

Original article

Preschool wheeze among a retrospective cohort of Egyptian children

Background: Prevalence of recurrent wheeze in the preschool age was reported to affect one third of children in the developed world, with even more frequency and severity in the developing countries. Epidemiological studies on this subject in Egypt are lacking. We sought to investigate the frequency and different phenotypes of preschool wheeze (PSW) among a group of Egyptian children and their relation to different risk factors.

Methods: A retrospective cohort study was conducted on 1209 children, aged 6-10 years, recruited from the Outpatients' Clinics of Ain Shams University Hospitals from March 2019 to March 2021. Children with underlying chronic disease or suspected to be immunodeficient were excluded. The main study tool was a survey composed of 30 questions and presented to the parent/caregiver via direct interviewing by the investigator and included sociodemographic data details of wheezing episodes before the age of 6, wheezing risk factors and comorbidities. Skin prick test (SPT) was done for the prolonged early, persistent early and late onset wheezers, while pulmonary function tests were done for the currently asthmatics patients.

Results: History of PSW was positive in 298/1209 (24.6%) of the participants. According to the onset, duration and course of wheezes, preschool wheezers were classified as transient wheezers (10.4%), prolonged early wheezers (3.9%), late onset wheezers (3.2%) and persistent wheezers (7.1%) relevant to the whole cohort. Fifty percent of PSW were multi-trigger wheeze while 39.3% were episodic viral wheeze. Twenty-five patients out of 148 wheezers (16.9%) who underwent SPT were found to be atopic. **Conclusion:** PSW is commonly reported among Egyptian children, paralleling international reports with transient and persistent early wheezing being the most common phenotypes in Egypt.

Keywords: Preschool wheezes, transient, persistent, Children.

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INTRODUCTION

The term "preschool wheeze" (PSW) has not been appropriately defined, and it varies considerably among countries as regards the age of patients, however, wheezes before the age of 6 years is the most commonly accepted definition.¹ Wheezing in preschool children has tripled in prevalence over the past 30 years. At present, nearly 50% of all preschool children experience at least one episode of wheezing before 6 years of age and up to 40% of these children have recurrent wheezing episodes during early life.² Children who experience PSW only when they get respiratory tract infections, are usually non-atopic, and outgrow symptoms by 6 years of age.^{3,4} Compared to childhood asthma, recurrent PSW is nearly twice the rate of outpatient clinic and emergency department visits; and more than 5 times the rate of hospitalization.²

Phenotype classification of PSW depends mainly on the natural history and possible triggers.⁵

Multiple cohort studies were designed as proposals to identify PSW appropriately, such as The Tucson Children Respiratory Study (TCRS),⁶ The Avon Longitudinal Study of Parents and Children (ALSPAC)⁷ and the international multicenter birth cohort study.⁸

The incidence of all PSW disorders has increased (including viral wheeze). Factors unrelated to atopy are implicated in the changing epidemiology of wheeze in childhood. Therefore, young children with PSW may either have viral-associated respiratory problems that may not persist into later childhood or may have an asthmatic pattern of airway inflammation that may subsequently turn into asthma.⁹ Genetic, environmental, developmental, and host factors and their interactions may contribute to the development, severity, and persistence of the asthma over time.¹⁰⁻¹²

Definite figures of PSW among Egyptian children are lacking, and thus we were stimulated to

study the frequency, phenotypes, and severity of PSW as well as its natural history among a sample of Egyptian children using a retrospective model.

METHODS

This retrospective cohort study was conducted in the Outpatient' Clinics and the Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University Hospitals in the period from March 2019 to March 2021.

Study population: Egyptian children aged between 6 and 10 years were consecutively recruited during their visits to the Outpatient' Clinics. Verbal consent was obtained from the parent/caregiver/ of each participant. Patients with chronic illness or suspected immunodeficiency were excluded from the study. The sample size was calculated employing the standard sample size calculation method by **Nam, 1987**.¹³ Assuming a prevalence of recurrent wheeze in the population of about 25%, a sample size of 1000 was required to be 95% certain of estimating an overall prevalence in the sample within a mean of 2-5% of its true value. We therefore recruited 1209 children in our cohort.

The survey instrument (annexed) was constructed based upon the data in the medical history relevant to the studied topic. The survey was administered by the same investigating physician via direct interviewing of parent/caregiver to ensure consistency of the collected data.

