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REVIEW ARTICLE

What lessons can be learned about asthma phenotypes in children from cohort studies?

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Abstract

'Phenotyping' asthma by multivariate analyses and more recently by unsupervised analysis has been performed in children cohorts. We describe the key findings that have emerged from these cohorts. It would appear that there are three wheeze phenotypes in children of preschool age: the mild episodic viral wheeze phenotype; the multitrigger atopic wheeze; and, less often encountered, the severe non-atopic wheeze. Early onset of allergy in asthma (more prevalent in boys) is associated with poor prognosis unlike the severe non-atopic wheeze phenotype which has a female predominance. The prognosis of the severe non-atopic wheeze depends on time of onset (early or late) of allergic expression. At school age, the risk of severe asthmatic exacerbations is associated with eosinophil predominant inflammation frequently related to allergic asthma, whereas neutrophil inflammation is associated with moderate-to-severe asthma with poorer lung function. Nevertheless, allergic asthma is also a heterogeneous disease with a severe allergic phenotype strongly associated with atopic dermatitis and very high eosinophil-driven inflammatory markers. Further studies are required to find non-invasive biological markers in very young children to better define wheezing phenotypes associated with an elevated risk of developing severe asthma with a view to personalizing treatment.

Asthma is the most common disease during childhood (1). It is a heterogeneous disease in terms of triggers, severity, inflammation and age of onset (2). To date, asthma classification has mainly been related to asthma severity: It is generally accepted that phenotypes related to asthma severity follow a track during childhood and even during the whole of life (3).

Asthma severity is also an important parameter because the major healthcare burden of this disease is related to severe asthma. Nevertheless, severe asthma includes multiple features, and it is important to distinguish between the different severe phenotypes to determine targeted and effective treatment (4).

Anti-inflammatory treatment is the pedestal of asthma treatment, but there is ongoing debate about whether children should be treated with continuous or intermittent inhaled corticosteroid treatment (5). On the other hand, uncontrolled asthma despite high levels of controlled medication should be treated with an additional treatment such as an anti-IgE (6) or various anticytokine treatments.

There is currently growing evidence that personalized medicine based on phenotypes and endophenotypes (characterized by physiopathological pathways) is important in the management of all chronic diseases (7).

Against this background of 'phenotyping' asthma, multivariate analyses and, more recently, unsupervised analyses have been performed in birth cohorts (8–16). In the same manner, phenotyping analyses have also been performed in cohorts of children comprising moderate-to-severe asthma phenotypes (17–24). In relation to these data, it appears that age of onset, hyperresponsiveness, asthma controlled by treatment and multiple sensitizations are important parameters to define phenotypes of asthma during childhood. In this article, we highlight the main results which have emerged from these cohorts in preschool (Table 1) then in school age (Table 2) children.

Table 1 Asthma phenotypes in very young children

	Gender Predominance	High risk of exacerbation	Prognosis in term of asthma persistence during childhood	Predominant inflammation/ Response to corticosteroid
Episodic Viral Wheeze	Male (29)	No (21, 22, 29)	Good (24, 28, 30, 39)	None (21)/High (21)
Multiple-Trigger Wheeze	Male (21, 30, 32)	Yes (21, 29, 32)	Poor (21, 24, 30–32, 36, 37, 41–44)	Eosinophilic (21, 22, 29)·/ Intermediate (21)
Nonatopic wheeze phenotype	Female (21, 35)	No (21, 22, 29)	Intermediate (depending of late onset of allergic expression) (24, 30)	Neutrophilic ?/Low (21)

Table 2 Asthma phenotypes in children at school age

	Gender Predominance	Age of asthma onset	High risk of exacerbation	Prognosis in tem of lung function decline	Predominant inflammation/ Response to corticosteroid
House dust mite Sensitization and Mild Asthma	M	Early (23, 38, 54)	_	_	Eosinophil/High (23)
Pollen Sensitization with Severe Exacerbations	M	Late (23)	Yes (23, 47)	_	Eosinophil (23, 54–56)/High (23)
Multiple Allergic Sensitizations and eczema associated with Severe Asthma	M	Early (23, 32, 46, 53)	_	Poor (23, 52, 53)	High Eosinophil (23, 46)/Low (23)
Multiple Allergic Sensitizations and Mild Asthma	M	Early (23)	_	_	Eosinophil (23)/High (23)
Severe asthma with bronchial obstruction	F	Late (45, 46, 50, 51)	_	Poor (45, 51)	Neutrophil (46)/Very low (46, 50, 51)

In preschool children, asthma phenotypes exist and are related to gender

The European Task Force proposes to use the terms episodic (viral) wheeze (*EVW*) to describe children who wheeze intermittently and are well between episodes, and multiple-trigger wheeze for children who wheeze both during and between distinct episodes (25). *EVW* consists of children with wheeze related to cold only and can be considered as mild disease (26).

