Congenital CMV infection, An imaging perspective: A case report.

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Abstract:

Brain imaging is most important tool for the accurate diagnosis of various congenital CNS infections. Infections of the foetal nervous system results in spectrum of findings that depends upon the inciting agent and the timing of infection. As a general rule earlier the infection, more severe are the findings. Congenital CMV infection can be diagnosed with accuracy with its specific features identified on brain imaging. We present a case of congenital CMV infection in an 8-months-old boy, its clinical presentation, imaging findings and laboratory reports. Specific literature review is included in order to point out major goals achieved in the diagnosis and prognosis of congenital CMV infection.

Key Words: CMV, Congenital, Cytomegalovirus, Neuroimaging.

Case Report:

An 8-months-old male boy of 2nd issue of non-consanguinous parents was brought to the paediatric OPD by the parents for the chief complaints of baby not responding to them. Patient had not achieved neck holding yet. Parents also gave history of two episodes of seizures at the age of 7 months, which were generalized tonic clonic type, not preceded by fever and lasted for 1 minute, followed by post-ictal unconsciousness.

The mother G2P1L1A0 had an uneventful antenatal period. Baby was delivered in hospital at term by a normal vaginal delivery with a birth weight of 2.1 Kgs. Baby cried immediately after birth and there was no history of NICU/ PICU stay. Baby was immunized normally till date. Family history was unremarkable.

On examination the patient had increased muscle tone in bilateral lower limbs and microcephaly.

The baby was subjected to USG brain, followed by MRI and NCCT brain. On intracranial USG, ventriculomegaly was evident as well as multiple tiny puctate echogenic foci with post-acoustic shadowing along periventricular as well as parietal cortical-subcortical white matter.

On MRI Brain, there was evidence of multiple punctate linear and curvilinear foci of intra-cranial calcifications as evidenced by blooming on FFE images along ependymal surface of bilateral lateral ventricles, bilateral parietal occipital lobes in cortical and sub-cortical locations as well as few in bilateral cerebellum, mid brain and

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frontal-occipital areas. These findings were later confirmed on NCCT Brain study.

MRI also revealed ventriculomegaly involving all four lateral ventricles, periventricular cyst formation and neuronal migration anomaly in the form of pachygyria (Lissencephaly Spectrum).

These findings were suggestive of the congenital CNS infection- congenital cytomegalovirus infection, which was later confirmed with the serum CMV specific anti-IgG antibody titers.

Discussion:

Neonatal CNS infections, whether acquired *in utero* (congenital), intrapartum or postnatally remain an important cause of acute and long-term neurological morbidity. Pathologic features and associated imaging patterns depend upon the stage of development of the CNS, the affinity of a specific infective agent for a specific CNS cell type, and the ability of the host to respond to that insult.[6] Neuroimaging is crucial in visualization of typical & atypical lesion patterns, which not only allows for a rapid diagnosis but also subsequent therapeutic decisions.[1, 6]

The mechanism of infection and damage is also different amongst the infectious agents, leading to more specific imaging and pathologic appearances. Viruses, for example, tend to produce a selective necrosis of specific cell types, whereas bacteria and fungi are less selective. Also, different patterns of calcifications on CT or pathologic specimens are typical for the various STORCH (syphilis, toxoplasmosis, rubella, CMV, human immunodeficiency virus (HIV) and herpes simplex) infections.

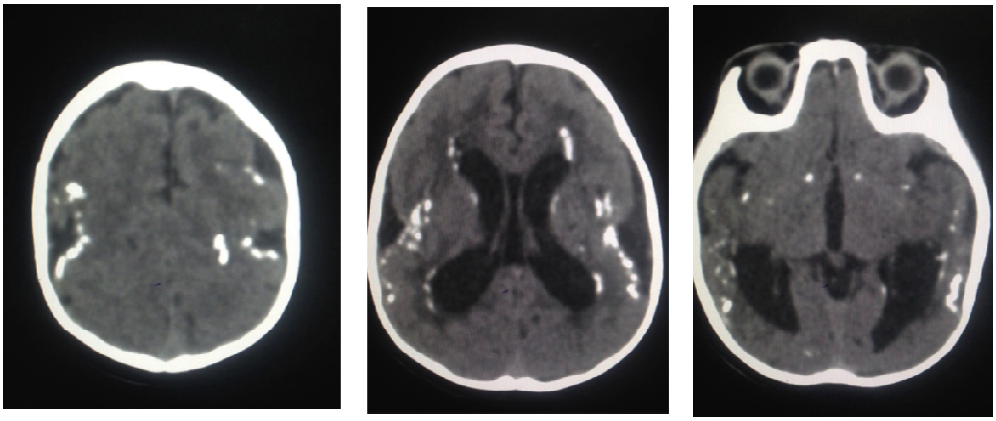
Congenital CMV infection is one of the most common congenital viral infections in the world. Foetal infection results from transmission of the virus across the placenta and is particularly common in women who experience primary infection during pregnancy. Approximately 7%–10% of neonates with CMV infection exhibit symptoms of cytomegalic inclusion disease such as microcephaly, hepatosplenomegaly, thrombocytopenic purpura, hearing loss, and intracranial calcifications. Other symptoms include low birth weight, hepatitis, pneumonitis, and neurologic and hematologic abnormalities. Foetuses that are infected at a younger gestational age generally have a poorer outcome than those infected at a later stage of development. Infections that occur postnatally are less severe, and these patients may even be asymptomatic. Sensorineural hearing loss is common in children with congenital CMV infection and is present in 10%–15% of infected infants who were symptomatic at birth. Asymptomatic infants develop hearing loss less often than do infants who were symptomatic at birth, but asymptomatic infants account for most cases of CMV-related sensorineural hearing loss because of the large number of these patients.[2]

