

Congenital Cytomegalovirus in Algiers, Algeria, a Descriptive Case Series Study

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ABSTRACT

Cytomegalovirus (CMV) is an endemic ubiquitous herpes virus transmitted through saliva, urine, genital secretions, mononuclear blood cells, and transplanted tissue. It is a common infection with mild symptoms or asymptomatic in the immunocompetent individuals but can be severe in the immunocompromised individuals, e.g., HIV-infected individuals, transplanted and cancer patients, and fetuses. CMV is the leading cause of congenital viral infection and the leading non-hereditary cause of sensorineural hearing loss and mental retardation in early childhood. Here, we describe the clinical and laboratory monitoring of four congenital CMV (cCMV) cases referred to Pediatric Belfort Establishment in Algiers in 2019, 2020, and 2021. All the patients had developed signs and symptoms of postnatal CMV infection with intrauterine growth retardation. The clinical manifestations differed; some presented cytopenia with or without hepatosplenomegaly and others a clinical and biological cholestasis syndrome. All our patients had intrauterine growth retardation. A CMV PCR of a urine sample was positive. Treatment for six weeks based on ganciclovir, with a relay by valganciclovir.

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INTRODUCTION

Cytomegalovirus (CMV) is an endemic ubiquitous herpes virus transmitted through saliva, urine, genital secretions, mononuclear blood cells, and transplanted tissue. It is a common infection with mild symptoms or asymptomatic in the immunocompetent individuals but can be severe in the immunocompromised individuals, e.g., HIV-infected individuals, transplanted and cancer patients, and fetuses. CMV is the leading cause of congenital viral infection and the leading non-hereditary cause of sensorineural hearing loss and mental retardation in early childhood, with a ~0.65% prevalence. Transmission of the CMV from mother to child may occur during pregnancy (congenital CMV infection), during childbirth (perinatal CMV infection), or after birth (postnatal CMV infection) [1]. The seroprevalence might be affected by various epidemiological factors, exhibiting significant variation [2]. The 15%-50% fetal transmission rate in mothers' primary infection decreases to 0.15%-1% with recurrent maternal infections [3]. Congenital CMV (cCMV) infection is asymptomatic in 90% of cases, while the rest of the patients present typical symptoms.

ELISA has at least 95% sensitivity and specificity for detecting CMV-specific IgG antibodies [4, 5]. Postnatal

infection can occur after exposure to human milk, blood products, or transplanted organs. Human milk-associated CMV infections are typically asymptomatic in term infants due to passively acquired maternal antibodies [6].

Infected breast milk is the primary source in the postnatal period. Recent studies utilizing the highly sensitive polymerase chain reaction (PCR) assays have demonstrated the virus DNA in breast milk from more than 90% of seropositive women. CMV infection acquired postnatally in a healthy, full-term infant is typically asymptomatic and without sequelae [7]. In contrast, the very low birth weight (VLBW) preterm infants who acquire CMV postnatally may be completely asymptomatic or have a sepsis-like syndrome with abdominal distention, apnoea, hepatomegaly, bradycardia, poor perfusion, and respiratory distress [4,1]. Approximately 10–15% of congenitally-infected infants have signs and symptoms of the disease at birth, and approximately half experience long-term sequelae [8,9]. Among asymptomatic infants with congenital CMV, an estimated 10–15% develop long-term sequelae; the most common long-term sequela is hearing loss [10, 11].

Here, we describe the clinical and laboratory monitoring of four cCMV cases to address the essentials for diagnosing and prognoses of this infection.

All four patients were referred to Pediatric Belfort Establishment in Algiers, Algeria, in 2019, 2020, and 2021.

Cases' reports

We discuss four cases of newborns and infants diagnosed with congenital CMV infection. All four patients were referred to Pediatric Belfort Establishment in Algiers, Algeria, in 2019, 2020, and 2021. Serological diagnosis of primary CMV infection was performed based on serum-CMV specific-IgM antibodies and urine samples PCR. The maternal infection was asymptomatic, as it is for most infections in immunocompetent patients.

