Original Article / Özgün Araştırma

Clinical Characteristics of Fungal Sensitization in Children with Allergic Respiratory Diseases

Allerjik Solunum Yolu Hastalıkları Olan Çocuklarda Küf Mantarı Duyarlılığının Klinik Özellikleri

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Abstract

Objective: The aim of the study was to evaluate the prevelance of fungal sensitization among school-aged children with allergic respiratory diseases who attended our outpatient clinic and to evaluate its clinical impact on disease severity.

Materials and Methods: Children with allergic symptoms during mould season, who attended our outpatient clinic between January 2014 and August 2015, were evaluated for allergic respiratory diseases. Skin prick testing with fungal and other commercial standardized solutions of aeroallergens was performed in all children. Spirometry was performed in children with asthma. Serum total immunoglobulin E (IgE) and aeroallergen specific IgE (sIgE) levels were measured.

Results: A total of 112 children were included in the study. The prevelance of fungal sensitization was 6.4%. *Alternaria alterna* was the most common fungal allergen in both mono and polysensitized groups (p=0.002, p=0.004, respectively). *Alternaria alterna* sensitization was significantly higher in patients with persistent allergic rhinitis compared to those with intermittant allergic rhinitis (p=0.002). The patients with mild asthma were mostly monosensitized (p=0.003), but cases with severe asthma (SA) were polysensitized (p=0.007). In polysensitized cases, *Alternaria alterna* and *Cladosporium spp.* coexistance was the most common combination compared to other fungal combinations (p<0.001). The sensitivity rate of sIgE was found to be 88%. In spirometric analysis, forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity values were lower in polysensitized children with asthma and in children with asthma coexisting allergic rhinitis compared to children with allergic rhinitis only (p=0.004, p=0.001, respectively).

Conclusion: The most common fungal allergen was *Alternaria alterna* in children with mono or polysensitization. Polysensitization with fungal allergens was closely associated with SA and lower spirometric parameters.

Keywords
Asthma, allergy, allergic rhinitis, mould, sensitization, pediatrics

Anahtar Kelimeler
Astım, allerji, allerjik rinit, küf mantarı, duyarlanma, pediatri

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Öz

Amaç: Çalışmanın amacı polikliniğimize başvuran okul çağındaki allerjik solunum yolu hastalıkları olan çocuklarda küf mantarı duyarlılığının sıklığının araştırılması ve duyarlılığın hastalığın ağırlığındaki öneminin tespit edilmesidir.

Gereç ve Yöntemler: Küf mantarı sezonunda allerjik semptomları olan çocuklardan polikliniğimize Ocak 2014-Ağustos 2015 tarihleri arasında başvuranlar allerjik solunum yolu hastalıkları açısından değerlendirildi. Küf mantarı ve ticari standardize

edilmiş aeroallerjenler ile deri prik testi yapıldı. Astımlı çocuklara spirometri uygulandı. Serum total immünoglobulin E (IgE) düzeyine bakıldı ve spesifik IgE (sIgE) düzeyleri ölçüldü.

Bulgular: Çalışmaya 112 çocuk alındı. Küf mantarı duyarlılığının sıklığı %6,4 bulundu. *Alternaria alterna* hem mono hem de polisensitize çocuklarda en sık küf mantarı allerjeni idi (sırasıyla, p=0,002, p=0,004). *Alternaria alterna* duyarlılığı persistan allerjik riniti olanlarda intermittan olanlara göre belirgin yüksekti (p=0,002). Hafif astımı olan hastalar daha çok monosensitize (p=0,003) iken, ağır astımı olanlar polisensitize (p=0,007) idi. Polisensitize olanlarda *Alternaria alterna* ve *Cladosporium spp.* birlikteliği diğer küf mantarlarına göre daha sıktı (p<0,001). sIgE'nin sensitivitesi %88 bulundu. Spirometrik değerlendirmede, sadece polisensitize çocuklarda zorlu ekspirasyon hacmi 1/zorlu vital kapasite değerleri astımı ve astıma eşlik eden allerjik riniti olanlarda tek başına allerjik riniti olanlara göre daha düşük saptandı (sırasıyla, p=0,004, p=0,001).

Sonuç: Mono ve polisensitize olan çocuklarda en sık rastlanan küf mantarı allerjeni *Alternaria alterna* idi. Küf mantarı ile polisensitizasyon ağır astım ve düşük spirometrik değerler ile ilişkili gibi gözükmektedir.

