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Predictors of persistent asthma among preschooler wheezers: a retrospective case series study

Hager Barakizou^{1*}

Abstract

Background Early childhood wheezing can evolve to different asthma phenotypes. Prediction of persistent asthma during the preschool years has proven challenging. Through this study, we aimed to identify predictors of persistent asthma in preschooler wheezers.

Methods This was a retrospective case series study over 10 years. Patient data from 98 infants diagnosed with infantile asthma were obtained from their medical records. A multivariate logistic regression model was developed to determine predictors of persistent asthma in preschooler wheezers.

Results The sex ratio was 1.72. The mean age at the first episode of wheezing was 7 ± 3.17 months. The mean age at diagnosis was 14.82 ± 4.28 . Asthma was well controlled in 71 cases (72.44%) and partly controlled in 27 cases (27.56%). Two groups were identified: transient wheezers (61.33%) and persistent wheezers beyond the age of 5 years old (38.77%). The average age for wheezing disappearance was 24.28 ± 4.1 months.

Four predictive factors for persistent asthma were identified: familial atopy (adjusted odds ratio [OR] 4.76; 95% confidence interval [CI] 2.52–12.45; p < 0.001), passive smoking (adjusted OR 5.98; 95% CI 2.48–13.64; p < 0.001), poor control of asthma (adjusted OR 5.23; 95% CI 2.47–14.76; p 0.0013), and aerosensitization (adjusted OR 7.38; 95%CI 3.87–17.84; p < 0.001).

Conclusions The main predictors for persistent asthma among preschooler wheezers were aerosensitization, family history of atopy, early exposure to passive smoking, and poor control of asthma. The detection of such factors allows for earlier diagnosis and targeted prevention strategies.

Keywords Allergens, Asthma, Preschoolers, Predictors

Background

Prevalence of asthma is in perpetual progress with an average cumulative value of about 10% [1]. This disease appears before the age of 5 years in 75% of cases and more than half asthmatic children are symptomatic during the first 2 years of life [2].

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Infantile asthma constitues a particular entity. Its definition and diagnosis are the subject of controversy, due to reasons such as the difficulty of performing objective pulmonary function tests or the high frequency with which the symptoms subside in the course of childhood. Used definitions and medical approaches can vary greatly among different guidelines or studies [1–5]. One of the most accepted definition in our country is the one proposed by the French High authority of Health as any infant, aged less 36 months, with three or more episodes of wheezing, regardless of the age of onset, stigmas of atopy and precipitating causes [2]. Early childhood



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wheezing can evolve to different asthma phenotypes. Two groups can be mainly individualized: transient wheezers and persistent wheezers [6, 7]. Many children present symptoms consistent with asthma in the first years of life, and the course of the disorder over the subsequent years is highly variable, making it difficult to predict persistence or remission with sufficient reliability. Few studies related to the course of infantile asthma had been conducted in in middle and low-income countries. To help filling this knowledge gap, we conducted the present study.

Methods

A retrospective case series study was conducted at the pediatrics department of the Military Hospital of Tunis, Tunisia over a period of 10 years [2013–2022].

Sample selection Inclusion criteria

- Children of both genders aged 5 years.
- Patients with a prior diagnosis of infantile asthma according to the French High Authority for Health definition [2].

Non-inclusion criteria

- Patients with other diagnosis of wheezing other than infantile asthma
- History of prematurity, neonatal respiratory distress, chronic lung disease, congenital cardiopathy
- Patients with comorbidities type obesity, gastroesophageal reflux, adenoid and tonsil hypertrophy

Data collection and definitions

Medical records of children classified "Infantile asthma", "recurrent wheezers", "hyperreactive airway disease" were extracted from the archive data base of the pediatrics department.

One hundred six medical records were extracted. Epidemiological, clinical, paraclinical and therapeutic features were collected and analyzed. An episode of wheezing during the two first years of life was retained if meeting one or more of the following criteria: physiciandiagnosed wheezing at an office visit or per admission in the pediatric department, an illness given the specific diagnosis of bronchiolitis or asthma exacerbation.

Ninety-eight infantile asthma cases responded to the French High Authority for Health (HAS, 2009) definition were included in the study (Fig. 1). Two groups were identified. Group 1 (G1 = persistent wheezers) was

defined as children who still have, by the age of 5 years, respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity. Group 2 (G2=transient wheezers) was defined as those who were, by the age of 5 years, symptoms free at least since 1 year.

