

The Etiology of Recurrent Pneumonia with Onset During Infancy, and the Effect of Risk Factors on Age at First Episode and Episode Frequency

Başlangıcı Süt Çocukluğu Döneminde Olan Tekrarlayan Pnömoni Nedenleri ve Risk Faktörlerinin İlk Atak Yaşı ve Atak Sıklığı Üzerine Etkisi

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ABSTRACT

Objective: To determine the etiology of recurrent pneumonia in infants and to identify the factors associated with age at first episode and episode frequency.

Material and Methods: Children that had their first episode of pneumonia at age 1-24 months and met the diagnostic criteria for RP were included in the study. Their records were screened for conditions that may have been associated with pneumonia, including aspiration syndromes, congenital disorders, airway obstruction and secretion clearance disorders, immune deficiencies, and pulmonary hemosiderosis. The correlation between risk factors, and age at first episode and the frequency of episodes were evaluated separately for patients with and without an underlying etiology.

Results: In all, 60 patients (33.9%) had congenital birth defects, 55 (31%) had aspiration syndrome, 19 (10.8%) had airway obstruction, 7 (4%) had immune deficiency, 4 (2.3%) had cystic fibrosis, 2 (1.1%) had pulmonary tuberculosis, and 1 (0.6%) had pulmonary hemosiderosis. Of the patients; 29 (16.3%) had no specific etiology. In the patients without a discernible underlying disorder, risk factors (a history of exposure to cigarette smoke, ≥ 5 household members, insufficient breastfeeding) were significantly associated with a higher frequency of pneumonia episodes. Multiple logistic regression analysis showed that exposure to cigarette smoke was a risk factor for recurrent pneumonia episodes, independent of the other risk factors evaluated

Conclusion: Exposure to cigarette smoke, an overcrowded household, and insufficient breastfeeding were determined to be highly probable risk factors associated with the higher frequency of episodes in the RP patients without an underlying disorder.

Key Words: Pneumonia, Recurrent pneumonia, Children

ÖZET

Amaç: Süt çocuklarında tekrarlayan pnömoni nedenlerini ve risk faktörlerinin ilk atak ve atak sıklığına etkilerini belirlemek.

Gereç ve Yöntemler: İlk pnömoni atağını 1-24 ay içerisinde geçiren ve tekrarlayan pnömoni tanı kriterlerine uyan hastalar çalışmaya alındı. Pnömoni ile ilişkili olabilecek aspirasyon sendromları, konjenital bozukluklar, havayolu obstrüksiyonu, sekresyon temizleme bozuklukları, immün yetmezlik, pulmoner hemosiderozis gibi birliktelikler incelendi. Altta yatan hastalığı olan ve olmayanlar arasında risk faktörleri, ilk atak yaşı ve atak sıklığı arasında korelasyon varlığı değerlendirildi.

Bulgular: Hastaların 60'ında (%33.9) konjenital bozukluklar, 55'inde (%31) aspirasyon sendromları, 19'unda (%10.8) havayolu obstrüksiyonu, 7'sinde (%4) immün yetmezlik, 4'ünde (%2.3) kistik fibrozis, 2'sinde (%1.1) pulmoner tüberküloz ve 1'inde (%0.6) pulmoner hemosiderozis saptandı. 29 (%16.3) hastada kesin etioloji belirlenemedi. Altta yatan nedeni belirlenemeyen hastalarda sigara dumanına maruziyet, evde ≥ 5 kişi bulunması, yetersiz anne sütü alımı gibi risk faktörleri pnömoni atağı sıklığı ile ilişkili bulundu. Multipl lojistik regresyon analizi ile diğer risk faktörlerinden bağımsız olarak sadece sigara dumanının pnömoni sıklığı artışı ile ilişkisi saptandı.

Sonuç: Sigara dumanına maruziyet, kalabalık ev ortamı, yetersiz anne sütü alımı, altta yatan hastalığı olmayan hastalarda pnömoni atağı sıklığını artıran önemli risk faktörleridir.

