

Wheezing in Preschool Children and Total IgE Levels: A Birth Cohort Study

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Objectives: To evaluate association between total IgE levels and wheezing in preschool children from India. **Methods:** Data were collected in a prospective birth cohort study related to wheezing till three years of age. Total IgE was measured at enrolment, at one year and two years of age and correlated with wheezing episodes. **Results:** A total of 310 (167 boys) children were enrolled. Total IgE levels increased with age ($P<0.001$). Overall, 101 (32.6%) children had 182 episodes of wheezing. The median (IQR) total IgE levels in children with wheezing and without wheezing were similar at one year [42.1 (12.7, 93.5) vs 41.9 (17.1, 96.7) kU/L; $P=0.39$] and two years of age [62.8 (32.4, 212.0) vs 75 (25.8, 173.0) kU/L, $P=0.92$]. **Conclusion:** Total IgE levels increased with age and were not different in preschool children with and without wheezing.

Keywords: Immunoglobulin E, Rhonchi, Under-five wheezer.

About 50 % children report at least one episode of wheezing by six years of age [1]. It is postulated that events including viral infections in first few years of life determine the occurrence of wheezing and asthma later in life [2,3]. There is a strong correlation of IgE levels and asthma at least in older children, but limited information about association of IgE levels and wheezing in preschool children viral respiratory tract infections are common. Studies from developed countries show variable association show between IgE levels and wheezing in young children [4-8]. Similar data are lacking from developing countries where atopy is not so common. The aim of our study was to evaluate association between total IgE levels and wheezing in preschool children from a birth cohort in India.

METHODS

This study was a part of a prospective birth cohort study where term appropriate for gestational age babies without adverse perinatal events were enrolled at birth. Baseline data (demographic profile, gestational age, anthropometry, physical findings, family history of asthma or allergy etc.) were collected. Acute respiratory infection (ARI) was defined as presence of cold or cough with or without fever, fast breathing or breathing difficulty. Children were followed-up at the hospital every 6 months. Parents were additionally asked to report to the hospital whenever they had ARI (breakthrough visit). Parents were contacted

telephonically for any respiratory symptoms monthly. Each episode of respiratory symptoms was evaluated for presence of wheezing and for etiology. The primary objectives of the birth cohort study were to evaluate development of asthma at five years of age following ARI during infancy, to assess effect of ARI on pulmonary function, to generate normative data for infant pulmonary function test (PFT), and to study etiology of ARI. The data on etiology have been already published [9]. For index study, total IgE levels and episodes of wheezing were evaluated to assess for association. Total IgE levels were measured at enrolment, at one year of age, and at two year of age using ImmunoCAP Phadiatop (by Thermo Scientific, Sweden). Secondary outcomes were: total IgE levels in children with no, single or multiple episodes of wheezing; demographic characteristic in children with and without wheezing; and total IgE levels by onset of age of wheezing.

The episodes of illness when child had wheezing were recorded in follow-up till three years of age and were correlated with total IgE levels at different ages. Each wheezing episode was confirmed by a pediatrician and was managed as per unit's policy. Blood samples were collected within two weeks of schedule time. If there was wheezing on the scheduled date of sampling, blood sample was collected after recovery. Elevated value of total IgE at birth, one year of age and two years of age was defined as values of more than 1.28 kU/L, 15.3 kU/L and 29.5 kU/L, respectively [10].

The study was approved by the ethics committee of our institute, and parents' consent was taken before enrolment in the study.

Statistical analysis: Continuous data were reported as mean (SD) if normally distributed otherwise as median (IQR) and were compared using parametric and non-parametric tests as appropriate. Categorical data were presented as percentage and were compared using chi-square test. Total serum IgE levels at different age were compared in children with and without wheezing. STATA 12 software was used to analyze the data.

RESULTS

A total of 310 (169 male) children with mean (SD) gestational age of 267.9 (22.6) days and mean (SD) birth weight of 2648.2 (689.2) g were enrolled. One infant died of an unrelated cause. One hundred one (32.6%) children had 182 episodes of wheezing up to three years of follow up, of which 50 children had a single episode of wheezing. Majority (139, 76.4%) of wheezing episodes were detected during breakthrough visit and 43 (23.6%) episodes were detected during six monthly visits. The frequency of wheezing was not different in boys and girls.

Total IgE levels were available for 288, 255, and 219 children at baseline, one year, and two years of age, respectively and at all three time points for 189 children. A total of (9.0%), 191 (74.9%), and 159 (72.6%) children had abnormal total IgE levels at baseline, one year, and at two years of age, respectively. The median (IQR) total IgE values were significantly higher at two year than one year of age [72.7 (26.3, 184.0) and 42.1 (15.2, 94.8), respectively; *P* <0.001]. The total IgE levels were not different in boys and girls. The serum IgE levels in children with and without wheezing are shown in **Table I**.

