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Atopic Dermatitis May Be Linked to Whether a Child Is First- or Second-born and/or the Age of the Mother

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Five hundred and thirty families with at least 1 child who had been referred to a dermatologist with atopic dermatitis were interviewed in an effort to determine whether factors such as the age of the mother when a child is born and/or birth rank can contribute to the development of atopic dermatitis. The families interviewed had a total of 1,084 children, or an average of 2 children per family. Sixty per cent of the children with atopic dermatitis were under 5 years of age. Ninety-one per cent of them had developed the disease before the age of 3; those most severely affected had developed the disease during the first year of life. In families with 2 children, but only 1 child with atopic dermatitis, the odds ratio for the second child to develop atopic dermatitis was 1.379 ($0.025 < p < 0.05$). The average maternal age was 24.8 to 25.2 years when giving birth to the first child and 28 years when giving birth to the second child, irrespective of the status of the child. Thus, atopic dermatitis can be related to birth rank or to the age of the mother. ***Key words: birth rank; maternal age.***

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The incidence of atopic dermatitis has increased over the past two decades (1–8). This is somewhat surprising, as the disease has a strong genetic background (9, 10). It has been hypothesized that atopic dermatitis is related to genetically determined dysmaturation of ectodermal tissue (11). This may mean that children born to older mothers have an increased risk of developing atopic dermatitis due to the mother's reduced capacity to mature the child *in utero*.

In Denmark, the age of first-time mothers increased from a mean of 23.1 years in 1960 to a mean of 26.9 years in 1992, with the first child often born to women between the ages of 25 and 34 (12). This increase in the age of first-time mothers corresponds to an increase in the incidence of atopic dermatitis in Denmark and led us to consider whether this relationship might be more than coincidental.

If it can be shown that whether a child is first- or second-born has little significance for the development of atopic dermatitis, then the higher risk of atopic dermatitis among second-born children may be related to the age of the mother and her capacity of *in utero* maturation of the second child. This relationship is known to exist in Down's syndrome (13).

SUBJECTS AND METHODS

A study of 552 consecutive children with atopic dermatitis ranging in age from 0 to 16 years was carried out by dermatologists at dermatology clinics in Aarhus, Aalborg and Fredericia, Denmark. At the first consultation, the person accompanying the child was interviewed, and answers to the questions listed in Table I were recorded. The study was conducted over a period of 1 year from April, 1992 to April, 1993. For 22 of the children the information recorded could not be used for various reasons: the child was a twin, was adopted or was older than 16 years at the time of the interview, and in a few cases, the interview form was incorrectly completed. The data collected was analyzed and described using the odds ratio and McNemar's chi-square tests.

In order to determine whether the age of the mother or whether or not a child was first- or second-born could influence the occurrence of atopic dermatitis, the subpopulation of families with 2 children, only 1 of whom had atopic dermatitis, was also considered.

The study was approved by the Ethics Committee of the County of Aarhus and the Danish Data Protection Agency.

RESULTS

A total of 530 case children, 246 boys and 282 girls, were included in the study, giving a boy:girl sex ratio of 1:1.15. No information about sex was available for 2 children. The 530 families interviewed had a total of 1,084 children, or an average of 2 children per family (Fig. 1). Six hundred and seventy-one children had the diagnosis of atopic dermatitis.

The age distribution of the 530 case children included in the study showed that 60% were 5 years old or younger when the study was initiated (Fig. 2). Ninety-one per cent of these children had developed atopic dermatitis before the age of 3 (Fig. 3). There were approximately equal numbers of children in each of the categories: mild and moderate dermatitis (Table I and Fig. 4). Sixteen per cent of children had severe atopic dermatitis and one-third of children in this catagory had developed the disease within the first year of life. No significant differences were seen among boys and girls with regard to age at onset of disease or disease severity.

Table I. *Questions asked at the initial interview*

Sex of the child?	
Age of the child at the time of the interview?	
Age of the child at the onset of eczema?	
Number of siblings and their ages?	
Atopic diseases (atopic dermatitis, asthma, rhinitis) of the child, parents and siblings?	
Severity of atopic dermatitis?	
mild dermatitis–	defined as atopic dermatitis for which intermittent topical hydrocortisone therapy was sufficient.
moderate dermatitis–	defined as atopic dermatitis requiring the use of intermittent topical therapy with steroids of moderate potency.
severe dermatitis–	defined as atopic dermatitis requiring the use of potent topical corticosteroids.
Duration of breast-feeding?	

