International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 21-04-2019; Accepted: 24-05-2019
www.medicalsciencejournal.com
Volume 5; Issue 6; June 2019; Page No. 103-108

Manifestations of symptomatic congenital cytomegalovirus infection and Valganciclovir HCL effect: A study in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh

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Abstract
Introduction: Herpes (CMV) is recognized because the most typical inborn virus infection in humans and a crucial explanation for morbidity and mortality in upset hosts. This recognition of the clinical importance of invasive herpes virus malady within the setting of immunological disorder and in child with inborn herpes virus infection has light-emitting diode to the event of recent diagnostic procedures for the fast identification of herpes virus. it's calculable that regarding 40,000 child (0.2 to 2%) of all deliveries area unit born with herpes virus leading to regarding four hundred fatalities annually.1 most youngsters (60 to 90%) with symptomatic infection and (10 to 15%) of these with symptomless infection, develop one or additional long-run medicine seqeuls, like subnormality, cognitive content retardation, SNHL and ophthalmologic abnormalities.
Objective: To work out the clinical manifestation of inborn herpes (CMV) infection and also the result of Valganciclovir HCL.
Methodology: Twenty newborns with inborn herpes virus infection were admitted at Queen Rania Hospital (KHMC) between Gregorian calendar month 2009 and Gregorian calendar month 2010 and were treated with Valganciclovir HCL were enclosed within the study.
Result: The most typical clinical presentation was intrauterine growth retardation (45%), Hepatosplenomegaly (35%), Chorioretinites (35%) and purpuric roseola (25%). Brain magnetic resonance imaging was positive in two hundredth. Complete blood count was abnormal in two hundredth. Over seventy fifth patients improved with Valganciclovir HCL with none complications.
Conclusion: Intrauterine growth retardation, hepatosplenomegaly and chorioretinites were commonest clinical manifestations of herpes virus infection. Valganciclovir HCL was effective. Hindrance of inborn herpes virus infection by immunisation of symptomatic girls who area unit in danger of primary infection throughout gestation ought to be emphasised.

Keywords: Cytomegalo virus, CMV, Valganciclovir HCL. Bangladesh

1. Introduction
Cytomegalovirus (CMV) is recognized because the most typical inherent infection in humans and a crucial explanation for morbidity and mortality in upset hosts. This recognition of the clinical importance of invasive herpes illness within the setting of immunological disorder and in youngsters with inherent herpes infection has LED to the event of recent diagnostic procedures for the speedy identification of herpes. Designation of acute maternal herpes infection by the presence of (Ig) M and low-avidity immune globulin needs confirmation of vertebrate infection, that is often performed mistreatment enzyme chain reaction (PCR) assays for herpes on humour. Microorganism culture of the piddle and spittle obtained at intervals the primary period of life continues to be the gold commonplace for designation of congenitally-infected infants. PCR assays of dried blood spots from newborns are shown to lack sufficient sensitivity for the identification of most neonates with inherent herpes infection for universal screening functions. However, spittle PCR assays area unit presently being assessed as a helpful screening technique for inherent herpes infection. Within the upset host, newer speedy diagnostic assays, like protein 65 antigenemia and herpes period PCR of blood or plasma have allowed for preventive treatment, reducing morbidity and mortality. However, lack of standardized period PCR protocols hinders the comparison of information from totally different centers and also the development of uniform tips for the management of invasive herpes infections in upset people.

2. Literature review
It is calculable that concerning 40,000 youngsters (0.2 to a pair 2%) of all deliveries square measure born with herpes virus leading to concerning four hundred fatalities annually [1]. Most children (60 to 90%) with symptomatic infection and (10 to 15%) of these with symptomless infection, develop one or a lot of long-run neurologic sequels, like backwardness, cognitive content retardation, SNHL and ophthalmologic abnormalities [2-4]. This incidence of herpes virus is way bigger than that of known childhood disorders,

like retardation (4000/year), foetal alcohol syndrome (5000/year), or spinal bifida (3500/year), creating this infection the foremost common reason for birth defects and childhood disabilities within the u. S [5, 6]. Considering the general public health significance of CMV-related long-run neurologic disabilities, it's shocking that adequate attention isn't being paid to understanding the neuropathogenesis of inherent herpes virus infection. The aim of this study was to work out the clinical manifestation of inherent herpes virus infection and its response to Valganciclovir HCL medical care.

