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Main Article

Effect on hearing of ganciclovir therapy for asymptomatic congenital cytomegalovirus infection: four to 10 year follow up

A Lackner, A Acham, T Alborno, M Moser, H Engele*, R B Raggam†, G Halwachs-Baumann‡, M Kapitan**, C Walch

Abstract

Background: Congenital cytomegalovirus infection is the leading identified nongenetic cause of congenital sensorineural hearing loss. Most of the infections are asymptomatic but may be detected from umbilical cord vein and/or newborn serum positivity for human cytomegalovirus immunoglobulin M, and from urine positivity (on polymerase chain reaction) for human cytomegalovirus deoxyribonucleic acid in the newborn period. Children infected by cytomegalovirus may later develop sensorineural hearing loss. In symptomatically infected infants, ganciclovir therapy administered in the neonatal period prevents hearing deterioration. However, preventative therapy of asymptomatic congenital cytomegalovirus disease with ganciclovir is controversial, as side effects such as severe neutropenia may occur during treatment.

Methods: The study population consisted of 23 asymptomatic children with congenital cytomegalovirus infection. Twelve children were treated just after diagnosis of cytomegalovirus infection in the newborn period, with ganciclovir 10 mg/kg bodyweight for 21 days. The other 11 children were observed without therapy. Over a four to 10 year follow-up period, we evaluated all the children's hearing status using pure tone audiometry.

Results: All 23 children had normal sensorineural hearing at one year follow up. Five of the 23 children (21.7 per cent) were lost to follow up over the four to 11 year follow-up period. Of the remaining 18 children, sensorineural hearing loss occurred in two (11.1 per cent). Neither child had been treated with ganciclovir in the newborn period. An eight-year-old boy showed bilateral high frequency loss and a 10-year-old girl showed severe unilateral sensorineural hearing loss. In the ganciclovir-treated group (nine children), none showed sensorineural hearing loss. During ganciclovir therapy, moderate neutropenia occurred as a side effect in two out of 12 (16.6 per cent) treated children. Speech and general development were normal in all children.

Conclusion: Asymptomatic congenital cytomegalovirus infection is likely to be a leading cause of sensorineural hearing loss in young children. Intravenous ganciclovir therapy seems to offer a medical option to prevent subsequent sensorineural hearing loss. Further studies including a greater number of children are needed. Cytomegalovirus screening models are mandatory if medical therapy is to be implemented in time.

Key words: Sensorineural Deafness; Child; Cytomegalovirus; Ganciclovir

Introduction

Cytomegalovirus (CMV) is the leading nongenetic cause of congenital sensorineural hearing loss (SNHL) in developed countries.[1,2] The prevalence of congenital CMV infection in our region of Austria is about 0.22 per cent.[3,4] Other reports from Europe and the US show prevalence rates of between 0.2–2 per cent.[5,6] Therefore, approximately one per cent of all neonates are congenitally infected with CMV.[7]

Ten per cent of infants with congenital CMV are symptomatic, and SNHL accompanies these symptoms in 30 to 65 per cent,[1,8] whereas 90 per cent of congenital CMV infections are asymptomatic. However, SNHL occurs from 7 to 15 per cent in this primary asymptomatic group during the first six years of life;[9] thus, the prevalence of SNHL caused by CMV infection in childhood ranges from 20 to 30 per cent.[10]

From the Department of Neurotology, ENT University Hospital, the *Department of Neonatology, Hospital for Paediatrics, the †Institute of Hygiene, Microbiology and Environmental Medicine, the ‡Department of Clinical Chemistry and Laboratory Medicine, and the **Institute for Medical Informatics, Statistics and Documentation, Graz Medical University, Austria.
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The virus remains latent in the organism for the lifetime of the host, and it can be reactivated periodically.[11] A large virus burden during the first month of life is associated with SNHL.[12] However, until now, it has been unclear whether the development of SNHL in childhood is caused by the reactivation of the virus, the immunological response of the host or the delayed clinical appearance of symptoms.

