

Thymus size and head circumference at birth and the development of allergic diseases

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Summary

Background The positive association between a large head circumference at birth and total serum IgE levels has been suggested to be due to negative associations between head circumference at birth and thymus development and between thymus development and total serum IgE levels.

Objectives To examine the associations between head circumference and thymus size at birth and the development of allergic disease.

Methods The size of the thymus was assessed by sonography during the first week of life in 149 healthy term infants. Information on birth characteristics and mode of delivery was collected at delivery. The presence of allergic disease was assessed 5 years later by mailed questionnaires, which were returned by 85% of the eligible families.

Results At birth, head circumference was positively associated with thymus size ($P < 0.001$). In all, 27 (23%) of the children had developed at least one allergic disease. Multivariate analysis revealed that both parental allergy (Prevalence Ratio and 95% CI) = 3.18 (1.49–6.78) and caesarean delivery (2.62 (1.48–4.64)) were independently correlated with allergic disease, whereas thymus size was not.

Conclusions Our study does not support that a large head circumference is associated with a small thymus size, nor that a small thymus size is associated with allergic disease. Whether thymus size at birth is related to total serum IgE levels still remains to be elucidated.

Keywords: allergic disease, birth characteristics, thymus size, head circumference, caesarean delivery

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Introduction

Several studies have shown associations between a large head circumference at birth and elevated levels of total serum IgE (S-IgE) [1–5]. Godfrey *et al.* who were the first to report this association, suggested that babies with a large head circumference have a rapid intrauterine growth, making them particularly susceptible to undernutrition in late gestation

and thereby to disproportionate growth and impaired thymus development. Impaired thymus development would in turn favour T helper (Th)2 cell populations and, as a consequence of this, also result in higher total S-IgE levels (Fig. 1) [1].

Godfrey's hypothesis has been invoked several times [4–11], and extended further to suggest associations between thymus development and both atopy and allergic disease. However, neither the possible relationship between head circumference and thymus development, nor the association between thymus size at birth and total S-IgE levels or other markers of atopy or allergic disease have been studied directly.

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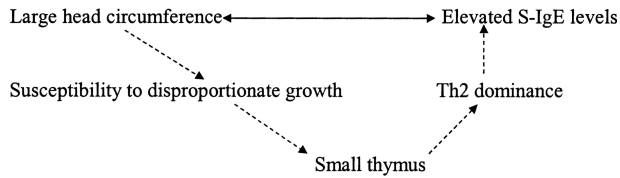


Fig. 1. Hypothesized relationship between head circumference, thymus size and S-IgE levels.

In a prospective study we have therefore tested the relationship between head circumference and thymus size at birth. We were not able to test the association between thymus size at birth and total S-IgE levels or other blood markers of atopy, but looked at the association between thymus size at birth and the development of allergic disease during the first 5 years of life.

Materials and methods

The size of the thymus was assessed during the first week of life in 149 healthy term infants (63 girls and 86 boys) from September 1993 to November 1994. One radiologist (HH) measured the thymus, using a B & K sonographic scanner type 1846 and a 7 MHz probe type 8534 (B & K Medical, Gentofte, Denmark). At sonography, the thymus appears as a well-delineated echo-poor structure in the anterior mediastinum. A transsternal approach was used to measure the largest transsternal diameter of the thymus. Perpendicular to that, the largest sagittal area (longitudinal scan plan) was depicted on the monitor and measured by the computer. The two measurements were multiplied and recorded as the thymus index. The results were expressed as the average of two determinations. The index is an estimate of the volume of the thymus, and postmortem examinations have shown a high correlation between the thymus index and the thymus weight and volume [12]. Information on mode of delivery, gestational age, birth weight, birth length, and head circumference was collected at the time of delivery. A follow-up was done in August 1999, when the children were between 4.8 and 5.9-years-old.

Questionnaire

Six of the originally included children were unavailable for follow-up. Twins were excluded from the study because of the effect of multiple birth on fetal growth. The parents of the remaining 139 children received a mailed questionnaire on symptoms, diagnoses and family history of allergic diseases (atopic dermatitis, rhinitis and/or asthma), parental education, breastfeeding, number of siblings, pets and smoking in the household, and day-care attendance. Atopic dermatitis and rhinitis were defined as affirmative answers to the questions used in the International Study of Asthma

and Allergies in Children (ISAAC) [13], i.e. 'Has your child ever had eczema?' and 'Has your child ever had hayfever?', respectively. Asthma was defined according to the question 'Has your child ever had asthma or asthmatic bronchitis?' (asthmatic bronchitis is a commonly used term for wheezing in early childhood in Denmark) combined with an affirmative answer to the question 'Has your child had wheezing or whistling in the chest in the last 12 months?'. Food allergy was defined as a positive response to the question 'Has a doctor ever said that your child had food allergy?' combined with milk and/or egg and/or fish as the triggering food. Allergic disease was defined as having at least one of the above diseases.