Asthma was classified as intermittent, mild persistent, moderate persistent and severe persistent. This classification is based on the type of medication needed to control asthma. These different stages of asthma corresponded respectively to stages 1, 2, 3, and 4 of the treatment of asthmatic children aged 5 and under according to the GINA 2022 recommendations [4].

We adopted the Pediatric Respiratory Assessment Measure (PRAM) for grading asthma exacerbation severity (mild asthma exacerbation = score 0-3, moderate asthma exacerbation = score 4-7, severe asthma exacerbation = score 7-12) [8]. We adopted the GINA 2022 criteria for assessment of asthma control in children 5 years and younger [4].

Tunisia is a lower-middle income country according to World Bank Data [9]. Socioeconomic level was evaluated based on average household income per month. It was considered low if the average household income per month was under 180 USD. It was considerate middle or high if at least one of the parents respectively earns monthly between 180 and 550 USD or more than 550 USD.

Statistical analysis

Odd ratios (OR) and 95% confidence intervals (CI) were estimated. The chi-square test and Fisher's exact test were used for the comparison of categorical data between the two groups. Statistical significance was identified with a p value < 0.05. A logistic regression analysis was used to evaluate independent risk factors of persistent wheezing. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 21.

Ethical considerations

Ethical considerations in this paper were carried out.

Results

Characteristics of the population of study

We gathered 98 cases of infantile asthma. Main sociodemographic and environmental characteristics are summarized up in Table 1.

A familial atopy was noted in 51.02% of cases (Table 2) with a first-degree relative in 70% dominated by maternal atopy (48%). The newborns were breastfed in 71 cases (72.44%) with a medium length of 6.2 ± 1.3 months. The proteins of cow's milk were introduced in the first 2 months of life into 41 cases (41.83%). Only 19 newborns

Extraction of medical records (MR) from the archive data base



Fig. 1 Flowchart of patient inclusion

Table 1	Socio-demographic	and	environmental	characteristics
of study	participants			

	n (%)
Gender	
Male	62 (63.26)
Female	36 (36.74)
Consanguinity	
Yes	40 (40.81)
No	58 (59.19)
Socio-economic level	
Low	15 (15.3)
Medium	73 (74.4)
High	10 (10.2)
Humidity	38 (38.7)
Passive smoking	44 (44.89)
Pets	29 (29.59)

 Table 2
 Familial atopy manifestations in study participants

Familial atopy type	n (%)
Allergic asthma	27 (27.55)
Allergic rhinitis	15 (15.3)
Allergic conjonctivitis	5 (5.1)
Atopic dermatitis	3 (3.06)
Total	50 (51.02)

were exclusively breastfed until the age of 6 months. Personal atopic dermatitis was noted in three cases.

The mean age at the first episode of wheezing was 7 ± 3.17 months (extremes 3–11 months). The age at the third episode of wheezing was 14.82 ± 4.28 months (extremes 6–20 months). Asthma was classified as intermittent, mild persistent and moderate persistent respectively in 32 cases (32.65%), 50 cases (51.02%), and 16 cases (16.32%). Asthma was well controlled in 71 cases

(72.44%) and partly controlled in 27 cases (27.56%). Worsening during the cold season was noted in 66 cases (67.34%). During the fourth year of live, 26 children (26.5%) had two asthma attacks or more with a PRAM score more than 8 in 6 of them.

Prick tests (PT) were done by allergists and used extracts from *Stallergenes* Laboratory. These tests were positive in 57 cases (58.16%). PT were done at a mean age of 29.7 months (extremes 18 months–4.1 years). The frequency of aerosensitization and food sensitization was respectively of 53.06 and 5.1%. The sensitization to house dust mites came at the first rank of aerosensitization (75%) followed by dog hair (11.5%) and cat hair (5.7%). A multiple sensitization was noted in four cases.

Respiratory outcome

The medical follow-up reported in patient records was mainly of 4.58 ± 1.72 years. The transient wheezers counted for 61.23% and the persistent wheezers for 38.77%. The medium age at disappearance of wheezing was 24.28 ± 4.1 months (extremes 15-39.5 months). In persistent wheezers, asthma was moderate persistent, mild persistent, and intermittent respectively in 68.36%, 20.4%, and 10.2% of cases. Asthma was partly controlled in 81.57% of all persistent wheezers.

Eleven factors were identified as associated with a risk of asthma in preschoolers (Table 3).

