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ORIGINAL ARTICLE

The Natural History of Fatal Childhood Asthma—A Case from the Isle of Wight Birth Cohort

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Subjects with severe and unstable asthma are at high risk of fatal asthma attack. We describe a case of fatal childhood asthma in an 11-year old girl whose asthma was apparently stable with supranormal lung function and identify additional characteristics that should be considered as increasing the risk for fatal asthma. This opportunity was provided by this girl's participation in the Isle of Wight Whole Population Birth Cohort Study. Prospectively collected data identified her as an early-onset persistent wheezer with significant allergic comorbidity. She was highly atopic with multiple allergen sensitization and a total IgE exceeding 5000 Ku/L (normal range: 0–180 ku/l) at 10 years. Additionally at that age, whilst possessing normal lung function (FEV₁ 2.15 Litres; 110% predicted), she was found to have marked bronchial hyper-responsiveness (PC₂₀ Methacholine 1.71 mg/ml). At the age of 11 years, despite apparent clinical stability and use of regular controller asthma therapy, she suffered a fatal acute asthma attack that may have been related to acute allergen exposure. This report provides further insight into factors associated with fatal childhood asthma. We propose that highly atopic children with early onset persistent asthma are at a higher risk of fatal asthma even if their asthma is apparently stable and lung function is normal. Marked bronchial hyper-responsiveness provides a clue and should be assessed if there is concern.

Keywords asthma phenotypes, allergen sensitivity, allergen exposure, bronchial hyper-responsiveness, childhood asthma, fatal asthma

INTRODUCTION

Recent advances in childhood asthma management have reduced associated morbidity and mortality (1, 2). However, severe and sometimes fatal cases still occur (3, 4). Recognition that childhood asthma comprises numerous phenotypes has aided understanding of this complex disease (5). Despite such progress, severe childhood wheezing phenotypes conveying possible fatality risk remain poorly understood.

We report a case of acute fatal asthma in an 11-year-old girl with persistent but apparently stable atopic asthma. She was a participant of the Isle of Wight Whole Population Birth Cohort Study—a prospective study assessing the natural history of asthma and allergic disease. That participation has provided an opportunity to increase understanding of fatal childhood asthma.

CASE STUDY

The subject was recruited at birth into our Cohort ($n = 1456$) and underwent regular Study reviews (1, 2, 4 and 10 years). There was no childhood domestic exposure to tobacco smoke or animals. There were background histories of paternal asthma and of a paternal Aunt dying of acute severe asthma aged 19 years.

Our subject was delivered at term weighing 2.9 kg. She was breast-fed for the first 5 weeks of life with introduction of cows' milk at 4 weeks and solids at 3 months. She demonstrated early evidence of atopy (Table 1) with egg sensitisation at 1-year skin prick test (SPT). One-year clinical assessment recorded recurrent wheeze, atopic dermatitis, and

egg allergy (vomiting and rash). Over the next year she had continuing wheeze (diagnosed as asthma), atopic dermatitis, egg allergy, plus rhinitis while 2-year SPT found aeroallergen but not food sensitisation (Table 1).

Her asthma deteriorated in the preschool period, with several exacerbations and 3 overnight hospitalizations, despite therapy with inhaled cromoglycate and salbutamol syrup. Study review at 4 years confirmed ongoing asthma, atopic dermatitis, and rhinitis but no further food allergy. SPT detected aeroallergen plus peanut sensitisation (Table 1).

Her asthma stabilised after reaching school age and she enjoyed physical activities like cycling and gymnastics, unaffected by her asthma. By 10 years she was controlled on inhaled budesonide (200 micrograms bd) and salmeterol (50 micrograms bd). Compliance with therapy was reportedly good. Three courses of oral corticosteroid “ever” for acute asthma therapy were reported by then. At that review in response to the ISAAC questionnaire she described 4–12 wheezing attacks, only infrequent nocturnal asthma awakening and at least one episode of speech limitation due to severe wheezing in the past year. Reported asthma triggers included infection, dust, pollen, and animals (once developing wheezing, angioedema, and urticaria at a Donkey Sanctuary).

Ten-year review confirmed ongoing atopic dermatitis, perennial rhinitis, and development of adverse reactions to peanut. While avoiding overt nut ingestion, consumption of “hidden” peanut was followed by itchy lips and nausea, but never more generalised symptoms. No other significant comorbidities were reported. SPT demonstrated aeroallergen and food sensitisation (Table 1). Total IgE was grossly elevated (Table 2), spirometry normal (FEV₁ = 110% predicted) with no hint of airway obstruction (FEV₁/FVC: 96%), and methacholine challenge detected significant bronchial

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TABLE 1.—Atopic sensitisation through childhood for subjects.

