

Original Article

Evaluation of allergic sensitization and gastroesophageal reflux disease in children with recurrent croup

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Abstract *Background:* Croup, which is seen commonly in childhood, is a disorder that can be recurrent and progress to bronchial asthma. In the present study the prevalence of gastroesophageal reflux (GER) and atopy and the response to therapy were investigated in children with recurrent croup.

Methods: Between October 2003 and June 2004, 57 patients with acute stridor were admitted to the emergency room. The patients who had at least three croup episodes and patients with first croup episode were compared.

Results: Thirty-two children had recurrent croup history, GER was found in of 62.5%, and atopy in 17.2%. Atopy was not found in any children with first croup episode. The difference was significant. In addition it was found that atopic dermatitis, previous history of wheezing and established atopy increased the risk of croup recurrence. Alone or combined inhaled corticosteroids and GER therapy were administered, and 77.7% of the patients responded very well.

Conclusion: GER and atopy should be investigated in patients with recurrent spasmodic croup. Recurrent croup is a non-specific manifestation of atopy. Patients with atopy should be followed closely for developing bronchial asthma.

Key words atopy, gastroesophageal reflux, recurrent croup.

Croup is seen frequently in childhood and is characterized by barking cough, hoarseness and inspiratory stridor. It can be caused by infectious or non-infectious etiology. Infectious croup (laryngotracheobronchitis) is most commonly caused by viruses. Unless a child is infected by an immunologically different strain of the virus, it is not typical to have more than one episode per year.^{1–3} Nevertheless, recurrent croup may be related to gastroesophageal reflux (GER) or hyperreactivity of tracheobronchial mucosa and may result in the development of asthma.^{1,4–12} In addition, non-specific irritating agents, foreign bodies, C1 esterase inhibitor deficiency and psychological factors also may cause recurrence of croup episodes.⁵ Although recurrent croup is unexpectedly common in the pediatric population, etiological factors have not been identified in detail. The objective of the present study was therefore to evaluate the rate of GER and allergic sensitization in children with recurrent croup and the response to the treatment according to etiology.

Methods

Ninety-one patients who were admitted to the Emergency Department of Dr Sami Ulus Children's Hospital with acute stridor between October 2003 and June 2004 were studied. Croup was accepted as an episode of barking cough, inspiratory stridor, hoarseness with or without dyspnea, cyanosis and retractions.

Recurrent croup was defined as at least three episodes of croup.

Thirty-four of 91 patients were excluded because of wrong addresses and phone numbers or not presenting to hospital for the investigations. The remaining 57 patients were divided into two groups: group 1 consisted of 32 children with recurrent croup; and group 2, 25 patients with first croup episode. Allergy skin prick testing were performed for all of the patients in group 2, and in 29 in group 1. The following allergens were tested: cow's milk, egg white, mixed grasses, mixed tree pollens, *Dermatophagoides pteronyssinus*, *D. farineus*, cockroach, cat fur, *Artemisia vulgaris*, *Alternaria alternata*, *Aspergillus fumigatus* (Soluprick Allergen extract, ALK-Abellø, Hørsholm, Denmark and Alyostal Stallergenes, SA-Antony Cedex, France). A positive reaction was considered as a wheal reaction of ≥ 3 mm to the allergen.

In group 1, 30 of 32 patients were investigated for GER on scintigraphy, in addition 24 h double probe Ph monitoring was used in only three patients who had GER symptoms but in whom scintigraphy was normal. Four of the patients with a history of GER symptoms in group 2 were also investigated for GER on scintigraphy. On the scintiscan the presence of at least two episodes of reflux was considered as GER.¹³ Double probe pH monitoring was performed via two probes; the distal one was placed 5 cm above the lower esophageal sphincter, and the proximal one 2 cm above the upper esophageal sphincter. Daily activities and feeding times were recorded during 24 h. At the proximal probe, at least one reflux episode was accepted as positive with the presence of symptoms suggesting laryngopharyngeal reflux (LPR). Boix-Ochoa and Vandenplas reflux scoring systems were used for evaluating distal probe results.^{14,15} Complement 4 (C4)

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Table 1 Patient details vs recurrence of croup