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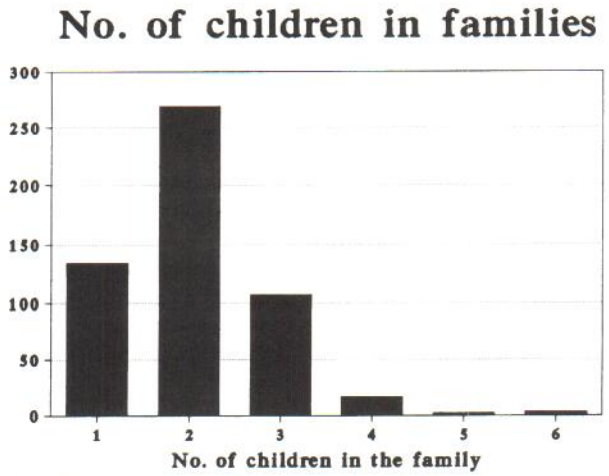

Fig. 1. The number of children in the families. The total number was 1,084 children in 530 families.

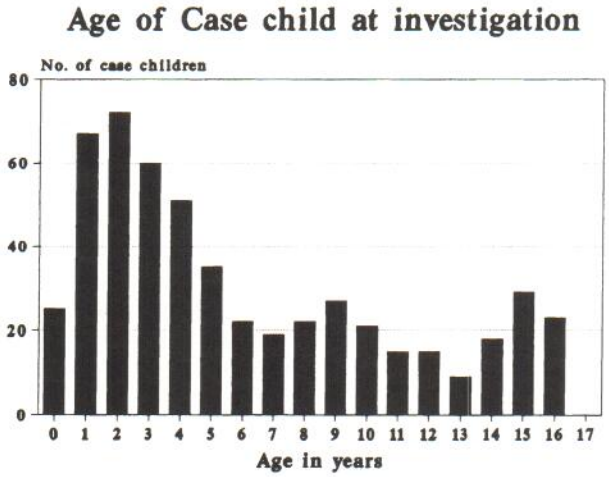

Fig. 2. The age distribution of 530 case children. Sixty percent were 5 years or younger.

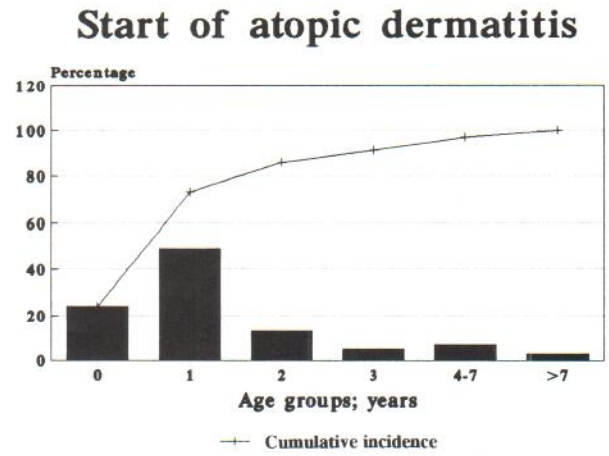

Fig. 3. Age at start of atopic dermatitis among 530 case children. Ninety-one percent started within the first 3 years of age.

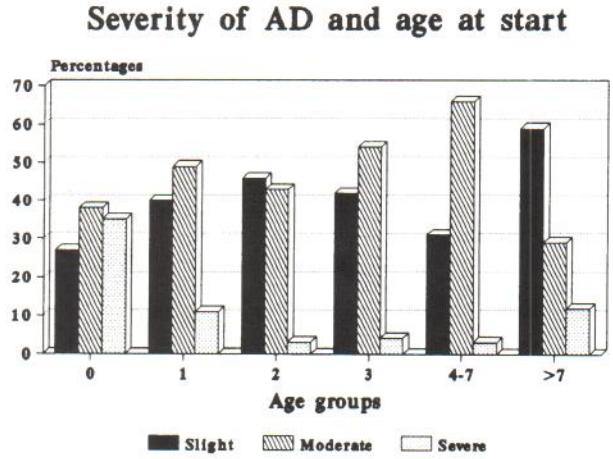

Fig. 4. The relation between severity of atopic dermatitis (see Table I) and age of start of the disease.