	1-year	2-year	4-year	10-year
SPT positive	Egg (++++)	House dust mite (++++) Cat (++++) Dog (++++)	House dust mite (4) Alternaria (3) Peanut (3)	House dust mite (6) Peanut (11) Hazelnut (5) Almond (3) Cat (7) Dog (5) Cod (4) Grass pollen (9) Horse (9) Haydust (3) Cladosporium (3)
SPT negative	House dust mite Grass pollen Milk	Egg Grass pollen Milk	Egg Grass pollen Milk Walnut Brazil nut Hazelnut Almond Wheat Pea Cod Soya Cat Dog Cladosporium	Egg Tree pollen Milk Walnut Brazil nut Cashew Cocoa Wheat Cheese Alternaria Soya

Figures in parentheses refer to recorded mean wheal diameter (mm) for positive (>3 mm) skin prick test (SPT) results that were available from study records.
+++ Denotes >3 mm mean wheal diameter in infancy.

hyper-responsiveness (BHR). Subsequently she was assessed in an Outpatient Clinic and given adrenaline pens, topical emollient and corticosteroid for her food allergy and atopic dermatitis.

Twenty months later she suffered a fatal asthma exacerbation while visiting a friend on a mild, damp winter day. Her parents felt that her disease had been stable in the interim. Livestock including horses were present nearby and the children visited them when playing. Food was not consumed. While outdoors, she developed breathlessness, wheeze and nausea. She took inhaled bronchodilator but deteriorated, rapidly progressing into respiratory arrest. Cardiopulmonary resuscitation was initiated and continued during ambulance transfer to hospital. There she was pronounced dead approximately 90 minutes after collapsing. Post-mortem examination demonstrated congested large airways. The lungs were hyperinflated with visible rib markings on their surface. Sectioning revealed widespread tenacious mucus plugs within large and small order bronchi typical of severe asthma. There was no evidence of significant food residue (including nuts) within the stomach. Death was attributed to bronchial asthma related to acute allergic reaction.

DISCUSSION

This case provides timely reminder that while uncommon, fatal childhood asthma still occurs. Indicators of such outcomes are sparse. Assessment of asthma severity generally relies on level of symptoms, medication use and exacerbation frequency and most asthma clinics would additionally check lung function as an objective marker. On all these grounds, this girls' asthma was stable and she would not be regarded as high risk for adverse outcome. Understanding of the importance of phenotype to asthma outcome is still in its infancy. Characterisation of early onset persistent asthma and atopy is still emerging and assessment of BHR is not routinely done. However, this girls' participation in our birth cohort study offers insight in this regard. From prospective records we identified a strong allergic phenotype with co-existent atopic dermatitis, food allergy, and perennial rhinitis. Though physically active, with supranormal lung function, she possessed marked BHR and numerous allergen sensitisations both of which may have been relevant in her fatal outcome.

Work from this Cohort (6–9) has previously characterised childhood asthma phenotypes. Using those criteria our child was an early-onset persistent wheezer (6), a state associated

TABLE 2.—Characteristics of subject compared to mean values for early-onset persistent wheeze phenotype at 10-years.

	Case Subject	Early-Onset Persistent Wheeze Phenotype	Whole Population Sample at 10 years
Height (metres)	1.40	1.38 (1.37–1.39)	1.39 (1.39–1.39)
Weight (kg)	29.40	34.50 (33.10–35.90)	35.16 (34.71–35.61)
Body Mass Index (Weight/Height ²)	15.00	18.10 (17.57–18.62)	18.11 (17.93–18.29)
FEV ₁ (Litres)	2.15	1.97 (1.91–2.03)	2.02 (2.01–2.04)
FEV ₁ /FVC	0.96	0.86 (0.85–0.88)	0.89 (0.88–0.88)
Modified PC ₂₀ Methacholine (mg/ml)	1.71	13.00 (10.40–15.60)	20.91 (19.96–21.85)
Inverse Slope (BHR)	0.008	0.031 (0.025–0.037)	0.051 (0.048–0.053)
Total IgE (ku/L)	>5000	586.60 (376.40–760.80)	328.72 (284.16–373.27)