Anahtar Sözcükler: Pnömoni, Tekrarlayan pnömoni, Çocuk

INTRODUCTION

Pneumonia is an acute inflammation of the lung parenchyma that develops due to both infectious (bacteria or viral) and non-infectious causes. Community-acquired pneumonia is an important cause of morbidity and mortality in children worldwide. In 2010, over 25% of childhood deaths worldwide were attributed to pneumonia and meningitis (1). The incidence and mortality rate of childhood pneumonia are 10 times higher in developing countries (2). A subgroup of children suffers from recurrent pneumonia (RP). It is defined as ≥ 2 episodes in 1-year period or ≥ 3 episodes during any time period with radiographic clearing between episodes (3). RP was determined in 6.4–9% of children with pneumonia (4-7).

Recurrent pneumonia usually occurs due to an underlying disorder that negatively affects local or systemic defense mechanisms and the underlying cause is identified in 80-90% (8). Recurrent pneumonia episodes may lead to the development of chronic respiratory morbidity. The potential burden of RP on the healthcare system, in terms of frequent hospitalizations, is significant. Early recognition and management of the underlying cause(s) is expected to reduce the number of pneumonia-related hospital admissions, morbidity and mortality (9). The aim of the present study was to determine the prevalence, underlying causes and risk factors of RP in infants and to identify the factors associated with age at first episode and episode frequency.

MATERIAL and METHODS

This study was conducted at Dr. Sami Ulus Maternity and Children's Education and Training Hospital, Ankara, Turkey. The study protocol was approved by the Hospital's ethics committee. The medical records of children that were admitted to the infant ward with a diagnosis of pneumonia between January 2005 and 2010 were systematically reviewed. Patients who had their first episode of pneumonia at age 1-24 months were identified and the records of those that met the diagnostic criteria for RP were included in the final analysis. Pneumonia was diagnosed based on the presence of tachypnea (with a respiratory rate of ≥ 60 /min for infants aged < 2 months, ≥ 50 / min for infants aged 2-11 months, and ≥ 40 / min for infants aged 11-24 months), labored breathing, reduced bronchial breath sounds or crackles on chest auscultation and/or radiological findings (pulmonary consolidation or infiltrate) (10).

Recurrent pneumonia is defined as 2 or more episodes of pneumonia in a year, or three or more episodes in any time frame. Children with protracted and persistent pneumonia and those aged > 24 months at the time of diagnosis were excluded from the study.

Patient demographics (gender, age at diagnosis of RP, age at first episode, number of episodes per year, and number of

episodes prior to diagnosis of RP) and details pertaining to the etiology of and risk factors for RP (presenting symptoms, history of mechanical ventilation, foreign object aspiration, frequent infections, prematurity, vaccination history, exposure to cigarette smoke, number of household members, method of home heating, duration of breastfeeding, parental consanguinity, family history of atopy or other chronic disorders, and exposure to tuberculosis) were recorded for each patient on forms. Physical examination findings and the results of diagnostic tests (chest X-ray, sweat test, PPD skin test, hemosiderin-laden macrophages in gastric aspirate, immunological evaluation, barium meal, gastroesophageal reflux scintigraphy, thoracic CT, and acid-fast staining of fasting gastric aspirate) were also recorded. In addition, medical records were screened for underlying conditions that may have been associated with pneumonia such as aspiration syndromes, congenital disorders, airway obstruction disorders, immune deficiencies, disorders of secretion clearance, and pulmonary hemosiderosis. The correlation between risk factors, and age at first episode and the frequency of episodes were evaluated separately for patients with and without an underlying etiology.

All statistical analyses were performed using SPSS v.15.0 for Windows. Two-way comparisons were made by dividing the patients into subgroups according to the presence or absence of each factor evaluated. Subgroups were compared in terms of age at first episode and episode frequency using the Mann-Whitney U test. Numerical variables are given as mean \pm SD or median (range), where appropriate. Categorical variables are expressed as frequencies and percentages. The level of statistical significance was set at $p < 0.05$. The effect of risk factors on age at first episode and episode frequency was evaluated using logistic regression analysis.

RESULTS

Among the 2120 patients with a diagnosis of acute lower respiratory infection during the study period, 177 (8.3%) were diagnosed as RP. In this group, 103 (58.2%) were male and 74 (41.8%) were female. The most common presenting symptom was cough (95.5%), followed by fever (59.9%) and wheezing (47.9%). The most commonly noted risk factor was exposure to cigarette smoke ($n=101$ [57.1%]). The patients' demographic and clinical characteristics are summarized in Table I.

