Mucosal Immune Response in a Case of Sudden Infant Death Syndrome

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ABSTRACT. A prospective study to define the normal patterns of development of mucosal immunity in 263 children provided a unique opportunity to study the mucosal immune response in an infant who unexpectedly died from sudden infant death syndrome. The subject initially had a normal pattern of mucosal immune function, which was perturbed after a transient mild upper respiratory tract infection at 3½ wk of age. After the upper respiratory tract infection, there was an increase in mucosal permeability and the appearance of IgA and IgM in saliva. The unusual features in this case were the degree and the duration of the increases in salivary IgA and IgM after resolution of the illness. The marked abnormalities suggested a persistent stimulation of the mucosal immune response. The case provides informative data on potential mechanisms of sudden infant death syndrome and supports a role for involvement of upper respiratory tract infection. (*Pediatr Res* 33: 554–556, 1993)

Abbreviations

SIDS, sudden infant death syndrome
URTI, upper respiratory tract infection

SIDS has been reported to occur after a mild URTI (1–4). As there is no epidemiologic, clinical, pathologic, or microbiologic evidence that favors infection by a particularly virulent pathogen, it is likely that a high degree of stimulation of the immune system may be one important link in the chain of events that culminates in respiratory arrest. Previous studies have suggested that secretory component was absent or reduced in bronchopulmonary epithelium in SIDS (5) and that overstimulation of the mucosal immune response occurs in the respiratory and gastrointestinal tracts (6–9). IL-1 has also been suggested as a mediator between sleep apnea and SIDS during URTI (10). However, the limitations associated with retrospective data collected on postmortem material, as well as the quality of control studies, have presented major difficulties with interpretation of SIDS research.

A prospective study from birth of a cohort of 263 children to determine normal patterns of development of mucosal immunity (11, 12) provided an opportunity to study the mucosal immune response in an infant who unexpectedly died from SIDS. We describe in this infant the mucosal immune response after a URTI and postulate that a disturbance in immune regulation and/or mucosal permeability may constitute a link in the chain of events that lead to respiratory arrest.

Received July 7, 1992; accepted January 19, 1993.

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The study was partially funded by the National Health and Medical Research Council of Australia. The data on the incidence of viral illness in NSW, Australia, were kindly provided by Professor Richard Barry (Department of Virology, University of Newcastle).

MATERIALS AND METHODS

Clinical history. The female infant was delivered at term by spontaneous vaginal delivery to a 24-yr-old mother (gravida 4, para 2) after an uncomplicated pregnancy. She weighed 3620 g and had Apgar scores of 8 at 1 min and 10 at 5 min. She was breast-fed until 5 wk of age, but received complimentary formula feeding on the first 2 d of life, and was then totally formula-fed from 5 wk of age. She had not received any childhood vaccinations.

A mild respiratory tract infection (symptoms were a “runny nose” and difficulty breathing) was diagnosed at 3½ wk of age by the local doctor. The subject shared a bedroom with two older siblings, one of whom had a prior respiratory tract infection. Her father was atopic, but otherwise there was no family history of specific illness. Both parents smoked more than 10 cigarettes/d. Her mother did not smoke during the pregnancy but resumed smoking immediately after the birth.

The subject was born at the beginning of the Australian autumn and was followed prospectively during the months of March to May. In March, there was an increase in the incidence of mycoplasma pneumonia in the state of New South Wales, whereas respiratory syncytial virus and parainfluenza virus showed normal background incidence during the same period (Australia Communicable Diseases Intelligence Bimonthly statistics).

The infant died at home at 10 wk of age. The postmortem findings confirmed the infant death classification of SIDS, and the examination showed cerebral and pulmonary edema with some shedding of the alveolar lining cells. No acute bronchitis or bronchiolitis was demonstrated.

Immunological investigations. Saliva samples were collected from the SIDS infant 2 d after birth and during wk 2, 3, 4, 6, and 8 after birth. Salivary IgA, IgM, IgG, and albumin were measured by electroimmunodiffusion (13). The reference levels for each analyte were calculated for weekly age groups as the 10th, 50th (median), and 90th percentiles and are represented as shaded areas on Figure 1. Salivary Ig responses during URTI have been previously studied in this cohort of children (14), and the relevant findings have been summarized in this report.

RESULTS

Albumin. The salivary albumin level was initially low near birth (10th percentile for 2 d) but showed a rise and subsequent fall in the 2nd and 3rd wk of life (Fig. 1A); the concentrations remained within the normal age-related reference ranges for wk 1 to 3. The albumin level was significantly increased in the 4th wk, being 7 times higher than the age-related median level. The albumin levels in the 6th and 8th wk declined but remained above the 90th percentile for each age group.

In the control study examining salivary protein responses during URTI (14), the geometric mean albumin levels within any individual child did not differ between periods of URTI and noninfection periods.

Fig. 1. Albumin (A), IgG (B), IgA (C), and IgM (D) concentrations in saliva collected from birth to 8 wk of age in an infant who died of SIDS. Age-related reference ranges are represented as shaded areas.

IgG. The salivary IgG level was within normal age limits at birth (0.031 g/L) and decreased to a nondetectable level at 3 wk of age (Fig. 1B). The IgG level rose at 4 wk of age to 0.054 g/L, a level above the 90th percentile for this age group. The IgG level declined in the 6th wk but at 8 wk was again above the 90th percentile for this age.

