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Evaluation of the Children with Recurrent Respiratory Tract Infections

MD. Günseli Bozdoğan, MD. Ismail Reisli, MD. Figen Doğu, MD. Aydan Ikincioğulları and MD. Emel Babacan

The aim of the present study is to evaluate the main causes underlying recurrent respiratory tract infections during childhood retrospectively. The records of 204 patients out of 6935 subjects who were admitted to our clinic between the years 1994-1999, with complaints of recurrent respiratory tract infections were examined. The patients were divided into three groups depending on their complaints during admission: Children with symptoms of only upper respiratory tract infection (group I), children with symptoms of only lower respiratory tract infection (group II) and children with symptoms of upper and lower respiratory tract infection (group III). The subjects consisted of 204 children, 132 male and 72 female with a median age of 3 years. Asthma and allergic diseases were the most common causes (45%) of recurrent complaints of respiratory tract while primary immunodeficiencies were determined as the second frequent cause (37.2%). Anatomic-obstructive diseases (9.3%) and the nutritional deficiency of micronutrient (8.3%) were determined as the other primary factors causing recurrent complaints of respiratory tract. Asthma and allergic diseases, primary immunodeficiencies and anatomic-obstructive factors, as well as nutritional zinc and iron deficiencies seems to be the major causes underlying recurrent respiratory tract infection in childhood.

Key words: Children, recurrent respiratory tract infection

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For further information about this article or if you need reprints, please contact:

Figen Doğu, MD
Sancak Mah., 219.
Sokak, 8/12, Yildiz,
Ankara, 06550, Turkey

Fax:+90 312 3620581
Ph:+90 312 3623030-ext 6346
e-mail:esin.figen@veezy.com

ANSInet
Asian Network for Scientific Information

Ankara University School of Medicine,
Department of Pediatric Immunology and Allergy, Ankara, Turkey

Introduction

Every pediatrician is faced with the fact that some children have more infections than others (Paul and Shearer, 1999). Children with a history of recurrent infections present a diagnostic challenge to their pediatricians because of the expectations of the parents for an explanation regarding the increase in the frequency of infections (Woroniecka and Ballow, 2000). Pediatricians should maintain a high index of suspicion because early diagnosis and treatment improve the quality of life of these patients and their parents (Herrod ***et al.***, 1995 and Paul and Shearer, 1999). Sometimes the type or severity of infection, family history, or physical examination provides a clue that the immune system is not functioning properly (Paul and Shearer, 1999) in these children, revealing some serologic abnormalities (Becker, 1999 and Herrod ***et al.***, 1995) as result of its evaluation. On the other hand, some factors such as atopy or asthma, gastroesophageal reflux and structural anatomic factors contribute to the risk for infections during childhood (Becker, 1999 and Woroniecka and Ballow, 2000). The development of new diagnostic tests in recent years has raised the issue of which studies are indicated for evaluating this patient population (Becker, 1999 and Herrod ***et al.***, 1995).

The objective of the present study is to evaluate the main causes underlying recurrent respiratory tract infections during childhood.

Materials and Methods

In this study, the records of 204 patients out of 6935 patients who were admitted to Pediatric immunology-Allergy Outpatient Clinic at Ankara University School of Medicine between the years 1994-1999 with complaints of recurrent respiratory infections were examined retrospectively. Children with infections involving the upper respiratory tract with a history of more than eight episodes were defined as recurrent upper respiratory tract infection while recurrent pneumonia were defined as at least two radiologically and clinically proven episodes of pneumonia. A work-up which included detailed personal and family history, physical examination and laboratory studies was done to evaluate patients for recurrent respiratory tract infections. Laboratory studies included complete blood count and blood smear to determine absolute neutrophil and lymphocyte counts; measurement of serum immunoglobulin(Ig) and IgG subclass levels and isohemagglutinin titers and if indicated, monoclonal antibodies for lymphocyte subgroups and prolipherative responses to mitogens.

In this study, all the patients have been evaluated for anatomic-obstructive diseases with detailed personal history and if indicated, ENT consultation was made. Since zinc deficiency is one of the well known cause of recurrent infections (Arcasoy, 2001); serum zinc levels were measured for all patients The diagnosis of asthma was made based on the criteria of international Pediatric Asthma Consensus Group Reports and criteria of the Martinez for patients under 2 years of age (Castro-Rodriguez ***et al.***, 2000). The atopic status of asthmatic patients was defined through positive skin-prick test to extracts of common aeroallergens and/or serum specific IgE by CAP-System (Pharmacia, Sweden).

Patients with IgA serum levels of less than 7 mg/dL were defined as selective whereas, levels that fell more than two standard deviations below the mean serum level for their age were defined as partial IgA deficiency (Schroeder, 2001).

