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Case Series

Congenital Cytomegalovirus Infection in Children: A Retrospective Case Series Study at Resource Limited Setting with Literature Review

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Abstract

Congenital cytomegalovirus infection (cCMVI) is the most common viral infection during pregnancy, affecting 0.5-1% of live births in the West and three to four-fold increased incidence in Low to middle income countries (LMIC). This retrospective case series study analyzed eleven cases of cCMVI in children under five years, highlighting the clinical spectrum from asymptomatic to full blown clinical presentation with neurological impairments. Key findings include periventricular calcification, ventriculomegaly and elevated anti-IgG and IgM antibodies. Early detection through universal maternal and neonatal screening combined with serological testing and neurosonogram, is crucial for early detection and intervention in resource limited settings (RLS). Antiviral treatments like Ganciclovir and valganciclovir show promise in reducing disease severity. The study underscores the importance of maternal education, early therapeutic intervention, and regular follow up to mitigate long term sequelae in affected children.

Keywords: Congenital Cytomegalovirus Infection (cCMVI); Resource Limited Settings (RLS)

Abbreviations

AHW: Anterior Horn Width; BRUE: Brief Resolved Unexplained Event; CCMVI: Congenital Cytomegalovirus Infection; CMV: Congenital Cytomegalovirus; cUSS: Cranial Ultrasound Scan; CT Scan: Computerized Tomography Scan; CDC: Centre for Disease Control; DNA: Deoxyribonucleic Acid; EEG: Electroencephalogram; LMIC: Low to Middle Income Countries; MRI: Magnetic Resonance Imaging; NICU: Neonatal Intensive Care Unit; NDD: Neurodevelopmental Delay; OAE: Otoacoustic Emission; PICU: Pediatric Intensive Care Unit; PTI: Preterm Infant; PCR: Polymerase Chain Reaction; RLS: Resource Limited Setting; SNHL: Sensory Neural Hearing Loss; TORCH: Toxoplasmosis, rubella, Cytomegalovirus and Herpes; WHO: World Health Organization

Introduction

Congenital cytomegalovirus infection is the most common viral infection during pregnancy and accounts for affecting 0.5 – 1% of live births in the western countries and about 3 – 4 times more prevalent in LMIC [1]. Most of these infections are asymptomatic (90%) at birth and only 10% neonates' manifest symptoms like jaundice, brain' abnormalities and rash [2]. At least 24% of symptomatic CCMVI in children experience late onset hearing loss [3]. Other potential issues include central nervous system disease, neurodevelopmental delays (NDD), sensory neural hearing loss (SNHL), microcephaly with or without hydrocephalus, seizures, visual impairment (choreoretinitis) and behavioural problems, though these are debated in asymptomatic cases. While initially asymptomatic, 2% of them may develop SNHL months to years later [4].

Standard newborn screening guidelines can help assess the percentage of asymptomatic CCMVI in children at risk of adverse outcomes. Differentiating congenital infection from early acquired Cytomegalovirus (CMV) infection needs testing at birth and retesting 3 weeks after birth [1]. Pediatric literature offers guidelines for diagnosing congenital CMV but often lacks details on early treatments. Recognizing CMV epidemiology and infant presentation is essential for pediatricians.

Early recognition and early initiation of therapeutic interventions have been associated with better clinical outcomes [5]. Bedside cranial ultrasound screening (cUSS) and MRI brain scan results in finding the cCMVI cases, in both symptomatic and asymptomatic. This paper presents retrospective study of cCMVI as case series with review of literature on epidemiology and suggests strategies for clinical presentation and investigation of affected infants.

Methods

All clinically diagnosed cases of CCMVI in children from neonatal to under five years during the last three years were collected. They were further analysed with case history, clinical findings, imaging, and serological study and presented as retrospective case series study from a single centre in resource limited area. There were seven cases of < 1 year and four cases more than one year.