Introduction

The most important bioaerosols in indoor environment are mold, fungal spores, endotoxins and fungal glucans. Many factors like warmth, wind condition, and location of the living area affect the reproduction of fungi (1). Domestic bioaerosols, house dust mites, animal feather epithelium, cockroaches, cigarette smoke and gases emerging during cooking are closely linked to respiratory diseases (2). Particularly, mold and humidity in the home environment have been shown to have an important effect on the prevelance of asthma and/or allergic rhinitis.

The atmospheric mould spore season is spring and summer is the season for *Alternaria alterna* and Claudosporium spp. in Turkey. The concentration of the mould spores vary according to geographical location, humidity, rainfall, and meteorological conditions (3,4). Exposure to mould increases asthma exacerbations and wheezing attacks in childhood period (4,5). Fungal sensitization is closely associated with asthma severity and reduced pulmonary functions in adults (4). Similarly, in children, fungal sensitization causes worse asthma severity and more frequent exacerbations (5). Recently, the causal association with asthma severity and fungal sensitization was demostrated and *Alternaria alternata* exposure was found to increase T-helper 2 (Th2) type immune reactions and steroid-resistant bronchial hyperreactivity. Interleukine-33 was the most important cytokine for such an inflammatory reaction in the lungs (6).

The data on the clinical presentation of fungal sensitization in children with allergic respiratory tract diseases are limited (7). In the present study, it is aimed to investigate the prevelance of fungal sensitization in school-aged children with allergic respiratory tract diseases and to evaluate the association of fungal mono/polysensitization with disease severity.

Material and Methods

Study Subjects

The study was performed in a prospective and cross-sectional design. Children aged between 6 and 18 years, who were diagnosed with allergic respiratory tract diseases in our outpatient clinic between January 2014 and August 2015, were evaluated.

Asthma was diagnosed according to the Global Initiative for Asthma recommendations and based on clinical asthma symptoms and lung-function tests. Asthma severity was determined according to the same guidelines, via the analysis of the following parameters: symptoms, nocturnal awakenings, rescue medication use, activity limitation, and Forced expiratory volume in 1 second ($FEV_{1)}$. As a result, asthma patients were divided into three groups: mild asthma, moderate asthma, and severe asthma (SA). This classification always took into account the most severe clinical or functional manifestation (8).

The diagnosis of allergic rhinitis and assessment of its severity were conducted according to the Allergic Rhinitis and its Impact on Asthma guidelines (9). Patients with no sleep disorder, daily activity restriction, school attendance problems and symptoms without causing any problems were evaluated as "mild"; the cases were assessed as "moderate/severe" in the presence of any of these symptoms. Symptoms lasting more than 4 days in a week and more than 4 weeks were regarded as persistent allergic rhinitis.

Exclusion Criteria

Children with isolated cough, swallowing difficulty, wheezing, palpitation, pain in the chest and shortness of breath not compatible with asthma symptoms, chronic pulmonary disease, malignancy, primary

immune deficiency, and bleeding problems were excluded from the study.

Evaluation of Sensitization

Children who have allergic respiratory system symptoms in mould season were evaluated for atopy with skin prick testing (SPT). SPT was standardized according to the Europe Allergy and Clinic Immunology Academy guidelines (10). SPT was applied to the volar surface of the arm. Histamine hydrochloride (10 mg/ml) was used as positive and NaCl 0.9% as negative control. Standardized commercial allergen solutions for 4 fungi (*Alternaria alterna*, *Cladosporium herbarum*, *Aspergillus fumigatus* ve *Penicillium* crhysogenum) and other commercial aeroallergens those selected in conformity with the pollen map of the west region of our country as grass pollen mix, tree pollen mix, olive pollen, house dust mites (*Dermatophagoides farinae* ve Dermatophagoides pteronyssinus), cockroaches, and cat and dog allergens (Stallergenes SA, France) were administered to the participants. During the test, allergen solution was dropped by at least 2-cm intervals and the result was evaluated 15 minutes later and, the widest edema diameter formed was measured with a ruler. In SPT, in case enduration diameter was ≥3 mm (≥9 mm^2), the situation was evaluated as sensitized. The tests were evaluated by an allergy expert since positive reaction could manifest itself by its smaller edema diameter in very little children. In the case the timing of the symptoms and sensitization in SPT was compatible; those cases were defined as allergic to fungal aeroallergens and were included in the study. The patient was regarded as monosensitized upon responding to single fungal allergen positively and considered as polysensitized upon being susceptible to more than one fungal allergens in SPT (11,12).