3. Patients and methods

Between January 2016 and December 2017 twenty newborns were admitted at Hepatology & Nutrition Dept, Dhaka Shishu (Children) Hospital Dhaka, Bangladesh. All had symptom of congenital CMV at birth. Baseline history was obtained and physical examination performed [2]. The history included mother's pregnancy course, including fever, lymphadenopathy, and development of a mononucleosis syndrome, hepatitis, or rash. The history of the newborn included Apgar scores; associated diseases, medications administered, method of feeding, appearance of general anomalies, lethargy, anorexia, Moro's reflex, seizures, pneumonia, and disseminated intra vascular coagulopathy. The weight, length, and head circumference were documented at the time of admission. All newborn suspected to have congenital CMV had serum analyses of CMV IgG, IgM and urine sample for CMV by PCR. The definitive method for diagnosis of congenital CMV infection was virus isolation or PCR, performed at or shortly after birth. All patients proved to have congenital CMV were started on parenteral Valganciclovir HCL for six weeks at a dose of 10mg in two divided doses. After three weeks of treatment, follow up by previous method to show if the test becomes negative. A monthly follow up was performed on all patients by hearing assessment, ophthalmological examination, complete blood count, abdominal ultrasound, and developmental assessment.

Serological analyses

IgG antibodies specific for cytomegalovirus were detected by fluorescence microscopy, victimisation business reagents (Merifluor cytomegalovirus Ig, US) in step with the manufacturer's directions. Samples were more to a layer of human fibroblasts mounted on glass slides on that more or less 100 percent of cells area unit infected with cytomegalovirus strain AD169, and therefore the formation of antigen-antibody complicated is viewed employing a dyestuff clean fibroblasts on constant slide were used as an interior management of the specificity of the take a look at. The tests were valid with negative and positive management sera. The employment of reference sera ensured the reliability of results between batches in step with the manufacturer, the take a look at has ninety seven sensitivity, 100% specificity, and 100% prognosticative worth of a positive take a look at and ninety nine prognosticative worth of a negative take a look at.

Statistical analysis

Statistical analysis consisted within the determination of absolute and relative frequencies (percentages). Binomial confidence intervals were calculated victimisation the precise technique that uses the connection between the F and Binomial distributions attributed to elation and Brownlee as delineated by Zar [40]. Transmission and Prevention: folks with cytomegalovirus could pass the virus in body fluids, like spittle, urine, blood, tears, semen, and breast milk. Cytomegalovirus is unfold from AN infected person within the following ways:

- From direct contact with spittle or pee, particularly from babies and young youngsters
- Through sexual contact
- From breast milk to nursing infants
- Through transplanted organs and blood transfusions

A woman who is infected with herpes virus will pass the virus to her developing baby throughout gestation. Female could also be able to reduce their risk of obtaining herpes virus by reducing contact with spittle and excretion from babies and young child. The spittle and excretion of child with herpes virus have high amounts of the virus. A pregnant girl will avoid obtaining a child's spittle in her mouth by, for instance, not sharing food, utensils, or cups with a toddler. Also, she ought to wash her hands once ever-changing diapers. These cannot eliminate her risk of obtaining herpes virus, however might reduce the possibilities of obtaining it.