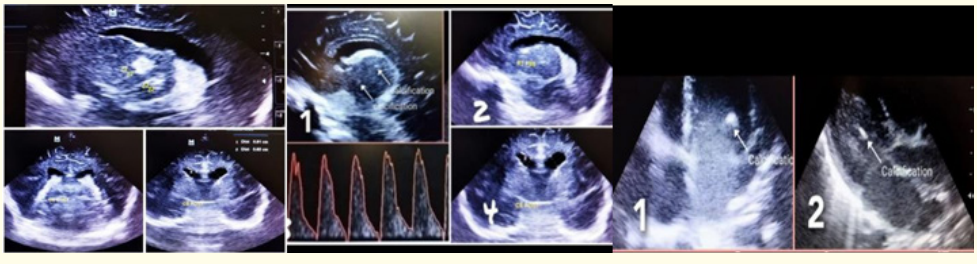

Figure 1: Case 1 (figure 1). Shows periventricular calcification, calcification of thalamus (top), dilated lateral ventricles with increased anterior horn width (bottom), Case 2 (figure 2 and 3). Periventricular calcification and dilated lateral ventricles (top) increased peak flow velocity and decreased diastolic flow of anterior cerebral artery (bottom) and increased AHW of LV Figure 3: Calcification in left ventricle of heart (1 and 2).

Results

Case 1: A female baby brought by parents on 18th day of life for seizures, multi focal, transient, recurrent, more than 15 episodes in less than 12 hours for the first time. This baby is a product of non consanguineous parents, uneventful pregnancy G1P1L1, 2.3 kg at birth, small for gestational age, and delivered at term by LSCS (extramural). Initial Appar scores were normal followed by sudden apnea and needed NICU (extramural) admission for 3 days. Cranial USS showed periventricular calcification, calcification at thalami's area, lateral ventriculomegaly with irregular margins, increased anterior horn width of left LV 8.3 mm and right LV 6.7 mm and echogenic brain. Similar features were found on MRI brain, serology showed elevated anti CMV IgG and IgM antibodies and polymerase chain reaction (PCR) test for urine sample was positive for CMV. On follow up, baby developed neuro developmental day, intellectual disability, microcephaly, gait abnormality, dystonia, squint, and diminished vision. Child is on anti seizures medication.

Case 2

A female baby of 56 days old presented with history of apnea and unresponsiveness with altered body colour change transiently and resolved to normal after few minutes and before reached the health care facility. On reaching our casualty, baby had normal vitals, skin perfusion and alertness. On further evaluation, cUSS screening revealed periventricular calcification, enlarged anterior horns of lateral ventricles, and increased systolic peak flow velocity with decreased diastolic flow on cranial Doppler study of anterior cerebral artery. Echocardiogram showed left ventricular calcification. Left ear passed and right ear failed/repeat with OAE screening. Both anti CMV IgG and IgM antibodies were elevated. Further progression of AHW of lateral ventricles over serial cUSS scan noticed and referred for neurosurgical opinion.

Case 3

Three months old female infant referred for evaluation of cardiac murmur and echo revealed mild branched pulmonary artery

stenosis. Serological tests showed grossly elevated anti CMV IgG antibodies. Further evaluation with cUSS showed periventricular calcification and mildly dilated anterior horns of lateral ventricles. This baby was a product of young non consanguineous parents belonging to low socioeconomic strata. Baby delivered at term by spontaneous vaginal delivery at a health care facility. Baby was low birth weight of 2.1kg at birth and history of photo therapy for neonatal hyperbilirubinemia.

Case 4

Three-year-old male child developed sudden unresponsive state with loss of posture followed by fluttering of both eye lids that lasted for > 3 minutes followed by drowsiness. EEG showed generalised spike waves. Serology showed grossly positive anti CMV IgG antibodies. OAE screening passed for right ear but not for left. This Toddler had seizures and intracranial calcification with > four-fold increased anti IgG antibodies for CMV.

Case 5 and 6

Female twins toddlers presented for speech delay. Both babies were reached language skills of only mono syllables at 3 years. However, other milestones were right for the age. Both babies had periventricular calcification on CT brain and elevated anti IgG antibodies for CMV. Both children had not passed OAE testing and they were referred for further evaluation and intervention by audiologist and speech therapist.