Specific IgE measurement was analyzed by using the radioallergosorbent test method and standardized aeroallergen panel including grass pollen mix, tree pollen mix, fungi mix, olive, house dust mites and cockroaches and regarded as positive when it was >0.35 kIU/L. Serum total IgE level was analyzed with enzyme-linked immunosorbent assay method. According to the manufacturer's recommendation, a value of <100 kU/L was considered normal.

Spirometric Analysis

Pulmonary function tests were performed using a spirometer (MasterScreen™ Pneumo; Jaeger, North Rhine, Westphalia, Germany). FEV_1, forced vital capacity (FVC) and maximum mid-expiratory flow (MMEF25–75%) were measured according to the American Thoracic Society/the European Respiratory Society guidelines (13). The patients conducted three consecutive manoeuvres and the best result was retained.

Ethical Concerns

The protocol was approved by the local ethics committee of our institution with a protocol number of 2013/10. Informed consent was obtained from the parents of each participant for the scientific reporting of the data based on the study protocol.

Statistical Analysis

Data were analyzed by using SPSS for Windows, Version 18 (SPSS Inc., Chicago, IL, USA) program. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Descriptive analyses were presented with using mean±standard deviation for normally distributed variables. The descriptive frequencies were given as (%). A chi-square test was used for comparison of proportions. Student's t-test was used for the comparison of normally distributed independent numerical variables. Comparisons between two groups of non-normally distributed independent variables were analyzed by using the Mann-Whitney U test. Pearson's correlation coefficient was used to assess the correlation between normally distributed independent variables. A p value of less than 0.05 was considered statistically significant.

Results

3.120 children admitted to our outpatient clinic were recruited into the study. 1.750 SPTs were carried out in children with allergic respiratoy diseases within 18 months. Of those, 112 children had respiratory tract symptoms in mould season and had at least one fungal sensitization with a rate of 6.4% and the rate of sensitization to *Alternaria alterna* was found to be 5%. The demographical characteristics and descriptive parameters of children with mould allergy are summarized in Table 1.

The age, age at onset of symptoms, and age at diagnosis in patients with allergic rhinitis were significantly higher than in those with asthma ($p<0.05$). The age at diagnosis in children sensitized to *Penicillium spp.* was higher than in those with

Table 1. Characteristics of children with mould allergy

Characteristics (n=112)	Values
Age (month) Mean ± SD	 107.46±47.21
Age of the symptoms (month) Mean ± SD	 61.08±41.64
Diagnosis age (month) Mean ± SD	 89.76±46.8
Gender (%) Male	 63 (56.2%)
Parental atopy history (%)	28 (25%)
Diagnosis (%) Asthma only Allergic rhinitis only Asthma and allergic rhinitis Allergic conjunctivitis	 19 (16.9%) 33 (29.4%) 48 (42.9%) 12 (10.8%)
Asthma (%) Mild Moderate Severe	 27 (40.2%) 27 (40.2%) 13 (19.4%)
Allergic rhinitis (%) Intermittant Persistant	 28 (34.5%) 53 (65.5%)
Sensitization type Monosensitization Polysensitization	 43 (38.3%) 69 (61.7%)
Total IgE Mean ± SD	 527.6±160.1
Fungal allergen sensitization by SPT (%) Fungal aeroallergens *Alternaria alterna* *Cladosporium herbarum* *Penicillium spp.* *Aspergillus fumigatus* Non-fungal aeroallergens Grass Olive Dust mite Animal dander	 51 (45.5%) 36 (32.1%) 18 (16 %) 7 (6.2%) 42 (82.3%) 32 (62.7%) 23 (45%) 19 (37.2%)
Spirometric analysis FEV_1% FEV_1/FVC PEF% MF25-75%	 89.3±21.51 91.53±23.11 83.97±20.31 94.77±18.95

SD: Standard deviation, IgE: Immunoglobulin E, FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, PEF: Peak expiratory flow, SPT: Skin prick testing

other fungal sensitizations (p=0.033). There was no statistically significant difference between patients with different fungal sensitizations in terms of patients' age, age at onset of symptoms, age at diagnosis, and having asthma and/or allergic rhinitis (p>0.05).