IgG subclass deficiency was defined as a serum IgG subclass levels more than two standard deviations below the normal mean for age (Ballow, 2002). in our practice for transient hypogammaglobulinemia we have used a definition based on major immunoglobulin isotype levels that fall at least two standard deviations below the mean for age according to the reference values with normal production of isohemagglutinin (Doğu ***et al.***, 2003). No patient with a recognized severe immunodeficiency was included in the study. None of the patients had an asthma diagnosis before being evaluated for recurrent respiratory tract infections. Symptoms related to the structures of the respiratory tract above the larynx were accepted as upper respiratory tract infections while those below the larynx were accepted as lower respiratory tract infections (Arnold, 1996). The 204 children were divided into three groups based on their complaints at admission as follows: children with symptoms of only upper respiratory tract infection (group I), children with symptoms of only lower respiratory tract infection (group II), and children with symptoms of upper and lower respiratory tract infection (group III). These three groups were compared according to age and gender distribution and after the final diagnosis following laboratory studies.

Chi-square test and Kruskal Wallis analysis of variance were used for statistical analysis. Statistical significance was determined as $p< 0.05$.

Results

Of these 204 children, 132 are male and 72 are female and the median age is 3 years. The age and gender distribution according to each group of children with recurrent respiratory infections at admission are given in Table 1. There is no difference in gender distribution between the three groups. However, the median ages of children in group I are higher than in group II and III ($p<0.05$) while the age ranges of children in all groups are similar. Admission with complaints of the upper respiratory tract infection was more common (43.1%) than admission with complaints of lower respiratory tract infection (19.1%).

The final diagnosis of the patients according to the groups are shown in Table 2. The most common diagnosis in group I was primary immunodeficiency while asthma and allergic diseases were most common in groups II and III. Anatomic-obstructive diseases and nutritional deficiency of micronutrient were prominent in group I compared to groups II and III (Table 2).

As shown in Table 3, asthma and allergic diseases were the most common entities (45%) causing recurrent complaints of respiratory tract infections, with a higher prevalence of non-atopic asthma (78%). The ages of the patients with non-atopic asthma were lower than atopic asthmatics ($p<0.05$). Primary immunodeficiencies were determined as the second group of frequent diseases (37 %) causing recurrent complaints of respiratory tract infections. The most common primary immunodeficiency disease was IgA deficiency (51.3%). The anatomic-obstructive diseases (9.3%) and the nutritional deficiency of micronutrient (8.3%) are determined as the other primary factors causing recurrent complaints of respiratory tract infections (Table 3). in addition, the association of nutritional zinc and/or iron deficiencies are also determined in 24.5% of all

Table 1: Age and gender distribution of the patients

	Group I	Group II	Group III
n (%)	88 (43.1)	39 (19.1)	77 (37.8)
Male (n)	54	25	53
Female (n)	34	14	24
Age (year)			
Median	4	2	2.5
Range	0.4-13	0.5-12	0.75-14

Table 2: The final diagnosis according to the groups

	Primary immuno deficiency (n)	Asthma- allergic diseases (n)	Anatomic-obstructive diseases (n)	Nutritional deficiency of micronutrient (n)
Group I	43	20	10	15
Group II	11	25	3	-
Group III	22	47	6	2

Table 3: The final diagnosis of the children admitted with recurrent complaints of respiratory tract

Diagnosis	n	%	Age (yr) Median (Mean±SD)
ASTHMA AND ALLERGIC DISEASES	92	45	3 (4.1 ± 3)
Asthma	87		3 (4 ± 3)
Atopic asthma	19	22	7 (7.3 ± 3.4)
Non-atopic asthma	68	78	2.2(3.2 ± 2.1)
Allergic Rhinitis/rhinoconjunctivitis	5		7 (6.7 ± 1.9)
PRIMARY IMMUNODEFICIENCY	76	37	2.5 (3.4 ± 2.7)
IgA deficiency	39	51,3	3 (3.9 ± 2.6
Partial	35		
Selective	4		
Transient hypogammaglobulinemia	25	32,8	1.8 (1.9 ± 0.9)
IgG Subclass deficiency	11	14,4	6 (5.6 ± 3.4)
IgG1 deficiency	5		
IgG2 deficiency	3		
IgG3 deficiency	2		
IgG4 deficiency	1		
SPECIFIC ANTIBODY DEFICIENCY	1	1,3	2
ANATOMIC-OBSTRUCTIVE DISEASE	19	9,3	3 (3.8 ± 2.5)
Adenoidal enlargement	13		4 (4.9 ± 2.3)
Gastro-esophageal reflux	4		1.5 (1.4 ± 0.1)
Vascular ring	2		1.8 (1.8 ± 1.8)
NUTRITIONAL DEFICIENCY OF MICRONUTRIENT	17	8,3	3 (4.4 ± 2.9)

Table 4: Nutritional deficiency of micronutrients

	n	%	Age (yr) Median(Mean±SD)
Zinc deficiency	**29**	**58**	4 (4.8 ± 2.6)
Pure	11		
With other diseases	18		
Iron deficiency (with other diseases)	**13**	**26**	1.5 (1.6 ± 0.6)
Zinc+iron deficiency	**8**	**16**	2.8 (3.5 ± 2)
Pure	6		
With other diseases	2		
Total	**50**	**24,5**	3 (3.7 ± 2.5)

children (Table 4). There is no difference between the three groups according to nutritional deficiencies.

