

Original article

Evaluation of Risk Factors for Recurrent Wheezing Episodes in Children After 3 Months of Age

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Abstract

Recurrent wheezing is a common clinical problem in children and a common cause of emergency department visits and hospitalization. The aim of this study was to investigate the characteristics and risk factors of recurrent wheezing in children admitted to Misurata medical center. A cross-sectional study was conducted on 115 patients older than 3 months admitted to the pediatric department in Misurata medical center who presented with recurrent attacks of wheezing during 1 year period from 1/1/2022 to 31/12/2022. The study included 115 patients, of those, 71 (62%) males and 44 (38%) females. The average age of was 2 years (SD 2.7 years). The first attack of asthma occurred at the age of 6 months in most cases (58%). URTI was the most common risk factor (80%), followed by a family history of bronchial asthma (60%), introduction of cow's milk before 3 months (60%), and family history of allergic rhinitis (55.6%). While allergy to cow's milk was the least frequent risk factor (6.95%). The most significant risk factors for recurrent wheezing episodes in children are wheezing at a younger age (early-life factor), male sex, a history of URTI particularly during the first 3 months of life, is a major risk factor, family history of atopy and cow's milk introduction before 3 months.

Keywords. Congenital Epulis, Granular Cell Tumor, GCT, Mouth Tumors.

Introduction

Wheezing is a high-pitched whistling sound that is caused by air passing through constricted or narrowed airways, [1] or so-called bronchospasm which is the most common cause of wheezing [2]. Bronchospasm can be made worse by inflammation of the small and medium airways, which results in edema and more airway narrowing [2]. In newborns and early toddlers, respiratory virus infections are typically the cause of an acute wheezing episode; however, allergies or inhaled irritants (such as tobacco smoke) can also cause (or exacerbate) airway inflammation. Allergies, asthma, or recurrent viral respiratory infections can all lead to wheezing. Chronic dysphagia leading to recurrent aspiration, gastric reflux, airway malacia, a retained aspirated foreign body, or heart failure are less prevalent reasons of recurrent wheeze. Recurrent wheeze frequently may have an unknown etiology [2,3].

In developed as well as developing countries, wheezing problems are the primary cause of ER visits and hospital stays during the first few years of life, which has a significant financial impact. [4] According to reports from the past decade, between 33% and 50% of children have experienced wheezing at least once before turning three years old, with 20% experiencing it frequently [5]. According to another study, the majority of children with asthma (over 85%) developed their asthma before the age of three, and the majority of these children's lung function impairments happened during preschool [6]. Additionally, the researchers reported that 60% of children had wheezing by the time they were six years old, and that at least 40% of the toddlers who had wheezing before the age of three still experienced episodes by then. Simultaneously, preschoolers experiencing wheezing episodes had a 50% rise in outpatient visits, a two-fold increase in emergency visits, and a three-fold increase in hospitalization rates when compared to other typical children [7].

Many prospective studies have linked a number of risk factors of early wheezing in children with the subsequent development of asthma, including a family history of allergies, [8] a personal history of rhinitis or eczema, [9-10] Viral respiratory infections caused by the rhinovirus or respiratory syncytial virus (RSV), [11] maternal smoking with pregnancy or passive exposure following delivery, [12] male gender [9] and daycare attendance [13].

Also, throughout infancy, frequent use of drugs like paracetamol and antibiotics has been linked to the development of asthma [14].

Additionally, children whose first symptoms of asthma are recurring wheezing episodes will continue to wheeze throughout later childhood or adolescence. Whereas other children, whose wheezing fits end by the time they are 6 to 10 years old, are not considered asthmatic [2,3].

This research is warranted due to the high incidence and prevalence of wheezing in infants, which can have detrimental effects on both the family and the child. Additionally, recurrent wheezing in asthmatic children can indicate a more advanced stage of the child's development, making it a public health concern that necessitates a thorough investigation of its risk factors. Thus, we set out to identify the variables related to personal allergies or allergies related to family history that is associated with increased risk of wheezing in children until 6 years' old.

