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CLINICAL REPORT

Atopic Dermatitis Is Increased Following Vaccination for Measles, Mumps and Rubella or Measles Infection

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The prevalence of atopic dermatitis increased markedly in the period 1960s to the 1990s. Earlier findings indicate that infections acquired in early life enhance or suppress the expression of atopic disease as a result of a change in immune reactivity. Our objectives were to examine the association between measles, mumps and rubella vaccination, measles infection and the risk of atopic dermatitis. A random sample of 9,744 children were followed up from birth to 3–15 years. Their parents responded to a questionnaire including highly structured questions on atopic dermatitis, measles, mumps and rubella vaccination and measles infection. Information on parental educational level was obtained from Statistics Denmark. The cumulative incidence of atopic dermatitis at age 14 was 19.7%. The confounder adjusted incidence ratio of atopic dermatitis among measles, mumps and rubella vaccinated children versus children not subjected to measles, mumps and rubella vaccination and measles infection was 1.86 (95% CI 1.25–2.79); the incidence ratio for measles-infected children was similar. The incidence of atopic dermatitis increased after measles, mumps and rubella vaccination and measles infection, which is surprising in view of the hygiene hypothesis. We suggest further study of the possible short-term and long-term effects of virus and bacteria on the immune responses and expression of atopic disease. ***Key words: atopic dermatitis; hygiene hypothesis; measles infection; measles, mumps and rubella vaccination.***

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Atopic dermatitis is a skin disease of unknown aetiology with a peak prevalence in early childhood (1). Epidemiological studies suggest that the prevalence of atopic dermatitis among children and young adults increased from 3% in the early 1960s to approximately 20% in the 1990s (2–5).

Earlier reports of an inverse association between atopic disease and family size have given rise to the hygiene hypothesis of Strachan (6), who proposed that infections acquired in early life may prevent atopic disease. This has been indirectly substantiated in many studies (7–10). Furthermore, the findings by Shaheen et al. (11, 12) concerning changes in skin prick positivity and cell-mediated immunity towards delayed-type skin test among African children have supported the hypothesis that absence of infections in early life can affect the development of cell-mediated immunity, resulting in predominance of Th-2 responses (13). The predominance of Th-2 responses may enhance expression of atopic disease (14).

The measles, mumps and rubella (MMR) vaccination with live-attenuated virus was introduced as part of the public health immunization programme in Denmark on 1 January 1987. The programme is free of charge and the child is offered the vaccination twice, i.e. at 15 months and at 12 years. The vaccination rate of the first MMR vaccination was 85% between 1989 and 1998 (15).

The aim was to study whether the MMR vaccination and measles infection affect the risk of atopic dermatitis.

MATERIAL AND METHODS

Participants

The study included a random sample of 10,000 children (between 3 and 15 years of age) drawn from the Danish Medical Birth Registry (16). Data were collected from questionnaires mailed to the families. The information from different registers was linked to the study cohort file by means of personal identification numbers.

The random sample served the dual purpose of providing a population base for studying associations between atopic dermatitis and a few selected risk factors, and of being a reference group in a case-control study concerning association between atopic dermatitis and insulin-dependent diabetes mellitus (5).

We obtained information on deaths, emigration, first-grade family members and the address of the mother from the Danish National Population Register. The information was collected in May 1998, at which time 256 of the 10,000 families were no longer living in Denmark. Information on participation and selected information on symptoms and diagnoses was linked by Statistics Denmark to information on parental educational level 1 January 1998, but owing to legal restrictions this information could not be incorporated in the main database.

Questionnaires were sent to the 9,744 families from May

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Table I. *The main topics of the Danish questionnaire sent to 9,744 families in Denmark*

Questions related to: atopic dermatitis (AD)	measles, mumps and rubella (MMR) vaccination
Ever had itchy skin rash	Ever vaccinated against measles*
Age at onset	Date of first vaccination
History of flexural involvement	Date of second vaccination
Visible flexural involvement	Ever had measles infection†
History of AD, asthma or hay fever – a doctor's diagnosis	Age when child had measles
History of AD, asthma or hay fever among first-grade family members	
Dry skin	

*The parents were told that measles vaccination was part of a triple vaccine called MMR or 'umbrella-vaccination' in Denmark.
†The typical manifestations of measles infection described in ordinary Danish terms.

to October 1998, and a reminder was sent to non-responders one month later.

