Neurodevelopmental assessment after congenital cytomegalovirus infection

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SUMMARY The neurodevelopmental state of 41 children with congenital cytomegalovirus infection and their controls was assessed at 2 years using the Griffiths scale. The scores achieved by children with congenital cytomegalovirus but with no associated neurological abnormality (asymptomatic) were similar to those of the control children, whereas the mean score of the five children with congenital infection and neurological impairment (symptomatic) was significantly lower. This study, which has the statistical power to detect differences in developmental quotient as small as five points, gave no evidence that at 2 years cytomegalovirus infection was associated with mental retardation in the absence of other neurological impairment. Thus 90% of children with congenital cytomegalovirus infection at 2 years are neurologically and developmentally normal.

Congenital cytomegalovirus infection, which occurs in three to four of every 1000 live births in the United Kingdom, may cause severe handicap in up to 10% of cases. In addition to causing cerebral palsy or sensorineural deafness, or both, it has been claimed that cytomegalovirus is a major cause of mental retardation. There is little evidence, however, to confirm or refute this, and there are few reports of congenital cytomegalovirus infection presenting with isolated mental retardation. As part of an ongoing prospective study to determine the consequences of congenital cytomegalovirus infection the intellectual development of 41 infected children and their controls was assessed at 2 years of age using the Ruth Griffiths developmental scale.

Patients and methods

In a prospective study, details of which have been described elsewhere, infants were screened for the presence of cytomegalovirus as soon as possible after birth. Isolation of virus within the first 3 weeks of life was the criterion for the diagnosis of congenital cytomegalovirus infection. Details of maternal age, race, marital state, occupation, and parity were obtained from all mothers. For each infected child two control infants were selected matched for sex, maternal age (<20, 20–24, 25–29, and >30 years), race (white, black, or Asian), parity, and social class (manual, non-manual, or other, this latter group mainly including single mothers with no classifiable employment or women whose partners were unemployed).

The children who were congenitally infected and the controls were followed up at regular intervals and children with neurological damage such as spastic quadriplegia or sensorineural deafness identified. At 2 years of age a neurodevelopmental assessment was carried out using the Griffiths scale. The overall developmental quotient was calculated as the mean of five subscales, where locomotor function, personal social skills, language development skills, eye-hand coordination, and fine motor performance skills were assessed.

The development quotients of children with congenital cytomegalovirus and specific neurological abnormalities (that is, symptomatic) were analysed separately from those with no neurological abnormalities (asymptomatic) and from the controls. None of the controls suffered from specific neurological abnormalities. Children with psychomotor delay but who had no specific neurological abnormalities were included with the children in whom neurological examination was normal. For
children who were unable to complete the full test the mean score of three or more subscales was used to calculate the overall development quotient. If less than three subscales were completed the overall development quotient was not calculated. Means and standard deviations were calculated for each subscale for symptomatic, asymptomatic, and controls. In a further analysis multiple regression was used to examine the possible effect on overall development quotient of matching variables such as social class and to remove any variation association with them.

Results

By December 1984, 42 congenitally infected children and 75 controls had reached 2 years of age. Two of these children (one case and one control) were unable to complete any subscale of the Griffiths assessment and were excluded altogether. Both children have subsequently been found to be developing normally.

Subscale scores were therefore available for 41 cases and 74 controls and overall development quotient scores for 40 cases and 73 controls. None of the 74 control children had detectable neurological abnormalities, and none were detected in 36 of the 41 congenitally infected infants. This asymptomatic group included one child with congenital cytomegalovirus with mild psychomotor delay and the additional stigmata of fetal alcohol syndrome and one control with mild psychomotor delay but no specific neurological abnormalities. Five congenitally infected children had pronounced neurological abnormalities: two unilateral sensorineural deafness, two bilateral sensorineural deafness, and two spastic quadriplegia and epilepsy (associated in one child with bilateral sensorineural deafness). Of the three children with no neurological abnormalities other than deafness, two had essentially normal Griffiths scores, except on the Hearing and speech subscale. The third, with unilateral deafness, had uniformly low Griffiths scores, averaging 81.

The Table shows the overall development quotient and the subscores of the three groups. The scores achieved by children with asymptomatic congenital cytomegalovirus were similar to those of the control children. In addition, the subscores showed no specific area of development to be affected. The mean score for the five symptomatic congenitally infected children was 69, which was more than 30 points below the control group and the asymptomatic group. This suggests that only symptomatic congenital cytomegalovirus is associated with psychomotor delay.

Because some of the variation in development quotient scores may be associated with the maternal factors used in matching cases and controls, multiple regression analysis was carried out on the overall development quotient scores. The development quotients of children with symptomatic congenital cytomegalovirus was 35-6 points lower than that of the controls, which is highly significant ($t_{40}=-6.2$, $p<0.0001$). In contrast, children with asymptomatic congenital cytomegalovirus had marginally higher development quotients than the controls ($t_{45}=0.1$, $p>0.5$). Congenital cytomegalovirus infection, therefore, had no significant effect on developmental achievement at 2 years when it was not associated with neurological abnormality. Furthermore, the narrowness of the 95% confidence interval, −3·0 to +7·2 development quotient points, suggests that if asymptomatic cytomegalovirus has an effect it is unlikely to be of educational significance (Figure).

