

Annotations

Respiratory syncytial virus and the infant immune response

The pattern of disease caused by respiratory syncytial (RS) virus is distinctive. Severe lower respiratory tract infection, commonly bronchiolitis, is most prevalent among infants between 1 and 6 months of age. Primary infection outside of this age range is fairly common and well documented, but both neonates and children tend to handle the virus more successfully. One infection is insufficient to engender complete protection, but the severity of disease diminishes with successive infections as the child grows older.¹

The search for an explanation of this unique epidemiological pattern has centred on the infant's immune response: effectively, all mothers will have encountered this ubiquitous virus and vulnerable infants passively acquire maternal immunity both transplacentally and, in some cases, through colostrum and breast milk. In addition, they are capable of mounting their own primary local and systemic responses. For babies who develop bronchiolitis the complex interaction of these passive and active defences results in an aggregate response insufficient to protect the lung from damage. Recent research has revealed several subtle defects, some age related and some RS virus specific, which together may begin to explain why patients with this virus fill our paediatric wards each winter.

Transplacental antibody

Babies acquire serum antibody passively from their mothers, and there is evidence that high maternal antibody concentrations may protect.² The incidence of severe infection rises, however, from the second month of life when concentrations of maternal antibody in infant serum are still high. No satisfactory explanation for this phenomenon is yet available, but there are several ways in which maternally acquired antibody may be inadequate.

It has been suggested that protection of the infant lung against RS virus is mediated by antibody of the IgG3 subclass. IgG3 forms a minor component of the antibody acquired transplacentally, has a short half life, and declines to a nadir in infant serum at four to six weeks of life.³ Acute serum samples from

infants infected with RS virus have been found to contain IgG3 anti-RS virus antibodies, albeit at low concentrations, but it might be argued that these have declined below a threshold necessary for protection.⁴ Alternatively, transplacentally acquired antibody may lack specificity for the strain of virus infecting the infant. RS virus is not monotypic and at least two subtypes have been described that have co-circulated during recent years.⁵ Studies in animals indicate that cross protection does occur but does not correlate with neutralising antibody concentrations and may depend on cross reactive cell mediated immunity, which does not cross the placenta.⁶

To protect the infant, antibody present in the blood must gain access to the site of infection. Enhanced transudation of serum immunoglobulin on to the mucosa occurs during the early inflammatory response to virus. Exposure of human macrophages to RS virus, but not influenza virus, stimulates production of an interleukin 1 inhibitor, which in vivo may delay inflammatory changes at the site of infection and thus hinder mobilisation of serum antibody.⁷

Bronchiolitis and breast feeding

Immunity to RS virus may also be acquired passively from the mother through breast milk, and breast feeding reduces the risk of lower respiratory tract disease.⁸ Colostrum and milk contain large amounts of IgA antibody, some of which is RS virus specific, and breast fed but not bottle fed neonates have IgA in their nasal secretions, which is probably passively acquired. Lower concentrations of anti-RS virus IgG antibodies are also found in milk and RS virus reactive T lymphocytes are present in the colostrum of up to 40% of mothers. Mothers of infants with severe RS virus bronchiolitis were no more likely, however, to have low anti-viral IgA or IgG antibody concentrations or lymphocyte reactivity in their colostrum and milk than mothers of infants with mild disease or infants of similar age with no evidence of infection.⁹ Animal studies have indicated that breast feeding may accelerate the maturation

tion of the infant mucosal immune response, but in human infants we have found that nasal antibody responses in breast and formula fed infants with RS virus infection were similar both in timing and concentration. The mechanism of protection afforded by breast feeding thus remains obscure.

The infant's systemic immune response

Detailed recent comparisons of serum antibody responses of infants and older children have shown no significant qualitative differences in either immunoglobulin subclass or antigenic specificity.^{10 11} After primary infection with RS virus, however, serum antibody responses of infants are less efficient than those of older children. Some fail to respond at all and the low level and inconsistency of their systemic response probably contributes to their vulnerability to the virus.¹⁰ The poor serum antibody response of infants may, at least in part, result from an immunosuppressive effect of transplacentally acquired maternal antibody.¹²

Cell mediated immune responses are likely to be of considerable importance in recovery from infection as suggested by the severity of infection in patients with congenital T cell defects and by studies of cytotoxic T lymphocytes in animal models.¹³ Unfortunately, ethical and technical difficulties in the collection of blood samples from infants have restricted the range of investigations and further studies of human infants are required to assess their ability to mount a cytotoxic T cell response and assess its relevance to the pathogenesis of infection.

Local responses in the respiratory tract

While it is clear that high concentrations of nasal antibody protect adult volunteers against RS virus infection¹⁴ and stopping of virus shedding in the nasal secretions of infants coincides with the appearance of sIgA antibodies,¹⁵ the effect of local immune responses on the pathogenesis of virus infection of the lung has not been established. Measurement of nasal responses may have little relevance to lower respiratory tract infection and we have failed to detect any discernible relation between concentrations of nasal virus and severity of chest infection in RS virus infected infants (unpublished results). Nasal secretions are, however, accessible and may give a picture of the general level of immunoresponsiveness in the infant.

Local, like systemic, responses are sluggish in the very young. This poverty of response may be particularly dangerous as nasal interferon¹⁶ and IgM antibody responses in RS virus infected infants are considerably lower than those in infants of the same

age infected with other respiratory viruses (unpublished results). Suppressed local responses may reflect the immunosuppressive abilities of RS virus described by Domurat¹⁷.

Although these subtle defects may render young infants particularly vulnerable to RS virus infection, other factors seem to determine the outcome of individual infections, as neither nasal interferon nor secretory antibody responses correlate with disease severity (unpublished results). Welliver *et al*, however, report an association between early and high nasal anti-RS virus IgE antibody secretion and lower respiratory tract disease.¹⁸ They have postulated that bronchiolitis results when a suppressor cell defect in RS virus infected infants leads to uncontrolled local IgE synthesis, degranulation of mast cells, and bronchoconstriction. Unfortunately, antigen specific IgE assays have proved difficult to establish elsewhere and these exciting results have not been confirmed in other laboratories.

References

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