Hearing loss in children with congenital cytomegalovirus infection

Original Article

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Abstract

Objective: To study the prevalence of hearing loss in children with congenital Cytomegalovirus infection and the influence of the type of maternal infection, symptoms and neonatal treatment with valganciclovir.
Study design: Retrospective cohort
Material and Methods: Data was collected through computerized processes of children with congenital Citomegalovirus, followed in Hospital de Guimarães, between 2017 and 2022. Hearing evaluation was performed between 2 months and 2 years old. The type of maternal infection and treatment with valganciclovir were assessed.
Results: Twenty-two children were enrolled in this study. Global prevalence of hearing loss was 50%, greater in symptomatic children and children born to mothers with primary infection. After treatment with valganciclovir, 41.6% of children presented with hearing loss.
Conclusion: The risk of hearing loss is greater in symptomatic children and children born to mothers with primary infection. A screening programme should be implemented regarding the high prevalence of hearing loss in asymptomatic children.

Keywords: Cytomegalovirus, CMV, hearing, valganciclovir, children, screening.

Introduction

Cytomegalovirus (CMV) infection is the most common congenital infection and the main cause of non-genetic sensorineural hearing loss in the newborn (NB). Its incidence is 0.6%–0.7% in developed countries[1] and 0.2%–2.5% worldwide[5] . In Portugal, its estimated prevalence is 1.05%.

However, there is no screening for CMV, either universal or associated with the universal neonatal hearing screening (*Rastreio Auditivo Neonatal Universal* - RANU); therefore, the diagnosis is made after the initial incidental finding of maternal seroconversion or when presented with a NB with symptomatic illness, as reported by Sousa[2].

Vertical transmission occurs during pregnancy in both primary or secondary maternal infection, which may result from reactivation of a latent infection or reinfection by a new strain of CMV in a woman with antibodies against CMV[3]. In a meta-analysis conducted in 2007, Kenneson and Cannon found that the rates of vertical transmission were 32% and 1.4% for primary and secondary maternal infection, respectively[6]. There is a higher risk of transmission and greater probability of severe illness when the infection occurs in the periconceptional period or first trimester of pregnancy and in cases of primary maternal infection.

The clinical manifestations at birth vary from asymptomatic infection to potentially fatal multiorgan disease. Only 10% of NBs with congenital CMV infection are symptomatic at birth and may present with delayed growth, microcephaly, petechial rash, brain microcalcifications, hepatosplenomegaly, retinitis, thrombocytopenia, or hepatitis. About half of symptomatic NBs will have long-term sequelae.

The majority of NBs (approximately 90%) are asymptomatic at birth. However, approximately 10%–15% of asymptomatic NBs develop long-term sequelae, with sensorineural hearing loss being the most frequent[1]. The prevalence of sensorineural hearing loss is reportedly 30%–65% in symptomatic NBs and 7%–15% in asymptomatic NBs. The onset and progression of hypoacusis are highly unpredictable[4]. It may manifest at birth or develop over the years, and is responsible for 25% cases of hearing loss among 4-year-old children[2].

Treatment with ganciclovir or valganciclovir is indicated for symptomatic congenital CMV infection, and the latter is more commonly used because of its lower risk of adverse effects and possibility of oral administration. Treatment with one of these antivirals has been associated with improved performance in hearing tests in the long term[10]. Valganciclovir is recommended at a dose of 16 mg/Kg, twice a day, for a minimum period of six weeks. Its adverse effects include neutropenia, anemia, thrombocytopenia, and more rarely, elevated liver enzymes, creatinine, and urea.

The objective of the present study was to analyze the prevalence of hypoacusis in children with a diagnosis of congenital CMV infection, in addition to examining whether the symptoms at birth, type of maternal infection, and neonatal treatment with valganciclovir influence the course of the disease.

Materials and Methods

This retrospective study was conducted at the Hospital da Senhora da Oliveira in Guimarães. The data were obtained from the electronic records of children who were diagnosed with congenital CMV and followed-up at the childhood deafness clinic between 2017 and 2022. The diagnosis was made by the detection of viral DNA in the urine by polymerase chain reaction (PCR). A diagnosis of congenital CMV infection was made when a NB aged ≤14 days had a positive urine test.

The children with a diagnosis of congenital CMV infection were referred to the childhood deafness clinic. Hearing evaluation was performed between the ages of two months and two years using brainstem auditory evoked potentials (BAEP). When more than one hearing evaluations were performed, the results of the most recent evaluation were used. The CMV infection was deemed to be symptomatic if the NB exhibited at least one of the following signs in the first two weeks of life: microcephaly, petechial rash, brain microcalcifications, hepatosplenomegaly, retinitis, thrombocytopenia, or hepatitis.

The type of maternal infection (primary or secondary) was determined by the detection of serum IgM, IgG, and IgG avidity for CMV.

Statistical analysis was performed using the IBM SPSS Statistics v. 28.0.1.0 software.

