Neurological Manifestations of Congenital Cytomegalovirus Infection at a Tertiary Care Centre from Southern India

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Abstract

Background Cytomegalovirus (CMV) is a ubiquitous herpes virus. It is the most common congenital viral infection. Data on congenital CMV in India are lacking and hence the present study was undertaken.

Objectives The aim of the study is to evaluate the clinical and radiological profile of neurological manifestations of congenital CMV infections in tertiary care hospital.

Methods This is a retrospective chart review of the clinical and laboratory profile of congenital CMV infections presenting from January 2018 to February 2020 to a tertiary care hospital in Southern India. Details of clinical profile, serological and neuroimaging data were obtained and analyzed.

Results A total of 42 cases with female preponderance (57%) were reported during the study period. The mean age of presentation was 2.9 years. Clinical features were developmental delay (81%), microcephaly (93%), seizures (33%), intrauterine growth restriction (19%), neonatal encephalopathy (10%), anemia (9%), jaundice (10%), hepato-splenomegaly (7%), and eye abnormalities (14%). Antenatal maternal fever was reported by 12%. Sensorineural hearing loss was present in 57%. Neuroimaging showed periventricular calcification (79%), cerebral atrophy (69%), ventricular dilatation (55%), malformations (26%), dysmyelination (12%), and temporal lobe cysts (5%). CMV-immunoglobulin-M positivity was seen in 14 cases (33%), urinary polymerase chain reaction for CMV was positive in 21 cases (50%), and clinical diagnosis was done in seven cases (16%).

Conclusion Common findings in congenital CMV are microcephaly, developmental delay, seizures, anemia, and sensorineural hearing loss. Common neuroimaging findings are periventricular calcification, cerebral atrophy, malformation, white matter signal changes, and cysts. CMV can mimic like cerebral palsy, malformations of the brain, demyelinating disorders, and calcified leukoencephalopathies like Aicardi-Goutières syndrome.

Keywords

- cytomegalovirus
- congenital
- developmental delay
- India
- central nervous system

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Introduction

Cytomegalovirus (CMV) is an omnipresent herpesvirus. It spreads by close contact through saliva, blood, breast milk, genital secretions, or urine. It has been seen to infect up to 90% of the United States population. It remains latent in monocytes and granulocytes for the lifetime.¹⁻³ Yearly approximately 20,000 to 40,000 infants in the United States are born with congenital CMV infection, corresponding to an incidence of 0.6 to 0.7% of deliveries, thus, making CMV the most common congenital viral infection.⁴⁻⁷ In various serological surveys in India, an incidence of 80 to 90% seropositivity with CMV IgG is shown in mothers.⁸ However, data regarding the frequency and various neurological manifestation of congenital CMV from India are lacking and commonly mistaken for other neurological disorders. The overall incidence of congenital CMV ranges from 0.5 to 3.0% in all live births.⁹ Most children (approximately 85–90%) do not have clinical findings at birth (asymptomatic CMV infection).^{10,11} The CMV infection, can present with symptoms in the newborn period or with long-term neurodevelopmental sequelae. According to two large meta-analyses, congenital CMV presented symptomatically in 11 to 12.7% of all neonates.^{4,5} Some prospective studies have shown that approximately half of the children born with asymptomatic infection will develop sensorineural hearing loss (SNHL), intellectual disability with intelligence quotient less than 70, and microcephaly.^{4,12} Congenital CMV infection is commonly mistaken for other causes of developmental delay like cerebral palsy, leukodystrophies, and malformations. Hence, it becomes important to estimate the neurological (both clinical and radiological) key points which will aid early diagnosis, treatment, and rehabilitation to prevent morbidity and mortality. The present study was undertaken with objectives to estimate the neurological (both clinical and radiological) profile of congenital CMV-infected cases in a tertiary care hospital in South India.

