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Short Communication

Treatment of symptomatic congenital cytomegalovirus infection beyond the neonatal period

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ABSTRACT

Background: Congenital cytomegalovirus (CMV) is an important cause of sensorineural hearing loss. Ganciclovir treatment in the neonatal period may prevent hearing deterioration in infants with central nervous system (CNS) involvement. However, there are hardly any data regarding antiviral treatment begun beyond the neonatal period.
Objectives: To describe the hearing outcome of infants with congenital CMV infection and CNS involvement treated beyond the neonatal period. To assess the tolerability and toxicity of prolonged valganciclovir treatment in these patients.
Study design: Retrospective case series of infants with congenital CMV infection and CNS involvement who started antiviral treatment beyond the neonatal period in Spain between 2008 and 2010. Hearing was tested by brainstem-evoked response at the time of diagnosis, 6 and 12 months after the beginning of treatment.
Results: Thirteen cases were included. All received oral valganciclovir, and 4 also intravenous ganciclovir. Median valganciclovir treatment duration was 6 months and it was well tolerated. Six patients developed neutropenia, none requiring granulocyte colony-stimulating factor. Eleven children (85%) had hearing defects at baseline, compared to 50% at 12 months. By ears, 18 ears showed hearing loss at baseline (7 mild, 3 moderate, 8 severe). At 12 months, 9 remained stable, 7 had improved and none had worsened. In 8 normal ears at baseline, no deterioration was found at 12 months.
Conclusions: Valganciclovir treatment is well tolerated. It may improve or preserve the auditory function of congenitally cytomegalovirus-infected patients treated beyond the neonatal period for at least one year after the beginning of antiviral treatment.

1. Background

Cytomegalovirus (CMV) is the most common congenital infection and the leading nongenetic cause of sensorineural hearing loss in developed countries.[1] Long-term sequelae occur in 40–58% of infected children with CMV-specific symptoms at birth and in 13.5% of asymptomatic infants.[2] Treatment with intravenous ganciclovir for 6 weeks, starting in the neonatal period, may prevent hearing deterioration in symptomatic infants with central nervous system (CNS) involvement.[3] Newborn CMV screening is not performed on a population basis, so infants with asymptomatic and some with oligosymptomatic infections are not usually diagnosed at birth.[4] However, there are hardly any data regarding antiviral treatment begun beyond the neonatal period, and its efficacy to prevent hearing deterioration is unknown.[5]

2. Objectives and study design

A multicenter, retrospective case-series of infants with congenital CMV infection with CNS involvement who started antiviral

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; DBS, dried blood spots; PCR, polymerase chain reaction; BAER, brainstem auditory evoked response; GCV, ganciclovir; VGC, valganciclovir; dB, decibels; G-CSF, granulocyte-colony stimulating factor; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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treatment beyond the neonatal period in 6 tertiary hospitals in Spain between 2008 and 2010 is presented.

Diagnosis of congenital CMV infection beyond the neonatal period was made by CMV-PCR in dried blood spots (DBS-PCR). Cases in which DBS-PCR was not available were considered as having suspected congenital CMV infection provided they fulfilled all the following conditions: (1) positive urine CMV-PCR, (2) suggestive clinical and neuroimaging findings, and (3) exclusion of other congenital infections and neurological disorders.

CNS involvement was defined as the presence of any of the following: microcephaly, chorioretinitis, abnormal visual or auditory evoked responses, neurologic signs or abnormal neuroimaging findings consistent with congenital CMV infection.

Patients were treated with valganciclovir (VGC) oral solution at 32 mg/kg/day (b.i.d.) under compassionate use. Some also received intravenous ganciclovir prior to VGC, at 12 mg/kg/day (b.i.d.), as decided by the physician in charge of the patient. Written informed consent was obtained from parents before starting VGC therapy. A close follow-up during antiviral therapy was performed, with monthly controls including physical examination, complete blood count and liver and kidney function tests. Toxicity assessments were quantified using the DMID pediatric toxicity tables, 2007.[6] Hearing was tested by brainstem auditory evoked response (BAER) at the time of diagnosis, 6 and 12 months after the beginning of antiviral therapy. Results were analyzed considering total evaluable ears and hearing loss degree was categorized as follows: normal hearing (≤20 dB), mild hearing loss (21–45 dB), moderate hearing loss (46–70 dB) or severe hearing loss (≥71 dB). Hearing improvement was defined as BAER change by at least one gradation (e.g., moderate hearing loss at baseline and mild hearing loss at follow-up). Patients were categorized as stable when there was no change in BAER gradation between baseline and follow-up. All infants were periodically evaluated by a pediatric Ear, Nose & Throat specialist who assessed middle ear by otoscopy and timpanometry and ruled out other etiologies of hearing impairment before the beginning of antiviral therapy, such as congenital anomalies, hereditary hearing loss, ototoxic drugs and neonatal hyperbilirrubinemia.