Valganciclovir: Valganciclovir is associate medicinal drug. It works by preventing infectious agent cells from multiplying in your body. Valganciclovir is employed in adults to forestall infection with CMV (CMV) that will occur once associate surgical operation (heart, kidney, or pancreas). Valganciclovir is additionally accustomed treat herpes virus infection of the attention in adults with nonheritable immunological disorder syndrome (AIDS).is used in child a minimum of four months previous to forestall herpes virus infection once a urinary organ transplant. Valganciclovir is additionally employed in child a minimum of one month previous to forestall herpes virus sickness once a heart transplant. Valganciclovir won't cure herpes virus however it will facilitate management the infection. Valganciclovir isn't for treating herpes virus that a baby is born with. Valganciclovir may be used for functions unlisted during this medication guide. If you've got signs of infection such as: fever, chills, tiredness, grippe symptoms, mouth sores, skin sores, pale skin, simple bruising, uncommon harm, shortness of breath, or feeling light-headed. Valganciclovir (Valcyte) and ganciclovir (Cytovene) must not ever be taken along.You should not use this drugs if you're allergic to valganciclovir or ganciclovir (Cytovene).Valganciclovir (Valcyte) and ganciclovir (Cytovene) must not ever be taken along. victimisation valganciclovir might increase your risk of developing cancer raise your doctor concerning your specific risk. To form certain valganciclovir is safe for you, tell your doctor if you've got ever had:

a. Kidney sickness (or if you're on dialysis);
b. A blood corpuscle disorder (such as anemia or low levels of platelets in your blood); or
c. Treatment with radiation or medicine that weaken your system (such as cancer drugs or steroids).
d. You might have to own a negative bioassay before taking valganciclovir.

Valganciclovir will hurt associate unhatched baby. Don't use this drugs if you're pregnant. Use effective contraception to forestall gestation, whether or not you're a person or a girl. Men ought to use condoms. The employment of this drugs by either parent might cause birth defects.

a. If you're a girl, keep victimisation contraception for a minimum of thirty days once your last dose of valganciclovir.
b. If you're a person, keep victimisation condoms for a minimum of ninety days once your last dose.
c. Tell your doctor quickly if a gestation happens whereas either the mother or the daddy is victimisation this drugs.

This drugs might have an effect on fertility (ability to own children) in each men and ladies. However, it's vital to use contraception to forestall gestation as a result of valganciclovir might hurt the baby if a gestation doe's occur.HIV are often passed to your baby if you're not properly treated throughout gestation. Take all of your HIV medicines as directed to regulate your infection. Valganciclovir won't stop innate (inherited) herpes virus during a newborn. You must not breast-feed whereas you're taking valganciclovir. Female with HIV or AIDS shouldn't breast-feed a baby. Even if your baby is born while not HIV, the virus is also passed to the baby in your breast milk.Do not provide this drugs to a baby while not medical recommendation.

Valganciclovir aspect Effects: Get emergency medical facilitate if you have got signs of associate degree allergic reaction: hives; troublesome breathing; swelling of your face, lips, tongue, or throat. Serious infections might occur throughout treatment with valganciclovir decision your doctor promptly if you have got signs of infection such as:

a) Fever, chills, tiredness, flu-like symptoms;
b) Feeling light-headed or in need of breath;
c) Mouth sores, skin sores;
d) Pale skin, cold hands and feet; or
e) Simple bruising, uncommon harm (nose, mouth, vagina, or rectum).
f) Additionally decision your doctor quickly if you have:
g) A seizure (convulsions);
h) Pain or burning once you urinate;
i) Pain or swelling close to your transplanted organ; or
j) Excretory organ problems--little or no urinating; painful or troublesome urination; swelling in your feet or ankles; feeling tired or in need of breath.
k) Excretory organ issues is also a lot of possible in older adults.
l) Common aspect effects might include:
m) Fever or alternative signs of infection;
n) Nausea, vomiting, diarrhea;
o) Headache;
p) Tremors, loss of balance or coordination;
q) Sleep issues (insomnia); or
r) Cold symptoms like stuffy nose, sneezing, and inflammatory disease.

Valganciclovir Interactions: Avoid being close to people that area unit sick or have infections. Tell your doctor quickly if you develop signs of infection. Avoid activities which will increase your risk of harm or injury. Valganciclovir might impair your thinking or reactions watch out if you drive or do something that needs you to be alert.

Valganciclovir will hurt your kidneys: This result is enhanced once you additionally use sure alternative medicines, including: antivirals, therapy, injected antibiotics, drugs for gut disorders, drugs to stop operation rejection, injectable pathology medication, and a few pain or inflammatory disease medicines (including acetylsalicylic acid, Tylenol, Advil, and Aleve). Alternative medication might move with valganciclovir, as well as prescription and over-the-counter medicines, vitamins, and seasoning product. Tell your doctor regarding all of your current drugss and any medicine you begin or stop victimisation.