Values for early onset wheeze phenotype are mean with their 95% Confidence Intervals in parentheses. Modified PC₂₀ Methacholine refers to a measure of PC₂₀ where a value of 32 mg/ml has been assigned to cases where bronchial challenge failed to yield a detectable PC₂₀. Inverse slope refers to a continuous measure of bronchial hyper-responsiveness (BHR) calculated using least-squares regression analysis. Low values thus reflect greater BHR.

with significant morbidity, airflow obstruction, BHR, allergen sensitisation, rhinitis, atopic dermatitis, and food allergy. Such disease initially manifests in infancy. Early atopic sensitisation, asthmatic family history, recurrent chest infections in infancy plus absent nasal symptoms in the 1st year of life can distinguish (7) these from commoner transient infantile wheezers. Alternative classification based on atopy defined our subject as chronic childhood atopic (8), which is associated with early, persisting, severe allergic disease. It is specifically associated with troublesome childhood asthma (9) with high treatment needs. Such chronic disease has previously been linked to sudden childhood asthma death (10).

Though these phenotypes highlight groups with increased mortality risk, more specific features are needed to identify particular at-risk individuals. Only limited understanding of such factors exists. A survey of paediatric asthma admissions to Intensive Care Units (ICU) (11) identified frequent Emergency Department attendances, initial hypoxia, elevated total IgE, and longer asthma duration as independently significant risk factors for ICU admission. Our child had markedly raised IgE and chronic asthma. Her raised IgE was matched by extensive allergen sensitisation. Correlation has been drawn between severe asthma, allergen sensitisation, and exposure to sensitising allergen (12). Our subject had strong horse sensitisation plus potential horse allergen exposure when playing outdoors prior to collapsing. Horse allergen is a recognised contributor to difficult childhood asthma (13) and has been previously implicated in asthma fatality (4). Whether that may have been a relevant trigger for severe bronchospasm or even anaphylaxis in our subject is open to speculation.

Our child had significant BHR at 10 years—something previously noted (14–16) in fatal childhood asthma, both with (15) and without (14) peak flow variability. Unlike prior reports, she had deceptively normal spirometry and was not a typical “brittle asthmatic.” ISAAC responses at 10 years suggested “partial asthma control.” Our records do not include peak flow readings in the final year of life, but her parents report that she was symptomatically stable and had no history of significant exacerbation in that time. Allergen exposure in a highly, sensitised asthmatic with significant background BHR could provide plausible reason for her outcome despite apparent clinical stability.

Studies (4, 17, 18) have linked asthma death to inadequate treatment. Our patient was known to be compliant with prophylactic inhaled corticosteroid and long-acting β_2 agonist. Her symptoms at 10 years indicated “partial” rather than “total” control. Perception of “asthma control” by patients and health professionals may not be as good as it should be. Even “controlled asthmatics” possess significant ongoing airway inflammation (19) which, as here in a less controlled case, could credibly presage fatal asthma in the wrong circumstances. There may, therefore, have been scope for some treatment escalation in this case, both for her asthma and for relevant comorbidities such as rhinitis.

Table 2 compares our child to the average early-onset persistent wheezer in our Cohort ($n = 139$), while providing overall averages for these indices in the whole population (3rd column). She was smaller in size, had higher total IgE and BHR than her counterparts. Lower weight and BMI is consistent with prior demonstration (11) of lower growth in

childhood asthma fatalities and may reflect disease chronicity. Bronchial challenge data is given as modified PC₂₀ (with designation of 32 mg/ml for cases without measurable PC₂₀) plus continuous measure of dose-response slope (20) since not all children demonstrate sufficient reactivity to derive PC₂₀ measurement. Both indicate marked BHR in our subject. Our findings suggest that markedly raised total IgE and BHR herald adverse outcome in early-onset persistent wheezers.

Asthma arises (21) through genetic and environmental influences; strikingly this case was the second asthma related death within the index family. The earlier fatality of a 19-year-old paternal Aunt of the subject was similarly sudden, questioning whether specific genetic traits confer such risks. Understanding of such susceptibility is primitive but candidate genes for characteristics like BHR in the setting of atopy are already recognised (22).

In conclusion, we urge recognition of the early-onset persistent wheeze phenotype plus associated factors including marked BHR, significant specific allergen sensitisation, and allergen exposure that together may enhance the risk of fatal childhood asthma. In judging this risk it is important not to be deceived by normal spirometry and apparent symptom control as indicators of low mortality risk in such children. Instead recognise that risk by detecting marked BHR in the presence of highly atopic early-onset asthma.

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