These phenotypes are similar to those found in the Tucson Children's Respiratory Study (27). This study was the first to describe early transient wheeze with rare episodes of wheeze apart from colds in infants compared to persistent wheezers (28). The French Trousseau Asthma Program (TAP) cohorts, independent cohorts of several hundred consecutive children explored in a cross-sectional and prospective manner by unsupervised analysis, also identified similar phenotypes. In one TAP cohort study of 551 early wheezers with an average age of 18 months described by cluster analysis, a mild *EVW* phenotype emerged in comparison with severe phenotypes (21) (Figure 1). This phenotype was validated by another independent TAP cohort (22) which also included exhaled nitric oxide (FeNO) determinants. In the same manner, The Pollution and Asthma Risk an Infant Study (PARIS), a birth cohort composed of 3500 full-term newborns recruited in Paris, described a similar mild non-atopic wheezer phenotype (29). Furthermore, Spycher et al. (30). in two independent cohorts (nested samples of a total population of 1650 white children recruited at the age of 0–5 years in Leicestershire, UK) showed a similar phenotype with mild, virus-triggered symptom wheeze.

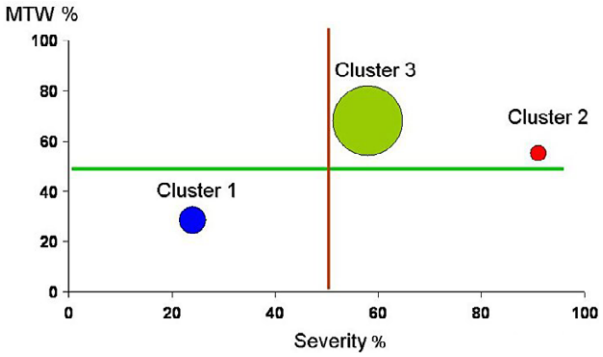

Figure 1 Representation of the three clusters according to the percentage of Multiple-trigger wheeze, severity and atopy for the entire population (n = 551). MTW (multiple-trigger wheeze) is defined as wheezing during colds and with other triggers such as house dust, grass, pets, tobacco smoke, exercise, or cold air; Severity is defined as percentage of moderate-to-severe asthma according to GINA classification; Circled area represents the percentage of atopy defined as percentage of positive Phadiatop Infant® ≥0.35 U/ml (21).

A second phenotype is the multiple-trigger wheeze identified using various approaches. For example, in the Avon Longitudinal

Study of Parents and Children (ALSPAC) (6), a birth cohort in which the children of 14,541 pregnancies were recruited antenatally, two phenotypes characterized by early and intermediate onset of wheeze persisting during childhood were characterized by allergy features (with skin prick test positivity) and severity of the disease (with bronchial hyper-responsiveness and reduced lung function) (31). This description was also confirmed across two independent cohorts of children previously described by Spycher et al.(30). In a British birth cohort, The National Asthma Campaign Manchester Asthma and Allergy Study (MAAS cohort), parents were screened at antenatal visits. The main result of this cohort was the impact of early-onset al.lergy on asthma prognosis. Effectively, Belgrave et al. (32). showed that children with frequent asthma exacerbations and multiple early atopy are at risk of progressive loss of lung function from 3 to 11 years, and this effect is also more marked in boys. Similarly, in the TAP cohorts, the multiple-trigger wheeze phenotype (called atopic multiple-trigger phenotype) includes more children (more frequently boys) with allergic diseases such as eczema, allergic rhinitis (AR) food allergy and more specific IgE positivity. Finally, the well-known association between male gender and allergic diseases is described in numerous studies (33, 34).

A third non-atopic severe wheezer phenotype at preschool age is more rarely described. Spycher et al. (30). showed an intermediate phenotype between the atopic multiple-trigger phenotype and the *EVW* in terms of prognosis. In the TAP cohorts, a similar phenotype was found as follows: the non-atopic uncontrolled wheeze phenotype characterized mainly by moderate-to-severe disease and uncontrolled wheeze despite high doses of ICS and a higher proportion of parental asthma. This last phenotype is more prevalent in girls. Similarly, Isozaki et al. (35). also demonstrated a gender difference in phenotypes with a non-allergic wheezing resistant to treatment more prevalent in girls.