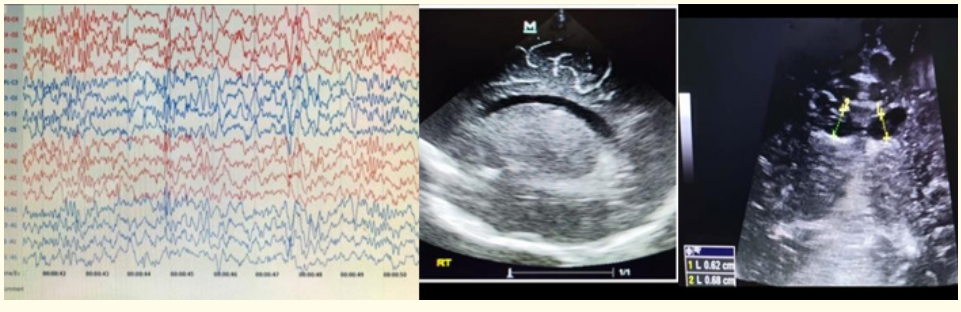

Figure 2: Case 4 – abnormal EEG pattern with generalised spikes (left) and Case 7 - dilated lateral ventricle (left) with periventricular calcification on day 7 and case 10 increased AHW of lateral ventricles with internal septation of right anterior horn.

Cases 7, 8, 9 and 10

All these neonatal infants had abnormally dilated lateral ventricles on fetal neurosonogram during pregnancy and all these mothers were serological TORCH positive for antiCMV IgG antibodies. On postnatal neurosonogram, these babies had mildly dilated lateral ventricles with periventricular calcification. All babies had high titres of anti CMV IgG antibodies, and two babies had borderline anti CMV IgM antibodies. Urine sample PCR test not undergone due to non availability of the same at the health care facility and inability to afford the test from the extra mural laboratory by the families.

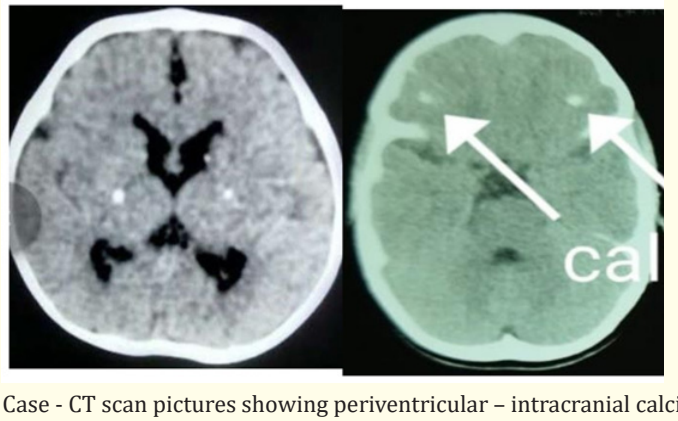

Figure 3: Case - CT scan pictures showing periventricular – intracranial calcification.

INTERPRETATION OF IgM & IgG in CMV INFECTION DURING PREGNANCY				
So. No.	IgM	IgG	STATUS	COMMENTS
1.	—Ve	-Ve	Sero –Ve mother	Repeat monthly upto 20Wk GA & at term
2.	+ Ve	-Ve	Early seroconversion / false +Ve	Repeat after 2wks. If IgG +Ve. Primary infection. Immunoblot test best
3.	—Ve	+Ve	Past infection or recurrent infection	
4.	+Ve	+Ve	Perform IgG avidity test	Primary infection if Ig avidity test low or intermediate in 1st 16 Aks GA. High IgG avidity test indicates past infection.

Table 1: Showing interpretation of antenatal serological tests among pregnant women.

Case	Age	Sex	CF	IgG	IgM	PCR	CALCIFICATION- NSG	VENTRICULOMEGALY	Hearing tests	CT / MRI imaging	OTHERS
Case 1	18 days	Fe	Seizures microcephaly, SGA	Raised	Raised	Positive	+	+	Failed	Cal	AbN vision&hearing, NDD
Case 2	56days	Fe	BRUE,SGA	Raised	Raised	-	+	+	Failed	Cal	Echo LV cal
Case 3	3 Mns	Fe	Heart murmur,SGA	Raised	Equivocal	-	+	+	Rt ear failed	-	Echo BPAS
Case 4	3yrs	Me	Seizures	Raised	-Ve	-	+	-	Failed	Cal	AbN EEG
Case 5	3yrs	Fe	-	Raised	-Ve	-	+	-	Failed	Cal	
Case 6	3yrs	Fe	-	Raised	-Ve	-	+	-	LT ear failed	Cal	
Case 7	7days	Fe	FetalUSS AbN	Raised	-Ve	Denied	+	+	Passed	-	
Case 8	6days	Fe	-do-	Raised	-Ve	-do-	+	+	Passed	-	
Case 9	11days	Me	-do-	Raised	-Ve	Urine +	+	+	Passed	-	
Case 10	14days	Me	-do-	Raised	-Ve	-do-	+	+	Passed	-	
Case 11	2yrs	Me		Raised	-Ve	-do-	+	+	Failed	Cal	Deafness

Table 2: Showing clinical, laboratory and imaging features of study population.

