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Symptomatic congenital CMV infection after recurrent maternal infection

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Title figure:
Cytomegalovirus (Source: www.nature.com)

Cytomegalovirus (CMV) is probably the most common congenital viral infection; approximately 10% of congenitally infected neonates display symptoms at birth. In the past, symptomatic congenital CMV infection was thought to occur almost exclusively after primary infection of the mother during pregnancy, whereas preexisting maternal CMV immunity was thought to protect the unborn child from infection in the case of maternal re-infection. However, this has been proven to be incorrect by cases of symptomatic congenital CMV infection in infants of mothers who had been seropositive before pregnancy. Treatment of symptomatic infants with intravenous ganciclovir can decrease the risk of hearing loss, the most common neurological sequela, and reduce the risk for neurodevelopmental delay in infancy. However, strategies regarding the route and duration of treatment differ widely due to a lack of randomized controlled trials.

We present the case of a term baby girl born to a healthy 38-year-old G2/P2 at 40 2/7 weeks of gestation. Pregnancy had been uneventful until 26 weeks of gestation, when fetal ultrasound examination revealed bilateral subependymal cysts. This finding was confirmed by magnetic resonance imaging (MRI), which in addition showed slightly dilated lateral ventricles (Fig. 1A). At 36 weeks of gestation, another fetal MRI examination demonstrated focal white matter lesions (Fig. 1B). The mother had been CMV-IgG positive prior to this pregnancy, but CMV-PCR from amniotic fluid was positive. Therefore, maternal recurrent CMV infection during pregnancy was suspected.

The girl adapted well with Apgar scores of 8, 8 and 10 at 1, 5 and 10 minutes, respectively. The umbilical cord pH values were 7.20 (arterial) and 7.34 (venous). Birth weight was 3140 g (P19), length was 50 cm (P29), and head circumference was 33 cm (P8). On physical examination, extensive petechiae, hepatosplenomegaly and jaundice were noted.

Congenital CMV infection was confirmed by PCR in infant blood and urine samples, and therapy with intravenous ganciclovir was initiated. Postnatal MRI on day of life 5 revealed persistence of the abnormalities documented on fetal MRIs; however, neither calcifications nor polymicrogyria were seen (Fig. 2 A, B). Severe thrombocytopenia was treated with multiple platelet transfusions (Fig. 3). Profound hepato-

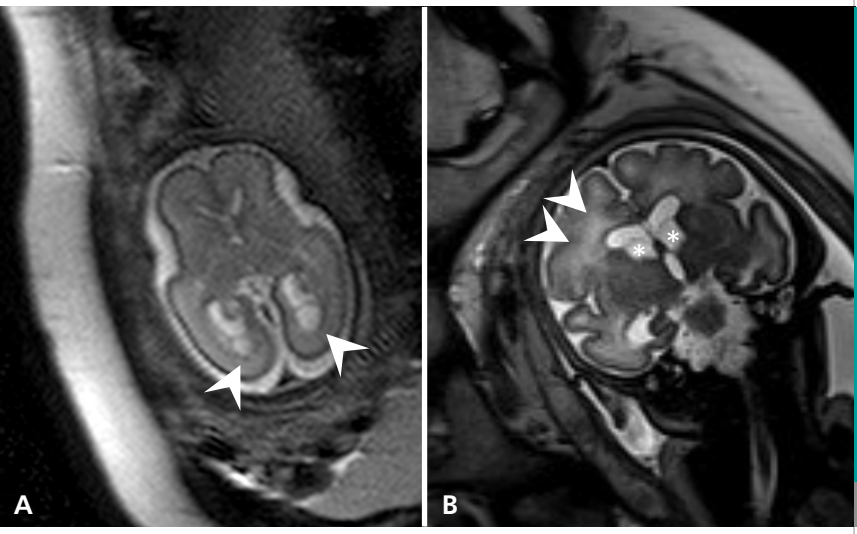

Fig. 1

A) Fetal MRI at 26 weeks of gestation (axial T2 haste weighted sequence): intraventricular cysts in the dorsal horns of slightly dilated lateral ventricles (arrow heads); B) Fetal MRI at 36 weeks of gestation (coronal T2 haste weighted sequence): intraventricular cysts (asterisks) and focal white matter lesions with increased T2 intensity (arrow heads).

