

*Original articles*

# Congenital cytomegalovirus infection

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**SUMMARY** Clinical details of 50 infants with congenital cytomegalovirus infection identified in a prospective study are reported. The mean birthweight, gestational age, and head circumference of children with congenital cytomegalovirus infection were not significantly different from those of controls. Three (6%) had symptoms at birth—two neurological and one pneumonitis. In the first four months of life transient hepatosplenomegaly occurred in two infected children and six suffered interstitial pneumonitis. Three congenitally infected children have major neurological handicaps including spastic quadriplegia, microcephaly, and psychomotor delay, and five (10%), including the one with quadriplegia, have sensorineural deafness which is bilateral in three (6%). Estimates based on these findings suggest that the impact of congenital cytomegalovirus infection is comparable to that of congenital rubella in the era before vaccination.

Of the 42 children where the nature of maternal infection was classifiable, congenital infection followed primary maternal infection in 32 (76%) and recurrent infection in 10 (24%). Neurological defects followed exposure to primary maternal infection in all three trimesters of pregnancy and also recurrent maternal infection.

Cytomegalovirus is the most common, known congenital infection in man, and in Britain occurs in 3 to 4 per 1000 live births.<sup>1-3</sup> Five to 10% of infants with congenital cytomegalovirus infection are symptomatic at birth<sup>4</sup> and a further 10 to 20% may develop late sequelae.<sup>2 5-7</sup> The incidence and severity of congenital infection varies widely throughout the world,<sup>8</sup> depending on the population studied and the predominant type of maternal infection (that is primary or recurrent).<sup>9</sup> Hence estimates of handicaps due to congenital cytomegalovirus infection such as deafness and mental retardation cannot be extrapolated from one population to another.

In 1980 a prospective study was initiated to provide information on the incidence of congenital cytomegalovirus infection in a British population and to assess the frequency and severity of sequelae.<sup>1</sup> We now report the clinical findings in the first 50 congenitally infected infants and relate these to the type of maternal infection and the stage of pregnancy at which maternal infection occurred.

## Subjects and methods

Infants born in three London hospitals were

screened for cytomegalovirus infection by throat swab, collected in the first week of life. This has been shown to be as effective as urine culture in the diagnosis of cytomegalovirus infection in the neonatal period.<sup>2</sup> When cord blood samples were available in infants found to be excreting cytomegalovirus, these were tested for specific IgM antibody by solid phase radioimmunoassay.<sup>10</sup> A urine sample was collected in addition to a throat swab from those infants born to women who had acquired cytomegalovirus antibody during pregnancy. As no single method will identify all cases of congenital cytomegalovirus infection<sup>2 10</sup> this increased the likelihood of diagnosis in those infants at highest risk of infection. A diagnosis of congenital infection was made when virus was isolated from either a throat swab or urine sample collected within three weeks of birth<sup>11</sup> or cytomegalovirus specific IgM was found in cord blood. In infants with congenital infection, the type of maternal infection, primary or recurrent, was defined according to the criteria previously described.<sup>1</sup>

Each congenitally infected infant was examined at home, with the cooperation of the general practitioner, as soon as the diagnosis had been made.

Thereafter the child was seen at 3, 9, 18, 24, and 36 months. At each visit a physical examination was carried out and measurements of height, weight, and occipitofrontal circumference were recorded. Developmental progress was assessed using the Stycar sequences.<sup>12</sup> At 2 years of age, a Griffiths developmental assessment was performed<sup>13</sup> and at 3 years items from the Stott test of motor impairment<sup>14</sup> were used to assess fine motor coordination. At 9 months and at 3 years, full audiological assessment was performed by an audiological physician. At 9 months hearing was assessed by distraction tests and at 3 years conditioning tests and a Kendal toy test were used. On both occasions middle ear function was assessed by tympanometry.

Two children from the study population, in whom congenital cytomegalovirus infection had been excluded, were selected as controls for each infected infant. They were matched for mother's age, parity, race, country of origin, social status, infant's sex, and birth date, but not for birthweight or gestation. Control children were initially visited at home at approximately 3 months of age (with the consent of their general practitioner). Thereafter the follow up of controls and congenitally infected children was identical. No congenitally infected infants have been lost to follow up but six controls withdrew from the study at ages ranging from 5 to 32 months.