Case 1

An 18-day-old boy was admitted for treatment of persistent jaundice with discoloration of the stools. The clinical examination found hypotrophy and microcephaly. The length and head circumference were also below 0.4th centile. Physical examination indicated a cholestasis syndrome with total bilirubin at 90 mg/l and conjugated bilirubin at 7 mg/l, cytolysis with ASAT at 100 IU/l, ALAT at 90 IU/l, and the 45% TP. The remainder of the laboratory tests were normal. We prescribed vitamin K for three days, leading to an elevated prothrombin level. TORCH serology showed an IgM positivity titer of 1:123 for CMV and 55566 copies/ml of CMV in the urine sample. The cerebral MRI had objectified cortical atrophy localized to the left sylvic region. Severe CMV infection was diagnosed, and parenteral ganciclovir was prescribed at 6mg/kg/day for six weeks twice daily, followed by oral valganciclovir at a dose of 16 mg/kg twice daily for six months. The follow-up included fortnightly monitoring of viral load, liver enzymes, creatinine, and blood urea. The urine viral load fell from 55566 copies/ml on day 18 to 100,000 copies/ml on day 40. Blood viral load was 1056 copies/ml on day 18, and after one month of antiviral therapy, no virus was detected. Biochemistry was normal and exhibited no adverse effects following the treatment.

The infant is currently two years old and keeps a slight hypotrophy but a good psychomotor examination. The long-term follow-up did not reveal any hearing or ocular abnormalities.

Case 2

A three-month-old boy with jaundice was admitted for weight and psychomotor delay. The anthropometric measurements indicated that the infant had severe failure to thrive and could not hold his head yet. Laboratory data showed anemia with 9g/dl of hemoglobin, leukopenia 8510/ μ L, markedly decreased platelets to 50000/ μ L, hepatic cytolysis, ALAT 200U/L, ASAT 100U/L, total bilirubin of 160 mg/l, direct bilirubin 120 mg/l, and

biological cholestasis, alkaline phosphatase (ALP) of 180; Gamma glutamyltransferase of 200UI/l, and prothrombin time (PT) of 50%. Abdominal ultrasound revealed hepatosplenomegaly. The echocardiography showed unrestricted ventricular septal defect, but transfontanellar ultrasound and cerebral MRI were normal. Fortunately, the ophthalmological examination did not find any ocular involvement. TORCH serology tests were negative for toxoplasmosis, rubella, herpes simplex, and HIV. The CMV IgM was positive for both the baby and the mother. ELISA test for CMV IgM in the mother and baby and PCR test for CMV genome of the baby were positive. Due to very positive CMV PCR (44300UI/ml) in the urine, and given the richness of the clinical symptomatology, moderate CMV disease was diagnosed, and CMV infection was considered the leading cause of this delay. Intravenous ganciclovir administration (12 mg/kg/day) twice a day was started and continued for six weeks, relayed by oral valganciclovir for six months at a dose of 6 mg/Kg/day in two doses. The number of viral copies in PCR reduced to 100 after one month, the hepatic assessment returned to normal, and icterus disappeared within one month of development. We did not find any side effects inherent in the prescription of ganciclovir. We had to adjust the doses of valganciclovir because of a slight increase in transaminases. The infant is currently still on valganciclovir. He is six months old and still has hypotrophy without psychomotor retrading. He has undergone an audiometric examination without any particularities.

Case 3

A sixty-day-old boy born prematurely at 35 weeks of pregnancy with intrauterine growth retardation and second-degree consanguineous presented with jaundice and hepatosplenomegaly. The admission examination found cutaneous jaundice, cutaneous hemorrhagic, and hepatosplenomegaly. Biologic exploration found bicytopenia, anemia 8.4 g/dl, thrombocytopenia 19000/ mm^3 , disturbed blood crust, and cholestasis with frank cytolysis alanine transaminase 567 UI/l, aspartate transaminase 734 UI/l. Serum electrolytes, blood gases, and serum ammonia were within normal limits. TORCH screening showed positive CMV-IgM titer 1: 520 and a positive urinary viral load of 7,100,000 copies /ml. MRI showed objective diffuse involvement with hypomyelination of the white substance with bleeding marks of the left choroid plexus stigmas. We diagnosed severe CMV disease and started intravenous ganciclovir (10 mg/kg/day) twice daily for six weeks, then relayed by oral valganciclovir, with close monitoring of the complete blood counts and renal function tests and the enrichment of the milk in medium-chain triglycerides, in fat-soluble vitamins A, D, E, and K. The patient is currently eight months old with good psychomotor acquisitions.