	Group 1 (Recurrent croup)	Group 2 (First croup episode)	<i>P</i>
Gender (female/male), <i>n</i>	5/27	8/17	0.14
Age at first episode (years), average $\pm$ SD	1.7 $\pm$ 1.75	2.7 $\pm$ 2.18	0.22
Age at admission (years), average $\pm$ SD	4.35 $\pm$ 2.66	3.03 $\pm$ 2.55	0.64
Duration of symptoms (h), average $\pm$ SD	68.7 $\pm$ 50.39	83.7 $\pm$ 46.6	0.25
Hospitalization, <i>n</i>	6	0	0.02

levels were also studied for C1 inhibitor esterase deficiency in 29 children in group 1. The patients were followed up at least for 6 months. Ethics committee approval was received and informed consent forms were signed by the parents of all patients.

Age at first croup episode; number of episodes; days that it continued; symptoms accompanying the episodes; and symptoms of GER were investigated for all patients. The findings of complete physical examination were noted. All of the tests were performed after the patients were symptom free for at least 1 month.

The translated version of the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire was used to evaluate symptoms for allergic disorders. Questions on history of asthma, allergic rhinitis and atopic eczema in first degree relatives were asked.

SPSS 11.00 (SPSS, Chicago, IL, USA) was used for statistical analysis. Nominal data were analyzed on χ^2 test, while means were compared on Student's *t*-test. Statistical significance was taken as *P* < 0.05. Association between symptoms and risk factors were expressed as odds ratios (OR), with 95% confidence intervals (CI).

Results

In the present study 57 children aged between 4 months and 10 years were investigated. The age at first croup episode ranged between 2 months and 7 years (mean $\pm$ SD, 1.8 $\pm$ 1.91 years) in group 1 and 2.5 months and 8 years (mean $\pm$ SD, 2.3 $\pm$ 1.86 years) in group 2. The mean age at first croup episode and mean age at admission, average duration of stridor and the hospitalization history for both groups are listed in Table 1. In group 1, six patients needed hospitalization for previous attacks and this difference between the two groups was significant (*P* = 0.02).

When the symptoms and physical examination findings were assessed, we found that hoarseness and retractions in group 1,

fever, rhinorrhea and vomiting in group 2 were seen more often than in the other group (*P* < 0.05; Table 2).

According to the patients' previous history, the prevalence of GER symptoms such as vomiting and regurgitation were significantly different between the two groups (*P* = 0.02, *P* = 0.007, respectively; Table 3).

The history of frequent upper respiratory infections (URI; one or more time/1 month), family history of atopic disease (bronchial asthma, allergic rhinitis and atopic eczema) and personal history of atopic eczema and wheezing were found to be significantly different in group 1 (Table 4). According to results of the ISAAC questionnaire, 16 children had at least one previous wheezing episode in group 1 (*P* < 0.001). We found an increased risk for croup recurrence in children with wheezing history (OR, 2.07; 95%CI: 1.39–3.09). Based on these wheezing episodes, seven patients in group 1 and one in group 2 were diagnosed with bronchial asthma by another physician, but this difference was not significant (*P* = 0.054). History of atopic eczema was seen more frequently in group 1 than in group 2, and the difference was significant (*P* = 0.022). Five (17.2%) of the 29 patients who had allergy skin prick tests in group 1 had reaction to at least one common allergen. There were no positive results for skin prick tests in group 2. The difference was significant (*P* = 0.022). In addition, positive family history for atopic disease was found to be a risk factor for the recurrence of croup (OR, 3.30; 95%CI: 1.08–10.11).

Twenty of 32 patients in group 1 were diagnosed as having GER. In addition, GER was also diagnosed in four patients in group 2 because of the presence of GER symptoms. The two groups, however, were not compared for GER on scintigraphy or double probe 24 h pH monitoring. PH monitoring was used in only three patients who had GER symptoms but in whom scintigraphy was normal.