Statistical analyses

Due to a skewed distribution of the thymus index, a logarithmic transformation of the thymus index was used in the statistical analyses. To study the effect of disproportionate growth, we calculated the head circumference/birth weight ratio and the head circumference/birth length ratio. Correlations between head circumference and other birth characteristics on one hand, and thymus index on the other hand were analysed by linear regression using SAS version 6.12. The linear regression models were described by the regression coefficient. Furthermore, in order to obtain unit-free measures, the difference in thymus index between the 25th and the 75th percentile of the distributions of birth measurements was calculated from the regression coefficients. To adjust for birth weight, the infants were split into three birth weight subgroups, obtaining the least discrepant number of subjects in each group. The correlation between age and allergic disease was analysed using Wilcoxon 2-sample test. The correlations between selected known or suspected risk factors and allergic disease were analysed by logistic regression using SAS 6.12. A large head circumference was defined as 37 cm or more, as this cut-off was employed in most previous studies reporting a relationship to elevated S-IgE levels [2,3,5]. The other birth characteristics were split into three subgroups, obtaining the least discrepant number of subjects in each group. The prevalence ratios for each parameter were calculated using the high category as reference. *P*-values for trend were calculated using logistic regression on the continuous values of the variables. Correlations between parental allergy and head circumference were calculated using Chi-square and Fishers two-tailed exact test.

Ethical aspects

The study received approval from the Ethical Committee for Copenhagen and Frederiksberg County.

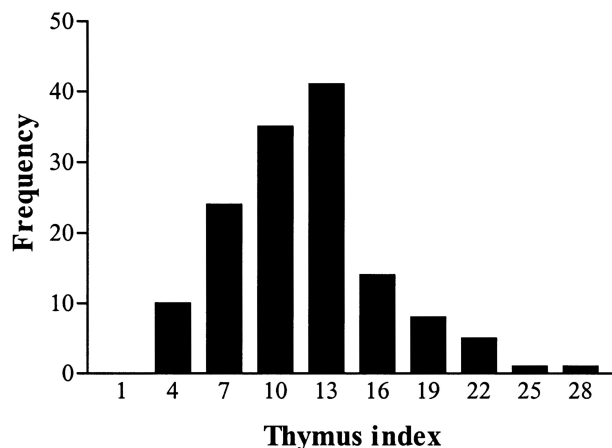


Fig. 2. Distribution of the thymus index.

Results

The median thymus index at birth was 11.9 (range 3.8–29.1; 25th–75th percentiles = 8.7–14.4) (Fig. 2). Birth weight, birth length, and head circumference all correlated with the log transformed thymus index to some extent (Table 1). Head circumference/weight ratio (HC/BW) was negatively correlated with the thymus index, whereas head circumference/length ratio (HC/BL) was not. Adding the squared value of each of the parameters into each model gave no further information (data not shown). Based on 'goodness-of-fit', birth weight was the best determinant of thymus index, but it only explained 20% of the variation. There was a borderline significant interaction between birth weight group (birth weight < 3.4, ≥ 3.4 and < 3.75, and

≥ 3.75 , respectively) and HC/BW ($P = 0.05$). Stratifying for birth weight group showed that the negative association between HC/BW and thymus index was only significant among infants with the highest tertiles of birth weight. There were no significant interactions between birth weight group and any of the other birth characteristics. Adjusting for birth weight group showed that the positive associations between head circumference and birth length, respectively, and thymus index, were partly explained by birth weight.

The questionnaires regarding 85% (118/139) of the children were returned. Eighteen (15%) of the children had atopic dermatitis, 3 (3%) rhinitis, 8 (7%) asthma, and 3 (3%) food allergy, and 27 (23%) had at least one allergic disease. Allergic disease was not associated with age (data not shown). Therefore, age was not included in the further analyses.

To control for possible confounding from other risk factors, we assessed a number of factors related to known or suspected risk of allergic disease (sex, parental allergy and education, mode of delivery, breastfeeding, number of siblings, pets and smoking in household, and day-care attendance). Only parental allergy (51 of 111 children) and caesarean delivery (14 of 118 children) were significantly related to allergic disease. In multivariate analyses the prevalence ratio for parental allergy was 3.18 (1.49–6.78) and for caesarean delivery 2.62 (1.48–4.64). Controlled for parental allergy and caesarean delivery, there were no associations between the different birth characteristics and the development of allergic disease (Table 2). Parental allergy was associated with a head circumference of 37 cm or more ($P < 0.05$). The tendency was seen for both maternal and paternal allergy, but only reached statistical significance for paternal allergy.

Table 1. Associations between birth characteristics and thymus index at birth

	Range	25th to 75th percentile range	Regression coefficient (P)	Factor for increase in thymus index from 25th to 75th percentile	Regression coefficient adjusted for birth weight group (P)	Factor for increase in thymus index from 25th to 75th percentile adjusted for birth weight group
Head circumference (cm)*	31.5–39.0	34.0–36.0	0.09 (< 0.001)	1.20	0.05 (0.07)	1.11
Birth weight (kg)	2.4–4.8	3.2–3.9	0.37 (< 0.001)	1.30		
Birth length (cm)	45–57	51–54	0.06 (< 0.001)	1.20	0.03 (0.12)	1.09
Head circumference/weight (cm/kg)*	7.6–13.5	9.1–10.7	– 0.14 (< 0.001)	0.80	Low bw: – 0.08 (0.21) Med. bw: 0.14 (0.26) High bw: – 0.25 (0.01)	0.88 1.25 0.67
Head circumference/length*	0.58–0.76	0.66–0.69	– 0.70 (0.57)	0.98	0.26 (0.82)	1.01

*16 infants with missing values of head circumference were excluded from analyses.

