Evaluation of Infants Hospitalized in Intensive Care Unit Due to Acute Severe Bronchiolitis in Terms of Recurrent Wheezing or Asthma Development

Yoğun Bakım Ünitesinde Akut Şiddetli Bronşiolit Nedeniyle Yatırılan İnfantların Tekrarlayan Hışıltı veya Astım Gelişimi Açısından Değerlendirilmesi

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ABSTRACT

Objective: Bronchiolitis stands out as the most prevalent lower respiratory tract infection among young children.Severe bronchiolitis, or bronchiolitis requiring admission to the hospital, affects 2-3% of all infants. The aim of this study was to evaluate individuals who were followed up in the pediatric intensive care unit (PICU) due to severe bronchiolitis in terms of asthma development.

Material and Methods: Patients who were admitted Ankara Bilkent City Hospital PICU between January 2013 and December 2022, who were diagnosed with severe bronchiolitis and who had no additional systemic disease were included in the study. Demographic and clinical characteristics of patients, intensive care support treatments, duration of hospital stays, atopic conditions, and respiratory viral panel cultures was documented. The current clinical condition of the patients was documented through hospital records and telephone interviews conducted with their caregivers. The existence of asthma symptoms and the utilization of treatments within the last 12 months were evaluated according to the guidelines of the Global Initiative for Asthma (GINA) and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

Results: The mean age of the 60 patients admitted to the intensive care unit who met the study criteria was 13.5±7.2 months. The mean age of the children at the time of the study was 42.5 months. Male gender was more predominant (n=39, 65%). The mean number of days that respiratory support was received in intensive care was 4.9 (±3.5) days and the mean number of days of systemic steroid therapy was 3.8 (±1.7) days. In the viral respiratory tract, Respiratory Syncytial Virus (RSV) was isolated at the highest frequency in 27 patients, accounting for 45%, followed by rhinovirus (n=6, 10%) and Bocavirus (n=5, 8.3%). The number of patients receiving current asthma treatment was (n=33, 55%). Upon assessing the current status, it was found that there had been 25 (41.6%) patients with asthma attacks over the past 12 months.

Conclusion: This study revealed that over half of the patients who experienced severe bronchiolitis subsequently developed asthma, with some not being referred to an allergy clinic. Furthermore, it was observed that certain patients, despite presenting with asthma symptoms, were unaware that these symptoms were attributable to asthma. We recommend that

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patients admitted to the PICU with a diagnosis of severe bronchiolitis be closely monitored for the potential development of asthma and that families be thoroughly informed at the time of discharge.

Keywords: Asthma, Infants, Pediatric Intensive Care, Severe Bronchiolitis, Wheezing

ÖZ

Amaç: Bronşiolit, çocuklar arasında en yaygın alt solunum yolu enfeksiyonu olarak öne çıkmaktadır. Hastaneye yatış gerektiren ağır bronşiolit, tüm infantların yaklaşık %2-3'ünü etkilemektedir. Bu çalışmanın amacı, ağır bronşiolit nedeniyle çocuk yoğun bakım ünitesinde (ÇYBÜ) takip edilmiş olan bireyleri astım gelişimi açısından değerlendirmektir.

Gereç ve Yöntemler: Ocak 2013 ile Aralık 2022 tarihleri arasında Ankara Bilkent Şehir Hastanesi ÇYBÜ'ye kabul edilen, ağır bronşiolit tanısı almış ve ek sistemik hastalığı olmayan hastalar çalışmaya dahil edilmiştir. Hastaların demografik ve klinik özellikleri, aldıkları yoğun bakım destek tedavileri, hastanede kalış süreleri, atopi durumları ve solunum yolundan izole edilen viral panel sonuçları değerlendirilmiştir. Hastaların mevcut klinik durumu, hastane kayıtları ve bakım verenler ile yapılan telefon görüşmelerinden elde edildi. Astım semptomlarının varlığı ve son 12 ay içinde tedavi kullanımı, GINA ve Uluslararası Çocukluk Çağı Astım ve Alerjileri Çalışması (ISAAC) anketine göre değerlendirildi.

