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Clinical Analysis of Children Diagnosed with Recurrent Croup

Tekrarlayan Krup Tanısı Alan Çocukların Klinik Analizi

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ABSTRACT Objective: Croup is a common disease in childhood, characterized by barking cough, hoarseness and inspiratory stridor. When symptoms show recurrent and/or persistent characteristics, attention must be paid in terms of other underlying diseases. Our aim is to retrospectively review the long term results of our follow-up patients with recurrent croup and to discuss the etiology and final diagnosis and treatment of this clinic description in the light of the literature. **Material and Methods:** This study included patients who had 3 or more croup attacks per year. The patients' frequency of attacks, triggers, persistancy of the complaints, atopic dermatitis, rhinitis symptoms, family history of atopy were derived from their medical records. Laboratory results [total eosinophil count, immunoglobulin E levels, skin prick test, gastroesophageal reflux (GER) tests] and treatments were evaluated. **Results:** 100 patients aged between 7 months and 14 years with recurrent croup diagnosis were evaluated. Of them, 77 were males, the median frequency of attacks was 4 (3-10) times a year. In 17% of the patients, upper respiratory infection, in 24% spasmodic character, and in 59% both were determined as triggers. In 12% atopic dermatitis, in 42% rhinitis, in 36% atopy, in 33% GER disease, in 26% persistant croup, in 55% laryngotracheobronchitis (LTB) was detected. When laryngoscopy was performed on persistant croup patients, laryngomalacia was detected in 9% and GER findings were found in 15%. Of the patients, 48 were given inhaled steroid treatment, 7 were given reflux treatment and 26 received combination of inhaled steroid and reflux treatments, 8 were treated only during attacks. **Conclusion:** Recurrent croup is generally a benign clinical picture. Atopy, LTB and GER may be associated with recurrent croup. The patients who are detected to be atopic, and/or respond well to inhaled steroid must be closely monitored in terms of reactive airway disease. Persistent cases necessitate a multidisiplinary approach.

Keywords: Allergy and immunology; cough; gastroesophageal reflux; pediatrics; croup; endoscopy

ÖZET Amaç: Krup, çocukluk çağında sık görülen havlar tarzda öksürük, ses kısıklığı, stridor ile karakterize bir hastalıktır. Semptomlar tekrarlayıcı ve/veya persistan özellik gösterdiğinde altta yatan farklı hastalıklar açısından dikkatli olunmalıdır. Amacımız, tekrarlayan krup ile takip edilen hastalarımızın uzun dönem sonuçlarını retrospektif olarak gözden geçirmek; bu klinik tanımlamanın etiyolojisini, nihai tanılarını ve tedavisini literatür ışığında tartışmaktır. **Gereç ve Yöntemler:** Çalışmaya, yılda 3 veya daha fazla krup atağı geçiren hastalar alındı. Hastaların tıbbi kayıtlarından atak sıklığı, tetikleyiciler, yakınmaların persistan olup olmadığı, atopik dermatit, rinit bulguları, ailede atopi öyküsü kaydedildi. Laboratuvar sonuçları [total eozinofil sayısı, immünglobulin E seviyeleri, deri prick test, gastroözofageal reflü (GÖR) tetkikleri] ve tedavileri değerlendirildi. **Bulgular:** Yaşları 7 ay-14 yaş arasında olan, tekrarlayan krup tanılı 100 hasta değerlendirildi. Hastaların 77'si erkek, atak sıklığı yılda 4 (3-10) idi. Krup atakları, hastaların %17'sinde üst solunum yolu enfeksiyonu ile %24'ünde spazmodik karakterde, %59'unda her ikisi de tetikleyici olarak saptandı. Hastaların %12'sinde atopik dermatit, %42'sinde rinit, %36'sında atopi, %33'ünde GÖR hastalığı, %26'sında persistan krup, %55'inde laringotrakeobronşit (LTB) tespit edildi. Persistan kruplu hastalara uygulanan laringoskopide %9 laringomalazi, %15 GÖR bulguları görüldü. Hastaların 48'ine inhale steroid tedavisi, 7'sine reflü tedavisi, 26'sına reflü tedavi ile inhale steroid tedavisi, 8'ine sadece atak sırasında tedavi verilmişti. **Sonuç:** Tekrarlayan krup, genelde iyi seyirli bir klinik tablodur. Atopi, LTB ve GÖR tekrarlayan krup olguları ile birliktelik gösterebilir. Sık tekrarlayan ya da yakınmaları persiste olan olgularda multidisipliner yaklaşım gereklidir. Atopisi saptanan, inhale steroid tedavisine yanıtı iyi olan hastalar, reaktif havayolu hastalığı açısından yakın takip edilmelidir.

