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Symptomatic congenital Cytomegalovirus deafness: the impact of a six-week course of antiviral treatment on hearing improvement

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SUMMARY

Congenital Cytomegalovirus infection is the leading non-genetic cause of neurosensory deafness. We compared the outcomes of a treated group of children to an untreated group.
The effect of antiviral therapy on hearing improvement between baseline and 2-year follow-up was statistically significant. These results suggest that the benefit of 6-week therapy is not limited to preventing further hearing deterioration.

Keywords: Cytomegalovirus, congenital deafness, ganciclovir, valganciclovir.

INTRODUCTION

Congenital Cytomegalovirus (CMV) infection is the leading nongenetic cause of neurosensory hearing loss in developed countries, including Italy, where the 0.6-1% of all infants born alive are infected with CMV [1]. The 10-15% of infants with congenital CMV are symptomatic at birth and approximately 90% of symptomatic survivors show long-term neurologic sequelae, including sensorineural hearing loss in the 30-65% of cases [2-5].
According to current clinical recommendations, the most common drugs accepted for the treatment of children with congenital CMV infection are intravenous ganciclovir (GCV) and its oral prodrug valganciclovir (val-GCV), both administered over a period of 6 weeks, although a strong evidence for a specific therapeutic regimen has not been established yet [6-9]. Up to now, scientific literature has provided evidences that the administration of 6-weeks antiviral therapy is effective in preventing further hearing deterioration [6].

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PATIENTS AND METHODS

This study analysed retrospectively the medical records of neonates born between January 2007 and December 2014 at Verona University Hospital, who were diagnosed of symptomatic congenital CMV infection with hearing impairment at birth. Patients were excluded if there were evidences of CMV disease involving central nervous system structures other than hearing, such as microcephaly, hydrocephaly, ventriculomegaly, intracranial calcifications, chorioretinitis or other ophthalmological signs, abnormal cerebrospinal fluid for age or other neurologic abnormalities.
All the study participants had CMV detected from

urine or blood specimens by means of culture, shell-vial culture or polymerase chain reaction assay. Once the informed consent was provided by parents or legal guardian, a 6-weeks antiviral treatment with either intravenous GCV (at a dose of 6 mg per kilogram of body weight, twice daily) or oral val-GCV (at a dose of 16 mg per kilogram of body weight, twice daily) was administered to all of them within the first 10 days of life.
Review of medical records included birth history, clinical presentation leading to diagnosis of congenital CMV infection and subsequent radiological and laboratory investigations to determine the burden of disease, duration of antiviral treatment, laboratory assessments (complete blood counts, aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine measurements), which were performed at the beginning and at the end of treatment and audiological evaluations, which were performed at birth, 6, 12 and 24 months with auditory brainstem responses (ABR). Hearing thresholds were defined as follows: 20 dB or lower for normal hearing, 21 to 45 dB for mild hearing loss, 46 to 70 dB for moderate hearing loss and 71 dB or higher for severe hearing loss.
Trends in hearing status of treated cases were compared with the ones of children whose parents or legal guardian refused the therapy. A change in hearing above 10 dB was considered significant.
All statistical analyses were performed using SPSS software, version 24.0 (SPSS, Inc., Chicago, IL, USA). Data were analysed using Fisher's exact test. p values <0.05 were considered significant.
The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of the World Medical Association.

RESULTS

13 patients were identified as having symptomatic congenital CMV infection with hearing impairment at birth. The male/female ratio was 7/6. Table 1 summarizes the demographic and the baseline clinical characteristics of our population. All study subjects had serial audiological examinations: all of them completed the follow-up. Table 2 documents the hearing assessments performed before initiation of antiviral therapy and at 2-years follow-up. ABR at birth recorded a complete bilateral deafness (CBD) in 4 cases and a partial or single-sided hearing loss in 9 children. Therapy

Table 1 - Baseline characteristics of the studied population.

Patient	*Sex*	*Gestation age (week + day)*	*Body weight (kg)*	*Involvements other than CNS*	*Impaired in laboratory assessment*
1	F	37+3	2.5	Thrombocytopenia	PLT 92000/µL
2	F	35 + 6	2.1	Thrombocytopenia, hepatitis	PLT 45000/µL/ALT 167 UI/L
3	M	38 + 2	2.7	None	
4	F	38 + 5	3.1	None	
5	M	33 + 3	2.5	None	
6	M	30 + 1	2.8	Hepatitis	ALT 183 UI/L
7	M	30 + 6	3.2	Thrombocytopenia	PLT 113000/µL
8	F	34 + 1	2.9	None	
9	M	37 + 2	2.4	Thrombocytopenia	PLT 74000/µL
10	M	39 + 4	3.5	None	
11	F	38 + 6	2.9	None	
12	M	40 + 2	3.4	None	
13	F	39 + 5	3.2	None	

ID: pat
F/M: female/male
PLT: platelet count
ALT: alanine aminotransferase

Table 2 - Hearing outcome in the study population.