Methods

Study design and setting

A retrospective cross-sectional design was used. This study was conducted in the pediatrics department at Misurata Medical Center during a 3 months' period from August until November 2023. The study reviewed the medical records of the pediatric patients with wheezy chest from January-2022 until December-2022.

Patients

The records of 115 pediatric patients aged 3 months and older who presented with recurrent attacks of wheezy chest and admitted with it were analyzed retrospectively.

Variables

The study included basic demographic data (sex and age), as well as the medical history specific to lower respiratory symptoms (age at diagnosis, and the age at the first wheezy chest attack) and the general history of fever, number of out-patient treatments or admissions prior to the last admission. Risk factors were also included in the study as follows: Indoor smoking, animal contact, personal and family history of atopy, and early introduction to cow milk (at the age of 3 months).

Statistical analysis

The open-source software for statistical analysis, Jamovi version 2.4.14 for windows was used to perform the basic statistical measure of frequency, central tendency, and dispersion. The software was also used to perform the tests of logistic regression, t-tests, and ANOVA tests for the difference in means between numeric variables, and chi-square tests, OR, and likelihood ratio for categorical variables. The association was considered significant at ($p < 0.05$).

Ethical considerations

The research was conducted with the permission of the Committee of Scientific Affairs at Misurata's Medical Center.

Results

The study included 115 patients, of those, 71 (62%) males and 44 (38%) females. The average age of was 2 years (SD 2.7 years). The majority of cases were younger than 3 years 80 case Table 1 with only two cases having a late onset asthma i.e., asthma onset at an age older than 6 years. persistent asthma was reported in 24 patients (20%) of the cases.

The first attack of asthma occurred at the age of 6 months in most cases (58%) Table 2.

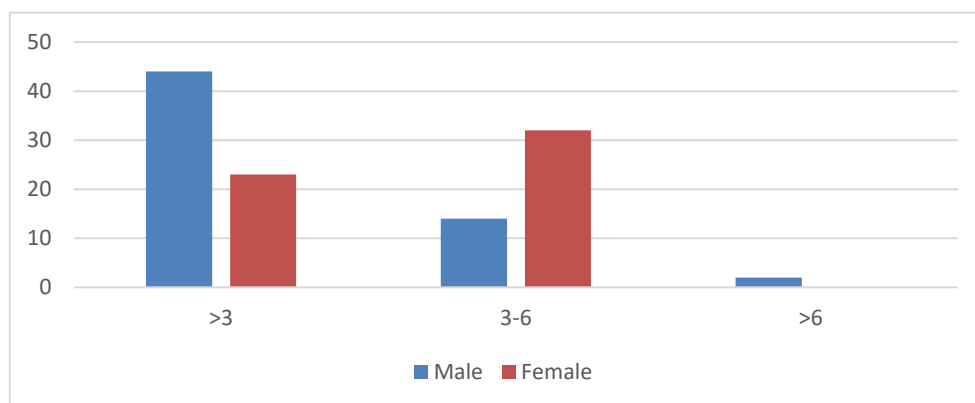
Table 1 Age distribution

Age group	No. of patients	Percentage
<3 years	80	69.5%
3-6 years	24	20.8%
>6 years	11	9.56%

Table 2. Treatment method used according to age

Treatment method	<3	3 – 6	>6
Bronchodilators through Nebulization	64	29	16
Bronchodilators through inhalers	0	2	5
Oral bronchodilators	0	0	0

There difference in age of onset was not significantly different between males or females ($p < 0.654$) (Figure 1).

**Figure 1. Age at the Time of the First Attack of Asthma**

More cases already had fever at the time of admission 89 cases (77%) while only 25 had fever after admission. Most patients have received a form of outpatient treatment for asthmatic attacks 99 patients, while 16 patients have received no previous treatment. The median duration of the outpatient treatment was 3 days. Nebulization with steroids and bronchodilators was used to treat 94% of the patients followed by salbutamol inhaler (Ventolin®) 5.2%, no use of oral bronchodilators or steroids was documented (Table 2).

The risk factors investigated in the study were split according to the age group. An upper respiratory infection was the most common risk factor found in the studied population (80%) while allergy to cow's milk was the least frequent risk factor, only in 8 patients (6.95%) (Table 3).

