

Patterns of allergic respiratory disease in children with a past history of bronchiolitis

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Sequential annual examinations have been carried out in a group of children who were hospitalized 5 years previously for bronchiolitis. During the subsequent 5 year study period, 40 to 50 per cent of the children were observed to wheeze recurrently. There was a high incidence of positive family histories of allergy, atopic rhinitis and dermatitis, and increased eosinophils in the nasal secretions and peripheral blood. Strong skin test responses to allergens were seen predominantly in the wheezing subjects and increased in frequency during the 5 year period. Wheezing episodes were generally associated with respiratory infections but were also observed during exposure to skin test reactive antigens as the children became older. The relationship of the bronchiolitis episode to childhood asthma is discussed.

Acute bronchiolitis in infancy is a clinically defined disorder in which various etiologic factors have been postulated.¹ Several studies¹⁻³ have reported an increased incidence of asthma in children with a past history of bronchiolitis. Starting in 1964, an annual follow-up investigation was made at this institution of a group of children hospitalized here in 1960 to 1962 with a diagnosis of bronchiolitis. Interval histories, physical examinations, and certain laboratory studies were carried out wherever possible in every child of this group who could be located. After the initial year of follow-up, it was found⁴ that approximately 50 per cent of the children had recurrent or continuous wheezing following the episode of bronchiolitis. Several clinical features were found to characterize a large majority of persistently wheezing children as contrasted to the non-wheezing group. These were: (1) a strong family history of allergy, (2) other allergic manifestations in the patient, and (3) increased numbers of eosinophils in the nasal secretions. The limited number of positive skin test responses to a panel of common allergens were seen only in the persistently wheezing children.

The present report describes several interesting clinical patterns which developed as these children have been studied annually over a 5 year period.

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MATERIALS AND METHODS

Patient study group

Thirty-five children had been hospitalized on the Pediatric Service of the Hospital of the University of Pennsylvania for a double-blind study of the effect of dexamethasone on the duration and morbidity of acute bronchiolitis. The criteria utilized at that time for the diagnosis of bronchiolitis have been described previously.⁴ In brief, these included: (1) the acute onset of respiratory distress with sibilant rales and/or wheezes, (2) evidence of obstructive pulmonary hyperinflation on physical and radiologic examination, (3) normal temperature or low-grade fever, and (4) absence of a past history of wheezing or allergies.

Follow-up studies

Annually, starting in 1964, an assiduous attempt was made to obtain yearly follow-up study of each child to the fullest degree possible. With succeeding years, such attempts became progressively more difficult because many of the population involved moved frequently without leaving forwarding addresses. Three of the children could not be located at any time. In some instances, information concerning the interval history and physical examination were obtained during home visits by the investigators, but the mother failed repeatedly to bring her child to the clinic for some of the laboratory studies. It should be emphasized, however, that the complete exclusion of a child from statistical analysis of any of the annual examinations occurred only when the family could not be located despite intensive search.

Interviewing of parents, physical examination, and laboratory studies were carried out as noted previously.⁴ Total and differential white blood counts, smears of nasal secretions for eosinophils, chest roentgenograms, and screening reaginic skin tests by the scratch and intradermal technique were carried out wherever possible. Scratch test antigens were in the dried defatted form (Hollister-Stier Laboratories, Spokane, Wash.) except for pollen extracts, 40,000 protein nitrogen units (PNU) per milliliter of aqueous solution, made in the laboratory of the Allergy and Immunology Clinic, Hospital of the University of Pennsylvania, from dried pollen supplied by Greer Laboratories, Inc., Lenoir, N. C. Intradermal tests were carried out with: (1) dust (Hollister-Stier, 1,000 PNU per milliliter); (2) mixed tree extract, mixed grasses extract, and mixed ragweed extract, all prepared in aqueous solution of 1,000 PNU per milliliter; and (3) standard intradermal testing extracts of cat dander, dog dander, feathers, egg, milk, *Alternaria*, and *Hormodendrum* (supplied by Hollister-Stier Laboratories, Spokane, Wash.). Readings of skin tests were made at 20 minutes and were expressed in wheal diameters as compared to a control (Coca's solution).

In recording the data, several clinical and laboratory features were tabulated: (1) the incidence of persistent wheezing; (2) atopic syndromes such as allergic rhinitis and atopic dermatitis; (3) the incidence of major allergies in the immediate family (parents and/or siblings); (4) increased eosinophils (at least 20 per cent of the inflammatory cells) in the nasal secretions; (5) increased eosinophils (more than 3 per cent) in a differential white blood count; (6) chest roentgenogram abnormalities; (7) strongly positive allergy skin tests. Criteria for strongly positive skin tests, read at 20 minutes, were: (1) scratch test with wheal diameter at least two times that of a control and accompanied by definite flare, (2) intradermal test with wheal diameter at least three times that of a control, or (3) intradermal test with a definite "pseudopod" reaction.