The Danish questionnaire was a modified version of the UK Working Party's questionnaire for atopic dermatitis (17–20). The Danish questionnaire included questions on itchy skin rash, the child's age at the start of symptoms, MMR vaccination and measles infection (Table I). Atopic dermatitis was defined according to the UK Working Party's algorithm as an itchy skin rash at least once and fulfilling another 3 out of 4 criteria (children less than 4 years of age) or 3 of 5 possible criteria (children 4 years or older). Questions on asthma and hay fever were included, but no information on timing and severity was collected; these diseases will not be considered further in the present paper.

Validation of the Danish questionnaire revealed a sensitivity concerning active atopic dermatitis of 90% (95% CI 74–98%) and a specificity of 97% (95% CI 82–99%) compared to an interview and a standardized clinical examination (21).

Vaccination data were obtained from parental recall using the vaccination booklet kept by the parents. A short description of the typical clinical appearance of measles infection was included in the questionnaire, and the parent was asked whether the child had ever had measles infection.

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

Statistics

Data entry was performed with SPSS Data Entry 1.0. A random sample of 5% of the questionnaires was entered twice, and 99.1% of the questionnaires were recorded without errors. This was found to be an acceptable level. Response rates were age-adjusted by direct standardization before comparisons. For studying the relationship between incidence of atopic dermatitis and exposure to MMR vaccination and measles infection we calculated time at risk and number of incident atopic dermatitis cases before and after exposure. In cases where the recorded ages of exposure and incidence of atopic dermatitis were identical, and it could not be determined whether it was an exposed or unexposed case, we decided to censor the observation 3 months before the recorded age. The accumulated incidence among exposed and unexposed from age 2 to age 12 was estimated from the age-specific incidence rates. Incidence ratios adjusted for age and other potential confounders were estimated by Cox proportional hazards regression.

The analysis was performed with SPSS for Windows, version 10.0 and Stata 7.0. We used 95% confidence intervals and $p<0.05$ was considered significant.

RESULTS

The participation rate was 79% (7,693 of 9,744 families); 51.7% were boys and 48.3% were girls. The age-adjusted response rate was significantly associated with maternal educational level ($p<0.001$) (Table II). Direct standardization by age modified the estimates only slightly (data not shown).

The cumulative atopic dermatitis incidence up to the age of 14 was 19.7% using the UK Working Party questionnaire algorithm, and 21.8% using a doctor's diagnosis of atopic dermatitis (Fig. 1).

Among responders, 7,178 (93.3%) children had received at least one MMR vaccination. A total of

Table II. *Educational level of the mother, non-response rate, atopic dermatitis incidence and measles, mumps and rubella (MMR) vaccination rate*

Educational level of the mother*	Non-response rate	Atopic dermatitis†	MMR vaccination rate‡
Missing information	35.3% (171)	–	–
Elementary school (10 years)	31.4% (835)	18.2% (333)	91.2% (1655)
Elementary school +1 to 3 years	17.8% (715)	17.6% (580)	95.5% (3147)
Elementary school +4 to 5 years	14.7% (130)	19.2% (145)	93.6% (706)
Elementary school +6 to 7 years	12.7% (159)	19.6% (215)	94.0% (1030)
Elementary school +8 years +	9.3% (41)	15.8% (63)	95.5% (381)
p value (trend)	<0.001	0.77	0.006

*The highest educational level of the mother on 1 January 1998.
†The UK Working Party Criteria for atopic dermatitis.
‡The first MMR vaccination.

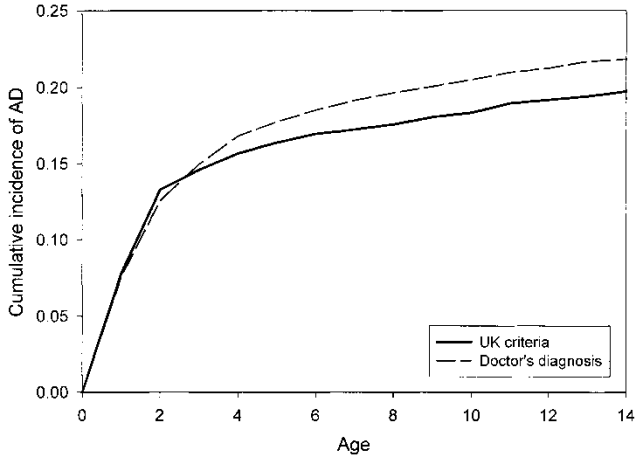

Fig. 1. Cumulative incidence of atopic dermatitis (AD) among 0–14-year-old children using the UK diagnostic algorithm and a doctor's diagnosis.

483 (6.3%) children had never received an MMR vaccination and MMR data were missing for 32 (0.4%) children. The MMR vaccination rate was lowest among responders with low educational level, and there was no association between educational level and incidence of atopic dermatitis (Table II). The median age at the first MMR vaccination was 15 months, and 86.3% of the vaccinated children received their first vaccination during the second year of life. Atopic dermatitis developed after MMR vaccination in 415 children, and 955 children developed atopic dermatitis while unvaccinated.

