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CLINICAL REPORT

Thymus is Enlarged in Children with Current Atopic Dermatitis. A Cross-sectional Study

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Atopic dermatitis is a common skin disorder of unknown aetiology with peak incidence in early childhood. The disease is associated with peripheral T-cell accumulation in the skin. The thymus is a key organ of the cellular immune response early in life. We hypothesized that atopic dermatitis is associated with an unbalanced establishment of the peripheral T-lymphocyte system. This cross-sectional study was performed to compare thymus sizes in patients with atopic dermatitis and healthy controls. Thirty-seven children with current atopic dermatitis were enrolled and compared with 29 healthy controls. An interview and medical examination were performed by one doctor, an ultrasound scan was performed within 3 days of the examination, and the thymus index, a marker of thymus size, was measured. The thymus index was on average 32% higher (95% CI 3%–67%) in children with active atopic dermatitis compared with healthy controls. It declined with age in both children with atopic dermatitis and healthy controls, but the reduction in size was only significant for healthy controls. We demonstrate increased size of thymus among children with active atopic dermatitis compared with healthy controls. The larger size of thymus is compatible with increased thymic activity and emission of T lymphocytes. ***Key words: atopic dermatitis; increased size of thymus.***

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The thymus is essential for the establishment of a normal peripheral T-lymphocyte immune system. Its size and function are highest in infants (1–3). Re-establishment of the peripheral T-lymphocyte system after chemotherapy is directly related to the age at therapy, as children 3 years of age have 90% of their CD4+ T cells in blood compared with pre-treatment values, whereas persons around 25 years of age at the time of chemotherapy only have 10% of CD4+ T cells in blood after treatment (4).

Atopic dermatitis (AD) is a common skin disorder of unknown aetiology with a peak incidence in early childhood (5). It includes immune deviations such as T-cell accumulation and activation in the skin resulting in active eczema (6, 7). A doubling of lymphocytes in normal-looking skin and a four- to five-fold increase of lymphocytes in active eczema is observed in patients with AD (8). This means that a person with active eczema has more lymphocytes in the skin than in blood (9). We hypothesized that AD is associated with an unbalanced establishment of the peripheral T-lymphocyte system. We set out to compare thymus size in children with current AD and healthy controls.

MATERIALS AND METHODS

Participants

Sixty-six children aged 0–6 years were enrolled in the study from October 1998 to December 1999. Thirty-seven children had current AD, and 29 were healthy controls without any atopic disease. The AD cases were recruited from in-patient and out-patient clinics of the Department of Dermatology. The AD cases were admitted to the hospital. All the study investigations were done within the first 3 days after admittance to the hospital. None of the children had received therapy with topical steroids 2 weeks prior to the day of admittance to the hospital but their treatment was launched without delay on the day of admittance. The healthy controls were recruited from a combined nursery and kindergarten and among children of colleagues. Cases and controls were recruited at the same time in all seasons of the year. All children and their parents were interviewed, and a clinical examination of the children was performed by one doctor (A.B.O.). Information concerning birth factors, breastfeeding and introduction of other foods, and earlier and current diseases including infections was obtained. The clinical examination included measurements of weight, height and rectal temperature, signs of infections and a thorough examination of skin. If the child had AD, a SCORAD measure was performed. Children who had either a history of infection within 2 weeks prior to the examination or signs of infection were excluded from the study.

The study was approved by the Ethical Committee of the county of Aarhus, Denmark.

Thymus index

Sonography of the thymus was performed within 3 days of the clinical examination. One radiologist (G.A.) performed all ultrasound scans using a Siemens sonographic scanner 7.5 MHz section transducer. The method has been described

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elsewhere (1, 10). A trans-sternal approach is used to measure the largest trans-sectional diameter of the thymus and, perpendicular to that, the largest sagittal area (longitudinal scan plan) is depicted on the monitor and measured by the computer. The thymus index is the product of these two measurements. Two independent measurements were performed with less than 15% deviation. Post-mortem examinations have shown good correlation between the thymus index and the volume and weight of the thymus (10).

Statistical analysis

Due to a skewed distribution of the thymus index, a logarithmic transformation of the thymus index was used in the statistical analyses. A linear regression model was used to predict thymus index by current AD and age. The association between thymus index and SCORAD was determined using the Spearman rank correlation.

Comparison between AD cases and healthy controls concerning duration of breastfeeding and family size was done by a two-sample Wilcoxon rank sum test and with regard to daily care with a Pearson chi-squared test.

RESULTS

The thymus index declined with age in both children with AD and controls (Fig. 1). The decline was significant for the healthy controls ($p=0.03$), but not for the AD children ($p=0.16$); however, the association with age was not significantly different for the two groups. When considering the association with age to be the same for the two groups, the thymus index was on average 32% higher (95% CI: 3%–67%) in children with AD compared with the healthy controls ($p=0.03$). There was a large variation in thymus index in both groups of children (Fig. 1). There was no association between the thymus index and SCORAD when adjusting for age (linear regression; $p=0.46$).

Children with AD and healthy controls did not differ with regard to duration of breastfeeding ($p=0.64$), family size ($p=0.68$) and daily care of the child ($p=0.17$) and these factors were not included in the linear regression model.

