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Contents

A New Global Journal for Our Specialty

It gives me great pleasure to introduce to you our newly established *Journal* which will serve as the platform to disseminate the latest information from the basic research to the most up-to-date clinical practice in the field of pediatric respirology and critical care medicine. We aspire to become one of the best international journals in our discipline and the source of most trusted information for our clinical practice. Members of the Editorial Board recognize that there is an unmet need regarding the possible international journals for papers in our field. This journal is the joint efforts of the Asian Paediatric Pulmonology Society, Hong Kong Society of Paediatric Respirology and Allergy, and the Taiwan Society of Pediatric Pulmonology and Critical Care Medicine. Instead of publishing individual journal from each society, we believe our joint effort will result in a journal of higher quality attracting interesting and informative papers from around the world. Initially, there will be 4 issues per year. *Pediatric Respirology and Critical Care Medicine* accepts submissions of original articles, editorials and commentaries, review articles, and instructive case reports embracing studies of both basic and translational research in our discipline. In this inaugural issue, Professor Andrew Bush's review article "Asthma: what's new, and what should be old but is not!" is a must read review for all pediatricians who treat so many people with asthma in their clinical practice. Prediction of asthma among the preschool wheezers has been one of the most important areas of research. Dr. Ng and his colleagues studied a large group of children who presented with wheezing illness at a young age and provide convincing data to show the possible predictive factors for subsequent diagnosis of asthma by 6 years of age. Dr. Yu and colleagues reported a large cross-sectional study showing the important relationship of severe allergic rhinitis and exhaled nitric oxide level. Abnormal chest wall protuberance is a common reason for referral for assessment. Dr. Wong and his colleagues reported a very informative series of 12 patients describing the detailed clinical and radiological findings responsible for the abnormal protuberance. I am sure these 4 articles will be helpful for your clinical practice and provide inspirations for your research. We look forward to reading your submission to our *Journal* in the near future.

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Review Article

Asthma: What's New, and What Should Be Old but Is Not!

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Abstract

Asthma is a common condition, which is commonly, badly diagnosed and badly treated, leading to unnecessary morbidity and even death in childhood, despite which complacency about management at all levels of care persists. Asthma is an umbrella term like anaemia and arthritis and should not be used as an unqualified diagnosis. It is suggested that airway disease should be deconstructed into treatable and untreatable components, such as fixed and variable airflow obstruction and airway inflammation and infection. Every effort should be made to make an objective diagnosis, and treatment should be individualised accordingly. Objective testing for airway inflammation may include determination of atopic status, blood eosinophil count and exhaled nitric oxide; physiological testing includes peak flow measurement, comprising response to exercise and short-acting β-2 agonists. Most school-age atopic children with recurrent wheeze respond well to low-dose inhaled corticosteroids if these are regularly and correctly administered. The provision of an asthma plan is mandatory. If response is poor, rather than uncritically escalating therapies, a review of adherence and any adverse environmental factor should be considered. Asthma attacks are a red flag sign of a bad prognosis, and should prompt a full review, and changes in the asthma plan as necessary. Also, regular reviews of progress and treatment need are mandatory, even in the well child with asthma. In all contexts, the importance of getting the basic rights cannot be overemphasised; still, asthma deaths are attributed to neglect of this principle. Other issues discussed in this review include the approach to the child who is breathless on exercise and the diagnosis of exercise-induced laryngeal obstruction; the so-called habit/honk cough; the problem of breathlessness and airway disease in the obese child, including the airway as the target of systemic inflammation; and the problem of 'asthma' complicating other airways diseases such as cystic fibrosis and extrapulmonary diseases such as sickle-cell anaemia. Overall, the main message of this review is that it should never be forgotten that asthma is a disease which kills children and should always be taken seriously.

Keywords: Atopy, cough, eosinophil, exercise-induced laryngeal obstruction, exhaled nitric oxide, obesity, peak flow

Introduction

Asthma is one of the most common conditions in children, and in many parts of the world, it is probably managed with more complacency and less care and attention to detail than almost any other illness. All paediatricians and primary care physicians think that they can diagnose and manage asthma, many without thinking they actually need to do any objective testing, and the result is often the prescribing of unnecessary, potentially hazardous and expensive treatments to normal children, and sometimes tragically, preventable death as a result of mismanagement.[1] The trivialising of the diagnosis of asthma,[2] as a result of overdiagnosis both in primary[3] and secondary care,[4] has led to attention being diverted away from children at high risk. The purpose of this review is to describe some of the pitfalls to be avoided in school-age children; although many of the same principles apply to preschool wheeze, this will not be discussed in this article. The underpinning message is that asthma is a potentially fatal disease, which needs to be treated with respect by families and paediatricians. Unfortunately, many general principles of basic care which were delineated years ago, and should be yesterday's news, are still not being applied, hence the present study was conducted.

What Is This Thing Called 'Asthma'?

Asthma is no more than an umbrella term, covering a multiplicity of airway diseases, not unlike 'anaemia' and 'arthritis' in terms of lack of specificity. It is better as far as

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possible to consider the components of the airway disease in the individual child.[5] These are as follows:

- Fixed airflow obstruction: This may be developmental[6] or secondary to airway remodelling.[7] This is not treatable but is overtreatable. There is no point escalating treatment to try to reverse the irreversible
- Variable airflow obstruction: This is usually secondary to airway smooth muscle constriction in asthma, but bronchoconstriction is not specific to asthma, and variable obstruction may be due to other causes such as airway mucus
- Airway inflammation: In children with asthma, this is usually eosinophilic but may be absent. In our hands, neutrophilic inflammation suggests an alternative diagnosis such as cystic fibrosis[8]
- Airway infection: This is usually in the context of an acute attack of asthma and traditionally was thought to be viral. However, bacterial infection is at least as common as viral in this context.[9] However, whether bacterial infection is causative of attacks or secondary to a transient airway immunosuppression by viruses is not clear
- Other components of airway disease, which are uncommon in childhood asthma and will not be discussed further, are altered airway sensitivity leading to enhanced or blunted cough, and altered airway liquid. This may manifest as a dehydrated airway, for example, cystic fibrosis,[10] or rarely an overhydrated one as in pseudohypoaldosteronism,[11] and also increased airway mucus disproportionate to any irritant stimulus.

It is better to consider the components of airway diseases, and especially what is treatable,[12] rather than use antiquated umbrella terms. Clearly, the extent of documentation of these different components will vary with the severity of the presenting illness, the context in which the child is seen and the response to simple treatment. However, it is a useful discipline at least mentally to consider the nature of the airway disease being treated

Diagnosis of Asthma

The first issue is to determine whether the child has a disease at all, and if so, whether it is an airways disease. The diagnosis of 'normal child' is the hardest of all and requires the most experience. All children have intermittent respiratory symptoms; a normal child may have more than ten colds and three attacks of otitis media in a year,[13] and troublesome respiratory symptoms often last for more than 2 weeks after the start of a cold,[14] which may be a surprise to first-time parents. Clearly, a selective approach to diagnostic testing is required. Asthma should be suspected if there is significant breathlessness, wheeze and sometimes cough. If there is no breathlessness, the child does not have asthma; of course, there are many more causes of breathlessness than asthma. Wheeze is a term that is frequently used imprecisely by families and children,[15-18] and it is important to determine exactly what noise is being described; a video questionnaire may help,[17,18] or even asking the parents to video in attack of wheeze (discussed in more detail below). Isolated dry cough is rare if ever due to asthma and is normally non-specific in a community setting.[19] Although cough variant asthma exists, it has undoubtedly been overdiagnosed in the past. There may be a history of other atopic disorders, including eczema, allergic rhinitis and food allergy, and a positive family history of asthma and atopy in first-degree relatives.

There is a wide differential diagnosis of asthma, and clinical history and examination must be used to determine what focused testing is indicated. Important alerts that another diagnosis needs to be considered are given in Table 1, and a scheme of differential diagnosis is shown in Table 2. In particular, chronic productive cough (daily cough for 8 weeks) is rarely due to asthma, and alternative diagnoses must be sought.[20] It should be stressed that a 'do every test in every child' approach is incorrect.

If the paediatrician feels a diagnosis of asthma is likely, then further testing to establish the diagnosis is mandatory in school-age children.[1] In what other chronic disease in which objective testing can be performed is long-term treatment instituted without performing those tests? Blind treatment of a putative diagnosis of asthma in school-age children is inexcusable. It is accepted that not all tests are available in every setting, but some tests are available in all but the most deprived settings. These can be divided into tests characterising the presence and nature of any inflammation and tests documenting the presence and temporal variability of airway obstruction. None is diagnostic of asthma, but the general principle should be that the more tests are negative, the more carefully the possibility of an alternative diagnosis should be considered.

Airway inflammation

These are largely indirect except in the most severe cases and in specialist settings, where sputum induction and bronchoscopy may be performed.

Table 1: Diagnostic clues on history or examination suggesting that there is a diagnosis to be made

History	Physical examination
The breathing noises have been misdiagnosed as wheeze	Clubbing
Prominent upper airway symptoms	Weight loss or failure to thrive
Symptoms from 1st day of life	Nasal polyps (highly suggestive of cystic fibrosis)
Sudden onset symptoms, suggestive of foreign body aspiration	Other upper airway disease, such as adenotonsillar hypertrophy
Chronic moist cough or production of sputum	Unusually severe chest deformity
Symptoms of a systemic illness	Abnormal auscultation: Fixed monophonic wheeze, stridor, asymmetrical signs
Continuous and unremitting symptoms, especially if worsening	Signs of cardiac or systemic disease

Table 2: Some of the important differential diagnoses of asthma

Class of diagnosis	Examples
Local immunodeficiency	Cystic fibrosis, primary ciliary dyskinesia, persistent bacterial bronchitis
Systemic immunodeficiency	Any, including B-cell and T-cell dysfunction
Intraluminal bronchial obstruction	Foreign body, carcinoid, other tumour
Intramural bronchial obstruction	Bronchomalacia, complete cartilage rings, intramural tumour
	In low- and middle-income countries, bronchiectasis due to severe infection in an otherwise healthy child is particularly important
Extraluminal bronchial obstruction	Vascular ring, pulmonary artery sling, congenital lung cyst, enlarged lymph nodes due to tumour or tuberculosis, other mediastinal masses
	In low- and middle-income countries, tuberculosis is a particularly important cause
Direct aspiration due to uncoordinated swallow	Bulbar or pseudobulbar palsy; laryngeal cleft; laryngeal neuropathy or myopathy
Aspiration by direct contamination	H-type fistula, which may not present until adult life
Aspiration secondary to gastro-oesophageal reflux	Any cause of gastro-oesophageal reflux, including hiatus hernia and oesophageal dysmotility (e.g. achalasia or after neonatal repair of tracheo-oesophageal fistula)
Complications of prematurity	Bronchomalacia, structuring secondary to intubation, vocal cord palsy secondary to surgery for patent arterial duct
Congenital heart disease	Bronchial compression from enlarged cardiac chambers or great vessels; pulmonary oedema
Interstitial lung disease	Any not presenting with neonatal respiratory failure
Dysfunctional breathing	Vocal cord dysfunction, hyperventilation syndromes (usually a co-morbidity in a known asthmatic, but may present in isolation)

This table is by no means exhaustive

- Skin prick tests for atopic sensitisation (or more expensively, specific IgE): If a school-age child is not atopic, then eosinophilic airway inflammation is unlikely although not absolutely impossible. Of course, not every atopic child has airway disease
- Blood eosinophil count: There is increasing evidence that peripheral blood eosinophilia reflects airway eosinophilia.[21,22] This test can be performed on a finger-prick sample. Of course, a raised blood eosinophil count may be a manifestation of other atopic disease, but the absence of peripheral blood eosinophilia is a strong pointer that there is no airway eosinophilia
- Exhaled nitric oxide (FeNO): This is elevated in children who are not prescribed inhaled corticosteroids (ICS),[23] but also in atopy without airway disease.[24]

Underpinning the approach of documenting infection is the principle that there is no point in prescribing anti-inflammatory medications such as corticosteroids if there is no airway inflammation present, any more than anti-hypertensives should be prescribed to patients with a normal blood pressure.