Bulgular: Çalışma kriterlerini karşılayan 60 hastanın, yoğun bakımda yatışı yaş ortalaması 13.5 (±7.2) aydı. Çalışma sırasında çocukların ortalama yaşı 42.5 aydı.ekleyelim. Erkek cinsiyet daha baskındı (n=39, %65). Mevcut astım tedavisi alan hasta sayısı 33 (%55) olarak belirlendi. Mevcut durum sorgulandığında, son 12 ayda astım atağı geçirmiş olanların sayısı 25 (%41.6) olarak tespit edildi.

Sonuç: Bu çalışmada, şiddetli bronşiolit geçiren hastaların yarısından fazlasında astım geliştiği ve bazı hastaların alerji polikliniğine yönlendirilmediği görülmüştür. Ayrıca, bazı hastaların astım semptomları olmasına rağmen, bu semptomların astımdan kaynaklandığının farkında olmadıkları belirlenmiştir. Ağır bronşiolit tanısı ile ÇYBÜ'ye yatırılan hastaların, astım gelişimi açısından yakından izlenmesi ve taburculuk sırasında ailelerin bilgilendirilmesi gerektiğini öneriyoruz.

Anahtar Sözcükler: Astım, Bebek, Çocuk Yoğun Bakım, Ağır Bronşiolit, Hışıltı

INTRODUCTION

Bronchiolitis stands out as the most prevalent lower respiratory tract infection among young children. Almost all children are exposed to viral agents during the first two years of life. Severe bronchiolitis, or bronchiolitis requiring admission to the hospital, affects 2-3% of all infants (1, 2), and of these, 3-11% require admission to the (PICU) (3). There is a lack of extensive data in the existing literature concerning the relationship between experiencing severe bronchiolitis in infancy and its impact on the development of recurrent wheezing or asthma later in life (4).

Asthma is a heterogeneous disease characterized by chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Asthma affects 1-18% of the population in different countries (5). According to the modified International Study of Asthma and Allergies in Childhood (ISAAC) study conducted in Turkey, the cumulative prevalence of childhood asthma was found to be between 13.7-15.3% (6). Families are most concerned about the risk of wheezing children developing asthma later in life. Currently, there is no definitive laboratory test that can predict which wheezing children will develop asthma. Real-life data on the proportion of severe bronchiolitis cases that progress to wheezing infant and/or asthma are limited. The primary objective of our study was to ascertain the rates of recurrent wheezing and the development of asthma during the follow-up period for children who were hospitalized in the PICU with a diagnosis of severe bronchiolitis.

MATERIALS and METHODS

The study included patients admitted to Ankara Bilkent City Hospital PICU between January 2013 and December 2022 who were diagnosed with severe bronchiolitis within the first 24 months of life, according to the classification outlined in the Turkish Thoracic Society Diagnosis and Treatment Consensus Report (7). Patients with a prior diagnosis of wheezing infant syndrome and those with additional systemic chronic diseases were excluded from the study. Patients' demographic characteristics, intensive care support treatments, duration of hospital stays, atopic conditions, and respiratory viral panel cultures have been recorded. Medical records of the patients were evaluated for follow-up results. The current clinical status of the patients was recorded by telephone interviews conducted by the caregivers, with the interviews being carried out by the researchers themselves. The presence of asthma symptoms and the use of treatment in the last 12 months were assessed using the Global Initiative for Asthma (GINA) guidelines and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The control status of those with asthma was also evaluated using the GINA asthma control questionnaire. The prevalence of asthma was investigated using the ISAAC questionnaire, validated in Turkish (8, 9). The primary questions include "wheezing in the past 12 months," "history of asthma," and the presence of symptoms within the past 12 months. "four or more attacks of wheezing," "cough with no cold or respiratory infection," "sleep disturbed due to wheezing ≥1 night per week," "wheezing due to exercise," and "speech limited due to wheezing." Four additional questions were included to investigate the severity of asthma and use of medications: "number of asthma attacks in the last 12 months," "attendee in emergency service in the last 12 months because of asthma," "hospitalization in the last 12 months due to asthma," and "daily use of medications used to treat asthma". Factors that could pose a risk for the development of recurrent wheezing or asthma were assessed, including