Patient	*Sex*	*Hearing assessment at birth*	*Therapy*	*Hearing assessment at 2-year follow-up*	*Hearing change from baseline to 2-year follow-up**
1	F	L-severe (80 dB) R-severe (75 dB)	GCV	L-severe (82 dB) R-severe (75 dB)	No change
2	F	L-severe (90 dB) R-severe (80 dB)	GCV	L-severe (93 dB) R-severe (75 dB)	No change
3	M	L-severe (80 dB) R-moderate (49 dB)	GCV	L-mild (41 dB) R-normal (18 dB)	Improved
4	F	L-mild (30 dB) R-normal (16 dB)	GCV	L-normal (18 dB) R-normal (18 dB)	Improved
5	M	L-severe (90 dB) R-mild (38 dB)	val-GCV	L-moderate (68 dB) R-normal (20 dB)	Improved
6	M	L-mild (40 dB) R-moderate (50 dB)	val-GCV	L-normal (16 dB) R-normal (18 dB)	Improved
7	M	L-mild (35 dB) R-mild (28 dB)	val-GCV	L-normal (13 dB) R-normal (15 dB)	Improved
8	F	L-severe (100 dB) R-severe (80 dB)	Refused	L-severe (105 dB) R-severe (90 dB)	No change
9	M	L-severe (88 dB) R-severe (90 dB)	Refused	L-severe (95 dB) R-severe (90 dB)	No change
10	M	L-normal (17 dB) R-mild (40 dB)	Refused	L-normal (15 dB) R-mild (30 dB)	No change
11	F	L-normal (14 dB) R-mild (34 dB)	Refused	L-normal (16 dB) R-mild (40 dB)	No change
12	M	L-moderate (50 dB) R-mild (40 dB)	Refused	L-moderate (55 dB) R-mild (31 dB)	No change
13	F	L-mild (28 dB) R-moderate (60 dB)	Refused	L-mild (35 dB) R-moderate (55 dB)	No change

*Hearing change is defined as a change of 10 dB or more.

was administrated for 6 weeks to 7 of them, 2 with a CBD (both treated using GCV) and 5 with a partial or single-sided hearing loss (treated using val-GCV in 3 cases and GCV in 2 cases), while it was refused by 6 newborns' parents, 2 with a CBD and 4 with a partial or single-sided hearing loss. Discontinuation or lowering of therapy was not necessary in any treated case because no relevant signs of drug toxicity occurred. Regardless of the therapy, none of the patients presenting a CBD showed hearing changes during follow-up. Considering cases with a partial or single-sided hearing loss, all the 5 treated ones achieved a significant hearing improvement after 2 years, whereas the impairment enhanced in none of the 4 untreated children (p=0.0079). Overall, hearing improvement was significantly associated with antiviral therapy (p=0.0163).

DISCUSSION

This is the first Italian report about hearing impairment in infants with symptomatic congenital CMV infection who received early diagnosis and antiviral treatment.

The effect of GCV or val-GCV on hearing improvement between baseline and 2-year follow-up was statistically significant. These results suggest that the potential benefit of 6 weeks of therapy is not limited to the prevention from further hearing deterioration.

Kimberlin et al. performed a phase III, multicentre, randomized, controlled trial, enrolling 42 newborns affected by symptomatic congenital CMV infection involving a sensorineural hearing loss. This prospective study compared intravenous GCV with no treatment, both adminis-

tered for 6 weeks within the neonatal period. The 6-month assessment showed that antiviral therapy protected from further hearing loss [7].
A more recent multicentre trial, headed by Kimberlin once again, compared 6 months *versus* 6 weeks of val-GCV in 96 infants, showing a significant hearing improvement in the 6-month group between baseline and 12-month follow-up and between baseline and 24-month follow-up [10]. To date, this is the only controlled study that shows a favourable effect of antiviral treatment in terms of hearing improvement, even though it is obtained in patients who have completed 6 months of therapy, a long-term treatment that involves a higher onset of side effects and a higher dropout rate.
Furthermore, a retrospective study investigated 54 infants with congenital CMV and hearing impairment at birth, who received 12 months of antiviral treatment, showing a significant improvement in hearing status after at least one year of follow-up with a worse outcome in those with a severe impairment at birth [11].
Our results support the hypothesis that therapeutic efficacy is achieved only in children with partial or single-sided hearing loss. Otherwise, antiviral treatment did not seem to work in those who were affected by CBD. Considering that the level of deafness is inversely related to the time of foetal infection, these findings suggest that therapy has a favourable impact on hearing only when CMV infection does not occur at a very early gestational age [11].
While our data are encouraging, this study has important limitations regarding the retrospective design, small sample size of our cohort and single-centre experience. Further prospective trials, with a greater sample size and a longer follow-up, are needed to confirm these results. Moreover, a controlled study design, which stratifies children by severity of deafness, should be considered to identify patients who may effectively benefit from antiviral therapy, eventually avoiding unnecessary treatments.

Conflicts of interest and source of funding
None to declare.

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