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Neurodevelopmental Outcome of Treatment of Symptomatic CMV Infection with Ganciclovir

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Abstract

Rationale: Cytomegalovirus (CMV) infection is a common cause for neurodisability among poor populations in developing countries, including Bangladesh. Some studies have shown that ganciclovir therapy is effective in reducing neurodevelopmental morbidity; while others remain equivocal.

Objective : The objective of this study was to evaluate neurodevelopmental outcome of children with symptomatic CMV treated with ganciclovir compared to matched control.

Methods: Out of 218 children seropositive for CMV admitted into the neurology ward between 2003-2006, 91 were treated with intravenous ganciclovir for 2-3 weeks; of whom 43 came for follow-up at an interval of 3 months to 1 year. At each visit neurodevelopmental status was recorded for cognition, vision and hearing. 41 untreated age-matched cases with follow-up records were retrospectively enrolled as control.

Results: Among treated children compared to untreated controls, there was significant improvement in hearing (58% vs. 27%; p value=.012). Improvement remained consistent, without statistical significance, for vision (53% vs. 39%; p value=.071)) and cognition (51% vs. 54%; p value=.344).

Conclusion: Ganciclovir treatment improved neurodevelopmental outcomes of very young children with symptomatic CMV infection. In a country where limited resources are available for children with disability, early recognition and treatment of CMV infection is recommended.

Keywords: *CMV infection, ganciclovir, neurodevelopment*

Introduction

Cytomegalovirus (CMV) infection is the most common viral disease to be transmitted *in utero* and affect the central nervous system.[1-5] Fewer than 10% of infected infants are symptomatic at birth; while about 15% of asymptomatic infants are at risk of developing neurological complications within the first two years of life.[2-7] Only 5% of all congenitally infected infants have severe cytomegalic inclusion disease, 5% have mild involvement, and 90% are born with subclinical infection.[8-9] Transmission is transplacental due to maternal viremia, although perinatal infection may also occur during passage down the birth canal, via breast milk, or by blood transfusion.[10] Commonest sequelae of congenital neonatal CMV infections include microcephaly, intellectual impairment and sensorineural hearing loss;[11] and an estimated 5-10% of congenitally infected asymptomatic infants develop neurological problems later in life, the commonest being unilateral or bilateral sensorineural hearing loss.

For detection of CMV-specific IgG antibodies, ELISA has sensitivity and specificity of at least 95%.[12] A study in Bangladesh showed that the prevalence of CMV- specific IgG antibodies was significantly higher (35.84%) among children with cognitive, motor and sensory deficits compared to developmentally age-appropirate controls (6.67%) (p value=.0001) .[13]

The anti-viral agent Ganciclovir, which interrupts active replication of CMV by competitively interfering with elongation of the viral DNA chain, is the drug of choice and has been used successfully, especially for those

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with neurologic disease or hearing impairments[14]. It is important to note that postnatal ganciclovir is unlikely to be useful for severe forms of CNS injury associated with early *in utero* acquisition of infection[15]; and in addition, severe side effects i.e myelo-supression (e.g., granulocytopenia, anemia, thrombocytopenia) may be a side-effect, especially in immunocompromised patients.[16]

This study aimed to determine and compare the neurodevelopmental outcome of children with evidences of CMV infection treated with Inj. Ganciclovir, compared to a similar, but untreated, population.

Methods

Study design

A retrospective analysis was conducte to evaluated neurodevelopmental outcomes of children admitted into the neurology ward who were positive for serum antibody titer for CMV and treated with Inj. Ganciclovir. A set of children untreated for the condition during the same time period, were also analysed.

Study population

Children admitted into the Child Development and Neurology Unit of Dhaka Shishu Hospital during the period of 1994 to 2007 with features of a combination of impairments in cognition, speech, motor development, vision and hearing, seizure, microcephaly, stiffness, dyskinetic movement, were screened for CMV antibody titre in serum. All IgM positive cases and those with an IgG positivity >4 times of the laboratory's cut-off value were considered for treatment. The titer marker was taken from a previous study in Bangladesh[13]. Age range of included children were from birth to 60 months.

Treatment

Intravenous ganciclovir 6mg/kg 12 hourly as a 1-hour infusion was given for 3 weeks after proper counseling. Information on the functional neurodevelopmental status before starting treatment and after a follow up period of 3 months to 1 year were recorded. For the present study neurodevelopmental status for vision, hearing and cognition were considered. The same information were recorded from the children who were not treated with inj. Ganciclovir but had regular stimulation & followed up at the same centre.

Monitoring drug toxicity

Laboratory assessments (complete blood counts, alanine aminotransferase (ALT), bilirubin, uric acid, creatinine) were performed before initiating treatment with ganciclovir. Thereafter, weekly assessments of complete blood count was performed to monitor ganciclovir toxicity.

Neurodevelopmental assessment

A multidisciplinary team comprising of a child health physician, a developmental theraphist and a child psychologist, assessed children for their neurodevelopmental status. Improvement in vision, hearing and cognition were noted from follow up records. For vision assessment near-visual acuity was tested;[17-18] for hearing assessment distraction or performance test was conducted;[19-20] and for cognitive function age appropriate psychometric tests were administered according to the age-appropriateness of the child.[21]

Data analysis:

All information was tabulated in the SPSS. 11 + PC software program was used for data analysis.