Airway physiology

These tests may also be negative if the child is well, but failure to demonstrate any evidence of variable airflow obstruction should call into question the diagnosis of asthma.

- Peak flow or preferably spirometry in the consulting room: Both may be normal if the child is well at the time, but if reduced, the acute response to a short-acting β-2 agonist (SABA) should be determined
- Home peak flow monitoring: 'Monitoring fatigue' is common so the duration should be kept short, probably no more than 2–4 weeks.[25] Measurements should be made morning and evening. If the child is breathless after exercise at home, a measurement of peak flow should be made. It is legitimate for the child to have SABA during this time, and if administered, peak flow response should be measured
- Challenge testing: A field exercise test with peak flow monitoring is available to everyone, albeit it may be non-specific.[26] Histamine and methacholine challenge are the province of special centres; their role is to rule out asthma if the test is normal. A degree of bronchial hyper-reactivity may be seen in normal children
- Oral corticosteroid trial, with spirometry or peak flow monitoring, may be legitimate in a child who is thought to have fixed airflow obstruction at baseline or documented very variable airflow obstruction. Neither the dose nor duration of therapy has been standardised in paediatrics.[27] A 5–10-day course of prednisolone 1 mg/kg to a maximum of 40 mg/day is reasonable.

It is perfectly possible to deploy at least some objective testing in any setting to try to confirm or refute a diagnosis of asthma. In any event, the possibility of a wrong diagnosis, no matter how eminent the diagnostician, should always be considered during follow-up, in particular, if there is a poor response to standard therapy.

Treatment of Paediatric Asthma Characterised by Variable Airflow Obstruction and Presumed Eosinophilic Airway Inflammation

Numerous evidence-based guidelines have been published,[28,29] and will not be recapitulated here, beyond noting that, as guidelines have become more evidence based, asthma outcomes (below) remain largely unchanged. The aims of treatment include control of current symptoms, prevention of acute attacks (risk reduction), optimising lung growth (which is still an unmet need; a number of asthmatic children have abnormalities in airway growth) and minimising side-effects of medications. It must be emphasised to the

families that asthma is potentially a killing disease which must be taken seriously.

Pharmacotherapy

Initial treatment is with intermittent SABA. The decision to escalate to ICS is based on frequency of SABA use, but with no evidence base to guide the actual numbers of doses. If the decision is made to escalate treatment, first-line preventive therapy is ICS. There is a worrying tendency for the combination of ICS and long-acting β-2 agonists (LABA) to be used as first-line prevention.[30] Not merely is there no evidence to support this practice, but it may also actually be deleterious.[31]

If ICS are prescribed, the absolutely key principle is that most children will respond to a dose of fluticasone equivalent of 100 mcg twice daily. The BADGER study[32] showed that very few children got any benefit from escalating the dose above this level, and furthermore, the benefits of add-on therapy were not striking. Hence, before escalating therapy above this ICS dose, it should be back to basics in a detailed review [Table 3]. The cardinal sin in asthma treatment is escalating treatment uncritically without considering that the whole approach is wrong, or being misapplied, or being held back by environmental or psychosocial factors.[33]

Of great importance is that an appropriate medication delivery device is selected, and the child and family shown how to use it.[34] Techniques should be checked at every health-care encounter because repeated teaching sessions are usually necessary.[35]

If escalation of treatment beyond low-dose ICS is considered appropriate, the choices include high-dose ICS, ICS plus LABA in a combination inhaler or ICS plus leukotriene receptor antagonist (LTRA). ICS-LABA is more likely to be beneficial, but a trial of ICS-LTRA may be quicker (needs be no longer than 2 weeks) and cheaper in at least some contexts. Previous fears about LABA safety[36] have largely been laid to rest by a recent big study.[37,38] If the treatment does not work, it should be discontinued. All too often children remain in primary care, prescribed ICS in moderate to high dose, and LABA and LTRA. Such children by definition have problematic severe asthma[39] and should have been referred for specialist evaluation much sooner.[40] Treatments such as omalizumab and other monoclonals should only be administered in tertiary care settings, after a detailed evaluation of the child.

Table 3: Suggested areas for review before escalating treatment in a child who has not responded to low dose inhaled corticosteroids

Education: Do the family really understand the seriousness of asthma, the triggers and the asthma plan
Adherence: Ideal is electronic monitoring or directly observed therapy. Failing that, check prescription uptake and talk to the local pharmacist. Consider a trial of directly observed therapy at school
Environmental tobacco smoke: Measure urinary or salivary cotinine if available
Allergen exposure: Check for sensitisation (usually skin prick tests), ask about pets, and a home visit by an experienced nurse is often illuminating
Psychosocial: Depression, anxiety and denial are common in asthma. If available, consider asking for review from a clinical psychologist

Beyond pharmacotherapy – more to life than medicines

It is essential that children with all but the most trivial symptoms have an asthma management plan,[1] with detailed instructions about what to do in the event of deterioration or an asthma attack, which should be based on peak flow measurements. The family need to understand the asthma triggers and what can be done to avoid them; asthma education is essential. The role of peak flow monitoring in the well asthmatic is controversial. It is highly unlikely that children will slavishly measure their peak flow twice a day, every day, but measurements should be made at times of high risk, such as viral colds or unavoidable increase in exposure to allergens to which the child is sensitive, and perhaps a few times a month when the child is well, to ensure that lung function is not drifting imperceptibly. Attention should be paid to the child's environment – passive exposure to tobacco is all too common, and in the UK, to pets to which the child is sensitised.[41] Both can cause relative steroid insensitivity,[42,43] and both should be addressed before escalating medications.

Management – iterative not instantaneous

Whatever treatment plan is settled upon, regular review of all aspects of care is essential. It may be possible to reduce treatment if the child is well. Spirometry or peak flow, inhaler technique and height and weight should be measured and plotted on an appropriate centile chart. Asthma knowledge should be checked.

Asthma Attacks – Should Be a 'Nearly Never' Event

The word 'exacerbation' does patients a disservice and should not be used, implying as it does that the event is a trivial, and readily recoverable event.[44,45] In asthma[46,47] as with other airway diseases such as cystic fibrosis[48-50] and primary ciliary dyskinesia,[51] attacks are associated with a less favourable long-term course in terms of evolution of lung function and prognosis, but more importantly, in asthma, they should be a significant immediate red flag as signalling a high risk of future attacks and asthma deaths. In the UK, there has been another National Review of Asthma Deaths[1] which makes depressing reading. In summary, the lessons of the past have not been heeded and the basics have not been done right, and children have died. Importantly, 57% were not under specialist care, so primary care has to identify those at risk. Using current definitions,[40] 60% of those who died did not have 'severe' asthma (although it is difficult to think of a worse outcome than death!). In primary care, alerts should include those who had been prescribed more than six SABA canisters/year;[52] recent discharge from hospital, especially if they have had a really severe asthma attack; those who have attended emergency

departments especially in the previous year; and those who repeatedly do not attend follow-up consultations. All these patients can be readily detected in primary care.

The response to an asthma attack should be an immediate and focussed review. This should include whether recovery is complete – the fixed course of 3 or 5 days of prednisolone may not have been sufficient. The seriousness of the situation must be stressed to the family. The events around the attack should be reviewed in detail. Was the asthma plan followed, and should it be modified in any way? Was the attack monitored objectively with peak flow measurements, both by the family and also in the emergency care facility? Do the family understand the triggers for asthma, including smoking if this is a factor? Is their asthma undertreated[53] – baseline control may not have been as good as it should have been. Prescription uptake should be reviewed as a marker of adherence;[41] for sure, merely collecting a prescription does not equate to inhaling the medication correctly, but failure to collect any prescription certainly does not inspire confidence in adherence! A big uptake of SABA canisters is another warning sign. Technique with the medication delivery device must be checked. There should be a review of previous attendances – is there a history of failing to bring the child, or psychosocial factors such as denial or disorganisation within the family? Should the child be referred for a specialist assessment? The importance of asthma attacks as a signal event cannot be overstressed.

What is very clear is that we can make a difference with proper management. The stellar example is from Finland,[54] where attention to education of the families and professionals, and the aggressive use of ICS drove down asthma morbidity and mortality. Although pharmacological treatment costs rose, the overall cost of asthma, counting days lost from work and other health-care costs, and overall the fiscal burden of asthma fell.

Having been the basics of good asthma care covered above, the remainder of this review covers airways disease in special circumstances: Unexplained breathlessness on exercise, habit cough, the obese asthmatic and asthma complicating other airways diseases.

Breathless on Exercise – But Is It Really Asthma?

Exercise-induced bronchoconstriction is a common feature of poorly controlled asthma and usually comes on a few minutes after exercise. It is usually abolished by pre-exercise SABA and improvement of baseline asthma control. However, it is a cardinal error to assume that just because a child with even correctly diagnosed asthma is breathless, the cause of the breathlessness is asthma; it would be just as logical to assume firefighters are arsonists just because they are found at the site of fires. The differential diagnosis of exertional breathlessness is shown in Table 4.

A common misdiagnosis is exercise-induced laryngeal obstruction (EILO), which may also complicate asthma.