Case 4

A two months infant girl was referred for exploration of bicytopenia with hepato-splenomegaly. We found a notion of hypotrophy at a birth weight of birth 1800 g. On examination, we found exophthalmos with an anterior fontanel admitting the fingertip, microcephaly, and opisthotonos attitude. We also found hepatomegaly (hepatic arrow at 6 cm), splenomegaly, biological abnormalities type anemia with thrombocytopenia, conjugated hyperbilirubinemia, cholestasis, and cytolysis. Medullogram did not find malignant cells. TORCH screening showed IgM CMV titer 1:594 and a high urinary positive CMV load of 8999 copies/ml. Magnetic Resonance Imaging (MRI) showed calcifications, periventricular cysts, ventricular dilatation, subependymal, pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, and lenticulostriate vasculopathy. We started gancyclovir 10 mg/kg/day for 21 days, twice daily. Unfortunately, the infant experienced hypertonic convulsions at the first infusion of gancyclovir, resulting in discontinued treatment. We administered anticonvulsants and took over with valgancyclovir at a dosage of 6mg/kg/day. The infant presented significant sequelae with psychomotor delay, spastic quadriplegic type of cerebral palsy, and epilepsy. He received intensive physiotherapy and speech and language therapy. He also had impaired central vision and preservation of some peripheral vision.

DISCUSSION

Cytomegalovirus, a ubiquitous agent, is one of the crucial causes of intrauterine infections. The infection is usually asymptomatic in adults but often with a significant impact during pregnancy [12]. This infection is endemic worldwide, affecting most people, but the seroprevalence for CMV-IgG antibodies varies significantly with various epidemiological factors such as age, geographical distribution, socioeconomic status, marital status, and parity [13]. CMV occurs in the saliva or urine of infected people. Excretion of the virus, particularly at high titer, occurs more frequently in children under two, particularly in daycares [14,15]. The virus might be excreted, ranging from months to years. Also, CMV can be transmitted from urine and saliva to hands and then to mucosal surfaces (e.g., mouth) or directly to the mucosal surfaces. High-risk groups include parents with a child in daycare with a 23% risk of seroconversion per year if they have children who are shedding CMV. Parental excretion of CMV occurs from the cervix, in semen, and other bodily fluids [16].

The highest likelihood of mother-to-child transmission (MTCT) is following primary maternal infection during the first trimester, associated with a 30-40% risk of intrauterine transmission. Of the infected fetuses, around one-third (~10% overall) will have some disease [17]. Infants are not necessarily viremic at birth. Therefore, a

negative CMV PCR test for the whole blood or plasma or newborn dried blood spots (DBS) does not exclude CMV [18, 19]. We concluded that intrauterine transmission had occurred for all four patients presented here.

The cCMV diagnosis is established by detecting the virus DNA using PCR in body fluids in the first three weeks of life. If detection occurs after three weeks, whether the infection is congenital (antenatal infection) or postnatal cannot be concluded. [20]. After the birth, the sooner the tests are performed, the more confident are the cCMV diagnosis. Infants older than three weeks with symptoms of potential cCMV should still be examined as their management may still center on the diagnosis. Urine and saliva are the preferred samples due to greater sensitivity, but blood (including the newborn blood spot) can also be used in addition to, but not in place of, urine or saliva. A negative blood PCR does not exclude cCMV, and it is only helpful if positive. Detecting anti-CMV IgM antibodies is not conclusive as it is not as sensitive or specific as CMV PCR. CMV IgG is not helpful among infants under one year because it can reflect maternal antibodies owing to placental transfer. Urine and saliva samples are a priority, and blood is not a substitute; therefore, a TORCH screen should include urine/saliva for CMV [21]. Our patients all benefited from a CMV PCR in the urine. Evidence that premature babies have a higher incidence of cCMV is limited. At birth, clinical features of symptomatic cCMV include microcephaly, intrauterine growth restriction (IUGR), hepatosplenomegaly, petechial rash, jaundice, and seizures [22,23]. Infants with symptomatic cCMV should be identified promptly such that appropriate management can be instituted as early as possible to improve outcomes.