In all, 60 patients (33.9%) had congenital birth defects (congenital heart disease, laryngomalacia-tracheomalacia, an extra lung segment, tracheoesophageal fistula, cleft palate, congenital lobar emphysema, diaphragmatic hernia, lung hypoplasia), whereas 55 patients (31%) had ≥ 1 aspiration syndrome (gastroesophageal reflux disease, foreign object aspiration, neuromuscular disorders, velopharyngeal insufficiency). In total, 19 patients (10.8%) had symptoms suggestive of wheezing/airway obstruction, 7 patients (4%) had an immune deficiency

syndrome (transient hypogammaglobulinemia of infancy, Kostmann syndrome, Bruton's disease, or common variable immune deficiency (CVID), 4 patients (2.3%) had cystic fibrosis, 2 patients (1.1%) had pulmonary tuberculosis, and 1 patient (0.6%) had pulmonary hemosiderosis. In 29 (16.3%) of the patients with RP, no specific etiology was determined. The distribution of underlying disorders among the 177 RP patients is shown in Table II.

Mean age at first episode in the present study was 10.37±6.45 (1.50-24.00) months. Data regarding pneumonia episodes, including age at diagnosis of RP, age at first episode, number of episodes per year, and number of episodes prior to diagnosis of RP, are provided in Table III.

The correlation between risk factors, and age at first episode and the frequency of episodes were evaluated separately for patients with and without an underlying etiology. There was no significant

correlation between risk factors, and age at first episode and the frequency of episodes in patients with an underlying disorder (p>0.05). In patients with a discernible underlying disorder, the evaluated risk factors were not significantly correlated with age at first episode (p>0.05), whereas a history of exposure to cigarette smoke, an overcrowded household (≥5 household members), and insufficient breastfeeding were significantly associated with an higher frequency of pneumonia episodes (p<0.05). Multiple logistic regression analysis showed that exposure to cigarette smoke was a risk factor for recurrent pneumonia episodes, independent of the other risk factors evaluated (p=0.004, Beta:0.515 B:0.429) (Table IV).

DISCUSSION

The present study investigated the demographic characteristics and underlying etiologies in patients with RP, as well as episode characteristics, and risk factors and their effect on pneumonia episodes. Among the 2120 patients diagnosed with pneumonia, 8.3% had RP, which is in agreement with earlier reports, as was the gender distribution (4,6 8,11). Mean age at diagnosis in the present study was 10.37 months, and this is comparable to previous reports from Turkey (12,13). Patients with pneumonia commonly present with cough, tachypnea, dyspnea, and fever. Of the patients with RP, 95.5% had cough and 59.9% had fever, which is in agreement with the literature (13). The most frequently noted risk factor in the present study was exposure to cigarette smoke (57.1%), followed by insufficient breastfeeding and an overcrowded household. Other risk factors observed in the present study were parental consanguinity, history of mechanical ventilation, prematurity, and a family history of atopy. Low birth weight (<2500 gr), insufficient breastfeeding, and an overcrowded household were considered definitive risk factors for pneumonia, whereas exposure to cigarette smoke was accepted as a highly probable risk factor (14,15).

Table I: Underlying risk factors for RP in children*.

Risk factor	n (%)
Exposure to cigarette smoke	101 (57.1)
Insufficient breastfeeding (<6 months)	91 (51.4)
Overcrowded household (≥5 household members)	84 (47.4)
Parental consanguinity	62 (35)
History of mechanical ventilation	24 (13.6)
Prematurity	22 (12.4)
History of prolonged oxygen use	11 (6.2)
Family history of atopy	19 (10.7)
Contact with animals at home	5 (2.8)
Exposure to tuberculosis	5 (2.8)
Delayed clearance of meconium	5 (2.8)
History of foreign object aspiration	1 (0.6)
History of frequent otitis/sinusitis	1 (0.6)

*Patients may have more than one risk factor

Table II: Distribution of patients with RP according to underlying disorder.