Valganciclovir Dosage: Follow all directions on your prescription label. Don't take this drugs in larger or smaller amounts or for extended than suggested. Take valganciclovir with food. Drink lots of liquids whereas you're taking whereas victimisation valganciclovir, you'll would like frequent blood tests.

a) You ought to have your eyes checked a minimum of each four to six weeks whereas you're victimisation valganciclovir for CMV.

b) Use valganciclovir frequently to induce the foremost profit. Get your prescription refilled before you run out of medication fully.

c) Store valganciclovir tablets at temperature off from wet and warmth.

d) Store valganciclovir liquid within the white goods don't freeze. Throw away any unused when forty nine days.

Take the incomprehensible dose as presently as you keep in mind. Skip the incomprehensible dose if it's nearly time for your next regular dose. Don't take additional drugs to create up the incomprehensible dose. Valganciclovir is associate degree anti-viral drug. It's modified within the body to the active style of the drug referred to as ganciclovir. It's wont to stop malady caused by a scourge referred to as herpes virus (CMV) in people that have received organ transplants. CMV malady will cause serious infections within the body, as well as associate degree infection within the eye, referred to as CMV redness which will cause cecity. Valganciclovir works by deceleration the expansion of the CMV virus. It helps stop the fold of infection to alternative areas of the body. Valganciclovir is also used to treat CMV retinitis in people with advanced HIV disease (AIDS). This medication helps control CMV retinitis and decrease the risk of blindness. Valganciclovir is not a cure for CMV disease.

4. Results

This study out of 20 patients, 11 (55%) were below the age of one month and the other 9 (45%) were below three month. Nine (45%) patients were born with birth weight less than 2.5 Kg and hepatosplenomegaly and chorioretenites were commonest features (Table 1). Brain MRI showed calcification in five (25%) patients. PCR in urine was positive in all 20 patients (100%).

Table1: Clinical and laboratory manifestation of congenital CMV before treatment (n=20).

Percentage	Number	Clinical Finding
45%	9	IUGR
35%	7	Hepatosplenomegaly
35%	7	chorioretenites
25%	5	Purpuric skin rash
25%	5	Calcification of brain
15%	3	SNHL
20%	4	Nutropenia*
15%	3	Thrombocytopenia
30%	6	CMV, IgG and IgM
100%	20	PCR