Table 4: Differential diagnosis of exercise-induced breathlessness

Exercise-induced bronchoconstriction
Vocal cord dysfunction/exercise-induced laryngeal obstruction
Deconditioning/obesity, etc.
Exercise-induced anaphylaxis (ask what the child ate or drank before exercise)
Pulmonary hypertension – consider this especially in the child who faints while exercising

Typically, the symptoms of EILO are seen in high-achieving athletes and come on during exercise. Characteristically, the sound heard is stridor, not the expiratory polyphonic wheeze typical of asthma, and the pathophysiology is of vocal cord adduction or various types of laryngeal and supraglottic obstruction, which of course do not respond to asthma treatments. A video recording of an episode may be very informative.[55] If direct confirmation of the diagnosis is needed, laryngoscopy can be performed during most exercise[56] (such as running and rowing,[57] but perhaps not swimming!) and the laryngeal abnormalities demonstrated to the patient. EILO may also be late sequelae of neonatal laryngomalacia[58] and is also described in survivors of preterm delivery who have left recurrent laryngeal nerve damage secondary to surgical ligation of the ductus arteriosus in the neonatal period.[59]

The most important survey of exercise-induced breathlessness was recently carried out in Norway.[60] The authors performed a questionnaire study in 3838 adolescents; the prevalence of exercise-induced bronchoconstriction was 19.2%, and of EILO 5.7%. A sub-sample (n = 99 with exercise dyspnoea, n = 47 without) underwent standard treadmill exercise-induced bronchoconstriction and EILO tests (the latter including laryngoscopy on exercise). Nearly half the patients had neither exercise-induced asthma nor EILO, but many were being prescribed SABAs and other asthma medications; they were presumably deconditioned, but they were not more obese than the rest of the group. Six per cent of patients had isolated EILO, 5% had EILO and exercise-induced bronchoconstriction and the remainder had exercise-induced bronchoconstriction alone. The message of this large study is that exercise-induced asthma is overdiagnosed and, rather than escalating treatment for asthma when the patient complains of exercise dyspnoea, it is vital to understand the root cause of the problem.

'Habit' Cough

As discussed above, cough on its own is rarely if ever due to asthma, but it is often treated as such with escalating doses of ICS. A variant which is particularly prone to this is 'habit' (sometimes also called 'honk') cough. This is a repeated, loud and explosive cough, non-responsive to any medication, and quite unlike any cough relating to underlying disease. The key question is what happens when the child is asleep? Whereas asthma and most respiratory disorders are worse at night, the habit cough disappears completely. The

initial step is to explain the nature of the symptoms, and stop any inappropriate medication. Very often the symptoms will respond to intervention from a skilled physiotherapist or speech therapist. Occasionally, they may be a manifestation of some deep-rooted problem, such as impending parental divorce, and then the intervention of a psychologist may be helpful.

The Obese Breathless Child: Asthma or Not?

Obesity is overtaking us as a major epidemic. Globally, in 2013, there were an estimated more than 42 million overweight children under age 5 years age, and it is estimated that this will rise to more than 70 million by 2025.[61] The majority of overweight children live in developing countries; stunting is well known as being caused by poverty, but poverty also results in the consumption of cheap junk food, and hence obesity. Obesity may be part of a constellation of adverse factors, including smoking, poverty and overcrowding, and it may be difficult to determine causality of a particular factor.

Important information comes from the ISAAC study.[62] They reported on 10,652 children aged 8–12 years from 16 affluent and 8 non-affluent centres, using ISAAC phase two methodology. Both being overweight (OR 1.14, 95% confidence intervals [CIs] 0.98; 1.33) and obese (OR 1.67, 1.25; 2.21) related to wheeze. Both being overweight and obese were associated with a reduction in forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC); −0.90 (−1.33%; −0.47%) for being overweight and −2.46% (3.84%; −1.07%) for being obese. There was no association with any other objective markers including atopy. The lack of association with atopy must mean either they were a reporting non-asthma sound, which is perfectly feasible, or the asthma of obesity is a different phenotype to the usual childhood atopic asthma. However, in another study,[63] obese children with asthma were more likely to be admitted, and more likely to go to the intensive care unit, suggesting an association of obesity with asthma severity and/or treatment resistance. This latter was supported by data from the CAMP study, which suggested that obese asthmatic children had a worse response to ICS treatment than lean children.[64]

There are increasing data that obese children may have an airway disease, but it is phenotypically different from atopic asthma. In a recent study,[65] overweight and obese children had a lower FeNO (suggesting that airway eosinophilia was not a feature of their disease) and were less methacholine responsive, but reported increased β agonist use, worse asthma symptoms and more often reported breathlessness rather than wheeze as the primary symptom of an asthma attack. They less often reported cough and displayed poorer 'asthma' control and a distinct pattern of symptoms. The authors pointed out that the obese asthmatic may falsely attribute exertional dyspnoea to asthma rather than deconditioning, leading to excess rescue medication use, and clearly measuring what actually happens on exercise (bronchoconstriction vs. fatigue, above) is especially crucial in the obese.

There are pathophysiological data suggesting that obesity-asthma is a distinct condition. Dysanapsis is defined as normal flows in large lungs, so FEV_1 is normal or high, and FVC is high, so the FEV_1/FVC ratio is reduced. Airway length but not airway calibre is thought to be determined by lung size. The hypothesis that obesity may lead to dysanapsis was tested in six separate cohorts pooled (4 with longitudinal data).[66] The authors calculated body mass index (BMI) and looked at asthma outcomes. Four thousand one hundred and twenty-one children, aged 6–20 years, 1084 of whom were dysynaptic, were studied. They found that obesity was associated with greater likelihood of dysanapsis, and this was associated with a lower FEV_1 and higher total lung capacity, and with severe exacerbations (hazard ratio 1.95, 95% CIs 1.38–2.75) and use of systemic steroids (3.22, 2.05–5.14). The interpretation of these data is not easy, but these anatomical changes are not likely to be susceptible to ICS therapy. Whether obesity is associated with eosinophilic airway inflammation is controversial,[67,68] and again atopic status, blood eosinophil count and preferably exhaled nitric oxide should be measured before escalating treatment with ICS.

An interesting and novel concept is the airway as the target of systemic inflammation. Obesity and obstructive sleep apnoea are both pro-inflammatory states, and recent data suggested that interleukin-6 (IL-6) in particular could be an important mediator of airway damage.[69] Two cohorts of adult patients were studied, a total of 636 in all. Blood IL-6 was measured as a marker of systemic inflammation and related to asthma outcomes. 111/138 IL-6 high asthmatics were obese, and 178/289 of obese asthma patients were IL-6 low. Metabolic dysfunction as measured by IL-6 was not exclusive to the obese, but irrespective of BMI, IL-6 high patients had worse outcomes, which were not mediated via type 2 inflammation.

The treatment of the airway disease of obesity should clearly start with weight reduction, either dietary, with the aid of pharmacotherapy[70] or with bariatric surgery.[71] Three groups were compared in a longitudinal study in adults: Asthma and bariatric surgery ($n = 27$), bariatric surgery no asthma ($n = 39$) and asthma not treated with bariatric surgery ($n = 12$). Patients undergoing bariatric surgery lost weight, improved their FEV_1 and small airway function (especially if they were asthmatic); those with asthma who underwent bariatric surgery improved airway hyper-responsiveness, but changes in inflammatory profile were merely minor reduction in airway mast cell numbers. As well as weight reduction, it is clearly essential to be clear (a) that the symptoms reported are truly due to an airway disease and (b) what are the treatable components of that airway disease.

Asthma Plus – Does It Exist?

The final topic is how to answer the vexed question of diagnosing 'asthma' in the presence of another disease which may be airway based (e.g., cystic fibrosis) or systemic (e.g., sickle-cell anaemia). The question immediately becomes

Table 5: Some causes of airway obstruction in school age children, deconstructed and with proposed treatments

Disease	Inflammation? Eosinophilic, neutrophilic, both	Variable airflow obstruction? Bronchospasm, oedema, mucus, loss of tone, loss of alveolar tethering	Fixed airflow obstruction?	Infection? Bacterial, viral, both	Treatment
Persistent bacterial bronchitis	Neutrophilic, bacteria	Mucus	No (?)	Bacterial, ?viral	Antibiotics, airway clearance
Cystic fibrosis, primary ciliary dyskinesia, bronchiectasis	Neutrophilic	Yes, mucus obstruction	Usually	Bacterial predominant	Antibiotics, mucolytics, airway clearance
Obliterative bronchiolitis	None	No	Yes	No	Supportive
Sickle-cell anaemia	None	Yes, bronchoconstriction	Yes	Not known	Bronchodilators
Post-premature birth	None	Yes, bronchoconstriction	Yes	Not known	Bronchodilators
Primary airway malacia	None	Yes, loss of airway wall tone	+/−	Secondary	Airway clearance, continuous positive airway pressure, antibiotics, mucolytics, ?tracheostomy

meaningless if the asthma label is abandoned and the airway disease is described in terms of its component parts. There are many causes of airway obstruction in childhood, some of which are summarised in Table 5. Hence, for example, instead of asking 'does this cystic fibrosis patient have evidence of asthma?', the proper question is does this cystic fibrosis patient have evidence of eosinophilic airway inflammation which would justify the prescription of ICS?'. This then guides the response – is the child atopic, what is the exhaled nitric oxide, what is the peripheral blood eosinophil count and are there eosinophils present in spontaneously expectorated or induced sputum. The same approach can be used in, for example, the survivors of preterm birth. Instead of asking 'do they have asthma?', the airway disease is characterised. This shows evidence of fixed and bronchodilator responsive airflow obstruction,[72] but no evidence of type 2 inflammation.[73,74] Hence, treatment should be with bronchodilators and not ICS. Similarly, with sickle-cell anaemia, our data[75] showed fixed airflow obstruction, but no increase in atopy, evidence of allergic sensitisation or elevation of exhaled nitric oxide, suggesting that the airway phenotype will be resistant to conventional asthma therapies. Thus, the approach of defining treatable components of airway disease rather than sterile debates about umbrella terms is an approach that is widely applicable in paediatric airway disease.

Summary and Conclusions

The term asthma has outlived its usefulness as an unqualified diagnosis, and the era of diagnosing and treating this disease with potent ICS without any objective diagnostic testing or monitoring should have long passed. This review proposes deconstructing the components of airway disease and identifying treatable and untreatable components to individualise treatments. Asthma attacks are important red flag events and should lead to a detailed review of all aspects of care. This approach is applicable to all forms of airway disease, including the vexed question of 'asthma' complicating other airway diseases such as cystic fibrosis and systemic disease such as sickle-cell anaemia and is the first step to personalised care of many airway diseases. Ultimately, the target should be to identify abnormal pathways driving disease, and use specific molecular treatments rather than non-specific anti-inflammatory medications such as ICS. However, while looking to the future of pathway-based, designer molecule therapy for individually characterised airway disease, it should never be overlooked that at the present time, asthma is a disease which kills children, and getting the basics of care right is essential.

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Conflicts of interest

There are no conflicts of interest.

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The Predictive Factors in Preschool Wheezers for Subsequent Asthma Hospitalization after the Age of 6 Years

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Abstract

Background: Preschool children with wheeze may develop asthma later at school age. Positive skin prick test (SPT) to common aeroallergens in preschool wheezers may be associated with a higher chance of developing asthma at school age. **Methods:** All patients with SPT performed for the indication of preschool wheeze, i.e., before the age of 6 years, were included in the study from 1999 to 2011. Outcome measures including asthmatic attack requiring emergency hospitalization and the need for asthma controller prescription after the age of 6 years were retrieved from the hospital database. Potential risk factors including gender, family history of asthma, blood eosinophilia, environmental tobacco exposure, personal eczema, and allergic rhinitis were also retrieved for analysis. Multiple logistic regression was performed to identify independent risk factors. **Results:** Altogether, 463 children were included for analysis with mean age at SPT of 3.1 ± 1.36 years and 64.6% were male. Positive SPT results were obtained in 60.5% of patients. For preschool children with wheeze, female gender (odds ratio [OR] = 1.90, 95% confidence interval [CI]: 1.04–3.46, $P = 0.036$), positive SPT (OR = 2.96, 95% CI: 1.40–6.24, $P = 0.004$), and late-onset preschool wheeze hospitalization (OR = 2.82, 95% CI: 1.42–5.61, $P = 0.003$) were associated with a higher chance of asthmatic hospitalization after the age of 6 years. Allergic rhinitis (OR = 4.58, 95% CI: 2.16–9.71, $P < 0.001$) and family history of asthma (OR = 1.82, 95% CI: 1.09–3.02, $P = 0.022$) were associated with higher chance for asthma controller prescription. **Conclusion:** For preschool wheeze, female gender, positive SPT, and late-onset preschool wheeze index are associated with a higher chance of asthmatic hospitalization after the age of 6 years while allergic rhinitis and family history of asthma are associated with a higher chance for asthma controller prescription after the age of 6 years.