Fig. 2 shows the cumulated incidence from age 2 to age 12 of atopic dermatitis after MMR vaccination, after measles infection, and among children not yet exposed to MMR vaccine or measles infection. Most MMR vaccinations took place before the age of 2, but because of imprecise information on timing, with many ties, we consider the estimates before the age of 2 to

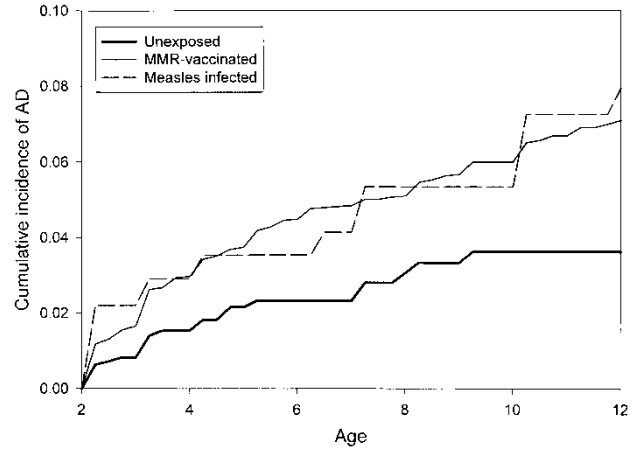

Fig. 2. Cumulative incidence of atopic dermatitis (AD) among 2–12-year-old children after exposure to measles, mumps and rubella (MMR) vaccination, measles infection and among unexposed children.

Table III. *Atopic dermatitis cases and time at risk after the age of 2, by exposure to measles, mumps and rubella (MMR) vaccination or measles infection*

Exposure	AD cases	Time at risk (years)	Annual incidence per 1000 (95% CI)
None	26	4,714.0	5.5 (3.8–8.1)
MMR vaccination	298	33,980.7	8.8 (7.8–9.8)
Measles infection	11	1,498.6	7.3 (4.1–13.3)

*Crude incidence rate.
AD: atopic dermatitis.

be unreliable. The main analysis was therefore carried out from ages 2 to 12. Table III gives the unadjusted atopic dermatitis incidence after the age of 2, according to exposure status. Compared to unexposed children, the incidence of atopic dermatitis was increased after MMR vaccination and measles infection. The incidence ratio adjusted for age, gender, gestational age, parity and maternal age after MMR vaccination was 1.86 (95% CI 1.25–2.79) and after measles infection 2.08 (95% CI 0.98–4.42). The incidence of atopic dermatitis among those measles-infected and vaccinated was not significantly different, adjusted incidence ratio 1.13 (95% CI 0.61–2.06). Using a doctor's diagnosis of atopic dermatitis gave similar results (data not shown). Among children with atopic dermatitis, we observed no difference in severity among those exposed and those not exposed to measles infection or MMR vaccination (data not shown).

DISCUSSION

The main finding of this study was an increased incidence of atopic dermatitis after MMR vaccination compared to unexposed children and a similar association with measles infection. Our findings are in agreement with the observations of both Paunio et al. (22) and Bager et al. (23), who found that atopic disease manifestations (eczema, asthma or allergic rhinitis) were significantly more prevalent among those who had a report of a measles infection.

The hygiene hypothesis as proposed by Strachan (6) suggests that eradication of common infectious diseases of childhood leads to a skewing of the immune system with increased development of atopy, i.e. an increased frequency of IgE-mediated reactions. This has been supported in many epidemiological studies. Shaheen et al. (11) observed that previous measles infection in African children is associated with a significant reduction in type I reactivity towards house dust mite antigen. Likewise, young Italian men drafted for military service with the presence of antibodies to hepatitis A had a significant reduction of type I reactivity to aeroallergens (24). However, IgE production and type I reactivity are not necessarily associated with atopic

dermatitis. In a recent African study on schistosomiasis infestation, type I reactivity was significantly reduced in children with chronic infestation in contrast to non-infested children (13). However, none of the children had clinical symptoms or signs of atopic dermatitis.

