

Croup, recurrent croup, allergy, and airways hyper-reactivity

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SUMMARY One hundred and ten children were studied 9 years after each had been in hospital for croup. They were evaluated with a questionnaire, physical examination, allergy skin testing, pulmonary function tests, and a histamine inhalation challenge. Fifty-seven of them had recurrent episodes of croup, and 33 were defined as allergic. The association between allergy and recurrent croup was highly significant. Airways hyper-reactivity was found in 23 of them, and was associated with allergy and recurrent croup. The group of children with a history of recurrent croup could be distinguished from the group with one or two episodes by male predominance, onset of the disease at a younger age, familial predisposition, a significantly greater association with allergy and airways hyper-reactivity, slightly lower expiratory flow rates in pulmonary function tests, and a tendency towards the subsequent development of asthma.

Viral croup (acute laryngotracheobronchitis) is a common childhood respiratory infection characterised by inspiratory stridor, hoarse voice, and barking cough. Some children have multiple episodes of croup. This recurrent, or spasmodic, croup generally has a distinctive pattern with acute episodes of inspiratory stridor occurring at night, lasting several hours, and often responding to humidified air.¹⁻⁴ The cause of recurrent croup is not known; mild viral infections, allergy, and psychological factors have been suggested.¹

Croup has been considered a self-limiting disease. However, a high incidence of a history of croup was found in children with asthma.⁵ Airways hyper-reactivity to exercise challenge was demonstrated in a group of 27 children with a history of croup, which suggested some possible association with asthma.⁶

The present study investigated the presence of allergic factors and bronchial hyper-reactivity in children who had been admitted to hospital with croup 9 years previously.

Materials and methods

During 1970, 331 children (237 boys, 94 girls) spent some time in the respiratory unit at the Royal Children's Hospital, Melbourne because they had croup. Medical records showed that 62 children had major congenital anomalies or chronic disease, and that some lived a great distance from the hospital; these were excluded from the study. The remaining 269 families were communicated with by letter. One

hundred and ten children attended and were studied. Eighteen children were excluded because of a recent respiratory infection or trauma. Fifty-six families did not reply to the letters, and 26 families made an appointment but failed to attend. The remaining 59 families could not be traced.

Each child was seen with at least one parent. A questionnaire which included information about the one episode, or multiple episodes of croup and allergic illness in the child and in 1st-degree relatives was completed. A routine physical examination was carried out.

Allergy skin prick tests were performed using 8 common local antigens.⁷ A weal of 3 mm in diameter was taken as a minimum positive response.

Functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV), maximum expiratory flow-volume (MEFV), and maximum inspiratory flow-volume (MIFV) curves were recorded in an integrated-flow body plethysmograph. Maximum expiratory flow at 50 ($\dot{V}_{E_{max50}}$) and 25% ($\dot{V}_{E_{max25}}$) of vital capacity (VC), and maximum inspiratory flow at 50% VC ($\dot{V}_{I_{max50}}$) were measured. MidVC-ratio was calculated by dividing $\dot{V}_{E_{max50}}$ by $\dot{V}_{I_{max50}}$. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and mean forced expiratory flow during the middle half of the FVC (FEF_{25-75}) were measured using a water-filled spirometer (Godart Expirograph) in accordance with standard guidelines.⁸ Results were expressed as percentage predicted normal.⁹⁻¹¹

A standard histamine challenge was performed.¹² A positive response was defined as a 20% fall in FEV₁ or greater. The test was terminated if a positive response was observed or, if the child did not respond, with the highest concentration. At the end of the histamine challenge the patient was immediately resealed in the body plethysmograph and a second flow-volume loop obtained.

Statistical analysis was performed using Student's *t* test, Fisher's test, and Yates's modification of the χ^2 test.

