Physical and intellectual development in children with asymptomatic congenital cytomegalovirus infection: A longitudinal cohort study in Qinba mountain area, China

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Abstract

Background: Although about 90% of congenital cytomegalovirus (CMV) infection is asymptomatic in newborn, some of them could show sequelae later in life. Qinba mountain area is a place with high incidence of mental retardation and a high rate of CMV intrauterine transmission in China. The correlation between asymptomatic congenital CMV infection and developmental outcomes of children in this area remain unclear.

Objectives: To investigate the impact of asymptomatic congenital CMV infection on physical and intellectual development of children during the first 6 years of life in Qinba mountain area.

Study design: Longitudinal cohort study. Forty-nine of all the 54 children with asymptomatic congenital CMV infection were followed prospectively in a study for surveying physical growth and intellectual developments.

Results: Either in neonatal or in infant period, no significant difference was noted between the asymptomatic congenital CMV infection children and the controls in average weight, height and head circumference (both \( p > 0.05 \)). The intellectual development was disproportion in asymptomatic congenital infected children. Compared with the control group, both global development quotient (DQ) and full-scale intelligence quotient (IQ) scores of asymptomatically infected children were worse (\( t = 2.19, p = 0.031; t = 2.48, p = 0.015 \), especially on language DQ scores (\( t = 3.25, p = 0.002 \)) and verbal IQ scores (\( t = 3.88, p = 0.000 \)). However, the incidence rates of mental retardation (DQ/IQ < 70) were similar in two groups (\( \chi^2 = 1.03, p > 0.05 \)).

Conclusions: Although asymptomatic congenital CMV infection did not have significant influence on the neonatal physical development or incidence of mental retardation later in life, it is obviously an important factor correlating with long-time cognitive outcomes, especially on the development of language. It is necessary to survey CMV congenital infection and monitor the early intellectual development of children with asymptomatic congenital CMV infection in this area.

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Keywords: Cytomegalovirus; Congenital infection; Asymptomatic; Physical development; Intellectual development

1. Introduction

Cytomegalovirus (CMV) is one of the most common congenital infection viruses. It is also one of the most common causes of mental retardation and non-hereditary congenital deafness in developed countries (Dahle et al., 2000; Griffiths, 2002). Human cytomegalovirus (HCMV) infection varies with the economic level of a nation or region (Numazaki and Chiba, 1997). Of the newborns with congenital CMV infection, 10% are symptomatic, with clinical symptoms at birth, and the rest 90% are asymptomatic, some of them do not show sequelae until several months or even several years after birth. Many studies have proved that congenital HCMV infection is closely related to sensorineural hearing loss (SNHL), whether it is symptomatic or asymptomatic (Fowler et al., 2006; Rivera et al., 2002; Williamson et al., 1992). However,
it remains controversial about the influences of congenital CMV infection on the children’s physical growth and intellectual development (Conboy et al., 1987; Ivarsson et al., 1997; Li et al., 2003; Noyola et al., 2000). Qinba mountain area is a place with high incidence of mental retardation (Zhang et al., 1999). The area also had high incidence of CMV active infection in pregnancy and high rate of intraterine transmission (Yan et al., 2000). This study, by following-up the children with asymptomatic congenital CMV infection in this area, is to discuss the influences of asymptomatic congenital cytomegalovirus infection on children’s physical growth and intellectual development in low socioeconomic regions.