Cranial ultrasonography (USG), magnetic resonance (MR) imaging, and computed tomography (CT) have been used for diagnosis and characterization of congenital CMV infection, and each modality has its advantages and disadvantages.[2]

Intracranial calcification is a common finding on neuroimaging in paediatric neurology practice. In approximately half of all cases the calcification occurs in damaged, neoplastic, or malformed brain. For the large number of other disorders in which intracranial

calcification occurs, no common pathogenetic mechanism can be suggested. Congenital infection, particularly with cytomegalovirus, accounts for a significant proportion of all cases. However, some genetic diseases, in particular Aicardi-Goutières syndrome, Band-like calcification, and RNASET2-related disease, may mimic congenital infection; therefore, a full consideration of the radiological and clinical features is necessary before concluding that congenital infection is the cause.[3]

Image 1: NCCT Brain showing intracranial calcifications, predominantly in periventricular location



In spite of a relative paucity of published CT data, characteristic features of intracranial calcification in CMV can be defined. Calcification is often thick and chunky, truly periventricular, in the ependymal or subependymal region, and seen as spots or lines or, on occasions, completely outlining the ventricles. Spots of calcification in the basal ganglia, white matter, or cortex may occur, and are often asymmetrical.[3] Elsewhere, including within the basal ganglia and brain parenchyma, calcification generally appears faint and punctate, a characteristic that helps distinguish basal ganglia calcification due to congenital CMV infection from that due to other causes, which tends to be more florid. Although calcification is extremely common in patients with congenital CMV infection, it is not always present; an absence of calcification should not exclude a diagnosis of congenital CMV infection.[2]

Migrational abnormalities are a heterogeneous group characterized by an abnormal structure of the cerebral cortex. They are caused due to genetic causes.[2, 4] These disorders may occur during the stages of proliferation, migration, or organization of the cortex. The clinical manifestations of these disorders vary considerably, and they depend largely on the stage of arrest.[4] A variety of migrational abnormalities have been reported in patients with congenital CMV infection, and such abnormalities may be present in as many as 10% of patients. Lissencephaly, pachygyria, and diffuse or focal polymicrogyria are the most common migrational abnormalities. Schizencephaly is rare, and cortical dysplasia was described in one patient with congenital CMV infection and concomitant white matter disease.[2]

