Clinical Profile of Episodic Wheezing and Multiple Trigger Wheezing in Preschool Children: A Cross-Sectional Study

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Abstract

The objectives of our study were to identify the relative frequency of episodic viral wheeze (EVW) and multiple trigger wheeze (MTW) in preschool children of 1 to 5 years of age with recurrent wheezing and to compare the relevant clinical and sociodemographic parameters in the above phenotypes. This cross-sectional study included 165 children aged 1 to 5 years with recurrent wheeze. Participants were categorized into EVW and MTW based on history according to European Respiratory Society Task Force recommendations 2008. Symptom control was assessed by Global Initiative for Asthma guidelines 2015. Of the total participants, EVW was seen in 55% and MTW in 45%. Children with MTW were significantly older than those with EVW, more atopic, and had higher eosinophil counts. The dominant phenotype seen in our study was EVW. The absence of ocular/nasal allergy and exclusive breastfeeding predicted well-controlled symptoms in EVW and in all preschool wheezers, respectively.

Keywords

- atopy
- children
- EVW
- MTW
- phenotype
- preschool
- wheeze

Introduction

Preschool wheezers are twice more likely to visit hospitals and thrice more likely to be admitted compared with older children.[1] An essential requirement for better management of these children is to classify them as either episodic viral wheezers (EVWs) or multiple trigger wheezers (MTWs) based on European Respiratory Society (ERS) Task Force recommendations 2008.[2] Although these phenotypes were found by some authors to change over time,[3–5] a recent study by Spycher et al indicates that they remain stable.[6] A significant number of them, particularly the MTW, are likely to have symptoms consistent with asthma and reduced lung capacity later in life.[7,8] The identification of these phenotypes help in predicting long-term outcomes and also to identify high-risk children who might benefit from secondary preventive interventions. There are only few studies comparing the clinical and sociodemographic profiles of these two phenotypes and none among Indian children. Hence, this study was performed to identify the relative frequency of EVW and MTW in preschool children 1 to 5 years of age with wheezing and to compare the relevant clinical and sociodemographic parameters in the above phenotypes.

Methods

This cross-sectional study was conducted in the Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, a tertiary care teaching institute from December 2015 to December 2017 after obtaining approval from our institute ethics committee. Preschool children (1–5 years of age), who were on follow-up in the childhood asthma clinic for at least 3 consecutive months and diagnosed by a doctor to have recurrent wheeze participated in this study. Children with pneumonia, history

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suggestive of gastroesophageal reflux disease, congenital heart disease, stridor, history suggestive of foreign body, bronchopulmonary dysplasia, bronchiectasis, immunodeficiency, and anatomic abnormalities leading to recurrent aspiration were not enrolled.

We recruited 165 children, who fulfilled the inclusion criteria during the study period (►**Fig. 1**). The participants were classified into EVW and MTW as per ERS Task Force guidelines 2008. Children who had history of wheezing during discrete time periods, following viral infections, with absence of wheeze between episodes were categorized as EVW. Children who had history of discrete exacerbations of wheeze and also had symptoms in between episodes of viral infections were categorized as MTW.[2]

For all participants, data on rural or urban location and parental literacy were recorded. Socioeconomic status (SES) was classified based on modified Kuppuswamy scale 2014.[9] History regarding the age of onset, frequency of symptoms, bronchiolitis in the past, frequency of wheeze exacerbations, triggers, seasonality, personal and family history of atopy, exposure to environmental smoke, prematurity, low birth weight, neonatal respiratory distress, breastfeeding status, immunization status, investigation, and treatment details were noted. Weight and height were measured and classified according to the World Health Organization guidelines.[10] Symptom control was assessed based on Global Initiative for Asthma (GINA) 2015 guidelines.[11] In our study, we classified the well-controlled symptom group in GINA 2015 as "well-controlled symptom group" and the partly and uncontrolled groups together as "uncontrolled symptom group." The Institute Ethics Committee—Human Studies of our institute approved the study (JIP/IEC/2015/22/776).

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR). Categorical variables were expressed as proportions. Mann–Whitney's *U* test was done for quantitative variables and chi-square test was used for categorical variables. Multiple logistic regression analysis was done for factors associated with symptom control for both EVW and MTW and also for all the participants combined. For statistical analysis, Statistical Package for the Social Sciences (SPSS) version 19 by International Business Machines (IBM) Corporation was used.

