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Original

Are cytokines and cortisol important predictors for the severity of pediatric croup: A case control study

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SUMMARY: Üzüm Ö, Çağlar A, Küme T, Sayıner A, Er A, Akgül F, Ulusoy E, Yılmaz D, Duman M. Are cytokines and cortisol important predictors for the severity of pediatric croup: A case control study. Turk J Pediatr 2017; 59: 281-287.

The aim of this study is to investigate the role of cytokines (TNF-α, IL-6, IL-10, and PAF), cortisol, and IgE in the pathogenesis of croup and the factors determining its clinical severity. Patients diagnosed with croup at the Pediatric Emergency Department were included and thirty healthy children were included as a control group. Patients' demographic characteristics, clinical findings, recurrent croup history, and patient-family atopy history were recorded. Patients were grouped according to the Westley croup scoring system. Blood samples were taken from the control group and the patients for cytokines and cortisol. Respiratory pathogens were studied with PCR. Sixty-nine pediatric cases who were diagnosed as croup were included in the study (34 mild, 31 moderate, 4 severe). Group comparisons were made in terms of mild and moderate/severe groups. In the moderate/severe group, IL-10 and cortisol levels were higher than the mild group. The moderate/severe cortisol levels between 12:00 am-6:00 pm were found to be higher. PAF and TNF-alpha levels were detected to be higher in patients with a history of atopy. Viral agents were isolated in 45 patients; rhinovirus PCR tests were positive in 22 patients.

In this study, rhinovirus was the most common etiology for croup. Increased levels of IL-10 and cortisol in the moderate/severe group indicate that different systemic and local mechanisms may play a role in the pathogenesis of croup.

Key words: children, croup, cytokines, cortisol.

Croup is a respiratory disease characterized by inspiratory stridor and respiratory distress. It affects young children between 6 months and 36 months of age more commonly than other ages[1,2]. Croup is caused by a viral infection of the respiratory tract, and parainfluenza virus is the most common pathogen. Other viral factors include respiratory syncytial virus, adenovirus, human coronavirus, influenza virus, rhinovirus, enterovirus, herpes simplex virus, and metapneumovirus. Bacterial factors are extremely rare, *Mycoplasma pneumoniae* is the most commonly observed bacterial pathogen[2].

The pathophysiology and disease severity predictors of croup has not been determined definitely. Viral agents cause inflammation in the nasal and pharyngeal mucosal epithelium. Erythema and swelling of the lateral walls of the trachea are observed upon laryngoscopic examination. Histiocytes, plasma cells, and neutrophil infiltration were observed in the larynx and trachea lamina propria, as well as the submucosa and adventitia layers in postmortem examinations of pediatric patients diagnosed with laryngotracheitis[3,4]. In the inflammation process, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and platelet activating factor (PAF) show pro-inflammatory activity; meanwhile, interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13), transforming growth factor-beta

(TGF-*β*), and cortisol show anti-inflammatory activity[5]. Eosinophil granule proteins cause damage in the epithelial cells, contraction in the airway smooth muscle. The mediators released by the effect of immunoglobulin E (IgE) cause bronchoconstriction[6,7]. The relationship between the beginning times of symptoms with cortisol circadian rhythm is not clearly known yet.

The number of studies conducted on the pathogenesis of croup and the factors determining the clinical severity is quite limited. The aim of this study is to investigate the role of cytokines (TNF-α, IL-6, IL-10, and PAF), cortisol, and IgE in the pathogenesis of croup and the factors determining its clinical severity.

Material and Methods

Study population

Pediatric patients who were diagnosed with croup and admitted to the Pediatric Emergency Department between October 2013 and October 2014 were included in the study. The demographic data (age, gender) of all patients were recorded at the time of admission. Admission times were evaluated as time units of six hours. Patients with two or more recurrent histories of croup were accepted as the recurrent group. History of an atopic disease (atopic dermatitis, asthma, allergic rhinitis, food allergy) was also recorded. Patients were categorized according to the Westley Croup Score as mild (0–2), moderate (3–8), or severe (>8)[8].

Patients with congenital or acquired structural airway disorders (subglottic stenosis, laryngeal web, laryngomalacia, respiratory hemangioma) and history of intubation were excluded from the study.

The control group consisted of 30 children who visited Pediatric clinics for routine well care without any acute illness and without a history of atopy who were similar with patients in the study group by age and gender.