Several studies of medical treatment with ganciclovir (an antiviral agent administered to affected, symptomatic infants in the neonatal period) document the possibilities for prevention of hearing deterioration[13] and the improvement of other neurological symptoms.[14,15] As neutropenia and thrombocytopenia occur due to high dose and/or long term ganciclovir therapy,[13,16] these possible side effects are dose-related and can be easily managed by dose reduction.[3,16]

Deafness, severe SNHL or deterioration of existing, moderate, congenital SNHL directly affects the child's intellectual skills. Therefore, use of ganciclovir to treat neonatal congenital CMV infection should enhance the child's learning possibilities and promote a higher quality of life. Secondary prevention strategies (such as active human CMV immunisation or secondary passive immunisation of infected pregnant women) are currently undergoing clinical trials but are not currently in clinical use, to our knowledge.[17]

Therefore, low dose ganciclovir therapy for asymptomatic congenital CMV-infected newborns, as secondary prevention of early childhood SNHL or neurological deficits, should be helpful in order to minimise the prevalence and development of SNHL in asymptomatic congenitally CMV-infected children.

In order to estimate the impact on SNHL development of early ganciclovir therapy in asymptomatic congenitally CMV-infected children, we evaluated the hearing status of already randomly treated children from a former study group over a four to 10 year follow-up period (from 1993 to 2000), by performing pure tone audiometry.[3]

Materials and methods

Study subjects

This study examined 23 children with documented, asymptomatic congenital CMV infection, born between January 1993 and December 2000 at the authors' hospital. Fourteen of the children had taken part in a previous prospective CMV screening and diagnosis study; in addition, nine others were included, up to December 2000.[3] These 23 asymptomatic children were randomly allocated to receive either ganciclovir therapy or no therapy, as soon as CMV was detected. Congenital CMV infection was screened by detection of CMV immunoglobulin M (IgM) in maternal serum or newborn umbilical cord vein blood, and identified by isolation of the virus in urine during the first postnatal week.

Twelve of the children were treated with ganciclovir. In their first year, none of the 23 children developed severe, CMV-induced handicaps such as microcephaly, hydrocephaly, ventriculomegaly, chorioretinitis or other ophthalmological symptoms, hepato-splenomegaly, thrombocytopenia, neutropenia, anaemia, jaundice, or hearing disorders.

At the age of one year, normal bilateral hearing was documented in all 23 children by measurement of bilateral transient evoked oto-acoustic emissions and by behaviour observation audiometry. Follow-up data for five children were unavailable because they moved to unknown addresses. Parental consent for examination of the remaining 18 children was obtained beforehand.

Follow up

Assessment of the medical history of each study subject included a review of their birth history and previous study protocols and medical reports (including radiographic investigations if available). The results of hearing screening tests performed at one year of age were retrieved from each child's medical record. Data on developmental status, health status and hearing level were obtained by the entries in each Mother-Child-Booklet.

Assessment of each child's hearing threshold was performed using ear microscopy, middle-ear impedance tests and behavioural observation audiometry until the age of four years; pure tone audiometry was used for older children.

Sensorineural hearing loss was defined as a median sensorineural decrease in hearing of $\geq$10 dBHL at low (125 to 1000 Hz), middle (1000 to 4000 Hz) or high (4000 to 16 000 Hz) frequencies and was graded as mild (25 to $\leq$40 dBHL), moderate (41 to $\leq$65 dBHL), severe (66 to $\leq$96 dBHL) or profound ($>$96 dbHL).

Therapy

Intravenous application of ganciclovir was commenced within the first 10 days of life. The dosage was 10 mg ganciclovir per kg body weight for 21 days. If any signs of toxicity occurred (such as leucopoenia or diarrhoea), the dosage was lowered to 5 mg per kg body weight; therapy was stopped if side effects did not resolve.

Results

At our hospital between January 1993 and December 2000, a total of 23 children were identified as having asymptomatic congenital CMV infection. Normal hearing was documented for all 23 children before the age of one year.