Disorders	n	Frequency (%)
Congenital heart diseases	44	24.9
Gastroesophageal reflux disease	32	18.1
Other aspiration syndromes	23	12.9
Other anomalies of the respiratory system	16	9.1
Asthma	16	9.1
Other causes of airway obstruction	3	1.7
Immune deficiency	7	4.0
Cystic fibrosis	4	2.2
Bronchopulmonary dysplasia	2	1.1
Pulmonary hemosiderosis	1	0.6
Diseases of unknown etiology	29	16.3
Total	177	100

Table III: Characteristics of episodes of pneumonia in patients with RP.

Characteristic	Mean ± SD (range)
Age at diagnosis (months)	10.37±6.45 (1.50-24.00)
Age at first episode (months)	4.92±4.61 (0.50-23.00)
Episodes per year	1.16±0.91 (0.28-5.49)
Number of episodes before diagnosis	2.68±1.05 (1.00-8.00)

Table IV: Comparison of the frequency of episodes in patients with RP(n=177), according to the presence or absence of certain risk factors.

Risk factor	n (frequency)	Frequency of episodes	
		Mean±SD (range)	p
Exposure to cigarette smoke			
Present	21 (11.8%)	1.06 (0.72-2.31)	<0.001
Absent	8 (4.5%)	0.63 (0.50-0.76)	
Number of household members			
<5	9 (5%)	0.70 (0.50-1.00)	0.001
≥5	20 (11.3%)	1.05 (0.60-2.31)	
Breastfeeding duration			
≥6 months	16 (9%)	0.76 (0.50-1.12)	0.001
<6 months	13 (7.3%)	1.16 (0.72-2.31)	
Home heating method			
Stove	20 (11.3%)	0.98 (0.54-1.90)	0.010
Radiator	9 (5%)	0.85 (0.50-2.31)	

According to logistic regression analysis, exposure to cigarette smoke, an overcrowded household, and insufficient breastfeeding were strongly associated with an increase in the frequency of episodes ($P < 0.05$ for all).

In the present study, the most frequent underlying disorders associated with RP were congenital anomalies (congenital heart diseases, followed by malacia disorders, diaphragmatic hernia, tracheoesophageal fistula, and pulmonary malformations) (4-6,8,11). The percentage of patients with congenital heart disease was higher than previous reports, which might have been due to the fact that our hospital is a tertiary center with sophisticated cardiology and cardiovascular surgery departments that accept patients from all over Turkey. The second most frequently encountered underlying disorders were aspiration symptoms; the most common was gastroesophageal reflux disease, followed by wheezy infant.

Evaluation of risk factors based on the presence or absence of an underlying disorder showed that exposure to cigarette smoke, an overcrowded household, and insufficient breastfeeding were risk factors strongly associated with the frequency of episodes in patients without a discernible underlying disorder. According to multivariate logistic regression, only exposure to cigarette smoke was an independent risk factor. A significant correlation was not observed between the method of home heating and

pneumonia episode frequency. Furthermore, a significant correlation between these factors (exposure to cigarette smoke, an overcrowded household, and insufficient breast feeding) and age at first episode of pneumonia was not noted.

Among the patients with an underlying disorder, none of the risk factors were significantly associated with the frequency of episodes or age at first episode, which might be attributable to the fact that underlying disorders independently increase the risk of episodes of pneumonia, regardless of the presence of other risk factors. Mean age at first episode in the present study was nearly 5 months and most patients were diagnosed after their third episode. In 2 patients, an underlying disorder was noted upon presentation with their first episode; clinical and laboratory evaluation indicated the presence of cystic fibrosis, and the diagnosis was confirmed via the sweat test. In 2 other patients that had transient hypogammaglobulinemia of infancy and gastroesophageal reflux disease, RP was diagnosed after their eighth episode, probably due to delayed referral to a tertiary center. The mean number of episodes per year in the present study was 1.16±0.91.

CONCLUSION

In the present study, patients with RP were evaluated in terms of associated risk factors and underlying etiologies, as well as pneumonia episode characteristics. The most frequent underlying disorders were congenital anomalies, followed by aspiration syndromes. Exposure to cigarette smoke, an overcrowded household, and insufficient breastfeeding were determined to be highly probable risk factors associated with the higher frequency of episodes in the RP patients without an underlying disorder. Educating families about the negative effects of cigarette smoke and the importance of breastfeeding, as well as implementation of policies that may improve the factors that contribute to an overcrowded household may help to decrease the risk of recurrent pneumonia.

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