Stability of asthma phenotypes in very young children during preschool age depends on allergic expression

Several tools have been developed to predict whether preschool children will have asthma at school age such as the Asthma Predictive Index (API) in the Tucson Cohort (36). The Prevention and Incidence of Asthma and Mite Allergy (PIAMA), a birth cohort study which enrolled children born to allergic mothers (37), also developed a score with predictions comparable to the original Tucson study. However, these prediction scoring systems are difficult to apply in clinical practice because of an overall low positive predictive value (38).

Another approach was to investigate whether prospectively defined phenotypes could have a different course during childhood and thus improve prediction of the course of asthma. The TAP cohort revealed that children classified as having the *EVW* phenotype had a good prognosis: at 5 years, 69% were still in the *EVW* group or were asymptomatic (24). This finding is in accordance with many other studies which demonstrate that recurrent viral-induced wheeze has a good prognosis with a low risk of asthma (39) or mild asthma. Spycher et al. (30). in particular noted that despite mild symptoms in early life, children with transient wheeze were more likely than controls to continue to have mild recurrent wheeze in preadolescence. This finding underlines the fact that remission or mild recurrent symptoms can occur in this phenotype, a fact which is important for the clinician in the management of early wheezing.

The prognosis of the initial severe phenotypes is worse than for *EVW*. Kappelle et al. (40). identified a severe *EVW* phenotype at preschool age with a high risk of asthma at age 5–10 years, reinforced by a positive family history of asthma and elevated FeNO levels.

The poor prognosis of allergic asthma with early onset has already been described in numerous prospective birth cohorts (41, 42). The MAAS (43, 44) demonstrated that atopy, and especially early onset of multiple sensitizations, increases the risk of persistence of asthma with severe exacerbations during childhood. In a TAP cohort, none of the children in the 'atopic multiple-trigger' phenotype became asymptomatic at 5 years and more than half of 'Non-atopic uncontrolled wheeze' children were still severe at 5 years (Figure 2). The third wheeze phenotype identified by Spycher et al. (very similar to the 'Non-atopic uncontrolled wheeze' phenotype of TAP findings (30)) is associated with a poor prognosis in preadolescence. Possibly, this phenotype is associated with persistent wheezing during preschool and school age in relation with late-onset atopy.

Overall, the lesson to retain about the prognosis of 'early wheezers' is that changes observed in each initial phenotype in

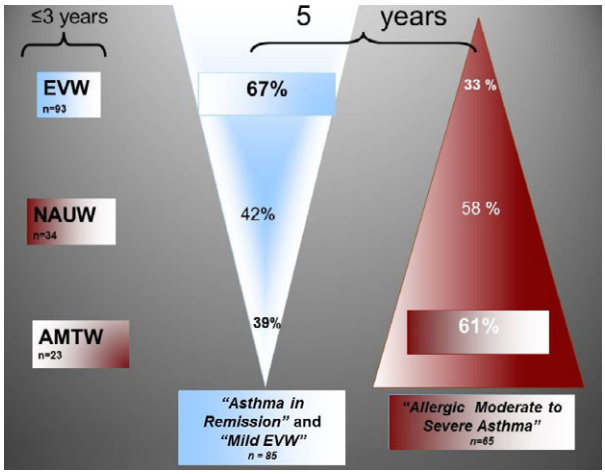

Figure 2 Change of wheeze phenotypes from under 3 years until 5 years of age. Y axis represents change (expressed in percentage) of separate 3 clusters toward the 4 clusters at 5 years of age. At 3 years of age: *Mild EVW*: episodic viral wheeze (wheezing only during colds and asymptomatic between episodes), Atopic *MTW:* multiple-trigger wheeze (wheezing during colds and with other triggers such as house dust, grass, pets, tobacco smoke, exercise or cold air), *NAUW:* non-atopic uncontrolled wheeze. The Fisher's exact test rejects the independence assumption ($p < 0.001$) (24).

preschool aged children depend not only on the expression of allergy but also on the time of onset (early or late).