All procedures performed in this study which involves human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Permission for this study was granted by the Ethical Committee of Clinical Investigations of the Medical Faculty of Dokuz Eylül University with the decision number 2013/18-09 and date 16.05.2013. Informed consent was received from all patients and control group. Financial assistance was received from Scientific Research Projects Unit of the Medical Faculty of Dokuz Eylül University with the decision number 2013140.

Biochemical measurements

All venous samples were taken before treatment and were stored at -80 °C. Samples were studied all together at the end of the study. Serum TNF-α, IL-10, IL-6 (catalogue numbers: EK0525, EK0416, and EK0410; Boster Biological Technology Co., Ltd., Wuhan, China), and PAF (catalogue number: 201-12-1157; Sunred Biological Technology Co, Ltd., Shanghai, China) levels were measured according to the commercial audience manufacturer recommendations based on the ELISA (enzyme-linked immunosorbent assay) method. Serum cortisol and total IgE levels were measured using the immunochemiluminescence method by using original kits in two auto analyzers (the Immulite 2000 XPi, Siemens Healthcare

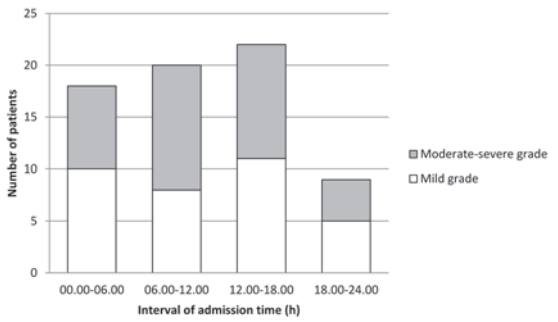

Fig. 1. Distribution of Patients According to Admission Time.

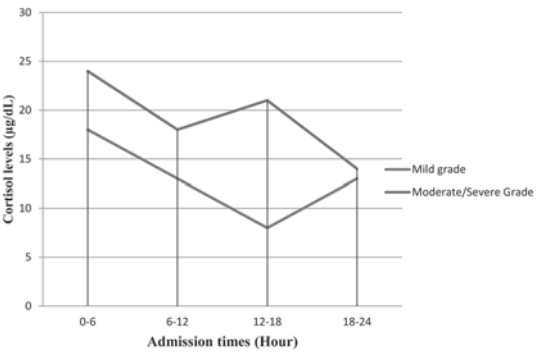

Fig. 2. Relationship Between Admission Time and Cortisol Levels of Patient Groups.

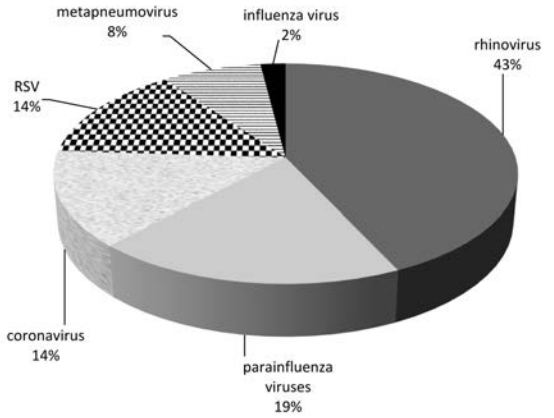

Fig. 3. Distribution of respiratory tract viruses in patients. RSV: Respiratory syncytial virus

Diagnostics, GmbH, Eschborn, Germany; and the UnicelDxI 800, Beckman Coulter Inc., CA, USA). The samples taken by the nasopharyngeal aspirate method were studied with the FilmArray multiplex nested PCR method in terms of twenty-one respiratory pathogens, which included adenovirus, bocavirus, coronavirus (229E, HKU1, OC43, NL63), human metapneumovirus, human rhinovirus/enterovirus, influenzas A (subtype H1, 2009 H1, 2009 H3) and B, parainfluenza 1-2-3-4, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Packages for the Social Sciences) Software 16.0 (Chicago, IL, USA). If numerical data fit the normal distribution, mean ± standard deviation were calculated, and when it did not fit a normal distribution median and interquartile range 25-50 percentile (interqualityrang - IQR) were calculated. The Mann–Whitney U test was used in order to compare the variables that did not fit to the normal distribution. The definitive chi-square test was used for the numerical variables, while Student's *t*-test was used for the numeric variables fitting the normal distribution. Statistical significance was accepted as $p < 0.05$ for all tests.