Results

The 110 children were assigned to groups according to the number of episodes of croup and the presence of allergy (Fig. 1). Croup (C) was defined as 1 or 2 episodes. Forty-three children had had 1, and 10 children had had 2 episodes. Recurrent croup

(RC) was defined as more than 2 episodes. The number of episodes in RC children ranged from 4 to 60 with a mean of 12. Allergy (A) was defined either by a clear history of an allergic disorder (eczema, urticaria, hay fever, asthma) or by at least 2 positive skin tests. A child was termed asthmatic only if he had been diagnosed previously as such by a physician. Twenty-one children had a clear history of an allergic disorder and each had at least 1 positive skin test. Twelve further children were defined as allergic on the basis of at least 2 positive skin tests. Five children had only 1 positive skin test each, but all had a history of allergic disease.

Four subgroups resulted (Fig. 1): croup without allergy (CNA), croup with allergy (CA), recurrent croup without allergy (RCNA), and recurrent croup with allergy (RCA). The association of allergy with recurrent croup was found to be highly significant ($P < 0.001$).

	Croup	Recurrent croup	
Non-allergy	Croup without allergy 46	Recurrent croup without allergy 31	77
Allergy	Croup with allergy 7	Recurrent croup with allergy 26	33
	53	57	

Fig. 1 Distribution of subjects into groups and subgroups.

Clinical data. Clinical data are summarised in Table 1. Eighty-two were boys and 28 girls. There was a significantly higher number of boys in RC than in C ($P < 0.01$) and also in A than in NA ($P < 0.02$). The mean age at the time of study for all children was 133 (range 113–195) months. There was no significant age difference between groups and subgroups. The mean age at the first episode of croup was significantly lower for RC than for C ($16.5 \text{ months} \pm 11.3$ compared with 24.1 ± 17.2 , $P < 0.01$). As the difference in the mean age between A and NA was not significant this did not relate to the coexistence of allergy.

The interval between the last episode of croup and the study was much longer in C (9 years) than in RC (5 years), a finding to be expected by the design of the study. There was no significant difference in this interval between CNA and CA and also none between RCNA and RCA. The age at the last episode of recurrent croup as well as the interval between the first and last episode in RC showed no significant difference between RCNA and RCA. The mean number of episodes for RCA was higher than

Table 1 Clinical data

Group	Age at last attack (months)		Time between first and last attack (months)		No of attacks		Croup in siblings*
	Mean	Range	Mean	Range	Mean	Range	
Croup without allergy (boys n=27, girls n=19)							4 (2C, 2RC)
Croup with allergy (boys n=6, girls n=1)							2 (2)
Recurrent croup without allergy (boys n=25, girls n=6)	68	(18–121)	51	(3–105)	9	(4–40)	6 (2C, 6RC)
Recurrent group with allergy (boys n=24, girls n=2)	78	(18–137)	62	(11–110)	15	(4–60)	11 (1C, 13RC)

* Number of cases.

for RCNA but this just failed to reach significance at the 5% level. The average duration of stridor in recurrent episodes, as estimated by the parents, also failed to show any significant difference between RCNA (6.3 hours) and RCA (8.6 hours). There was a significantly more frequent history of croup in siblings in RC compared with C ($P < 0.05$) as well as in A compared with NA ($P < 0.01$). Seven siblings had had 1 or 2 episodes and 21 had had multiple episodes of croup. The percentage of siblings with recurrent croup was significantly higher in RC than in C ($P < 0.05$). The comparison NA with A gave no significant result.

The manifestations of allergy are listed in Table 2. Seven children with asthma were in RCA. The parents of 3 of these children described a gradual change from typical croup to a picture in which wheezing became more prominent. A positive family history of atopic disease was more common in RC than in C, but the difference was not statistically significant. The association between a positive family history and children defined as A was highly significant ($P < 0.001$).