Keywords: Allergens, asthma, child

Introduction

Preschool wheeze has been reported to occur in 30% of children within the first 3 years of life and up to 50% of children before the age of 6 years.[1,2] In Hong Kong, it was reported that acute wheeze accounted for 10% of all emergency admissions to public hospitals.[3] Martinez *et al*. and Brooke *et al*. suggested that about 40% of children with preschool wheeze would develop persistent wheeze after the age of 6 years.[1,4] Early allergic sensitization was one of the identified risk factors for subsequent asthma development among preschool wheezers.[5-7] Skin prick test (SPT) is an easily available, safe, and simple test for allergic sensitization. Kurukulaaratchy *et al*. had shown that a positive SPT was one of the risk factors to predict persistent wheeze in children who had wheeze during early life.[8] Sensitization to aeroallergen was included in the Asthma Predictive Index developed from the Tucson cohort.[9] However, similar data were not available for Asian children. In the current study, we aimed to investigate whether SPT performed in preschool wheezers could predict asthma hospitalization and the need for asthma controller medication after the age of 6 years.

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Methods

Study population

This was a retrospective observational study targeting preschool wheezers who had SPTs performed in the Department of Paediatrics, Kwong Wah Hospital, from January 1999 to

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December 2011. During the study period, patients with preschool wheeze, who were either seen in the outpatient clinics or hospitalized, were offered SPT to check whether the wheeze was recurrent or severe. The inclusion criteria of the study included: (1) SPTs performed for the investigation of preschool wheeze in children aged <6 years and (2) participants completed at least 2-year follow-up in the pediatric specialist outpatient clinic after they turned 6-year-old. In the authors' department, SPTs were arranged for patients with two or more wheezes or wheezes requiring hospitalization. The exclusion criteria included (1) invalid SPTs, such as positive control test that was negative; (2) SPT performed for other or undocumented indications (e.g., suspected cow milk protein allergy, food allergy, recurrent urticarial, etc.); and (3) patients with chronic lung disease (e.g., bronchopulmonary dysplasia associated with prematurity, bronchiectasis, bronchiolitis obliterans, etc.) [Figure 1]. A flowchart of the study cohort is shown in Figure 2.

Data retrieval

Medical records of all the included patients were retrieved from the Hong Kong Hospital Authority (HKHA) computer medical systems. Data on the incidence of wheeze requiring emergency admissions to public hospitals under HKHA before and after the age of 6 years and potential confounding factors including gender, family history of asthma in the first-degree relatives, history of allergic rhinitis and eczema, environmental tobacco exposure, and peripheral blood eosinophilia (≥4%) were obtained. All electronic data were kept in encrypted spreadsheet and stored in a password-protected computer. Hard copies of records were stored in a locked cabinet. Wheeze without cold was not included because nasopharyngeal aspirates for respiratory virus were not routinely performed for all children

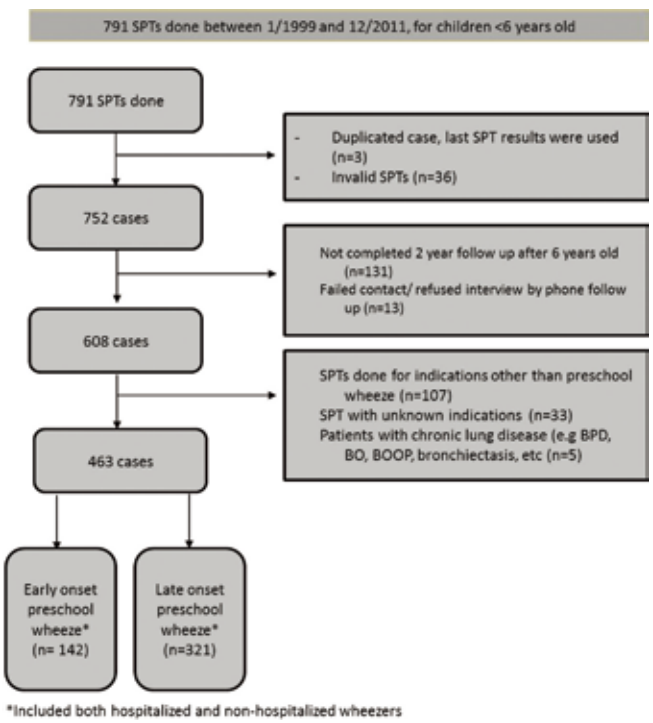

Figure 1: Flow chart for case recruitment.

who were admitted for wheeze in our hospital. Data on asthma controller prescription as listed in Appendix 1, prescribed at the age of 6 years or older, were retrieved from the hospital Clinical Data Analysis and Reporting System. For those who did not have regular pediatric specialist outpatient follow-up at the age of 6 years or above, a phone follow-up with standardized questions concerning asthma controller prescription by private doctors was conducted by one of the authors (PTY).

Outcome measures

The primary outcome was emergency asthma admissions to public hospitals after the age of 6 years. The secondary outcome was prescription of asthma controller medications after the age of 6 years.

Skin prick test

SPTs were performed according to the guideline described in the allergy diagnostic testing by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the ACAAI.[10] Patients were asked to withhold medications such as antihistamine, oral/topical steroid, and herbal medicine, 1 week before the test. The tests were performed by trained medical staff. The ventral part of forearm was pricked gently after the relevant allergens were placed onto the skin with a lancet or Stallerpoint®, used since January 2010. In addition to a positive control (histamine 1 mg/ml) and a negative control (saline), six aeroallergens were tested, including house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*), cat, dog, grass, and feather mix, which are the common aeroallergens in Hong Kong.[11,12] The results were interpreted 15 min later. The wheal size was measured as the summation of the longest transverse line and the corresponding longest perpendicular line divided by a factor of 2.

Definitions

SPT was defined as positive for an aeroallergen if the wheal size was 3 mm or greater than the negative control. SPT positivity was defined if SPT was positive for at least one tested aeroallergen.

Wheeze was classified as early-onset preschool wheezer (defined as the first wheeze before the age of 2 years) and late-onset preschool wheezer (defined as the first wheeze between the age of 2 years and 6 years).

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. in Armonk, NY, USA). The relationship between SPT positivity and emergency asthma admission/asthma controller prescription after the age of 6 years was investigated using Pearson's Chi-squared test. For continuous variables, normality was tested by Shapiro–Wilk test. Wilcoxon rank-sum test with continuity correction was used if continuous variables were not normally distributed. Univariate analysis was conducted to identify the potential risk factors for emergency asthma admission and asthma controller prescription after the age of 6 years. Multivariate logistic regression analysis was

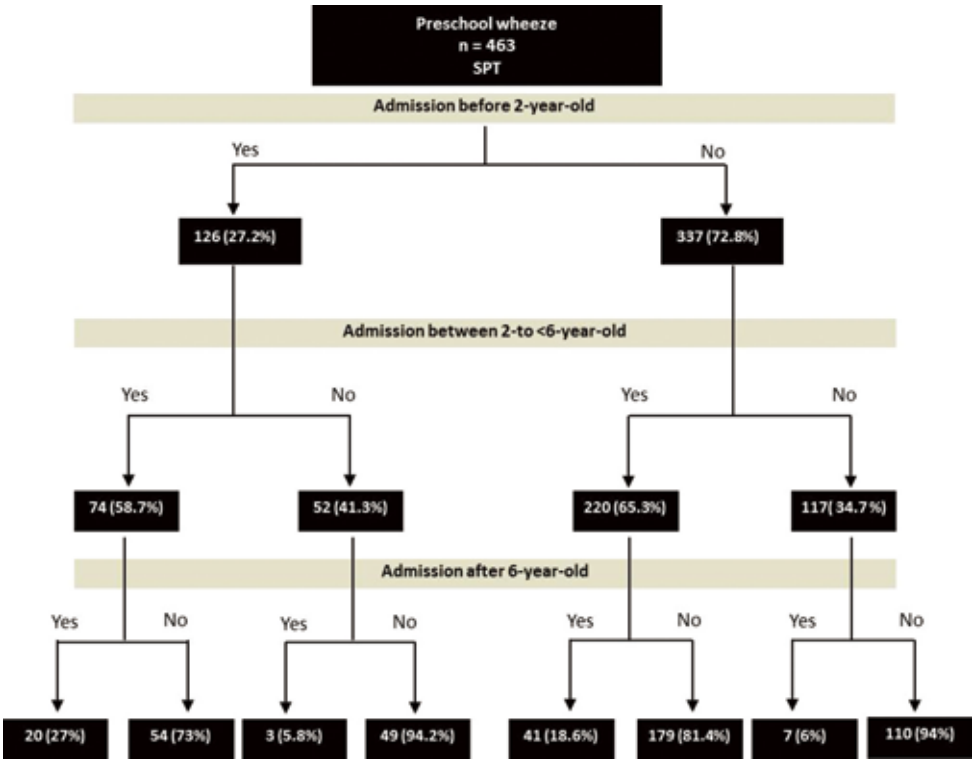

Figure 2: Flow chart for hospitalization of preschool wheezers.

performed to identify the independent risk factors. The variables with $P < 0.2$ were put into the final regression model.

Results

Patient characteristics

A total of 791 SPTs were done during the study period. Altogether 463 children were selected to be included in the study cohort [Figure 1], while 299 (64.6%) of them were male. Mean age at SPT was 3.1 ± 1.36 years. Majority were late preschool wheezers (n = 321, 69.3%) while 142 (30.7%) were early preschool wheezers.

Summary of skin prick test results

Among the 463 patients, 280 (60.5%) had positive SPT and 183 (39.5%) had negative results. Majority of the patients were sensitized to *D. pteronyssinus* (n = 266, 95%) and *D. farinae* (n = 245, 87.5%). Only a small proportion of children were sensitized to cat, dog, feather mix, or grass [Table 1].

