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Case Series

Paediatrics Section

Effects of Perinatally Acquired Cytomegalovirus Infection on Growth Hormone Axis

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ABSTRACT

Cytomegalovirus (CMV) is one of the most common causes of perinatally acquired infection worldwide. It affects almost every organ system with varied type of clinical manifestation. In this case series, effect of perinatally acquired cytomegalovirus infection was studied on relatively unexplored area i.e, on growth hormone axis. Effect of standard antiviral treatment was also studied in these children. Five children were diagnosed to have perinatally acquired cytomegalovirus infection and it was found that all of these children were suffering from growth hormone deficiency (as evidenced by low insulin-like growth factor 1 and insulin-like growth factor binding protein 3 level as well). Some of the children were also found to have other endocrine manifestations like hypothyroidism and hypoglycaemia. They were treated with intravenous Ganciclovir followed by oral Valganciclovir and most of them responded well.

Keywords: Endocrine manifestation, Hepatosplenomegaly, Insulin growth factor

INTRODUCTION

Cytomegalovirus (CMV) is one of the most important agents causing perinatal infection. Most commonly, symptomatic CMV infection is acquired congenitally through transplacental transmission or perinatally during birth or through breast milk [1]. CMV infection can also occur later in life, but mostly they remain asymptomatic (in 90% cases) in normal individual [2]. The manifestation of congenital CMV infection is manifold, and it affects almost every system of our body. The most common features in a case of congenital CMV are hepatosplenomegaly, direct hyperbilirubinaemia, petechial haemorrhage, microcephaly, Intrauterine Growth Restriction (IUGR) [3]. This case series highlighted a relatively unexplored area of possible association of the disease and suppression of the growth hormone axis, as manifested by reduced serum Insulin like Growth Factor 1 (IGF 1) and Insulin-like Growth Factor Binding Protein 3 (IGFBP 3) [4], and by little to no response of growth hormone level to various challenge tests. All of these five cases presented within the first 4 months of their chronological age, with different clinical pictures and various endocrine manifestations. But one thing was common in them, that is, suppression of the growth hormone axis.

CASE SERIES

Case 1

A 3-months-old (chronological age) male child was admitted in the hospital with complaints of not gaining weight along with huge hepatosplenomegaly. Previously the child was admitted in Neonatal Intensive Care Unit (NICU) because of prematurity (33 weeks), low birth weight (1.8 kg), perinatal asphyxia {Hypoxic-Ischaemic Encephalopathy (HIE) stage 2},, sepsis, shock, and had required ventilator support [Table/Fig-1]. Magnetic Resonance Imaging (MRI) brain had been done which revealed bilateral haemorrhagic infarct in temporoparietal region. During discharge from NICU at 17th day of life child had a weight of 2 kg and length of 45 cm. At that time child did not have hepatosplenomegaly.

On admission, the child had a weight of 2.7 kg and a length of 56 cm, conjugated hyperbilirubinaemia, anaemia, and had recurrent episodes of hypoglycaemia in absence of sepsis. Blood sample for hormonal assay were collected during two different occasions of hypoglycaemia revealed low insulin (0.16 µU/mL), borderline cortisol (5.1 µg/dL), and low growth hormone (0.7 ng/mL) levels. Serum IGF1 and IGFBP3 values were also significantly low [Table/Fig-1]. Child also tested positive for CMV Immunoglobulin

Cases	Presenting age (in months)/ Gender	Birth history	Nutritional status at presenting age	CMV IgM (Index) (≥1.0 reactive)	Urinary CMV DNA PCR (copies/mL)	Growth hormone (N ≥5 ng/mL) (stimulation)	IGF 1 (N=55-327 ng/mL)	IGF BP3 (N=0.7-3.6 µg/mL)	Other associated co-morbidities
Case 1	3/male	PT, LBW (1.8 kg), NVD, HIE Stage 2	Failure to Thrive	8.39	18000	0.7 (Hypoglycaemia)	16.9	0.58	Cholestatic jaundice, Secondary Hypothyroidism, Cortisol deficiency
Case 2	3/male	2.8 kg, NVD, uneventful neonatal period	Normal Nutritional status	6.37	724000	0.9 (Clonidine at 1 hr)	32.4	<0.5	Hypocalcemia, Hypovitaminosis D3
Case 3	4/male	2.65 kg, NVD, uneventful neonatal period	Normal Nutritional status	1.05	1500000	1.1 (Clonidine at 1 hr)	22.3	0.62	Autoimmune haemolytic anemia, Central Hypothyroidism
Case 4	2/male	3.1 kg, LUCS, uneventful neonatal period	Normal Nutritional status	2.1	22000	1.3 (Clonidine at 1 hr)	<15	<0.5	Secondary HLH
Case 5	4/male	Home delivery, Average sized baby	Failure to Thrive	3.24	20000	0.9 (Hypoglycaemia)	48.1	0.69	Tuberculosis

[Table/Fig-1]: Clinical settings and laboratory values.
N: Normal value: PT: Preterm: LBW: Low birth weight: NVD: Normal vaginal delivery: LUCS: Lower uterine caesarean section

M (IgM), and he had a urinary CMV Deoxyribonucleic Acid (DNA) Polymerase Chain Reaction (PCR) of around 18000 copies/mL. The mother was diagnosed with hypothyroidism during 1st trimester, and the child was also diagnosed to have secondary hypothyroidism for which he was started on levothyroxin supplements. MRI was repeated, which showed sequelae of congenital infection, but there was no definite involvement of sella or parasellar structures. Retinal examination was normal.

