Case report

Severe fetal intracranial hemorrhage: Congenital Cytomegalovirus infection may play a role? A case report and review of literature

Letizia Capasso*, Clara Coppola, Maria Vendemmia, Serena Salomè, Valentina Esposito, Chiara Colinet, Carolina Porfito, Francesco Raimondi

Neonatology and NICU, Department of Translational Medical Sciences, University Federico II, Naples, Italy

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ABSTRACT

Cytomegalovirus (CMV) is the most common cause of congenital infection, with a wide spectrum of clinical manifestations and different grade of severity. We report the case of a male baby born at term with an early prenatal diagnosis of severe intracranial hemorrhage (ICH), with no other evident risk factors. Urine and blood sample were tested for CMV-DNA, and diagnosis of congenital CMV infection was established. This case describes intracranial hemorrhage as uncommon although possible sign of early fetal CMV infection. Considering that pathogenic factors cannot be defined in 25% of term neonates with ICH, this case report highlights the importance of CMV screening in pregnant women and in term infants with prenatal ICH of unknown origin.

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Introduction

CMV is the most common cause of congenital infection with a wide spectrum of manifestations. Approximately 10% of neonates with congenital CMV (cCMV) infection are symptomatic at birth with clinical manifestations including jaundice, petechiae, purpura, hepatosplenomegaly, microcephaly and neurological symptoms, including intracerebral calcifications (typically periventricular), sensorineural hearing loss, cerebellar and hippocampal hypoplasia, cortical dysplasia (such as pachygyria, microgyria and lissencephaly) and retinitis. Neurodevelopmental impairment in childhood is common [1-3]. Intraventricular hemorrhage is a rare complication of cCMV infection and has been reported either in very premature infants or in association with thrombocytopenia [4,5]. We report a rare case of fetal ICH diagnosed at birth as cCMV infection without thrombocytopenia. The diagnosis of cCMV infection in neonates include real-time PCR of saliva, urine or both, as soon as possible after birth within the first 3 weeks of life. Valganciclovir treatment for 6 months in congenitally infected neonates with moderately to severely symptomatic disease could improve audiological and neurodevelopmental outcomes at 2 years of age [6,7]. Early diagnosis of cCMV is mandatory to start therapy within the first month of life.

Case presentation

MR was born at 38 weeks of gestational age (GA) from elective cesarean section. At birth: weight 2350 g (5–10th pt), length 45 cm (5th pt), head circumference 31 cm (<5th pc). Doppler flow at obstetric ultrasounds was regular. Placenta normal in shape and perfusion. The Apgar score was 8 at 1st min., 9 at 5th min.

At beginning of pregnancy, the mother was diagnosed as immune to rubella and she was negative for toxoplasmosis specific antibodies (IgG and IgM) throughout all the pregnancy. Only one determination of serological status for CMV at 11th week of GA was available(IgG positive and IgM negative). A maternal febrile episode in peri-conceptive period was reported. No maternal trauma reported in early pregnancy. Parents were not consanguineous and there was no family history of any bleeding disorders or stroke. No maternal use of cocaine or warfarin or anticonvulsant was reported.

A prenatal diagnosis of ICH was suspected during an ultrasound performed at 20th week of GA and it was confirmed at 25th week of GA through a fetal brain Magnetic Resonance Imaging (MRI) scan (Fig. 1).The prenatal MRI showed a porencephaly in the right fronto- temporal and insular zone with dilatation of the right lateral ventricle, reduced volume of the right cerebral hemisphere. In addition, it showed anomalous development of the right frontal cortex with a polylobulated aspect due to reduced amplitude of the furrows and increased number of turns (suspect of microgyria). No arterial nor venous abnormalities were reported.

* Corresponding author.
E-mail address: letizia.capasso@gmail.com (L. Capasso).

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Because of these prenatal findings, immediately after birth the neonate was admitted in our Neonatal Intensive Care Unit for further evaluations.

At birth physical examination revealed micro-purpuric elements on face and upper thorax, microcephaly, mild upper limbs muscular hypertonicity, abnormal deep tendon reflexes (plantar cutaneous reflex in extension bilaterally, absent left knee jerk), jaundice.

Laboratory evaluations were performed, including complete blood cell count, coagulative profile and liver and kidney function tests. Examinations for suspected congenital coagulopathy causing cerebral bleeding were performed (i.e. protein C and S, dosage of coagulative factors II, V, VII, X, XI, XIII, von Willebrand, IX, alf2 antiplasmin, APC resistance, lupus anticoagulant and anti-cardiolipin/beta 2 glycoprotein antibodies): all these exams resulted normal. Moreover, gene sequencing for MTHFR/Leiden Factor polymorphism resulted wild type. Screening for metabolic diseases at birth was negative.