Twenty four children among 76 primary immunodeficiencies (10 with transient hypogammaglobulinemia of infancy, 10 with IgA deficiency, 2 with IgG1 subclass deficiency, 1 with IgG2 subclass deficiency, 1 IgG3 deficiency), 3 children with gastro-esophageal reflux and 2 children with adenoidal enlargement had also an additional diagnosis of non-atopic asthma (data not shown in Table 2). in addition, 3 male children with transient hypogammaglobulinemia of infancy had an adenoidal enlargement.

Discussion

A wide spectrum of diseases influence the respiratory tract directly or indirectly, by causing recurrent infection. Pediatricians should make a differential diagnosis because early diagnosis and treatment improve the quality of life of these patients and their parents. Differentiation between frequent infections caused by common risk factors such an asthma, anatomic factors, and nutritional factors versus primary and secondary immune dysfunctions should be based on a detailed history and physical examination and, if indicated, established with appropriate laboratory studies (Woroniecka and Ballow, 2000). Sometimes a child who has a history of recurrent respiratory infection has allergic rhinitis (Becker, 1999 and Paul and Shearer, 1999). Atopy affects 15% to 20% of the children and causes chronic inflammation of the airways that can mimic recurrent or chronic upper respiratory tract infections (Becker, 1999 and Woroniecka and Ballow, 2000). in this study, we found that the most common reason causing complaints of respiratory tract infection was asthma and allergic diseases while primary immunodeficiency diseases came second. We have shown that the anatomic and nutritional factors can be a cause for recurrent respiratory symptoms therefore, should also be taken into consideration.

Many studies have found that prevalence of childhood asthma and allergic diseases has been increasing over the last decades in most countries (Becker, 1999 and Anonymous, 1998). it has also been shown that airway infections in early life are associated with asthma and reduced lung function (Clark ***et al.***, 2000; Martinez ***et al.***, 1995; Nystad ***et al.***, 1999 and Von Mutius ***et al.***, 1999) although it has also been suggested that such infections may have a protective effect on later asthmatic disease (Cookson and Moffatt, 1997 and Jarvis ***et al.***, 1997). in this study, we found that

non-atopic asthma is the more common cause of respiratory tract symptoms compared to atopic asthma. This finding is believed to be originated from the young age of our patients. This group may correspond to the "benign infantil wheezing" which is defined as recurrent wheezing episodes triggered by viral infections only, whereas asthma is considered as a wheeze triggered by a wide array of factors such as allergen exposure, exercise, physical stimuli, etc...(Von Mutius ***et al.***, 1999). Since the present study was done retrospectively, the number of patients having persistent wheezing phenotype could not be determined. However, the high ratio of asthma in this study suggests that careful follow up of such patients is worthwhile because recurrent respiratory infections could contribute to persistent wheezing and asthma in children.

The immune system is not at its full maturity at birth and may not be totally developed until a child reaches school age (Dalal and Roifman, 2001 and Woroniecka and Ballow, 2000). When patients with recurrent respiratory infections are evaluated, some immunologic abnormalities can be determined. in one study (Herrod ***et al.***, 1995); the most common serological abnormality in children with recurrent infections was reported as partial IgA deficiency. in another study, it was reported that IgG subclass deficiency was determined in 33% of 125 children with recurrent infection (Sanal ***et al.***, 1993). Similarly, partial IgA deficiency was the most common primary immunodeficiency disease in the present study. We have shown that the other humoral immunodeficiency diseases such as transient hypogammaglobulinemia of infancy and IgG subclass deficiency were also a common problem in the present study. Since children with these disorders have increased susceptibility to recurrent infections (Becker, 1999; Doğu ***et al.***, 2003; Herrod ***et al.***, 1995; Pan and Hammarström, 2000); we suggest that serum immunoglobulin and IgG subclass levels should be determined in children suffering from recurrent respiratory tract infections.

Several factors contribute to the risk of infections during childhood (Woroniecka and Ballow, 2000). Patients with anatomic defects and nutritional deficiency can exhibit recurrent respiratory tract infections (Becker, 2002; Woroniecka and Ballow, 2000). Anatomic-obstructive factors including adenoidal enlargement, gastroesophageal reflux and vascular ring were determined as the third group of common causes in the present study. Micronutrient deficiency is also associated with increased incidence of infections, especially the respiratory one (Paul and Shearer, 1999; Woroniecka and Ballow, 2000). We have also shown in this study that one fourth of the patients had micronutrient deficiency including zinc and iron with or without another disease causing recurrent complaints of respiratory tract infections. We suggest that anatomic-obstructive factors and nutritional deficiencies should also be evaluated in children with recurrent infections.

In conclusion asthma and allergic diseases, primary immunodeficiencies and anatomic-obstructive factors, as well as, nutritional zinc and iron deficiencies should be taken into consideration in the evaluation of a child with recurrent complaints of respiratory tract infections.

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