The survey covered the following main parts: Sociodemographic data: details of the wheezing episodes before the age of 6, risk factors of preschool wheeze and comorbidities. Number of inhabitants per room was calculated and referred to as (crowding index).¹⁴

The survey was revised by expert allergists and pilot-tested on a sample of 100 caregivers, and accordingly, modifications were done for some questions to make them clearer.

Full physical examination was carried out for detection of current chest signs, calculating body mass index (BMI) (Kg/m^2)¹⁵ and to exclude chronic illnesses.

Classification of preschool wheeze:

Patients' classification was adopted from AVON classification¹⁶ as follows:

- Never/infrequent wheezers
- Transient (wheezing attacks started in the first 3 years of life and ended around age of 3 years)
- Prolonged early wheezers (those who started to wheeze in the 1st 3 years of life but stopped wheezing around age of 5 years)

- Late onset wheezers (started to wheeze beyond 3 years and persisted beyond 6 years)
- Persistent early onset wheezers (started to wheeze before age of 3 years and persisted beyond 6 years).

Patients with persistent wheezes at time of enrollment, whether they were late-onset wheezers or persistent wheezers, were referred to as asthmatics. Asthma was diagnosed in 125 children (10.3% of all the participants). These were assessed at the time of enrollment with respect to severity, degree of control and treatment according to the GINA, 2019. Pulmonary function tests were performed for the currently asthmatics at enrollment using JAEGER- VLASYS Healthcare GmbH. Leibnizstrasse 7 spirometer at the Pediatric Pulmonology Unit, Children's Hospital, Ain Shams University.

Skin prick test was performed for the prolonged early, persistent early and late onset wheezers using standardized extracts (Omega Laboratories, Montréal, Canada) of the following allergens: aspergillus, mite mix, cat epithelium and pollen mix. Additional allergens were tested guided by the patient's history.

Statistical Analysis: Data were collected, revised, coded, and entered to the statistical package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges. Categorical variables were presented as number and percentages.

Ethical consideration: The study protocol gained approval of the Research Ethics Committee of the Department of Pediatrics, Ain Shams University (Number: FMASU 227918).

RESULTS

We evaluated 1,209 children in our study. Children's age ranged from 6 to 10 years (mean \pm SD: 7.9 ± 1.5); 657 (54.3%) of them were boys and 552 (45.7%) were girls. BMI of studied children ranged between 12.7th and 27.7th centiles (mean \pm SD: 15.5 ± 1.5), where 18 children (1.5%) exceeded the 95th centile.

Based on the study questionnaire, 298/1209 (24.6%) participants were considered preschool wheezers. Those patients were classified according to the onset, duration, course, and frequency of wheezes into transient wheezers (10.4%), prolonged early wheezers (3.9%), late onset wheezers (3.2%) and persistent early onset wheezers (7.1%) (table 1). Associated allergic manifestations were reported in 148/1209 (12.2%) of the whole cohort: 77/298

(25.8%) of the wheezers and 71/911 (7.8%) of the non-wheezers. Allergic rhinitis was the most predominant feature of allergy in 112/1209 (9.3%) (figure 1).

Episodes of preschool wheezes were frequently recurrent (> 6 times per year) in 40.3% of patients, and less frequent (3-6 episodes/year) in 53% of participants. Two hundred and twenty-three episodes did not necessitate hospital admission (74.8%) while 75 (25.2%) required hospital admission.

Concerning the suspected triggers of preschool wheeze, viral infections were reported in 39.3% (episodic viral wheeze, EVW) of preschool wheezers, seasonal variation in winter and spring in 6%, aeroallergen exposure in 2.7%, and multi-trigger wheeze (MTW) in 50% (table 2).

Sociodemographic data and exposures among the preschool wheezers are described in tables 3 and 4.

Evaluation of specific IgE in prolonged early, persistent, and late onset wheezers (n=172):

This was performed via skin prick test (SPT) in 148/172 of the prolonged early wheezers, persistent and late onset wheezers, and showed that 123/148 (83.1%) of those tested had positive results and thus were considered atopic. Table 6 and figure 2.

