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Cytomegalovirus in the neonate

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Cytomegalovirus infection in early life may be congenital, or acquired during delivery or in the post natal period. The incidence of congenital infection varies widely throughout the world and ranges from 0·2 to 2·2% of live births; rates in the United Kingdom are between 0·3 and 0·4%. While fewer than 10% of congenitally infected infants have clinical manifestations of CMV infection at birth, most of this group will have serious neurological handicap. Of those with no symptoms at birth about 5% will subsequently manifest CMV-related problems, the most common being sensorineural hearing loss. Most congenitally infected children are neurologically and intellectually normal.

Infection is acquired early in a high proportion of infants. In one study where 50% of mothers had CMV antibodies, 12% of their infants had acquired infection by three months and 20% by one year. The mothers' gestational status and whether the infants were breast fed were major factors associated with infection. Transfusion of CMV-infected blood is another important source of CMV infection and screened blood should be given to premature infants.

Introduction

Cytomegalovirus (CMV) infection may be acquired *in utero*, at the time of delivery through contact with infected cervical secretions (Reynolds, Stagno & Mosty, 1980), or after birth. Important sources of postnatal infection include breast milk (Stagno *et al.*, 1980), and transfusion of seropositive blood products (Adler *et al.*, 1983). Congenital CMV infection, which is the commonest congenital infection, is an established cause of handicap (Hanshaw, Dudgeon & Marshall, 1985). When acquired after birth, however, infection is usually asymptomatic or associated with non-specific illness, and only in premature infants or immunocompromised individuals are the consequences sometimes serious.

The proportion of women with CMV antibodies varies widely between populations. In the United Kingdom about 50% of women of childbearing age remain susceptible to a primary CMV infection, whereas in Africa and the Asian subcontinent close to 100% of the adult population are seropositive. The risk of a susceptible woman acquiring infection during pregnancy is about 1% and of those infected about 40% will give birth to an infant with congenital infection.

Congenital infection

The incidence and severity of congenital infection vary widely throughout the world; incidence ranges from 0·2 to 2·2% of live births, depending on the population studied.

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There is no evidence of a seasonal variation. The varying rates of congenital infection are likely to reflect the seroprevalence of infection in the community. After a primary infection periodic episodes of reactivation occur and recurrent infection in a pregnant woman with previous immunity can result in congenital infection. In populations with a high rate of seropositivity, most congenital infections will result from a recurrent maternal infection (Stagno, Pass & Dworsky, 1982). Although recurrent infections are less likely to result in fetal damage than primary infections (Stagno *et al.*, 1982), defects compatible with CMV infection have been reported in infants with congenital CMV born to women who are known to be seropositive before conception (Ahlfors *et al.*, 1981; Rutter, Griffiths & Trompeter, 1985).

As most women with CMV infection have no symptoms and over 90% of congenitally infected infants have no clinical signs of infection in the neonatal period, most congenital infections pass unrecognized. In order to provide information on the incidence and long term consequences of congenital infection large prospective studies of infants systematically screened for CMV infection at birth and found to be infected are required.

Clinical manifestations of congenital CMV infection in the neonate include hepatomegaly, splenomegaly, petechiae, thrombocytopenia, prolonged neonatal jaundice, pneumonitis, growth retardation, microcephaly, and, occasionally, cerebal calcifications. Only a small proportion of congenitally infected infants, about 5%, manifest these symptoms at birth and the likelihood of them surviving with normal intellect and hearing is small (Pass *et al.*, 1980). Later complications include cerebral palsy, epilepsy, mental retardation, choroidoretinitis, optic atrophy, delayed psychomotor development, expressive language delay, learning disability and sensorineural deafness. However, most congenitally infected infants have no neonatal manifestation of infection and develop normally.

Evidence derived from prospective studies carried out in the United States, Canada, Sweden and the United Kingdom (Ahlfors *et al.*, 1982; Saigal *et al.*, 1982; Preece, Pearl & Peckham, 1984) have shown that a small proportion of clinically normal neonates (fewer than 10%) may later manifest problems. These include sensorineural hearing loss, mental retardation and motor defects such as spastic diplegia or quadriplegia. The single most important late-appearing abnormality is sensorineural hearing loss and the hearing impairment may develop or become more severe after the first year of life (Dahle *et al.*, 1979).

In an continuing prospective follow-up study in London (Peckham *et al.*, 1983), about 35,000 newborns were systematically screened for CMV and 103 infants with congenital CMV were identified, a rate of 0.3% of live births. Only four children presented with CMV-related problems in the neonatal period and the remaining 99 had no clinical evidence of infection. All four symptomatic neonates developed handicaps which included cerebral palsy, microcephaly, severe mental retardation and severe bilateral hearing loss. In addition, four of the 99 asymptomatic neonates subsequently manifested bilateral sensorineural hearing loss, associated with mild cerebral palsy in three, and one had a unilateral hearing loss. Ten other congenitally infected infants developed pneumonitis and two had transient hepatosplenomegaly. The onset was usually around three months of age and the respiratory problems have resolved without sequelae.