Table 1: Results of skin prick tests for different aeroallergens

Antigens	Total number of children	Number of children with positive results (%)
Dermatophagoides pteronyssinus	463	266 (57.4)
Dermatophagoides farinae	463	245 (52.9)
Dog	463	36 (7.8)
Cat	463	43 (9.3)
Grass mix	463	14 (2.8)
Feather mix	463	4 (0.9)
Any positive	463	280 (60.5)

Risk factors associated with emergency asthma admission after the age of 6 years

Univariate analysis showed that gender, SPT positivity, environmental tobacco exposure, eosinophilia, early preschool wheeze admission index per year (age <2 years), late preschool wheeze admission per year (age 2–<6 years), wheeze admission before the age of 6 years were the potential risk factors for asthmatic attack requiring emergency hospital admission after the age of 6 years [Table 2]. After adjusting for the potential confounding factors in the multivariate logistic regression analysis, it was found that independent risk factors included female gender (odds ratio [OR]: 1.90, confidence interval [CI]: 1.04–3.46, P = 0.036), SPT positivity (OR: 2.96, CI: 1.40–6.24, P = 0.004), and late preschool wheeze admission index (OR: 2.82, CI: 1.42–5.61, P = 0.003) [Table 3]. Using the aforesaid model, the probability of asthma admission after the age of 6 years will be as follows:

$$P = \frac{\text{Prediction Index A}^*}{1 + \text{Prediction Index A}^*}$$

*Prediction Index A = Exp (−3.1 + 0.5 × female gender + 1.0 × SPT positivity + 1.4 × late preschool wheeze admission per year).

Using the above model, the OR of future asthma admission comparing children with various risk factors can be calculated.

Table 2: Univariate logistic regression analysis on the risk factors contributing to emergency asthma admission after the age of 6 years

Potential risk factors	Crude OR (95% CI)	*P*
Gender (female)	1.98 (1.19-3.30)	0.009*
Environmental tobacco exposure	1.45 (0.86-2.44)	0.164
Eosinophilia	1.53 (0.89-2.60)	0.121
Family history of asthma	0.97 (0.55-1.74)	0.930
Eczema	0.96 (0.56-1.62)	0.867
Allergic rhinitis	1.20 (0.65-2.22)	0.557
SPT positivity	3.08 (1.66-5.75)	<0.001*
Early preschool wheeze admission index†	1.42 (0.98-2.05)	0.061
Late preschool wheeze admission index‡	4.61 (2.49-8.53)	<0.001*
Admission for preschool wheeze before the age of 6 years	3.57 (1.59-8.02)	0.002*

*P<0.05, †Number of admissions for preschool wheeze at age <2 years divided by the number of years, ‡Number of admissions for preschool wheeze at age between 2 and <6 years divided by the number of years. OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

Table 3: Multivariable logistic regression analysis on the risk factors contributing to emergency asthma admission after the age of 6 years

Potential risk factors	Adjusted OR (95% CI)	*P*
Gender (female)	1.90 (1.04-3.46)	0.036*
Environmental tobacco exposure	1.16 (0.64-2.11)	0.618
Eosinophilia	1.19 (0.66-2.17)	0.562
SPT positivity	2.96 (1.40-6.24)	0.004*
Early preschool wheeze admission index†	1.53 (1.0-2.35)	0.053
Late preschool wheeze admission index‡	2.82 (1.42-5.61)	0.003*
Admission for preschool wheeze before the age of 6 years	2.68 (0.75-9.52)	0.128

*P<0.05, †Number of admissions for preschool wheeze at age <2 years divided by the number of years, ‡Number of admissions for preschool wheeze at age between 2 and <6 years divided by the number of years. OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

For instance, a child with female gender, SPT positivity, and a late preschool wheeze admission index of 1 will be almost 11 times more likely to be admitted for asthma after the age of 6 years than a child with male gender, SPT negativity, and a late preschool wheeze admission index of 0 [Appendix 2].

Risk factors associated with the prescription of asthma controller medications after the age of 6 years

Univariate analysis showed that gender, allergic rhinitis, family history of asthma, eosinophilia, SPT positivity, and late preschool wheeze admission were the potential risk factors for asthma controller prescriptions after 6 years of age [Table 4]. After adjusting for the potential confounding factors in the multivariate logistic regression analysis, it was found that independent risk factors were allergic rhinitis (OR: 4.58, CI: 2.16–9.71) and family history of asthma (OR: 1.82, CI: 1.09–3.02) [Table 5]. Using the aforesaid model, the probability of requiring asthma controller prescription after the age of 6 years will be:

Table 4: Univariate logistic regression analysis for prescription of asthma controller after the age of 6 years

Potential risk factors	Crude OR (95% CI)	*P*
Gender (female)	1.65 (1.10-2.48)	0.016*
Environmental tobacco exposure	1.06 (0.69-1.60)	0.783
Eosinophilia	1.39 (0.91-2.13)	0.127
Family history of asthma	1.87 (1.19-2.95)	0.007*
Eczema	1.12 (0.77-1.75)	0.463
Allergic rhinitis	4.23 (2.27-7.85)	<0.001*
SPT positivity	2.29 (1.48-3.54)	<0.001*
Early preschool wheeze admission index†	1.10 (0.79-1.53)	0.555
Late preschool wheeze admission index‡	1.76 (1.07-2.89)	0.024*
Admission for preschool wheeze before the age of 6 years	1.02 (0.65-1.61)	0.930

*P<0.05, †Number of admissions for preschool wheeze at age <2 years divided by the number of years, ‡Number of admissions for preschool wheeze at age between 2 and <6 years divided by the number of years. OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

Table 5: Multivariable logistic regression analysis for prescription of asthma controller after the age of 6 years

Potential risk factors	Adjusted OR (95% CI)	*P*
Gender (female)	1.34 (0.82-2.20)	0.239
Eosinophilia	1.02 (0.65-1.73)	0.814
Family history of asthma	1.82 (1.09-3.02)	0.022*
Allergic rhinitis	4.58 (2.16-9.71)	<0.001*
SPT positivity	1.55 (0.91-2.63)	0.106
Late preschool wheeze admission index†	1.51 (0.87-2.64)	0.143

*P<0.05, †Number of admissions for preschool wheeze at age between 2 and <6 years divided by the number of years. OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

$$P = \frac{\text{Prediction Index C}^*}{1 + \text{Prediction Index C}^*}$$

*Prediction index C = Exp (−2.8 + 0.6 × family history of asthma + 1.5 × allergic rhinitis)

Using the above model, the OR of prescription of asthma controller comparing children with various risk factors can be estimated. For instance, a child with allergic rhinitis and family history of asthma will be nearly 6 times more likely to be prescribed with asthma controller after the age of 6 years than a child without allergic rhinitis and family history of asthma [Appendix 3].

Discussion

Early life allergic sensitization was well known to be a risk factor for developing subsequent asthma in later childhood.[6,7] SPT is an easily available tool for identifying sensitization in young children. In the present study, our results suggested that SPT positivity may have a prognostic role in identifying those preschool wheezers who may have a higher chance to develop subsequent asthmatic attack requiring emergency

hospital admission after the age of 6 years. Emergency hospital admission was a surrogate marker for a relatively severe asthmatic attack after the age of 6 years. Previous studies demonstrated the association between SPT positivity and wheeze persistency after preschool age.[7-9,13] Kurukulaaratchy *et al*.[8] suggested that recurrent chest infections at 2 years old, family history of asthma, SPT positivity at 4 years old, and the absence of nasal symptoms at 1 year old were the four risk factors predicting the persistence of early life wheezing in later childhood. In the multivariate logistic regression model, female gender, SPT positivity, and late preschool wheeze admission index were the significant risk factors for asthma hospitalization after the age of 6 years. Female gender as a significant risk factor for asthma admission beyond the age of 6 years was consistent with the fact that females have lower specific airway resistance for the first 2 years of life.[14,15] Therefore, girls, who wheezed despite their larger airway, were more likely to have asthma than boys who wheezed because of their smaller airway, hence more likely to outgrow it with time as the lower airway grows rapidly in the first 2 years of life.[15] Those with allergic rhinitis and family history of asthma were more likely to require asthma controller medication beyond the age of 6 years.

This study has several limitations. As it was a retrospective study, data retrieved from the hospital's clinical management system were not as comprehensive and complete as a prospective study using a standardized questionnaire. Potential confounding factor concerning concurrent viral infection was not included due to practical difficulties. In the present study, our primary outcome was based on data in emergency asthma admission to public hospitals only. Those patients with asthmatic attack who were admitted to private hospitals would have been missed even though HKHA accounted for 80.3% of the total inpatient service in Hong Kong.[16] Therefore, the association between SPT positivity and subsequent asthmatic attack requiring hospitalization may have been underestimated.

Regarding generalizability, SPTs were arranged for patients with two or more wheezes or a moderate-to-severe wheeze requiring hospitalization. Therefore, the findings would be more applicable to those preschool wheezers with more frequent or severe wheeze.

Conclusion

The current study shows that female gender, SPT positivity, and number of preschool wheeze admissions after the age of 2 years predict asthma hospitalization after the age of 6 years. Furthermore, those with allergic rhinitis and family history of asthma are more likely to require asthma controller medication beyond the age of 6 years.

Acknowledgment

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Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendixes

Appendix 1: List of asthma controllers

Alvesco (ciclesonide)
Becloforte/becotide (beclomethasone dipropionate)
Flixotide (fluticasone)
Pulmicort (budesonide)
Seretide (fluticasone/salmeterol)
Serervent (salmeterol)
Singulair (montelukast)
Symbicort (budesonide and formoterol)
Vannair (budesonide and formoterol)

Appendix 2: Probabilities of emergency asthma admission after the age of 6 years comparing children with various risk factors

Late preschool wheeze admission index† / Risk factors	0	0.5	1	1.5	2	2.5	3
Female							
SPT +ve							
Probability*	0.16	0.28	0.44	0.61	0.76	0.86	0.93
SPT -ve							
Probability*	0.07	0.13	0.22	0.37	0.54	0.70	0.83
Male							
SPT +ve							
Probability*	0.11	0.19	0.32	0.49	0.66	0.8	0.89
SPT -ve							
Probability*	0.04	0.08	0.15	0.26	0.42	0.59	0.74

*Probability of having asthma admission after the age of 6 years, †Number of admissions for preschool wheeze at age between 2 to 5.9 years divided by the number of years. SPT: Skin prick test

Appendix 3: Probability of asthma controller prescription after the age of 6 years comparing children with various risk factors

	Allergic rhinitis positive	Allergic rhinitis negative
Family history of asthma positive	0.35*	0.11*
Family history of asthma negative	0.23*	0.06*

*Probability of requiring asthma controller prescription after the age of 6 years

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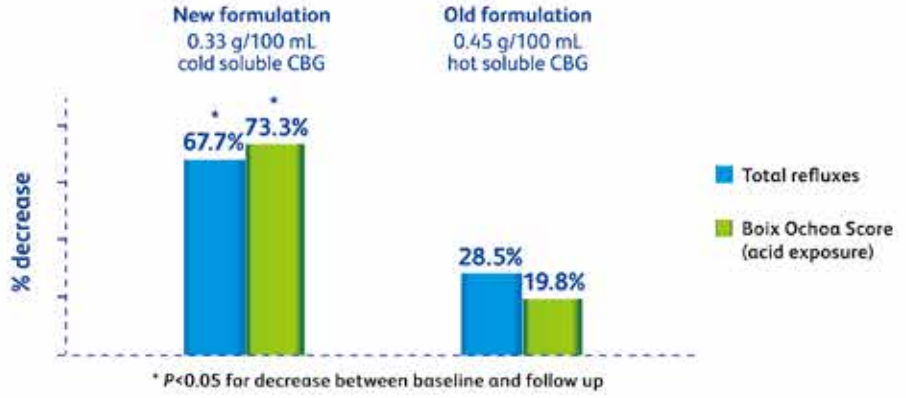

* *P*<0.05 for decrease between baseline and follow up

A randomized, partly double blind clinical trial conducted in the University Hospital "St. Marine" Varna, Bulgria
Fifty-six eligible infants (1-6 mo old) were randomly allocated to receive for two weeks a formula with either 0.33 g/100 mL or 0.45 g/100 mL of cold soluble CBG galactomannans respectively or a formula with 0.45 g/100 mL of hot soluble CBG galactomannans.
Reference: Georgieva M, Manios Y, Rasheva N, Pancheva R, Dimitrova E, Schaafsma A. Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices, *World J Clin Pediatr*, 2016 February 8; 5(1): 118-127.