Table 2 Croup symptoms vs croup recurrence

Symptoms	Group 1 (Recurrent croup) <i>n</i> (%)	Group 2 (First croup episode) <i>n</i> (%)	<i>P</i>
Fever	7/32 (21.9)	17/25 (68.0)	0.001
Vomiting	5/32 (15.6)	11/25 (44.0)	0.022
Fatigue	4/32 (12.5)	6/25 (24.0)	0.25
Rhinitis	8/32 (25.0)	17/25 (68.0)	0.001
Nasal Obstruction	6/32 (18.8)	8/25 (32.0)	0.249
Hoarseness	28/32 (87.5)	16/25 (64.0)	0.036
Retractions	24/32 (75.0)	10/25 (40.0)	0.008

Table 3 GER symptoms vs croup recurrence

Symptoms of GER	Group 1 (Recurrent croup) <i>n</i> (%)	Group 2 (First croup episode) <i>n</i> (%)	<i>P</i>
Vomiting	3/32 (9.4)	1/25 (4.0)	0.02
Globus pharyngeus	0/32 (0.0)	1/25 (4.0)	0.43
Regurgitation	8/32 (25.0)	0/25 (0.0)	0.007
Halitosis	9/32 (28.1)	4/25 (16.0)	0.28
Hypersalivation	1/32 (3.1)	1/25 (4.0)	0.86
Throat Clearing	7/32 (21.9)	2/25 (8.0)	0.15
Hiccups	1/32 (3.1)	1/25 (4.0)	0.86

GER, gastroesophageal reflux.

Table 4 Risk factors for croup recurrences

Personal and family history	Group 1 (Recurrent croup) (n = 32) (%)	Group 2 (First croup episode) (n = 25) (%)	P	OR (95%CI)
Frequent URI	13/32 (40.6)	2/25 (8.0)	0.045	
Wheezing history	16/32 (50.0)	2/25 (8.0)	0.001	2.07 (1.39–3.09)
Atopic eczema	6/32 (18.8)	0/25 (0.0)	0.022	
The diagnosis of asthma previously	7/32 (21.8)	1/25 (4.0)	0.054	
Family history of atopic disease	18/32 (56.2)	7/25 (28.0)	0.033	3.30 (1.08–10.11)

CI, confidence interval; ISAAC, International Study of Asthma and Allergy in Childhood; OR, odds ratio; URI, upper respiratory infection.

Various combinations of therapy were administered to patients with GER. Although 14 of them became symptom free on follow up, in one patient symptoms decreased <50% and in five they decreased >50%. Three of the nine patients who were accepted as having bronchial asthma in group 1 were lost to follow up. Eighteen of the remaining 26 patients responded to treatment very well. In four of six patients who were treated with inhaled corticosteroids, recurrent croup episodes were not seen. In one patient symptoms decreased below 50%. In another patient, recurrences of croup attacks continued despite inhaled corticosteroid treatment. In addition, GER was also diagnosed in four patients in group 2 because of the presence of GER symptoms.

C4 levels were studied for 29 patients in group 1, in two of them C4 levels were below the cut-off but C1 esterase inhibitor levels were in the normal range at the time of the croup episodes in these two patients.

Eight patients in group 1 were examined on direct laryngoscopy. Seven of these patients had normal findings, and one had adenoid hypertrophy.

Finally, bronchial asthma was diagnosed in nine patients; five of them had allergic sensitization; four of these five responded to asthma treatment and these four patients also had a family history of asthma. In conclusion, in group 1 GER was diagnosed in 20 children (62.5%) and bronchial asthma in nine (28.1%). The remaining three patients did not come to hospital for further investigations (Table 5).

Discussion

Recurrent croup is not a diagnosis and it is important to determine the primary or contributing non-viral causes. In the present study we investigated the prevalence of GER and atopy in 57 patients with croup. We found that 20 of 32 patients with recur-

rent croup were diagnosed with GER and five of 32 had skin test positivity. Zach *et al.* proposed that children with recurrent croup had their first croup episode at an earlier age than those with only one or two episodes.^{4,5} We found no difference, however, in age at first croup episode between the two groups. Fever and upper airway infection findings accompanying croup episode were more prevalent in group 2, indicating that infectious etiology was more common in the first croup episode group. Likewise, we found that vomiting and regurgitation with regard to GER were more frequent in group 1, indicating that a diagnosis of GER should be considered in patients with spasmodic croup.

Because the retractions were more frequent in group 1 than group 2, this suggested that the patients with recurrent croup had more abrupt and serious croup attacks. Based on the physical finding that hoarseness was more prevalent in patients with GER in group 1, it might be thought that GER causes tracheobronchial mucosal damage and that this affects not only the subglottic area but also the vocal cords.