The patient was started on hormone replacement therapy with hydrocortisone and thyroxin. The child was also treated with Inj. Ganciclovir for 4 weeks followed by oral Valganciclovir for next 4 months. Subsequently there was a gradual improvement of the general condition of the patient along with complete resolution of hypoglycaemia. His growth parameters were followed at 6th, 9th and 12th month (chronological age) and his weight and height were 4.2 kg and 61 cm, 5.8 kg and 67 cm, 7.1 kg and 71 cm, respectively.

Case 2

A 3-month-old male child presented to emergency with three episodes of generalised tonic clonic seizure within last 24 hours. The child was delivered vaginally at term with a birth weight of 2.8 kg and had uneventful neonatal period [Table/Fig-1]. Management was done as per protocol and he was found to have low serum calcium level, which was subsequently corrected by calcium and vitamin D3 supplementation (child also had low vitamin D3, and borderline elevated alkaline phosphatase). The child had a weight of 5.2 kg and length of 60 cm at the time of admission. There was hepatosplenomegaly, and both CMV IgM and Urinary CMV DNA PCR (7.24 lakh copies/mL) were positive. Retinal examination was normal. Accordingly, the child was started on Inj. Ganciclovir for three weeks, later to be replaced by oral Valganciclovir for next three months. Serum IGF1 and IGF-BP3 were also low [Table/Fig-1], and growth hormone level after clonidine challenge test was 0.9 ng/mL. The child had a weight of 9.2 kg at one year of age and sizes of liver and spleen were reduced almost to normal.

Case 3

A 4-month old male child presented with severe anaemia, jaundice, and hepatosplenomegaly. The child was delivered vaginally at term with a birth weight of 2.65 kg and neonatal period was uneventful [Table/Fig-1]. Investigations revealed autoimmune haemolytic anaemia (high reticulocyte count and positive direct coombs test). He also had three episodes of convulsion during hospital stay. His nutritional status was normal at the time of admission (weight was 4.9 kg and length was 61 cm). The mother was diagnosed with hypothyroidism during first trimester, and the child's thyroid profile revealed central hypothyroidism, with low levels of FT4 and TSH (0.21 µIU/mL). The child also tested positive for CMV IgM and had a high urinary CMV DNA load (15 lakh copies). Clonidine stimulation test was done to assess growth hormone levels, which were found to be consistently low. Serum IGF1 and IGFBP3 were also low [Table/Fig-1]. Retinal examination was normal.

The child was put on Ganciclovir initially for three weeks followed by oral Valganciclovir for next four months. His liver function returned to normal by six months of age. Child had maintained normal growth parameters throughout the period (weight was 8.9 kg and length was 72 cm at one year of age). Hepatosplenomagaly also regressed considerably at one year of age. Also, during this one year of follow-up, he maintained a normal haemoglobin level.

Case 4

A 2-month-old male child presented with fever for four days along with watering of eyes. Examination revealed significant pallor and huge hepatosplenomegaly. Mother had a history of fever with rash in first trimester. The child was delivered at term by caesarean section with a birth weight of 3.1 kg [Table/Fig-1].

At the time of admission, the child had a weight of 4.8 kg and a length of 58 cm. Investigations revealed positive CMV IgM [Table/Fig-1], and urinary CMV DNA PCR showed 22000 copies. Serum IGF1 (<15 ng/mL) and IGF-BP3 (<0.5 µg/mL) were also low [Table/Fig-1]. Clonidine stimulation test also showed low level of growth hormone. Retinal examination was normal. The child was treated with Inj. Ganciclovir for four weeks in view of recurrent blood transfusion within a short span. Initially, the child responded well, fever subsided, and the blood transfusion requirement went down, size of the liver and spleen also started to reduce. The child was discharged in stable condition with oral Valganciclovir for the next four months. But after about three months, the child was readmitted with features suggestive of Haemophagocytic Lymphohistiocytosis (HLH) including fever >5 days, splenomegaly, pancytopenia (haemoglobin was 5.4 gm/dL, total leucocyte count 1800/cumm with 10% neutrophil, platelet 60000), high ferritin, high triglyceride, low fibrinogen. Genomic sequencing was done and it showed the familial form of HLH. The child was started on steroid and other drugs as per protocol, but he succumbed at the age of 9 months.