Five of the 23 (21.7 per cent) children were lost to follow up during the four to 10 year follow-up period. The remaining study population (18 children) had an average age of 8.1 years, an age range of 4.2 to 11.2 years and a male:female ratio of 11:7.

Ten (55.5 per cent) of these 18 children received intravenous ganciclovir therapy within the first 10 days of life (Table I). None of the other eight children received any kind of medical treatment.

Speech and general development were normal in all the study children throughout follow up.

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TABLE I

PATIENT CHARACTERISTICS

Parameter	Treatment group	Control group
Asymptomatic congenital CMV (*n*)	12	11
Normal hearing ≤1 yr (*n*)	12	11
Lost to follow up (*n*)	2	3
Age (mean ± SD (yrs))*	7.4 ± 2.5	9.0 ± 1.6
Gender (male/female)*	5/7	6/5
Urine CMV titre†‡		
Copies – median (*n*)	3.83E + 05 (11)	6.59E + 03 (5)
Copies – range	1.06E + 05 − 1.17E + 07	2.00E + 03 − 8.28E + 05

n refers to patient numbers throughout. *$n = 18$ complete observations. †Includes patients lost to follow up. ‡In first postnatal week. CMV = cytomegalovirus; yr = year; SD = standard deviation

The children were followed up for a mean of 7.1 years (standard deviation (SD) 2.2; range 3.2–10.3). In the treatment group, the mean duration of follow up was 6.4 years (SD 2.5; range 3.2–10.3) and the median duration was 5.9 years. However, in the control group, the mean duration of follow up was 8.0 years (SD 1.6; range 4.6–9.8) and the median duration was 8.2 years. This difference in the observation times was not statistically significant according to the Wilcoxon exact test, performed because of tied data, ($p = 0.18$).

Statistical evaluation of the urine CMV titre in both groups was not performed, because follow-up data for only four control group patients were available.

Sensorineural hearing loss occurred in two of the 18 (11.1 per cent) children (Table II). Neither had been treated with ganciclovir as neonates. One eight-year-old boy showed bilateral, mild, high frequency hearing loss with a maximum of 30 dBHL at 8000 Hz (Figure 1). One 10-year-old girl showed unilateral, moderate to profound SNHL (Figure 2). These two children's follow-up periods were greater than five years. The difference between the SNHL incidence in the treated and untreated groups did not achieve statistical significance ($p = 0.18$, Fisher's exact test).

None of the 10 children in the ganciclovir treatment group showed signs of SNHL.

During ganciclovir therapy, moderate neutropenia (i.e. neutrophil cell count $1.0–1.5 \times 10^9$/l; normal range $1.5–10.0 \times 10^9$/l)[18] occurred in two of the 12 (16.6 per cent) treated children. After lowering the dosage to 5 mg ganciclovir per kg body weight, the leukocyte rate normalised within a few days. All 10 study patients receiving intravenous ganciclovir had finished their therapy after three weeks.

Discussion

In symptomatic cytomegalovirus (CMV)-infected infants with symptoms involving the central nervous system, systemic ganciclovir therapy administered in the neonatal period prevents hearing deterioration or maintains normal hearing in early childhood.[13,19] On the other hand, symptomatic CMV-infected infants receiving no such treatment develop sensorineural hearing loss (SNHL) in early childhood significantly more often, compared with ganciclovir-treated children.[13] The results of our study suggest that

TABLE II

INDIVIDUAL PATIENT CHARACTERISTICS AND HEARING RESULTS OVER 4–10 YEAR FOLLOW UP

Pt no	Age (yrs)	Gender	Ganciclovir	FU (yrs)	Diagnosis after FU
1	4.2	M	Yes	3.2	NH
3	9.7	F	No	8.7	NH
5	10.6	M	No	9.6	NH
6	8.8	M	No	7.8	NH
7	8.5	M	No	7.5	Bilat HF SNHL
8	8.1	F	Yes	7.1	NH
9	4.3	M	Yes	3.3	NH
10	5.6	M	No	4.6	NH
11	5.9	F	Yes	4.9	NH
12	5.9	F	Yes	4.9	NH
15	11.3	F	Yes	10.3	NH
16	9.7	M	Yes	8.7	NH
18	10.4	M	Yes	9.4	NH
19	8.6	M	No	7.6	NH
20	9.5	F	No	8.5	Unilat severe SNHL
21	7.1	F	Yes	6.1	NH
22	6.7	M	Yes	5.7	NH
23	10.8	M	No	9.8	NH