Cranial ultrasound performed on first day of life showed left cerebral hemisphere prevailing on the right, a poroencephaly (2.3 cm of diameter) on the right side with "ex vacuo" ventricle enlargement (Ventricular Index 1.4 cm, Occipital Thalamus Distance 2.5 cm) till Silvian fissure. A germinolytic cyst on the left side and hyperechoic spots in the left peritrigonal parenchyma were found. Corpus callosum was poorly visible in its anterior portion. Third and fourth ventricles were normal-sized (Fig. 2).

A postnatal MRI scan confirmed the previous finding. It showed poroencephaly in the right fronto-temporal and insular zone with
“ex vacuo” ventricle enlargement, reduced volume of the right cerebral hemisphere, with striatum nucleus and thalamus partially involvement with wallerian degeneration of the corticospinal bundle. MR angiography did not show arterial and venous malformations nor thrombosis. An abnormal development of the middle-lower right frontal cortex was highlighted, which showed a polylobate appearance due to reduced furrows width and increased number of turns confirming the micropolgyria extended up to the right parietal lobe (Fig. 3).

The electroencephalogram showed cortical abnormal activity in frontal-temporal-parietal cortex.

Abdomen and cardiac ultrasound examinations, audiological (TEOAE) and ophthalmological evaluation were performed and all were normal.

Considering the micropolgyria at MRI scan, on the fifth day of life we searched for CMV DNA in body fluid and we detected in urine 10,273,900 copies/mm³ and 449 copies/mm³ in blood. Therefore, the patient received diagnosis of congenital CMV infection and it was classified as a severe symptomatic one because of central nervous system involvement (microcephaly, micropolgyria and a wide malacic area in right half brain as consequence of ICH, with “ex vacuo lateral ventricle enlargement”). According to current guidelines on the 15th day of life he started antiviral treatment with oral valganciclovir (16 mg/kg/dose, administered orally twice daily) for 6 months.

Discharged at the 17th day of life, the patient was admitted in our outpatient program for perinatal infectious diseases. No side effects were reported as consequence of the antiviral therapy. Evoked auditory brainstem response and ophthalmological evaluations were performed and resulted normal. Neurological examination at three months of age underlined persistence of neurological impairment more evident at the left side and he was admitted to physio-kinesiotherapy and neuro developmental follow up. At 18 month of life he presented global delay in development with pyramidal signs in the left hemisphere. In particular he achieved head and trunk control and from the supine position he reached the prone and vice versa; with double support he maintained the standing position and took a few steps. His language were characterized by lallation and some simple bisyllabic phonemes. The EEG trace showed anomalies with potential epileptiform significane on the right hemisphere without critical episodes so that he did not start antiepileptic therapy.

**Discussion**

Intracranial hemorrhage is a rare complication of cCMV infection. Two different hypotheses have been advanced to explain this condition.

One hypothesis considers CMV as cause of direct neuronal damage, due to its neurotropic nature, especially in early gestational age, resulting in cortical dysplasia and hippocampus and cerebellum hypoplasia.

A second hypothesis considers CMV as cause of vasculitis that can affect blood vessels of the central nervous system, triggering thrombotic or hemorrhagic processes, even in absence of apparent coagulopathy \[8,9\]. This type of complication has been reported mostly in extremely premature infants \[10\] and less frequently in term neonates. As differential diagnosis, fetal stroke has been reported also in association with thrombocytopenia, prothrombotic disorders, bleeding diathesis, metabolic diseases, maternal trauma and use of warfarin, anticonvulsant and cocaine \[11–13\] that were excluded in our patient. ICH has also been reported in fetuses proven to have COL4A1 mutations but the absence of positive familiar anamnesis for stroke and the normality of eye exam led us to exclude it \[13\].

Suksumek et al. \[14\] reported a case of term neonate with congenital CMV infection and intraventricular hemorrhage with a normal platelet count and coagulation profile. It was diagnosed later in pregnancy at 38 weeks of gestation, in a baby without growth retardation.

Our case, apparently very similar to this one, differs however for the earlier gestational age at CMV infection. In fact, the intracranial hemorrhage in utero was suspected at 20th week of GA and the earlier infection is in line with the finding of micropolgyria, microcephaly with global growth retardation and the severe neurological impairment showed since birth. The two cases may share the common origin but the early onset in our case lead to a different and more severe clinical picture. Moreover, in our case there was a very complex cerebral picture not only consequence of an intraventricular hemorrhage. In fact, cerebral fetal damage did not probably originate from the germinal matrix, related for example to the immaturity of its vessels, because it would have been restricted to the germinal matrix or at least extent into the lateral ventricles. We speculated that our patient suffered from a complex ischemic-hemorrhagic phenomenon in utero caused by CMV infection, which covered a wide area of parenchyma, including also but not only germinal matrix, where neural
precursors originate. In prenatal MRI, an abnormal signal pattern in
sub plate was reported and it may correlate with an anomalous
cortical organization, which results in the micropolygyria in the
same areas detected in the post-natal MRI.
Maternal history may suggest a very early infection in the first
trimester or a reinfection [15] in the early second trimester for the
presence of micropolygyria that is expression of an early brain
damage associated to cCMV infection.
Parents of neonate received a full prenatal counseling on ICH
diagnosis otherwise, they decided to continue pregnancy and
asked for the full medical care for the neonate.
In conclusion, in our patient, diagnosis of fetal ICH forerun the
diagnosis of congenital CMV. ICH affects 0.5/1000 of symptomatic
term infants and in 25 % of these cases, pathogenic factors cannot
be defined. This case report highlights the importance of testing
pregnant women and neonate for CMV infection in case of
unexplained fetal intracranial bleeding as a possible etiology.