Anahtar Kelimeler: Alerji ve immünoloji; öksürük; gastroözofageal reflü; pediatri; krup; endoskopi

Croup is a childhood disease characterized by barking cough, hoarseness and inspiratory stridor. That is a benign disease generally, but sometimes progressive that requires hospitalization and even intubation.[1-3] While acute croup mostly occurs due to an infectious etiology; recurrent croup (RC) may be associated with different problems. Rankin et al. emphasized that 6.4% of children suffer from RC.[2] Although RC is relatively common; its clinical features and the causes of RC are not defined clearly.[4]

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Croup has been considered as a self-limiting disease. However, recurrent symptoms should alert physicians to assess the etiological relationship between RC and some serious upper respiratory diseases. These diseases include reactive airway disease, asthma, allergy, gastroesophageal reflux disease (GERD), subglottic stenosis and other diseases with airway stenosis.[2,5-8] Lin et al. claimed that children with RC should be closely monitored for asthma development.[5] Also there are some studies showing that the children with sensitivity to some allergens have the risk of RC.[6]

Since, the cause of RC is uncertain in many children, there is no definitive treatment and the prognosis may not be fully predicted. Treatment should be managed according to the potential etiology of RC.[4]

The aim of this study is to retrospectively review the clinical results of children who are treated in our clinic with the diagnosis of RC and to discuss the etiology and management of this disease in the light of the literature.

MATERIAL AND METHODS

This study included patients presenting with RC at the Department of Pediatric Allergy and Immunology Adana Research and Training Hospital, Faculty of Medicine, Başkent University, from February 2009 to December 2013. Prior to the study, written approval was obtained from the Başkent University Institutional Review Board and Local Ethics Committee in 2009 (Project no: KA16/197). The written consents of the patients' parents were obtained for the study.

The inclusion criteria were three or more episodes per year of barky cough, hoarseness, and inspiratuary stridor in previously healthy children. The exclusion criteria were premature labour, history of intubation, known presence of cardiac and immunodeficiency disease, neuromotor developmental delay and growth retardation.

DEFINITIONS

Recurrent croup: Three or more episodes of barky cough, hoarseness, and inspiratuary stridor per year.[2]

Laryngotracheobronchitis (LTB): Croup episodes associated with bronchitis in children with symptoms of cough, tachypnea and rhonchi.[9]

Persistent croup: Presence of croup symptoms lasting for more than three weeks.[9]

Atopy: Presence of positive skin prick test.

Family history of atopy: The presence of doctor-diagnosed asthma, atopic dermatitis (AD), and/or allergic rhinitis in at least one of the parents and/or siblings.

Gastroeosephageal reflux disease (GERD): Clinical manifestation of the excessive reflux of gastric contents into the esophagus; causing heartburn, regurgitation, dysphagia, pulmonary and laryngopharyngeal symptoms that is confirmed with GER scintigraphy, and/or barium esophagography and resolves with antireflux treatment.[10]

Spasmodic croup: Type of afebrile croup with a sudden onset.[9]

Rhinitis: The presence of nasal congestion, runny nose and/or sneezing, nasal itching lasting more than three weeks.

Atopic dermatitis: AD is described as clinical manifestation of eczema when the patients have a positive skin prick test.

DATA COLLECTION

These following informations were obtained from the patients'medical records:

- Frequency of attacks, number of applications to the hospital due to RC attacks, presence of known causes that triggered episodes, and family history for atopy were evaluated from medical records. Accompanying findings such as laryngotracheobronchitis (LTB), GERD, rhinitis, and AD were investigated.

- Total immunoglobulin E (IgE) and specific IgE levels are quantitatively measured in the blood by ELISA (Enzyme-linked ImmunoSorbent Assay). ImmunoCAP® kit in sera was used for the detection of food and phadiotop allergens. A positive screening test prompted the analysis of IgE levels specific to cow's milk, hen's eggs, soy, wheat, fish, peanuts, and inhalant panel levels >0.35 kU/l were considered positive.