When testing has confirmed cCMV, symptomatic infants require ophthalmological and hearing evaluation and head imaging [24, 5]. A head ultrasound (HUS) is usually sufficient for asymptomatic or minimally symptomatic infants. Both MRI and CT scan neuroimaging are superior to ultrasound (US) for identifying abnormalities that predict less favorable outcomes [25]. In our four patients, the damage was moderate in three and severe in one case. In our opinion, the elements of poor prognosis were the delay in diagnosis and starting the treatment. In the patient who experienced convulsions due to gancyclovir infusion, we observed a poor prognosis with significant sequelae following discontinuing the administration of the antiviral agent. MRI is preferred over CT and should be performed in infants with significant neurological features or abnormal findings in the cranial US. MRI can better detect findings that predict neurodevelopmental morbidities, e.g., dysplasia of the hippocampus, cerebellum, and polymicrogyria [26]. Head ultrasound is recommended in the neonatal period and has excellent sensitivity for demonstrating periventricular calcifications, structural lesions, and ventriculomegaly [27].

Cases of cCMV are classified at or around the time of birth by symptom severity as asymptomatic, mild, and moderate to severe disease [28]. Mild cCMV is characterized by transient or minor abnormalities in one or two organ systems with no CNS involvement. Managing mild CMV cases which are later confirmed to have sensorineural hearing loss (SNHL) should involve ID consultation. The management may be individualized, considering the presence and severity of sensorineural hearing loss SNHL [29, 30]. Currently, treatment is reserved for infants with symptomatic congenital infection and those with apparent signs of neurological involvement at birth, including microcephaly, radiographic abnormalities consistent with cCMV central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or CMV DNA in cerebrospinal fluid. Moderate-to-severe diseases are characterized by CNS involvement, including microcephaly, seizures, positive CSF CMV PCR, abnormal head imaging, chorioretinitis, multisystem disease (≥ 3 organs/systems involved) with significant non-transient abnormal laboratory values (e.g., hepatosplenomegaly, intrauterine growth restriction (IUGR) and moderate-to-severe hepatitis and moderate-to-severe or persistent thrombocytopenia), and severe single organ disease [31,5]. The impairment was considered severe for all of our patients, and treatment was initiated upon diagnosis.

A complete blood count and differential leukocyte count are important since thrombocytopenia in the neonate is a predictive biomarker for an increased risk of neurodevelopmental sequelae [32].

Data from two trials have provided support for treating severely symptomatic infants with antiviral agents [33, 34]. Oral valganciclovir should be administered for six months. Parenteral ganciclovir may be substituted for the first 2 to 6 weeks of treatment when the infant is very ill [35, 25]. Adverse effects (AEs) associated with antiviral therapy include neutropenia, thrombocytopenia, transaminitis, and elevated urea and creatinine. While on therapy, infants need to be monitored serially for AEs. There is no evidence to support routine viral load monitoring, as viral loads do not consistently correlate with treatment response [36, 37]. A remarkable adverse effect for one of our patients was convulsions just after the ganciclovir infusion, which resulted in the treatment discontinuation and reappeared as soon as the same infusion was repeated. The data on this side effect is poor; we found two cases reporting convulsive seizures after using ganciclovir in a man diagnosed with acquired immunodeficiency syndrome and a disseminated cytomegalovirus infection patient who experienced seizures following ganciclovir administration. Seizures began one month after initiation of therapy and worsened with increasing dosages [38, 39].

For all congenital CMV infections, a neurodevelopmental, neurosensory, and ophthalmological follow-up is required. Close dental follow-up may also be needed. Enamel hypoplasia occurs in up to 40% of children with symptomatic CMV [40, 41].

Late-onset, progressive SNHL has a median onset of 27 months of age but has been reported to develop as late as 44 months [42]. For our only patient who had presented this delay, we started to notice it already around 8-9 months with a psychomotor delay, then around the age of one year, the delay was apparent. Serial hearing evaluations should be conducted regularly over the first 4 to 5 years. Children with extensive CNS involvement may experience seizures, cerebral palsy, and intellectual delay [43-44].

The cCMV is the leading cause of non-genetic sensorineural hearing loss and a significant cause of neurodevelopmental and neurosensory morbidity. Basic hygienic measures are highly effective in preventing maternal infection. Early laboratory cCMV identification in infants (within the first 21 days after birth) is essential to determine disease severity and initiate antiviral therapy in moderate to severe cases. All infants with symptomatic cCMV and asymptomatic infants with isolated hearing loss should be referred to infectious disease specialists. When indicated, valganciclovir therapy, initiated in the neonatal period days and administered for six months, has been shown to improve hearing and developmental outcomes. Affected infants require multidisciplinary follow-up.

Future research should address newborn screening, treatment outcomes in children with isolated SNHL or mild disease, CMV vaccine development, and diagnostic and prognostic strategies.

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