Original Article

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Quick Response Code:

Website: www.jehp.net

DOI: 10.4103/jehp.jehp_138_17

Association of childhood croup and increased incidence of airway hyperreactivity in adulthood

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Received: 07-11-2017
Accepted: 06-02-2018

Abstract:

BACKGROUND: Some evidence suggests that childhood croup could be associated with increased incidence of adulthood bronchial reactivity, but its significance is uncertain. The aim of the present study was to evaluate the long-term outcome of early life croup.

PATIENTS AND METHODS: This case–control study was conducted in 2010–2012 in Isfahan, Iran. The case group consisted of 164 adolescents with a history of severe croup in early life and an equal number of healthy controls without any history of croup or other chronic or recurrent respiratory diseases. The two groups were compared according to pulmonary function tests and bronchial reactivity (exercise challenge test). Statistical analyses were performed using the SPSS software package, version 20 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

RESULTS: Baseline spirometric values (forced expiratory volume in 1st s (FEV1), forced volume capacity (FVC), FEV1/FVC, and forced expiratory flow at 25%–75% (FEF25–75) were similar in case and control groups. A reduction in FEV1 and FEF25–75 after exercise challenge test was seen in 9% and 12.8% of patients, respectively, whereas this was reduced in only 4.2% and 6.1% of the controls ($P = 0.034$ and $P = 0.021$, respectively).

CONCLUSION: Our findings suggest that childhood croup might be a predisposing factor for bronchial hyperreactivity in adulthood. Longitudinal studies are necessary to confirm the clinical significance of these findings.

Keywords:

Children, croup, pulmonary function test

Introduction

Croup or laryngotracheobronchitis is a common viral respiratory tract illness seen in the pediatric population. It is an acute illness and usually lasts for 1 week. It is estimated that 3% of children have been afflicted with croup before the age of 6. Croup results mainly from airway obstruction caused by viral infection.[1,2] Some studies have shown that allergens may play a role in recurrent croup. Some children with viral infections may develop sensitivity to viral allergens, which, in turn, leads to recurrent croup. Asthma is characterized by bronchial inflammation and airway hyperreactivity.[2,3] Viral infections, smoking, socioeconomic status, urbanization, and bronchiolitis are risk factors of asthma in children. Approximately one-third of children with childhood asthma have a family history of asthma and croup.[1-3] Long-term effects of croup and its association with asthma are not well described.[3,4] Recently, the role of respiratory infections as a risk factor for asthma has been conflicted.[5,6] Based on a medical theory (hygiene hypothesis), frequent respiratory infections stimulate the immune system and might reduce the

How to cite this article: Modaresi M, Pourvali A, Azizi G, Taher RR, Alinia T, Reisi M. Association of childhood croup and increased incidence of airway hyperreactivity in adulthood. J Edu Health Promot 2018;7:97.

incidence of atopy. This theory has been questioned recently.[3,7]

Several studies have confirmed the direct relationship between lower respiratory tract infections and the incidence of asthma.[5,7,8] However, the relationship between upper respiratory tract infections, such as croup and asthma, is controversial.[9,10] It is demonstrated that childhood croup may increase the incidence of asthma at the age of 10.[11] However, this relationship was not confirmed by other studies.[12] On the other hand, any association between croup in early life and pulmonary function test abnormalities in adolescence is confusing. Children who experienced croup had had a lower mean percentage predicted forced expiratory flow (FEF) at both 50% and 75% of forced vital capacity than those who had not. No clinical study has evaluated the effect of the duration and severity of croup on asthma development. Therefore, this study was designed to evaluate the relationship between croup and asthma development.

Patients and Methods

This case–control study was performed in Al Zahra Hospital, the main referral hospital affiliated to Isfahan University of Medical Sciences, Iran, in 2010–2012. Inclusion criteria included age <4 years old at admission time, Westley croup score of at least 6, access to patients, and their complete records. Westley croup score was the sum of points allotted for each of the following: inspiratory stridor, intercostal recession, air entry, cyanosis, and level of consciousness [Table 1]. The exclusion criteria consisted of previous history of bronchiolitis, active or passive smoker, and inability to perform spirometry. One hundred and sixty-four patients with a history of severe croup who had been admitted in the hospital between 1998 and 2001 were recalled and reevaluated by spirometry and exercise challenge test. Patients' information was collected from the archived files of the hospital. The control group was selected from the middle school adolescents by easy sampling method. They had no history of hospitalization due to respiratory problems and were matched with the case group. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (ID number: 4531). Before starting the study, written informed consent was obtained from the patients' parents or legal guardians. Spirometry was performed before and after 10 min of exercise in both groups.[11] Forced expiratory volume in 1st s (FEV1), forced volume capacity (FVC), FEV1/FVC, and FEF at 25%–75% (FEF25–75) were calculated. According to the American Thoracic Society criteria, a reduction of more than 12% in FEV1 was considered as bronchial hyperreactivity.