Pt no = patient number; yrs = years; FU = follow up interval; M = male; F = female; NH = normal hearing; bilat HF = bilateral high frequency; SNHL = sensorineural hearing loss; unilat = unilateral

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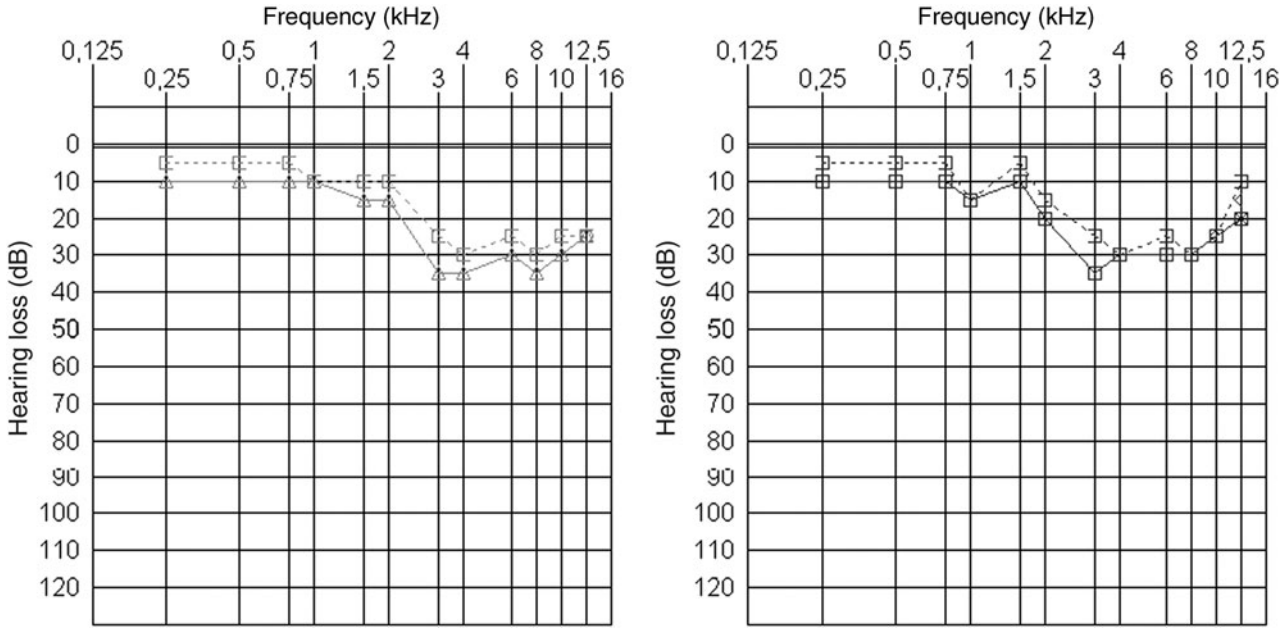

FIG. 1

Pure tone audiogram of an eight-year-old boy with primary, asymptomatic congenital cytomegalovirus infection, showing bilateral, mild hearing loss in the high frequencies.

ganciclovir given intravenously within the first 10 days of life for a total of three weeks helps maintain normal hearing during childhood in asymptomatic congenital CMV-infected children.

The total detection rate for SNHL in our study group was 11.1 per cent; this is similar to previous studies,[1,9] which have found rates of up to 7.4 per cent, and rates of 18.2 per cent for delayed SNHL onset up to the age of 62 months.[20] Although a statistical bias may be evident in this study, due to the small group of investigated children, the detection of SNHL in two children without treatment is significant.