Social class was the only other variable to show a significant effect on development quotient ($F_{2,100}=4.97, p=0.009$). Compared with the children of non-manual parents the development quotient of children whose parents were of manual social class was lower by 6-6 (95% confidence interval: 0·3–12·9) and children of unclassifiable social class by 9·0 (95% confidence interval: 2·7–15·3). Maternal age, race, parity, and infant sex did not have a significant effect on development quotients ($p>0.06$). Statistical tests for interactions showed that the effect of asymptomatic cytomegalovirus was the same irrespective of social class and of all other variables ($p>0.2$).

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Children with asymptomatic cytomegalovirus</th>
<th>Children with symptomatic cytomegalovirus</th>
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<tbody>
<tr>
<td></td>
<td>Score</td>
<td>SD</td>
<td>n</td>
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<tr>
<td>Total score</td>
<td>101.2</td>
<td>10.3</td>
<td>73</td>
</tr>
<tr>
<td>Locomotor</td>
<td>106.8</td>
<td>8.8</td>
<td>74</td>
</tr>
<tr>
<td>Social</td>
<td>106.9</td>
<td>13.3</td>
<td>73</td>
</tr>
<tr>
<td>Hearing and speech</td>
<td>97.0</td>
<td>9.4</td>
<td>72</td>
</tr>
<tr>
<td>Eye/hand coordination</td>
<td>99.2</td>
<td>9.7</td>
<td>71</td>
</tr>
</tbody>
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Table Mean scores on Griffiths subscales
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44 congenitally infected children who were asymptomatic at birth from an original sample of 53 children. Their development was assessed at ages ranging from 3.5 to 7 years using the Wechsler’s Pre-school Primary Scale of Intelligence. The congenitally infected children had significantly lower mean IQs than both their matched controls and a group of random controls. The results of this study have suggested that cytomegalovirus may be an important cause of mental handicap and poor school performance.

The different methods of diagnosis used to identify children with congenital infection in these prospective studies may have accounted in part for the conflicting findings. Pass et al have suggested that symptomatic newborns with a raised cord blood IgM concentration may have a more severe form of congenital infection than those identified by virus isolation. Griffiths and his colleagues also reported that the concentrations of cytomegalovirus specific IgM related to severity of infection and that those children with higher concentrations were more likely to have neurological damage. Cord blood IgM was used to identify children with congenital infection in the studies by Reynolds et al and Hanshaw and his colleagues, whereas in both the present study and that by Saigal et al congenital infection was diagnosed by virus isolation.

Although cytomegalovirus may cause severe neurological damage, there was no evidence in our study, which had the statistical power to detect an effect as small as five development quotient points, that congenital cytomegalovirus caused mental retardation in the absence of other neurological handicaps. The intellectual assessment of these children, however, will be repeated at 5 years to ensure that deterioration of intellectual function does not occur subsequently.

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Fifty years ago

**Meningitis in the newborn**

W S Craig (Edinburgh)—*Arch Dis Child* 1936;11:171–186

'Infection constitutes the most serious threat to survival with which the newborn infant has to contend.' Twenty one children were studied and postmortem examinations were carried out in 18 cases, permission being refused in three. Seven were four weeks and eight were more than six weeks premature. Delivery was instrumental in one and spontaneous in the rest, including four breech presentations. The condition of 17 was unsatisfactory at birth; four were severely asphyxiated, and the remainder were very feeble and never rallied.

'In nine cases a spongy sensation was appreciated on palpation of the fontanelle; due to fullness rather than increased tension. Three infants showed no fever, and in the others the temperature was subnormal for some time after birth but rose two to four days before death. Meningitis is usually part of a generalised septicaemia and is frequently the result of *E. coli* infection. A morbid condition of the skin, subcutaneous tissues or surface mucous membranes was present in 15 cases and constitutes a definite risk of meningitis, and infection of the mouth and nasal passages is a special risk. In this series the pathological and bacteriological findings leave little doubt that the primary foci of infection were present in the skin, scalp, and eyes, and emphasises the importance of meticulous attention to the hygiene of these parts, especially among premature infants.'

(Dr Craig saw these children at the Royal Maternity and Simpson Memorial Hospital, Edinburgh. The account is a reminder of the problems in the pre-antibiotic era but, although times have changed so much, there is still a need to stress the importance for early diagnosis on which mortality and morbidity still depend. As Dr Craig says 'Neonatal meningitis cannot always be diagnosed. The classical signs of meningitis are often absent. Signs of intracranial disturbance occurring after the first week of life should always suggest meningitis and lumbar puncture is essential for a final diagnosis.' NEIL GORDON.)
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