■ All of the skin prick tests were applied epidermally. Allergen solutions of Allergopharma (Reinbek, Germany) at standard activity and concentration (positive control, negative control, D. farinae, D. pteronyssinus, pine, olive, tree mix1, tree mix II, grass mix, mediterranean herbs, grass mix+cereals, alternaria, aspergillus, cladosporium, cat, dog, sheepswool, budgerigar, latex, cockroach) were used in skin prick tests. Atopy was accepted as positive in the presence of at least 3 mm indurations compared with the negative control.

■ The eosinophil percentage count in the whole blood was performed by closed system tube method (Abbott Cell Dyne 3700), and if the number of eosinophils in the blood is >450/μL or its rate is >4%, it is accepted as eosinophilia.

■ If it was present in medical records, radiologic examination results of esophagus with barium sulphate (Radiobaritsüspansiyon, Recordati®, Turkey) were also noted for GER diagnosis.

■ Otolaryngological examination was done by the same otolaryngologist using fiberoptic endoscopy and/or direct rigid laryngoscopy. None of the patients had undergone bronchoscopy.

We divided the patients into age groups such as under 2 years old, 2-6 years old, and >6 years old. We analysed the patients' features (atopy, family history or GERD) according to the age groups. We also analyzed the patients with LTB according the age groups, gender, history of bronchitis, and the presence of atopy.

We compared all the patients with atopy and non-atopy according to the gender, the presence of LTB, persistent croup (PC), the level of IgE, and family history for atopy.

The treatment which started for each patient and response to treatment were evaluated from medical records. Nebulised adrenalin, inhaled steroid (flixotide nebules 0.5 mg/2 mL; Glaxo Smith Kline Ilaç, Philadelphia Pennsylvania, USA) and/or systemic corticosteroid (prednol-L ampul; Mustafa Nevzat İlaç, İstanbul, Turkey) were given to all of the patients during the attacks.[9] If GER findings were present, than antireflux treatment was added [lansoprazol (15 mg/day, lansoprol 15 mg/capsul; Nobel İlaç, İstanbul; Turkey), domperidone (1 mg/kg/day, motilium süsp; Johnson İlaç, İstanbul, Turkey)].[10] Inhaled steroid treatment was given to some selected patients (frequent and/or severe attacks, family history of atopic diseases, atopy positivity), and the patients were followed-up for asthma development.

STATISTICAL ANALYSIS

Normality of distribution of variables was tested with Kolmogorov-Smirnov test. As the variables were not normally distributed, results were presented as median (25% and 75% interquertile range) or percentages (%). We used Mann-Whittey U test to compare the differences between groups in countable variables. Qualitative variables were assessed with chi-squared test. A p value <0.05 (2-tailed) was accepted as significant. We analysed the data using SPSS for Windows version 17.0.

RESULTS

One hundred patients with RC were evaluated in our clinic. Of them, 77% were boys. Median patient age at referral to clinic was 4 years-old (range;7 month-14 years) but the median age at onset of symptoms was 12 months (range; 2,4-120 months). Median frequency of attacks was four times/year (range; 3-10). Of the patients 26% had PC, 55% had LTB. Patients' symptoms were triggered by upper respiratory tract infection in 17%; were spasmodic in 24%; both triggered by upper respiratory infection and spasmodic in 59%. There was AD in 12 (12%), family history of atopic disease in 45 (45%), rhinitis in 42 (42%) of patients. Atopy was detected in 36 (36%) by skin prick test. When 74 patients were evaluated for GERD, the percentage was found to be 33%.

We also analysed the patients according the age groups (such as under 2 years old, 2-6 years old, and >6 years old). Eighteen patients were under 2 years-old, 5 patients were under 12 months-old and we did not find any significant feature increasing attack frequency in each group (p=0.832). Characteristic findings of the patients with RC were summarized in Table 1.

The patients with PC were evaluated by an otolaryngologist with flexible and/or direct laryngeal endoscopy. We found that four of them had

TABLE 1: Characteristic findings of the patients with reccurent croup.