Results

Seventy-two patients diagnosed with croup were originally included in the study. Three patients were excluded from the study, as they did not accept respiratory pathogen samples or the blood drawing process. Thirty-four croup patients (49%) were grouped as mild, 31 (45%) were moderate, and 4 (6%) were severe according to the Westley croup scoring system. Group comparisons were made in terms of mild and moderate-severe groups. Thirty children were included in the study as the control group.

The age and gender characteristics of children

Table I. Demographic and Clinical Features of the Patients.

Parameters	Total n=69 (100%)	Mild grade n=34 (49%)	Moderate-Severe grade n=35 (51%)	p[a]
Sex				
Male	52 (75.4)	24 (70.6)	28 (80)	0.373
Female	17 (24.6)	10 (24.4)	7 (20)	
Age (months)*	32.0 (16.5–52.0)	35.5 (15.5–72.0)	26 (11.0–49.0)	0.107
Age groups				
≤6 months	9.0 (13.0)	1.0 (2.9)	8.0 (22.9)	0.049
6–36 months	29.0 (42.0)	16.0 (47.1)	13.0 (37.1)	
>36 months	31.0 (45.0)	17.0 (50.0)	14.0 (40.0)	
Fever	17.0 (24.6)	9.0 (26.5)	8.0 (22.8)	0.472
Atopy				
Atopic dermatitis	2.0 (2.8)	1.0 (2.9)	1.0 (2.8)	0.545
Allergic rhinitis	2.0 (2.8)	2.0 (5.9)	-	
Asthma	4.0 (5.7)	2.0 (5.9)	2.0 (5.8)	
Recurrent croup	33 (47.8)	18 (52.9)	15 (42.8)	0.405

*Values shown as median with interquartile range.
[a]The Mann–Whitney U test and chi-square tests were used to compare the two groups.

Table II. Comparison of Cytokines/Hormone Levels of Groups.

Parameters	Control n=30	All patients n=69	Mild Grade n=34	Moderate-severe Grade n=35	p value
Leukocyte (x 10^3/ml)	9400 (7000–11925)	11900 (9800–14700)	11300 (10400–14125)	12800 (9100–16300)	[1]0.005 [2]0.440
Eosinophil (x 10^3/ml)	218 (176–474)	244 (182–403)	237 (202–388)	312 (172–428)	[1]0,785 [2]0.265
IL-6 (pg/ml)	10.8 (9.6 –13.2)	10.7 (8.8 –12.8)	11.1 (9.4 –13.3)	10.1 (8.4 –12.6)	[1]0.208 [2]0.253
IL-10 (pg/ml)	18.6 (10.0 –39.2)	22.5 (14.4 –50.1)	21.3 (9,9-29,9)	23.0 (17,0-22,7)	[1]0.204 [2]0.019
PAF (ng/ml)	43.2 (27.2–70.5)	35.1 (22.9–63.8)	31.3 (18.1–53.6)	37.8 (26.0–107.6)	[1]0.592 [2]0.195
IgE (mg/dl)	53.1 (10.4–192.2)	30.3 (11.2–93.0)	33.2 (11.8–150.0)	27.2 (8.0–39.9)	[1]0.178 [2]0.086
TNF- α (pg/ml)	15.7 (11.7–24.3)	17.6 (12.1–23.7)	18.5 (12.0–24.2)	14.8 (12.1–22.7)	[1]0.555 [2]0.920
Cortisol (μg/dl)	6.2 (4.7–8.6)	16.4 (9.9–22.7)	11.0 (4.2–19.1)	20.0 (15.0–26.9)	[1]<0.01 [2]0.012

Values are median (interquartile range).
[1]The Mann–Whitney U test was used to compare the patient and control groups.
[2]The Mann–Whitney U test was used to compare the mild and moderate-severe groups.
Interleukin-6: IL-6
Interleukin-10: IL-10
Platelet activating factor: PAF
Immunoglobulin E: IgE
Tumor necrosis factor-alpha: TNF-α

in the patient and control groups were similar (p>0.05). The demographic and clinical characteristics of the patients in the mild and moderate-severe groups are summarized in Table I. Fifty-five percent of the patients were younger than 36 months; in particular, patients under six months of age had a more severe clinical score. Five of the eight patients with history of atopy had a history of recurrent croup, but there was no statistically significant difference observed between recurrent croup and no recurrent croup with history of atopy (p>0.05).