The patients with mild asthma were mostly monosensitized (p=0.003), but with SA were polysensitized (p=0.007). *Alternaria alterna* sensitization was significantly higher in persistent allergic rhinitis compared to intermittent allergic rhinitis (p>0.05). *Aspergillus spp.* sensitization was higher in children with allergic rhinitis and conjunctivitis (p=0.038).

Alternaria alterna was the most common fungal allergen in both mono and polysensitized groups (p=0.002, p=0.004, respectively). *Cladosporium spp.* sensitization in monosensitized group was higher than in polysensitized group (p=0.032). In polysensitized cases, *Alternaria alterna* and *Cladosporium spp.* coexistence was the most common combination compared to other fungal combinations (p<0.001). Sensitization to *Alternaria alterna* and grass pollen mixture was signicantly higher than other fungal and non-fungal combinations in polysensitized children (p=0.048). The comparison of the characteristics of monosensitized and polysensitized children is summarized in Table 2.

Serum total IgE was high in 88 (78.5%) participants. No statistically significant difference was determined in serum total IgE levels among different types of fungal sensitization (p>0.05). sIgE measurement was performed in 90 patients (80.3%) and the sensitivity rate was found to be 88% compared to SPT. Children, whose sIgE levels were determined as negative, were monosensitized, however, there was no statistical significance (p>0.05). sIgE levels were correlated with SPT diameter in patients with allergic rhinitis sensitized to fungal allergens (r=0.466, p<0.001), however, there was no correlation between the two parameters in children with asthma and children with asthma and coexisting allergic rhinitis (p=0.092, p=0.258, respectively).

In spirometric analysis, FEV_1 and FEV_1/FVC values were lower in polysensitized children with asthma and children with asthma and coexisting allergic rhinitis compared to children with allergic rhinitis only (p=0.004, p=0.001, respectively). There was no correlation between each of spirometric parameters

of FEV_1, FEV_1/FVC, peak expiratory flow, MEF25-75 and the type of fungal sensitivity (p>0.05).

Discussion

The most remarkable findings of the present study were the high rates of fungal sensitization in school-aged children and its close relevance with the clinical findings. The most common fungal allergen was *Alternaria alterna*. More than half of the children were polisensitized with fungal allergens. Although, there was no significant difference between having asthma and allergic rhinitis in terms of fungal sensitization, *Alternaria alterna* sensitization was found to be the most common in persistent allergic rhinitis. Lastly, polisensitization with fungal allergens was closely associated with lower spirometric parameters in children with asthma.

In the present study, the rate of fungal sensitization determined by SPT in school-aged children was 6.4%.

Table 2. Comparison of demographic data and parameters between mono and polysensitized children to fungal allergens

Characteristics	Monosensitization (n=43)	Polysensitization (n=69)	p values
Age (month) Mean ± SD	93.05±41.86	116.75±49.44	0.013
Age of symptoms (month) Mean ± SD	4.70±3.52	5.49±3.46	0.293
Age of diagnosis (month) Mean ± SD	6.28±3.49	8.44±4.00	0.006
Gender (%) Male	24 (55.8%)	39 (56.5%)	>0.05
Parental atopy history (%)	11(25.6%)	17 (24.6%)	>0.05
Diagnosis (%) Asthma only Allergic rhinitis only Asthma and allergic rhinitis Allergic conjunctivitis	 7 (16.3%) 14 (32.6%) 21 (48.8%) 1 (2.3%)	 12 (17.4%) 19 (27.6%) 27 (39.1%) 11 (15.9%)	 >0.05 >0.05 >0.05 <0.001
Asthma (n=67) (%) Mild Moderate Severe	 7 (10.4%) 16 (23.9%) 3 (4.5%)	 12 (18%) 19 (28.3%) 10 (14.9%)	 0.003 >0.05 0.007
Allergic rhinitis (n=81)(%) Intermittant Persistant	 11(13.5%) 24 (29.7%)	 17 (21%) 29 (35.8%)	 >0.05 >0.05
Total IgE (IU/mL) Mean ± SD	353.4±62.0	655.1±65.2	0.024
Fungal allergen sensitization by SPT (%) *Alternaria alterna* *Cladosporium herbarum* *Penicillium spp.* *Aspergillus fumigatus*	 26 (60.5%) 10 (23.2%) 7 (16.3%) 0	 25 (36.2%) 26 (37.7%) 11 (16%) 7 (10.1%)	 >0.05 0.033 >0.05 <0.001
Spirometric analysis FEV_1% FEV_1/FVC PEF% MEF25%-75%	 91.65±19.68 89.55±20.33 85.99±19.76 95.66±19.45	 89.78±21.33 92.11±18.76 87.43±20.32 93.49±22.18	 >0.05 >0.05 >0.05 >0.05

