Childhood Cytomegalovirus Infection: Case Series and Literature Review

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Introduction and Objectives

Cytomegalovirus is a DNA virus which in its congenital form is the most frequent infectious cause of sensorineural hearing loss and the commonest viral etiology of mental retardation [1]. Intra-partial transmission or acquisition during breast feeding can lead to perinatal disease, though associated with much less sequelae than congenital CMV infection, especially in term deliveries. During the post-organ-transplant period and immune-compromised states like HIV infection, CMV can lead to life-threatening complications like pneumonia, hepatic failure, retinitis, esophagitis, bone marrow suppression, etc. [2-4].

Prevalence of CMV infection in the Ethiopian population is high. A study on maternal CMV and Rubella infections in Addis Ababa concluded that 15.5% of pregnant women studied were IgM positive for CMV while 88.5% were IgG positive [5]. Testing for species-specific CMV IgG among Ethiopian workers in Jeddah, Saudi Arabia revealed an 88.9% prevalence among 72 samples tested [6]. A number of studies have reported on prevalence of CMV retinitis of 1%–2% among HIV infected Ethiopian adults with ophthalmologic complications [7-11]. Distribution of CMV antibodies reaches up to 100% in healthy blood donors from developing countries; posing a high risk of transfusion related infection [12].

Data on pediatric CMV infections in Ethiopia is hard to come by. Thus we present this case series of four children evaluated at Tikur Anbessa Specialized Hospital, Addis Ababa with the objective of sharing their clinical features and how each was diagnosed and managed.

Abstract

Introduction and objectives: Early life Cytomegalovirus infection is an under-recognized disease. Infection can present as congenital, perinatal or acquired forms. Though mostly asymptomatic, it can lead to fatal complications.

Case presentation: The clinical presentations of four Ethiopian children with acute Cytomegalovirus infections are reviewed. Three had neonatal disease while one had an acquired infection. Two of the neonatal infections involved preterm deliveries while all three presented with persistent direct hyperbilirubinemia. Serologic tests were used to diagnose their infections.

Discussion: Childhood Cytomegalovirus infections involve multiple organs. Viral DNA detection and serologic tests are utilized to diagnose infection at different ages of childhood. Treatment was provided to one of our patients based on existing recommendations while the other three did not receive anti-viral drugs.

Conclusions: Early diagnosis and management of pediatric Cytomegalovirus infections will prevent long-term hearing and neurologic disabilities.

Keywords Cytomegalovirus; Congenital; Perinatal; Neonatal; Acquired; Childhood

Case Representation

The first infant was a preterm delivery via a cesarean section because of abruptio placentae. The infant spent the first week of life at our neonatal ICU for respiratory distress syndrome. The anthropometric measurements were normal. In the second month of life, decreased urine output, fever and un-sustained sucking were noted with bilateral pitting edema.

Investigations revealed a urinary tract infection due to Klebsiella pneumoniae and nephrotic syndrome (hypoalbuminemia, +3 proteinuria and hypertriglyceridemia). Voiding cystourethrogram was normal; Ultrasound showed bilateral moderate hydronephrosis with uretero-pelvic junction obstruction.

Work-up for secondary etiologies of nephrotic syndrome showed negative serum VDRL, hepatitis B surface antigen, hepatitis C and HIV antibody tests. Quantitative toxoplasma IgM and IgG titers were normal. Qualitative CMV IgM was positive and IgG was 14.6 IU/mL (normal<6 IU/mL). The mother's CMV IgG determined at the same time was >250 IU/mL. The infant's CMV IgG elevated to more than 8 times (121 IU/mL) by 3 months of age. An acute CMV infection of congenital or perinatal origin was diagnosed.

There were no evidences for pneumonia. Edema, serum albumin and urinary abnormalities later corrected. Coagulation profile was normal. Retinal screening and imaging of the brain could not be done for economic reasons. In the absence of testing for virus in body fluids in the first 2 weeks of life, differentiating between congenital or perinatal infection was not possible. Based on available clinical data, treatment was not indicated. The patient subsequently was lost from follow-up.
The second infant was also delivered at preterm; a cesarean section delivery for severe preclampsia with failed induction. Microcephaly was present at birth and throughout follow-up. The infant had a prolonged admission to the neonatal ICU for respiratory distress, neonatal sepsis and bictcytenia. Packed red blood cell and platelet transfusions were given during stay.

Soon after discharge from neonatal ICU, parents noted yellowish discolouration and a direct hyper-bilirubinemia was confirmed. Liver enzymes were elevated while an abdominal ultrasound was normal. Serum albumin, coagulation profile, HIV antibody, chest x-ray and brain ultrasound were normal. Quantitative CMV titer tests showed IgM of 1.9 IU/mL (normal<0.85 IU/mL) and IgG 69.5 (normal<6 IU/mL). Ophthalmologic examination was normal.

Due to microcephaly since birth, jaundice and positive serology, the most likely transmission method for this acute CMV infection is thought to be congenital. Perinatal CMV is largely asymptomatic though preterm perinatal infection is more likely to be symptomatic. Oral Valganciclovir 35 mg twice daily for 6 weeks was initiated.

This child probably acquired infection due to the multiple blood transfusions received. Treatment was not indicated because CMV infection was an improbable cause of the initial pancytopenia.