2. Materials and methods

2.1. Study population

In a prospective study, the neonates, who were born in Qinba mountain area during the 4-year period from January 1997 to December 2000, were screened for the presence of CMV in urine at the first week of life. Congenital CMV infection was diagnosed if a specific fragment of HCMV-DNA was found by means of polymerase chain reaction (PCR) as previously described (Zhang et al., 2007). The authors evaluated the symptomatic and asymptomatic infants according to the medical records. The asymptomatic congenital CMV-infected infants were followed-up clinically at least for 6 years. Physical and intellectual development outcomes were repeated evaluated at certain age intervals. Forty-nine of all 54 children with asymptomatic congenital CMV infection had completed the whole follow-up visit and were enrolled in infection group. Stratified sampling was used to choose other 55 normal newborns, which were born at the same period as those in the infection group. Fifty of all 55 children had completed the whole visit and constituted the control group. The two groups matched in age, sex, race, school grade, education background of the parents, and socioeconomic status. It was made sure that all the children did not suffer any complications of pregnancy, or any familial hereditary diseases like mental retardation, psychonosema, deafness, or any other factors related to diseases. All the children had never taken ototoxic drugs, nor had suffered head injury, or infectious diseases in the central neural system (CNS).

The study was approved by the Ethics Committee of the First Affiliated Hospital, Medical School of Xi’an Jiaotong University.

2.2. Laboratory methods

Following the instructions of the PCR kit (Gene Diagnosis Center, China), we detected the urine from newborns to confirm congenital CMV infection. Enzyme linked immunosorbet assay (ELISA) reagent kit (Human Corpo-

ration, Germany) was used to detect HCMV-IgG and IgM antibodies in the serums of the pregnant women.

2.3. Assessment of physical development

Head circumference, length and weight were measured within 24 h of birth by a trained examiner, and these values were followed-up each year until the baby reached 3 years old. The norm were referring to “Values (± s) for physical development of normal children under 7 years old from outskirts of 9 cities in China in 1995”. If the value we got was smaller than the corresponding referred median subtracting 2 standard deviation (M – 2S.D.), the baby would be judged as hypogenesis.

2.4. Assessment of intellectual development

Based on different period of age, different scales were chosen for measurement. Gesell Developmental Schedule was used to assess the development quotient (DQ) of the infants between 18 and 36 months of corrected age on motor skills (DQ1), adaptive capacity (DQ2), language development (DQ3) and personal–social skills (DQ4). The intelligence quotients (IQ) of the preschool children between 48 and 72 months were tested verbal IQ and performance IQ with Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Outcome variables were normal intelligence (IQ/DQ ≥ 90), mental retardation (IQ/DQ < 70), severe mental retardation (IQ/DQ < 50).

2.5. Data analysis

A professional examiner who was unaware of the children’s status administered the original test. Geometric means and S.D. were used to summarize the results. The serial data were recorded on standardized case report forms and maintained in SPSS13.0 for Windows data sets. Means were compared using T-test, and frequencies were compared using the correction Chi-square test.

3. Results

3.1. Epidemiologic characteristics of the subjects

Congenital CMV infection was diagnosed in 71 (6.13%) of 1159 infants born during 1997–2000 in Qinba mountain areas. Fifty-four (76.1%) were asymptomatic and 17 (23.9%) were symptomatic at birth. There were 38 (53.5%) boys and 33 (46.5%) were girls.

3.2. Comparison of physique outcomes

Five (10.20%) babies were born before 37 weeks’ gestational age in the infection group and 4 (8%) in the control group. At birth, 6 (12.24%) children weighed less
than 2500 g in the infection group and 4 (8%) in the controls. Though the infection group had higher incidence of premature or low-weight babies, there had no significant difference between the two groups on the average of birth weight \((3137 \pm 361 \text{ g vs. } 3241 \pm 402 \text{ g, } p = 0.18)\), length \((49.63 \pm 2.45 \text{ cm vs. } 50.12 \pm 2.55 \text{ cm, } p = 0.34)\) and head circumference \((33.89 \pm 0.82 \text{ cm vs. } 34.07 \pm 0.67 \text{ cm, } p = 0.22)\), respectively.

In infancy, according to age and gender, the weight, height and head circumference were also similar in both groups of infants.

### 3.3. Comparison of infants’ development quotient

Frequencies of the infants’ distribution are shown in Fig. 1 for comparison, and they were normal distribution according different grade of Gesell Developmental Quotient in both of two groups. The mental developments of motor skills, adaptive capacity, language development and personal–social skills were disproportion in asymptomatic congenital CMV infection infants (Fig. 2). The global DQ was significantly lower in infection group than in controls \((t = 2.19, p = 0.031)\), and the slowness in language development was of statistic significance \((t = 3.25, p = 0.002)\), shown in Table 1.

