

## Etiological Role of Cytomegalovirus in Type 1 Diabetes Mellitus

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### ABSTRACT

Cytomegalovirus is a double stranded DNA virus belonging to herpes virus family. The infection once acquired persists lifelong. The transmission of cytomegalovirus infection from mother to child may occur either in utero or perinatally. The risk of transmission to the fetus as a function of gestation age is uncertain, but infection during early gestation carries a higher risk of severe fetal disease. The incidence of Type 1 diabetes mellitus is rising continuously all over the world and this may be due to multiple factors. The role of cytomegalovirus in the etiology of diabetes mellitus is controversial. Here, we report a case of 35 months female child having Type 1 diabetes mellitus with congenital cytomegalovirus disease.

**Keywords:** Congenital infection, Cytomegalovirus, Type 1 Diabetes Mellitus.

The incidence of diabetes mellitus (DM) is rising continuously all over the world and this may be due to many reasons that can collectively or separately lead to the disease. These factors include genetic factors, obesity, autoimmunity and infection [1]. Molecular mimicry is one of the principal immunological mechanisms that lead to destruction of the pancreatic beta cells. This mimicry could be involved in cytomegalovirus (CMV) induced diabetes by inducing islet cell autoantibodies.

The loss of T cell tolerance to self (GAD65) may be due to processing and presentation of molecular mimicry of CMV protein pUL57 by dendritic cells [2]. CMV is a double stranded DNA virus belonging to herpes virus family. The transmission of CMV infection from mother to child may occur either in utero or perinatally [3]. In this case, the child had congenital CMV infection and was diagnosed as type 1 DM at a very early age. This strongly implies that CMV infection has an etiological role in the causation of type 1 DM.

### CASE REPORT

A 35 month old female child was brought to our hospital with altered sensorium, increased work of breathing and cold extremities. Child was stabilized with oxygen supplementation and fluid bolus. Child's random blood sugar (RBS) was high. Primary history taken from mother revealed that the baby had been diagnosed as Type 1 DM 6 months back. At this time, she was suffering from high grade fever, multiple episodes of non projectile, non bilious vomiting, and polyuria for 3 days. On general examination, child had signs of severe dehydration with oral and vaginal candidiasis.

A provisional diagnosis of uncontrolled type 1 DM with Diabetic Ketoacidosis was made and relevant investigations were sent and treatment was started simultaneously. Complete urine analysis revealed glycosuria and ketonuria. Complete blood count revealed leukocytosis (total count 22000/mm<sup>3</sup> with 85% neutrophils). Repeat RBS was 400mg/dl. Serum

electrolyte report showed hyperkalemia (6 mmol/l). With these investigations, Diabetic Ketoacidosis was confirmed.

After stabilization of the condition of the child, further detailed medical history of the child was taken from the mother. She was born out of non-consanguineous marriage and first in birth order. She belonged to upper lower socioeconomic class according to modified Kuppuswamy classification. Antenatal history revealed that the mother had fever without rash in the first trimester which subsided with medication. Ultrasonography, done in the last trimester of pregnancy, showed intra uterine growth retardation (IUGR) of the fetus. An emergency caesarean section was done in the 8<sup>th</sup> month of gestational age due to premature rupture of membranes. Baby had weak cry at birth and birth weight was 2 kg. Breast feeding was started after 6 hours and was continued till 2 years of age. Postnatal period is uneventful. Development milestones of the child were delayed in all the fields. Child received all the vaccines given under universal immunisation programme.

On anthropometric examination, she had microcephaly (head circumference - 37 cm, <3<sup>rd</sup> percentile for the age and sex). Her weight was 8 kg (<3<sup>rd</sup> percentile for the age and sex) and length was also less than 10<sup>th</sup> percentile for the age. Child had auditory, visual and speech defects with mental retardation. There is no family history of diabetes mellitus. Based on this history and anthropometry, congenital infection was suspected and TORCH profile was sent. Her CMV IgG antibody titres (159 RU/ml) were raised (<16 RU/ml- negative; 16-22 RU/ml – Borderline; >22RU/ml- positive). CT scan head showed cerebellar atrophy and tiny punctuate hyperdensities in bilateral parieto-occipital regions. With this information, congenital CMV infection was considered as the cause of Type 1 DM.

## DISCUSSION

CMV is a double stranded enveloped DNA virus with lifelong infection. It is a member of herpes virus family and is found only in humans. CMV is the most common congenital infection affecting 1% to 2% of all newborns. The rate of infection in a fetus of a mother with primary infection is between 40% and 50%, the rate of infection is less than 1% in the mother who had reactivated infection [4]. Infections can be transmitted from mother to developing foetus transplacentally or at the time of

delivery. Infected babies may be asymptomatic or minimally symptomatic when born, only to develop symptoms and disabilities in the following weeks, months or even years [4].

Type 1 DM is a chronic T cell mediated autoimmune disease that results from the destruction of pancreatic islets. The onset of Type 1 DM occurs predominantly in childhood, with age of 7 to 15 years, but it may present at any age [5]. Genetic predisposition and environmental factors lead to the initiation of an autoimmune process against the pancreatic islets [5]. Certain viruses can infect humans and cause diabetes through a different mechanisms such as pancreatitis or hepatitis and their subsequent complication [6,7]. Cytomegalovirus is one of the most important factors that are thought to be associated with DM owing to its ability to induce immunological beta cell damage [8].

Previous studies have shown contradictory results on the association of CMV infection with Type 1 DM. One recent study revealed significant correlation between IgG of CMV and Type 1 DM in children [9]. Hjelmesaeth et al showed that CMV infection is associated with increased risk of new onset type 1 DM [10]. Nicoletti et al also reported a significant association between high titre of anti-CMV and anti islet cell antibodies [11]. In contrast to these reports, Hiltunen et al did not find any correlation between the presence of Anti CMV IgG antibodies and newly diagnosed type 1 DM in children [12].

In the present case, TORCH profile of the baby showed raised CMV IgG antibody titres at the age of 35 months. The interpretation of a positive IgG titre in infant is complicated by the presence of transplacentally derived maternal IgG. Uninfected infants usually show a decline in IgG within 1 month and have no detectable levels by 4 to 12 months; whereas, infected infants continue to produce IgG throughout the time period [3]. Also the history, clinical features such as microcephaly, mental retardation, hearing defects and CT scan findings strongly support congenital CMV infection in this baby.

Therefore, occurrence of type 1 DM in this baby with congenital CMV suggests the possible etiological role of CMV in the occurrence of Type 1 DM. However as the number of studies on the possible correlation between CMV infection and type 1 DM are limited, these results

are still controversial and needs further evaluation in larger studies.

## CONCLUSION

We conclude that there may be an association between CMV infection and type 1 diabetes mellitus as suggested by the occurrence of type 1 DM in this 35 month old baby with congenital CMV infection.

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