gender, multiple intensive care hospitalizations, duration of active intensive care treatment, mechanical ventilation, total length of hospitalization, eosinophil percentage, presence of atopy, presence of RSV infection, birth weight, and delivery method. The recorded respiratory viral panel results for the patients were obtained through the application of PCR techniques.

Statistical analysis

All statistical analyses were performed with the SPSS 25.0 program (IBM Corp, Armonk, NY). Categorical variables were expressed as frequency and percentage. Continuous data that demonstrated a normal distribution were presented as mean and standard deviation. Logistic regression analysis was conducted to evaluate the independent effects of variables on asthma development. A p value of <0.050 was considered statistically significant.

RESULTS

The mean age of the 60 patients admitted, who met the study criteria, was 13.5±7.2 months. Male gender was more predominant (n=39, 65%). The mean follow-up period after discharge for the patients was 34.5±20.2 months. The mean age of the children at the time of the study was 42.5 months. The mean number of days that respiratory support was received in intensive care was 4.9 (±3.5) days and the mean number of days of systemic steroid therapy was 3.8 (±1.7) days, details in Table I. It was observed that 21.7% (n=13) of the patients experienced an episode requiring intensive care admission following a severe bronchiolitis attack. Among respiratory supports, the number of patients receiving invasive treatment, including Noninvasive Mechanical Ventilation (NIMV), High-Frequency Oscillatory Ventilation (HFOV), and Intubation, was a total of 52 (86.7%) (Table I). Total of 32 (53.3%) patients receiving magnesium treatment and 31 (51.7 %) ipratropium bromide treatment. In the respiratory viral panel results, pathogens were isolated in 42 patients. Among these, the most frequently isolated viruses were respiratory syncytial virus (RSV) in 27 patients, followed by rhinovirus (6, 10%) and bocavirus (2, 3.3%) (Table II). During the follow-up, 23 (38.3%) patients were admitted to the pediatric allergy outpatient clinic.

Table I: The characteristics of PICU admission and treatment

Follow-up period from discharge (month)*	34.5±20.2 (16-108)
Number of intensive care admissions*	1.3±0.84 (1-6)
Intensive care effective treatment time (day)*	4.9±3.5 (1-20)
Steroid treatment time (day)*	3.8±1.7 (0-9)
Total duration of admission (day)*	10.6±8.7 (1-66)
Receiving treatment†	
Magnesium treatment	32 (53.3)
Ipratropium Bromide treatment	31 (51.7)
Free flow oxygen delivery	2 (3.3)
Nonrebreathing mask	6 (10)
HFOV	37 (61.7)
NIMV	6 (10)
Intubation	9 (15)

***:** *mean ± standart deviation (minimum-maximum),* **†:** *n(%),* ***HFOV:** High-frequency oscillation ventilation,* ***NIMV:** Non-invasive mechanic ventilation*

Table II: Respiratory viral panel results

RSV*	27 (45)
Rhinovirus*	6 (10)
HboV*	5 (8.3)
Adenovirus*	2 (3.3)
nCoV2*	2 (3.3)