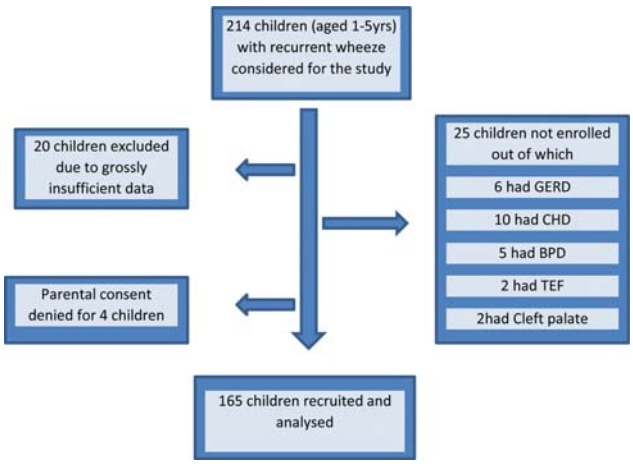

Fig. 1 Study flow diagram depicting the inflow of subjects into the study.

Results

The median age of the study population was 42 months with an IQR of 27.5 to 51.5. Boys were 110 (66.7%) in number; children belonging to rural areas were 98 (59.4%). Two children (1.2%) belonged to lower, 38 (23%) belonged to upper lower, 72 (43.8%) belonged to lower middle, 35 (21%) belonged to upper middle, and 18 (11%) belonged to upper socioeconomic classes. Majority were born at term (91.5%) with normal birth weight (78.1%), were exclusively breastfed (92.1%) in the first 6 months, and were completely immunized (97%) for age as per national schedule. EVW was seen in 91 (55%) and MTW in 74 (45%) children. Median age was significantly higher in the MTW group. The two groups did not significantly differ in breastfeeding status, immunization status, prematurity, low birth weight, neonatal respiratory distress, bronchiolitis in infancy, age of onset, and duration of treatment (►**Table 1**). The number of children on montelukast was higher in EVW group; those on inhaled corticosteroids (ICSs) were higher in MTW group and this finding was statistically significant. A significantly higher proportion of parental atopy and high absolute eosinophil count (AEC) was seen in children with MTW. Seasonality of exacerbation was present in 35 (47.3%) children with MTW. Viral infections in 67 (90.5%) children, dust allergy in 46 (62.1%) children, environmental smoke exposure in 23 (31.1%) children, and food allergens in 21 (28.3%) children were the common triggers identified in MTW group. Out of 91 children with EVW, 79 (86.8%) had well-controlled symptoms, whereas 12 (13.2%) had uncontrolled symptoms. Among the 74 MTW, 58 (78.4%) had well-controlled symptoms and 16 (21.6%) had uncontrolled symptoms. There was no significant difference in the symptom control among EVW and MTW.

On univariate analysis of factors associated with symptom control in EVW group (►**Table 2**), it was found that children with either parent or both graduates had a higher percentage of uncontrolled symptoms with an odds ratio (OR) of 8.5 (95% confidence interval [CI]: 2.2–32.1). Those with history of ocular/nasal allergies had more uncontrolled symptoms (OR: 12.8, 95% CI: 1.8–87.3). Other factors such as gender, SES, anthropometric parameters, prematurity, birth weight, breastfeeding, neonatal respiratory distress, bronchiolitis, environmental smoke exposure, AEC, and type and duration of treatment were not significantly associated. Among MTW (►**Table 3**), only exclusive breastfeeding in the first 6 months of life predicted well-controlled symptoms (OR: 6.1, 95% CI: 1.2–30.9).

On univariate analysis among all participants (►**Table 4**), wheezers with both parents being graduates had higher chance of having uncontrolled symptoms (OR: 2.5, 95% CI: 1–5.9), and so were those who had nasal/ocular allergy (OR: 2.5, 95% CI: 1–5.9) and those not exclusively breastfed (OR: 5, 95% CI: 1.5–16.4). On multiple (binomial) logistic regression