Methods

This was a retrospective chart review of the clinical and radiological profile of children with congenital CMV infection, presenting to a tertiary care hospital in South India from January 2018 to February 2020. Children aged between day one and 18 years were included. Congenital CMV was defined as IgM (immunoglobulin M) positive status for CMV, and/or urinary CMV positive status by polymerase chain reaction (PCR) method and those with clinically suspected static encephalopathies with CT scan (computed tomography) showing periventricular calcification after ruling out other secondary causes, were included in the study. Data regarding the age of presentation, sex, presenting complaint, consanguinity, family, birth, and developmental history, and examination findings were recorded from computer-based data. Relevant investigations that were done were noted. The laboratory investigations for CMV by IgM titers and urinary PCR were documented. Neuroimaging with magnetic resonance imaging (MRI) brain/

CT brain/ultrasonography (USG) cranium was traced. In the absence of any information, parents were contacted telephonically and history, investigations collected. Data were collected on a predesigned pretested proforma, analyzed, and presented in frequencies. Ethical clearance was obtained from the Institutional Ethical Committee.

Results

Forty-two cases from January 2018 to February 2020 were included in the study aged between day one and 18 years. Various clinical features are shown in **Table 1**. Mean age at presentation was 2.9 years. Female preponderance was present with females being 57%, and female to male ratio of 1.3:1. Consanguinity was seen in 19% of the cases. Serological markers showed, CMV-IgM positivity in 14 cases (33.33%), urinary PCR for CMV was positive in 21 cases (50%). The clinical diagnosis was done in seven cases (16.66%).

Neuroimaging was done in all cases. CT brain was done in 15 cases and MRI brain was done in 36 cases. In nine cases both CT and MRI were done, as the initial CT scan was

Table 1 Clinical features of congenital cytomegalovirus infections

Parameter	Frequency in figures (percentages)
Maternal fever with rash	05 (11.90)
Intra uterine growth retardation (IUGR) babies	08 (19.04)
Neonatal encephalopathy	04 (09.52)
Neonatal pneumonitis	01 (02.38)
Developmental delay	34 (80.95)
Seizures	14 (33.33)
Generalized	09 (21.42)
Myoclonic jerks	03 (07.14)
Focal seizures	02 (04.76)
Dysmorphism	07 (16.60)
Microcephaly	39 (92.85)
Skin rashes: petechiae/purpura	03 (07.14)
Anemia	38 (90.47)
Jaundice	04 (09.52)
Pyramidal signs	34 (80.95)
Hemiplegia	04 (09.52)
Hepatosplenomegaly	03 (07.14)
Ocular abnormality	06 (14.02)
Strabismus	03 (07.14)
Cataracts	02 (04.76)
Chorioretinitis	01 (02.38)
Sensorineural hearing loss	24 (57.14)
Bilateral	16 (38.09)
Left	03 (07.14)
Right	05 (11.90)

Abbreviation: IUGR, intra uterine growth retardation

Table 2 Neuroimaging findings of CT scan and MRI of brain

Finding on imaging	Frequency (percentages)
Periventricular calcification	33 (78.57)
Ventricular dilatation	23 (54.76)
Cortical atrophy	29 (69.04)
Migration abnormality	11 (26.19)
Pachygyria/agyria	06 (14.28)
Lissencephaly	05 (11.80)
Dysmyelination	05 (11.90)
Temporal lobe cysts	02 (04.76)
Cerebellar hypoplasia	02 (04.76)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

normal, and strong clinical suspicion of central nervous system involvement entailed a further MRI. The details are summarized in ►Table 2. Periventricular leukomalacia and cerebral atrophy were commonest findings.