3. Results

Thirteen cases were included, 10 of them confirmed (1 by blood and urine PCR at birth, 9 by DBS-PCR) and 3 with suspected diagnosis. Median (range) age at diagnosis was 3 months (0–8 months), four infants had intrauterine growth restriction and two were premature. Patients were screened for congenital CMV infection because of: microcephaly (4 patients), failure to pass newborn hearing screening tests (3), ventriculomegaly detected during pregnancy (2), hepatosplenomegaly (2), cholestasis (1), and intracranial calcifications in a skull X-ray obtained for cephalohematoma (1). All patients had neurological signs and symptoms at the time of diagnosis, including sensorineural hearing loss (11), abnormal neuroimaging studies (9), microcephaly (5) and psychomotor retardation (5). Neuroimaging findings included ventriculomegaly, periventricular calcifications, abnormal white matter echogenicity or MRI signal intensity and lenticulostriate vasculopathy.

Median (range) age at the beginning of treatment was 3 months (1.8–8.8 months). All children received oral VGC, and 4 also intravenous ganciclovir. Median (range) ganciclovir treatment duration was 4 weeks (3–6 weeks), whereas median VGC treatment duration was 6 months (3.5–12 months). Data regarding antiviral treatment and hearing outcomes are summarized in Table 1. VGC therapy was well tolerated and no treatment was interrupted due to side effects. Six patients developed neutropenia (all grade 1 or 2; lowest neutrophil count: 660 cell/mm^3) that resolved with VGC dose adjustment, none requiring G-CSF. Four patients had transiently raised aminotransferases (maximal values: AST 238 IU/L and ALT 246 IU/L). Urine CMV shell vial culture and/or urine CMV-PCR was negative after 8 weeks of treatment in all cases and remained negative during antiviral therapy. Eleven children (85%) had hearing defects at baseline, compared to 50% at 12 months. By ears, 18 out of 26 ears (69%) had hearing loss at the initial assessment: 7 mild, 3 moderate and 8 severe, compared to 46% at 12 months: 3 mild, 1 moderate, 7 severe. In 7 of the 18 baseline-affected ears (3 with mild hearing loss, 3 moderate, 1 severe), an improvement in hearing was noted. None of the remaining showed deterioration in hearing. Only 1 ear out of 8 with severe hearing loss at baseline improved, compared with 6 out of 10 with mild or moderate hypoacusia. In 8 normal ears at baseline, no worsening was found at 12 months.