Authors’ contribution

Conceptualization: LC, FR.
Supervision. LC, FR.
Writing and editing: LC, CCoppola, MV, SS.
Data Collection: VE, CCollinet, CP.
Review: LC, MV, SS.

Ethical approval

Not applicable.

Consent

The parents of the neonate gave as consent for publication of
the clinical history and images.

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Declaration of Competing Interest

The authors declare that the research was conducted in the
absence of any commercial or financial relationships that could be
construed as a potential conflict of interest.

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References

[1] Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S,
et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus
recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017;17
[June(6)]:e177–88.
[2] Giannattasio A, Bruzzone D, Di Costanzo P, Capone E, Romano A, D’Amico A,
et al. Neuroimaging profiles and neurodevelopmental outcome in infants with
congenital cytomegalovirus infection. Pediatr Infect Dis J 2018;37(October
[10]):1028–33.
[3] Giannattasio A, Di Costanzo P, Milite P, De Martino D, Capone E, Romano A,
et al. Is lenticulostriated vasculopathy an unfavorable prognostic finding in
infants with congenital cytomegalovirus infection? J Clin Virol 2017;91
[June]:31–5.
[4] Negro G, La Torre R, Sali E, Auteri M, Mazzocco M, Maranghi L, et al.
Intraventricular hemorrhage in a fetus with cerebral cytomegalovirus
infection. Prenat Diagn 2002;22:558–61.
[5] Dallar Y, Tiraz U, Catakli T, Gulal G, Sayar Y, Selvar B, et al. Life-threatening
intracranial bleeding in a newborn with congenital cytomegalovirus infection:
late-onset neonatal hemorrhagic disease. Pediatr Hematol Oncol 2011;28
[February(1)]:78–82.
[6] Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav–Boger R, Michaels MG,
et al. Valganciclovir for Symptomatic congenital cytomegalovirus disease. N
Engl J Med 2015;372:933–43.
[7] Salomé S, Giannattasio A, Malesci A, Marciano E, Dolce P, Portella G, et al. The
natural history of hearing disorders in asymptomatic congenital
cytomegalovirus infection. Front Pediatr 2020;8:217. doi:http://dx.doi.org/
10.3389/fped.2020.00217.
[8] Persoons MCJ, Stals FS, Van dam Mieras MCE, Bruggeman CA. Multiple organ
involvement during experimental cytomegalovirus infection is associated with
disseminated vascular pathology. J Pathol 1998;184:103–9.
[9] Golden MP, Hammer SM, Wainke CA, Allrech MA, Cytomegalovirus vasculitis:
case reports and review of the literature. Medicine 1994;73:246–55.
[10] Moinuddin A, McKinstry RC, Martin KA, Neil JJ. Intracranial hemorrhage
progressing to porencephaly as a result of congenitally acquired
cytomegalovirus infection—an illustrative report. Prenat Diagn 2003;23:797–
800.
[11] de Vries LS, Gunardi H, Barth PG, Bold LA, Verboom-Maciele MA, Groenendaal
F. The spectrum of cranial ultrasound and magnetic resonance imaging
abnormalities in congenital cytomegalovirus infection. Neuropediatrics
2004;35:113–9.
[12] Muñoz N, Pinzón H, Vizcalino H, Moneriz C. Cerebrovascular hemorrhage
associated with acquired cytomegalovirus infection in an infant. Biomedica
2014;34(October–December(4)):521–7.
[13] Kirkham FJ, Zefferino D, Howe D, et al. Fetal stroke and cerebrovascular
disease: advances in understanding from lenticulostriate and venous imaging,
alloimmune thrombocytopenia and monochorionic twins. Eur J Paediatr
Neur Orpol 2018;22(6):989–1005. doi:http://dx.doi.org/10.1016/j.
ejon.2018.08.008.
[14] Suksumek N, Scott JN, Chadha R, Yusufa K. Intraventricular hemorrhage and
multiple intracranial cysts associated with congenital cytomegalovirus
infection. J Clin Microbiol 2013;2013:2466–8.
[15] Giannattasio A, Di Costanzo P, De Matteis A, Milite P, De Martino D, Bucci L,
et al. Outcomes of congenital cytomegalovirus disease following maternal
primary and non-primary infection. J Clin Virol 2017;96(November):32–6 in
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