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Identification of asthma phenotypes in children

Educational aims

- › Aid understanding of the complexity of linking clinical disease presentation of asthma with underlying mechanisms
- › Outline possible advantages of improving this understanding

Summary

The lung is a highly complex organ that can only be understood by integrating the many aspects of its structure. There is increasing interest in defining childhood asthma phenotypes, following decades of research into understanding mechanisms of asthma development and their genetic background without significant breakthroughs. Despite the medical profession's best efforts to define asthma, identify risk factors and natural development of asthma in birth cohorts, and find characteristics that distinguish one type of asthma from another, we still do not know the relevant characteristics of the various subgroups of childhood asthma. This review will briefly describe the importance of identifying childhood asthma phenotypes, the observable characteristics of the disease, and the previous and current approaches used to find them.

Why define asthma phenotypes?

Asthma in early childhood is difficult to diagnose [1], probably more so than in later childhood or in adults. The clinical presentation of asthma varies through childhood, and recently there has been increasing interest in trying to define different asthma phenotypes [2, 3]. One of the most problematic areas of understanding childhood asthma is probably related to "wheezy" disorders in the first few years of life. On one hand, asthma often starts as wheezing within the first few years of life; while, on the other hand, wheeze may appear early in life without a later diagnosis of asthma.

The concept of phenotypes suggests a link to specific genotypes, whereby one individual could be distinguished from another. Furthermore, gene-environmental interactions are likely to modify the associations between genes and clinical presentation. Clearly, this is not the

case today for childhood asthma. The current lack of understanding of underlying mechanisms and our inability to predict prognosis or to tailor medicines individually stem from the difficulty in characterising distinct subgroups of childhood asthma [2, 4, 5].

Classical phenotypes

The classical approach has been to define asthma by various diagnostic criteria, and to add allergic or atopic features to try to separate subgroups of asthma. Thus, traits commonly appearing with (but not limited to) asthma, such as bronchial hyperresponsiveness (BHR) or atopic sensitisation, are often added to "asthma" in order to try to distinguish one group from another. This approach is flawed, however. For a start, there is no common agreement upon diagnosis of asthma that includes all asthma and excludes all without asthma [1, 6–8]. Thus, various pragmatic asthma definitions are used,

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reflecting the variety of asthma outcomes in asthma research. Most problematic is probably the term "wheeze", a concept relevant for the English-speaking parts of the world only, without relevant linguistic correlates in most countries. This sign of bronchial obstruction is a hallmark of early asthma, but it may also have other pathophysiological origins. Furthermore, a single or a few episodes only of wheeze are common in the first one to two years of life. They usually occur with lower respiratory tract infections, often respond poorly to anti-asthmatic treatment [9, 10] and are reported to resolve for more than half of children [11]. Although the term appears useful for objective correlates in many studies [11–13], it appears less useful in others [14–16].

Most asthma definitions combine the presence of symptoms and reversible airflow obstruction, and other features vary in studies as well as in doctors' diagnosis of asthma.

A wide range of other features, including asthma symptoms, exacerbations, response to treatment, lung function, BHR, allergic sensitisation, allergic comorbidities and triggers as well as varying markers of inflammation have been proposed to sub-characterise childhood asthma [3, 17–19]. Adding markers of inflammation has not greatly improved matters, but rather has highlighted the need for new approaches to

phenotype definitions [20]. An obvious problem with this approach is that very few subjects will eventually be classified within each phenotype, reducing statistical power to detect statistically and clinically meaningful risk factors and biological correlates (fig. 1) [3].