Table 3. The Distribution of Immunological Condition in Each Age Group

Risk factor	<3 years	3-6 years	>6 years	Total
Personal dermatitis	9 (7.8%)	1 (0.9%)	2 (1.74%)	12 (10.4%)
Personal allergic rhinitis	4 (3.48%)	3 (2.6%)	3 (2.6%)	10 (8.7%)
Personal cow's milk protein allergy	8 (6.95%)	0	0	8 (6.95%)
Family history of dermatitis	17 (14.9%)	4 (3.48%)	5 (4.35%)	26 (22.6%)
Family history of Bronchial asthma	53 (46%)	9 (7.8%)	7 (6.1%)	69 (60%)
Family history of allergic rhinitis	46 (40%)	12 (10.4%)	6 (5.2%)	64 (55.6%)
Indoor smoking	19 (16.5%)	7 (6.1%)	3 (2.6%)	29 (25.2%)
Upper respiratory tract infection	69 (60%)	16 (13.9%)	7 (6.1%)	92 (80%)
Cow's milk introduction <3 months	52 (45.2%)	11 (9.6%)	6 (5.2%)	69 (60%)
Animal contact	12 (10.4%)	7 (6.1%)	3 (2.6%)	22 (19.1%)

Discussion

About one-third of school-age children get recurrent wheezing chest episodes throughout their first five years of life, a condition that has a considerable morbidity. Wheezing in early children has been linked to a lower quality of life [15]. Our study looked into different risk

factors associated with recurrent wheezy chest episodes in children visiting Misurata medical center. Following are the most significant risk factors:

Wheezing at younger age (early-life factor)

Patients who initially encounter wheezing at a young age are more likely to endure recurrent wheezing episodes. 58% of our cases already had their first attack by the age of 6 months, the majority of cases were younger than 3 years. According to Moreno-Galdó et al [16], wheeze rates peak in the first two years of life and thereafter decrease, which is consistent with our study. Other studies also found that patients younger than six months and those between six and twelve months had the highest rate of recurrent wheezing, 45.8% and 28.6%, respectively [17]. This association is due to the immaturity of the innate and adaptive immunity [18].

Male gender

Males were predominant in our study. Males were more likely to have recurrent wheezy chest in other studies too [17, 19-23] including Libya [24]. This is explained by the fact that compared to girls, boys have higher serum IgE levels and allergic inflammation [25-26]. In addition, boys are more prone to wheezy chest due to dysanapsis which means smaller airway widths in relation to lung volumes [27]. Therefore, being male is a well-known risk factor in children, while the opposite is seen in adolescence [28], however, some studies did not find any significant difference between males and females [29].

Upper respiratory tract infection

Childhood wheezing is frequently brought on by upper and lower respiratory tract infections, especially those brought on by rhinoviruses and RSV. Although it is unclear how early infection affects the development of asthma later on [30], it has to do with how immature innate and adaptive immunity are [18]. The degree of anatomical and inflammatory involvement in the respiratory system increases with the early age at which infectious pathogens attack it. The immune response may promote the production of pro-inflammatory cytokines and the growth of T helper type 2 cells, depending on the infectious agent, which could aid in the development of asthma [31].

80% of our cases were affected with an URTI which makes it one of the major risk factors. According to a study which included 28,687 newborns from Latin American and European nations, one of the risk factors for sporadic and recurrent wheeze was the presence of URTI in the first three months of life [32]. Wheezing was shown to be highly likely among children who experienced common colds during the first three months of life, according to cohort research that examined 2,319 newborns up to the age of two [33].

Family history of atopy

According to reports, wheezing episodes are most likely to occur in the first 12 months of life in infants with a family history of asthma [34-35], allergic rhinitis, and allergic dermatitis [34]. This indicates that genetics is a significant risk factor for recurrent wheezing and the diagnosis with asthma later [21, 35].