It is suggested that frequent URI is associated with reactive airway disease.¹⁶ The present study was in agreement with this: the patients with recurrent croup had more URI per year than those in group 2. This implies that underlying reactive airway disease with triggering factors may cause either signs of URI or wheezing and/or croup.

As it is known, while viral croup tends to become less frequent with increasing age, the incidence of bronchial asthma increases with age.^{6,7} It is established that the occurrence of recurrent croup might be related to a more pronounced degree of hyperreactivity, also promoting the development of asthma.^{6,7} Nicolai and Mutius reported that asthma developed in 37.3% of children with a positive family history of asthma and croup, and in 7.2% of children without these risk factors.⁶ Similar to that study, we determined the incidence of asthma to be 28.1% in group 1. Nevertheless, Van Bever *et al.* found that children with recurrent croup did not have more positive skin prick tests than those without, indicating that recurrent croup does not relate to atopy.⁷ In contrast to that report, the difference in skin prick testing was significant between the two groups in the present study ($P = 0.022$). It is therefore possible that an underlying atopy makes children more susceptible to developing recurrent croup. In order to rule this out more studies with a larger number of patients are needed.

The present study found that a past history of wheezing and a family history of atopic disease were significantly associated

Table 5 Summary of the results

Risk factors	Group 1 (Recurrent croup)	Group 2 (First croup episode)
n	32	25
GER	20	3 (detected only symptomatic patients)
Bronchial asthma	9	0
Skin test positivity	5	0

GER, gastroesophageal reflux.

with recurrent croup, supporting the results of previous studies. It is assumed that children with a combination of allergic sensitization and recurrent croup tend to develop bronchial asthma later in life.^{1,17,18} In agreement with previous studies, the present study also supported these findings.

Association with recurrent croup, GER and airway hyperreactivity has been previously reported in the literature.^{19–22} In particular in patients under 2 years of age, pathologic GER with tracheal aspiration may cause loss of the natural protective mucosal barrier of the trachea, and this could cause the trachea to be more susceptible to viral and bacterial infections.²⁰ Waki *et al.* stated that there was a 47% incidence of GER in patients with two episodes of recurrent croup, but in patients with three or more episodes, 63% were diagnosed with GER.²⁰ Similarly, in another recent study, all 17 patients with recurrent croup had endoscopic and bronchoscopic findings of GER and LPR.²³ In the present study the incidence of GER was found to be 62.5% in patients with three or more croup episodes. Also, five of 20 patients with GER were diagnosed with bronchial asthma previously by another physician, and four of these five children had no skin prick test reaction and no response to the treatment for asthma. GER was thought to be a causative factor in these patients and their croup or wheezing episodes did not recur after GER treatment. This suggests that GER may cause or worsen reactive airway disease and may cause recurrence of the croup or wheezing episodes.

Recurrent croup shares many features with asthma. These include a male predominance; onset of the disease associated with viral respiratory tract infection early in life; genetic predisposition; frequent coexistence of allergy; tendency for episodes to occur at night; and non-specific bronchial hyperreactivity.⁴ Patients with recurrent croup who have atopy should be followed closely for development of bronchial asthma. It is suggested that if patients with recurrent croup are considered to have hyperreactive airway, it would be justified to treat them with inhaled corticosteroids, similar to patients with bronchial asthma.^{9–12} In the present study four of six patients who were treated with inhaled corticosteroids were symptom free on follow up. In agreement with these findings, it was thought that these patients had developed reactive airway disease. In addition, the manifestations of LPR occur without the typical symptoms of GER, including hoarseness, sensation of fullness at the back of throat, postnasal drip, chronic cough and laryngeal spasm. Although there is no ideal diagnostic tool for LPR detection, 24 h double probe pH monitoring is presently the accepted method to document LPR.^{24–26} Because it is an invasive test, however, we could not evaluate all patients on double probe pH monitoring, therefore this was a limitation of the present study.

In conclusion, the association between atopy, reactive airway disease and GER in children with recurrent croup is still controversial. In the present study it was not possible to confirm that the patients with first croup attack would not have another episode, therefore the number of patients and duration of follow up may not be sufficient. It is therefore necessary to conduct further studies to clarify this association with more detailed tests.

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