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Case Report

Cortical maldevelopment in congenital cytomegalovirus infection transmitted by a woman with preexisting immunity

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Although cytomegalovirus (CMV) congenital infection is more severe in children born to women with primary infection, neurological symptoms have also been observed in infants born to mothers with preconceptional immunity. The authors describe for the first time a case of severe cortical development disorder associated with multiple abnormalities of the white matter, occurring in the second-born child of a woman found to be positive for anti-CMV immunoglobulin G (IgG) before pregnancy. CMV DNA was detected in the urine and blood of the infant. These findings indicate that the neurological outcome of CMV infection may be severe also in infants born to women with preexisting immunity. *Journal of NeuroVirology* (2008) **14,** 173–176.

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Cytomegalovirus (CMV) is one of the most common causes of congenital infection and a leading cause of brain damage in developed countries (Boppana *et al*, 2002; Maher and Rajiv, 2004). Preconceptional immunity of the mother has a partial protective effect; in fact, the risk of vertical transmission is 30% to 40% in primary maternal infection yet less than 1% in recurrent infection (Raynor, 1993).

Congenital CMV infection may damage the central nervous system (CNS), causing abnormalities in the developing brain (e.g., schizencephaly, polymicrogyria, intracranial calcifications, and encephalitis), leading to seizure, psychomotor delay, cerebral palsy, sensorineural deafness, and other developmental disabilities (Asher and Orna, 2006; Iannetti *et al*, 1998; Malm *et al* 2000). Although the symptoms are more severe in children born to women with primary infection (Raynor, 1993; Fowler *et al*. 1992; Pass *et al*, 2006), severe disease can also occur in children born to mothers with preconceptional immunity (Boppana *et al*, 1999, 2002).However, the only CNS abnormalities reported in cases of secondary CMV infection are microcephaly, small periventricular hemorrhagic lesions, and intracranial calcifications (Asher and Orna, 2006; Manoura *et al*, 2006).

We describe a case of severe disorder of cortical development, associated with multiple abnormalities of the white matter, in a female child with congenital CMV infection born to an apparently healthy mother with preconceptional immunity (i.e., immunoglobulin G [IgG] positive and IgM negative at first pregnancy).

The girl is the second child of nonconsanguineous parents and was born at term through spontaneous vaginal delivery after a normal pregnancy. At birth the weight was 2420 g (25th centile), length 45 cm (25th centile), and head circumference 29 cm (<3rd centile). Bilateral congenital cataract (surgically corrected at 6 months of age) was diagnosed.

On the 2nd day of life, she began to present anemia (2.35 million/mm^3), jaundice with increased total serum bilirubin level (18.6 g/100 ml), and petechial rash (face, neck, and legs). At 10 days of age, the

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child received blood transfusion for severe anemia, persisting after 15 days (hemoglobin [Hb] 5.1 g/dl), when she also presented neutropenia (820 cell/mm^3). At this time, CMV DNA was detected in the urine by using a qualitative polymerase chain reaction (PCR), whereas negative results were obtained from leukocytes and plasma (i.e., using a real-time PCR with a cut-off of 400 copies/ml). PCR for rubella, toxoplasmosis, parvovirus B19, human herpes virus (HHV)-6, and herpes simplex virus (HSV)-1 and -2 was negative. Blood and urine screening for metabolic diseases yielded normal results.

At 2 months of age, CMV DNA was detected in blood (2200 copies/ml) and plasma (800 copies/ml); liver enzyme values were also increased (aspartate aminotransferease [AST] 309, alanine aminotransferase [ALT] 335, gamma-glutamyl transpeptidase [GGT] 83 IU/L). Gancyclovir was administered (10 mg/kg for 3 weeks), with resolution of hypertransaminasemia and neutropenia and significantly improved anaemia. During the following months, PCR for CMV DNA was repeatedly negative (under 400 cp/ml); the IgG antibody titer remained stable (around 45 UA/ml), and IgM were persistently negative.