The risk factors for wheezing, total IgE levels and the proportion of children having abnormally high IgE at birth, one year of age, and two years of age was not different among children with wheezing and without

Table II Comparison of Children With and Without Wheezing

Parameter	Wheezing (n=101)	No wheezing (n=310)
Male	57 (56.4)	112 (53.6)
Rural	15 (14.9)	21 (10.0)
Smoking at home	33 (32.7)	64 (30.8)
*Pet at home	12 (12.6)	25 (13.9)
†Family history	48 (47.5)	96 (45.9)
#Birthweight (g)	2793.9 (314.1)	2778.1 (401.6)

*Data shown for total 95 and 180 children, respectively; #Data expressed as mean (SD); all *P*>0.05; †History of asthma or atopy.

wheezing (**Table II**). The total IgE levels at one and two years of age were not different among children with or without history of asthma and other atopy in any family members (data not shown).

Total median (IQR) IgE levels were not different between no or one episode of wheezing (*n*=259) versus more than one episode of wheezing (*n*=51) at one year [41.1 (16.7, 96.4) vs. 42.5 (10.2, 75.6); *P*=0.34] and two years of age [77.4 (26.3, 184.0) vs. 54.3 (21.9, 147.0); *P*=0.43].

Out of total 182 wheezing episodes, 89 (48.9%) wheezing episodes occurred in 60 children below one years of age, 66 (36.3%) wheezing episodes occurred in 53 children in second year of life, and 27 (14.8%) wheezing episodes occurred in 20 children in third year of life. Total IgE levels were not different among children with and without wheezing by age of wheezing episodes (data not shown). Total IgE levels were above 100 kU/L in 58 (22.8%) and 90 (41.1%) children at one and two years of age respectively. There was no difference in wheezing in children having total IgE above 100 kU/L and less than 100 kU/L (*P*=0.84).

DISCUSSION

In this cohort study, about one-third children had at least one episode of wheezing by three years of age, most of

Table I Serum IgE Levels in Children With and Without Wheezing (N = 310)

	No.	With wheezing	No.	Without wheezing	<i>P</i> value
<i>Total IgE levels (kU/L), median (IQR)</i>					
At 1 y of age	95	42.1 (12.7, 93.5)	160	41.9 (17.1, 96.7)	0.39
At 2 y of age	82	62.8 (32.4, 212.0)	137	75.0 (25.8, 173.0)	0.92
<i>Elevated IgE, n (%)</i>					
At birth	101	10 (10.5)	209	16 (8.3)	0.53
At 1 y of age	95	65 (68.4)	160	126 (78.8)	0.07
At 2 y of age	82	63 (76.8)	137	96 (70.1)	0.28

WHAT THIS STUDY ADDS?

- The total IgE levels were not different in young children with or without wheeze suggesting that wheezing in preschool children may not be IgE-mediated.

which were associated with ARI. There was no difference in total IgE levels in children with wheezing and without wheezing suggesting that all wheezing may not be IgE-mediated.

A limitation of the study was that allergen-specific IgE levels and skin prick test to look for presence of atopy were not done. It is reported that pollen-specific IgE or mite allergen-specific IgE contribute most to total IgE [6]. Details of allergic rhinitis, atopic dermatitis, allergic conjunctivitis or food allergy, exertion precipitated cough/ dyspnea and frequency of use of paracetamol were not collected.

The association between total IgE levels and wheezing is not uniform. A few studies reported association between total IgE levels and wheezing [4,8,11-13] unlike other studies which reported no association [5,14-16]. Latter studies suggest that chronic airway inflammation triggered by a viral infection in early life may be risk factor for recurrent wheezing in young children. The absence of association between total IgE levels and wheezing in preschool children suggests that wheezing was a benign transient condition associated with viral respiratory tract infection and not related to asthma.

In the present study, the total IgE levels increased significantly with age unlike an earlier study [11]. In developing countries antibodies against parasitic infections like *Ascaris* have also been associated with wheezing and atopy in preschool children [17]. In the same study, active *Trichuris trichiura* infection was also associated with wheezing in preschool children [17]. Cross reactivity of IgE against *Ascaris* and mite has been described [18]. It is difficult to say if parasitic infections might have contributed to high total IgE levels in the present study as we did not look for helminthic infection and parasite specific IgE in this study.

Total IgE levels were high at birth possibly related to maternal factors, though maternal IgE levels were not measured.

Therefore, to conclude, wheezing in young children may not be IgE-mediated and it may be triggered by viral infections in congenitally small airways. It will be interesting to see whether development of asthma in this

cohort at 5 years of age has any association with total IgE levels at birth, one and two years of age.

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