Admissions were most frequently (48%) made in autumn. No significant difference was observed between the groups in terms of seasonal admissions (p>0.05). Distribution of the patients according to their admission time is shown in Figure 1. No statistically significant difference was observed among the clinical severities of patients according to the time gap of admission (p>0.05).

Comparison of the cytokine and cortisol levels of the patient and control groups is summarized in Table II. The number of leukocytes and level of cortisol were higher in the patient group compared to the control group. IL-10 and cortisol levels were found to be significantly higher in the moderate/severe group compared to the mild group. There was no statistically significant difference between the male and female patients' cytokines and cortisol levels. Although the highest cortisol levels in both groups were measured between 00.00 and 06.00, the cortisol levels of the moderate-severe group were observed to be between 12.00 and 18.00 at a statistically significant rate (p=0.001) (Fig. 2).

The cytokine/hormone levels of the patients who had or did not have atopy are summarized in Table III. PAF and TFN-α value were observed to be significantly high in the patients with history of atopy. Recurrence frequency was not significantly different between patients with or without history of atopy (p>0.05).

Table III. Comparison of Cytokines/Hormone Levels of Patients According to Atopy.

	With atopy n=8	Without atopy n=61	p value
Leukocyte (x 10^3/ml)	13700 (10950–17875)	11800 (9150–14490)	0.209
Eosinophil (× 10^3/ml)	318 (223–405)	240 (171–408)	0.476
IL-6 (pg/ml)	11.1 (8.6–13.8)	10.7 (8.8–12.7)	0.910
IL-10 (pg/ml)	16.3 (9.6–28.3)	23.0 (15.3–50.1)	0.202
PAF (ng/ml)	61.1 (49.1–109.2)	31.4 (21.2–61.0)	0.032
Cortisol (μg/dl)	23.0 (13.6–30.5)	15.6 (8.8–21.4)	0.121
Ig E (mg/dl)	27.2 (16.2–131.0)	31.5 (8.6–93.0)	0.814
TNF-alpha (pg/ml)	23.8 (19.6–55.7)	16.4 (12.1–23.2)	0.035

Values are median (interquartile range).
The Mann–Whitney U test was used to compare the two groups.
Interleukin-6: IL-6
Interleukin-10: IL-10
Platelet activating factor: PAF
Immunoglobulin E: IgE
Tumor necrosis factor-alpha: TNF-α

Viral agents were isolated in 45 (65%) of the patients. The most common viral agents were rhinoviruses, parainfluenza though the second most frequently detected only 19% of viral agent positive patients (Fig. 3). The combination of rhinovirus+coronavirus was present in four patients, while RSV+coronavirus was present in one patient and parainfluenza virus type 1+rhinovirus was present in one patient. No significant relationship was observed between respiratory pathogens and clinical severity ($p>0.05$). No statistically significant difference was observed between the cytokine/hormone levels of the patients whose respiratory pathogens were identified not identified.

Discussion

Croup is an important reason for admission to the pediatric emergency department. The hospitalization rate is about 8%, especially in children under the age of two; the rate of intensive care is around 1%[9]. It is not yet clear what the effect is of cytokines and hormones in determining clinical severity in the pathogenesis of croup. Croup is seen 1.5 times more often in boys[2]. It has been identified in large series studies in the literature that boys are more dominant at all ages and the most frequent admission age is between 6 and 12 months[10-12]. In this study, 75.4% of patients were male and most of them were 6 to 36 months old. Although age was not found to have a significant effect on clinical severity or cytokine/hormone levels, most of the children under the age of 6 months were observed to be in the moderate/severe group. Due to the narrowness of the subglottic areas, children under two years of age may be exposed to more frequent and more severe croup[1].

No correlation was observed between atopy and recurrent croup in this study. There are conflicting results in the literature regarding recurrent croup and atopy. Although a positive relationship was encountered in the study conducted by Cooper et al.[13], a negative relationship was observed in the study performed by Ramsey et al.[14]. No relationship was observed in the two other studies similar to the results of this study[15,16].