Wheezers at time of enrollment (asthmatic patients) (n=125):

Patients with persistent wheezes at time of enrollment, whether they were late-onset wheezers or persistent early onset wheezers, were considered asthmatic. These were 125 children (10.3% of all the participants). Of these, 84 (67.2%) children had mild asthma, 33 (26.4%) had moderate, and 8 (6.4%) had severe asthma. As for asthma control, 32 (25.6%) were well controlled, 57 (45.6%) were partially controlled and 36 (28.8%) were uncontrolled. According to GINA stepwise approach of treatment, 77 (61.6%) were on step 1 treatment (as needed short acting B2 agonists), 39 (31.2%) were on step 2 (daily low dose ICS), and 9 (7.2%) were on step 3 treatment (medium dose ICS or low dose ICS-LABA) (table 5). None of the enrolled patients was on biological treatment or allergen immunotherapy.

Evaluation of PFTs was attempted in the 125 asthmatic patients but was successfully performed in 76 only (60.8%), since 39 patients (31.2%) refused, and 10 (8%) failed to do the maneuver. The results showed an obstructive pattern in 32/76 (42.1%) patients, a restrictive pattern in 10, (13.2%) and a normal pattern in 34 (44.7%).

Table 1. Classification of preschool wheezing phenotypes among participants (n=1209)

Variable		Number	%
Preschool wheezes	Negative	911	75.4%
	Positive	298	24.6%
Phenotypes	Never wheezers	911	75.4%
	Transient wheezers	126	10.4%
	Prolonged early wheezers	47	3.9%
	Late-onset wheezers	39	3.2%
	Persistent early onset wheezers	86	7.1%

Table 2. Triggers of preschool wheezing episodes (n=298)

Variable		Number	%
Suspected triggers	Viral infection	117	39.3%
	Aeroallergens	8	2.7%
	Food allergens	0	0.0%
	Seasonal variation	18	6.0%
	Exercise	2	0.7%
	Multiple triggers	149	50.0%
	Unidentified	4	1.3%

Table 3. Sociodemographic data of preschool wheezers (n=298)

Variable	Wheezers (n=298)		
	Mean	SD	
BMI (kg/m ²)	15.9	2.2	
Crowding index	2.11	0.56	
Variable	N	%	
Sex	Male	165	55.4%
	Female	133	44.6%
Consanguinity	78	26.2%	
Residence	Rural	30	10.1%
	Suburban	74	24.8%
	Urban	194	65.1%

Table 4. Antenatal and Infantile risk factors among preschool wheezers (n=298)

Variable	Wheezers (n=298)		
	n	%	
Feeding in 1 st 4 to 6 months	<i>Exclusively breast fed</i>	206	69.1%
	<i>Mixed</i>	45	15.1%
	<i>Formula</i>	47	15.8%
Age day care attendance started	<i><6 months</i>	6	2.0%
	<i>6 months - <1 year</i>	12	4.0%
	<i>1 - <2 years</i>	48	16.1%
	<i>2 - <4 years</i>	141	47.3%
	<i>≥4 years</i>	3	1.0%
	<i>Never attended day care</i>	88	29.5%
Parental allergy	<i>Allergy of any type</i>	97	32.6%
	<i>Maternal BA</i>	26	8.7%
	<i>Paternal BA</i>	30	10.1%
	<i>Both maternal and paternal BA</i>	4%	1.34%
	<i>Allergic rhinitis</i>	34	11.4%
	<i>Food allergy</i>	5	1.7%
	<i>Atopic dermatitis</i>	2	0.7%
	<i>Exposure to fumes</i>	120	40.4%
<i>Exposure to pets</i>	77	25.8%	
<i>Exposure to passive smoking</i>	152	51.2%	
<i>Supplementary vitamin D during pregnancy</i>	140	47.0%	
<i>Cesarean delivery</i>	153	51.3%	
<i>MV in neonatal period</i>	44	14.8%	
<i>Supplementary vitamin D during infancy</i>	158	53.0%	

