh et al. (21) revealed that the prevalence of autoimmunity ranged from 4.2% to 39.2%. Aytekin et al. (1) investigated children who were diagnosed with selective IgAD and an autoimmune disease was reported to be present in 17% of children. However, they demonstrated that 31% of these patients had positive autoantibodies, and only a portion of them had an autoimmune disease. In Sweden, Ludvigsson et al. (22) conducted a national study in which 2,100 patients with IgAD were screened, and the results indicated that the rates of autoimmune diseases in patients from the age of four to adulthood were significantly higher than in society.

Celiac disease was identified as the most prevalent autoimmune disease in a meta-analysis (21). IgAD may also be associated with autoimmune thyroiditis, celiac disease, juvenile idiopathic arthritis, idiopathic thrombocytopenic purpura, hemolytic anemia, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus (23). According to Erkoçoğlu et al. (24), the most prevalent autoimmune disorder in children with selective IgAD was celiac disease (9.9%), followed by Type 1 diabetes mellitus (DM) (3.7%) and thyroiditis (2.5%). The most prevalent autoimmune condition among our patients was autoimmune thyroiditis, which affected 6.0% of individuals. This was followed by celiac disease, type 1 DM, inflammatory bowel disease, and juvenile idiopathic arthritis, which each affected 1.3% of our patients. Although the high occurrence of celiac disease has been extensively documented in studies, it is important to highlight that autoimmune thyroiditis was the predominant condition in our study, highlighting the necessity of diagnosing and subsequently monitoring these individuals.

IgM levels were above the normal limits for age in 15 patients (10.0%) at first admission, two of whom had autoimmunity. It is thought that this elevation occurred to compensate for the decrease in secretory IgA (4). When lymphocyte subgroups were assessed separately, it was noted that the proportion of B-cells and natural killer (NK) cells were within the normal ranges. In certain patients, the CD4/CD8 ratio was reversed, despite the fact that T-cells were within normal limits. Nechvatalova et al. (6) similarly reported that the number and ratio of CD4 + T lymphocytes were decreased and CD8 + T lymphocytes were increased in IgAD patients.

Our study showed abnormalities with differentiation in B-cell subgroups in 18.1% (4 out of 22) of the patients

investigated. Aghamohammadi et al. (7) put forward that those patients with problems in these stages of maturation, especially those with low class-switched memory B-cells, may have a more severe course, the development of autoimmunity and immunodeficiency (especially CVID) by evaluating the subgroups of B lymphocytes. B lymphocyte subgroup analysis is an essential biomarker in clinical prognosis according to recent studies. Bukowska-Straková et al. (25) showed that low CD27+IgD-class-switched memory B-cells are common in patients with CVID and IgAD. Nechvatalova et al. (6) also showed that in IgAD patients class-switched memory B-cells and IgM-plasmablasts were decreased, $CD21^{low}CD38^{low}$ B-cells were increased, and these anomalies were similar to patients with CVID. Celiksoy and Yildiran (26) studied patients with antibody deficiency and found that naive B-cells were increased in patients with CVID and IgAD, similar to our patients 2 and 4. Additionally, both class-switched and non-class-switched memory cells were decreased in CVID, and total memory cells and non-class-switched memory cells were decreased in IgAD. These studies showed that although it is more common in CVID, CD27+ IgD- class-switched memory B-cells are decreased in IgAD, similar to our patient 1. Given that patients 1 and 2 were siblings and considering the depletion of CD27+IgD-class-switched in patient 1 and the reduction of non-class-switched memory B-cells in patients 2 and 3, it is recommended that they be closely monitored and evaluated prospectively regarding CVID. This may be due to a common genetic predisposition, and this situation can guide the clinical prognosis and prediction of CVID (6,26).

Conclusion

Upon analyzing and comparing both selective and partial IgAD, this study revealed that infections were the predominant issue, however allergy symptoms and autoimmunity also exhibited notable frequencies. Although the frequency of infection was very high in both groups and there was no difference for accompanying allergic complaints and autoimmune diseases, in the selective IgAD group, sinusitis, LRTIs, hospitalizations and bronchiectasis occurred more frequently, and IgG subgroup deficiencies were only seen in the group with selective IgAD, so it can be concluded that selective IgAD must be monitored more closely and changes in patients' IgA levels are important in determining risk. As research on the study of B lymphocyte subgroups becomes more significant, it has been noted that several individuals who were examined had problems. Ultimately, patients diagnosed with IgAD should undergo extensive immunological and clinical monitoring during their follow-up.

Ethics

Ethics Committee Approval: Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa Clinical Research Ethics Committee approved this study (date: 15.12.2018, approval no.: 29430533-90399).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: A.A., H.Ç., Y.C., Design: A.A., H.Ç., Data Collection or Processing: A.A., Analysis or Interpretation: A.A., Y.C., Literature Search: A.A., Writing: A.A., H.Ç., Y.C.

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