Discussion

Reports on rates of CMV infections in Ethiopia suggest a high prevalence. Yeshwondm et al conducted a prospective cross sectional study in a tertiary hospital in Addis Ababa with the aim of investigating zero-prevalence of CMV and Rubella infections among pregnant women and stratifying the risks for infection. They concluded that 15.5% of the studied pregnant women were positive for IgM and 88.5% were IgG positive. No significantly associated risk factors were identified [5]. Another study conducted in Jeddah, Saudi Arabia tested for species-specific CMV IgG among Ethiopian workers plying their trade and revealed 88.9% prevalence among 72 samples tested. The findings confirmed that the Ethiopian workers tested were more affected than their counterparts from seven countries who originated from the Indian sub-continent, East Africa, Egypt and Yemen [6].

Another sub-set of patients which have been frequently studied are HIV infected Ethiopian adults. Prevalence of CMV retinitis is estimated to be 1%-2% among this group of patients. One patient was reported with bilateral blindness due to CMV retinitis [7-11]. An early WHO report comparing complement fixing antibodies against Cytomegalovirus in different parts of the world concluded their presence in up to 100% of healthy blood donors from developing countries. This high risk for transfusion related infection contributes to significant morbidities [4,12].

In-utero transmission of CMV occurs in 0.5%-22% of all live births. It is less frequent than perinatal transmission but more severe. Primiparious mothers, primary infection, infection during first and early second trimester of pregnancy and poverty are notable risk factors [2].

Multi-organ involvement is seen with congenital CMV infection due to inflammation occurring after viral invasion. These include persistent direct hyperbilirubinemia in the first months of life, hepatosplenomegaly, microcephaly, peri-ventricular intra-cranial calcifications, chorioretinitis, cognitive dysfunction, sensorineural hearing loss, blueberry muffin spots, petechiae, etc. Post-natal infection is rarely associated with long-term effects. Much more severe illness can be seen in transfusion related CMV infection [3]. Rare associations like persistent pulmonary pulmonary hypertension, intestinal malrotation, necrotizing enterocolitis and Menetrier's diseases have been reported [13-16].

Our case series of acute childhood cytomegalovirus infections consist of three patients in their early infancy and one aged 3 years and 8 months. The first three had neonatal disease while the last case had an acquired infection. Two of the neonatal infections were delivered preterm and presented in a few weeks with persistent direct hyperbilirubinemia. Serologic tests were used diagnose all cases. Table 1 shows the presentations and co-morbidities in the four patients.
Valganciclovir for 6 weeks. Other options include Foscarnet and detect CMV viremia or viruria. Viral excretion clinician would have to rely on the severity of manifestations and the transmission though it has little impact on the management. Positive IgM or demonstrations of rising IgG titers are useful in the absence of ophthalmologic abnormalities [17,18]. Direct hyperbilirubinemia was noted in two of our cases. Microcephaly was noted in one infant and it is a recognized complication, as echoed by Isikay and Yilmaz as well as Chowdareddy et al. [19,20].

Detection for virus in body fluids or CMV DNA PCR in the first two weeks of life is important in diagnosing in-utero acquired CMV. Most experience so far has come from testing urinary and salivary secretion samples. Viral excretion confirmed afterwards cannot differentiate between congenital or perinatal infection. Hence, the clinician would have to rely on the severity of manifestations and the presence of complications to distinguish between the two methods of transmission though it has little impact on the management. Positive IgM or demonstrations of rising IgG titers are useful in the absence of the aforementioned tests, though not as sensitive or specific [21].

Our patients all had quantitative or qualitative tests for both CMV-specific IgM and IgG which, tied up with their clinical features, enabled for diagnosis and treatment as acute CMV infections. Like most low resource countries, our center suffers from a lack of tools to detect CMV viremia or viruria. The unavailability of tests of DNA PCR and viral cultures holds us back from issuing a standard confirmation.

Main treatment options include intravenous Ganciclovir and oral Valganclovir for 6 weeks. Other options include Foscarnet and Cidofovir. Treatment is indicated for symptomatic children with neurologic findings, retinitis, pneumonia, hepatic dysfunction or immune-compromise.

The sole purpose of treatment is to improve long-term hearing and neurologic outcomes. Administration of Ganciclovir or Valganclovir should be initiated for neonatal disease early in infancy to have any meaningful use, as possible within the first month of life. Rates of severe neutropenia are seen in up to two-thirds of infants treated with intravenous Ganciclovir [22–26].

In conclusion, we are presenting four Ethiopian children with acute CMV infections diagnosed clinically and using quantitative and qualitative serologic tests. Our case series show that this viral infection should be considered as a possible etiology in early infancy persistent direct hyperbilirubinemia and of transfusion-related infections. It also reminds the myriad of possible presentations. We also underline the need for advanced diagnostic tools for congenital and acquired childhood CMV infections in Ethiopia.

**Table 1:** Presentations & co-morbidities seen in the four children.

<table>
<thead>
<tr>
<th>Retinitis</th>
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<tr>
<td>Pneumonia</td>
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<td>Hepatic failure</td>
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<td>Immune-compromise</td>
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<tr>
<td>Skin manifestations</td>
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<td>Petechiae</td>
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<td>Petechiae</td>
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</table>

Though half of newborns with congenital CMV have intracranial calcification on CT scanning, this was noted in none of our patients. Likewise, both children for whom ophthalmologic screenings were done had no findings suggestive of CMV infection. Similar reports of congenital CMV have also discussed a lack of imaging or ophthalmologic abnormalities [17,18]. Direct hyperbilirubinemia was noted in two of our cases. Microcephaly was noted in one infant and it is a recognized complication, as echoed by Isikay and Yilmaz as well as Chowdareddy et al. [19,20].

References