SD: Standard deviation, SPT: Skin prick testing, FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, PEF: Peak expiratory flow

In GA(2)LEN skin test study, which was performed in all over Europe, the fungal sensitization rate was determined as 5% in a group consisting of adults and children with asthma (11). This rate was found to be 10.9% in Iranian children with asthma (14), 8% in Argentinian children with wheezing (15) and 6.3% in a population of children and adults with allergic rhinitis (16). Fungal sensitization rates were ranging between 7.5% and 15% in adults with asthma (17-19). Our results were concordant with the data of the Europe, however, our rate was lower than that of the results of adults with asthma. We speculate that this might be a consequence of the longer annual exposure to sunlight in our residential district in the Mediterranean region with a latitude (North latitude between 37°30' and 38°03) in which annual sunlight exposure varies between 3.6 and 10.2 hours, and rarely rainy days ranging between 0.5 to 12.2 days/month. The other possible reason for lower sensitization rates might be related to the younger age of the study population. Supporting our results, a new meta-analysis showed that exposure to domestic fungal allergens in early ages was closely related to development of asthma and allergic rhinitis in childhood and, the incidence and severity of the disease and also increased with the duration of exposure (8). According to the general consensus on atopic march showing that years are needed to develop allergic respiratory tract diseases, this might be also true for fungal allergen sensitization and its clinical outcome.

In the present study, about two-thirds of the children were sensitized to *Alternaria alterna* and, subsequently, one-third of the children were sensitized to *Cladosporium spp.* Similarly, Torres-Rodríguez et al. (20) have reported that fungal sensitization in children with respiratory allergy was most commonly to *Alternaria alterna* followed by *Cladosporium spp.*, *Penicillium spp.* and *Aspergillus spp.* Kashef et al. (21) from Iran established that the sensitization rates of fungi in a population with allergic rhinitis were 9.8%, 3.7%, 2.2%, and 0.7%, for mixed fungi, *Alternaria alterna*, *Aspergillus spp.*, and Candida, respectively.

In the present study, the rate of sensitization to *Alternaria alterna* was found to be around 5%. However, in a previous study from Istanbul in 2005, Turkey, the rate of sensitization to *Alternaria alterna* was determined as 1.1% in children with allergic respiratory diseases (22). Thus, these two studies are more or less similar in methodological aspect; it might be thought that in our country, fungal aeroallergen sensitization increases in children by time. However, in the literature, we found no study in a prospective design at the same center to determine the increase in the prevalence of fungal sensitization. In Chile, *Alternaria alterna* susceptibility was determined as 11% in children with asthma (23) and 2.8% in a population of children and adults in a study conducted in six different research centers in France (24).

Surprisingly, more than half of the children were polysensitized during the school-age years. Moreover, the mean age and the age at diagnosis of polysensitized children were significantly higher than monosensitized ones. We could not find any evidence in the literature demostrating an increase in fungal sensitization by age. As known, depending upon the aeroallergen, susceptibility to aeroallergens seen in asthma and allergic rhinitis increases at an average of 2-7% annually (25). This increase is mostly seen in late childhood or adolescence (26). Increase in the number of sensitized aeroallergens starts after approximately 4 years of age. In other words, the number of sensitized allergens in the majority of children, who have been sensitized until the age 4, rises by time and detected at age 10 and 18 years (27).

