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Leukoencephalopathy In A Child With Congenital Cytomegalovirus Infection

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Introduction:

Most of infected infants presenting with Cytomegalovirus (CMV) remain asymptomatic[1]. Symptoms include growth restriction, microcephaly, seizures, cerebral ventriculomegaly, chorioretin is, hepatitis syndrome, thrombocytopenia, anemia, and pneumonitis[2]. Approximately 5 to 10% of these infants manifest signs of serious neurological defects at birth, including deafness, mental retardation, blindness, microcephaly, hydrocephalus, and cerebral calcification[3,4]. In addition, 10 to 15% of congenitally infected infants who are asymptomatic at birth subsequently develop brain disorders such as sensorineural hearing loss.[5] One case of congenital CMV disease with developmental delay and leukoencephalopathy has been reported here.

CMV is the largest and most complex member of the Herpesviridae family of DNA viruses.[6] The virus is named for the intranuclear and intracytoplasmic inclusions seen with symptomatic disease, cytomegalic inclusion disease. CMV is highly species specific, and humans are the only known reservoir for disease.[7] Congenital CMV infection results from transplacental transmission of the virus during maternal viremia.[8] Although CMV affects most cell types, it has a special affinity for epithelial cells, ependymal cells lining the ventricles, the organ of Corti, and the neurons of the eighth cranial nerve.[9] Congenital CMV infection is more prevalent in underdeveloped countries and among lower socioeconomic groups in developed countries, where overcrowding is more common[10,11]. Current estimates indicate that approximately 8,000 children are affected each year with some neurological sequelae related to CMV infection in utero[12].

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Case Report:

R, a one year old girl of nonconsanguinous parents, presented in Centre for Neurodevelopment and Autism in Children (CNAC) in Bangabandhu Sheikh Mujib Medical University with the complaints of delay in development. She has no history of convulsion, jaundice, fever , rash, visual or hearing impairment. Mother was on regular antenatal check up. However, she had an episode of fever without rash in her first trimester. Her developmental history reveals that neck control at 10 months and she learned to sit with support at 12 month. Other domains of development were age appropriate. R was an alert girl, mildly pale, anicteric, OFC on 10th centile (46 cm), Length 70cm, Wt Â 3rd centile (7 kg). Eye and ENT were normal with no organomegaly. Neurological examination revealed normal except delay in motor development. Fundoscopic examination was normal.

Her investigations showed: Hb 10.1 gm/dl, TC- 12000/ cumm, Platelet 4 lac/cu mm, N- 25%, L- 65%, PBF- Anisochromia with anisocytosis. TORCH screening showed that CMV IgG was positive (titre- 150 U/ml). CT scan of brain was suggestive of leuko-encephalopathy followed by MRI of brain- suggestive of leukoencephalopathy. Then CMV DNA was done which revealed 72.51 copies/ml (by RoboGene HCMV DNA Quantification Kit).

She was treated with I/V Gancyclovir 5mg/kg/dose 12 hourly for 3 weeks. Weekly blood film, liver function test and renal function test were done. She completed the treatment regimen without any significant adverse effect and discharged from hospital. At the end of the treatment a repeat CMV DNA detection test was done which revealed no detected CMV in blood. She came for follow up 3 times in next 12 months in the outdoor. Now she is well, can walk without support and speak a few words. Her repeat MRI revealed no improvement though her hearing assessment and psychological assessment was normal.