Table 2 Allergy manifestations in 110 children

Group	Positive family history of allergy	Clear history of allergic disease	Skin test (at least 2 positive results)
Croup without allergy (n=46)	6	0	0
Croup with allergy (n=7)	3	4	5
Recurrent croup without allergy (n=31)	5	0	0
Recurrent croup with allergy (n=26)	13	17 (Asthma --7)	23

Table 3 Lung volumes (mean \pm SD)

Group	FVC (% predicted)	FRC (% predicted)	TLC (% predicted)	RV (% predicted)	RV/TLC (%)
Croup without allergy (n = 46)	93.1 \pm 11.2	110.6 \pm 23.1	103.4 \pm 12.5	133.0 \pm 37.7 15(4)*	30.8 \pm 6.8 22(4)
Croup with allergy (n = 7)	92.1 \pm 10.1	120.8 \pm 28.9	104.8 \pm 14.9	144.0 \pm 54.0 2(1)	31.8 \pm 8.9 3(1)
Recurrent croup without allergy (n = 31)	92.4 \pm 9.1	112.1 \pm 18.2	102.3 \pm 11.1	128.6 \pm 33.1 9(4)	30.6 \pm 5.1 12(4)
Recurrent croup with allergy (n = 26)	92.5 \pm 8.2	113.6 \pm 18.4	104.6 \pm 9.8	139.1 \pm 32.8 11(8)	30.9 \pm 6.1 15(12)

* Number of subjects with increased residual volume (outside 95% confidence limits). 'Corrected' number (see text) in parentheses.

Table 4 Flow measurements (mean \pm SD)

Group	FEV ₁ (% predicted)	FEV ₁ /FVC (%)	FEF ₂₅₋₇₅ (% predicted)	V _E max50 (% predicted)	V _E max25 (% predicted)	Mid-VC ratio (%)
Croup without allergy (n = 46)	99.31 \pm 10.2	89.2 \pm 4.7	101.2 \pm 20.1	75.3 \pm 15.7	95.8 \pm 30.9	112.4 \pm 25.2
Croup with allergy (n = 7)	93.7 \pm 8.7	83.7 \pm 2.3	81.8 \pm 15.7	72.0 \pm 10.2	70.0 \pm 14.3	107.4 \pm 17.9
Recurrent croup without allergy (n = 31)	99.2 \pm 11.8	86.4 \pm 6.2	95.3 \pm 23.5	73.1 \pm 15.4	90.3 \pm 24.5	102.6 \pm 25.4
Recurrent croup with allergy (n = 26)	97.3 \pm 10.4	85.4 \pm 4.9	91.1 \pm 17.9	76.3 \pm 25.1	85.9 \pm 36.9	107.0 \pm 22.8

Virological studies were not done routinely in 1970. Physical examination was essentially normal in all 110 patients.

Pulmonary function tests. There was no significant difference between groups and between subgroups for FVC, FRC, and TLC (Table 3). RV and the RV/TLC ratio was increased in all groups and subgroups and there was no significant difference either between means or in the number outside the 95% confidence limits. In an attempt to explain this increase in RV, the MEFV curves of the 52 children with an increased RV/TLC ratio were studied. Thirty-one curves showed a rapid drop to zero flow at the terminal portion of the expiration suggesting a submaximal effort. In the remaining 21 the increase had to be accepted as genuine. This 'corrected' number of genuinely increased RV/TLC ratios now showed a significant association with RC ($P < 0.05$) and with A ($P < 0.01$).

Results of flow measurements are summarised in Table 4. There was no significant difference between groups in FEV₁ expressed as percentage predicted normal, V_Emax50, V_Emax25, and midVC-ratio. FEV₁/FVC however, was significantly lower in RC than in C (85.9 \pm 5.6 compared with 88.4 \pm 4.8, $P < 0.02$) and also in A than in NA (85.0 \pm 4.5 compared with 87.9 \pm 5.5, $P < 0.01$). The FEV₁/FVC ratio was significantly lower in RCNA compared with CNA ($P < 0.05$) and CA compared with CNA ($P < 0.01$). FEF₂₅₋₇₅ was significantly lower in A than in NA (89.1 \pm 17.6 compared with 98.8 \pm 21.6, $P < 0.05$) but the comparison RC with C was not significantly different.

