

EDITORIAL

Head circumference at birth and the development of allergic disease – more questions than answers

The concept of programming, whereby an early adverse stimulus operating at a critical period of fetal development results in an increased risk of disease, is now well established [1–3]. The best studied example is that of poor fetal growth resulting in small size at birth which is associated with an increased propensity to adverse health outcomes in adulthood including diabetes, hypertension, abnormal blood lipids and death from cardiovascular disease [4–7].

By comparison, knowledge of the fetal origins of atopy is limited and in many respects is conflicting. Interest initially centred on the observations of Godfrey *et al.* that large head circumference at birth was associated with raised serum immunoglobulin (Ig)E levels in adulthood [8]. The hypothesis was raised that the association reflected the effects of sustained fetal brain growth at the expense of other organs such as the thymus. It was proposed that the resulting impaired thymus growth might have long-term effects on the developing immune system.

In this edition of *Clinical and Experimental Allergy*, Benn and colleagues have examined the relationship between head circumference at birth and thymus size [9]. Contrary to the hypothesis of Godfrey *et al.* [8], they observed that the thymus index, a surrogate for volume and weight, varied positively with head circumference at birth [9]. Birth weight was the strongest predictor of thymus size and this explained a large part of the positive association between head circumference and thymus size. In this study there was no association between a history of reported hayfever, eczema or asthma and head circumference at birth. However, these latter observations are limited by the small power of the study, the limited clinical data and the age of the subjects who were studied, in whom episodes of wheezing are more likely to relate to small airway size and viral respiratory tract infection than to atopy [10,11]. In addition, there was no assessment of thymus function or of atopic sensitization with the measurement of either serum IgE levels or skin prick test sensitivity to specific allergens. It would be of interest to revisit these children in later childhood, measure their atopic status, and relate this to head circumference at birth.

Indeed, several studies have now observed a significant positive association between large head circumference at birth and raised total IgE in cord blood [12], childhood

[13], adolescence [13,14] and adult life [8,15]. In contrast, only one study has reported an association between a large head circumference at birth and asthma in childhood [16]. One interpretation of these findings is that while large head circumference is a marker of an enhanced risk of atopic sensitization, other atopic or non-atopic mechanisms may be predominant in terms of asthma risk.

If it is accepted that the currently available evidence indicates that large head circumference at birth is associated with a subsequent risk of developing atopic sensitization, then what is it a marker of? The findings from this study suggest that this relationship is not related to thymic size and therefore to disproportionate growth affecting the thymus. It is known that head circumference at birth is determined by the growth of the brain, which is influenced by numerous factors which are complex and vary depending on gestational age, including maternal factors such as nutritional status, uterine and placental function, and fetal factors such as genetic growth potential [17–22]. The role of these factors has not been addressed in the studies which have examined the associations between anthropometric measures at birth and the later development of atopy. However, the observation by Benn and colleagues that a large head at birth was associated with parental allergy is intriguing and suggests that the atopic state may confer some differential growth effect on the fetus. It also suggests that a relationship between head circumference at birth and atopy may be observed in these children as they age, and when their phenotype is fully expressed.

There is now sufficient evidence to suggest that during fetal development the risk of atopy and/or asthma may be programmed by numerous genetic and environmental factors. It is crucial that research now extends beyond simple associations with disease outcome and anthropometric measurements such as head circumference at birth and that prospective studies are undertaken which examine the materno-fetal environment, its resulting immunological effects and the expression of atopic disease in late childhood and adult life.

References

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