Wheezing phenotypes in childhood

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There can no longer be any doubt that, within the spectrum of wheezing disorders of childhood, several distinct phenotypes can be recognised. Although clinicians have been aware of this for decades, it is only through the painstaking recording and analysis of population cohorts over many years that convincing evidence has emerged.

It is worth reminding ourselves here of three important issues in long term studies of the natural history of disease. Firstly, studies which set out to test explicit hypotheses are especially important. Although valuable information can be gleaned from massive information gathering projects, this is often more by luck than design. Secondly, a long term approach to organisation and funding is needed to ensure the best gains from early investment. We detect a reluctance to plan far ahead in the UK, perhaps driven by the four yearly research assessment exercises in UK universities and by project grants of 2–3 years duration.

Thirdly, data must be stored in an accessible format. Written records are bulky but they are durable and retrievable over long periods. With advances in technology, will electronic archives be equally accessible in 60 years time, or will the decipherment of Linear B be re- enacted each time we try to analyse old data sets?

Papers in this issue of Thorax from two of the most influential recent cohort study groups – from Aberdeen, Scotland and Tucson, USA – address the subject of childhood wheezing phenotypes, their classification and heredity. While neither provides unambiguous results, both have important messages, methodological lessons, and interesting data. It is important to subject them to public scrutiny and debate. What can we make of them?

The Tucson cohort is younger but has the advantage of detailed information collected during early childhood – an age when many formative events occur, when the rate of developmental change is at its greatest, and when wheezing phenotypes are changing. The original Aberdeen cohort was recruited 30 years ago from children aged 10–14 years, the age at which the (current) Tucson data end. It is tempting – despite a generation time gap and 5000 miles – to treat them as providing a continuous account. This could be rash.

The report by Stein and colleagues from Tucson deals with clinical features of the 60% of the original birth cohort still living in the area at age 11, complementing data collected at birth, three years and six years. These data points arbitrarily divide childhood into age periods and we need to remind ourselves that changes occur gradually during childhood, not at fixed time points. A comprehensive set of clinical and physiological data was collected. The population may be atypical in that, at 11, 25% had a current history of wheezing and 60% were atopic on skin prick testing. Methacholine responsiveness, positive skin tests, and male sex were strongly linked with current wheeze at 11, but not with wheeze at younger ages. Again, this confirms previous observations in high risk populations. In contrast to other studies which found PEF variability to be weakly associated with measures of clinical disease in mild wheeze or stable asthma, PEF variability was not associated with current symptoms or bronchial responsiveness but bore a marginal relationship to former wheeze (at six years of age) in non-atopic children.

On this dubious basis, a third phenotype with a peak prevalence at six years was identified between the group of early transient wheezers and later atopic asthmatic subjects. The distinction between children who wheezed in the first three years and those who only wheezed in their sixth year is dependent simply on the time points which were chosen by the Tucson group. Bearing in mind the continual switching which occurs between the wheezing and non-wheezing sets in a population over the years, a full breakdown of the groups would be needed to make a judgement on the numbers of phenotypes. Our own estimate from tables 3 and 4 shows that atopy (by skin prick tests at the age of 11) was about 60% in currently non-wheezing children at all ages, while the proportion of atopic children in the wheezing groups rose steadily from 71% at three years of age to 76% of those wheezing at six years and to 90% at age 11. This suggests a steady enrichment of atopic children within (or a loss of non-atopic children from) the declining wheezing population. A further phenotype perhaps?

Rather than force each child into a particular phenotype, is it not more useful and logical to consider the risk factors which may be operating over different time periods in the population, and to which individual children may be variously susceptible? Figure 1 (adapted from Wennergren and Wilson) is an attempt to illustrate this point. The implications are that clinical phenotypes are not static so that transient viral wheeze can, for instance, occur in subsequently atopic wheezers. The cohort data can then be used to examine questions relating to interactions between these risk factors.

The latest instalment concerning the highly informative Aberdeen cohort considers their offspring 30 years after recruitment. Attrition, small and highly selected study groups, and statistically marginal outcomes present problems. For example, the conclusions that prepubertal male non-atopic offspring of probands with a childhood history of wheezy bronchitis have smaller spirometric values than controls, and that these children are less likely to suffer current (but not past) wheeze than the children of non-atopic controls, is based on tiny numbers and...
demonstrably flawed parental recall. Nevertheless, these data do weakly support the Tucson data – which were based on good quality childhood data but only retrospective information about parents – in suggesting familial clustering of the “wheezy bronchitis” phenotype. The fact that sex differences have been demonstrated in relation to many of the risk factors for early wheezing again surely provides the basis for hypotheses which can tease out causal mechanisms rather than simply identifying risk factors.

We should praise these groups for their efforts and for continuing to stimulate debate and research. With their experience it has become clear that very large random populations are needed to sort out the many processes in childhood wheezing. While such large epidemiological studies continue, perhaps there is room too for studies of suitably “enriched” groups to answer particular clinically important questions.

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