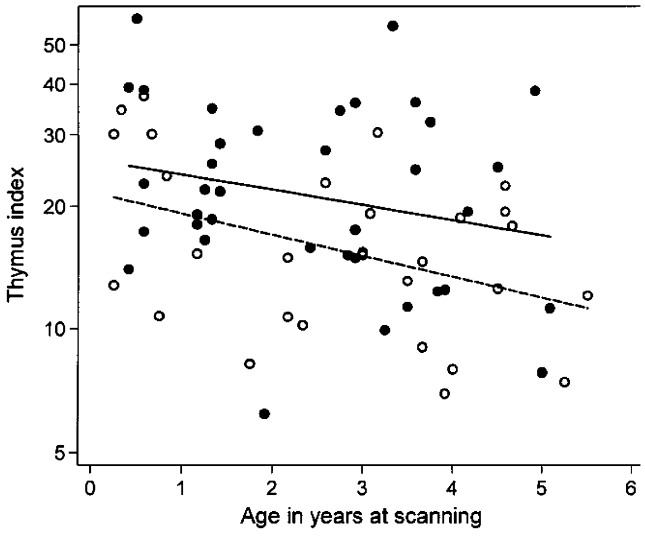

Fig. 1. Semi-logarithmic plot of the thymus index among children with atopic dermatitis (● —) and healthy controls (○----) at various ages.

DISCUSSION

We observed that the thymus index was significantly increased among children with current AD. The thymus index declined with age in both children with AD and healthy controls, but the reduction with age was only significant for the healthy controls. There was no association between the thymus index and the severity of AD.

A recent French investigation of 60 children using the same technique of thymus ultrasound scan reported no difference in the thymus index among children with AD compared to children with a high risk of atopy and healthy controls. However, the thymus was smaller among severe cases of AD (11).

The thymus is the organ responsible for a proper maturation of the T-lymphocyte system. Previous studies of the thymus index have shown that its size can be accurately assessed in small children (10, 12). The size of the thymus is sensitive to a number of factors. Drugs such as steroids and cyclosporine have thymolytic effects. Treatment with systemic corticosteroids 1 mg/kg for 5 days leads to disappearance or significant reduction of the thymus in 80–90% of cases within 3–4 days (13, 14). 'Stress' itself reduces the thymic volume via increased levels of corticosteroids (15). Desensitization in a guinea pig model led to a 30% reduction in the size of the thymus over 1 week (16). Earlier infections such as episodes of fever, measles and pneumonia have in some instances shown significant reduction of the thymus size (1, 17), whereas this was not found in other studies (2). A recent study reports that larger thymus index was associated with higher CD4+ cell counts among HIV-infected patients who had received highly active anti-retroviral therapy for 6–18 months (18), suggesting that the larger size of thymus is compatible with increased thymic activity and emission of T lymphocytes.

Hence, the size of the thymus in children with current eczema can be influenced by many factors of which stress from itching, lack of proper sleep, and/or an impact from the application of topical steroids are particularly relevant. These factors would probably lead to a reduction in the size of the thymus. However, it is unknown whether a chronic skin infection with *Staphylococcus aureus* may have influenced the size of thymus among the AD children in the study. Skin cultures were not collected, but the signs of infection in the skin recorded according to SCORAD were not associated with the thymus index. The contradiction between our observations and those of Boralevi et al. (11) may be due to the thymolytic effect of long-term

treatment with topical steroids and stress among children with AD in the French study, in contrast to our study where the children with current AD had their sonography done within the first 3 days after initiating therapy with topical steroids.

AD is a T-lymphocyte-driven disease of unknown origin. The fact that it occurs early in life and disappears in most children could support the hypothesis that it is related to an unbalanced establishment of the peripheral T-lymphocyte system (19). This is supported by the fact that there are 'too many T lymphocytes' in the periphery – at least in the skin (8). AD is mostly a Th2 disease, i.e. there is a strong propensity to develop type I allergies to environmental allergens. The Th2 skewing is reflected in the fact that children who later develop insulin-dependent diabetes mellitus (IDDM) and who are known to have primarily Th1 immune responses, do not contract AD to the same degree as non-IDDM children (20).

The T cells are activated in AD. An increased number of CD4+CD8+ T-lymphocytes have been observed both in blood and in the skin, but these cells do not seem to be immature thymocytes as they are CD45RO+ (9). Further, a significant decrease of the telomere regions in CD4+CD8+ T-cells in blood indicates an increased 'turn-over' of lymphocytes (21). Finally, some patients with active AD have increased values of T-cell receptor excision circles in peripheral blood, indicating the presence of recent thymic emigrants (Just H. et al., Department of Dermatology, University Hospital of Aarhus, personal communication).

The present result is the first to demonstrate that children with current AD have increased size of their thymus. This does not prove that these children have an increased emission of T lymphocytes into their peripheral system. However, it is compatible with the hypothesis that AD somehow is associated with an unbalanced establishment of the peripheral immune system. Investigation of this hypothesis is needed and calls for longitudinal prospective follow-up studies among children at risk of later development of AD.

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