Development of approaches to define asthma phenotypes

Moving onward from the classical clinically based phenotypes, the Tucson study [21, 22] initiated a new approach looking into the temporal presentation of wheeze. This approach has remained popular, and combined with allergic sensitisation led to proposed phenotypes that might have different underlying mechanisms as well as prognosis [22, 23]. Developing from these first observations with biological correlates to temporal patterns of wheeze, recent approaches have used more advanced statistical approaches such as latent class analyses [12, 17]. Although less biased than *a priori* group comparisons performed by researchers, these statistical approaches are nevertheless based upon one criterion only: "Did the child wheeze within the past year?". Despite remarkable similarities between the six and five classes, respectively, identified in the AVON and PIAMA studies, as well as their correlates with traits such as allergic sensitisation, lung function and asthma [12], this approach classifies based upon one criterion only. There are several disadvantages to this type of classification of asthma in childhood (fig. 1). First, the phenotypes are by nature retrospective, and are therefore not helpful for the clinician. Secondly, the time points of definition are arbitrary, depending upon the follow-up investigations. Risk factors may change with time, as was shown in the German Multicentre Allergy Study (MAS) study [24]. Third, the approach does not account for complex associations and interactions between the varying spectrums of factors likely to be involved in phenotype characteristics [2–4, 12, 25].

It has therefore been necessary to develop new ways to identify phenotypes using data driven analyses. SMITH *et al.* [26] described the use of data-driven principal component analyses in a population-based cohort to identify groups of children with similar characteristics. In this analysis, data from interviews, lung function (specific airway resistance), atopy and BHR at age 3 and 5 years identified five group variants

Figure 1
Defining childhood asthma phenotypes.

(components): wheeze; wheeze with irritants; wheeze with allergens; cough; and chest congestion, with correlates to atopy and BHR. Whether or not these groups at age 5 years represent specific future asthma phenotypes is yet to be determined. A limitation in many approaches is the fact that many of the traits determining underlying pathophysiology are likely to be quantitative, rather than qualitative [27, 28]. This is illustrated by demonstrating that quantitative measures of obstructive airways disease as well as of specific immunoglobulin E at age 2 years contributed increasingly to predict asthma 8 years later in boys in one birth cohort [29]. Allergic sensitisation is thus not an all-or-nothing phenomenon [28], and classification as allergic sensitisation or not was a poorer predictor.

Mathematical techniques such as latent class analysis [17], principal component analysis [26] and detrended fluctuation analysis [30] have been applied in asthma phenotyping and recently to identify children at risk for exacerbations [30]. Very recently, various approaches were suggested to predict immunological correlates to varying phenotypes of asthma. In the American Severe Asthma Research Program, BRASIER *et al.* [31] suggested an approach involving intermediate phenotypes and various statistical models to identify predictors of bronchoalveolar lavage (BAL) cytokines for severe asthma. This proof-of-principle study in adults used intermediate quantitative asthma phenotypes (determined by extreme values of BAL eosinophils and neutrophils, bronchodilator response and BHR), testing five statistical prediction models in order to identify multidimensional BAL cytokine profiles. Their data suggested that logistic regression and multivariate adaptive regression splines produced the best methods to predict asthma phenotypes. However, the optimal statistical approaches to identify underlying pathophysiology in different phenotypes are not clear.

New approaches such as the integrative systems biology strategy have been proposed to disentangle phenotypic characteristics reflecting underlying pathological mechanisms [2]. These approaches rely on the application of "omics" techniques (proteomics, metabolomics) with high-throughput measurement platforms integrated with biological and clinical data in order to develop new biomarkers of early diagnosis, phenotype definition, severity, response to therapy and drug toxicity. Further studies are necessary to evaluate the applicability of these new tools to characterise and monitor the dynamic and complex nature of asthma.

Phenotypes and risk factors

An important feature of phenotype description is to identify relevant risk factors. Contradictory results relating to the role of pet exposure in asthma and other allergic disease [32] are likely to stem from our inability to distinguish relevant phenotypes in which such exposure may have an impact compared to the (many?) phenotypes where pets do not matter. Other risk factors, such as exposure to tobacco smoke, parental atopic disease, dampness at home or reduced ventilation, allergic sensitisation, time of food allergen introduction and breastfeeding, to mention some, appear to exert a differential impact depending on when the outcome is determined. In the German MAS study, it was found that the associations between risk factor (exposure) and wheeze or asthma were much stronger in early than in later childhood [24]. This raises again the question of whether phenotypes are stable or alter over time. If the latter is true, then when and what are the underlying mechanisms that differentiate the changes in phenotypic expression?