Asthma severity at school age depends on inflammatory cell type

Asthma in children is highly heterogeneous and is related not only to lung function and atopy but also to systemic inflammation. The Severe Asthma Research Program (SARP) recruited subjects with asthma of all ages who met the American Thoracic Society (ATS) workshop definition of severe asthma with an additional group of subjects with non-severe asthma. A multivariate approach identified a severity spectrum related to sputum cellular inflammation from mild-to-moderate allergic asthma with minimal or eosinophil predominant inflammation to moderate-to-severe asthma with neutrophil-predominant or mixed granulocytic inflammation (45). Other group have also linked inflammation to asthma severity. For example, in a TAP cohort (46), the asthma phenotype with multiple allergies was more atopic, with more frequent severe exacerbations but relatively normal lung function. This type of severe asthma is associated with an inflammation predominantly of 'allergic type' (with eosinophil and basophil cells). Many studies, mainly in children, have confirmed that asthma at risk of severe exacerbations or difficult to control is associated with eosinophil inflammation related to allergic asthma (47).

Conversely, studies have shown an association between the severity of asthma and neutrophilic inflammation detected by induced sputum in particular in the adult (48, 49). The TAP results underline that neutrophilic asthma exists also in children and is characterized by a higher BMI, poorer lung function, higher IgG and IgA values and less atopy (46). This finding supports that of the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) which was performed in 388 French nuclear families and describes two asthma phenotypes: one with 'active-treated allergic childhood-onset asthma' associated with blood eosinophilia and another with 'active-treated adult-onset asthma' associated to blood neutrophils (50).

At school age, allergic asthma is a heterogeneous disease

It is generally accepted then that allergy expression defines the prognosis of asthma during childhood. The question that arises is how should atopy be defined? Atopy depends on allergic sensitization (single or multiple but also the type of allergen and the date of onset of sensitization) and the association with allergic comorbidities (AR, eczema, food allergy).

Moore et al. (51). also defined a large cluster (82% of the study population) of adults with early-onset mild atopic asthma. The Australian Childhood Asthma Prevention Study (CAPS) (14) included pregnant women whose unborn children were at high risk of developing asthma. Both this birth cohort study and MAAS (32, 52) identified an HDM monosensitized population which confers a better prognosis of asthma than children with multiple sensitizations. A TAP cohort study (23), performed in 125 children of school age with allergic asthma, described four phenotypes and especially a mild asthma phenotype associated with monosensitization to HDM in 98% of cases. In a previous study, another TAP cohort described a similar phenotype of asthma with few allergic sensitizations and mild asthma (46).

Conversely, in the MAAS cohort (32), children (especially boys) with persistent wheeze, frequent asthma exacerbations and multiple early atopy had diminished lung function throughout childhood and were at higher risk of progressive loss of lung function from age 3 to 11 years. Furthermore, Garden et al. (the CAPS cohort) (52) showed that asthma risk is related to the type of allergen sensitization, with a strong association between the mixed food and inhalant sensitization class and poor asthma control at age 8 years.

The German Multicentre Allergy Study (MAS) cohort consists of 1314 children followed at yearly intervals until the age of 13 (53). This cohort found that eczema associated with filaggrin loss of function mutations conveyed a greater risk of severe asthma phenotype with a significant decrease in pulmonary function at puberty. A similar finding was described in a TAP cohort in the multiple allergies and severe asthma phenotype which comprised children with multiple allergic features (100% of whom had eczema and multiple sensitizations) and a significant decrease in $FEF_{25–75}$.

Another severe allergic asthma phenotype at school age was described in the TAP cohort. This phenotype comprised 92% of children with severe exacerbations and pollen sensitization. Erbas et al. (54). showed a linear increase in asthma emergency department presentations correlated with an increased concentration of ambient grain of grass pollen ($p < 0.001$). More specifically, pollen-allergic children seem to be admitted due to food-induced anaphylaxis more often during the pollen season ($p = 0.015$) (55, 56).

To sum up, severe allergic asthma in children could consist of two phenotypes depending on the type of sensitization and the association with other allergic comorbidities: a severe phenotype constantly associated with eczema with multiple allergies and another severe phenotype with acute exacerbations related to pollen exposure.

Conclusions

As already suggested (57), our analysis confirms that existing cohort studies have provided useful data to ascertain early life asthma phenotypes. Further studies should be designed to find non-invasive biological markers to better define wheezing phenotypes in very young children associated with an elevated risk of developing asthma to define personalized medicine based on targeted treatment.

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