***:** *n(%),* ***RSV:** Respiratory syncytial virus,* ***HboV:** Bocavirus,* ***nCoV2:** Novel Coronavirus*

Table III: ISAAC Asthma Questionnaire

	Yes*
Wheezing in the last 12 months	25 (41.7)
Asthma attacks in the last 12 months 1-3 attacks 4-12 attacks	22 (36.7) 3 (5)
Wheezing due to exercise	20 (33.3)
Speech limited due to wheezing	12 (20)
Cough without cold or respiratory infection in the last 12 months	13 (21.7)
Sleep disturbance due to wheezing	18 (30)
Emergency room attendee due to asthma	20 (33.3)
Hospital admission due to asthma	11 (18.3)
Using steroids for asthma in the last 12 months	8 (13.3)
Using bronchodilators for asthma in the last 12 months	36 (60)
Current asthma treatment	33 (55)
Physician diagnosed asthma†	34 (56.7)

***:** *n(%)*

Table IV: Analysis table of risk factors for the development of asthma

	Univariate		
	OR	CI	p
Gender	1.17	0.4-3.41	0.765
Multiple intensive care admissions	2.15	0.58-7.98	0.25
Effective treatment duration (days)	0.95	0.82-1.1	0.572
Mechanical Ventilation	1.56	0.48-5.06	0.45
Total hospitalization duration	0.94	0.82-1.07	0.35
Percentage of eosonophils	1.03	0.77-1.4	0.8
Presence of atopy	0.59	0.05-6.95	0.68
RSV isolation	1.65	0.59-4.63	0.33
Birth weight	0.98	0.27-3.57	0.98
Delivery method	0.94	0.33-2.66	0.91

Patients were questioned according to the ISAAC asthma questionnaire for the last 12 months and the details are given in table III. The number of patients receiving current asthma treatment was 33 (55%). Upon assessing the current status, it was found that there had been 25 (41.6%) patients with asthma attacks over

the past 12 months (Table III). Out of the 34 patients diagnosed with asthma, 17 were being followed with an asthma diagnosis at our clinic; however, the diagnosis of the remaining 17 patients was determined through phone interviews. In the present study, we sought to examine the potential influence of various factors on the development of asthma following intensive care unit (ICU) admission. Our investigation encompassed a range of variables, including gender, the necessity for multiple PICU admissions, the duration of active treatment, the use of mechanical ventilation, eosinophil percentage, the presence of atopy, RSV isolation, mode of delivery, and birth weight. However, our analysis did not identify any statistically significant risk factors (Table IV).

DISCUSSION

The number of patients with asthma with a current doctor's diagnosis was 34 (56.6%), and the number receiving current treatment was 33 (55%). According to the ISAAC questionnaire, 25 (41.6%) patients had wheezing attacks in the last 12 months. Early-life viral respiratory infections have been linked to an elevated risk of developing recurrent wheezing and asthma (10, 11). Bronchiolitis is the most prevalent acute lower respiratory tract infection during infancy. Despite the majority of cases being mild to moderate, some children may experience severe symptoms necessitating hospitalization. Severe bronchiolitis significantly increases the risk of long-term respiratory issues; in fact, approximately 30–40% of hospitalized infants with bronchiolitis will later develop recurrent wheezing or asthma. However, the factors determining which infants will develop chronic respiratory conditions are not fully understood (12-14). The findings of our study indicate that the incidence of asthma development following severe bronchiolitis is comparable to that observed in the aforementioned studies. The factors influencing the development of asthma in infants with bronchiolitis remain ambiguous; our study aimed to assess the impact of bronchiolitis severe enough to necessitate PICU hospitalization on the subsequent development of asthma. In our study, when we evaluated 60 patients who were hospitalized for intensive care and questioned their current status with the ISAAC asthma questionnaire. The number of patients with asthma with a current physician diagnosis was 34 (56.6%) and 17 (28.3%) patients continue to be followed up with a diagnosis of asthma in our clinic. Since the diagnosis of 17 patients was based on their answers to the ISAAC questionnaire. This rate was found to be high compared to the prevalence of asthma in our country (6, 9, 15-19)