The observations of the previous double-blind study of dexamethasone effect during the original bronchiolitis episode in these children were then reviewed. The clinical response to corticosteroids or placebo therapy during this episode was then compared to the subsequent respiratory course for each child.

RESULTS

Although the number of children in whom studies were performed varied somewhat from year to year, the percentage of those found to be persistently

TABLE I. Prevalence of wheezing in children with a past history of bronchiolitis

Follow-up evaluation	Children wheezing	Children not wheezing
1st year	12	12
2nd year	15	17
3rd year	11	12
4th year	12	14
5th year	11	11

wheezing was fairly consistent (about 50 per cent) during the 5 years of the study (Table I). Three of the children who were noted to be wheezing during the first follow-up period were found to be free from wheezing during the subsequent 4 year study period. Conversely, 2 subjects who were found to be free from wheezing during the initial follow-up period subsequently exhibited wheezing.

A more detailed analysis of the clinical and laboratory findings during these studies is shown in Table II. In the group of children with persistent wheezing, there was a high prevalence (1) positive history of atopy in the immediate family, (2) atopic manifestations in the patient, and (3) increased eosinophils in the nasal secretions compared with the nonwheezing group ($p < 0.01$ for each parameter). There was no significantly greater incidence of peripheral blood eosinophilia in the wheezing children during the first year of study (67 per cent versus 42 per cent in nonwheezing children). However, during the subsequent years of the study, peripheral blood eosinophilia was significantly more common ($p < 0.05$ for each year) in those children with persistent wheezing. Abnormalities other than suggestive evidence of hyperinflation were quite unusual in the annual chest roentgenograms of both groups.

The results of skin testing with a selected panel of common allergens are shown in Tables II and III. Although data were limited here because of lack of cooperation on the part of some parents, a rather striking pattern became apparent over the 5 year study period. Initially, only a small percentage of the tests elicited positive responses; these were seen only in the children with recurrent wheezing. As the same children were tested annually, there was a progressive increase in the number of positive skin tests exhibited by the wheezing group. This increase reflected both an increased percentage of these children showing at least one positive test and increased numbers of positive tests per child. By contrast, there was a consistently low prevalence of positive skin tests in the nonwheezing children over the 5 year period.

Annual inquiries into the patterns of wheezing in these children also revealed interesting changes over the 5 year period. Initially, the only precipitating factors for wheezing episodes noted by the parents were either respiratory infections or nonspecific stimuli such as exertion, sudden weather changes, etc. As the children became older, histories of precipitation of asthmatic and nasal symptoms by exposure to inhalants such as dust, danders, and pollen were more common. It was also at this time that strongly positive skin tests to these inhalant allergens were seen more commonly in the same children; a good correlation between the emerging pattern of asthmatic symptoms and the pattern of skin test reactivity was seen in some subjects. Infections continued to be a common precipitating cause of asthmatic episodes. Since most of these

TABLE II. Clinical and laboratory parameters in wheezing and nonwheezing children over a 5 year period

Parameters	Year									
	1st		2nd		3rd		4th		5th	
	Wh-N/Wh		Wh-N/Wh		Wh-N/Wh		Wh-N/Wh		Wh-N/Wh	
Other atopic manifestations	58*	8	75	6	64	5	67	9	82	25
Family history of allergy	92	8	80	18	86	14	92	10	82	25
Eosinophilia										
Nasal secretion	58	0	82	15	78	10	83	12	91	17
Peripheral blood	67	42	64	22	78	10	83	12	91	33
At least one positive skin test	50	0	77	18	78	14	92	14	91	17

Wh, Children with persistent wheezing after bronchiolitis; N/Wh, children not wheezing after bronchiolitis.

*Per cent of positive responses in the subjects in whom information was available.

children were observed only during the annual re-evaluation examinations, no attempt was made to quantitate the severity of wheezing over the study period. However, from estimates given by the parent and the histories of hospitalizations for respiratory distress, it appeared that wheezing became less prominent in the majority of children with increasing age. In some, wheezing occurred only on excess exertion or with respiratory infections. Five of the wheezing group were actively symptomatic much of the time.

DISCUSSION

In the opinion of many investigators, more than one etiologic factor may be playing a role in the clinical entity called "bronchiolitis."⁵ The studies of Chanock and associates⁶ and Parrott and co-workers⁷ have revealed frequent evidence of infection with the respiratory syncytial (RS) virus in epidemics of bronchiolitis. More recently they⁸ have postulated that the RS virus-induced bronchiolitis in infants may be at least partially due to the formation of pathogenic antigen-antibody complexes. There is also evidence⁹ to suggest a synergistic effect of viral and bacterial agents in producing the clinical picture of bronchiolitis.

Yet, it still is difficult to discern whether one is dealing with bronchiolitis or asthma, especially when there are recurrent episodes³; an approach to these diagnostic difficulties has been well described recently by Wittig and Chang.¹⁰ These authors felt that the presence of increased eosinophils in nasal secretions and evidence of concurrent atopic manifestations would point to a child who is likely to develop asthma in later childhood.