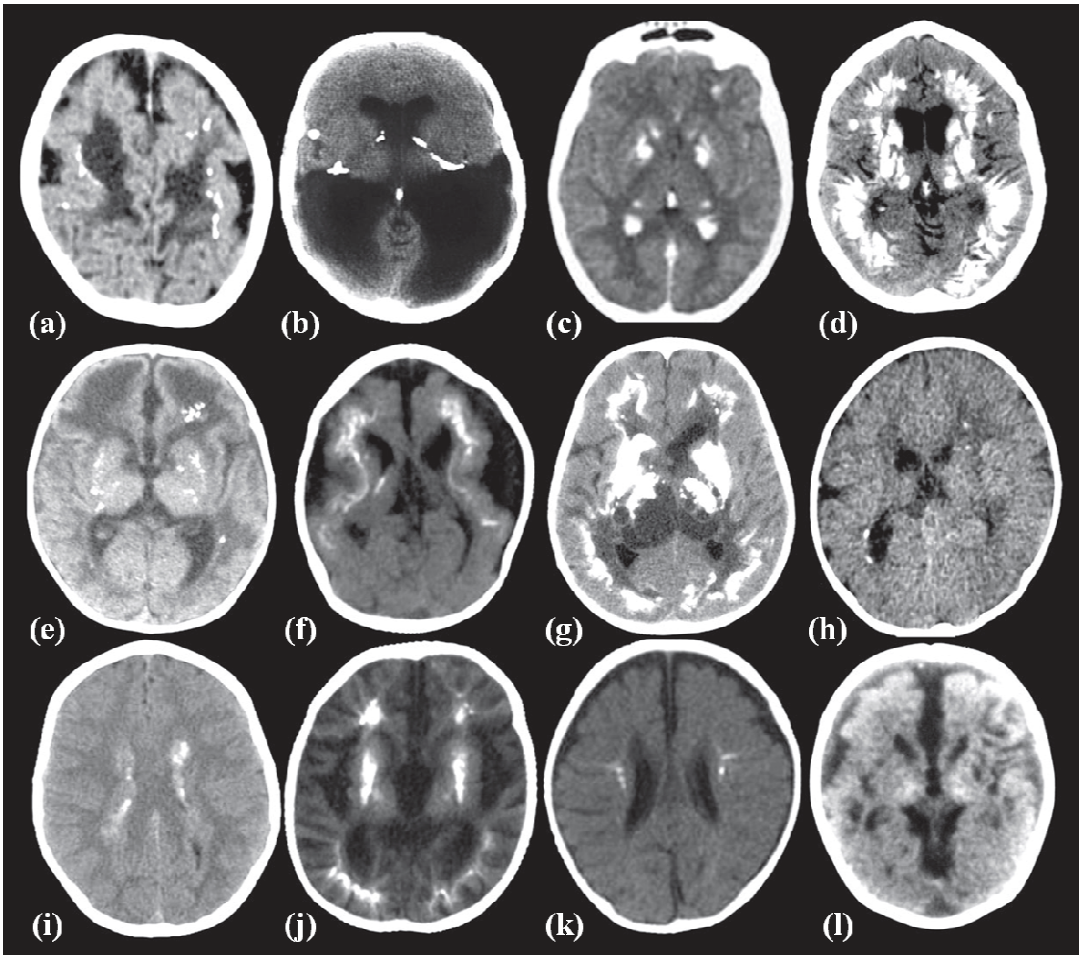


Image 2: Examples of intracranial calcification (ICC) patterns in specific diseases. (a) Congenital cytomegalovirus infection showing true periventricular and cortical calcification, and extensive cortical malformation. (b) Congenital toxoplasmosis demonstrating dense periventricular aggregates and hydrocephalus. (c) Hypoparathyroidism secondary to chronic iron toxicity in thalassaemia. Symmetrical calcification in globus pallidus, caudate, thalamus, and left frontal cortex. (d) Fahr disease: extensive symmetrical and predominantly grey matter calcification. (e) Classical Aicardi–Gouti_eres syndrome: calcification in basal ganglia and deep white matter with marked low density and swelling of frontal white matter. (f) Band-like calcification with simplified gyration and polymicrogyria secondary to OCLN mutations showing a malformed brain with frontoparietal polymicrogyria and linear or reticular calcification in the deep cortex. (g) Leukoencephalopathy with calcifications and cysts. Note that the calcification is largely in the grey matter, and is similar to that seen in some cases of Fahr disease in (d). There are, however, large cysts arising in the thalami. There is also low density of white matter indicative of leukoencephalopathy. (h) COL4A1 mutation showing spot calcification in the deep frontal white matter on the left and true periventricular calcification on the right. There are also features of periventricular leukomalacia. (i) Juvenile Alexander disease showing calcification within periventricular garlands. (j) Cockayne syndrome with widespread calcification in deep white matter, deep cortex, and basal ganglia in an atrophic brain. Calcification was not suspected from the MR appearances. (k) Infantile Krabbe disease showing calcification with the corona radiata. (l) Molybdenum cofactor deficiency demonstrating bilateral thalamic calcification in an atrophic brain with some cystic encephalomalacia.(Image curtsey: Livingston JH et al[3])