The measles virus has profound short-term effects on the immune system interfering with the survival and functioning of dendritic cells, T lymphocytes and thymic epithelial cells with a temporary lymphopenia and reduced or lacking cell-mediated immune reactivity of the skin (12, 25–29). In an earlier cross-sectional study by Alm et al. (30), an inverse association between atopy and measles infection was observed. Others have demonstrated that BCG vaccine is inversely associated with atopy, suggesting that in some instances vaccination may have a strong influence on the development of a specific Th1 immune response (31, 32). In another study, Alm et al. (33) found no association between BCG vaccination and atopy; however, since the unvaccinated children had a very special lifestyle, that particular study was vulnerable to confounding. Our observation indicates that both MMR vaccination and measles infection stimulate the clinical expression of an atopic disease: namely atopic dermatitis. Our observations are surprising in view of the hygiene hypothesis (6), but they do not rule out that a lack of certain bacterial infections or infestations is of significant importance to understanding the increased prevalence of atopic dermatitis.

Griffin & Ward (34) have shown that infection with the measles virus is associated with prolonged IL-4 elevation in plasma. The changes are similar after vaccination with live attenuated measles virus but less prolonged (35). Recently, Imani et al. (36) showed that the activation of Th-2 cells is associated with IgE induction in the presence of IL-4. These findings may support the notion that the measles virus induces expression of atopic disease, as observed in this study and others (22, 23).

In contrast, Pabst et al. (37, 38) found that interferon-gamma was the principal cytokine produced after measles immunization of infants, thus suggesting a Th-1 response. These findings are in keeping with the observations of Shaheen et al. concerning reduced type I reactivity (11) and by Bodner et al. (39).

The contradictory findings may indicate that exposure to the measles virus affects the immune system differently concerning atopic dermatitis compared with atopic diseases such as asthma and hay fever and IgE-mediated allergy. We observed no association between the other atopic diseases (hay fever and asthma) and MMR vaccination or measles infection (data not shown). However, the hay fever and asthma diagnoses were collected without information concerning age of onset, and it was not possible to make a proper statistical analysis including the sequence of events. Another explanation of the different findings may be that the immunological mechanisms induced by the measles virus differ in timing and intensity of exposure. Our results indicate that the MMR vaccination and measles act in the same manner and increase the risk of atopic dermatitis. However, the effects of the mumps and rubella virus and adjuvants in the MMR vaccine are so far unknown. A skin infection like measles may elicit another latent skin infection, i.e. atopic dermatitis.

The main strength of the present study is its large size, and the availability of registered information covering the entire population, thus providing a population-based setting with a unique opportunity for non-responder analysis and consistent information concerning educational level. We focus on atopic dermatitis incidence and take the sequence of events into consideration. Our validation of the Danish questionnaire has shown an acceptably high specificity and sensitivity of the diagnosis of active atopic dermatitis (21).

The weakness of our study is its retrospective design. We are dependent on parental recall for most of our information, and neither the information leading to diagnosis nor the information concerning timing can be considered perfect. The information on MMR vaccinations is less vulnerable to recall problems since the parents could consult the vaccination booklet. Before the age of 2, MMR vaccination and atopic dermatitis were frequently reported at the same age, leading to ambiguity concerning the sequence of events. After the age of 2 such occurrences become infrequent, and we therefore consider an analysis from the age of 2 onwards to be valid. We see no reason to assume that recall concerning atopic dermatitis experience was different among unvaccinated and vaccinated children, and the consequence of non-differentiated recall problems is invariably an underestimation of the true contrast.

Parental recall could give rise to misclassification of atopic dermatitis, but the associations between MMR vaccination, measles infection and atopic dermatitis did not change whether atopic dermatitis was defined as a doctor's diagnosis or according to the UK diagnostic algorithm.

When adjusting for gender, gestational age, parity and maternal age the estimates changed only slightly. Because of legal restrictions we could not incorporate social indicators directly in our database, and our main analysis concerning AD and MMR vaccination and measles infection could not directly be adjusted for maternal education. However, we found no association between maternal education and the incidence of atopic dermatitis, thus ruling out confounding from this source. The decision not to let a child be vaccinated may be associated with other lifestyle factors associated with the atopic dermatitis risk. If parents of non-vaccinated children are less attentive concerning health issues such as skin conditions, it could lead to bias.

However, in our study the tendency was that a doctor's diagnosis of atopic dermatitis was more frequent in families with low educational level (data not shown), and this refutes the suggested source of bias.

We observed an increased incidence of atopic dermatitis after MMR vaccination and measles infection, which is unexpected in view of the hygiene hypothesis. It is important to stress to all concerned parents that not only does our study support that MMR vaccination increases the risk of atopic dermatitis, but that the alternative, natural measles infection, had the same effect. We suggest that further studies focus on the short-term and long-term effects of virus and bacteria on the immune responses and their regulation in children with and without atopic disease, with a focus especially on the other IgE-mediated disorders and then follow-up on the relevant age groups of children and young adults.

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