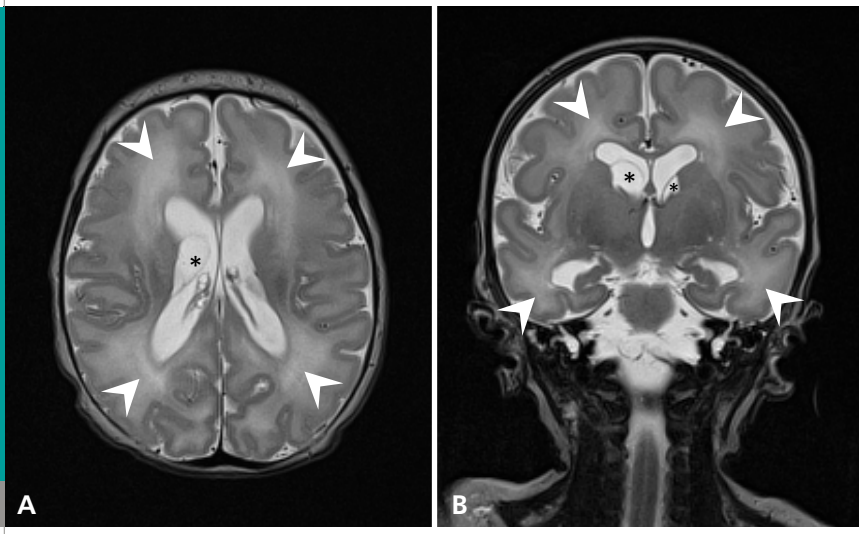

Fig. 2

Postnatal MRI on day of life 5: A) Axial and B) coronal T2-weighted sequences demonstrating cysts in the area of former germinal matrix (asterisks), slight dilatation of the lateral ventricles and frontal, as well as occipital white matter hyperintensities (arrow heads). Neither calcifications nor polymicrogyria can be seen.

pathy led to conjugated hyperbilirubinemia, coagulopathy, and progressive cholestasis within the first two weeks of life (Fig. 4). The latter was explained by functional bile duct obstruction due to CMV rather than an adverse effect of ganciclovir. Otoacoustic emissions and brainstem auditory evoked potentials were abnormal. Eye examination was unremarkable except for some minor pre-retinal hemorrhagic spots.

During 3 weeks of intravenous ganciclovir therapy, liver dysfunction improved, and CMV viral load in the plasma decreased significantly (Fig. 4,5). Thus, therapy was changed to oral valganciclovir, and the girl was discharged to home. The girl was regularly followed at the outpatient clinic, and treatment with oral valganciclovir was stopped after a total of six weeks of antiviral therapy. Viral load had decreased significantly, but viremia was still detectable at the end of the six-week course. Apart from transient mild muscular hypotonia and right-sided sensorineural hearing loss her neurological development was normal.

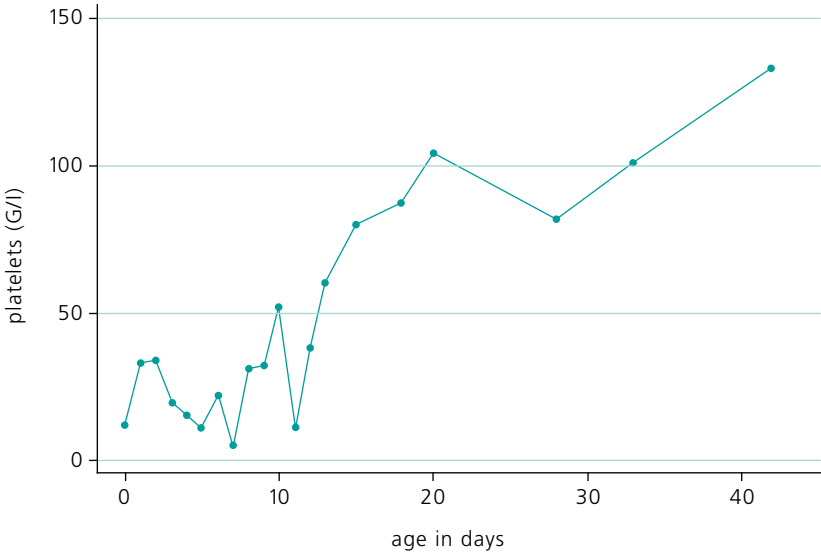

Fig. 3

Recovery of thrombocytopenia during antiviral treatment.