Image 3: Axial T2/FLAIR section showing Pachygyria

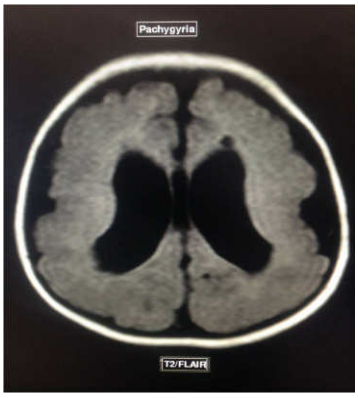
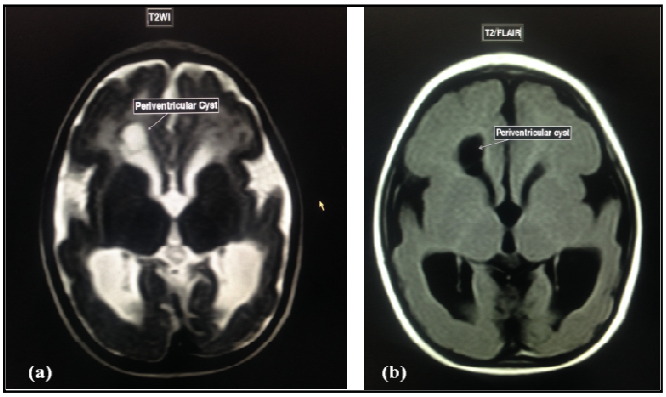


Image 4: Periventricular cyst (a) Axial T2WI (b) T2/FLAIR

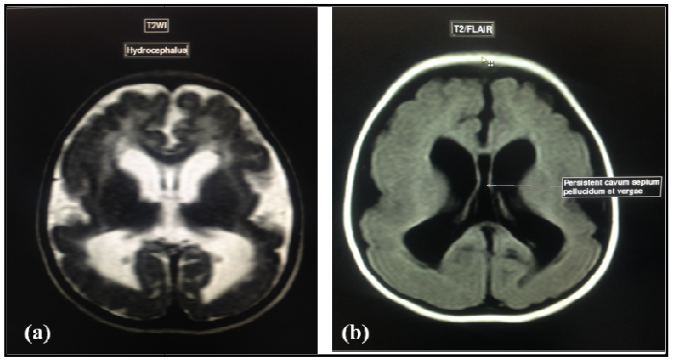


White matter abnormalities are common in those with congenital CMV infection, occurring in as many as 22% of patients. Delayed myelination is one manifestation of white matter disease in patients with congenital CMV infection. However, delayed myelination is nonspecific and may be seen in a variety of conditions. Disturbed myelination is more common in congenital CMV infection than generalized delayed or decreased myelination. White matter abnormalities may be the only imaging finding of congenital CMV infection in these children, and congenital CMV infection should be considered in the differential diagnosis of developmental delays and leukoencephalopathy. CMV-related encephalopathy is static and does not progress with time, a characteristic that may help distinguish congenital CMV infection from other progressive types of leukoencephalopathy.[2]

Periventricular cysts have been reported in patients with congenital CMV infection, and they may appear as cystic areas adjacent to the ventricles at CT, MR imaging, and US. Cysts have been reported in a variety of locations, but they are particularly common adjacent to the anterior temporal lobes, where they often are associated with white matter abnormalities. The differential diagnosis of leukoencephalopathy with anterior temporal cysts is very narrow and includes congenital CMV infection, leukoencephalopathy with subcortical temporal cysts and megalencephaly, and vanishing white matter disease.[2]

Other common but non-specific findings of congenital CMV infections includes cerebral atrophy, ventriculomegaly and lenticulostriate vasculopathy.[2]

Image 5: Hydrocephalus & Persistent cavum septum pellucidum (a) Axial T2WI (b) T2/FLAIR



The biochemical markers (Serum IgG and IgM) were performed for toxoplasma and CMV by capture ELISA method. The tests showed strongly positive Serum IgG titers for CMV infection and were negative for Toxoplasmosis. [Table 1,2]

Table 1 Test results for CMV Serum IgM and IgG

Test name	Result	Unit	Biological reference interval
Cytomegalo virus IgG	3.1	Index	<0.8: Negative ≥0.8 - ≤ 1.2: Equivocal >1.2: Positive
Cytomegalo virus IgM	0.6	Index	<0.8: Negative ≥0.8 - ≤ 1.2: Equivocal >1.2: Positive

Table 2 Test results for TOXOPLASMA Serum IgM and IgG

Test name	Result	Unit	Biological reference interval
Toxoplasma virus IgG	0.13	Index	<0.7: Negative ≥0.7 - ≤ 1.3: Equivocal >1.3: Positive
Toxoplasma virus IgM	0.37	Index	<0.8: Negative ≥0.8 - ≤ 1.2: Equivocal >1.2: Positive

Conclusion:

In conclusion, the presence of characteristic imaging findings such as intracranial calcification, migrational abnormalities, white matter disease, ventriculomegaly, and periventricular cysts may help diagnose congenital CMV infection in infants and children with neurodevelopmental deficits. In isolation, many findings of congenital CMV infection are nonspecific; however, patterns of abnormalities are indicative of the diagnosis.

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