Through the multivariate logistic regression analyses four predictive factors for persistent asthma were identified: familial atopy (adjusted odds ratio [OR] 4.76; 95%

Discussion

Infantile asthma constitutes a particular entity. Its definition is not consensual and one of the principal issues is the prediction of the respiratory outcome in such infants. Many children identified before the age of five as having asthma had symptom remission, making it difficult to identify those whose symptoms will linger [1, 2, 5].

Few studies have been conducted on this topic in low and middle income countries. Our study identified factors associated with persistent asthma, then our findings were compared to those of previous studies conducted in developed countries. Among the 98 children enrolled in our study, two groups were individualized: transient wheezers (61.33%) and persistent wheezers beyond the age of 5 years old (38.77%). Their asthma was well controlled and partly controlled respectively in 72.44% and 27.56%.

Four predictive factors for persistent asthma were identified: familial atopy (adjusted odds ratio [OR] 4.76; 95% confidence interval [CI], 2.52–12.45; p < 0.001), passive smoking (adjusted OR 5.98; 95% CI 2.48–13.64; p < 0.001), poor control of asthma (adjusted OR 5.23; 95% CI 2.47–14.76; p 0.0013), and aerosensitization (adjusted OR 7.38; 95%CI 3.87–17.84; p < 0.001).

Table 3 Risk factors for persistence of wheezing in preschoolers

	Persistent wheezers	Transient wheezers	p	OR [95% CI]
Consanguinity	15(37.5%)	25(62.5%)	0.82	_
Male gender	24 (38.7%)	38 (61.3%)	0.98	-
Familial atopy	29 (58%)	21 (42%)	0.0018	4.44 [1.74–11.33]
Maternal atopy	15 (62.5%)	9 (37.5%)	0.0077	3.69 [1.41–9.67]
Familial allergic asthma	17(65.51%)	10 (34.49%)	0.0018	4.58 [1.76–11.91]
Familial allergic rhinitis	11 (73.33%)	4 (26.66%)	0.0028	6.46 [1.9–21.96]
Passive smoking	26 (59.1%)	18(40.9%)	< 0.001	5.05 [2.09–12.17]
Non-exclusive breastfeeding during the first 6 months of life	37 (%)	42 (%)	0.82	-
Proteins of cow's milk before 2 months old	22 (53.65%)	19 (46.35%)	0.033	2.47 [1.07–5.69]
Age at the 1st episode < 6 months	18 (58.06%)	13 (41.94%)	0.009	3.25 [1.34–7.88]
Two asthma attacks or more with a PRAM score more than 8 during the 4th year of live	5 (83.3%)	1(16.7%)	0.031	3.25 [0.92–428.77]
Moderate persistent asthma	10 (62.5%)	6 (37.5%)	0.039	3.21 [1.05–9.75]
Partly controlled asthma	18 (66.66%)	9 (33.33%)	0.019	5.1 [1.96–13.22]
Inhaled corticosteroids during the first 3 years of life	37 (38.94%)	58 (61.06%)	0.196	-
Aero sensitization	31 (65.3%)	21 (34.7%)	< 0.001	6.11 [2.26–16.52]
Food sensitization	2 (40%)	3 (60%)	0.95	-

Exclusive breastfeeding until 6 months of age was noted in 19.38%. Neither the nonexclusive nature of breastfeeding nor the early introduction of cow's milk protein was retained in the multivariate analysis as predictive factors for the persistence of infantile asthma.

The Tucson study individualized four groups of different outcomes (group of precocious and transient wheezers (19.9%), group of precocious and persistent wheezers (13.7%), group of late wheezers (15%), and group of nonwheezers (51.4%). Among infants who had at least an episode of wheezing before 3 years old; 40% remained symptomatic at the age of 6 years. The persistent wheezers belonged to the group of atopic with a positive PT [6, 10].

Other epidemiological studies brought comparable information: Maltret, Delacourt, and Boussetta found a rate of persistent wheezers respectively of 30%, 37%, and 42.8% [11-13]. We found a similar rate of 38.77%.

Through these studies different factors were analyzed to predict the respiratory outcome [14]. The consanguinity does not constitute itself a predictive factor of persistent wheezing apart from familial atopy [15, 16]. In our study, consanguinity was noted in 40.81% of cases. It was not associated with persistent wheezing (p = 0.82).

The male gender, admitted by several authors as predisposing to atopy and asthma, does not seem to influence the respiratory outcome of asthmatic infants [17–19]. We did not find a significant link between male gender and persistent wheezing in preschoolers (p=0.98).