Case 11

Two years old male child presented with history of age-appropriate speech development up to 1 ½ years followed by arrest and non improvement in further speech and decreased response to verbal commands especially when the child was in noisy environment. Child tested and showed abnormal findings on audiometry tests, serological tests revealed high titres of anti IgG CMV antibodies with normal IgM levels and CT brain showed intracranial calcification.

Discussion

Eleven reported cases were analysed with respect of history, clinical findings, serological study, and imaging- CUSS and CT/MRI (when possible and affordable). There were seven cases belonging to infant age and four children above 1year age. Three cases were presented with seizures (two infants and one toddler) and one young infant (case 2) presented with brief resolved unexplained event (BRUE). Four infants were reported as dilated atria of lateral ventricles on antenatal ultrasound scan during pregnancy and one

infant was incidentally diagnosed while evaluating for a cardiac murmur. Three infants had seizures and abnormal EEG pattern. Two twin sister toddlers were presented with delayed speech. All infants showed grossly raised anti IgG antibodies and two cases with anti IgM antibodies against CMV. All cases had intra cranial calcification especially periventricular area with nonexistence for alternate diagnosis and showed dilated lateral ventricles on cUSS. The anterior horn width (AHW) of lateral ventricles on cUSS is normally <3mm in term infants [6] and <4mm in preterm infants (PTI) [7]**.** Higher values of AHW should be evaluated with cranial Doppler study of major cerebral arteries for raised intracranial pressure as denoted with either absent or reverse diastolic flow and interpret in conjunction with clinical manifestations. The CMV causing CNS infection will damage the periventricular germinal matrix during intrauterine life and produces periventricular and intracranial calcification. Two infants on follow up, had sequelae with developmental delay, gait abnormalities, lower intelligence, microcephaly, and hearing impairment.

This case series presents a spectrum of clinical presentation including asymptomatic cases to BRUE and full spectrum involving severe brain damage, microcephaly, ventriculomegaly, hearing loss, low intelligence, seizures, developmental delay, and diminished vision. Early detection, universal screening of mothers and newborns, maternal education, antiviral treatment during pregnancy and infancy with regular follow up plays key role in mitigating long term neurological sequelae. Universal antenatal serological screening of mothers and neonatal CUSS screening are cost effective in low resource settings and enables early detection and intervention in affected children. Primary CMV infection in pregnant women is suggested by raised anti CMV IgM antibody titres in 1st trimester (sensitivity >98%) with gradual fall over 2nd and 3rd trimester and low avidity test (<30%) in earlier <3 months (sensitivity 94-100%) for anti CMV IgG levels [8]. However, high titres of more than fourfold raise from upper limit of normal range of anti IgG CMV antibodies are also significant. Primary CMV infections occur in 1-4% of seronegative pregnant mothers with a fetal transmission of 30-40%. Reactivation CMVI occurs in 10-30% seropositive pregnant women at fetal transmission of 1-3%. High sensitivity and specificity for CMV DNA PCR test is clear after 21 weeks of GA. Sequelae is seen in 22-65% among symptomatic children with a mortality of 30% in severe cases [9].

Literature Review

Contextual framework and importance

Congenital cytomegalovirus (CMV) infection is the most common congenital infection and a leading cause of sensorineural hearing loss, more so than phenylketonuria and galactosemia [10]. Transmission to the fetus can occur from infected leukocytes in asymptomatic mothers. Understanding perinatal risk factors for vertical CMV transmission is essential for studying fetal infection and evaluating prenatal screening and treatment options. However, finding specific risk factors has been difficult, with uncertainties around infection timing, maternal infection types, and prior CMV immunity effects.

Etiology, mechanisms, and modes of transmission

Cytomegalovirus (CMV) is a double stranded DNA virus with a 230kb genome encoding >250 open reading frames and many microRNA genes from the herpesvirus family [11], prevalent worldwide and causing lifelong infections with phases of latency and reactivation especially in individuals with immature or altered immunity. In the U.S., CMV seroprevalence in adults ranges from 50–85%, varying by demographics. Infected individuals intermittently shed and transmit CMV, primarily through respiratory and excretory routes, oropharyngeally.