Case 5

A 4-month-old male child presented with complain of not gaining weight and length. There was history of gross weight loss and intermittent low-grade fever over last two months. The child was delivered at home and as per parents, he was born with average weight. There was no documentation about his nutritional status in his 1st 4 months. On examination, all the anthropometric indices were well below 3Z Score as per World Health Organisation (WHO) growth chart, and there was moderate hepatosplenomegaly. The child also experienced a few episodes of hypoglycaemia during the hospital stay. All episodes were asymptomatic and managed by allowing breast feeding. Investigations revealed presence of anaemia, and blood culture showed growth of *Staphylococcus aureus*.

He was started on F-75 starter diet along with appropriate antibiotics (vancomycin and amikacin for 14 days) and supportive treatment (vitamin A, D, K, B-complex including folic acid, potassium, magnesium sulphate as per management protocol of severe acute malnutrition). Chest X-ray showed few patchy infiltrates, and gastric lavage revealed very high load of *Mycobacterium tuberculosis*, for which the baby was started on antitubercular drug. The mother was also tested positive for tuberculosis. CMV IgM was positive and subsequently, urinary PCR showed around 20,000 CMV DNA copies/mL. Serum IGF1 and IGF-BP3 were found to be low [Table/Fig-1]. Blood sample for growth hormone obtained during hypoglycaemic episodes also found to be low. Retinal examination was normal. The child was also started on Ganciclovir for three weeks and then shifted to oral Valganciclovir. During the hospital stay, he started to gain weight and gradually become free of symptoms. The child was discharged in stable condition, but unfortunately, he was lost to follow-up. All the cases have been briefed together in [Table/Fig-1].

DISCUSSION

In the present case series, it was seen that CMV infection manifested as a myriad of clinical signs and symptoms. The patients were all male children, aged 2-4 months, and only one among the five patients hada history of prior hospital admission, before this diagnosis of CMV infection was made. Rest of the four patients were well from birth till the onset of the present disease. All the children had hepatosplenomegaly and anaemia, while others showed isolated findings like jaundice (cholestatic/haemolytic), microcephaly, classical MRI findings.

However, all these patients were also found to have a depressed growth hormone axis, as evidenced by a low level of serum IGF1 and IGF-BP3, which are independent markers of the level of growth hormone. Growth hormone challenge tests by induced hypoglycaemia (done in two patients) or by clonidine suppression

(done in three patients), which revealed persistently low growth hormone levels in all. Some other endocrine manifestations were-hypothyroidism in two children, recurrent hypoglycaemia not attributable to other causes in two children, altered vitamin D3-calcium metabolism in one child, and low serum cortisol level in one child.

Cytomegalovirus is known to cause intrauterine growth restriction in neonates [5], hence it can be hypothesised that similar action can also be exerted in the extrauterine life also. However, probably there were only two documentations of panhypopituitarism associated with CMV infection in children of similar age group [6,7] and some in immunocompromised adults [8]. Chan U et al., described a 2-month-old child with septo-optic dysplasia and acquired CMV infection presented with cholestasis, hepatosplenomegaly, panhypopituitarism and growth retardation. After treatment with Ganciclovir and hormone replacement therapy, there is improvement in cholestasis and growth rate [6]. Hara K et al., described a term infant with congenital CMV infection presented with recurrent hypoglycaemia and panhypopituitarism. This child also responded well with Ganciclovir and hormone replacement therapy [7].

As for the other endocrine manifestations, there are sporadic reports of each being associated with congenital CMV [9-11], but the data is inadequate to draw any conclusion. Tuli G et al., described two newborns with congenital hypothyroidism with congenital CMV infection [9]. Jayamanne MDCJP et al., described a newborn with congenital CMV infection with recurrent hypoglycaemic episodes [10]. Dinleyici EC et al., described two infants with CMV-associated adrenal insufficiency in childhood. Both of them responded well to appropriate adrenal substitution therapy and Ganciclovir [11].

Question remains as to whether these cases were congenital CMV infection or acquired. None of the children except one had any complications in the neonatal period, and the earliest age of presentation (except in one) was two months. CMV IgM may remain elevated for several months, thereby rendering the exact localisation of the time of infection difficult [12]. However, high values of CMV DNA copies isolated from urine via PCR is much stronger evidence of current infection, and may point more towards an acquired infection rather than a congenital one [13,14]. However, another contradictory factor is that the features like hepatosplenomegaly, anaemia is more common in congenital infections, as are the chances of long-term sequelae.

CONCLUSION(S)

To conclude, it can be stated that all the five infants with CMV infection discussed, showed growth hormone suppression, of which three had visible growth restriction. Once treatment with Ganciclovir was started, most patients responded well, while one required hormone replacement therapy. Whether this hormonal manifestation is caused by the CMV itself, or there are other confounding factors can only be concluded by further research into the pathophysiology of the disease. So, whenever any symptomatic CMV infection was found, possible suppression of growth hormone axis should be kept in mind and appropriate decision to be taken regarding treatment.

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