

Infantile natural immunization to herpes group viruses is unrelated to the development of asthma and atopic phenotypes in childhood

To the Editor:

The development of atopic diseases, including asthma, is influenced by factors such as atopic family background and exposure to allergens. Recent epidemiologic studies have shown geographic differences in the prevalence of atopic phenotypes between Eastern Europe and Western Europe and between industrial nations and developing countries. One possible explanation for these observations is differences in exposure to certain infectious agents in early life. ¹

Infections with herpes group viruses have high prevalence and induce a powerful T_H1-type immune response that might have an influence on the general human immune system. Whereas T_H2- type cytokines promote IgE production, T_H1-type cytokines, such as IFN- γ , inhibit the action of T_H2-type cytokines. ² Thus, early infection with herpes viruses might be protective for developing T_H2- type –dependent asthma and atopic disorders.

We analyzed the relationship between natural immunization to herpes virus infections—cytomegalovirus (CMV), EBV, and varicella-zoster virus (VZV)—in infancy by measuring the specific humoral immune response and the subsequent prevalence of atopic manifestations.

In a birth cohort study (MAS-90), a newborn population was prospectively examined for atopic characteristics. The cohort children were examined at 1, 3, 6, 12, 18, and 24 months of age and subsequently at yearly intervals up to the age of 7 years. Atopic symptoms, such as atopic dermatitis, bronchial asthma, rhinoconjunctivitis, allergic sensitization, and total serum IgE level, were recorded. ³

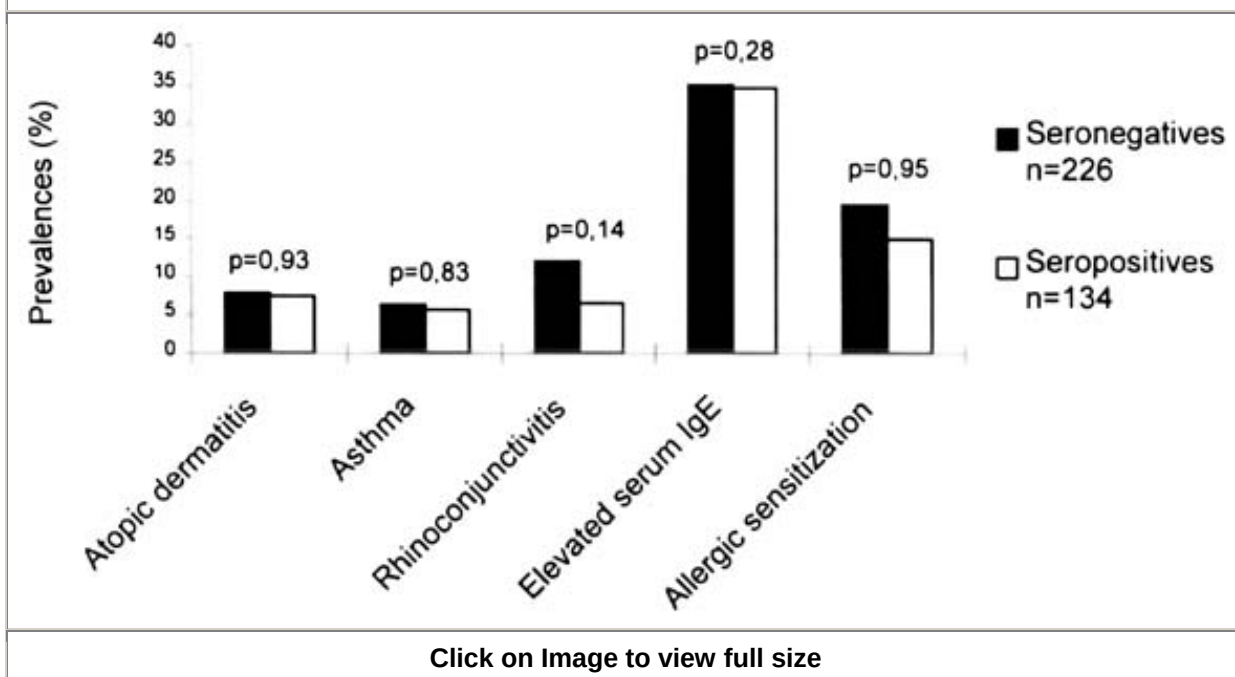
Of 1314 participating children, 1120 (85%) participated in the follow-up survey at 1 year of age and 939 (71%) participated in the final follow-up survey at 7 years of age. The participation rate for blood sampling at the age of 1 year was 65% (724/1120). During the final years of the cohort study, the samples were used for various investigations; as a result, only 362 of the original 724 serum samples taken at the age of 1 year were available for the present study.

