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Bronchial hyperreactivity after infantile obstructive bronchitis

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A follow-up study was performed on 406 patients treated for infantile obstructive bronchitis during the period between 1964 and 1973. Their mean age was 12.6 years at the time of the study. The male : female ratio was 1.7. Forty-three patients (11%) became asthmatic within 10 years after onset of the wheezy episode of infancy. In one-third of the 363 non-asthmatic children, bronchial hyperreactivity was shown by acetylcholine and histamine provocation. There was a significant correlation between the number of recurrent obstructive episodes and the length of the period of recurrent wheezing on the one hand and bronchial hyperreactivity on the other hand.

Obstructive bronchitis is a common disease during infancy and early childhood. It is characterized by fever, dyspnoea, expiratory wheezing, sometimes crepitation, dry, later productive cough, pulmonary hyperinflation, depressed position of the diaphragm, on X-rays hyperaeration of lungs, and sometimes atelectasis. Obstructive bronchitis is usually accompanied by upper airways catarrh and not infrequently by bronchopneumonia.

The condition is also termed spastic, asthmatic or wheezy bronchitis; Clark and Godfrey wrote of a "wheezy baby syndrome" [2]. Some Anglosaxon authors apply the term bronchiolitis to all forms of wheezing, but most experts distinguish the disease caused by respiratory syncytial virus from obstructive bronchitis [2, 5, 14, 22]. Williams and McNicol regard obstructive bronchitis as one extreme of the broad spectrum of asthmatic diseases [20]. Still, the phrase "all that wheezes is not asthma" [19] means that the symptom does not unequivocally mean asthma. Indeed, wheezing during childhood may be a manifestation of cystic fibrosis, tracheal or bronchial malformation, foreign body, heart defect, gastrointestinal reflux, etc. About 10% of all children experience at least one obstructive episode before their second birthday [1].

Ten to 27% of children affected by obstructive bronchitis during infancy develop asthma in subsequent years [1, 11, 12, 13]. Host factors may here play an important role [5, 14]. There may be hereditary factors at work since allergy is more frequent in the families of patients with infantile obstructive bronchitis; its prevalence, however, is not as high as in families of asthmatic children [2, 19, 20].

A characteristic feature of bronchial asthma is a hyperreactivity of the bronchial system [3]. Bronchial hyperreactivity has been found in both short and long-term follow-up studies performed in patients with infantile obstructive bronchitis; the provocative factor may be exercise [6, 7, 9], histamine [13] or acetylcholine [12]. Similarly, bronchial hyperreactivity has been observed after infantile bronchiolitis [4, 17]. Heredity of bronchial hyperreactivity occurring after "wheeze disease" has been assumed [4, 5, 16] and confirmed by family and twin studies [7, 8].

The present follow-up study on children having experienced obstructive bronchitis during infancy was initiated in 1979; its aim was to see whether bronchial hyperreactivity could be demonstrated 10 years or more after the primary wheezing episode and to examine its relationship to certain factors.

Material

During the period between 1964 and 1973, 27 724 infants and children were admitted to our department; in 744 instances (about 3%) the diagnosis was obstructive bronchitis, 660 patients were involved. 406 of these 660 patients (62%) answered positively to our request to participate in the follow-up. Their mean age was 12.6 years (range, 9—18 years) at the time of the study. The male : female ratio of the 406 participants was 1.70 while among the original 660 infants this was 1.73. No fatality due to obstructive bronchitis occurred. Two children had died of heart defect and one of eclampsia; in one child cystic fibrosis, bronchial anomaly, chronic foreign body, in another a heart defect was found. 98 healthy children, free from any chronic complaint and matching in age served as controls.

Methods

The children were asked in a letter to visit our outpatient department. A detailed case history was then taken, data of earlier admissions were reconsidered, physical examination and lung function tests were carried out. Provocation tests were performed in children free from symptoms and complaints for at least two weeks. Bronchial reactivity was examined after acetylcholine and histamine provocation. Acetylcholine provocation was carried out in all 406 participants, while histamine provocation only in 313 out of the 363 non-asthmatic patients.

First, resting FEV_1 (forced exspiratory volume in the first second) and PEFR (peak expiratory flow rate) were determined; the best value of three determinations was chosen. A 1% solution of acetylcholine, 0.02, 0.05 and 0.10% solutions of histamine were applied step-wise by a Tur-Usi 50 ultrasound nebulizer, each solution for maximum 3 minutes. Each time the loading test was interrupted after 4—5 initial inspirations in order to see if an early reaction occurred. The above mentioned parameters were measured 3, 5 and 10 minutes after the cessation of provocation. A value exceeding the initial value by more than 15% was regarded as a sign of bronchial hyperreactivity [15, 18]; in the control group no increment larger than 12% was encountered.

The data of the 406 children were fed to a Videoton R-10 (VT-1010) computer and analysed statistically by the t and χ^2 tests.

Results

(i) 43 children out of the 406 participants (11%) became asthmatic some time after the initial obstructive bronchitis episode and the time of the study. The diagnosis of asthma was based on our own data or on data obtained in other hospitals. In earlier years the diagnosis rested on clinical data, later, with increasing frequency, on skin tests, aspecific or specific airway provocation, etc. The male : female ratio of asthmatic children was 1.86, in the non-asthmatic subjects only 1.68. Seventeen children had asthmatic complaints at the time of study, 26 of the asthmatics had been free from symptoms for at least one year and had not received any kind of treatment.