Sensorineural hearing loss is the most frequent problem associated with congenital CMV and prospective studies suggest that about 6% of such children have a moderate

or more severe bilateral sensorineural deafness (Kumar *et al.*, 1984). The importance of congenital CMV as a cause of hearing loss was further supported by a study in which 1644 children aged between six months and four years, attending a hearing centre in London, were screened for CMV infection (Peckham *et al.*,1987*b*). The prevalence of CMV in the urine of children with sensorineural hearing loss but no immediate family history of deafness (13%) was nearly twice that found in other children with impaired hearing loss and those with normal hearing (7%). It was estimated that congenital CMV could account for about 12% of children with bilateral sensorineural hearing loss.

Recent studies have also shown that in the absence of neurological problems CMV does not appear to have a specific effect on intellectual development. This has important implications for the 90% of congenitally infected children who are apparently normal at birth. Pearl *et al.* (1986) using a *Griffiths assessment* on CMV infected infants and their matched controls, found no significant difference in the mean overall score or subscores, between the congenitally infected children with no obvious neurological abnormalities and controls. Preliminary examination of the same cohort at five years using the *Weschler Preschool and Primary Scale of Intelligence* test supports these findings and suggestions no subsequent deterioration (S. Logan, personal communication). Similar findings were reported by Conboy *et al.* (1986). These results are encouraging and suggest that children with no obvious manifestations of CMV develop normally.

Predisposing risk factors for congenital infection

Preece *et al.* (1986) compared the mothers of a group of congenitally infected infants with those of the screened population of women with non-infected infants. The age of the mother, her race and marital status were all individually stongly associated with the prevalence of congenital CMV. When these factors were accounted for neither social class nor parity had any additional effect. The overall rate of congenital CMV infection was 3/1000 live births, but it ranged form 25/1000 for single black women under 20 years old to 1·6/1000 in married or cohabiting white women over 25 years of age.

Early acquired infection

The rapid acquisition of CMV infection in the first months of life in children of seropositive mothers, and its relative absence among infants of seronegative mothers suggests that the mother is the major source of infection. Of 253 infants screened at birth to exclude congenital CMV, and followed up three-monthly for one year, 12% had acquired infection by three months and 20% by one year. In all children the infection was subclinical. The mother's serological status and whether the infant was breast fed were the major factors determining the risk of acquiring infection (Peckham *et al.*, 1987*a*). Thirteen of the infected infants were re-examined at three years and all were still shedding virus in their urine. This demonstrates that virus shedding persists for years in those that acquire infection early. Unless CMV is detected in the urine within three weeks of birth, congenital and acquired infection cannot be distinguished, even when clinical problems suggestive of congenital infection are present.

Reactivation of latent CMV infection with virus shedding from the cervix is common (Montgomery, Youngblood & Medearis, 1972) and there is a strong association between maternal shedding and transmission of infection to the offspring. Reynolds

et al. (1980) reported the early acquisition of CMV infection in 40% of infants of women from whom virus had been isolated from the cervix in late pregnancy.

Infected breast milk is an even more efficient source of early acquired infection. When virus isolates from mother's breast milk and infant's urine were typed for molecular relatedness by restriction endonuclease digestion analysis, the breast milk samples had similar DNA fragments to those isolated from respective infants' urine indicating that infection had occurred with the same CMV strain (Peckham *et al.*, 1987*a*). Virus has been isolated from breast milk in a substantial proportion of seropositive women. Hayes *et al.* (1972) isolated virus from milk or colostrum from 17 of 63 (27%) seropositive women and virus was isolated significantly more often after the first week than before. Stango *et al.* (1980) similarly reported high rates of isolation. In a population with a high seropositivity rate, transmission through breast milk is likely to be a major source of early infection.

Another important and preventable source of CMV infection is blood transfusion. Severe and even fatal disease may occur in premature infants who have been transfused with CMV positive blood and whose mothers' are seronegative (Yeager *et al.*, 1981). For this reason screened blood should be given to premature infants of seronegative mothers. However, as the mother's antibody status is often unknown and if the baby is extremely premature the restriction of screened blood to the offspring of seronegative mothers may not be appropriate. Mortality is likely to be related to immaturity of the immune system and to use gestational age of 32 weeks or less as the criterion for the use of CMV blood would seem reasonable (Logan, Barbara & Kovar, 1988).

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