It was shown in this study that being polysensitized to fungal allergens was closely associated with SA and persistent allergic rhinitis. In a systemic review evaluating the studies carried out in children, it was stated that earlier exposure to humidity or mold was associated with earlier onset of asthma and the higher exposure dose was associated with more SA (28). The presence of mold on walls at home,is associated with 2.4-fold increased risk of early-onset-asthma and mold odor, is related with 5-fold and 16.7-fold greater risk of early-onset-asthma and late-onset asthma, respectively (29). As a result, we suggest that fungal exposure duration as in other aeroallergens has an impact on fungal allergen polysensitization. Besides, the severity of allergic pulmonary diseases might be related to duration of exposure to fungi as the case with other aeroallergens, however, so far, an accurate conclusion can not be achieved.

Surprisingly, more than half of the children were polysensitized during the school-age years. Moreover, the mean age and the mean age at diagnosis of polysensitized children were significantly higher

than that of monosensitized ones. We could not find any evidence in the literature demostrating the increase in fungal sensitization by age. However, we know well that polysensitization to pollens and other aeroallergens developes by years (30,31). It was shown in this study that being polysensitized to fungal allergens was closely associated with SA and persistent allergic rhinitis. As a result, we suggest that fungal exposure duration as in other aeroallergens has an impact on fungal allergen polysensitization. Besides, the severity of allergic pulmonary diseases might be related to duration of exposure to fungi as is the case with other aeroallergens.

The relationship between fungal allergen sensitization and the severity of respiratory allegic diseases is still a matter of debate. Recently, it has been shown that fungal allergens play a role in SA, asthma exacerbations, earlier onset of symptoms and, asthmatic children were more frequently prescribed maintenance oral corticosteroids (32). Vicencio et al. (33) showed that 76% of asthmatic children sensitized to fungi were categorized as severe persistent than that of 33% of asthmatic children without any evidence of fungal sensitization with an OR of 6.33. However, Feliu et al. (34) could not observe any relationship between *Alternaria alterna* sensitization and asthma in patients aged 2-14 years. Nonetheless, in this study sensitization was evaluated by Alta-1 sIgE. Zou et al. (35) have reported that sIgE levels against fungi increased with the severity of asthma except for *Alternaria alterna*. In a study carried out in Spain, while no relationship of *Alternaria alterna* sensitization with asthma could be established; it was only correlated with allergic rhinitis (20). On the contrary, sensitization to *Alternaria alterna* was correlated with allergic rhinitis in monosensitized adult patients independently of asthma (36). Unlike all these study results, we found that polysensitization was closely associated with asthma severity and persistent allergic rhinitis. Distinct from the previous studies, the relability of our stuy is increased by performing SPT instead of sIgE test whose positive predictive rate was 88% and demonstrating the relationship between being polisensitized and lower spirometric analysis parameters.

The major strengths of the study were the evaluation of the patients by a pediatric allergy specialists and the determination of sensitization by performing SPT, which potentially increased the reliability of the results.

Study Limitations

The limitations of our study included the fact that patients who were referred to tertiary care services were included in the study, therefore, the real prevelance and the burden of the fungal allergen sensitization in the population cannot be estimated. Polysensitization was increasing with age and more than half of the children with SA were co-sensitized to non-fungal aeroallergens. It was not possible for us to estimate whether fungal or non-fungal sensitization has an impact on disease severity in this study due to its retrospective design. Further prospective studies are needed to investigate this point.

Conclusion

In conclusion, fungal sensitivity is a gradually increasing threat. To the best of our knowledge, the findings of this study are the first evidence showing the importance of fungal sensitization and its association with allergic respiratory tract diseases in school-aged children in our country. This study is the pilot study for large-scale prospective studies that will be conducted to understand the risk factors of fungal allergy in childhood period. Fungal allergy sensitization seems to be a burden for children with allergic respiratory tract diseases. Polysensitization appears to start in very early ages of life and is associated with the disease severity. Further prospective large-scale studies are needed in order to understand the role of fungal allergy and its importance for child health.

Ethics

Ethics Committee Approval: The study was approved by the Adnan Menderes University University of Local Ethics Committee, Informed Consent: Consent form could not be filled out by all participants because of the retrospective design of the study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Pınar Uysal, Duygu Erge, Ayşe Yenigün, Concept: Pınar Uysal, Duygu Erge, Design: Pınar Uysal, Duygu Erge, Data Collection or Processing: Duygu Erge, Analysis or Interpretation: Pınar Uysal, Literature Search: Pınar Uysal, Duygu Erge, Ayşe Yenigün, Writing: Pınar Uysal, Editing: Ayşe Yenigün.

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