RESULTS OF COCHLEAR IMPLANTATION IN CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION VERSUS GJB2 MUTATION

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Abstract

Background: Children with congenital cytomegalovirus (CMV) infection face a bigger risk of neurological deficits and developmental delays associated with sensorineural hearing loss (SNHL). Their rehabilitation with a cochlear implant (CI) may therefore be inferior to the paediatric population in general. This study describes post-implant outcomes in children with CMV-related deafness and compares them to children with genetic deafness caused by GJB2 mutation (connexin 26) rehabilitated at the Centro Hospitalar e Universitário de Coimbra, Portugal.

Material and method: We conducted a revision of 11 children with profound hearing loss caused by congenital CMV infection rehabilitated with a CI in our institution. The children were divided into 3 groups according to age of implantation (<2 years, 2–3 years, >3 years) and their performance was compared to a group of children with genetic hearing loss caused by GJB2 mutation. To compare performance the following tests were applied: SIR, CAP, vocal characteristics evaluation grid (VCEG), MAIS, and MUSS.

Results: We found no differences between the two groups in terms of hearing thresholds obtained with a CI. In spite of a wider spread of results in the CMV group, there were no significant statistical differences in the SIR and VCEG tests or in the MAIS and MUSS questionnaires. There was a significant difference in the CAP test (p=0.049) where the GJB2 group had superior results.

Conclusions: The present study has shown that the CMV group had poorer results for the CAP test and a wider spread of results in the other tests. However, the CMV group attained results comparable to children with profound hearing loss and no other deficit, and benefited from rehabilitation with a cochlear implant.

Keywords: cochlear implants • cytomegalovirus infections • deafness

RESULTADOS DE LA INSERCIÓN DE IMPLANTES COCLEARES EN NIÑOS CON LA INFECCIÓN CONGÉNITA CON EL CITOMEGALOVIRUS Y LA MUTACIÓN GJB2

Resumen

Introducción: Los niños con la infección congénita con el citomegalovirus (CMV) se enfrentan a un mayor riesgo de defectos neurológicos y retraso en el desarrollo asociado a la pérdida auditiva neurosensorial (SNHL). Su rehabilitación con el implante coclear (CI) puede ser más difícil que en el caso de otros niños. El presente estudio describe los resultados tras la inserción de implantes cocleares en los niños con sordera asociada con CMV y comprara estos resultados con los de los niños, cuya pérdida auditiva está condicionada por factores genéticos en la mutación de GJB2 (conexina 26), rehabilitados en el Centro Hospitalar e Universitário de Coimbra en Portugal.

Materiales y métodos: El estudio se ha realizado en 11 niños con pérdida auditiva profunda provocada por la infección por el CMV y rehabilitados en nuestro centro utilizando los implantes cocleares. Los niños han sido divididos en 3 grupos de acuerdo con la edad, en la que se llevó a cabo la implantación (2 años, de 2 a 3 años, >3 años), y sus resultados fueron comparados con pérdida auditiva condicionada genéticamente, provocada por la mutación del gen GJB2. Para el estudio comparativo se han utilizado las siguientes pruebas: SIR, CAP, VCEG, MAIS i MUSS.

Resultados: No se ha observado ninguna diferencia entre los dos grupos examinados respecto a los umbrales de audición en los usuarios de CI. A pesar de una mayor discrepancia de los resultados en el grupo de los niños con CMV, no se han producido diferencias estadísticamente relevantes en las pruebas SIR y VCEG o en las encuestas MAIS y MUSS. Se ha observado

una diferencia considerable en la prueba CAP (prueba de procesamiento auditivo central) (p=0,049), en la que el grupo GJB2 ha obtenido mejores resultados.

Conclusiones: El estudio ha demostrado que el grupo CMV obtuvo peores resultados en la prueba CAP, pero en todas las demás pruebas los resultados fueron más dispersos. Sin embargo, el grupo CMV ha obtenido resultados comparables con los de los niños con pérdida auditiva profunda y sin otro defecto, y también se ha beneficiado de la rehabilitación con el implante coclear.