*Neutropenia =ANC less than 1500/ml

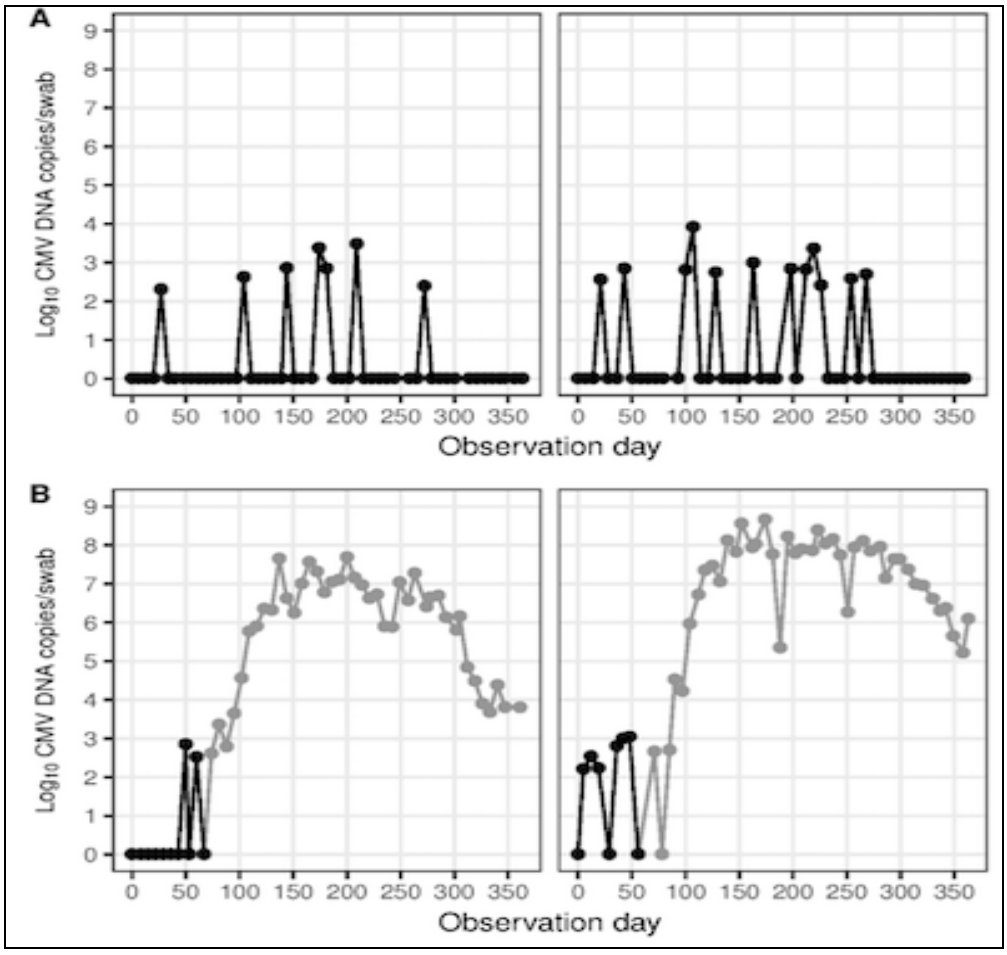

Fig 1: Cytomegalovirus causes transient prior to lifelong infection.

Human cytomegalovirus (CMV) is a common virus that infects almost half of people over 40, usually causing no symptoms. However, immunocompromised individuals can develop life-threatening disease. Once infected with CMV a person remains infected and the virus can reactivate many years after the initial event. Even though so many people have CMV, early events of infection are not well documented or studied. This is probably due to the fact that initial infection is mostly during childhood and asymptomatic. To better understand initial infection and spread, researchers at Fred Hutch in the Vaccine and Infectious Disease Division studied a cohort of 30 high risk infants over time, taking oral samples to test for the presence of CMV DNA, hoping to catch the initial infection stage and study viral spread. Dr. Schiffer and colleagues collected weekly swabs from infants and found 20 with primary infection and more that 130 self-limiting episodes that resulted in what they called transient infection. Transient infection was marked by swabs positive for up to 2 weeks that then returned to baseline after this time (figure 1A). These infections did not lead to long-term infection; thus they were termed transient. An infant was considered infected with a primary infection if the viral load increased and subsequent swabs returned positive for CMV by PCR (median time = 31weeks) (figure 1B). When the group compared infants that became primarily infected versus ones that are only transiently infected, the swabs prior to the onset of primary infection looked similar, suggesting that transient infection probably did not represent early primary infection.

Table 2: One year follow up after Valganciclovir HCL treatment (n=20).

Percentage	Number improved	Manifestation
80%	6	Chorioretenites
70%	5	Hepatosplenomegaly
75%	3	Neutropenia
66%	3	Thrombocytopenia
66%	2	SNHL
75%	50	PCR