Histamine inhalation challenge. Twenty-three children (21 boys, 2 girls), demonstrated a fall in FEV₁ of

20% or more with histamine (Fig. 2). There were significantly more responders in RC than in C ($P < 0.01$). The association of responders with A was highly significant ($P < 0.001$). There were significantly more responders in CA than in CNA ($P < 0.05$) and also in RCA compared with RCNA ($P < 0.02$). However, comparison of CNA with RCNA as well as CA with RCA showed no significant difference. There was no significant correlation of histamine response with the age at the last episode of croup, number of episodes, time span between first and last episode, and positive croup history in siblings. The mean age at study was significantly lower in responders compared with non-responders (122 compared with 136 months, $P < 0.01$). This corresponded with the finding that the mean age at the first episode of croup in the responders was significantly lower than in the non-responders (13 compared with 22 months, $P < 0.02$). The mean interval between the study and the last episode in responders

with RC was 54 months; in non-responders it was 61 months. The difference was not significant.

The MEFV curves after histamine of the responders were compared with the prehistamine tracings. In all there was a decrease of the maximum expiratory flow rate and increased convexity towards the volume axis suggesting lower airways obstruction. $\dot{V}_{E_{max50}}$, expressed as percentage change from baseline, showed a greater fall after histamine in RC than in C ($-14.0\% \pm 20.0$ compared with $-9.6\% \pm 19.5$) but the difference was not significant. There was however a significant difference when A was compared with NA ($-20.8\% \pm 21.6$ compared with $-8.1\% \pm 17.7$, $P < 0.01$). $V_{I_{max50}}$ also showed a greater fall in RC than in C ($-6.0\% \pm 18.5$ compared with $-1.2\% \pm 17.6$) and in A than in NA ($-7.7\% \pm 18.2$ compared with $-2.0\% \pm 18.0$) but the differences were not significant. All groups showed a small fall in their midVC-ratio but again the differences were not significant.

After histamine challenge 7 children (1 CNA, 1 CA, 2 RCNA, and 3 RCA) demonstrated a change in the shape of their MIFV curve suggesting a variable extrathoracic upper airways obstruction. Four of these were also histamine-responders based on the fall in FEV_1 . Three of the 5 children in RC with this deformity had each had their last episode of croup less than 12 months before study.

Discussion

This study of children with a history of croup demonstrates a significant association between recurrent croup, allergy, and airways hyper-reactivity. As a group, children with recurrent croup had their first episode at an earlier age than those with only 1 or 2 episodes. Correspondingly children with airways hyper-reactivity had a significantly earlier onset of episodes.

Previous studies have demonstrated airways hyper-reactivity to exercise and metacholine challenge in children with a history of croup.^{6,13} No correlation between airways hyper-reactivity and any other features of croup, and in particular recurrent croup, was found in these studies. Other authors have speculated on the role of allergy in recurrent croup.^{1-3,14} One group noted significantly more recurrent croup in children with a history of allergic disease.⁶ This is confirmed by the results of this study where the association between allergy and recurrent croup was highly significant. However, the nature of this association is unknown. Allergy could theoretically constitute the cause or the result of recurrent croup, or both allergy and recurrent croup might represent different manifestations of a basic underlying disorder.

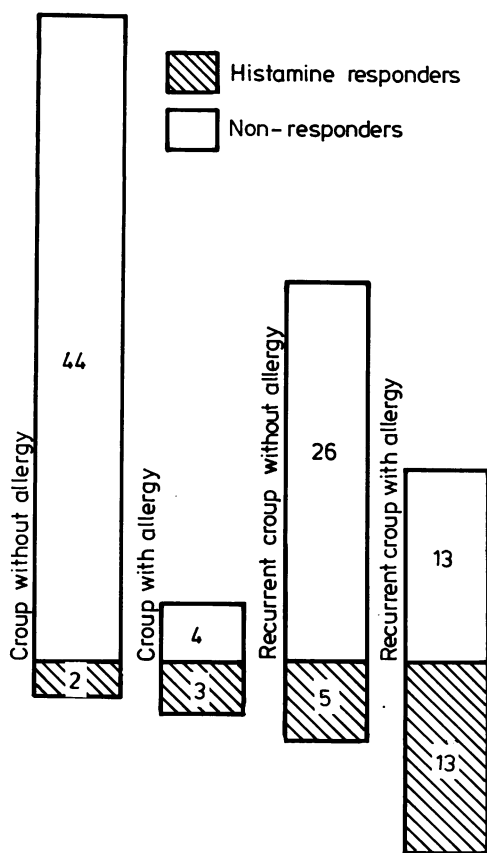


Fig. 2 Number of histamine responders and non-responders in the four subgroups.