Symptoms are typically seen at night hours, which may be related to the circadian rhythm of cortisol[1]. Two large studies that assessed admission time are available in the literature: although the peak admission time was found to be 3:00 am in the study conducted by Lee et al.[5,], and the peak admission time was found to be 9:00 am in a study conducted by Rosychuk et al [12]. In our study, the peak admission hour was 3:00 pm, and admissions were most frequently made between noon and 6:00 pm. Cortisol levels and admission times of the patients were not in convenience with physiological circadian rhythm, and the cortisol levels of the moderate/severe patients were high. The authors suggested that the higher

cortisol levels in the moderate/severe group was associated with the stress response.

Many studies in the literature have shown that the most frequent etiological agent in croup is parainfluenza virus[10, 12,17]. Interestingly, in our study, the most frequent etiological agent was detected as rhinovirus, and the second frequent was detected as parainfluenza virus. In a study conducted by Miller et al[18]. assessing viral etiological agents, the most frequent etiological agent was also detected as rhinovirus, and the second frequent was also detected as parainfluenza virus. Other studies conducted recently also support that rhinovirus isolation increases in croup patients and that rhinovirus should be considered a frequent agent[9,19-21].

The number of leukocytes and the level of cortisol in the patient group were significantly higher compared to the control group in this study. However, the number of leukocytes was within normal limits for the age ranges within the groups.

The levels of cortisol and serum IL-10 in the moderate/severe group were found to be significantly higher than the mild group. Although many studies exist in the literature investigating the effect of inflammatory cytokines in patients with bronchiolitis, pneumonia, respiratory distress, asthma and isolated from specific respiratory virus pathogens[22-25], no studies exist comparing the severity of croup and levels of cytokines. In a large study conducted by Tabarani et al.[22], which investigated patients with RSV-positive lower respiratory infection, it was shown that a positive correlation existed between inflammatory cytokines and disease severity. Similar results were obtained in a study conducted by Diaz et al.[24]. Respiratory distress severity and the nasopharyngeal inflammatory cytokine levels of 153 patients with parainfluenza virus were compared by Feghaly et al[23]. The nasal wash CXCL8 (IL-8) concentrations were elevated in patients with lower respiratory tract infection when compared those with upper respiratory tract infection. The moderate and severe nasal wash CXCL8 and CXCL10 (IL-10) concentrations were higher than mild group. The high concentration of local CXCL8 concentration of parainfluenza virus may offer a biochemical explanation for why glucocorticoids are effective at reducing severity of clinic[23]. Observing an increase in local pro-inflammatory cytokines in Feghaly's study and the low levels of systemic pro-inflammatory agents in the present study suggested that local inflammatory responses may play a more important role in croup. However, studying the both systemic and local agents can be a target of further studies in severity of croup.

Levels of PAF and TNF-α were identified to be higher at a statistically significant level in patients with history of atopy. PAF is a pro-inflammatory phospholipid released from mast cells, monocytes, and tissue macrophages[26]. There are studies in the literature suggesting that the lack of PAF acetyl hydrolase, which reduces the high level of PAF or the effect of PAF, is associated with allergy and anaphylaxis[27-29]. Studies showing the direct relationship between the TNF-α level and atopy are quite limited. Although the TNF-α and TNF receptor-I (TNFRI) levels were significantly high in patients with severe anaphylaxis, Brown et al[29]. determined that only the TNFRI level correlated with disease severity. Again, in the study performed by Brown et al.[29], a significant relationship was observed between anaphylaxis severity and TNFRI[29]. This suggested that the TNF-α level is demonstrating the systemic inflammation more than local inflammation. These results suggest that the levels of PAF and TNF-α may be high in the atopic patients, additional studies on this issue are necessary.

The current study has several limitations. The number of patients was small. The cytokine/hormone levels were studied without nasopharyngeal samples, and other cytokine and receptor levels were not studied. These measures should be the subject of further studies. Despite these shortcomings, our study has the methodological advantages of using both proinflamatory and antiinflamatory cytokines, and the samples taken by the nasopharyngeal aspirate method were studied with the Film Array multiplex nested PCR method in terms of twenty-one respiratory pathogens.

In contrast with other studies, rhinovirus was the most frequent causal agent for croup in this study. The inflammatory and anti-inflammatory cytokine/hormone levels in moderate/severe group, and the levels of PAF and TNF-α in the history of atopy group indicate that different

systemic and local inflammatory mechanisms may play a role in the pathogenesis of croup.

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