At 4 months, the infant began to present daily myoclonic seizures involving the head and the upper limbs; versive seizures, right hemiclonic seizures, and complex focal seizures with oroalimentary automatisms then appeared. The frequency of seizures varied (from daily to once every 2 weeks), showing a frequency reduction in the initial phase of antiepileptic treatment and a decreased responsiveness later in the course of epilepsy.

At 3 years of age, neurological examination showed bilateral spastic/dystonic tetraplegia, severe cognitive impairment with absence of expressive language, verbal comprehension limited to simple sentences of daily use, and severe visual impairment. Electroencephalograms (EEGs) showed a poorly organized background activity, with high-voltage slow activity prevalent in the right occipital region. Multifocal spike-wave complexes, sometimes polyspikes accompanied by segmental myoclonias, more pronounced in the right central-temporal leads, were recorded. Cerebral magnetic resonance imaging (MRI) revealed unilateral fused lip schizencephaly with double localization, white matter signal hyperintensity (Figure 1), unilateral temporal subependymal cyst, multiple calcifications, and corpus callosum hypoplasia. Visual-evoked potentials were impaired: electroretinogram (ERG) showed no a-b components bilaterally, and P100 showed increased latency on the left occipital electrode (167 ms), but normal latency and decreased amplitude on the right electrode. Otoacustic emissions (76 dB spl), performed when she was 3 months old, yielded normal responses bilaterally, indicating normal cochlear function.

Discussion

CMV is associated with a large spectrum of brain disorders, including cerebral malformations and white matter lesions (Van Der Knaap *et al*, 2004). Though maternal preconceptual immunity usually provides substantial protection, long-term neurological sequelae have been reported in children with congenital CMV infection born to mothers with preexisting immunity (Boppana *et al*. 2001). We describe, for the first time, severe cortical organization and migration disorders, and white matter abnormalities, in secondary/recurrent CMV infection. Congenital CMV brain disease is supposed to be related to the viral infection of rapidly dividing, susceptible, neural precursor cells (NCPc), which give rise to neurons, astrocytes, and oligodendrocytes (Odeberg *et al,* 2006). In fact, recent experimental models suggest that the primary mechanism underlying the development of brain abnormalities is NCP infection in the ventricular and subventricular zones and subsequent inhibition of neuronal differentiation, attenuated ability to proliferation, and enhanced apoptosis (Cheeran *et al*, 2005). Because the capacity of human CMV to prevent neuronal differentiation apparently decreases within 24 h of the initiation of differentiation (Odeberg *et al*, 2006; Cheeran *et al*, 2005), the timing of infection of the fetal brain may be an important determinant of brain-lesion severity. However, viral genotype and host immune response can also be implicated in the pathogenesis of CMV brain damage (Rasmussen, 1999). In particular, the neurotropism of different strains could differ and affect the severity of brain damage (Barbi *et al*, 2001). Finally, superinfection with a new CMV strain can lead to intrauterine transmission of CMV in infants of women with preconceptional immunity (Boppana *et al,* 2001).

Given the increasing interest in developing vaccines to prevent the damage associated with congenital CMV infection, it is important to determine whether the CNS disorders in children of immune mothers are due to reactivation or of reinfection with a different strain. Unfortunately, we were not able to determine whether secondary infection was due to a reactivation of endogenous virus or to reinfection with a different strain. Another limit of our study consists in the use of a PCR with relatively low sensitivity: this may have led to late detection of CMV DNA in blood and plasma, which resulted negative at the time of first evaluation.

This case report emphasises that brain abnormalities and the neurological outcome of secondary maternal CMV infection may be severe and that the clinical spectrum of CMV infection in offspring of women with preexisting immunity remains to be defined.