Male gender (n, %)	77 (77%)
Age at referral, years-old (median, minimum-maximum)	4 (0.6-14)
Age at onset of symptoms, months (median, minimum-maximum)	12 (2.4-120)
Frequency of attacks/year (median, minimum-maximum)	4 (3-10)
Family history of atopy (n, %)	45 (45%)
Croup with laryngotraceobronchitis (n, %)	55 (55%)
Persistent croup (n, %)	26 (26%)
Presence of GERD* (n, %)	33 (33%)
Atopy of patients (n, %)	36 (36%)
The patients with atopic dermatitis	12 (12%)
The patients with rhinitis	42 (42%)
Eosinophil count/mm^3 (median, minimum-maximum)	230 (25-1000)
Level of IgE (IU/L) (median, minimum-maximum)	108 (5-1086)

*GERD: Gastroesophageal reflux disease; Ig: Immunoglobulin.

adenotonsillar hypertrophy, nine of them had mild/moderate laryngomalacia (9/100, 9%) and one of them had vocal cord nodule. In 15 patients with the signs of erythema/hyperemia, vocal cord edema and diffuse laryngeal edema, GERD was also detected with flexible endoscopy. Seventy four patients were evaluated by GER scintigraphy, and/or barium esophagography, and there was reflux in 28 (30%) of them.

Fifteen patients showed GER symptoms in flexible endoscopy, 10 of these patients had positive GER scintigraphy while 5 of them had negative GER scintigraphy. Although the GER scintigraphy of these 5 patients were negative, they were started to be treated for GER as they had GER complaints and there were endoscopic findings of GER.

In children with reccurent croup, 55% (n=55) were diagnosed with LTB. These patients were analysed and it is found that 83.6% of LTB patients (46/55) were males (p=0.081) and most of them (54/55) had history of bronchitis (p=0.000). Also, 25 of them (45.5%) had atopy and this was found to be significant (p=0.037).

In Table 2, we compared the patients with atopy and non-atopy according to some features and we found that RC patients with atopy were mostly males, had high levels of IgE, and had high predisposition for LTB. These were found as statistically significant. On the other hand, atopy was detected in 5 (5/26) patients of PC.

The evaluation of the treatment protocols that applied to the patients is as follows; all the patients were given nebulised adrenalin and systemic corticosteroid during the attacks. Inhaled steroid treatment was regularly given to 48 (48%) of the patients, only antireflux therapy was given to 7 (7%), inhaled steroid plus antireflux therapy were given to 26 (26%). Eight (8%) patients were treated only during attacks as their attacks were less frequent and mild also not accompanied by any other risk factors. The patients which started to be treated with inhaled steroid are closely monitored for asthma development.

TABLE 2: Special features of recurrent croup patients with and without atopy (p<0.05 is significant).

	Atopy+ (n=36)	Atopy- (n=64)	p
Male (n, %)	32 (88.9%)	45 (70.3%)	0.027
Persistent croup (n, %)	5 (13.8%)	21 (32.8%)	0.039
Laryngotracheobronchitis (n, %)			
+	25 (69.4%)	30 (46.8%)	0.037
-	11	34	
Level of IgE (IU/L) (mean, SD)	285.5±297	125.7±155	0.001
Atopic family history (n,%)			
+	21 (58.3%)	24 (37.5%)	0.041
-	15	39	

Ig: Immunglobulin; SD: Standard deviation.

Twenty of our patients (20/100) did not come back for the evaluations. For that reason, 80 patients could be evaluated at follow-ups and half of these patients' (41/80) symptoms were resolved in three to six months after the treatment. Regarding all patients, median follow-up time was found as 12 months (range; 0-72 months). We significantly detected that the RC patients with LTB came to control regularly and had long follow-up time (p=0.025).

DISCUSSION

RC is a common illness among outpatients, but few cases require hospitalization.[11] The patients mostly apply during an attack and receive their treatment in ambulatory and emergency policlinic. RC symptoms are often preceded by symptoms like those of an upper respiratory tract infection. However, it manifests with signs such as afebrile sudden onset of barking cough, almost always at night or during sleep, substantialy correlated with inspiratory stridor and respiratory distress.[12]

Although upper respiratory infections commonly triggered RC attacks, some patients experienced relapsing attacks emerging with allergy, psychological causes and/or GERD.[2,5] Hiebert et al. showed that in patients with RC, incidence of a history of GERD is estimated as 20% and incidence of asthma/allergies is observed as 35%.[7]

In many studies, the relationship between RC and reactive airway diseases and/or asthma has been well demonstrated.[5,13] It is suggested that if patients with RC have hyperreactive airway, it would be justified to treat them with inhaled corticosteroids, similar to patients with asthma.[14] In our study, the majority of our patients had responded well to treatment with inhaled corticosteroid. Just like in asthma; male sex, family presence of atopic disease, and atopy were observed more frequently in patients with RC in our study. These findings suggest that there could be a relationship between RC and reactive airway disease and the patients with RC should be followed in terms of developing asthma. We gave inhaled steroid treatment to 48 selected patients (frequent and/or severe attack, family history of atopic diseases, frequently presence of spasmodic croup, atopy positivity) and they were observed for asthma development.