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台灣兒童胸腔暨重症醫學會第七屆第二次會員大會暨學術研討會時間表

時間：106 年 4 月 16 日(星期日)
地點：高雄醫學大學附設中和紀念醫院啟川大樓 6 樓第二講堂
主題：pediatric critical care
合辦單位：高雄醫學大學附設中和紀念醫院

TIME	TOPIC
08:40-09:10	報到
09:00-09:10	opening remark 主持人：戴任恭理事長；榮譽大會會長：劉景寬校長、鍾飲文院長、吳國強教授
09:10-09:50	專題演講 I： Pediatric airway commitee inSpain: organization and outcomes of team work in our center (西班牙)(40min) 講師：Prof. Carlos Gutierrez / 主持人：戴任恭理事長、周世華醫師
9:50-10:00	Discussion
10:00-10:30	Tea time
10:30-11:10	專題演講 II： Ciliary function: in health and disease (英國) (40min) 講師：Prof.Chris O' Callaghan / 主持人：謝凱生副理事長、黃健燊主任
11:00-11:20	Discussion
11:20-12:30	young investigator 1(less than 40 y/0) competition (約 1-2 題，可 case sharing)(9min/1 題) / 主持人：陳家玉教授、黃崇濱副院長 young investigator 2(less than 40 y/0) competition (約 1-2 題，可 case sharing)(9min/1 題) / 主持人：宋文舉主任、穆淑琪主任 young investigator 3 (less than 40 y/0) competition (約 1-2 題，可 case sharing)(9min/1 題) / 主持人：黃碧桃教授、林清淵教授
12:30-13:30	午餐及會員大會
13:30-14:20	醫學倫理(兩性平等議題)(50min) 講師：成令方 / 主持人：徐世達主任、詹秀玉主任
14:20-14:40	Tea time
	Update of critical care
14:40-15:05	第 1 主題：Overview of pediatric pulmonary hypertension 講師：戴任恭理事長 / 主持人：申昆玲教授、繆定逸教授
15:05-15:25	第 2 主題：Pulmonary hypertension in neonate (20min) 講師：林毓志主任 / 主持人：于鴻仁醫師、王德明主任
15:25-15:45	第 3 主題：Acute respiratory distress syndrome (20min) 講師：陳怡真醫師 / 主持人：呂克桓校長、牛震廣院長
15:45-16:05	第 4 主題：Renal failure (20min) 講師：蘇有村主任 / 主持人：林毓志主任、農寶仁醫師
16:05-16:25	第 5 主題：Sepsis (20min) 講師：農寶仁醫師 / 主持人：陳中明主任、何文佑醫師
16:25-16:45	第 6 主題：Hepatic failure (20min) 講師：于鴻仁醫師 / 主持人：徐仲豪主任、蘇有村主任
16:45-16:50	Discussion / 主持人：鄭玫枝主任、呂 立主任
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The Correlation of Exhaled Nitric Oxide, Atopy, and Severity of Allergic Rhinitis in Taiwanese Children with Moderate Persistent Asthma

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Abstract

Background: Allergic rhinitis (AR) is characterized by eosinophilic infiltration and immunoglobulin E (IgE)-mediated reaction after exposure to an allergen. Its severity may be correlated to fractional exhaled nitric oxide (FeNO). This study aimed to evaluate the correlation of FeNO and various parameters with severity of AR in Taiwanese children with moderate persistent asthma. **Materials and Methods:** The study enrolled 103 children aged 5–18 years with AR and moderate persistent asthma from the Outpatient Department, Mackay Memorial Hospital, Taipei. Based on Total Nasal Symptom Score (TNSS), the patients were divided into high-score group (TNSS ≥5) and low-score group (TNSS <5). Both groups were assessed and compared by FeNO, blood eosinophil percentage, serum total IgE level, specific IgE levels to 8 allergens, and pulmonary function tests. **Results:** The low-score group showed significantly lower FeNO (18.57 ± 14.47 vs. 26.83 ± 17.84 ppb; $P < 0.05$), lower blood eosinophil percentage (3.08 ± 3.43 vs. 4.53 ± 3.37%; $P < 0.05$), lower level of serum total IgE (232.64 ± 438.88 vs. 510.63 ± 732.64 IU/mL; $P < 0.05$), and lower specific IgE to *Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), and dog (1.80 ± 2.35 vs. 3.66 ± 2.23, $P < 0.05$; 1.78 ± 2.36 vs. 3.56 ± 2.31, $P < 0.05$; and 0.00 ± 0.00 vs. 0.29 ± 0.81, $P < 0.05$). There are no significant differences between two groups about forced expiratory volume in 1 s (FEV1) (96.95 ± 13.39 vs. 97.85 ± 14.98% predicted; $P = 0.75$), FEV1/forced vital capacity percentage (89.00 ± 9.78 vs. 90.20 ± 5.85%; $P = 0.47$), and forced expiratory flow 25%–75% (55.16 ± 18.48 vs. 56.75 ± 20.15% predicted; $P = 0.68$). **Conclusions:** Taiwanese children with moderate persistent asthma with more severe symptoms of AR are significantly associated with higher levels of FeNO, total IgE, specific IgE to *Der p*, *Der f*, and dog, and higher blood eosinophil percentage.

Keywords: Allergic rhinitis, children, fractional exhaled nitric oxide, moderate persistent asthma

Introduction

The human nasal cavity is an important airflow orifice and the gatekeeper of the human airway. Its functions are heating, humidification of inspired air, filtration of hazardous air pollutants and allergen particles, and protection of the peripheral airway. As such, it becomes the most vulnerable organ for accumulating allergic inflammation and the manifestation of clinical symptoms.

Allergic rhinitis (AR) is a chronic inflammatory disease of the nasal mucosa induced by an immunoglobulin E (IgE)-mediated reaction. It is defined by sensitization to inhaled allergens and symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing during exposure to relevant allergens.[1-3] Thus, AR has become one of the most common chronic disorders in childhood and adolescence, and its prevalence rate has doubled over the past decades such that the current prevalence rates in countries with the Western lifestyle may be as high as 40%.[1,4]

Fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker of eosinophilic airway inflammation.[5] It is produced by airway epithelial cells in response to inflammatory cytokines.[6,7] Evidence based on the previous studies supports the tight relationship between increased FeNO levels and allergic airway inflammation.[7-10] Recent opinions by the American Thoracic Society (ATS) and the European Respiratory

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Society (ERS) recognize the role of FeNO in the assessment and management of airway diseases. Recommendations for the standardized procedures of measurement have also been made.[11,12] Various studies have proven that AR is associated with increased FeNO levels.[8,9,13-17]

This study attempted to evaluate the correlation of the severity of AR, FeNO, and various parameters including atopy-related biomarkers in Taiwanese children with moderate persistent asthma. The results may help clarify the role of FeNO and other parameters in assessing the conditions of Taiwanese moderate persistent asthmatic children with AR.

Materials and Methods

Study design and subjects

This cross-sectional study enrolled 103 children aged 5–18 years old. All of them were first diagnosed with AR and moderate persistent asthma at the Outpatient Department, Mackay Memorial Hospital, Taipei. Besides, the enrolled children were not undergoing any known treatment of asthma and AR including oral drugs and inhaled agents. The diagnosis of AR was done based on a typical history of allergic symptoms and diagnostic tests by the Allergic Rhinitis and its Impact on Asthma guidelines.[18] Diagnosis of moderate persistent asthma was made according to the Global Initiative for Asthma 2008 guidelines.[19] The children's parents provided written informed consent whereas the children provide verbal assent.

After diagnosis had been established, evaluation of symptoms and measurement of parameters were performed before any treatment of asthma and AR including oral drugs and inhaled agents. The following symptoms of AR were evaluated in all children: sneezing, rhinorrhea, nasal itching, and nasal stuffiness. The severity of each symptom was evaluated using the Total Nasal Symptom Score (TNSS),[20,21] which had a 4-point scale (0, absent; 1, mild; 2, moderate; and 3, severe). Thus, each score ranged from 0 to 3 points, and possible total score ranged from 0 to 12 points. General characteristics, including age, sex, height, body weight, body mass index (BMI), gestational age at birth, and birth weight, were obtained from medical records and questionnaires completed by the patients and their parents. Symptoms of asthma including night cough, shortness of breath in the early morning, dyspnea or wheezing in daytime, and cough in daytime were also evaluated using asthma symptom score.[22] Each asthma symptom score ranged from 1 to 4 points, and possible total score ranged from 0 to 16 points.

Other parameters measured were FeNO, blood eosinophil percentage, blood absolute eosinophil count, serum total IgE level, specific IgE levels to eight allergens (i.e., *Dermatophagoides pteronyssinus* [*Der p*], *Dermatophagoides farinae* [*Der f*], cat, dog, cockroach, egg white, milk, and fish), and pulmonary function test.

After evaluating the symptoms and measuring the parameters, the children were divided into two groups arbitrarily as per the clinical practice of the authors. The high-score group included 59 children with TNSS ≥5 whereas the low-score group included 44 children with TNSS <5. Both groups were then compared.

Measurements of fractional exhaled nitric oxide

The FeNO was measured in all participants using a handheld, portable Nitric Oxide Analyzer (NIOX MINO, Aerocrine AB, Solna, Sweden) before pulmonary function testing by spirometry. All FeNO measurements followed the ATS/ERS recommendations.[12] Only measurement results from correctly performed procedures and under the correct conditions would be presented. The participants were asked to inhale to total lung capacity and then exhale through the NIOX MINO at a mouth flow rate of 50 mL/s over 10 s, assisted by visual and auditory cues.[23] The measurement range of NIOX MINO was 5–300 ppb.