## Results

**Diagnosis of congenital cytomegalovirus infection.** Between March 1980 and July 1983, 50 infants with congenital cytomegalovirus infection were identified. Throat swabs were available in 48 children and in 42 (88%) virus was isolated. In the remaining eight children who did not have a positive throat swab, cytomegalovirus specific IgM was present in the cord blood, and virus was also isolated from urine samples in five. Urine samples were collected from a total of 24 newborns and cytomegalovirus was grown in 23 (96%); in the remaining child, virus was isolated from throat swab. Cord blood samples were available for 19 children where virus was isolated and cytomegalovirus specific IgM was detected in 16 (84%).

Ninety seven controls were selected. Two children, living permanently abroad do not have controls, although both have been followed up.

**Neonatal presentation of children with congenital cytomegalovirus infection.** The mean birthweight, gestational age, and occipitofrontal circumference of congenitally infected infants were not significantly different ( $P > 0.05$ ) from controls when assessed by the Student's *t*-test (Table 1). Figs. 1 and

Table 1 Mean birthweight, gestation and head circumference of infants with congenital cytomegalovirus (CMV) and their controls

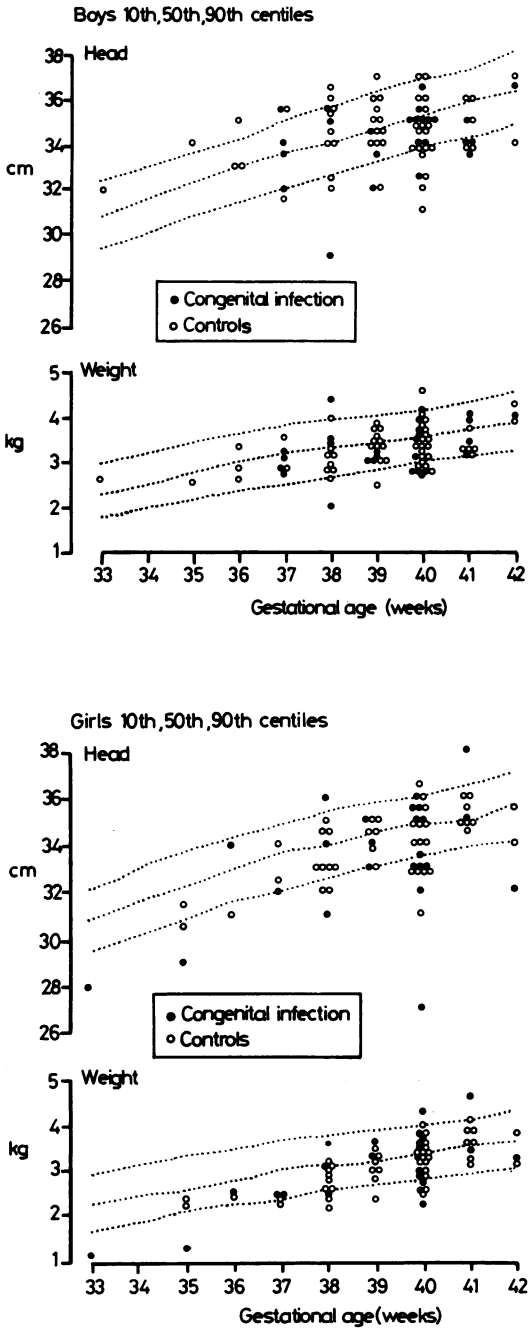
	Congenital CMV (n=50) Mean (SD)	Controls (n=97) Mean (SD)	P value
Birthweight (kg)	3.21 (0.67)	3.22 (0.48)	0.93
Head circumference (cm)	33.6 (2.16)	34.3 (1.47)	0.12
Gestation (weeks)	39.1 (1.78)	39.2 (1.62)	0.83

2 show the birthweight and head circumference by gestational age for boys and girls in both groups. There was no significant difference in the proportion of infected infants and controls with birthweight below the third centile ( $P = 0.07$  Fisher's exact test). Although a higher proportion of cases than controls (22% and 11%) had a head circumference below the third centile, this difference did not reach significance ( $\chi^2 2.94 0.1 > P > 0.05$ ) (Table 2). The high proportion with an occipitofrontal circumference below the third centile in both groups may be due to the number of non-Caucasian children in the study.