A familial predisposition towards recurrent croup has been suggested previously¹⁵ and was found in this study too. The percentage of cases of recurrent croup in siblings of children with recurrent croup was significantly higher than in siblings of children with croup.

It has been suggested that paediatric respiratory disorders in general may constitute important risk factors for the subsequent development of chronic airways disease in adult life.¹⁵⁻¹⁸ A high incidence of previous croup in asthmatic children has been reported.⁵ In the present study the finding of 7 children with asthma in the subgroup with recurrent croup and allergy suggests that children with this combination are at risk of developing asthma. The symptoms in 3 of these 7 children indicated a gradual transition from episodes of predominant inspiratory obstruction to a clinical picture where expiratory obstruction became the dominant feature. Children with recurrent croup and allergy also showed slightly lower flows during forced expiration, especially FEV₁/FVC, again suggesting some association with obstructive disease of the lower airways.

There might also be an association between recurrent croup, allergy, and an increased RV/TLC ratio. However, there were 2 possible mechanisms for the high values of RV. It could have been the result of submaximal effort or alternatively a manifestation of gas trapping. The method adopted to distinguish between the 2 however, was considered too subjective to allow clear conclusions. Other workers have also reported increases of RV/TLC in children with a history of croup.¹³

The flow-volume loops obtained after histamine indicated that all children with a significant fall in FEV₁ had a fall in maximal expiratory flow with increased convexity towards the volume axis suggesting obstruction in the lower respiratory tract.¹⁹ The degree of change in the MEFV curves may have been underestimated because of the delay in reseatting the child in the body plethysmograph after a positive response on the spirometric tracing.

Seven children, 4 of whom also had significant falls in FEV₁, showed decreases of inspiratory flow and plateau formation of the MIFV curve after histamine. Such a deformity has been attributed to a variable extrathoracic upper airways obstruction.²⁰ This is compatible with a narrowing of the airways above the thoracic inlet simulating the lesion of croup. Three of these children had each had their last episode of recurrent croup within the previous 12 months. The small number of children with this type of response to histamine makes any further conclusions difficult.

More than half the children in this study had

recurrent croup. This might not indicate the true incidence of recurrent croup. The method of recruitment of children for the study might have produced a biased selection. Patients with recurrent episodes are more likely to have had recent visits to the hospital and so their addresses would be correct. Furthermore parents of children with frequent episodes would be more likely to respond to an invitation to take part in a study.

This large number of children with a history of recurrent croup however, permitted the identification of some as yet unreported features of recurrent croup thereby further distinguishing this entity from croup. In comparison with children who only had had 1 or 2 episodes, the group of children with recurrent croup showed: (1) a greater proportion of males, (2) a tendency to experience the first attack earlier in life, (3) a greater association with allergy as documented by a positive history of atopic disease and positive skin tests to environmental allergens, (4) a tendency towards the subsequent development of asthma, (5) slightly lower flow rates in baseline pulmonary function tests, (6) a greater association with airways hyper-reactivity as assessed by histamine inhalation challenge, (7) a familial predisposition towards the development of recurrent croup.

These clinical features help to distinguish recurrent croup from croup. Recurrent croup however, shares many features with asthma. These include a male predominance, the possible onset of the disease with a viral respiratory tract infection early in life, a genetic predisposition, the frequent coexistence of allergy, a tendency for episodes to occur at night, and non-specific bronchial hyper-reactivity. This study raises the question as to whether recurrent croup and asthma could share, at least in part, the same pathophysiological basis.

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