Exacerbations play a crucial role in asthma, exerting a substantial impact on both the child and their family. In our study, when we asked the patients about asthma attacks in the last 12 months, we found that the number of patients who experienced an asthma attack in the past year was 25 (41.7%), and among these patients, three (5%) had experienced more than three attacks. Looking at surveillance studies conducted in the literature, the incidence of asthma attacks has been found to be approximately between 30-40% (20, 21). A survey of 753 children with asthma in seven European countries revealed that 36% of children require an unscheduled urgent care visit in the past 12 months (22). Engelkes et al. (23) determined the rate of asthma attacks in the asthma cohort observed in the last 1 year to be 25%.

When examining asthma prevalence studies conducted in Turkey using the ISAAC questionnaire, Topal et al. (15) reported the prevalence of wheezing in the last 12 months at 12.3%. In other prevalence studies conducted in different regions of our coutry, the wheezing prevalence in the last 12 months was determined as follows: Çelik et al.(18) reported 23.2%, Cetemen et al. (17) 19.3%, Ece et al. (16) 14.7% and Kalyoncu et al. (19) 11.9%. When we look at the prevalence studies conducted in different regions in our country, we found that the prevalence of wheezing in the last 12 months in the follow-up of patients with a history of intensive care unit hospitalization due to severe bronchiolitis was 41.7% in our study, which is approximately two times more frequent than the study with the highest prevalence. Therefore, if the patient is hospitalized in PICU due to severe bronchiolitis even once, the risk of wheezing will increase in the future. In other recent studies, it has been found that the rate of asthma development during intensive care unit hospitalizations for severe bronchitis is higher than in non-admitted patients (24, 25).

Some studies have found that approximately 10% to 20% of patients requiring hospitalization for bronchiolitis require intensive care support (26-28). However, when we compared the patients who received only oxygen therapy with those who received invasive respiratory support, we did not find a significant difference between them (p=0.795). Sonnaville et al. (24) evaluated 74 patients who required mechanical ventilation only because of severe bronchiolitis and found that the rate of current asthma development during follow-up was approximately 15% and stated that having severe bronchiolitis requiring mechanical ventilation poses a risk for future asthma development.

In our study, when examining the agents contributing to the development of bronchiolitis, RSV was identified as the most prevalent (n=27, 45%), followed by rhinovirus (n=6, 10%) and bocavirus (n=5, 8.3%). Likewise, in our exploration of bronchiolitis etiologies in the literature, the predominant findings across numerous studies revealed the prevalence of RSV, followed by rhinovirus (29-32). Examining the respiratory viral panel results in individuals who experienced wheezing attacks in the last 12 months revealed that RSV was isolated in the first place with a rate of 43.5%. In our study, RSV was the most frequently isolated virus with a rate of 45%. Many studies have been conducted on the relationship between RSV and the development of asthma. Also many long-term follow-up studies have shown that RSV-induced bronchiolitis is associated with the later development of asthma (33, 34). Recent literature data have demonstrated that Bocavirus infections have a tendency to manifest as severe cases, requiring prolonged respiratory support for affected patients (35-37). Corresponding data supporting this information are available in the literature (38). However, in our study, we did not observe a statistically significant difference, and we attributed this to the

possibility that Bocavirus was isolated from only 5 patients in the sample.

More studies are needed to say with certainty that admission of children in the PICU for severe bronchiolitis increases the risk of asthma in the future. However, caregivers should be informed of the high likelihood of wheezing and obstructive pulmonary disease at any stage of life. Therefore, it is important to monitor and evaluate children for the development of asthma.

CONCLUSION

In this study, more than half of the patients with severe bronchiolitis developed asthma and some patients were not referred to the allergy clinic. In addition, although some patients had asthma symptoms, they were unaware that these symptoms were caused by asthma. We suggest that patients hospitalized in PICU with a diagnosis of severe bronchiolitis should be closely followed up in terms of asthma development and families should be informed at discharge.

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