MV: Mechanical ventilation

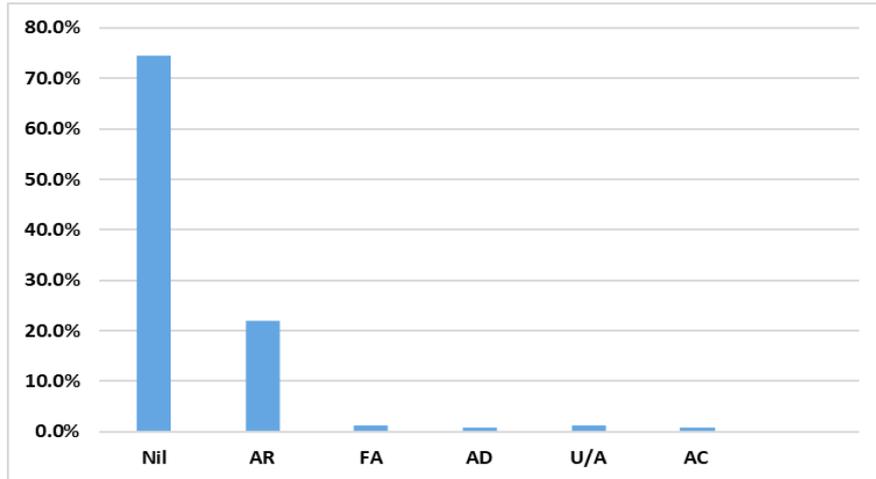


Figure 1. Allergic manifestations among patients with history of preschool wheeze (n=298)
 AC: allergic conjunctivitis; AD: atopic dermatitis; AR: allergic rhinitis; FA: food allergy; U/a: urticaria angioedema

Table 5. Asthma characteristics among the asthmatic group (n=125)

Variable		Number	%
Asthma severity	Mild	84	67.2%
	Moderate	33	26.4%
	Severe	8	6.4%
Asthma control	Uncontrolled	36	28.8%
	Partially controlled	57	45.6%
	Well controlled	32	25.6%
Asthma treatment according to GINA, 2019	Step 1	77	61.6%
	Step 2	39	31.2%
	Step 3	9	7.2%

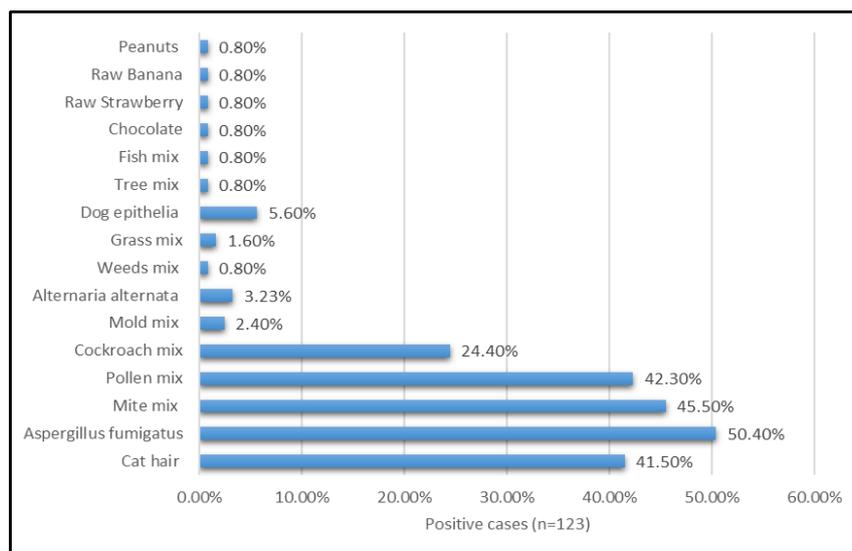


Figure 2. Distribution of sensitization to different allergens according to skin prick test results (n=148)

DISCUSSION

Appropriate identification or classification of PSW for the purpose of clinical assessment, therapeutic strategy, and preventative care is a primary unmet need.¹⁷ We observed a frequency rate of PSW of 24.6% in our cohort (298/1209). In a large UK population-based cohort, analysis of data obtained from primary and secondary medical records of children at the ages of 1-5 years revealed a prevalence of preschool wheeze in 7.7 % in 2017.¹⁸ This is while a cross-sectional analysis of the data from the International Study of Asthma and Allergies in Childhood (ISAAC)-modified self-administered questionnaire of parents of 4-month-old infants in Nagoya City, Japan, at well child visits, revealed that 7.6% infants experienced wheeze at least once within 4 months of age, with 1.3 % requiring hospitalization.¹⁹ The higher prevalence in our study might be related to racial factors, different age ranges of the studied population, and different approaches of data collection (prospective versus retrospective from patients' medical records or via recall as in our study, not to mention the impact of restrictions imposed by the COVID-19 pandemic.