The findings of the present study are in agreement with this impression and point to certain other rather consistent features in the children who go on to manifest asthma following an episode diagnosed as "bronchiolitis" in infancy. The high prevalence in this group of other atopic manifestations in the patient, positive family history of atopy, and increased eosinophils in nasal secretions

TABLE III. Prevalence of strongly positive skin tests during annual examinations

Evaluation	Dust	Cat	Dog	Feath- ers	Egg	Milk	Trees	Grass	Ragweed	Alter- naria	Hormo- den- dum
1st Year											
Wh(8)	0	1	1	0	0	0	0	1	1	0	0
N/Wh(7)	0	0	0	0	0	0	0	0	0	0	0
2nd											
Wh(14)	4	1	4	2	0	1	0	1	2	1	0
N/Wh(16)	2	1	0	1	0	0	0	0	0	0	0
3rd											
Wh(14)	5	2	2	1	1	1	3	2	4	3	1
N/Wh(14)	2	0	0	0	0	0	0	0	0	1	0
4th											
Wh(11)	8	3	0	3	2	1	4	4	4	6	2
N/Wh(7)	2	0	1	1	0	0	0	0	0	0	0
5th											
Wh(10)	9	4	1	3	1	0	2	1	5	4	1
N/Wh(6)	1	1	0	0	0	0	0	0	0	0	0

Wh, Subjects persistently wheezing; N/Wh, subjects without wheezing. Numbers in parentheses are subjects tested in each group.

noted during the initial follow-up evaluation has persisted through the four additional annual examinations. Peripheral blood eosinophilia has also become significantly more common in the recurrently wheezing group, although slightly elevated levels of blood eosinophils were not unusual in nonwheezing children. The 2 groups of children also showed quite different patterns of response to sequential allergy skin testing. The progressive increase over the years in the number of positive reactions was seen only in the wheezing group. Such skin test reactivity has been felt by some investigators^{11, 12} to be a hallmark of "atopic" reactivity." Annual sequential skin test reactivity, such as carried out here, has not been studied extensively in atopic children or in children with strong family histories of atopy. There is some information¹³⁻¹⁵ about the prevalence of positive skin test reactivity in individuals deemed to be atopic or nonatopic by history. In some of these studies, concern was expressed about nonspecific irritant effects when concentrated extracts were used for intradermal skin testing. However, a prior study at this clinic¹⁴ with the use of the extract concentrations described in the present report did not reveal a high incidence of positive reactions in a nonatopic population. The patterns of skin test responses seen in this study would be compatible with a postulated atopic diathesis being present in the wheezing group but not in the nonwheezing group. The progressive increase in the percentage of positive skin test responses in each wheezing child would suggest increasing sensitization to extrinsic antigens over the years, possibly associated with increased exposures. It is of significance that it was only in the later years of the study that we could obtain convincing histories of precipitation of wheezing episodes by exposure to such antigens.

Precise quantitation of the severity of the wheezing episodes was not feasible in this study, but the pattern in most cases was that of less prominent and disabling wheezing episodes as the children's ages increased. This pattern

would be similar to that reported¹⁶ in a 5 year follow-up of children with "asthma" in a large community survey.

The question remains as to whether the episodes diagnosed as "bronchiolitis" were the initial presentation of asthma in some of these patients. None of them had exhibited wheezing prior to the hospitalization for bronchiolitis. Wittig and Chang¹⁰ have proposed several clinical criteria to help distinguish between bronchiolitis and asthma in infancy with the understanding that distinction is not clear-cut in some patients. Review of the clinical characteristics of the past episode of bronchiolitis in these children did not show different patterns for those in the subsequent "recurrent wheezing" and "nonwheezing" groups. There were also similar patterns of response to corticosteroid treatment of the previous episodes of bronchiolitis in the two groups. This is similar to experience reported recently in a large controlled study.¹⁷ Unfortunately, virologic studies were not carried out in our study group during the hospitalization for bronchiolitis. Although Hyde and Saed³ have reported the occasional occurrence of two or three repeated episodes of bronchiolitis in the same child, the large majority of children with recurrent wheezing studied here have exhibited this pattern for up to 8 years. On the other hand, only 2 of the 17 children who reportedly were free from wheezing during the first 3 years after bronchiolitis subsequently manifested this symptom.

In reviewing some of the evidence at hand,^{18, 19} one gets the impression that in at least some of these children an episode indistinguishable from bronchiolitis was likely the initial manifestation of the asthmatic response. Recognition of this emerging pattern with its associated clinical characteristics may lead to more prompt investigation and management of etiologic factors. In addition, the presence of a strong family history of allergy may help alert the physician caring for an infant with bronchiolitis to the increased likelihood of future recurrent wheezing episodes in that child.

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