Symptoms were present in the neonatal period in three (6%) of the 50 congenitally infected infants (Table 2). One infant, with microcephaly and dystonia, was small for gestational age and the other, who fed poorly and developed stridor on the third postnatal day, was found on examination to have generalised hypotonia and hepatomegaly which resolved in two weeks. The third infant, in whom congenital infection was not clinically suspected, developed tachypnoea with non-specific infiltration on chest radiograph. Tachypnoea persisted for four weeks despite antibiotic treatment, and no pathogenic organism other than cytomegalovirus was isolated. The delay in clinical recovery prompted investigation of a heart murmur which was found to be due to a small ventricular septal defect. A diagnosis of fetal alcohol syndrome was considered in view of the facial appearance and maternal history of alcohol abuse. Two of the three infants with symptoms at birth were clinically suspected as cases of intrauterine infection. None of the infected infants presented with splenomegaly, rash, or thrombocytopenia and jaundice was no more frequent in cases than controls.

Eight of the 97 control infants (8%) had neonatal problems. These included four children with umbilical herniae, one with a ventricular septal defect, one with craniotabes, and two with congenital ptosis associated in one with glucose-6 phosphate dehydrogenase deficiency.

**Follow up of children with congenital cytomegalovirus infection.** There have been no deaths in either



Figs. 1 and 2 Birthweight and head circumference of children with congenital cytomegalovirus and controls (adapted from D Gairdner, J Pearson, Arch Dis Child 1971;46:783-7).

Table 2 Clinical manifestations at birth and at subsequent follow up in children with congenital cytomegalovirus infection (CMV) and controls

	At birth										At follow up									
	No	Birthweight < 3rd centile	Occipitofrontal circumference < 3rd centile	CNS defects	Hepatomegaly	Respiratory symptoms	Other*	Psychomotor delay	Spasticity	Visual handicap	Deafness	Pneumonitis	Hepato-splenomegaly	Conductive	Sensori-neural					
Abnormal at birth	3	+	+	+	-	-	-	+	+	+	-	-	-	-	-					
No specific abnormalities at birth but permanent neurological sequelae	4	-	-	-	+	+	-	-	-	-	+	+	+	+	+					
Sub total	7	3	3	2	1	1	1	3	2	1	5	2	1	0	6					
Normal at birth but without neurological sequelae	43	2	8	0	0	0	0	0	0	0	0	0	1	14	1					
Total	50	5 (10%)	11 (22%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)	3	2	1	5/47§	16/47§	2	6	0					
Controls	97	3 (3%)	11 (11%)	0	0	0	8	2	0	0	0/88§	27/88§	1	0	0					

\*See text. †Bilateral sensorineural deafness; ‡unilateral sensorineural deafness; §number with assessment.

the congenitally infected children or controls. Follow up information, available for all infants with congenital infection (Table 3) and their controls, is described in Table 2.

#### *Neurological findings including hearing assessment*

All three children with clinical signs in the neonatal period have adverse neurological sequelae. One aged 3 years has spastic quadriplegia, epilepsy, bilateral optic atrophy, and severe mental retardation; hearing could not be assessed by routine methods but electrocochleography is normal. The second child failed to thrive and is below the third centile for height and weight. Transient hepatosplenomegaly developed at 3 months of age and at 3 years mild psychomotor delay with no specific neurological defect was seen. The third child has a mixed bilateral (sensorineural and conductive) hearing loss and requires hearing aids.

A further child who was small for gestational age but otherwise normal in the neonatal period, later developed spastic quadriplegia associated with psychomotor delay, epilepsy, and bilateral hearing loss. At initial assessment (at 10 months) the hearing loss was moderate and was thought to be mixed in nature (conductive and sensorineural). Over the following six months deterioration in thresholds occurred despite resolution of the conductive element and a residual, moderately severe bilateral sensorineural loss persists requiring the use of hearing aids. Sensorineural deafness is present in a further three children, who were asymptomatic at birth and have normal psychomotor development; in one this is bilateral requiring hearing aids and in two unilateral.

Overall, five of 47 (10%) children who have had a full audiological assessment have sensorineural deafness, although hearing aids were required for only three (6%). Three children who have not completed a full audiological assessment are clinically normal. None of the controls have sensorineural deafness.

There was no significant difference in the prevalence of conductive hearing loss in the congenitally infected infants (35%) and controls (31%) ( $P > 0.05$ ).

#### *Hepatosplenomegaly*

Two infants developed hepatosplenomegaly at 3

months of age. In one, who was asymptomatic previously, this was associated with 'erythema multiforme' and although the rash resolved in a few days, the hepatosplenomegaly persisted until 18 months; this child is developing normally.