Virus-specific IgG antibodies to CMV, EBV, and VZV were analyzed in all sera by ELISA (ETI-CYTOK-G [P2860], AD 169, ETI-EBNA-G [P001607], synthetic peptide EBNA-1, and VZV-IgG-ELISA [DS5600], DiaSorin, Saluggia VC, Italy). Statistical significance values were calculated by means of χ^2 and Yates tests through use of a computer program

(SPSS version 8.0; SPSS, Inc, Chicago, Ill); *P* values less than .05 were considered statistically significant.

At the age of 12 months, seropositivity for CMV, EBV, and VZV was found in 33.4%, 1.3 %, and 3.1% of the 362 children, respectively; 37.3% of the children were seropositive for at least 1 of the 3 viruses (CMV, EBV, or VZV). We were unable to detect significant differences between children with and children without antibodies to CMV, EBV, and VZV at 1 year of age with regard to prevalence of atopic dermatitis, bronchial asthma, seasonal allergic rhinoconjunctivitis, total serum IgE levels, or allergic sensitization at the age of 7 years or before then. Elevated serum IgE was defined as total serum IgE levels greater than those of the 85th percentile. Allergic sensitization was defined as a specific IgE value of ≥ 0.35 kU/L (Fig 1 ■).

Fig. 1. Prevalence of atopic phenotypes at the age of 7 years in relation to the presence of serum antibodies to herpes group viruses at the age of 1 year.



Potential confounders, such as atopic family history, social status, and sex, showed no significant association with antibodies to CMV, EBV, or VZV.

An inverse association between viral infections and the prevalence of asthma and atopic disorders has recently been reported.⁴⁻⁶ Our group found that recurrent mild upper airway infections in infancy had a protective effect against the later development of asthma.³ This discrepancy could be explained by the use of a different study design. The children that we included in the present study are a subset of the children that had been analyzed previously.³ Illi et al³ defined herpes infection on the basis of clinical data (occurrence of cutaneous herpes infection—such as exanthema subitum, herpes simplex, stomatitis, or varicella zoster— during the first 3 years of life) reported by parents. Our study was designed to investigate systemic infections with herpes group viruses and their capacity to induce a powerful T_H1 immune response (much more than the local virus infections).

The diagnosis of herpes infection was made by detecting circulating antibodies to the virus in the blood. Theoretically, infections with herpes group viruses might also have a modulating effect on the immune response. The exposure to herpes viruses is known to

occur frequently in childhood, inducing lifelong immunity, which is mostly associated with a powerful T_H1 immune response representing more than 1% of the total T-cell repertoire.⁷

It has been suggested that the first months of life are important for the development of effective T_H1 immune responses that protect against viral infections and control the T_H2 response pattern. An inadequate development of the T_H1 response in infants might result in persistent dominance of the T_H2 response, which predisposes to atopy.⁸ In the present study we could not determine exactly when during the first year of life the seropositivity had occurred; this is because the serum samples were not collected before the age of 12 months. However, to test for potential differences between early and later exposure to CMV in the first year of life, we compared antibody titers to the viruses in atopic and nonatopic children. No statistically significant difference was found. These data provide indirect evidence that there are no differences regarding time of primary virus infection between atopic and nonatopic children. Recent studies suggest that only recurrent infections—not single viral infections—influence a T_H1/T_H2 deviation and the predisposition to atopy.⁹

In conclusion, our data do not demonstrate a protective effect of natural herpes virus infections in infancy on the subsequent development of atopic disorders. One reason for these results might be that infections with herpes viruses, unlike other viral or mycobacterial infections, have less influence on the development of atopic manifestations. In contrast to immunologic reactions caused by the herpes viruses analyzed in this study, immunologic reactions caused by infections with rhinoviruses—to take one example—take place directly in an organ of interest, the upper airway. Recent studies have suggested that herpes viruses induce not only a T_H1-type immune response but also a T_H2-type immune response, depending on the viral antigens.¹⁰ Further studies will show whether there are mechanisms by which certain viral infections protect against atopic disorders.

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