Ethical considerations

Verbal consent was taken before starting the treatment schedule. Possible side-effects of the treatment and treatment expenses were explained, including facts about neurodevelopment

The hospital provided free stay, investigations during the three week of treatment. In addition, full free treatment was provided for the low income families.

Results

Out of all children admitted with neurodevelopmental impairments, total 218 children were found to be seropositive for CMV antibody (table-I). Among them 61 (28%) were female and 157 (72%) were male.

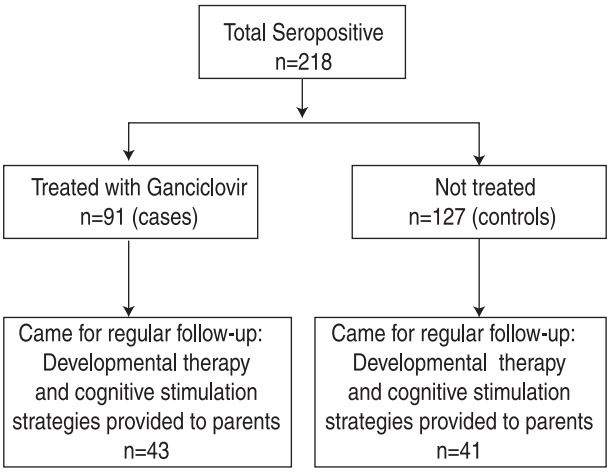

Fig.-1: *Numbers of cases selected for treatment and controls.*

Table-I

Age and gender of the total children found to be seropositive (n=218), and those subsequently treated with ganciclovir (n=91).

Patients profile	Children with CMV seropositive n = 218 (100%)	Treated n = 91 (100%)
Age in months		
1 mo – 6 mo	76 (35)	36 (40)
>6 mo – 12 mo	59 (27)	25 (27)
>12 months	83 (38)	30 (33)
Gender		
Male	157 (72)	57 (63)
Female	61 (28)	34 (37)

Table-II

Neurodevelopmental impairment and subsequent improvement of the followed up children (n=43) after treatment and matched controls (n=41).

Neurodevelopmental domains	Treated N=43 (100%)		Controls N=41 (100%)		p value
	Number of children with Impairments at admission	Improved After treatment	Number of Impairments at admission	Improved	
Hearing	30 (70)	25 (58)	22 (54)	11 (27)	.0128*
Vision	30 (70)	23 (53)	29 (71)	16 (39)	.071
Cognition	36 (84)	22 (51)	32 (78)	22 (54)	.344

*p value <.05

Among the seropositive children 76 (35%) were from age group 1 to 6 months , 59 (27%) from >6 – 12 months and 83 (38%) from age group >12 – 60 months. Total 91 children were treated with inj. ganciclovir, of whom 36 (40%) were from age group 1 to 6 months, 25 (27%) from age group >6 - 12 months, and 30(33%) from age group >12 – 60 months.

Neurodevelopmental improvement in the treated group and matched controls after a follow up of 3 months to 12 months showed significant difference in hearing (58% in cases vs. 27% in controls; p value = 0.0128) (table-III). Although a larger proportion of cases improved in visual functioning (ie, 53% in cases vs. 39% in controls), it was not statistically significant (p value=0.055), and cognitive improvement was marginally higher in the controls (ie 51% in cases vs. 54% in controls), with no statistically significance (p value=0.35). There was no significant difference in outcomes by age group.

Discussion

This study suggests that intravenous ganciclovir treatment for infants with seropositive CMV presenting with neurodevelopmental impairments may improve neurodevelopmental outcomes, especially their hearing. Visual improvement was noted among the treated group which was not significantly different from that of untreated group. This could be due to the small study size, especially as not all children came for follow up visits. The results also suggest that treatment with ganciclovir may not be able to prevent all neurodevelopmental impairments from occurring, as cognitive improvement seemed to be unaffected.

A randomized controlled study in neonates with symptomatic CMV disease involving the central nervous system, randomly assigned to receive 6 weeks of intravenous ganciclovir versus an untreated group, has shown to prevent deterioration in hearing

in the treated group at 6 months and 12 months of age.[22] However, treatment of very young children should be done with caution, as almost two thirds of treated infants had significant neutropenia during therapy. In another study conducted from 1991 to 1999, 100 neonates were enrolled in a controlled trial and randomized to 6 weeks of intravenous ganciclovir at 12 mg/kg/day delivered in two divided doses (*n* = 48) or to no antiviral treatment (*n* = 52). Results showed that treated subjects had fewer neurodevelopmental delays compared with subjects who did not receive antiviral therapy .[23] These two studies differs from our present study in that we treated children above the neonatal ages, although the majority were <12 months of age. None of our treated children developed neutropenia or any other hematological complication. This may be due to the shorter duration of therapy, ie 3 weeks in our present study, compared to six weeks treatment with ganciclovir in the above quoted studies.

This study suggests that all neonates and infants presenting with neurodevelopmental impairments should be screened for CMV infection if possible. Seropositive cases with symptoms may be given a course of injectable ganciclovir, whose main effect is in the prevention of hearing loss. Other neurodevelopmental outcomes may need further study in a larger population of children.

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