![Fig. 1. Frequencies of the infants’ distribution in different grade of Gesell test. The scales in x-axis is the different grade of DQ.](image)

![Fig. 2. Disproportion of the mental development in asymptomatic congenital CMV infection infants.](image)
Table 1
Comparison of the mean values of DQ scores between infants of the two groups in 10–36 months of age

<table>
<thead>
<tr>
<th>Feature</th>
<th>Infection group, N=49</th>
<th>Control group, N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor skills (DQ1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92.02 ± 12.80</td>
<td>95.76 ± 11.52</td>
</tr>
<tr>
<td>Adaptive capacity (DQ2)</td>
<td>87.47 ± 12.88</td>
<td>91.96 ± 10.91</td>
</tr>
<tr>
<td>Language development (DQ3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>81.57 ± 14.06</td>
<td>90.06 ± 11.77</td>
</tr>
<tr>
<td>Personal–social skills (DQ4)</td>
<td>93.41 ± 12.86</td>
<td>97.58 ± 11.66</td>
</tr>
<tr>
<td>The global DQ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>88.62 ± 13.09</td>
<td>94.03 ± 11.35</td>
</tr>
</tbody>
</table>

<sup>a</sup> All values are means ± S.D.
<sup>b</sup> p = 0.002.
<sup>c</sup> p = 0.031.

Table 2
Comparison of the mean values for Wechsler IQ scores between children of the two groups in 48–72 months of age

<table>
<thead>
<tr>
<th>Feature</th>
<th>Infection group, N=49</th>
<th>Control group, N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal IQ&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;b&lt;/sup&gt;</td>
<td>82.76 ± 12.68</td>
<td>91.98 ± 10.81</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>96.20 ± 12.98</td>
<td>98.56 ± 10.35</td>
</tr>
<tr>
<td>Full-scale IQ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89.43 ± 12.78</td>
<td>95.27 ± 10.51</td>
</tr>
</tbody>
</table>

<sup>a</sup> All values are means ± S.D.
<sup>b</sup> p = 0.000.
<sup>c</sup> p = 0.015.

3.4. Comparison of preschool children’s Intelligent Quotient

Fig. 3 shows the subscales of verbal IQ scores (information, vocabulary, mathematics, similarities, comprehension, and sentences) and performance IQ scores (animal house, picture completion, mazes, geometric design, and block design) in the asymptomatic congenital CMV infection children and control group children between 48 and 72 months of age.

Table 3
Comparison of the incidence rate of mental retardation between children of the two groups in infancy and preschool period

<table>
<thead>
<tr>
<th>Infancy (DQ)</th>
<th>Infection group, N=49</th>
<th>Control group, N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>4 (8.16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (2)</td>
</tr>
<tr>
<td>70–89</td>
<td>13 (26.53)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>≥90</td>
<td>32 (65.31)</td>
<td>42 (84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preschool period (IQ)</th>
<th>Infection group, N=49</th>
<th>Control group, N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>4 (8.16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>70–89</td>
<td>15 (30.61)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>≥90</td>
<td>30 (61.23)</td>
<td>40 (80)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Numbers in parentheses are percent.

3.5. Comparison of mental retardation in two groups

The comparison of incidence rates of mental retardation (IQ/DQ < 70) between the asymptomatic congenital CMV-infected children and the controls are shown in Table 3. Of the 49 children with asymptomatic CMV infection, 4 (8.16%) had an IQ/DQ of <70 either in infancy or in preschool period, and the incidence rates of mental retardation (DQ/IQ < 70) were similar in infected children and controls (χ² = 1.03, p > 0.05).