Family history of bronchial asthma was associated with 60% of our cases. This was also an important risk factor seen in other studies. [20,23] and a major criterion in asthma predictive index suggested by Coastro-Rodriguez et al. [36] Also, according to published studies, the most significant factors influencing the occurrence of asthma in children between the ages of 3 and 11 are the family history of allergies and the individual's past history of asthma [37]. In line with the findings of this study, Sheikh et al. found that among individuals with asthma aged 1 to 20 years, 71.4% had a family history of the condition; higher rates from the mother [38]. There has also been evidence of a link between childhood asthma and the medical history of distant relatives, including grandparents [38-39], and children are more likely to develop asthma if there are more family members with the condition [39].

Family history of allergic rhinitis was significantly present in 55.6% of the cases. This is in line with Aranda et al. [40] which reported that family history was significantly associated with both occasional and recurrent wheezing.

Cow's milk introduction <3 months

60% of our cases were introduced to cow's milk before the age of 3 months. There is an ongoing debate about the relation between the introduction of cow's milk and the provoking or worsening asthma symptoms. Multiple studies correlate with our finding and found the positive relation between cow's milk and asthma to be well known and proved [41-42].

Additionally, a recent study by Darougar et al. [43] suggested that a diet that excludes cow's milk protein is a wise strategy for treating individuals with resistant asthma and may be the missing piece in the puzzle of asthma care as 82% of the cases showed a significant improvement when they started a cow's milk free diet. In 4–8% of children with asthma, there is a high likelihood that foods may cause respiratory symptoms, even though any correlation between an acute food allergy and isolated respiratory symptoms has been deemed unusual. According to this, sensitivity to egg, cow's milk, peanuts, soy, fish, shellfish, and tree nuts may be associated with an increased chance of developing asthma in later life [43].

This means that children who exhibit signs and symptoms of airway inflammation, which are expressed as childhood asthma, may also have a hidden food allergy. This allergy may play a role by means of an underlying, hidden allergic gastroesophageal reflux, which is a comorbidity of asthma. Through this mechanism, food may enter the airway, stimulating airway mast cells and triggering vagal stimulation, which lowers the airway reaction. Given that GERD is a very common condition, the signs and symptoms of airway reactivity in these patients are caused by extra-gastroesophageal (respiratory) GERD manifestations [43].

In contrary, a meta-analysis study by Yuan et al. (2021) [44], reviewed and summarized the evidence about the relationship between the early cow's milk and cow's milk formula introduction and the development of atopic diseases, these relationships were not shown to be significant. Some significant confounders may be responsible for the conflicting results. For instance, respiratory virus infections linked to breastfeeding length are also linked to the emergence of wheezing and asthma. In the majority of the included studies, the definitions of asthma and wheeze were unclear. It's challenging to determine which one was genuinely allergy-related. Furthermore, breastfeeding cessation may raise the risk of wheezing-causing respiratory viruses, which may not be related to allergies [44].

Indoor smoking was present as a risk factor in 25.2% only in our cases. In contrary, smoking exposure was seen as a significant risk factor in different other studies, [20,21,23,40], Moreover duration of wheezing episodes was positively correlated with the amount of passive smoking. [20] Additionally, according to research by Wang et al., [45], children with asthma who are exposed to secondhand smoke are twice as likely to be hospitalized, to have recurrent wheezy chest, and be admitted to emergency rooms as children with asthma who are not exposed to smoking. Furthermore, another meta-analysis study found that children and young adults who are exposed to tobacco smoking have a 20% times higher risk of wheezing problems and asthma [46].

Animal contact was not a significant risk factor and was present in 19.1% of our cases. Aranda et al., [40] and Wellyne Alves Lustosa et al [21] also reported a non-significant association between animal contact and wheezing episodes, except if the contact since the time of birth were the prevalence doubled. [21] In the other hand, other studies seem to find pets at home a protective factor against recurrent wheezy chest [47-48]. Bozaykut et al., [20] reported that only 15.7% of the infants with pets at home, who are included in their study, had recurrent episodes of wheezy chest and that the number and duration of the episodes was significantly lesser and shorter. Moreover, these infants acquired their first bronchiolitis at an older age than infants who don't have pets at home.

Conclusion

In conclusion, the most significant risk factors for recurrent wheezing episodes in children are wheezing at a younger age, male sex, a history of URTI particularly during the first 3 months of life, is a major risk factor, family history of atopy and cow's milk introduction before 3 months.

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