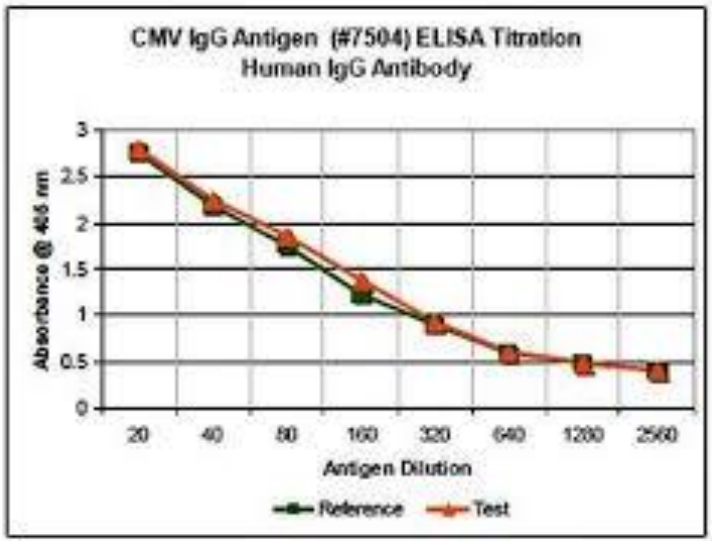

Fig 2: Cytomegalovirus IgM Antigen protein.

After 3 weeks of treatment, PCR for CMV were negative in 15 (75%) patients. Five (25 %) were still positive. All were continued on medication for another 3 weeks. In three patients (75%), netropenia and two (66%) thrombocytopenia improved after one week of treatment. Regression of hepatosplenomegaly was very slow, five of seven (70%) had mild hepatosplenomegaly after one year, and the other two (30%) had the same degree of hepatosplenomegaly. Chorioretenitis improved in six patients (85%) after 6 weeks of treatment, one patient lost his vision (15%). Two patients (66%) who had sensorineural hearing loss improved moderately. One patient (5%) passed away during treatment at the age of 5 weeks.

5. Discussion

This study was done to determine the clinical manifestations of CMV infection, and the effects of Valganciclovir HCL treatment. We found that 80% of anemia and thrombocytopenia improved after four weeks of treatment. Ganciclovir was selected for utilization in this protocol because of its significant antiviral activity [7, 8]. However, due to its known toxicity, particularly bone marrow suppression and gonadal effects, only children at exceedingly high risk for death or sever neurologic impairment were given the drug. All children enrolled in this study had evidence of severe disease, likely the consequence of fetal infection early in gestation [9]. From this study we learned that ganciclovir at 10mg /kg/day in two divided doses led to a significant reduction in the overall quantity of virus in the urine and other sites. The mortality rate directly attributed to CMV in this study was as low if not lower, than that reported in earlier studies [10]. In our series, mortality rate was 5%. Hearing loss is the most common sequel of congenital CMV infection, occurring in 10%-15% of all infected children and in our study, 15% had hearing loss. After gancicloviur treatment, 5% of them had permanent hearing loss. There is no data in Jordan regarding seroprevelance for CMV infection in women of child bearing age. In some countries, it is as high as 85% [11]. The virus can also be transmitted to the infant at delivery from contact with genital secretions or later in infancy through breast milk [12]. No vaccine for prevention of CMV infection is approved for use. A live attenuated vaccine using the Towne PCR 125 strains has been developed. However, the Towne vaccine was unable to prevent infection in women of childbearing age exposed to young children shedding CMV [13]. General recommendations for pregnant women with regard to CMV infection include practicing good personal hygiene, especially hand-washing with soap and water after contact with diapers or oral secretions, particularly with a child who is in day care center, as this was associated with a higher risk of maternal infection in pregnancy. It is believed that treatment of congenital CMV will require long periods of drugs administration, thus, the importance of developing a safe antiviral medication that can be administered orally rather than intravenously.

6. Conclusion

Cytomegalovirus (CMV) is recognized as the most common congenital viral infection in humans and an important cause of morbidity and mortality in immunocompromised hosts. This recognition of the clinical importance of invasive CMV disease in the setting of immunodeficiency and in children with congenital CMV infection. We found intrauterine growth retardation, hepatosplenomegaly and chorioretinites to be the commonest manifestations of CMV infection. Response to Valganciclovir HCL was satisfactory. The prevention of CMV infection by immunization of symptomatic women who are at risk for primary infection

during gestation should be emphasized. This study was done to determine the clinical manifestations of CMV infection, and the effects of Valganciclovir HCL treatment. We found that 80% of anemia and thrombocytopenia improved after four weeks of treatment.

Acknowledgement: We acknowledged the Dhaka Shishu (Children) Hospital authority, and related personnel who was engaged in the Crosse sectional**.**

Conflict of interest: The Author has no conflict of interest of the study.

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