4. Discussion

CMV can be transmitted to the fetus even if there is preconceptional maternal immunity, and the reinfection or reactivated latent infection might be an important determinant of some severe deficits in the offspring. Numazaki and Chiba (1997) reported the population of seropositive women during childbearing age in low socioeconomic community was about 85%, and was about 55% in high socioeconomic status. Children with symptomatic congenital CMV infection has been shown to predict the cognitive and motor impairments as evidenced by the presence of microcephaly, seizures, abnormal tone, or chorioretinitis at birth (Boppana et al., 1994, 1992;
Deorari et al., 2000; Noyola et al., 2001; Pass et al., 1980). However, the predictors of physical and mental development in children with asymptomatic congenital CMV infection have not been identified.

It is generally thought that CMV infection of placenta during pregnancy may damage the differentiation and invasion of cytotrophoblast and cause the decrease of synthesis or secretion of steroid hormone, therefore effecting the growth of fetus (Fisher et al., 2000). Obstruction of small blood vessels and capillaries in placenta caused by virus infection also affect, to some extent, the growth of fetus, even resulting in fetal growth restriction (Muhlemann et al., 1992; Pereira et al., 2003). Wang et al. (1996) reported that the average birth weight and height were significantly lower in newborns with congenital CMV infection than in controls. However, Zhang et al. (2005) made follow-up visits to children with CMV congenital infection when they were at birth, 1 month old to 8 years old and reported that, compared with the children without congenital infection, there were no statistic difference in average height, head circumference and weight in children with congenital infection. In view of the fact that after the period of infancy, acquired factors have greater influences on the physical growth of children, our study made follow-up visits to newborns and infants in 10–36 months of age. The results agree with the consequence that congenital CMV infection does not have significant influence on physical growth of the infants. We suppose that the damage in physical growth of a newborn with asymptomatic congenital CMV infection more likely be influenced by the intrauterine affection of the virus, and the latent infection does not have definitely interrelationship with the physical development of children.

Fetal brain is the main target of congenital CMV infection. Lipton and Gilden (1997) reported that neurotropic virus infection in the CNS tended to become persistent infection in neurons. Yoshifumi et al. (2003) obtained definite evidence that murine cytomegalovirus (MCMV) was tightly restricted to subpopulation of neurons in the CNS, and this neuron-specific activation may be associated with persistent infection in neurons and cause the neuronal disorders in congenital CMV infection. Tsutsui et al. (2002) suggested that the most preferential site of latent CMV infection may be neural stem or progenitor cells in the subventricular regions, which are pivotal sites for brain development, and the brain disorders that occur long after birth in individuals with congenital CMV infection may occur by intermittent reactivation of latent infection in the brains. Although asymptomatic at birth, the infants with asymptomatic congenital CMV infection will develop progressive SNHL or other neurodevelopmental difficulties within first 4 years of life (Barbi et al., 2003; Fowler et al., 1997), indicating that the infants had persistent infection in CNS.

Qinba mountain area is a place not only with high incidence of mental retardation, but also with high incidence of CMV active infection in pregnancy and high rate of CMV vertical transmission in China. After 6 years of follow-up visits, we found that though the incidence rates of mental retardation were not obviously high in children with asymptomatic congenital CMV infection, the latent infection takes an important role in the neonatal long-time cognitive outcomes, especially in language developments. We have no decision why the intellectual development of congenital infected children was disproportion in this area, whether is due to the direct injury of virus infection in CNS or to the indirect influence of hearing loss, but we suppose that asymptomatic congenital CMV infection is possibly a kind of latent, persistent and progressive risk in mental development of newborns in the future.

In conclusion, there are some correlations between asymptomatic congenital CMV infection and intellectual outcomes in Qinba mountain area by the fact that the intellectual development was worse in asymptomatic congenital infected children.

The neonatal screening maybe worthwhile setting up to find the congenital CMV infection in a child’s first weeks of life. Following-up the intellectual development of the newborns with asymptomatic congenital infection, especially language development, will be benefit on starting adjustment promptly. It is important to ensure as many children with congenital CMV infection as possible are given the chance for normal linguistic, cognitive and social development.

Acknowledgements

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References