In 50% of all the families, the person interviewed stated that neither of the parents had atopy defined as atopic dermatitis, asthma and/or hay fever. There were no significant differences between fathers and mothers regarding predisposition to atopy.

Two hundred and sixty-eight of the families had 2 children. These families were selected to test the hypothesis that birth rank and the age of the mother are related to the development of atopic dermatitis. In 74 of 176 families with 2 children and only 1 child with atopic dermatitis, the first-born child had the disease, whereas in 102 of these same 176 families, only the second-born child had atopic dermatitis (Table II). Thus, the odds ratio for the second-born to develop atopic dermatitis was 1.379 ($0.025 < p < 0.05$), McNemar's chi-square test.

The average maternal age in 2-children families was 25.2 years when giving birth to the first child classified as having atopic dermatitis and the average maternal age was 24.8 years when the first child was non-atopic. The average maternal age was 28 years when giving birth to the second child irrespective of whether the child had the diagnosis of atopic dermatitis or not.

Table II. *Atopic dermatitis in 268 families with 2 children and in 179 of the families in which both children were at least 3 years old*

	No. of families in which only the first-born child had atopic dermatitis	No. of families in which only the second-born child had atopic dermatitis	No. of families in which both children had atopic dermatitis	Total
All families with 2 children	74	102*	92	268
Families with 2 children both ≥3 years of age	39	78**	62	179

* $0.025 < p < 0.05$, McNemar's chi-square test.
** $p < 0.001$, McNemar's chi-square test.

One hundred and thirty-four families included in this study had only one child with atopic dermatitis. This opens the possibility of a sampling error, as families whose first child is atopic could later have a second non-atopic child. Furthermore, a second child under 3 years of age at the time of the study could develop atopic dermatitis later in life. Knowning that 91% of the children had developed atopic dermatitis within the first 3 years of life, we carried out a restriction analysis excluding families with 2 children, the younger of whom was under 3 years of age, and where only 1 child had atopic dermatitis. This exclusion left a total of 117 families. The results of this analysis are given in Table II. In 39 of the 117 families, only the first-born child had atopic dermatitis, compared with 78 of 117 families in which only the second-born child was affected. Thus, the odds ratio for the second child to develop atopic dermatitis was 2.0 ($p<0.001$), McNemar's chi-square test.

DISCUSSION

It was demonstrated that among the families included in the current study, the second-born child had a statistically significantly greater risk of developing atopic dermatitis than the first-born child. This observation supports the hypothesis that the occurrence of atopic dermatitis may be related to the age of the mother.

Interpretation of the results is complicated by the fact that whether a child is first- or second-born may in itself influence the occurrence of atopic dermatitis. It is not possible to separate the influence of the age of the mother and the order of birth of two or more children. Danish families have an average of 2 children, and this number has remained virtually stable over the past two decades. During this same period, the age of first-time mothers increased from a mean of 23.1 years in 1960 to 26.9 years in 1992 (12), and this increase paralleled a fourfold increase in the incidence of atopic dermatitis (14).

The long time span may in itself have influenced our findings in the form of a "period effect". The period effect is the summation of changes in our society as well as changes in individual life circumstances over the past 16 years that may have influenced the frequency of atopic dermatitis in our study group. It is impossible to estimate the importance of this effect by any statistical method in a study dealing with age as a risk factor. The period effect and the age of the mother cannot be separated.

The current study involved children ranging in age from 0 to 16 years, born in the period 1976 to 1993. One important confounder when dealing with this long span of time is the fact that the incidence of atopic dermatitis increased during the period in which the children were born. This fact alone could mean that the second-born child had a statistically significantly greater risk of developing atopic dermatitis than the first-born child. We know that the incidence of atopic dermatitis in Denmark increased from 3.2% in 1960–64 to almost 12% in 1979 and that the incidence of the disease stagnated from 1974 to 1979 (7). We have no comparable incidences of atopic dermatitis in Denmark for the 1980s and 90s.

However, we observed that approximately 90% of the children had developed atopic dermatitis within the first 3 years of life and that children who developed severe atopic disease did so within the first year of life. The average age of all second-born children included in the current study was 7.5 years, indicating that most of the children could at that age be described as either atopic or non-atopic. These results indicate that the children in our study were correctly classified as either having atopic dermatitis or being unlikely to develop the disease.