Measurement of blood eosinophils, serum total immunoglobulin E, and specific immunoglobulin E

Laboratory examination included blood eosinophil percentage, absolute eosinophil count, serum total IgE, and specific IgE to *Der p*, *Der f*, cat, dog, cockroach, egg white, milk, and fish. Serum total IgE concentration was determined by the IMMULITE chemiluminescent immunoassay system (Diagnostic Products Corporation, Los Angeles, CA, USA). The normal range of total IgE was <100 IU/ml. The Pharmacia CAP system (Modal Auto-CAP V1 Pharmacia, Uppsala, Sweden) was used to quantify specific IgE antibody concentration in the serum. The degree of hypersensitivity was classified according to the concentrations of specific IgE: Class 0 (<0.35 kuA/L), Class 1 (0.35–0.7 kuA/L), Class 2 (0.7–3.5 kuA/L), Class 3 (3.5–17.5 kuA/L), Class 4 (17.5–50 kuA/L), Class 5 (50–100 kuA/L), and Class 6 (>100 kuA/L).

Pulmonary function tests

Pulmonary function testing included assessments of the forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), forced expiratory flow (FEF) in 1 sec/FVC ratio (FEV1/FVC), and FEF rate over the middle 50% of the FVC (FEF 25%–75%). All pulmonary function tests were performed using an automated spirometer (Model 2130; SensorMedics, Yorba Linda, CA, USA). A well-trained, experienced technologist performed all of the procedures to ensure that the quality of tests fulfilled the ATS standards.[24,25]

Statistical analysis

Data from the total group of children were divided into the high-score group (children with TNSS ≥5) and low-score group (TNSS <5). Group data were expressed as means ± standard deviation (SD). Analysis was performed using SPSS 19 for Windows (SPSS Inc., Chicago, Illinois, USA). Variables of clinical parameters between the two groups were compared using Student's *t*-test and Mann–Whitney U-test, as needed. Variables of basic characteristics were compared using Mann–Whitney U-test and Chi-squared analysis, as

appropriate. The FeNO and serum total IgE values were log transformed before analysis to achieve a near normal distribution. For presentation, log-transformed means and SDs were reconverted to their original scale. Statistical significance was set at $P < 0.05$.

Results

Basic characteristics of patients

The low-score group ($n = 44$) had a mean age of 9.48 ± 2.77 years whereas the high-score group ($n = 59$) had a mean age of 9.74 ± 3.24 years. The ratio of boys to girls was 1.24:1.

In terms of basic characteristics, there were no statistically significant differences between the two groups with regard to sex (61.4% vs. 50.8% male; $P = 0.29$), age (9.48 ± 2.77 vs. 9.74 ± 3.24 years; $P = 0.87$), height (138.53 ± 17.38 vs. 137.60 ± 16.67 cm; $P = 0.78$), weight (36.20 ± 15.53 vs. 35.18 ± 14.39 kg; $P = 0.95$), BMI (18.88 ± 8.23 vs. 18.27 ± 3.11 kg/m^2; $P = 0.53$), birth gestational age (39.05 ± 1.37 vs. 38.84 ± 1.73 week; $P = 0.75$), birth body weight (3219 ± 458.49 vs. 3117 ± 413.55 g; $P = 0.26$), and asthma symptom score (4.16 ± 1.60 vs. 4.71 ± 1.89 g; $P = 0.31$) [Table 1].

Relationship between the two groups in terms of fractional exhaled nitric oxide

In terms of FeNO, the low-score group had significantly lower FeNO levels than the high-score group (18.57 ± 14.47 vs. 26.83 ± 17.84 ppb; $P < 0.01$) [Table 2].

Relationship between the two groups by eosinophil parameters or total immunoglobulin E levels

Comparing blood eosinophil percentage and serum total IgE levels, the low-score group had lower eosinophil percentage (3.08 ± 3.43 vs. 4.53 ± 3.37%; $P < 0.01$) and absolute eosinophil count (229.97 ± 244.42 vs. 352.08 ± 243.47/μL; $P < 0.01$) [Table 3]. The low-score group also had lower serum total IgE levels (232.64 ± 438.88 vs. 510.63 ± 732.64 IU/mL; $P < 0.01$).

Relationship between the two groups in terms of serum allergen-specific immunoglobulin E

The low-score group had significantly lower serum levels of specific IgE to *Der p* (1.80 ± 2.35 vs. 3.66 ± 2.23; $P < 0.01$), *Der f* (1.78 ± 2.36 vs. 3.56 ± 2.31; $P < 0.01$), and dog (0.00 ± 0.00 vs. 0.29 ± 0.81; $P = 0.01$) [Table 4]. There were no significant differences between the two groups in terms of serum levels of specific IgE to other agents such as cat, cockroach, egg white, milk, and fish.

Relationship between the two groups by pulmonary function tests

There were no significant differences between the low-score and high-score groups in terms of FEV1 (96.95 ± 13.39 vs. 97.85 ± 14.98% predicted; $P = 0.75$), FEV1/FVC (89.00 ± 9.78 vs. 90.20 ± 5.85%; $P = 0.47$), and FEF 25%–75% (55.16 ± 18.48 vs. 56.75 ± 20.15% predicted; $P = 0.68$) [Table 2].

Table 1: Basic characteristics of the two groups

Basic characteristics	High score (score ≥5)	Low score (score <5)	*P*
n	59	44	
Male sex, *n* (%)	30 (50.8)	27 (61.4)	0.29
Age (years)	9.74±3.24	9.48±2.77	0.87
Height (cm)	137.60±16.67	138.53±17.38	0.78
Weight (kg)	35.18±14.39	36.20±15.53	0.95
BMI (kg/m^2)	18.27±3.11	18.88±8.23	0.53
Gestational age (weeks)	38.84±1.73	39.05±1.37	0.75
Birth body weight (g)	3117±413.55	3219±458.49	0.26
TNSS	7.44±2.06	2.34±1.57	<0.01
Asthma symptom score	4.71±1.89	4.16±1.60	0.31

TNSS: Total Nasal Symptom Score, BMI: Body mass index

Table 2: Fractional exhaled nitric oxide level and pulmonary function tests between the two groups

Characteristics	High score (score ≥5)	Low score (score <5)	*P*
FeNO (ppb)	26.83±17.84	18.57±14.47	<0.01
FEV_1 (% predicted)	97.85±14.98	96.95±13.39	0.75
FEV_1/FVC (%)	90.20±5.85	89.00±9.78	0.47
FEF 25%-75% (% predicted)	56.75±20.15	55.16±18.48	0.68

FeNO: Fractional exhaled nitric oxide, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, FEF: Forced expiratory flow

Table 3: Eosinophil percentage and total serum immunoglobulin E levels between the two groups

Characteristics	High score (score ≥5)	Low score (score <5)	*P*
Eosinophil percentage	4.53±3.37	3.08±3.43	<0.01
Absolute eosinophil count (/μL)	352.08±243.47	229.97±244.42	<0.01
Total IgE (IU/mL)	510.63±732.64	232.64±438.88	<0.01

IgE: Immunoglobulin E

Table 4: Serum levels of allergen-specific immunoglobulin E between the two groups

CAP items	High score (score ≥5)	Low score (score <5)	*P*
Dermatophagoides pteronyssinus (grade)	3.66±2.23	1.80±2.35	<0.01
Dermatophagoides farinae (grade)	3.56±2.31	1.78±2.36	<0.01
Cat (grade)	0.12±0.46	0.16±0.61	0.96
Dog (grade)	0.29±0.81	0.00±0.00	0.01
Cockroach (grade)	0.29±0.70	0.27±0.82	0.51
Egg white (grade)	0.07±0.31	0.07±0.25	0.73
Milk (grade)	0.14±0.47	0.05±0.21	0.41
Fish (grade)	0.00±0.00	0.00±0.00	1.00

Discussion

This cross-sectional study integrated data from a detailed medical history with a variety of physiologic and laboratory

examinations in two groups of Taiwanese moderate persistent asthmatic children with AR of varying severities. The integrated approach suggests substantial differences between patients with high scores and those with low scores.

Various studies had described that higher FeNO levels were observed in patients with AR,[8,26,27] while AR was associated with increased FeNO levels mainly by the increased expression of inducible nitric oxide synthase.[11] Moreover, some reports also suggested a correlation of symptoms of AR and nasal FeNO or oral FeNO levels.[14,28] In the present study, oral FeNO level could reflect the degree of allergic inflammatory conditions in Taiwanese moderate persistent asthmatic children with AR of varying severities. The similar positive correlation between symptoms of AR and oral FeNO levels could be found in the study by Lee *et al*.,[28] which suggested that FeNO reflected an increase in the severity of lower airway inflammation according to increased upper airway inflammation.

Children with more severe symptoms of AR in this study had significantly higher blood eosinophil count. In previous reports, the relationship of blood eosinophil percentage and symptoms of AR was seldom investigated. However, the findings here were consistent with the reports by Droste *et al*. and Chen *et al*.[29,30] A previous study also suggested that simple tests such as blood eosinophil count may provide useful information for diagnosing and predicting the severity of AR.

Higher levels of serum total IgE and specific IgE of *Der p, Der f*, and dog showed significant association with more severe symptoms of AR. The results were consistent with those of a previous study that showed a significant association between symptom severity of AR and total IgE level.[30] About symptoms of AR and specific IgE levels, previous investigators found a positive association between specific IgE levels and clinical symptoms.[29,31,32] In the present study, results of pulmonary function tests showed no significant difference between the two groups of Taiwanese moderate persistent asthmatic children with different severities of AR. In previous studies which described correlation of AR symptoms and FeNO, workup of pulmonary function tests was not mentioned.[14,28] In our study groups, FeNO reflects higher severity of AR symptoms better then pulmonary function tests.

Conclusions

Higher eosinophil count, total IgE, specific IgE to *Der p*, *Der f*, and dog, and FeNO level are correlated to higher TNSS score in Taiwanese moderate persistent asthmatic children with AR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Focal Chest Wall Protuberance due to Forked Ribs or Cartilages: An Analysis of 12 Cases

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Abstract

Objective: The purpose of this article is to describe and summarize the clinical manifestations and radiographic features of focal bulging of chest walls in children using plain chest radiography and computed tomography (CT) scans. **Methods:** From 2008 to 2014, we identified 12 patients with forked ribs younger than 18 years of age. These patients received plain chest radiography and computed tomographic scans of the chest for focal anterior chest wall protrusion at the outpatient chest clinic of a children's facility. **Results:** A total of 12 patients (5 girls and 7 boys; age range, 2–12 years; median, 5 years) were enrolled in this study. Six patients had right-sided costal lesions, four had left-sided lesions, and two had anomalies on both sides. The most common rib involved was the 4th rib. Two patients with forked cartilages and one patient with forked rib were not detected in frontal radiograph but seen by CT scans only. Up to the time of this writing, the follow-up of patients revealed no progression of focal bulging. **Conclusion:** In otherwise healthy children with asymptomatic focal anterior chest wall bulging, forked ribs is a common cause of variation. The chest radiographs may be normal. Chest CT scans demonstrated forked ribs/cartilage as the cause of focal bulging of the chest wall unequivocally in such instances.

Keywords: Bifid sternum, chest wall, forked cartilage, forked ribs

Introduction

Protruding chest wall lesions in children are both worrisome for the parents and the primary care physicians alike. The diagnostic possibilities of focal bulging of the thorax include congenital costal or cartilaginous anomalies of developmental variations, infections, and benign and malignant neoplasms of soft tissue/bony origins.[1-5] Congenital chest wall anomalies can be observed as a single anomaly or as a symptom of various monogenic syndromes, chromosome aberrations, or disruption sequences.[6] Despite anatomical variations being the most common cause of chest wall protrusions in the pediatric population, the clinical manifestations of forked (or bifid) ribs were infrequently described.[7] This study described the experience of forked ribs in a single pediatric chest clinic and reviewed the literature.