Fig.-1

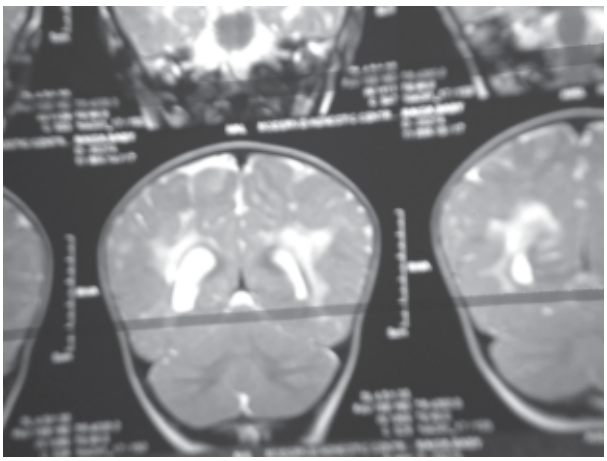

Fig.-2

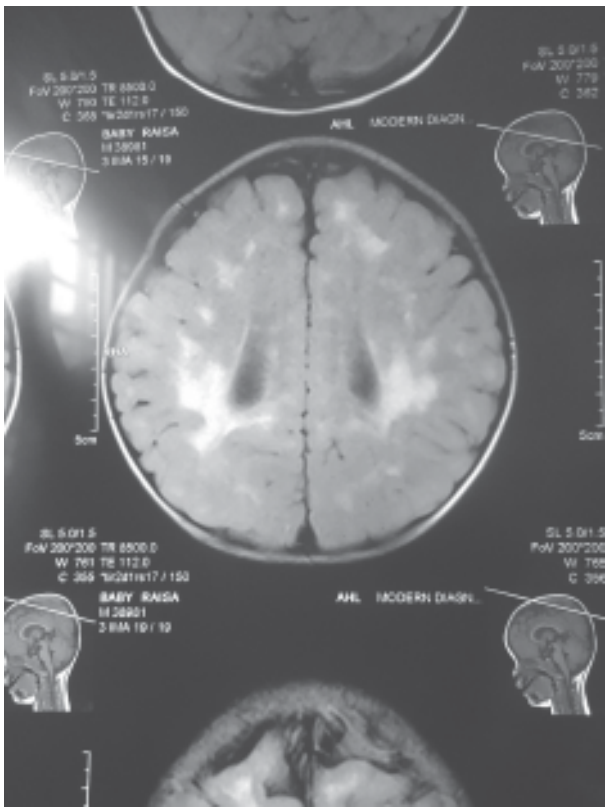

Fig.-3

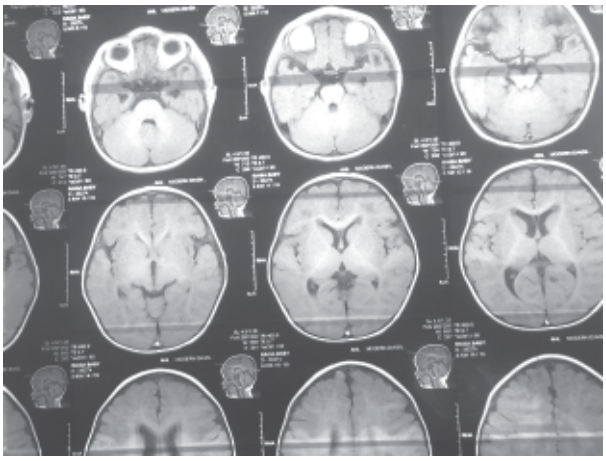

Fig.-4

Discussion:

Cytomegalovirus (CMV) has emerged as the most important cause of congenital infection globally. Congenital CMV infection may lead to hearing, cognitive, and motor impairment. In the US approximately one per cent of all neonates excrete CMV, of which 10% will be severely affected with a wide range of symptoms[13,14,15]. The diagnosis of congenital CMV sometimes produce dilemma as a good number of patient is asymptomatic . However, the rapid and correct diagnosis of congenital CMV infection in neonates/infants is very important to advocate the right therapy and proper management of the case. ELISA is the most common method employed for detection of CMV specific IgM class antibodies to establish current or congenital CMV infection. CMV afflicted babies are known to shed virus in various bodily secretions especially urine, blood and throat swab, in some cases, for months and years. Detection of cytomegalovirus from clinical samples like urine and blood, by PCR, also provides important information about the excretion of virus in the infected baby and prediction of the symptomatic disease[16].

In a study conducted in India, among clinical manifestations reported in the babies, hepatosplenomegaly was the most common feature. Other frequent symptoms were developmental delay, convulsions, pneumonitis, visual and hearing impairment. Intracranial calcification was also reported

in two positive cases[16]. Whereas, in a study conducted in Banglasdesh the presenting neurologic features were impairment in speech, cognition, motor delay, vision and hearing problem, seizures, microcephaly[17]. The child in this case report presented with unexplained developmental delay without any other manifestation. So in any case of delay in milestone, there should be search for CMV infection.

This case was diagnosed on the basis of high titre of IgG, positive CMV DNA and neuroimaging changes. In one study conducted in India, twenty seven serum samples, out of 125 tested (21.6%), were positive for CMV IgM antibodies indicating serological evidence of exposure to in-utero/perinatal CMV infection[18]. It has been suggested that therapy should be initiated in asymptomatic high-risk patients based on diagnostic test results indicating primary CMV infection (blood CMV DNA) [19].

Trials regarding anti-viral treatment of the symptomatic babies with Ganciclovir have shown that the infected babies' show positive response to the drug. 18 In Bangladesh many symptomatic infants might remain unreported and thereby remain unscreened for CMV infection and the true impact of the congenital CMV infection still remains under-appreciated.

This child had leukoencephalopahy in both CT scan and MRI of brain.In previous studies frequent neuroimaging findings are intracranial calcifications (in 33%–54% of patients), ventriculomegaly (in 10%–37% of patients), white matter abnormalities (in 0%–22% of patients), neuronal migration abnormalities (in 0%–10% of patients), and an extensive destructive encephalopathy (in 5%–13% of patients)[20] In 20%–30% of patients, no abnormalities are found .Williamson et al observed white matter abnormalities in 14% of the children with asymptomatic congenital CMV infection in their study, whereas no abnormalities were demonstrated in 86% of the children. None of the children had calcifications or ventriculomegaly[21]. In one study in Netherlands of 152 patients with static leukoencephalopathy of unknown origin CMV status was done and 12 patients were positive. They reported a distinct pattern of MR imaging abnormalities in a group of patients with neonatally asymptomatic but proved congenital CMV infection[22]. So leukoencephalopathy might be an important finding in CMV.

This child was treated with Inj Gancyclovir for a period of 3 weeks according to one report.[23] Although, there have been recommendations of gancyclovir for 2- 7 weeks duration, here duration was for 3 weeks to avoid severe side effects like bone marrow depression (chiefly neutropenia reported 2/3 of the patients), thrombocytopenia, anaemia, kidney and liver toxicity with laboratory abnormalities[24].

Conclusion:

A child with CMV infection may present with only developmental delay clinically and neuroimaging might reveal leukoencephalopathy. Treatment with gancyclovir results in clinical improvement.

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