Table 1 General characteristics of the study population

Variable		Episodic wheezer $n = 91$ (%)	Multitrigger wheezer $n = 74$ (%)	*p*-Value (chi-square)
Median age in mo (interquartile range)		36 (24–48)	42 (36–54)	0.003[a]
Male gender		64 (70.3)	46 (62.2)	0.268
Rural residence		52 (57.1)	46 (62.2)	0.514
Socioeconomic status	Lower	2 (2.2)	0	0.772
	Upper lower	19 (20.9)	19 (25.7)	
	Lower middle	39 (42.9)	33 (44.6)	
	Upper middle	21 (23.1)	14 (18.9)	
	Upper	10 (11)	8 (10.8)	
Prematurity		8 (8.8)	6 (8.1)	0.876
Low birth weight		17 (18.7)	20 (27)	0.201
Exclusive breastfeeding for 6 mo		85 (93.4)	67 (90.5)	0.568
Median duration of breastfeeding in mo (interquartile range)		13 (12–18)	18 (12–18)	0.261[a]
Complete immunization status		88 (96.7)	72 (97.3)	0.463
Neonatal respiratory distress		5 (5.5)	9 (12.2)	0.126
Bronchiolitis in infancy		47 (51.6)	32 (43.2)	0.282
Median age of symptom onset in mo (interquartile range)		10 (6–18)	12 (5.75–25)	0.547[a]
Frequency of exacerbations	≤2 in 6 mo	17 (18.7)	8 (10.8)	0.161[b]
	>2 in 6 mo	74 (81.3)	66 (89.2)	
Controller medications	Montelukast	39 (42.9)	8 (10.8)	0.001[b]
	ICS	49 (53.8)	66 (89.2)	
	None	3 (3.3)	0	
Median duration of treatment in mo (interquartile range)		3 (3–6)	3.5 (3–8.25)	0.119[a]
Median absolute eosinophil count (interquartile range)[c]		292 (132.5–485)	850 (260–1,630)	0.001[a]
H/o atopic eczema		2 (2.2)	16 (21.6)	0.001[b]
H/o ocular/nasal allergy		5 (5.5)	34 (45.9)	0.001[b]
Parental atopy		12 (13.2)	44 (59.5)	0.001[b]

Abbreviations: H/o, history of; ICS, inhaled corticosteroid.
[a]*p*-Value calculated using Mann–Whitney's *U* test.
[b]*p*Value calculated using chi-square test.
[c]For 94 children.

in the EVW group, absence of ocular/nasal allergies predicted well-controlled symptoms (OR: 20.4, 95% CI: 1.9–216.6). On multiple (binomial) logistic regression analysis among preschool wheezers in general, exclusive breastfeeding in the first 6 months of life predicted well-controlled symptoms (OR: 4.1, 95% CI: 1.2–14.4).

Discussion

From our study results, we find that EVW is the dominant phenotype. Children with MTW were older than EVW, were mostly on ICS, and had more parental atopy, personal atopy, and higher AEC. In the EVW group, symptoms were more likely to be significantly well controlled in the absence of ocular or nasal allergy. In preschool wheezers as a whole, exclusive breastfeeding in the first 6 months of life was associated with well-controlled symptoms.

It is generally known that the proportion of MTW increases and EVW decreases over time.[12,13] In a study involving 109 children in the age group of 2 to 6 years, Schultz et al found that 35% had EVW and 65% had MTW at baseline and 31% had EVW, 47% had MTW, and 22% had no wheeze at 1-year follow-up.[4] We did not find significant difference in the age of onset, frequency of exacerbations, or duration of treatment between EVW and MTW, but there was difference in the type of treatment, AEC, and parental

Table 2 Sociodemographic, clinical, treatment-related factors, and comorbidities associated with symptom control among episodic wheezers

Factors	Well controlled ($n = 79$)	Uncontrolled ($n = 12$)	Odds ratio (95% CI)	*p*-Value (chi-square)
Age > 3 y (%)	36 (45.6)	2 (16.7)	0.2 (0–1.1)	0.059
Male (%)	56 (70.9)	8 (66.7)	1.2 (0.3–4.4)	0.745
Rural (%)	46 (58.2)	6 (50)	0.7 (0.2–2.4)	0.592
Lower SES (%)	19 (24)	2 (16.7)	0.6 (0.1–3.1)	0.726
Father's education: graduate (%)	19 (24)	9 (75)	9.4 (2.3–38.6)	0.001
Mother's education: graduate (%)	19 (24)	8 (66.7)	6.3 (1.7–23.3)	0.005
Both parents' education: graduate (%)	15 (19)	8 (66.7)	8.5 (2.2–32.1)	0.001
Prematurity (%) (missing—1)	7 (9)	1 (8.3)	0.9 (0.1–8.2)	0.999
Low birth weight (%) (missing—4)	15 (20)	2 (16.7)	0.8 (0.1–4)	0.999
Exclusive breastfeeding (%)	75 (95)	10 (83.3)	3.7 (0.6–23.1)	0.177
Partial immunization (%)	3 (3.8)	0	NA	0.999
Neonatal RD (%)	4 (5)	1 (8.3)	1.7 (0.1–16.6)	0.515
Bronchiolitis in infancy (%) (missing—3)	40 (51.3)	7 (70)	2.2 (0.5–9.2)	0.327
Stunted (%)	6 (7.6)	2 (16.6)	2.4 (0.4–13.7)	0.284
Underweight (%)	20 (25.3)	2 (16.6)	0.6 (0.1–2.9)	0.723
H/o atopic eczema, rash, etc. (%)	2 (2.5)	0	NA	0.999
H/o nasal/ocular allergic symptoms (%)	2 (2.5)	3 (25)	12.8 (1.8–87.3)	0.015
Exposure to environmental smoke (%)	3 (3.8)	1 (8.3)	2.3 (0.2–24.1)	0.438
Family h/o allergy (%)	10 (12.6)	2 (16.7)	1.3 (0.2–7.2)	0.656
Treatment with inhaled corticosteroids (%) (missing—4)	43 (54.4)	6 (50)	1.3 (0.4–4.5)	0.634
Absolute eosinophil count > 500 (%) (missing—55)	5 (14.7)	0	NA	0.999
Duration of treatment > 3 mo (%) (missing—3)	31 (40.8)	5 (41.7)	1 (0.3–3.5)	0.999