Phenotypes of PSW were determined according to the onset and persistence of wheezes. Transient wheezes were detected in 10.4%, prolonged early wheezes in 3.9%, late onset wheezes in 3.2% and persistent early onset wheezes in 7.1%. On reviewing the international reports, Rusconi and colleagues reported a frequency rate of PSW of 17.2% in retrospective analysis of a study population composed of 16,333 children aged between 6 and 7 years. Transient early wheezers represented 7.5%, persistent wheezers represented 4.1% and late-onset wheezers were 5.6% of participants.²⁰ Although the frequency rate of PSW in their series is lower than ours, distribution of phenotypes is almost comparable, taking in consideration the 20 years difference between the 2 studies, and the different ethnic, climate and environmental factors.

Another retrospective cohort study conducted on 3,739 Spanish children aged 6 years, revealed incidence rate of PSW of 34.4%, distributed as follows: 18.3% as transient wheezers, 6.6% persistent wheezers and 9.7% late onset wheezers.²¹ On the other hand, a longitudinal birth cohort study was conducted on 6265 children since birth till the age of 7 years. PSW was elicited in 40.6% of the children, phenotypical distribution was as follows: 16.3% were transient early wheezers, 8.9% had prolonged early wheezes, 6% had late onset

wheezes and 6.9% had persistent wheezes. Children who experienced wheezes after the age of 18 months were referred to as intermediate wheezers, and they represented 2.7% of their participants.¹⁶

MTW and EVW, were evident in our study, recorded in 50.0% and 39.3% respectively. In the study of *Shultz et al*,²² 34.9% were classified as episodic EVW and 65.1% as MTW as determined by retrospective parental report at the start of the study.

In the study of *Tualzik and Chandrasekaran*,²³ EVW was seen in 55% and MTW in 45% of their studied patients. However, it was troublesome in many studies, as well as ours, to determine the actual trigger of PSW due to large overlap, and the retrospective nature of the study counting on the parent/caregiver recall of the events.²⁴⁻²⁷ It was observed that the proportion with EVW decrease, and the proportion with MTW increase with age.²⁸ Virus induced wheeze is considered the most common risk-based phenotype in the age group between 1 and 5 years of age.¹²

Associated allergies, particularly allergic rhinitis and conjunctivitis were significantly more frequent in children with PSW. This agreed with the results of other studies.²⁹⁻³¹ In general, sensitization to either food or airborne triggers was assumed to be associated with recurrent PSW through the T helper 2 mediated inflammatory response;^{2,32} and this is a logic explanation to the reported findings in many studies as well as in ours.

The majority of asthmatic children at enrollment had mild episodes of asthma (67.2%), followed by those who experience moderate (33%) or severe (6.4%) asthma. Asthma control at enrollment varied among patients, 25.6% were well controlled, 45.6% were partially controlled, and 28.8% were suffering from uncontrolled asthma, based on GINA 2019 guided evaluation

Among the 76 with successful pulmonary function testing, 10 had restrictive pattern. Those patients will require further evaluation and close follow-up to investigate the actual underlying illness, while the rest with normal/obstructive pattern will be followed up as asthmatic patients and their treatment will be adjusted for the partial controlled/uncontrolled cases.

From our retrospective study on a cohort of 2109 children, we conclude that PSW frequency mounts up to 24.6% of preschool children. We identified transient wheezers in (10.4%), prolonged early wheezers in (3.9%), late onset wheezers in (3.2%) and persistent early onset wheezers in (7.1%) relevant to the whole cohort.

The main limitation of our study is its retrospective nature which was adopted for several reasons: the time limit to perform the study, the fear of non-compliance of patients to follow up visits, had it been a prolonged retrospective one, the difficulty in reaching out to children, in addition to the restrictions imposed by the COVID-19 pandemic. We had to rely on history recalled by the parents/caregivers of patients presenting to the outpatients' clinics rather than population based electronic medical records which are not yet available in our health system setting., making our study population not the ideal representative of the same age group in the general population.

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