One control infant had a non-specific illness at age 9 months characterised by hepatosplenomegaly and lymphadenopathy. Infectious mononucleosis due to cytomegalovirus and Epstein-Barr virus were excluded and symptoms resolved in approximately one month.

#### *Interstitial pneumonitis*

Six congenitally infected infants who were asymptomatic at birth presented with respiratory symptoms at age 3 to 4 months. In each case the child was afebrile and the illness characterised by tachypnoea, hyperinflation, and non-specific chest radiological appearance. In all cases cytomegalovirus was isolated from pharyngeal aspirate during the acute phase of the illness, and apart from the isolation of chlamydia in one infant, bacterial culture, virus isolation, and serology were negative for other pathogens. The illness lasted less than one month in all but two children, who have continued to have intermittent respiratory exacerbations. None of the controls suffered from pneumonitis, although one child has had frequent lower respiratory infections.

#### *Additional problems*

Speech delay occurred in two congenitally infected children, associated with severe behavioural problems in one. One control child has vesicoureteric reflux, another, who had a febrile fit, has delayed speech, and a further two have mild psychomotor delay associated with delayed speech development. Lymphadenitis, requiring surgical drainage, and *Haemophilus influenzae* septicaemia respectively have occurred in two further control children.

**Type and time of maternal infection.** Thirty two of the 42 infants (76%) with congenital infection in whom the nature of the maternal infection was classifiable were born after a primary maternal infection: nine infections had occurred in the first 16 weeks of pregnancy, seven in mid-pregnancy, and 14 at 28 weeks or after. Two infections, occurring between 9 and 24 weeks and 13 and 40 weeks respectively could not be allocated to a particular trimester (Table 4). Neurological sequelae followed exposure to maternal infection in all three trimesters and the most seriously affected child was exposed at about 28 weeks.

Ten infants (24%) were born after recurrent

Table 3 Number of children assessed at each age

Age (months)	No	3	9	18	24	36
With congenital cytomegalovirus infection	50	50	47	30	29	18
Controls	97	97	90	65	54	34

Table 4 Type and timing of maternal cytomegalovirus infection in relation to outcome

Type of maternal infection	No (%)	Time of infection (weeks)	No (%)	Neurological sequelae
Primary	32 (64)	16	9 (28)	Bilateral sensorineural deafness. 1 (11%)
		16-27	7 (21)	Unilateral sensorineural deafness. 1 (14%)
		28	14 (43)	Spastic quadriplegia. 1 (7%)
		Not known	2 (8)	—
Recurrent	10 (20)			Spastic quadriplegia, bilateral sensorineural deafness. 1 } 2 (20%)
Nature of infection not classified	8 (16)			Bilateral sensorineural deafness. 1 } 2 (25%)
				Psychomotor delay only. 1 } 2 (25%)
				Unilateral sensorineural deafness. 1 }

infection. Two of these infants, both in the presumed recurrent group, have neurological sequelae.

Where the type of infection was defined, congenital infection resulting from a primary maternal infection was significantly more frequent in infants born to white mothers (25 (89%) of 28) than infants born to black mothers (7 (58%) of 12) ( $P=0.04$  Fisher's exact test). None of four congenitally infected Asian infants had been exposed to a primary maternal infection.

### Discussion

Major sequelae such as cerebral palsy or bilateral sensorineural deafness were present in 10% of the 50 congenitally infected children. A further five per cent have unilateral sensorineural deafness. As there was no selection bias in the screening of neonates, it is likely that these findings reflect the true risk of handicap after congenital cytomegalovirus infection in infants born in this population. These rates are lower than those reported by Reynolds and his colleagues<sup>5</sup> and Hanshaw *et al.*,<sup>6</sup> but similar to the findings of Saigal *et al* who followed up 47 children with congenital cytomegalovirus infection in Canada.<sup>7</sup>

Spasticity and psychomotor delay were evident in three children (6%). This rate of major central nervous system abnormality, which excludes deafness, is comparable to the two to seven per cent reported elsewhere<sup>5-7 15</sup> despite the differences in racial and socioeconomic background of the populations studied. The variations in rates of overall handicap reported between studies are largely accounted for by differing rates of sensorineural deafness (9 to 50%<sup>5 16</sup>) which is the most frequent complication of congenital infection. While the overall rate of deafness may reflect the frequency with which cytomegalovirus causes damage, only bilateral hearing loss of greater than 40 dB (averaged over the speech frequencies) in the better ear is likely to be a major handicap to the child. Using this criterion to calculate significant hearing loss in

previous studies<sup>5-7 16</sup> rates from 5 to 7.5% were obtained which are similar to the 6.5% reported in the present study.