In the control study (14), IgG was detected in saliva more frequently in samples collected during URTI (89%) than during noninfection periods (53%), but the concentrations did not exceed the 90th percentile for age for any subject.

IgA. Low (0.009 g/L) or nondetectable levels of IgA were measured in the saliva for the first 3 wk of life (Fig. 1C). The IgA level rose in the 4th wk of life (0.022 g/L) and continued to rise in samples collected in the 6th and 8th wk to a level (0.093 g/L) 5 times higher than the age-related median level for 8 wk of age.

In the control study (14), elevations of salivary IgA were observed during 18 of 20 URTI periods studied, and the IgA returned to noninfection mean levels within 10 d of disappearance of symptoms. The IgA peak level during URTI periods in three children studied under 6 mo of age did not exceed 0.020 g/L.

IgM. IgM was not detected in the saliva samples collected in the first 4 wk of life (Fig. 1D). IgM was detected in the samples collected in the 6th and 8th wk of life, at levels above the 90th percentile for age, and at 8 wk of age was 10 times higher than the age-related median level.

In the control study (14), there was no significant association between URTI and the detection of IgM in saliva.

DISCUSSION

We report results of investigations of mucosal immunity in an infant who died of SIDS. The cohort of 262 healthy infants had been prospectively studied from birth for 5 y, enabling a precise

definition of normal patterns of development of mucosal immunity and factors that alter the ontogeny (11–13), including the influence of URTI (14). Analysis of saliva protein levels in the SIDS infant demonstrated a prolonged period of increased mucosal permeability and an exaggerated and prolonged mucosal immune response after an URTI, both of which persisted until the assessment period 2 wk before the infant's death.

In the immediate postnatal period, the detection of IgG and high levels of albumin reflect a normal transient physiologic state of increased mucosal permeability (15). The subject of this report initially had a normal pattern of mucosal function, with a rapid disappearance of IgG, a decrease in albumin levels in saliva, and an absence of detectable IgA and IgM. The normally evolving saliva protein profile was perturbed after a transient mild respiratory tract infection. The reappearance of IgG and the increase in saliva albumin levels from the time of the URTI reflects an increase in mucosal permeability, which has been noted in normal infants after antigenic challenge, including infection of the respiratory tract (14).

The appearance of IgM and an increase in IgA in saliva is a normal event after URTI (14). The unusual features, unique in our experience in the SIDS infant, were both the degree and the duration of the increases in the salivary Ig levels. We have prospectively followed normal infants with URTI and commonly noted minor increases in IgA, IgG, and IgM, but they have been small in amount and have always returned to normal levels within 10 d of disappearance of clinical symptoms (14). The marked abnormalities in mucosal Ig in the SIDS infant suggested an enhanced immune response, possibly due to increased antigen influx.

Mature mucosal surfaces are down-regulated with respect to immune reactivity to environmental antigen, and control is probably mediated through suppressor T lymphocytes capable of restricting lymphocyte proliferation (16). Little is known about the maturation of mucosal immune control mechanisms, but an

apparent oscillatory pattern of salivary IgA levels early in life (13) would be consistent with a period of instability in the first few months of life. The appearance in the saliva of some infants at this time of IgD (17) and monomeric IgA (18) further suggests a period of mucosal immaturity. Infants genetically predisposed toward lability in the development of normally rigorous mucosal suppressor mechanisms may account for the abnormal response observed in the SIDS infant.

Previous studies have identified a genetic predisposition (19, 20) and a mild URTI (1–4) as risk factors for SIDS, whereas many of the other risk factors identified (20–29), such as social status, environmental temperature changes, infant overheating, and passive smoking (4, 30–33) may secondarily relate to infection or mucosal inflammation. Several of these potentially conditional risk factors were identified in the SIDS infant.

Recent studies (20, 21) have suggested that the pattern of infant feeding is a risk factor, with a decreased incidence of SIDS in breast-fed infants. Formula feeding in early life exerts a significant effect on mucosal function, extending the postnatal period of increased mucosal permeability and causing early activation of mucosal B lymphocytes (12, 15). The SIDS subject in this study changed from breast feeding to formula feeding at 5 wk of age, coinciding with the phase of enhanced mucosal immune response. The possible interaction between the effect of introduced food and a concurrent mucosal infection at a critical stage of mucosal maturation requires further study.

The protein changes in saliva were distant from the site of clinical infection. Whether these changes reflect a contiguous infection of oropharyngeal mucosa or a more generalized mucosal change cannot be stated. Nor can a direct or indirect link with respiratory arrest be proven. We would propose, however, the following hypothesis: infants genetically predisposed to transient labile mucosal suppressor mechanisms are particularly at risk should certain environmental events occur in the period of mucosal immaturity. An inappropriate or persistent mucosal immune response to antigen may activate vagal afferent nerve endings or chemoreceptors to induce reflex apnea.

Acknowledgments. The authors thank members of the research team, Professor Stephen Leeder, and Associate Professor Michael Hensley, and in particular Sister Sue Graf for collection of the saliva and Sharron Hall for technical assistance; also, Amanda Beisty for typing this manuscript.

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