Abbreviations: CI, confidence interval; H/o, history of; NA, not available; RD, respiratory disease; SES, socioeconomic status.

Table 3 Sociodemographic, clinical, treatment-related factors associated with symptom control among multitrigger wheezers

Factors	Well controlled ($n = 58$)	Uncontrolled ($n = 16$)	Odds ratio (95% CI)	*p*-Value (chi-square)
Age > 3 y (%)	37 (63.8)	11 (68.8)	1.2 (0.3–4)	0.713
Male (%)	37 (63.8)	9 (56.25)	1.3 (0.4–4.2)	0.582
Rural (%)	37 (63.8)	9 (56.25)	0.7 (0.2–2.2)	0.582
Lower SES (%)	14 (24.1)	5 (31.2)	1.4 (0.4–4.8)	0.538
Father's education: graduate (%)	15 (25.9)	3 (18.75)	0.6 (0.1–2.6)	0.746
Mother's education: graduate (%)	16 (27.6)	3 (18.8)	0.6 (0.1–2.4)	0.747
Both parents' education: graduate (%)	13 (22.4)	3 (18.8)	0.8 (0.2–3.2)	0.999
Prematurity (%)	5 (8.6)	1 (6.3)	0.7 (0–6.5)	0.999
Low birth weight (%) (missing—3)	18 (32)	3 (20)	0.5 (0.1–2.1)	0.527
Exclusive breastfeeding (%)	55 (94.8)	12 (75)	6.1 (1.2–30.9)	0.035
Partial immunization (%)	1 (1.7)	1(6.3)	3.8 (0.2–64.3)	0.388
Neonatal RD (%)	5 (8.6)	4 (25)	3.5 (0.8–15.1)	0.095
Bronchiolitis in infancy (%) (missing—1)	26 (45.6)	6 (37.5)	0.7 (0.2–2.2)	0.563
Stunted (%)	5 (8.6)	1 (6.3)	0.7 (0–6.5)	0.999

Table 3 (*Continued*)

Factors	Well controlled ($n = 58$)	Uncontrolled ($n = 16$)	Odds ratio (95% CI)	*p*-Value (chi-square)
Underweight (%)	11 (19)	5 (31.3)	1.9 (0.5–6.7)	0.315
H/o skin atopy (%)	14 (24.1)	1 (6.3)	0.4 (0.1–2.2)	0.496
H/o nasal and ocular allergy (%)	26 (44.8)	8 (50)	1.2 (0.4–3.7)	0.713
Exposure to environmental smoke (%)	19 (32.8)	4 (25)	0.6 (0.2–2.4)	0.762
Family h/o allergy (%)	36 (62)	8 (50)	0.6 (0.2–1.8)	0.384
Treatment with inhaled corticosteroids (%) (missing—1)	50 (87.7)	15 (93.7)	0.4 (0–4.1)	0.676
Absolute eosinophil count > 500 (%) (missing—41)	19 (73)	3 (43)	0.2 (0–1.5)	0.186
Duration of treatment > 3 mo (%) (missing—1)	28 (49.1)	9 (56.3)	1.3 (0.4–4)	0.614

Abbreviations: CI, confidence interval; H/o, history of; RD, respiratory disease; SES, socioeconomic status.