Table 2. Associations between birth characteristics and allergic diseases

	Allergic children	Non-allergic children	Adjusted prevalence ratio** (95%CI)
Head circumference (cm)			
< 37	22	68	1.5 (0.6–3.6)
≥ 37	4	12	1.0 (ref)
Birth weight (kg)			
≤ 3.3	11	26	1.4 (0.6–3.2)
> 3.3, < 3.8	9	35	1.3 (0.6–3.1)
≥ 3.8	7	30	1.0 (ref)
Birth length (cm)			
≤ 51	11	33	1.4 (0.6–3.4)
> 51, < 54	10	31	1.1 (0.4–2.7)
≥ 54	6	27	1.0 (ref)
Head circumference/birth weight (cm/kg)			
≤ 9.46	5	28	0.6 (0.3–1.5)
> 9.46, < 10.42	10	27	1.0 (0.5–2.1)
≥ 10.42	11	25	1.0 (ref)
Head circumference/birth length			
≤ 0.67	8	28	1.3 (0.6–2.8)
> 0.67, < 0.69	7	26	1.1 (0.5–2.6)
≥ 0.69	11	26	1.0 (ref)
Log Thymus index			
≤ 2.3	8	32	0.8 (0.4–1.7)
> 2.3, < 2.6	9	27	0.8 (0.3–1.7)
≥ 2.6	10	32	1.0 (ref)

*Adjusted for parental allergy and caesarean delivery.

#All *P*-values for trend were between 0.26 and 0.56.

Restricting analyses to children with atopic dermatitis, which was the largest group with allergic disease, did not add further information. Restricting analyses to children with atopic dermatitis, rhinitis and food allergy, excluding children ($n = 4$) whose only allergic symptom was wheezing, which could at this age be infectious, did not add further information either (data not shown).

Discussion

We found a positive association between head circumference and thymus size at birth.

Birth weight was, however, the strongest predictor of thymus size, and this explained a large part of the positive associations between head circumference, and birth length on one hand, and thymus size on the other hand. There was interaction between birth weight group and the head circumference/birth weight ratio. This marker of disproportionate growth was especially associated with a relatively smaller thymus among infants with high birth weights.

Allergic disease was assessed by means of an ISAAC-

based questionnaire. The response rate was high, and the percentages of children with different allergic diseases were similar to current Danish figures [14,15]. We found no association between a large head circumference and allergic disease when controlling for parental allergy and caesarean delivery. Previous studies reporting an association between a large head circumference at birth and elevated total S-IgE levels have not found any associations between head circumference and sensitization to common allergens [2–4], atopic dermatitis [2], rhinitis [2], or asthma [2–4]. Only one study has reported an association between a large head circumference at birth and asthma in childhood [6]. As previously pointed out [3], this is surprising, as elevated total S-IgE levels are normally associated with allergic disease in developed countries. We did not measure total S-IgE levels, and therefore cannot exclude a positive correlation between head circumference and S-IgE levels. Interestingly, parental allergy was associated with a head circumference of 37 cm or more. It has been suggested that allergic women, with their propensity towards Th2-skewing of the immune system, might have more successful

pregnancies, and it was even recently reported that allergic women have more children than non-allergic women [16]. It may be that allergic parents also have more successful pregnancies in terms of larger children. Three of the previous studies of head circumference and atopy did not control for parental allergy at all [1,3,4], one study just controlled for parental asthma [2], and only in the remaining studies other parental allergic diseases were recorded [5,6].

A small thymus index at birth was not associated with the development of allergic diseases. Godfrey hypothesized that impaired thymus development would result in a diminished population of Th1 lymphocytes [1]. This possibility is supported by the observation that neonatal thymectomy in animals abrogates the postnatal shift from a Th2 to a Th1 pattern [17]. In humans, a relationship between a widened roentgenographic mediastinal shadow, presumably indicating an enlarged thymus, and increased prevalence of allergic disease has been observed [18].

Parental allergy and caesarean delivery were the only risk factors for allergic disease detected in the present study. Caesarean delivery has previously been shown to influence the intestinal flora of the child at least 6 months after birth [19], and as the intestinal flora differs between allergic and non-allergic children [20], this could possibly explain a relationship between caesarean delivery and allergic diseases.

In conclusion, our study does not support that a large head circumference is associated with a small thymus size, nor that either a large head circumference or a small thymus size are major causes of allergic disease during the first 5 years of life. Whether thymus size at birth is related to total serum IgE levels still remains to be elucidated.

Acknowledgements

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