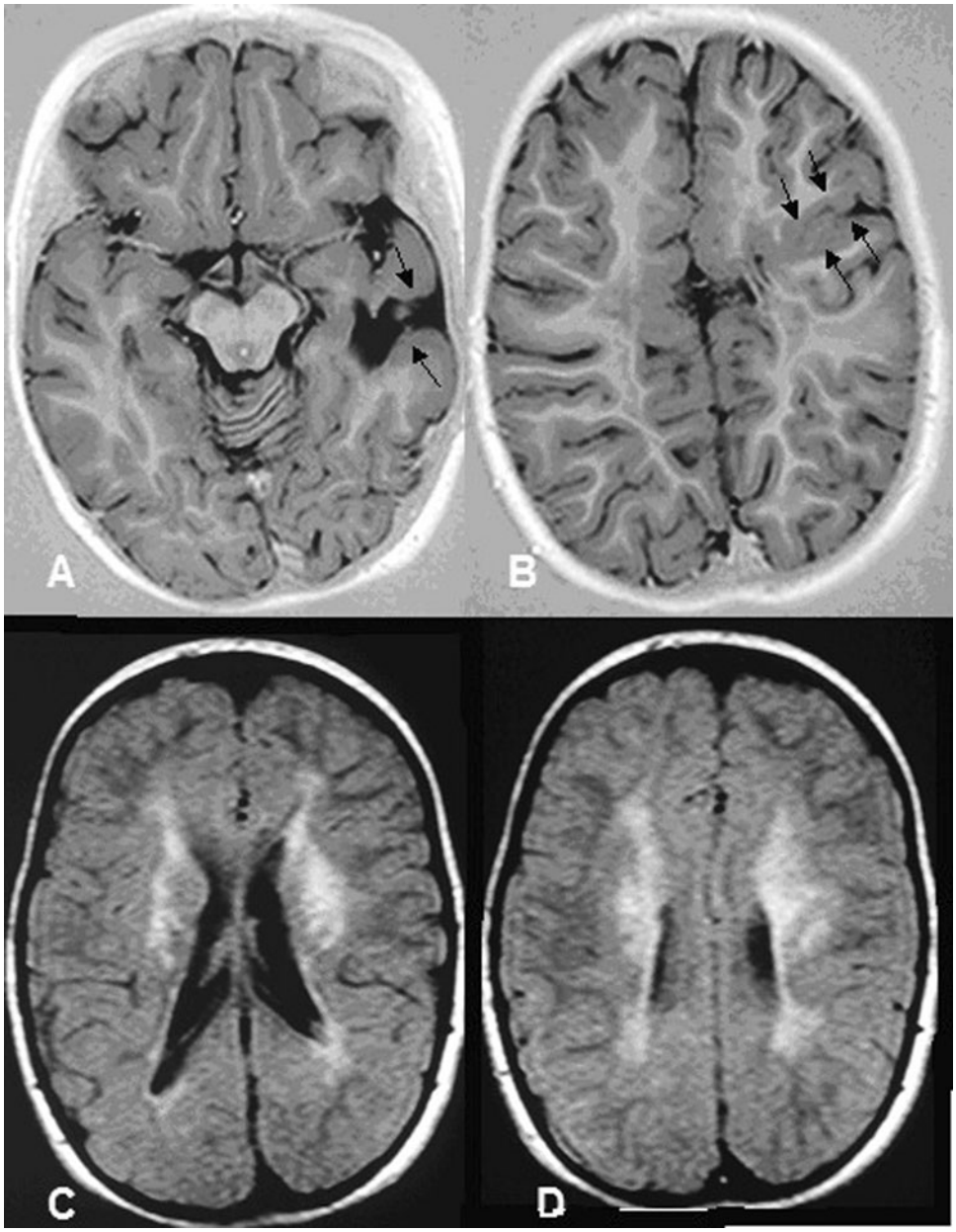

Figure 1 Axial MRI: Inversion recovery (**A**, **B**) and FLAIR-weighted images (**C**, **D**). Unilateral closed lip schizencephaly with double localization in left temporal (*arrow*, **A**) and frontal regions (*double arrows*, **B**). Both lips are surrounded by polymicrogyric cortex. White matter appears markedly hyperintense (**C**, **D**).

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