(*ii*) Bronchial hyperreactivity was observed in 122 children out of 363 non-asthmatic participants (33.6%). The distribution of positive results according to the kind of provocation was as follows.

only acetylcholine (363 children)	87	positive results
only histamine (313 children)	20	positive results
both (313 children)	15	positive results
all:	122	patients

The rate of hyperreactivity was identical for the two genders: 33.7% in boys, 33.3% in girls.

There were three pairs of twins, one of them uniovular. The monozygotic twins were concordantly negative, in one dizygotic pair both members exhibited a positive result, while in the other, one was positive and one was negative.

(*iii*) The number of episodes of obstructive bronchitis showed the following distribution.

one	91	children (25%)
two or three	118	children (33%)
more than three	154	children (42%)

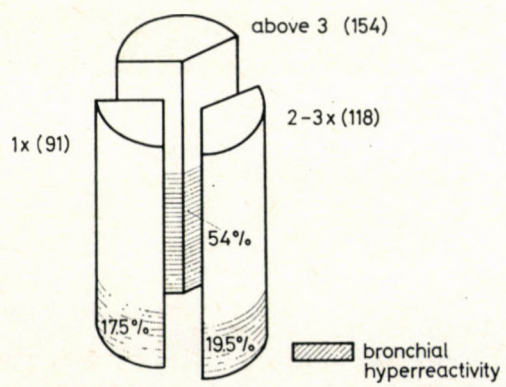

Fig. 1. Relationship between rate of bronchial hyperreactivity and number of episodes of obstructive bronchitis. In the group with more than 3 episodes, the rate is significantly higher ($p < 0.001$), $n = 363$

Figure 1 demonstrates the relationship between the number of obstructive episodes and bronchial hyperreactivity. In the group with more than three episodes bronchial hyperreactivity was significantly more frequent, $\chi^2 = 49.336$, $p < 0.001$. It is noteworthy that even in the group with a single obstructive episode, one fifth of the patients exhibited bronchial hyperreactivity.

(*iv*) The recurrent episodes disappeared by the age of ten years, only 7 children had obstructive symptoms accompanying respiratory infections beyond the seventh year of life. In 54% the obstructive symptoms disappeared by the end of the second year of life, in 85% by the end of the fourth year of life (see Figure 2). There was a certain relationship between the length of the period charged with obstructive episodes and the rate of bronchial hyperreactivity:

		Length of period	
		less than 4 years	more than 4 years
Bronchial hyperreactivity	present	97 (31%)	25 (47%)
	absent	213 (69%)	28 (53%)
	all	310	53

$\chi^2 = 5.114$, $p < 0.05$

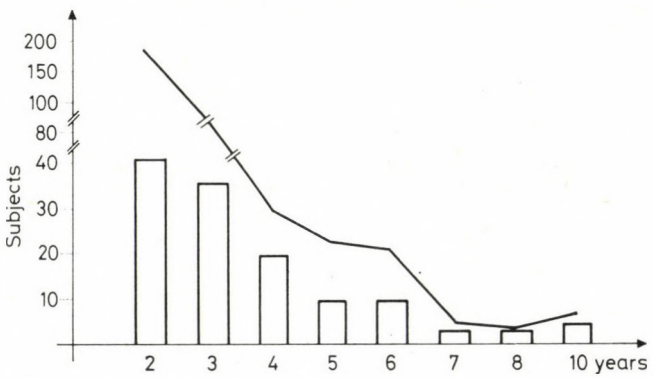

FIG. 2. Length of period with recurrent obstructive bronchitis and rate of bronchial hyperreactivity. In the group exhibiting recurrences beyond the fourth year of life there is a significantly higher rate of bronchial hyperreactivity ($p < 0.05$). The continuous line represents the patients in whom the recurrence ceased in the given year; this is 197 for two years and 84 for three years of age. The height of columns represents the rate of bronchial hyperreactivity

As can be seen, there was a significantly higher rate of bronchial hyperreactivity among children with recurrent episodes of obstructive bronchitis beyond the fourth year of life.

DISCUSSION

In a considerable proportion of infants affected by obstructive bronchitis, asthma develops during child-

hood. Conversely, in a proportion of asthmatic children the complaints begin before the age of two years [10]. The rate of asthma developing in subsequent years in infants with obstructive bronchitis has been found 11% in our study; this is in agreement with published data [1, 13], although the length of follow-up was not uniform.

Bronchial hyperreactivity is a characteristic feature of childhood asthma; it can be demonstrated by aspecific stimuli like provocation with cold air or body exercise. A similar hyperreactivity has been found in follow-up studies on infants with obstructive bronchitis, both shortly or a long time after the primary disease. Scislicki et al [13] found hyperreactivity on histamine provocation in 16% of 42 patients, König and Godfrey demonstrated hyperreactivity to exercise in 18 children [6, 7]. In patients with recurrent obstructive bronchitis, 87% hyperreactivity was found by Lenney and Milner while the patients were symptom-free [9]. The high rate (33%) of hyperreactivity found by us among 363 non-asthmatic children was significantly higher than that found among healthy children by acetylcholine and/or histamine provocation.

Inheritance of bronchial hyperreactivity has been suggested by König and Godfrey, on the basis of exercise provocation studies on family members and twins of patients with obstructive bronchitis [8]. The number of twins in our material was too small for conclusions in this respect.

Bronchial hyperreactivity was found to occur at a higher rate in children with more than three recurrences of wheezy bronchitis, respectively in those whose disposition persisted beyond the fourth year of life. Such a relationship has not yet been investigated according to the literature available to us. Further follow-up studies are necessary to determine whether this high rate of hyperreactivity, exceeding 50%, predicted an increased risk for chronic respiratory disease or bronchial asthma.

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