Table 1: Croup score-clinical scoring system

Inspiratory stridor
Not present - 0 points
When agitated/active - 1 point
At rest - 2 points
Intercostal recession
Mild - 1 point
Moderate - 2 points
Severe - 3 points
Air entry
Normal - 0 points
Mildly decreased - 1 point
Severely decreased - 2 points
Cyanosis
None - 0 points
With agitation/activity - 4 points
At rest - 5 points
Level of consciousness
Normal - 0 points
Altered - 5 points

Total possible score 0-17: <4=Mild croup, 4-6=Moderate croup, >6=Severe croup

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of quantitative variables. Values were expressed as frequency (number and percentage) and mean ± standard deviation. Fisher's exact test and Chi-square tests were used for 2 × 2 comparison of categorical variables, whereas *t*-tests were used to compare numerical variables. Pearson's and Spearman correlation coefficients were calculated for assessment of correlation between quantitative and qualitative variables, respectively. Statistical analyses were performed using the SPSS software package, version 20 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

During 1998–2001, 220 patients with severe croup were admitted in the emergency department of Al-Zahra Hospital in Isfahan, Iran. Forty children did not meet the inclusion criteria (28 were reevaluated as mild or moderate croup [Westley croup score <6], 7 were not available, and 5 had incomplete records). Sixteen children were excluded from the study (10 children were passive smokers and 6 were unable to perform spirometry). Finally, 164 patients were enrolled in the study. The mean age of the case group and the control group was 13.7 ± 2.2 and 13.1 ± 1.8 years, respectively. There was no difference in terms of age between the two groups ($P = 0.82$). The mean age of the patients with a history of croup at the time of diagnosis was 2.9 ± 1.3 years [Table 2]. In the case group, the prevalence of croup in boys was higher than in girls (92 vs. 72, respectively) ($P = 0.020$). Baseline spirometric values (FEV1, FEV1/FVC, and FEF25–75) were similar between the two groups. Nine percent of the cases and 4.2% of the controls had a significant reduction in FEV1 ($P = 0.034$), and 12.8% of the cases and 6.1% of

Table 2: Summary of the demographic information of survey participants

	Patient	Control
n	164	164
Age (mean±SD) year	13.7±2.2	13.1±1.8
Age of patients with history of croup (mean±SD) year	2.9±1.3	-

SD=Standard deviation

the controls had a significant reduction in FEF25–75 after exercise challenge test ($P = 0.021$).

Discussion

Asthma is a common chronic airway disorder characterized by periods of reversible airflow obstruction known as asthma attacks. Exposures for asthma include exercise, infection, allergens, occupational exposures, and airborne irritants.[13] In the United States, the prevalence of asthma has increased from 7.3% in 2001 to 8.4% in 2010.[14] The prevalence of asthma among Iranian children varied from 1.26% to 11.6%.[15] In our study, the prevalence of asthma in the control group was 10.4%; our result was similar to reports by Arshad *et al*. in 2005 and Castro-Rodriguez *et al*. in 2001.[5,16]

In this study, we determined the relationship of childhood croup (those which lead to hospitalization) with further bronchial hyperreactivity in adolescence. In our study, the incidence of croup was higher in boys. It was in agreement with other studies by Nafstad *et al*. in 2005 and Balemans *et al*. in 2006.[11,12] Other studies suggest that recurrent croup is a risk factor for asthma.[17,18] In a study by Castro-Rodriguez *et al*. in 2001, it is proposed that children who present with croup may or may not be at increased risk of subsequent recurrent lower airway obstruction, depending on the initial lower airway involvement, and preillness and postillness abnormalities in lung function associated with this condition. They concluded that if croup is associated with wheezing and lower airway involvement, the risk of asthma would be increased.[16]

In a study by Nicolai and Mutius, asthma was diagnosed in 37.3% of children with croup and a positive family history. In our study, the prevalence of asthma in the case group was 21.8%. However, in another study by Van Bever *et al*., the prevalence of asthma in children with croup was 7%.[19]

In our study, there was a significant correlation between the history of severe croup and the prevalence of asthma ($P = 0.01$). Moreover, we found a correlation between the croup in early childhood leading to hospitalization and a reduced FEV1 after exercise. However, this relationship was not reported in the study by Balemans *et al*. in 2004.[12] FEF25–75 is indicated as small airway obstruction and is not dependent on the cooperation of the patient in performing spirometry. A reduction of more than 12% of FEF25–75 in children is a sensitive criterion for the diagnosis of asthma.[20] Accordingly, in our study, this relationship (between croup in early childhood and reduced FEF 25–75) was significant. This relationship was also shown in a study by Balemans *et al*. in 2004.[12] The explanation for these findings was the older age and better cooperation of the participants when performing the spirometry.

However, Van Bever *et al*. reported no difference in the mean percentage predicted FEV1, FVC, and PEF between children with and without croup or recurrent croup. However, they reported a lower mean percentage predicted FEF50 and FEF75 in children who had suffered from croup in comparison to those had not.[19] Therefore, croup and recurrent croup are associated with bronchial asthma. The association seems essentially based on the presence of hyperreactive airways and to a lesser extent, on the presence of atopy, although the latter can be considered as an aggravating factor. The reduced FEF50 and FEF75 found in children with croup proposed small airway involvement.

It appears that inflammation related to upper and lower respiratory tract infections in the early years of life may cause a series of inflammatory processes in the air ducts (especially the small airways). It may lead to impaired immune breathing systems. Therefore, the patients will be at risk for chronic diseases (such as asthma) in the later years of life. Further studies are needed for establishing the relationship between upper respiratory tract infections and asthma. It seems that preventing the respiratory illnesses (including croup in early childhood) can reduce an individual's risk of asthma in the future. Regardless of the relationship between croup and asthma, our study showed that FEF changes with respect to FEV1 could be considered as a more precise criterion for the diagnosis of asthma in children. One of the advantages of our study is the review of older people and their better cooperation with spirometry.

Conclusion

Inflammatory diseases of the upper respiratory tract (e.g., croup) and lower respiratory tract (e.g., bronchiolitis and pneumonia) in early childhood could increase the risk of asthma in adolescence. It could be either as changes in clinical or spirometric indexes, particularly FEF25–75. Our findings suggest that childhood croup might be a predisposing factor for bronchial hyperreactivity later in life. Longitudinal studies are needed to confirm the clinical significance of these findings.

Acknowledgments

We wish to thank all the patients, family members, and staff from all the units that participated in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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