Evidence to date suggests that fetal damage after recurrent infection is rare and it is primary infection which results in handicap.<sup>9</sup> If the type of maternal infection is related to outcome, however, it is surprising that the prevalence of defects reported in different prospective studies of children with congenital infection are so similar when the populations from which they derive are so diverse. In populations with a high proportion of congenital infection most infected infants are born after recurrent maternal infection,<sup>17</sup> whereas in populations with a low prevalence most result from primary infections.<sup>1 9</sup> In only two studies<sup>9 18</sup> has the type of maternal infection been defined. In Sweden<sup>18</sup> the relative contribution of primary and recurrent infection was similar to that in the present study. In contrast, Stagno *et al*<sup>9</sup> in the United States reported that primary maternal infection accounted for 50% of congenital cytomegalovirus infections in the white population, but only 18% in the black. In the present study primary maternal infections accounted for 89% of infections in white infants and 58% in black, although the seropositivity rates of whites (55%) and blacks (82%) were the same as those reported by Stagno *et al.*<sup>9</sup> The rate of seropositivity is unlikely, therefore, to be the only factor determining the predominant type of maternal infection resulting in congenital cytomegalovirus infection.

There was no evidence from the present study that the type or timing of maternal infection was related to the frequency or severity of handicap, or both, in the offspring. Children who are damaged by cytomegalovirus infection may differ from those in whom congenital infection is asymptomatic, and other factors such as a deprived background, poor antenatal nutrition, or exposure to other agents such as alcohol and drugs may be important. It was notable that the mothers of two of the most seriously damaged children in this study had been exposed to adverse social circumstances during their pregnan-

cies. One spent some months in prison and the other was a heavy drinker. The combined effects of poor social background and congenital cytomegalovirus infection could be greater than the effect of either factor alone.<sup>6</sup> This may explain the differences reported in the effect of congenital infection on intellect<sup>5-7 15</sup> and the inconsistent association between congenital infection and low birthweight.<sup>5 19 20</sup> Although the number of individual children with birthweight and occipitofrontal circumference below the third centile was higher in congenitally infected infants than their controls, the difference was not significant: the number of control infants who fell into this category illustrates the importance of matching for racial and social variables.

The commonly reported presentations at birth of congenital cytomegalovirus infection—hepatosplenomegaly and rash—were not seen in this study. Transient problems, however, including hepatosplenomegaly and pneumonitis presented for the first time between age 3 and 4 months, a finding also noted by Starr *et al.*<sup>19</sup> It is possible that cytomegalovirus acts as an opportunist respiratory pathogen like chlamydia or pneumocystis carinii<sup>21</sup> since the age of presentation coincides with the waning of passive maternal immunity and cytomegalovirus may depress cellular immunity.<sup>22</sup>

The rate of handicap in this study is provisional since congenital infection may cause progressive disease.<sup>23</sup> A Griffiths developmental assessment, however, on 24 children from this study who have reached 2 years of age (Pearl *et al.*, in preparation) has shown no significant difference in developmental quotient between those congenitally infected infants with no major neurological defects and their matched controls. This suggests that the onset of serious new problems is unlikely to be great, although other problems such as language delay have been reported<sup>20</sup> as well as specific language disorders and learning difficulties in older children with normal intelligence.<sup>24</sup>

From these preliminary findings, we have estimated the impact of congenital cytomegalovirus infection in Britain. Assuming a birth rate of 650 000 per year and a rate of congenital infection of three to four per 1000 live births<sup>1 2</sup> between 1950 and 2600 congenitally infected infants will be born each year. Assuming that 10% have appreciable deafness, neurological defects, or both, 195 to 260 infants will be born each year with serious handicaps. Assuming that a further five per cent have minor handicaps such as unilateral deafness, the total number of affected children will be approximately 292 to 390. Hence the number of children with serious handicaps attributable to cytomegalovirus

is comparable to that of children born with congenital rubella defects in a non-epidemic year in the era before vaccination.<sup>25</sup>

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