4. Discussion

Congenital CMV infection causes very significant long-term disability due to hearing loss and mental handicap.[1,4] Diagnosis of congenital CMV infection is confirmed by virus isolation or identification of viral genome within the first 2 weeks of age.[7] Recently, the development of methods for detecting CMV DNA in DBS has enabled the retrospective diagnosis of congenital CMV in older children.[8] In a phase III randomized clinical trial, intravenous ganciclovir for 6 weeks prevented hearing deterioration in children with congenital CMV infection and CNS involvement. However, 21% of treated infants developed progressive hearing loss at the 1-year hearing assessment.[2] It is unclear whether progressive hearing loss is caused by viral reactivation, immune response or the delayed clinical onset of an already present damage. Nevertheless, longer antiviral treatment might sustain suppression of viral replication and slow down immune response as compared with the 6-week treatment course, potentially leading to a better auditory outcome.[9–11] Pharmacokinetic studies have shown that intravenous ganciclovir (6 mg/kg/12 h) and oral VGC (16 mg/kg/12 h) result in similar plasma concentrations of ganciclovir in neonates with CMV infection[12,13]; thus, VGC appears to be a good alternative for long-term antiviral treatment. There is a paucity of data on the treatment of children with congenital CMV infection beyond the neonatal period and on the efficacy and long-term outcome of prolonged antiviral therapy. A placebo-controlled, double-blind, randomized study (CASG 112) comparing 6 weeks vs. 6 months of oral VGC in congenital symptomatic CMV infection is currently ongoing.[14] The Spanish Society of Pediatric Infectious Diseases recommends intravenous ganciclovir followed by oral VGC in infants with congenital CMV infection with CNS involvement or organospecific disease. Cases diagnosed retrospectively should be individually assessed, and treatment considered in those with CNS involvement or progressive hearing loss.[7] However, the efficacy of antiviral therapy to prevent hearing deterioration in these patients is unknown. Some authors have reported hearing improvement in infants treated with oral VGC beyond the neonatal period,[5,15] but to our knowledge this is the first case series of such patients. Most infants presented hypoacusia at baseline and received long-term VGC. Antiviral treatment was well tolerated, neutropenia being its main side effect, but there were not any cases of grade 3 or 4 neutropenia.

Interestingly, hearing deterioration was not observed at the 12-month follow up in our series as compared to worsening auditory response at 1 year in 21% of the children treated with the 6-week ganciclovir course.[2] In a recent retrospective series, only 2% of infants receiving ganciclovir plus oral VGC up to 12 months of age showed hearing worsening at ≥1 year.[9] Prolonged antiviral treatment may also improve hearing in some cases. In our study, 6 out of 10 ears with mild or moderate hypoacusia at baseline improved during treatment, and this improvement was sustained at the 12-month control.

Table 1
Antiviral therapy and hearing outcomes.

Patient	Confirmed congenital CMV infection	Age at the beginning of any antiviral therapy (months)	Treatment with GCV[a]	Duration of VGC[b] treatment (months)	BAER threshold (dB) at baseline[c]		BAER threshold (dB) at 6 months		BAER threshold (dB) at 12 months[d]	
					Rt ear	Lt ear	Rt ear	Lt ear	Rt ear	Lt ear
1	Yes	2.2	Yes	6	40	≥80	30	≥80	30	≥80
2	Yes	3	Yes	6	≤20	40	≤20	≤20	≤20	≤20
3	Yes	4.5	No	7	≥90	≥90	≥90	≥90	≥90	≥90
4	No	2	Yes	6	40	≤20	≤20	≤20	≤20	≤20
5	Yes	7	No	7.5	50	≥90	20	60	20	50
6	Yes	2	No	8	40	≤20	≤20	≤20	≤20	≤20
7	Yes	8	No	7.5	≤20	≤20	≤20	≤20	≤20	≤20
8	Yes	5	No	12	50	80	50	80	40	80
9	Yes	8	No	4	30	80	30	90	30	90
10	Yes	8.8	No	3.5	≥100	≥100	≥100	≥100	≥100	≥100
11	No	1.8	Yes	4	30	30	30	30	–	–
12	No	3	No	6	50	≤20	30	30	≤20	≤20
13	Yes	3	No	6	≤20	≤20	≤20	≤20	≤20	≤20

[a] Ganciclovir.
[b] Valganciclovir.
[c] Brainstem-evoked response.
[d] Patient 11 was lost to follow-up after the 6-month visit.

The main limitations of our study are its retrospective design, the lack of a control group and the small sample size. Age at the beginning and duration of antiviral therapy varied among patients. Valganciclovir has been administered considering the neonatal dosage, due to the lack of pharmacokinetic data in infants.

In conclusion, our results show that prolonged VGC treatment is well tolerated and may preserve or even improve hearing in children with post neonatal-diagnosed congenital CMV infection and mild or moderate hypoacusia at baseline, even when therapy is started beyond the neonatal period. The follow-up duration of 12 months may be insufficient to determine whether this improvement in the auditory function is sustained, but it allows to acquire speech and oral language during early childhood, which is critical for central auditory development.[16] Additional studies are warranted to determine the optimal antiviral therapy for these patients and to assess the safety of long-term VGC use.

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None.

Competing interests

None declared.

Ethical approval

Not required.

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