A systematic sampling error may have been introduced by the fact that families with only one child, a child with atopic dermatitis included in the current study, may at a later date have a non-atopic child. A second child of under 3 years of age at the time of the study could later develop atopic dermatitis. For this reason, an analysis was carried out in which all families with a child younger than 3 years of age were excluded. The results of this analysis indicate that the bias had a limited effect on our results, as the odds ratio for the second child having atopic dermatitis actually increased from 1.379 to 2.0.

In a study conducted in Great Britain, 8,279 children with "eczema" were categorized according to social class. Eczema was found to be twice as prevalent among children in social classes I and II (15). Although many factors were taken into consideration in this study, the age of the mother at the time of birth was not one of them. It is our hypothesis that women in the more advantaged social classes were older when their children were born than women in the lower social classes.

The current study should be seen in context with our study in which it is shown that a selected group of children who later developed severe atopic dermatitis had increased gestational age ("gestational age" is equivalent to length of pregnancy) (16). Children with atopic dermatitis were shown to have higher than average birth weight (16). In this population-based study (16), we found a trend between high maternal age and atopic dermatitis but no statistical significance was observed. With reference to the information gleaned from these studies, we suggest that a long gestation period and an associated impaired capacity of the mother to mature the tissue of the foetus are aspects for further study in determining the aetiology of atopic dermatitis (11). The present findings, together with our previous observations, including the association of genetically aberrant T-cell clones with atopic dermatitis (17, 18), can perhaps add some pieces to the puzzle known as atopic dermatitis.

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REFERENCES

1. Carr RD, Meyer B, Becker SW. Incidence of atopy in the general population. Arch Dermatol 1964; 89: 27–32.
2. Taylor B, Wardsworth J, Wardsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. Lancet 1984; ii: 1255–1257.

3. Storm K, Haahr J, Kjellman N-IM, Østerballe O. The occurrence of asthma and allergic rhinitis, atopic dermatitis and urticaria in Danish children born in one year. Ugeskr Læg 1986; 148: 3295–3299.
4. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ 1992; 304: 873–875.
5. Åberg N, Engström I, Lindberg U. Allergic diseases in Swedish children. Acta Paediatr Scand 1989; 78: 246–252.
6. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol 1994; 30: 35–39.
7. Larsen FS, Hanifin JM. Secular change in the occurrence of atopic dermatitis. Acta Derm Venereol (Stockh) 1992; Suppl 176: 7–12.
8. Williams HC. Is the prevalence of atopic dermatitis increasing? Clin Exp Dermatol 1992; 17: 385–391.
9. Larsen FS. Atopic dermatitis. Etiological studies based on a twin population. Thesis. Copenhagen: Lægeforeningens Forlag, 1985.
10. Larsen FS, Holm NV, Henningsen K. Atopic dermatitis. J Am Acad Dermatol 1986; 15: 487–494.
11. Thestrup-Pedersen K, Ellingsen AR, Olesen AB, Kaltoft K. Atopic dermatitis may be a genetically determined dysmaturation of ectodermal tissue resulting in disturbed T lymphocyte maturation. A hypothesis. Submitted for publication.
12. Medical Birth Statistics 1991. Vital Statistics. Copenhagen: Danish National Board of Health, 1993.
13. Emery AEH. Principles and practice of medical genetics. Vol. 1. 2nd edn. Edinburgh: Churchill Livingstone, 1990.
14. Larsen FS. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. J Am Acad Dermatol 1993; 28: 719–723.
15. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? BMJ 1994; 308: 1132–1135.
16. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors. Submitted for publication.
17. Kaltoft K, Pedersen CB, Hansen BH, Lemonidis AS, Frydenberg J, Thestrup-Pedersen K. In vitro genetically aberrant T-cell clones with continuous growth are associated with atopic dermatitis. Arch Dermatol Res 1994; 287: 42–47.
18. Kaltoft K, Hansen BH, Pedersen CB, Pedersen S, Thestrup-Pedersen K. Continuous human T lymphocyte cell lines with solitary cytokine dependent growth and with common clonal chromosome aberrations. Cancer Genet Cytogenet 1995.