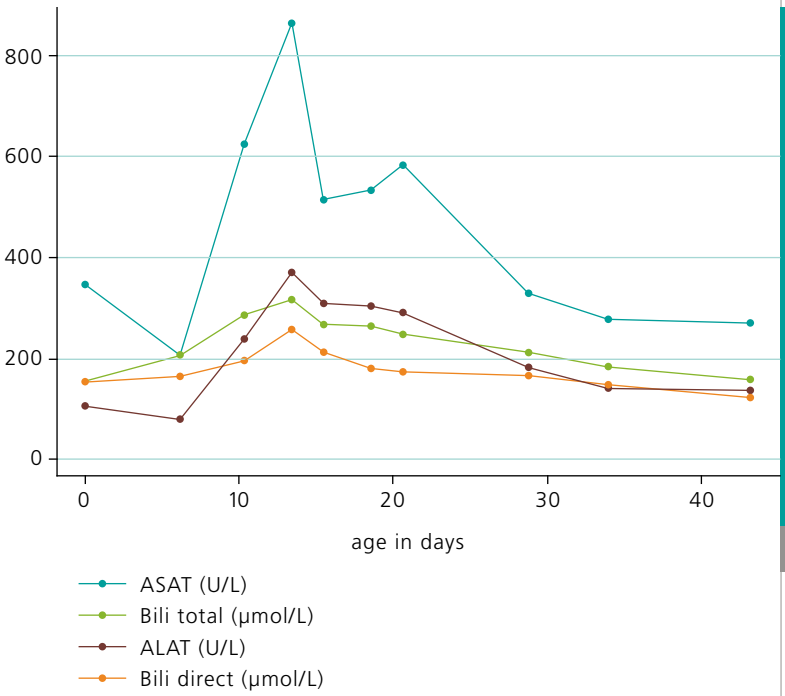

Fig. 4

Normalization of liver function tests during antiviral treatment.

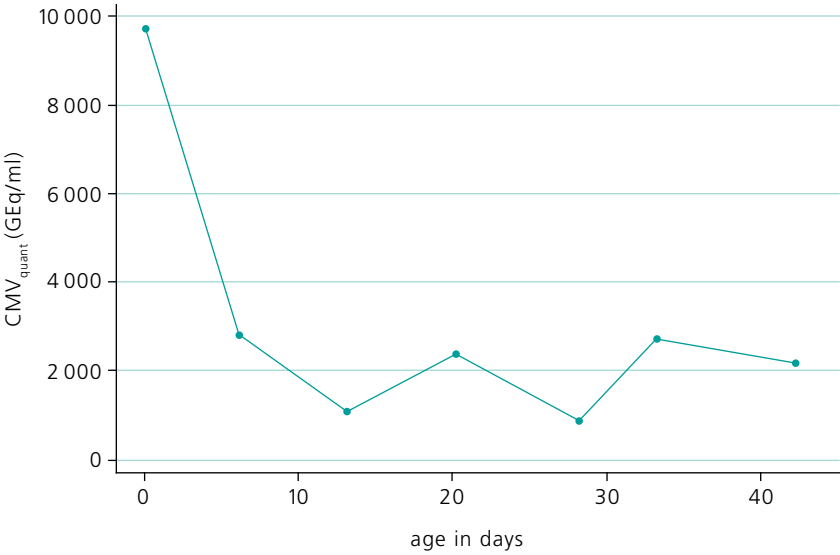

Fig. 5

Course of CMV viral load during antiviral treatment.

At the age of 4 years, she was seen in the emergency department because of acute onset of mild ataxia. Multiple laboratory examinations, including cerebrospinal fluid analysis and blood tests for viral or bacterial infections were negative. Cranial MRI showed regressive cerebral abnormalities with bilateral periventricular white matter lesions due to demyelination and gliosis, and intraventricular occipital adhesions (Fig. 6 A,B) but no signs of hemorrhage, infection or tumor. When mild signs and symptoms of upper respiratory tract infection developed, the neurological symptoms were felt to be parainfectious in origin rather than being related to her congenital CMV infection. She was last seen 6 months later: her overall neurodevelopment continued to be normal but severe right-sided hearing loss persisted (hearing threshold level > 90 dB).