In our study, 55% of the children with RC were diagnosed were LTB and 45.5% of these patients had atopy. This was found as statistically significant. LTB is a concomitant infectious disease which can affect the lower airways in patient with croup. LTB typically affects children who have underlying diseases such as asthma or atopy.[15,16] Inhaled steroid treatment was given to some selected LTB patients (family history of atopic diseases, atopy positivity) and we observed these patients had responded well to treatment with inhaled corticosteroid and we have followed them for asthma development.

GERD seen in childhood is a complex condition that should be evaluated in many ways. Although the role of laryngopharyngeal reflux disease is responsible for several pediatric diseases, it has not been sufficiently studied in RC. Laryngopharyngeal reflux coexists with a number of different symptoms depending on age. Infants typically present with vomiting, difficulty in swallowing, failure to thrive, apnea and RC.[5,10] School-age children tend to suffer from chronic cough, dyspnea, dysphonia, persistent sore throat, halitosis, and globus sensation.[17] In our study, we diagnosed 33 (33%) patients as GERD. However, Belafsky et al. showed in their studies that they were 95% sure that an individual had laryngopharyngeal reflux, if the patient had high "reflux finding score" according to laryngeal examination of the patient.[18] In this regard, we suggest that antireflux therapy may be effective in reducing the frequency of RC attacks if the patient has symptoms of reflux and has highly suspicious findings in the laryngeal examination. However, this idea should be supported by prospective studies.

Direct laryngotracheobronchoscopy is the most important approach used to detect anatomical airway abnormalities such as subglottic cysts, subglottic stenosis and tracheolarengomalacia that predispose to RC.[2] In addition, with the help of direct laryngotracheobronchoscopy, we show many problems ranging from vascular problems and mediastinal mass to findings suggesting GERD and extrinsic tracheal compression.[7,8] However, Hiebert et al. showed in

their systemic meta-analysis that, significant bronchoscopy findings were present only in 8.7% of 457 patients with RC.[7] In our study, laryngomalacia was detected as pathology with a percentage of 9% also similar to literature. Hiebert et al. concluded that the results of the laryngeal examination should guide physicians in selecting which RC patients are most at risk for significant findings.[7] In our study, laryngoscopy was performed by an otolaryngologist on the patients with PC for investigation of anatomical airway abnormalities. In the patients of PC, we detected atopy just in 5 (13.8%) patients. As anatomic defects generally associate with PC patients, we don't expect to detect atopy in this group. Our findings were also in favor of this thought. Pediatricians should be able to request laryngoscopy from an otolaryngologist in cooperation for etiological investigation of RC patient.

Our study has some limitations. Only the recorded data could be gathered because of retrospective nature of the study. Hence, it can be stated that responses to various treatments could not be objectively evaluated. Most of the patients with seasonal symptoms were not present for follow up after the improvement of their complaints, leaving doubts for adherence to treatment. The follow-up time of patients was irregular and we could not reach the data of patients treated only in the emergency room. We did not have the opportunity for 24-h pH-monitoring study, which is the gold standard for diagnosis of GER. We were not able to evaluate nonacid reflux episodes in patients received antireflux treatment.

CONCLUSION

As a conclusion, despite some limitations mentioned above, this study has been a comprehensive clinical analysis for RC. RC is a self-limited disease and it is highly responsive to treatment with inhaled corticosteroids. Atopy, LTB and GER often accompanies with RC. It is important to closely monitor the patients with RC in terms of asthma development, who are atopic, and/or respond to inhaled steroid. Persistent cases necessitate a multidisiplinary approach.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Belgin Usta Güç;* ***Design:*** *Belgin Usta Güç, Suna Asilsoy, Fulya Özer;* ***Control/Supervision:*** *Suna Asilsoy;* ***Data Collection and/or Processing:*** *Belgin Usta Güç, Fulya Özer;* ***Analysis and/or Interpretation:*** *Fulya Özer;* ***Literature Review:*** *Belgin Usta Güç, Suna Asilsoy;* ***Writing the Article:*** *Belgin Usta Güç;* ***Critical Review:*** *Fulya Özer, Suna Asilsoy;* ***References and Fundings:*** *Suna Asilsoy;* ***Materials:*** *Belgin Usta Güç, Fulya Özer.*

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