Methods

Patients

This is a retrospective observational study performed on patients aged below 18 years who had undergone chest radiography with/or without computed tomography (CT) scans with diagnoses of bifid ribs or cartilages. The patients were recruited from the database of patients visiting the chest clinic extended from January 2008 to December 2014. Our hospital is a university-affiliated hospital with walk-in-clinic serving the community. Patients presenting with primary pectus excavatum or carinatum were excluded from the analysis. Our Institutional Review Board approved the study with waiver of informed consent because the study only entailed a retrospective review of medical records (CGMH 102-3246B). From the medical charts, we retrieved demographic data, clinical presentations, underlying diseases, and confirmation of anomalies by helical CT scans with three-dimensional reconstruction if available.

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Results

A total of 12 patients were identified for the study (5 girls and 7 boys) with a median age of 5 years (range, 2–12 years) [Table 1]. Six patients had right-sided costal lesions, four had left-sided lesions, and two had anomalies on both sides [Figure 1a and b]. Multiple forked lesions were seen in two patients, one patient on the left side (Case 3) and one patient on the right side (Case 7). The most common ribs involved were 4th rib (6 times), 3rd rib (5 times), 5th rib (4 times), and once for 1st and 6th ribs, respectively. One patient had simultaneous fusion of the 1st and 2nd ribs together with the 3rd forked rib. Three patients with bifid rib were not detected in frontal radiograph but seen by CT scans only. Case 11 suffered from 47 XXY anomaly. Case 12 had right-sided forked cartilage together with a cleft sternum [Case 12 in Figure 2]. No patient required additional therapy for the forked ribs.

Discussion

Children presenting with focal bulging in the anterior chest wall are challenging to the clinicians because of the wide varieties of diagnostic possibilities.[1-5] Focal bulging of the chest wall can be caused by infections, such as empyema necessitates, osteomyelitis, or local abscess formations. However, most of these patients would show signs of infections including constitutional fever, local erythema, swelling, and tenderness.[4,5] With the advance of modern molecular diagnostics, sternal or costal osteomyelitis due to Bacille Calmette–Gue´rin had been reported in increasing frequencies in the past decade and should be considered in endemic areas of *M. tuberculosis* infection as in Taiwan.[8,9]

Primary neoplasms of the chest wall are uncommon and account for only 5%–10% of all bone tumors, metastases are even rarer.[1-3] Most of the patients with malignant soft-tissue masses in the chest wall present with painful masses, cough, dyspnea, and pleural effusion. Imaging studies are important for the diagnosis of treatable diseases and confirmation of malignant tumor or infection.[3-5]

In the study for asymmetrical chest wall bumps in children by Donnelly *et al*., only one patient had bifid rib among

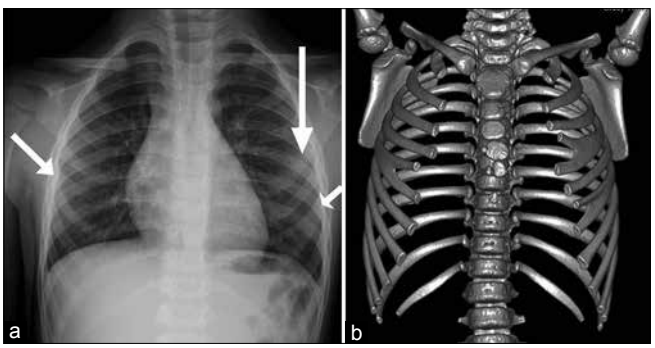

Figure 1: (a and b) The arrows in the figure demonstrate forked ribs in the right 5th, left 4th and 6th ribs, respectively (Case 8).

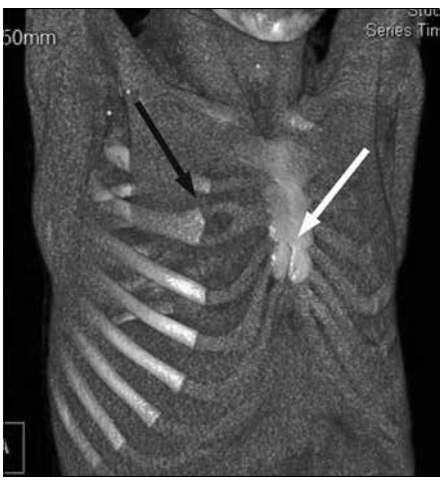

Figure 2: Black arrow in the right side demonstrates forked cartilage in the 3rd rib and white arrow in the left side reveals cleft sternum (Case 12).

Table 1: Summary of clinical and radiological findings

Case	Sex	Age (years)	Clinical presentation	Plain chest radiograph	3D reconstruction chest CT
1	Female	12	Right breast mass	Right 5th rib forked	ND
2	Male	3.5	Right chest wall protuberance	Right 4th rib forked, left 3rd rib forked	Clearly demonstrated
3	Male	11	Left clavicular enlargement	Left 1st–2nd rib fusion Left 3rd rib forked	Clearly demonstrated
4	Male	11	Left breast bony mass	Normal	Forked cartilage, 4th rib [Figure 3]
5	Male	8	Left chest wall elevation	Normal	Left 5th rib forked
6	Female	10	Right chest wall protuberance	Right 5th rib forked	ND
7	Female	5	Right parasternal protuberance	Right 3rd and 5th rib forked	ND
8	Male	3	Left anterior chest wall bulging	Right 5th rib forked, left 4th and 6th ribs forked	Clearly demonstrated [Figure 1]
9	Male	3	Right anterior chest wall bulging	Right 4th rib forked	ND
10	Male	3	Left anterior chest wall bulging	Left 4th rib forked	ND
11	Female	4	Left upper parasternal bulging	Left 4th rib forked	ND
12	Female	5	Right upper chest protuberance	Normal	Right 3rd cartilage forked and cleft sternum

3D: Three-dimensional, CT: Computed tomography, ND: Not done

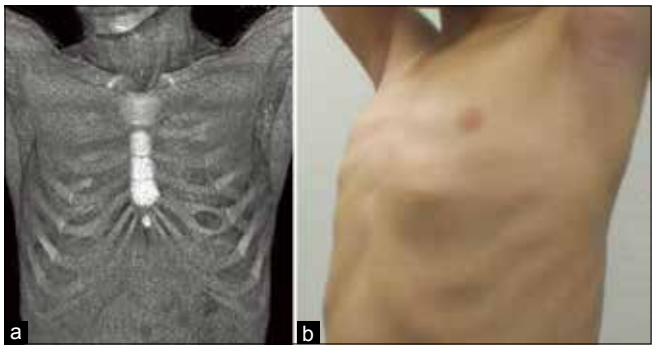

Figure 3: (a and b) Forked cartilage seen in the left 5th rib by three-dimensional reconstruction of axial computed tomographic images and photograph of the chest wall (Case 4).

26 reported patients.[10] Etter reported congenital rib anomalies in 544 (1.4%) men in the screening radiographs of 40,000 healthy young male military recruits; among whom 257 (0.6%) had fork ribs, usually the 4th rib was involved.[11] Bifid ribs were reported to occur in 0.15%–0.31% of the general population with a female predilection and occurred more frequent on the right side than the left side.[2,3,11] We found the most prevalent location of bifid ribs in this study to be the 4th rib (6 occasions), which was consistent with previous experience.[5] In this study of 12 patients, bifid rib anomaly was not mentioned in the routine report of frontal chest radiographs initially. Even with meticulous attention, three of the 12 patients had normal plain chest radiographs, and the true anomaly was not demonstrated even with bone reconstruction but well visualized with cartilage reconstruction algorithm only.

Only one patient had forked cartilage and associated cleft sternum in our study. Cleft sternum can be observed as a single anomaly or as a feature of various monogenic syndromes and chromosome aberrations.[12]

In the absence of pain, increasing size, or constitutional symptoms, physical examination is usually not rewarding, plain chest radiographs may reveal forked ribs if vigilantly looked for, but forked cartilages would be missed. No patient in this study had progression of the thoracic wall mass after a median follow-up of 3 years. Thoracic wall ultrasound was reported but the experience was limited.[13] With the availability of low-dose CT scans, it may be possible to demonstrate costal abnormalities with minimal radiation dosage with unequivocal diagnosis.

We were not able to calculate the true prevalence of forked ribs in a group of patients with chest wall bulgings because the total number of patients who had undergone investigations was not enumerated due to a retrospective analysis.

Conclusion

In children with an asymptomatic focal anterior chest wall bulging, forked rib is the common cause. It is commonly seen in preschoolchildren in the right side, sometimes with multiple site involvement either ipsilaterally or contralaterally. Chest CT scans demonstrated forked ribs/cartilages as the cause of focal bulging of the chest wall unequivocally if plain chest radiographs were normal.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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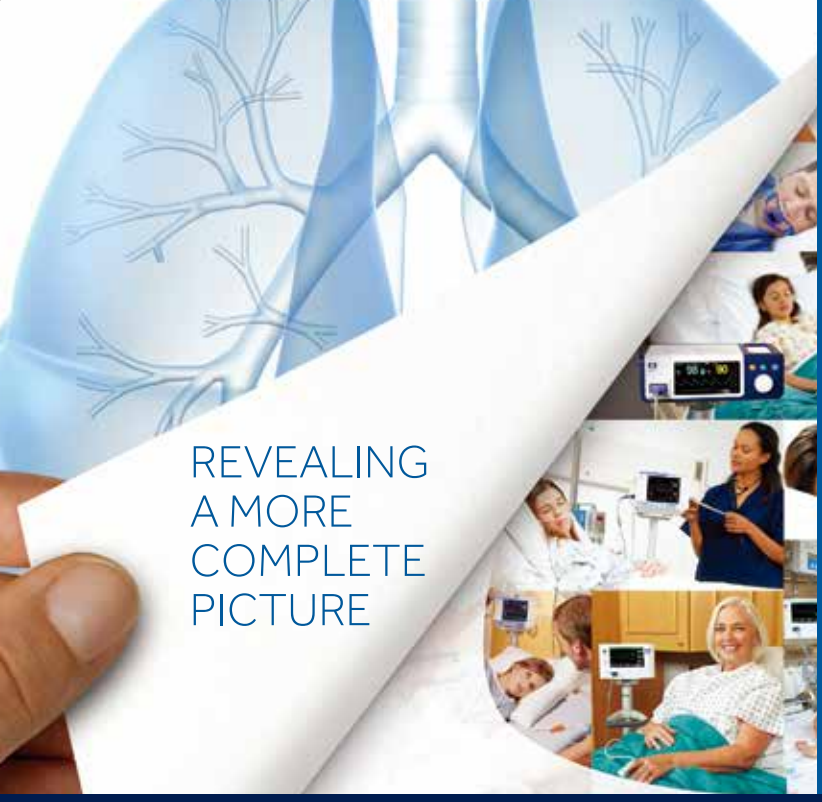

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