Results

The study included 22 children, comprising 10 boys (45.5%) and 12 girls (54.5%), with a mean age of 2.7±1.4 years. There were 11 cases of mild unilateral hypoacusis (50%) and no cases of bilateral hypoacusis. The

Table 1
Prevalence of hypoacusis according to the presence of neonatal symptoms and type of maternal infection

	Symptomatic (n)	Asymptomatic (n)	Primary Maternal Infection (n)	Secondary Maternal Infection (n)
Hypoacusis (n)	10 (58,8%)	1 (20%)	8 (66,7%)	3 (37,5%)
Without hypoacusis (n)	7 (41,2%)	4 (80%)	4 (33,3%)	5 (62,5%)

prevalence of hypoacusis was 50% overall, 58.8% in symptomatic patients, and 20% in asymptomatic patients (Table 1).

Seventeen children (77.3%) were diagnosed with symptomatic disease; six had microcalcifications in transfontanellar ultrasound, four had microcephaly, three had thrombocytopenia, three had prolonged jaundice, and one had hepatosplenomegaly.

The type of maternal infection was determined in 20 cases as follows: primary in 12 cases (60%) and secondary in eight cases (40%). With regard to the children with hypoacusis, eight (72.7%) were infected from primary maternal infection and three (27.3%) from secondary maternal infection. Eight of the 12 (66.6%) children born to mothers with primary infection and three of the eight (37.5%) children born to mothers with secondary infection had hypoacusis.

Twelve of the 22 children (54.5%) received antiviral treatment with valganciclovir, which was initiated in the first month of life and was administered for at least six weeks. Five children (41.6%) developed hearing loss later on. There was no statistically significant association between the antiviral treatment and later manifestation of hypoacusis (p=.525 , chi-square test).

Discussion

Because screening for CMV has not been implemented in Portugal, its diagnosis is usually made after a NB presents with symptoms of the disease[2]. Therefore, in our study, the prevalence rates of symptomatic disease (77.3% vs 10%) and hearing loss after primary infection (66.6% vs 32%) and secondary infection (37.5% vs 1.4%) were expected to be higher than those reported in the literature, namely in the meta-analysis of Kenneson and Cannon[6].

There were 11 cases of hypoacusis in the present sample, corresponding to a prevalence of 50%, which is in line with the prevalence of 30%–65% reported in symptomatic patients by Riga et al.[4] The absence of cases of bilateral hypoacusis can be explained by the small size of the sample.

Our results are consistent with those of a systematic review conducted by Goderis et al.[5] in that the prevalence of hypoacusis was significantly higher among symptomatic children.

The currently available data do not allow the accurate determination of the prevalence of hypoacusis in children after primary or secondary maternal infection. However, as expected, we found a higher prevalence of hearing loss in children whose mothers had primary CMV infection, which in line with the findings of Goderis et al.[5] and Puhakka et al.[1]

Unlike the results presented by Kimberlin et al.[9], our analysis did not show a relationship between hypoacusis and valganciclovir treatment in the neonatal period. However, the small sample size may have hindered the detection of a statistically significant relationship.

The present study has some limitations. Firstly, it was retrospective in nature and had a small sample size. Secondly, there was a clear selection bias as the hearing test was only performed in symptomatic children because there is no screening for CMV in Portugal, which resulted in a sample with a largely disproportionate number of symptomatic and asymptomatic children. Lastly, there was

some natural variation in the timing of the hearing evaluation.

The urine PCR test for CMV has a sensitivity between 93% and 100% and costs about 7.50 €, which makes it the ideal test for screening of congenital CMV infection[12]. Chen et al.[13] compared the cost/benefit relationship of universal screening, screening of a target population, and no screening and concluded that universal screening was more effective as it detected a higher number of children at risk of sequelae and demonstrated a superior cost/benefit relationship.

Furthermore, the diagnosis of congenital CMV infection in the first three weeks of life and starting antiviral treatment with valganciclovir in the first month can reduce the risk of hypoacusis associated with this disease, as shown by Kimberlin et al.[10] and Cannon et al.[11] Similarly, according to Mareri et al.[14], early treatment with an antiviral has a beneficial effect on manifestations such as chorioretinitis, thrombocytopenia, and anemia, and also reduces the risk of delayed neurocognitive development. In the absence of screening, most children who are asymptomatic at birth and at risk of developing hypoacusis are diagnosed at a later stage. By then there is no benefit of antiviral treatment, and language acquisition and adaptation to hearing aids is not as effective, which has a significant impact on the child's quality of life. Moreover, some children need to be referred for cochlear implant surgery, which is a much more costly treatment.

Therefore, universal screening is more appropriate because of the high prevalence of late-onset hypoacusis in NBs with asymptomatic CMV infection, which may not detected by screening only NBs who do not pass the RANU.

In fact, there are numerous reports in the literature on hearing loss in asymptomatic children that manifests only in adolescence or emerging adulthood. Thus, it is necessary to emphasize that screening in itself is not sufficient to improve the quality of life of these children, and long-term follow-up and frequent hearing testing until emerging adulthood are essential to maximize the benefits of treatment.

Conclusion

Congenital CMV infection remains one of the main causes of childhood hearing loss. Children whose mothers had primary CMV infection and symptomatic NBs were at a higher risk of developing hypoacusis. The hearing acuity of these children should be monitored in the long term. The implementation of screening is essential because of the high prevalence of hypoacusis in asymptomatic children.

Conflict of interest

The authors declare no conflict of interest regarding this article.

Data confidentiality

The authors declare that they followed the protocols in use at their working center regarding the publication of patients' data.

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Availability of scientific data

There are no publicly available datasets related to this study.

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