Phenotypes for treatment guidelines and severe asthma

The heterogeneity of asthma has been recognised for decades [33], but individualised asthma treatment is still not recommended. Most recent guidelines suggest some sort of phenotypic classification to guide initial treatment [1, 10, 34, 35], stressing the need for re-evaluation to assess treatment effect. However, trying to distinguish childhood asthma subgroups by symptoms, comorbidities, inflammatory markers, response to treatment or other features has so far not been very useful in the clinical setting [36]. Furthermore, recent studies have failed to predict treatment response to long-acting β -agonists or double dose of inhaled corticosteroids using exhaled nitric oxide fraction or forced expiratory volume in 1 s [36, 37]. As has been obvious in search of severe asthma phenotypes, it is difficult to target treatment for severe asthma in children according to their underlying disease [38, 39]. Several studies have demonstrated severe exacerbations with admissions to intensive care and even endotracheal intubation in children classified as mild-moderately severe asthmatics [40, 41]. Furthermore,

Table 1 Summary of issues related to approaches of phenotyping childhood asthma

Recent approaches are currently more useful for researchers than clinicians

Factors included into phenotype characteristics:

- Subjective *versus* data-driven (partially) objective
- How can we (or should we at all?) set limits or thresholds?

Recent developments in phenotyping are probably essential for determining the role of proteomics

Are there genetic correlates (genotypes) to novel phenotypes?

Optimal statistical methods are yet to be determined

Stability of phenotype is yet to be determined

- across populations
- over time

Better phenotyping is probably the only way forward to detect novel and individualised therapies

biological characteristics correlate poorly with severe asthma definitions as used today [19, 42, 43]. In the search for individualised therapy, novel treatments are likely to depend upon the identification of relevant phenotypes.

Phenotypes and prediction of prognosis

Childhood and even intra-uterine life [44, 45] represents a period in which immunology and pathophysiology undergoes decisive changes with lifelong consequences [46, 47]. Thus, exposure to risk factors at certain time-points may differentially influence the developmental path [48]. This indicates that asthma-related outcomes may not only vary according to early immunological and pathophysiological patterns, but may change with time. This begs the question of whether phenotypes of asthma are pre-determined or whether they change throughout life. The concept alluded to by Max Kjellman as "allergic march" suggests that one (allergic) event leads to another on a set path, with some scientific rationale [49]. If children set out on a pre-determined allergic developmental path, possibly starting *in utero*, it seems reasonable it should be possible with some confidence to predict asthma in childhood. Doing so has, however proved to be exceedingly difficult, whether from birth to

childhood [50], in early childhood for later childhood [11, 51] or in childhood for adult life [52]. It is likely that the lack of relevant phenotypes as outcomes substantiates our failure to predict the patient's prognosis. The optimistic view is that if a particular phenotype is not already a set pattern from birth, there should be a window of opportunity in early life not only for avoiding risk exposure, but also for preventive measures.

Summary

Identification of "true" phenotypes of childhood asthma is likely to improve our understanding of the pathophysiology of the disease, our ability to find new treatment targets and to individualise therapy. Mathematical approaches to find these phenotypes have moved from classical phenotypes involving the pattern of clinical presentation or traits of asthma, through statistical data-driven clusters of temporal presentation based upon recent wheeze, to new multidimensional statistical approaches oblivious to the researchers' preconception of traits that occur in clusters. The present approaches are probably essential to ascertain the role of proteomics, and to identify new therapeutic targets, but they are limited (table 1) by their lack of usefulness at present for the clinician, the lack of genotypic correlates to the identified phenotypes and uncertainty about the optimal statistical methods.

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