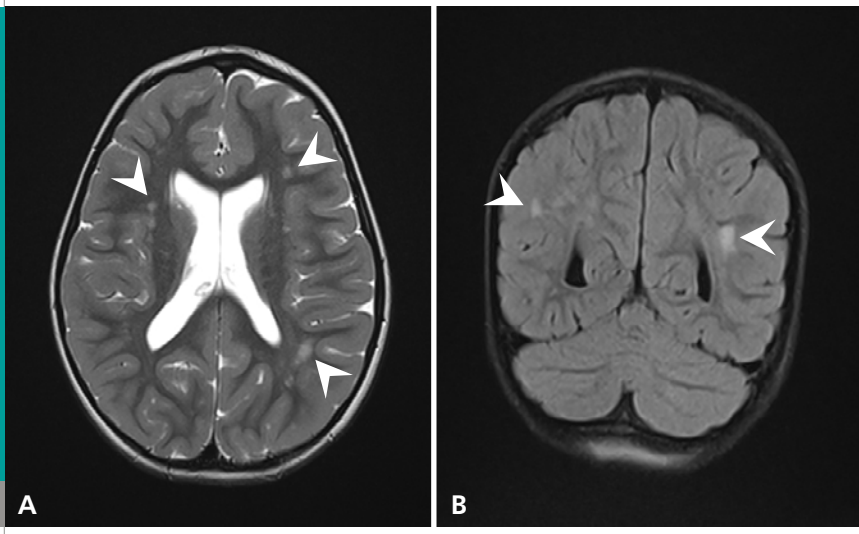

Fig. 6

MRI at age of 4 years: residual bilateral periventricular white matter hyperintensities (arrow heads; A) axial T2-weighted image, B) coronal T1-weighted image).

Fetal infection risk is highest with maternal primary CMV infection and less likely with recurrent infection due to the effect of maternal immunity. However, the observation of highest birth prevalence rates of congenital CMV infection in populations with high maternal seroimmunity indicates that CMV re-infections play an important role (1–4). It is unknown whether CMV reinfections in pregnancy are due to reactivation or infection with a different strain of CMV. Boppana et al. determined strain-specific IgG and clearly demonstrated that two-thirds of congenital infections in seropositive women were caused by exogenous reinfections (5). In contrast, reactivation as a route for symptomatic congenital infection has rarely been proven with molecular evidence (6).

Congenital CMV infection is the leading non-genetic cause of sensorineural hearing loss in early childhood, accounting for 21% of children with hearing loss at birth and 24% of those with hearing loss at 4 years of age (1). More sensitive screening methods for CMV have been developed in recent years (7), but treatment options for congenital CMV infections remain limited.

The current literature suggests that a six-week-course of ganciclovir, especially when started during the neonatal period, is effective in terms of decreasing the severity of neurological dysfunction and hearing loss in symptomatic and asymptomatic infants (8–10). Oral valganciclovir is more easily administered to infants

with congenital CMV-infection and results in similar plasma concentrations as with intravenous ganciclovir (11–13).

It was suggested that the benefit of a 6-week-course of ganciclovir therapy could wane over the first years of life (1). To address this issue, a randomized, placebo-controlled trial in neonates with symptomatic congenital CMV disease was recently performed, comparing 6 months with 6 weeks of valganciclovir therapy. The results showed that long-term treatment over 6 months had a moderately favorable effect on long-term audiologic and neurodevelopmental outcomes with no significant differences in the rate of adverse events between the two study groups (1). Whole blood viral loads decreased similarly in the two study groups during the first 6 weeks of treatment and then increased again in the 6-week-study group. Reduced viral loads correlated with better hearing outcomes at 6, 12, and 24 months among participants in the 6-month-group, whereas no such effect was observed in the 6-week group (1).

Symptomatic congenital CMV infection may be caused not only by re-infection but also by reactivation of CMV in seropositive mothers. There is still little knowledge on the frequency of reactivation-mediated congenital infection and its triggers during pregnancy. Although screening methods are advancing rapidly have become widely available, there is still limited evidence on treatment efficacy, particularly in cases with less severe disease. Further studies are needed to investigate the optimal route and duration of administration of antiviral drugs and to evaluate the course of hearing ability after cessation of antiviral treatment. Recent studies suggest improved outcome after long-term valganciclovir therapy.

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