Discussion

CMV infection is the most common cause of congenital viral infection in the Western world affecting 0.5 to 2.4% of newborns. Neurological signs include cognitive, motor impairments, SNHL, and chorioretinitis.^{13,14} Neuroimaging is a useful aid in diagnosis in older children in whom serology and PCR can be normal.¹⁵ In this retrospective review of 42 cases, the mean age of presentation was 2.9 years, with a female preponderance. Millichap et al reported a mean age of 20 months at presentation.¹⁶ The commonest mode of presentation was a developmental delay with pyramidal signs, as seen in 80.95% of the cases. This finding was much higher than the results of 10% as seen by Preece et al, Hanshaw and Dudgeon, and Reynolds et al.¹⁷⁻¹⁹ Ninety percent of these children had cerebral palsy in a study by Boesch et al.²⁰ Seizures were seen in 33.33% of the cases, which was similar to Millichap et al, who reported 37% seizure incidence.¹⁶ The maternal febrile illness was seen in 12%, in contrast to 54.8% as seen by Munro et al.²¹ The incidence of intrauterine growth restriction (IUGR) was 19%, which contrasted with a study done by Boppana et al where incidence was documented in 50% of the infants.²² Microcephaly was seen in 93% of children, whereas Boppana et al and Bale Jr et al deduced 53 and 70% incidence in their studies, respectively.^{22,23} Skin lesions like purpura/petechiae were seen in 7% of the cases. However, it was a major finding of up to 76% in a study by Boppana et al.²²

Anemia was a common finding in our study (90%), which was similar to Pemde et al, where anemia was documented in 89% of children.²⁴ Incidence of jaundice and hepatosplenomegaly was 9 and 7%, respectively. The incidence of jaundice and hepatosplenomegaly was 22 and 66%, respectively in a study by Gandhoke et al.⁸ Ocular abnormalities in the form of strabismus, bilateral cataracts, and chorioretinitis were

noted in 14% of children. This was similar to a study done by Coats et al, where ocular abnormalities were seen in 22% of the cases, but predominant causes were optic atrophy, macular scars, and cortical visual impairment. Strabismus was seen in 29% of their cases.²⁵ SNHL was seen in 57% of children in our study. The incidence of SNHL is reported to vary from 9 to 50%.¹⁷ Up to 30% rate of SNHL is seen in symptomatic infants at birth.²⁶ Bernard et al showed hearing abnormalities in 92% of the cases, bilateral in 33% and partial with unilateral in 23%.²⁷

Neuroimaging showed periventricular calcification to be the most common finding followed by cerebral atrophy, ventricular dilatation, migration abnormalities in the form of polymicrogyria/agyria and lissencephaly. Dysmyelination, temporal lobe cysts, and cerebellar hypoplasia were fewer common findings. Manara et al found white matter changes to be the commonest followed by ventriculomegaly in 64%, migration disorders in 43%, hippocampal dysplasia in 43%, and cerebellar hypoplasia in 28%.²⁸ Dilated lateral ventricles (100%) and subarachnoid space (80%), oligo/pachygyria (80%), delayed myelination (70%), periventricular cysts (60%), and intracerebral calcification in 10% were findings in a study by Boesch et al.²⁰

The limitations of this study are that it is retrospective in nature and confirmatory tests like CMV IgM antibody and PCR cannot be done in all children due to late presentation because of which both can be false negative. However, this is the largest study in this decade that shows that CMV continues to be a common problem in India and can present to neurologists with various clinical and radiological features that can be mistaken for various other neurological conditions.

Conclusion

Clinically, congenital CMV can present with global developmental delay, low birth weight, neonatal cholestasis, microcephaly, seizures, anemia, visual problems like cataract and chorioretinitis, SNHL, and hepatosplenomegaly. Radiologically congenital CMV infection should be considered in cases of bilateral periventricular and basal ganglia calcifications, white matter signal changes mimicking leukodystrophies, calcified cystic leukoencephalopathy especially in case of temporal and frontal lobe cysts, and malformation of the brain with associated calcifications.

Authors' Contributions

V. K. W. contributed toward supervision, guidance, and the review of the manuscript. P. K. was involved in the management of the child and the preparation of manuscript. D. K. V. has given valuable inputs in the management of this child.

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Conflict of Interest

None declared.

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