Familial atopy constitutes one of the main predictive factors for respiratory outcome. Maltret et al. found that 67.4% children with familial atopy continue to wheeze against only 17.1% of those who have no such family medical history [11]. Our results were similar; such infants belonged to the group of persistent wheezers in 58% of cases. Moreover, we found that familial atopy in relatives to the 1st degree was significantly and independently associated with persistence of respiratory symptoms in preschoolers (adjusted odds ratio [OR] 4.76; 95% confidence interval [CI] 2.52–12.45; p < 0.001).

Boussetta et al. find that infants with atopic mothers have 2.7 times more risk to keep wheezing at the preschool age. The paternal atopy does not influence, according to the same authors the respiratory outcome [13]. In our study, children had 3.6 times more risk to remain symptomatic in case of maternal atopy and no more risk in case of paternal atopy. However, this factor was not retained as an independent predictor of wheezing in preschoolers through multivariate analysis.

Maternal asthma constitutes, according to Boussetta and Martinez, a predictor of respiratory outcome [13, 20]. Concerning allergic rhinitis, the authors are not unanimous. Boussetta [13] and Martinez [20] do not keep it as a risk factor contrary to Maltret who establishes a significant relationship between maternal allergic rhinitis and persistent wheezing in preschoolers [11]. These differences can be explained by the heterogeneity of the population studies and by the heterogeneity of the diagnostic criteria of allergic rhinitis. In our study infants with familial allergic rhinitis belonged to the group persistent wheezers in 73.33% of cases but this factor was not kept as an independent predictor of wheezing in preschoolers.

Several studies conclude to the absence of preventive effect of the breast-feeding on allergy and even, for some, in its noxious effect. When a preventive effect is shown, it concerns only the non-allergic asthma [21, 22]. In our study, a non-exclusive breastfeeding during the first 6 months of life was not a risk factor for persistent wheezing (p=0.82). The precocious introduction of CMP was neither kept as an independent predictor of bad respiratory outcome.

Progressive atopic dermatitis is commonly admitted as a factor of persistence of wheezing [18, 23]. We had not established such correlation because of the few numbers of infants with atopic dermatitis enrolled in the study.

An early age at the first episode of wheezing is significantly linked to the persistence of respiratory symptoms. The age threshold remains however variable. It is 6 months for Wennergren [24], 7 months for Bousseta [13], and 12 months for Korppi [19]. In our study, wheezing before the age of 6 months was significantly associated with persistence of symptoms in preschoolers.

The poor control of asthma constitutes according to most authors a predictor of bad respiratory outcome [1, 13, 24]. Our results were similar, poor control of asthma was related to persistent symptoms (adjusted OR 5.23; 95% CI 2.47–14.76; p 0.0013).

Several studies established a link between precocious allergic sensitization specially towards pneumallergens and persistence of wheezing [24–26] with 7 times more risk according to Boussetta et al. [13]. Our results were concordant with those of these authors.

The Saudi Initiative for Asthma panel recommends for early identification of the risk for persistent asthma among preschool children, to use the modified asthma predictive index (modified API). This tool when used for children with a history of ≥ 4 wheezing attacks (at least one is diagnosed by physician) and either one major (parental physician-diagnosed asthma, physician-diagnosed atopic dermatitis, allergic sensitization to at least one aeroallergen) or two minor criteria (wheezing unrelated to colds, eosinophils $\geq 4\%$ in circulation, allergic sensitization to milk, egg, or peanuts) at 3 years of age, predicts a 4–tenfold increase in the risk of having asthma later in their childhood. On the other side, children with negative modified-API will have 95% chance of outgrowing their asthma later life [3].

Conclusions

In conclusion, we have demonstrated that four factors (aerosensitization, family history of atopy, early exposure to passive smoking, and poor control of the disease) increase probability of future asthma in preschoolers. This study conducted among a Tunisian pediatric sample may have some limitations: its retrospective design, the small numbers of included patients and the high consanguinity rate. It should be completed by a prospective and a multicenter national study to investigate specific epidemiological, environmental, and evolutive features of infantile asthma in our country. However, it was in accordance with the main international studies and with most of the predictive criteria used in the modified-API. Finally, our findings may help clinicians easily identify high risk children, allowing thus for earlier diagnosis and targeted therapeutic strategies.

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Author's contributions

Barakizou H: conception of the study, writing the manuscript. The author read and approved the final manuscript.

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Availability of data and materials

Available under reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares no competing interests.

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