CMV is transmitted both horizontally and vertically. Horizontal transmission occurs via direct contact with infectious body fluids like saliva, urine, and breast milk. Other transmission modes include sexual contact, hand–mouth contact, childcare environments, and blood transfusions. Risk varies depending on whether individuals are actively shedding the virus or have latent infections. Direct contact with children's secretions is the primary transmission method. In resource-poor areas, CMV spreads often between 12 and 48 months. Maternal–fetal transmission happens before this age, making children key in horizontal transmission [12]. Most mothers with prior infections do not experience reinfection or symptoms from shedding.

Pregnant women are the main source of CMV transmission to fetuses, with some already at risk due to primary infection. Pregnancy affects vertical CMV transmission notably; fetal infection may result in severe outcomes like miscarriage or symptomatic

infants. The virus in fetus produces tissue damage by viral replication, inflammatory reaction, and chronic hypoxia by altering placental perfusion. Congenital CMVI manifests as placentomegaly, produces chronic hypoxic condition in the fetus and responsible for extra medullary hematopoiesis with biliary obstruction and erythrocyte congestion, leading to hepato-spleenomegaly, growth restriction and blueberry muffin rash in neonates [13]. Recognizing fetal CMV exposure risks is vital for understanding other fetal loss causes. CMV is often present in fetal tissues, and real-time PCR testing in placental and fetal samples has significant clinical implications. The risk for symptomatic infants is greatest among women who seroconvert late, have chronic reactivations, or are infected at conception [3].

Clinical presentation, symptomatology, and complications

CMV is the most common viral infection affecting congenital, intrapartum, and postnatal periods in women and a significant cause of hearing loss in infants. About 10-15% of infants with CCMVI show symptoms at birth, while up to 60% may develop permanent conditions like SNHL, NDD, or impaired vision due to chorioretinitis [9]. Notably, 88% - 90% of those with CMV infection related hearing issues are asymptomatic at birth, making CMV the leading non-genetic cause of congenital SNHL. Congenital CMV infections are classified into symptomatic and asymptomatic cases. Most affected infants (asymptomatic) are found through positive CMV culture from urine or saliva within the first 2-3 weeks [14]. Symptomatic infections present with clinical or laboratory signs, including hepatosplenomegaly, hepatitis, jaundice, seizures, and microcephaly. These infants often show more severe clinical findings, such as cholestatic jaundice, hepatomegaly, and elevated liver enzymes [15]. Postnatal infection should be considered in PTI with transmission of CMV infection through breast milk.

Cytomegalovirus is increasingly being recognized as a major agent of viral congenital infection.

Various estimates for the incidence of CMV infection in the newborn agree with clinical observations. Vertical maternal transmission of CMV can occur during primary infection, reactivation in a CMV seronegative mother, or non-primary infection in previously seropositive women. The risk of fetal damage caused by maternal primary CMV infection is higher than the risk of sequelae in the infants of mothers with a history of earlier CMV infection.

In congenitally infected infants, congenital CMV infection can present with a series of symptoms. Congenital CMV infection should be suspected in all neonates presenting with petechiae, jaundice, hepatosplenomegaly, thrombocytopenia, anemia, microcephaly, intrauterine growth retardation, hepatic dysfunction, cerebral calcifications, chorioretinitis, sensorineural hearing loss, or post-term gestation, in the absence of any other cause for these clinical symptoms [15]. A 'significant risk' factor is represented by perinatal CMV infection, particularly in the newborn with prolonged lung disease. In newborns with symptoms suggestive of congenital CMV infection, a peripheral blood film should be performed to detect circulating blast cells, anemia, and low platelet count [16]. Early detection of cytomegalovirus in these infants would hasten the diagnosis.

Diagnosis and screening

Once the symptoms of CCMVI increase a clinician's suspicion, several definitive diagnostic tests should be performed. The most sensitive method is virus isolation from infants' specimens. If CMV is isolated from symptomatic young infants, it confirms the diagnosis. The virus can be found in the urine of infected babies' weeks after birth and is typically present in most congenitally infected infants early on <3weeks. Alternatives to viral culture include tests for specific CMV antigens, providing quicker results. CMV DNA detection through PCR testing may also be beneficial for assessing antiviral therapy in high-risk infants [17].