Table 4 Sociodemographic, clinical, treatment-related factors, and comorbidities associated with symptom control among wheezers in general

Factors	Well controlled ($n = 137$)	Uncontrolled ($n = 28$)	Odds ratio (95% CI)	*p*-Value (chi-square)
Age > 3 y (%)	73 (53.2)	13 (46.4)	0.7 (0.3–1.7)	0.508
Male (%)	93 (67.8)	17 (60.7)	1.3 (0.6–3.1)	0.463
Rural (%)	83 (61.3)	15 (53.5)	0.7 (0.3–1.7)	0.491
Lower SES (%)	33 (24)	7 (25)	1 (0.4–2.7)	0.918
Father's education: graduate (%)	34 (24.8)	12 (42.8)	2.2 (0.9–5.2)	0.052
Mother's education: graduate (%)	35 (25.5)	11 (39.2)	1.8 (0.8–4.4)	0.140
Both parents' education: graduate (%)	28 (20.4)	11 (39.2)	2.5 (1–5.9)	0.032
Prematurity (%) (missing—1)	12 (8.8)	2 (7.1)	0.8 (0.1–3.7)	0.999
Low birth weight (%) (missing—7)	33 (25.2)	5 (18.5)	0.6 (0.2–1.9)	0.460
Exclusive breastfeeding (%)	130 (95)	22 (78.5)	5 (1.5–16.4)	0.01
Partial immunization (%)	4 (2.9)	1 (3.5)	1.2 (0.1–11.4)	0.999
Neonatal RD (%)	9 (6.5)	5 (17.9)	3 (0.9–10)	0.06
Bronchiolitis in infancy (%) (missing—4)	66 (48.8)	13 (50)	1 (0.4–2.4)	0.917
Stunted (%)	11 (8)	3 (10.7)	1.3 (0.3–5.2)	0.709
Underweight (%)	31 (22.6)	7 (25)	1.1 (0.4–2.9)	0.786
H/o atopy (eczema, rash, etc.) (%)	16 (11.6)	2 (7.1)	0.5 (0.1–2.6)	0.741
H/o nasal and ocular allergic symptoms (%)	28 (20.4)	11 (39.2)	2.5 (1.–5.9)	0.032
Exposure to environmental smoke (%)	22 (16)	5 (17.8)	1.1 (0.3–3.3)	0.783
Family h/o allergy (%)	46 (33.5)	10 (35.7)	1. (0.4–2.5)	0.828
Treatment with inhaled corticosteroids (%) (missing—5)	93 (70.4)	21 (75)	0.8 (0.3–2)	0.629
Absolute eosinophil count > 500 (%) (missing—92)	24 (40)	3 (23)	0.4 (0.1–1.8)	0.348
Duration of treatment > 3 mo (%) (missing—4)	59 (44)	14 (50)	1.2 (0.5–2.8)	0.586

Abbreviations: CI, confidence interval; H/o, history of; RD, respiratory disease; SES, socioeconomic status.

atopy. Mutti et al in their study on 55 children have reported no significant difference between the age of onset, atopic status, and airway eosinophilia in EVW compared with MTW.[14] Significantly higher AEC and family history of atopy were seen in MTW in our study as MTW represents an atopic phenotype.[5,12,13,15–18] On univariate analysis, we found that more children whose parents were graduates had uncontrolled symptoms. These children also had higher parental allergy and environmental smoke exposure. Previous studies have found that parental allergies were independent risk

factors for developing persistent wheeze.[19,20] It is also known that lower parental education and low SES are associated with poorer symptom control.[19,21] However, in our study, we find that parents who were graduates were a risk factor for uncontrolled symptom on univariate analysis, but it was not confirmed in multiple logistic regression indicating that the discrepancy may be probably due to confounders. We also found that EVW without ocular/nasal allergy were more likely to have well-controlled symptoms. It is a well-known fact that allergic rhinitis can have a negative effect on symptom control.[22] Although atopy is more often associated with MTW, in our study, we found they may be associated with EVW also and further serves to support the observations of the ERS Task Force statement that there may be overlap between the two phenotypes.[2] Consistent with the conclusions of previous studies,[23–25] we also found that exclusive breastfeeding predicted well-controlled symptoms in all preschool wheezers in general.

The limitations of our study are that the sample was drawn from an asthma clinic and not from the community. It was a cross-sectional design and AEC was not available for 92 children. Information regarding breastfeeding and immunization was obtained based on history obtained from parents and information available in the case records (for immunization).

Conclusion

To conclude, EVW is the dominant wheezing phenotype found in preschool children. Children with MTW phenotype tend to be older than EVW phenotype and tend to have higher AECs. Atopy in the form of ocular and nasal allergies can also be seen in children with EVW and its absence predicts well-controlled symptoms. Exclusive breastfeeding predicts well-controlled symptoms in children with preschool wheeze in general irrespective of the phenotypes.

Authors' Contributions

Both the authors were involved in the study design, data collection, analysis, literature review, and drafting of the manuscript, and reviewed the manuscript for intellectual content and seen and approved the final draft. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

None declared.

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