The development of SNHL in congenitally CMV-infected neonates depends on a large virus burden during the first month of life. Higher amounts of infectious CMV in urine and the presence of CMV deoxyribonucleic acid (DNA) in the peripheral blood of children with asymptomatic congenital CMV infection during early infancy have

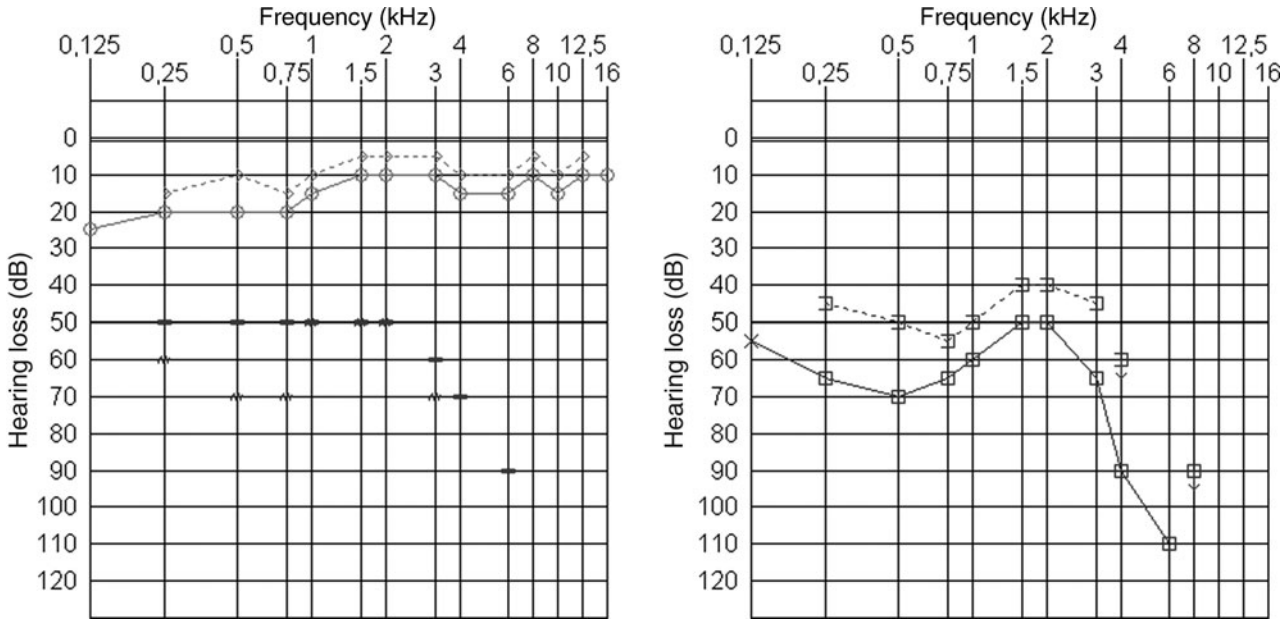

FIG. 2

Pure tone audiogram of a 10-year-old girl with primary, asymptomatic congenital CMV infection, showing unilateral, moderate to profound hearing loss.

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been found to be associated with an increased risk of subsequent SNHL development.[12,20] Ganciclovir applied in the first week of life lowers the virus burden in the peripheral blood;[12] a reduced urine virus load reflects the positive effect of ganciclovir therapy on the prevention of organic symptoms.[14]

In our study group, SNHL was observed in two children: bilateral, mild hearing loss in the high frequencies in one case; and unilateral (left ear), moderate to severe hearing loss in all frequencies in the second case. The latter case, a 10-year-old girl, was handicapped in bidirectional hearing but did not complain of it in everyday life. Neither child showed delayed speech or general development, nor were such delays found in any other study patient. The late diagnosis of SNHL in both affected cases, at eight and 10 years of age, was perhaps due to these children being previously investigated only by their general practitioner. As no other symptoms of reactivation of CMV infection were evident and the hearing loss in both cases was unremarkable, both sets of parents unfortunately withheld consent for peripheral blood venepuncture in order to analyse CMV DNA virus load, and for further magnetic resonance imaging head scans. However, these children's clinical histories indicated no other relevant aetiological factors for SNHL, so we believe that their hearing loss was due to their congenital CMV infection. Because of lack of evidence of a new CMV reactivation, subsequent ganciclovir therapy was not performed.