Imaging and laboratory tests

Neurosonogram and MRI imaging studies might show cerebral leucomalacia, calcifications, ventriculomegaly, or microcephaly [18]; however, these can be attributed to other causes. Unlike other infectious agents, serologic tests and PCR do not decide the timing of CMV infection or show the variety of clinical issues it may cause in neonates. Tissue biopsy or autopsy may reveal CMV inclusion bodies, typically found in central nervous system tissue, aiding postmortem diagnosis.

Laboratory tests for CMV infection in infants include urine or saliva cultures. Saliva / Urine antigen analysis is preferred within first 3 weeks of life as a positive result indicates CMV in the blood and signals severe symptoms like hepatosplenomegaly and jaundice. Maternal samples, including vaginal swabs or placental samples, help verify prior CMV infection. Neonatal IgG levels say passive

transmission from maternal side and only considered little significant if the titres are rising over time or existence of high titres of more than 4-fold than normal upper limit range. Neonatal IgM has weak response and absent in many infected infants. We opine that in the post neonatal infancy, serological tests of IgG and IgM in clinically suspected infants, alongside neurosonogram and testing for sensory neural deafness may get some value in low resource settings where other costly investigations neither available nor affordable and referral is not possible. If infants show organ-specific symptoms, further imaging tests, such as chest X-rays, echocardiograms, audiometry for hearing loss, head ultrasounds for intracranial calcifications, and brain MRIs or CT scans for CMV-related brain abnormalities, are necessary.

Management

Currently, no therapy is recommended for asymptomatic congenital cytomegalovirus infections. Ganciclovir is the primary treatment for symptomatic infants, but its use is limited due to significant myelosuppression, particularly granulocyte count reduction, and potential viral resistance from extended treatment [19]. Enhancing intravenous ganciclovir administration for six weeks and minimizing myelosuppression are key interests. Letermovir, a new anti-herpesvirus drug included in international guidelines for post-transplant CMV prophylaxis and preemptive therapy, has not been studied in congenital cases.

Studies show ganciclovir can improve outcomes for symptomatic congenitally infected infants with significant myelosuppression. Valganciclovir 16mg/Kg, an oral form [20], has similar efficacy to intravenous ganciclovir 6mg/Kg twice in a day and may be preferred for its ease of administration. However, ganciclovir is potentially teratogenic, targeting CMV-DNA polymerase while disrupting human DNA synthesis, leading to birth defects and fetal distress. Given its penetration into fetal organs, antenatal therapy should be considered alongside amniocentesis or fetal blood sampling. Intravenous ganciclovir should be administered in alternating daily doses for safety and the use of granulocyte-colony stimulating factor is recommended for infants [21,22].

Cidofovir and CMX001 are therapeutic alternatives, but their long-term safety is debated. Letermovir is a new CMV drug for stem cell transplants, but its effectiveness in preventing congenital CMV disease in infants is still uncertain.

Conclusions

1. CMVI is usually asymptomatic in immunocompetent individuals and symptomatic with sequelae in immunocompromised patients. 2. Universal maternal serological screening preferably during first trimester and confirmation with proper specimen with DNA polymerase chain reaction test yields reliable results. 3. Both antenatal and postnatal parenteral gancyclovir and oral valgancyclovir are effective in reducing the severity of disease. 4. Children are potential source of CMVI to pregnant women. 5. During neonatal life <3weeks, saliva and urine are reliable sources for viral detection especially viral DNA by PCR test. 6. Early therapeutic intervention in symptomatic infants prevents the CMV disease. 7. Prevention of CCMVI is possible with universal maternal and neonatal screening, maternal health education, early detection of CCMVI and therapy and vaccination.

- **What is already known about this topic**: CCMVI is the most common congenital viral infection during pregnancy with potential devastating consequences in fetus and children.
- **What is not known**: Clear evidence-based guidelines are not available for early detection in resource limited settings.
- **What this paper adds**: Combined clinical suspicion, serological testing, and ultrasonography evaluation of children especially with neuro-sonogram, in the absence of alternative clinical diagnosis is an easy and effective approach in detecting CCMVI at resource limited setting.

Conflict of Interest

There are no conflict of interest in preparing this manuscript.

Consent of Parents

Oral consent taken from parents for scientific publication of the images.

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