- **Congenital cytomegalovirus (CMV) disease is the leading identified nongenetic cause of congenital sensorineural hearing loss**
- **In symptomatic CMV-infected infants, ganciclovir therapy administered in the neonatal period appears to prevent hearing deterioration**
- **Preventive therapy with ganciclovir for asymptomatic congenital CMV disease is controversial, as side effects such as severe neutropenia may occur during therapy**

Administering antiviral treatment does however involve potential risk.[16,20] In animal models, gonadal toxicity and carcinogenicity has been observed following ganciclovir therapy.[16] Therefore, some authors[13,19] have refused paediatric antiviral therapy in settings other than symptomatical CMV infection. All 12 of our study patients who received intravenous ganciclovir finished their therapy by three weeks; this cumulative dosage would appear to be more tolerable. In our group, no evidence of neoplastic lesions was found, neither from the history nor from the clinical investigations.

The side effects of ganciclovir therapy are dose-dependent and mostly affect the haematological system, manifesting as transient to severe and as isolated neutropenia to pancytopenia. In our study group, only moderate neutropenia occurred, in two out of the 12 (16.6 per cent) ganciclovir-treated children. After lowering the dosage to 5 mg ganciclovir per kg body weight, the leukocyte rate normalised within a few days. Kimberlin *et al.*[13] and Michaels *et al.*[19] administered ganciclovir 10 mg/kg/day for between six weeks[13] and 18 months,[19] and observed significant haemotoxicity in up to two-thirds of their treated patients. For this reason, antiviral therapy must be carefully and accurately monitored during drug administration, and periodically afterwards.

Antiviral therapy of asymptomatic congenital CMV-infected neonates depends on a reliable screening programme and adequate diagnosis. From 1993 to 2000, in order to obtain objective evidence of congenital CMV infection in neonates, we used the detection of CMV-IgM in maternal serum or neonatal umbilical cord vein blood as a screening investigation, with subsequent diagnosis depending on identification of CMV virus from neonatal urine (isolating the virus using polymerase chain reaction) during the first postnatal week.

Recent advances in the diagnosis of congenital CMV infection offer even more possibilities to detect fetal or maternal CMV infections at a much earlier stage.[21] Therefore, in the future, antiviral therapy for CMV infection may be used not only in neonates. In 2007, Jacquemard *et al.*[22] reported the results of an uncontrolled, non-randomised therapeutic study of oral valaciclovir administration to pregnant women carrying a fetus with confirmed CMV infection. In this study, the CMV viral load in fetal blood decreased significantly after one to 12 weeks of treatment, and outcomes were better in the treated group than in the untreated group.

Other clinical trials have investigated intravenous[23] or intrauterine[24] application of CMV immunoglobulin. However, there is currently no established modality for treating a pregnant woman with CMV infection.

Conclusion

Asymptomatic congenital CMV infection is likely to be a leading cause of SNHL in young children. Assuming a routine screening programme with appropriate testing for congenital CMV infection at birth, our results suggest that, in asymptomatic congenital CMV-infected neonates, hearing deterioration in early childhood could be prevented by early (within the first week of life), intravenous administration of ganciclovir. Using low dose ganciclovir therapy minimises specific side effects and seems to be as effective as high doses. However, further studies including a greater number of children are needed to substantiate our results.

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Address for correspondence:
Dr Andreas Lackner,
Dept of Neurotology,
Medical University Graz,
Auenbruggerplatz 26-28,
A-8036 Graz, Austria.

Fax: +43 316 385 7643
E-mail: andreas.lackner@meduni-graz.at

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