РЕЗУЛЬТАТЫ УЛИТКОВОЙ ИМПЛАНТАЦИИ У ДЕТЕЙ С ВРОЖДЕННОЙ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИЕЙ И МУТАЦИЯ GJB2

Изложение

Введение: Дети с врожденной цитомегаловирусной инфекцией (CMV)вынуждены бороться с увеличенным риском неврологических нарушений и задержкой развития, связанной с рецептивной тугоухостью (SNHL). Их реабилитация с помощью улиткового имплантата (CI) может быть труднее, чем в случае других детей. Это исследование описывает результаты после имплантации у детей с глухотой, связанной с CMV, и сравнивает эти результаты с результатами детей с генетически предопределенной глухотой при мутации GJB2 (конексин 26), реабилитированных в Centro Hospitalar e Universitário de Coimbra в Португалии.

Материал и методы: Исследование проведено на 11 детях с глубокой тугоухостью, вызванной инфекцией CMV и реабилитированных в нашем центре с помощью CI. Дети были разделены на 3 группы согласно возрасту, в котором отбылась имплантация (<2 года, 2–3 года, >3 лет), а их результаты были сравнены с генетически предопределенной тугоухостью, вызванной мутацией GJB2. Для сравнения использованы следующие тесты: SIR, CAP, VCEG, MAIS i MUSS.

Результаты: Не отмечено никакой разницы между исследованными группами в области порогов слышания у пользователей CI. Несмотря на больший разброс результатов в группе CMV, не было статистически существенных различий в тестах SIR и VCEG или анкет MAIS и MUSS. Была замечена существенная разница в тесте CAP (p=0,049), в котором группа GJB2 получила лучшие результаты.

Итоги: Исследование показало, что группа CMV имела худшие результаты теста CAP, но во всех других тестах результаты были более широкие. Однако, группа CMV получила результаты, сравнимые с результатами у детей с глубокой тугоухостью и отсутствием других нарушений, а также она черпала пользу из реабилитации с использованием улиткового имплантата.

WYNIKI IMPLANTACJI ŚLIMAKOWEJ U DZIECI Z WRODZONYM ZAKAŻENIEM CYTOMEGALOWIRUSEM A MUTACJA GJB2

Streszczenie

Wprowadzenie: Dzieci z wzrodzonym zakażeniem cytomegalowirusem (CMV) muszą zmierzyć się ze zwiększonym ryzykiem wad neurologicznych i opóźnieniem rozwoju związanym z niedosłuchem odbiorczym (SNHL). Ich rehabilitacja za pomocą implantu ślimakowego (CI) może być trudniejsza niż w przypadku innych dzieci. Badanie to opisuje wyniki po implantacji u dzieci z głuchotą związaną z CMV i porównuje te wyniki do u dzieci z głuchotą uwarukowaną genetycznie przy mutacji GJB2 (koneksyna 26) rehabilitowanych w Centro Hospitalar e Universitário de Coimbra w Portugalii.

Materiał i metody: Badanie przeprowadzono na 11 dzieciach z głębokim niedosłuchem spowodowanym zakażeniem CMV i rehabilitowanych w naszym ośrodku przy pomocy CI. Dzieci były podzielone na 3 grupy zgodnie z wiekiem, w którym odbyła się implantacja (<2 lata, 2–3 lat, >3 lat) a ich wyniki były porównane z niedosłuchem uwarunkowanym genetycznie spowodowanym mutacją GJB2. Do porównania wykorzystano następujące testy: SIR, CAP, VCEG, MAIS i MUSS.

Wyniki: Nie odnotowano żadnych różnic pomiędzy badanymi grupami w zakresie progów słyszenia u użytkowników CI. Pomimo większego rozrzutu wyników w grupie CMV, nie było statystycznie istotnych różnic w testach SIR i VCEG lub ankiet MAIS i MUSS. Zauważono istotną różnicę w teście CAP (p=0,049), w którym grupa GJB2 osiągnęła lepsze wyniki.

Wnioski: Badanie pokazało, że grupa CMV miała gorsze wyniki testu CAP, ale we wszystkich innych testach wyniki były rozleglejsze. Jednakże, grupa CMV osiągnęła wyniki porównywalne do wyników u dzieci z głębokim niedosłuchem i brakiem innych wad, a także czerpała korzyści z rehabilitacji za pomocą implantu ślimakowego.

Background

Cytomegalovirus (CMV) is estimated to be the leading environmental cause of congenital hearing loss in developed countries [1,2]. Its physiopathology is largely unknown [3]. Sensorineural hearing loss (SNHL) is the most common sequel following congenital CMV infection (10–15% of all infected children). Two clinical situations can be distinguished [1,2,4,5]. 1) Children with a *symptomatic CMV infection* (10%) presenting mental retardation, motor disability, haematological changes, coetaneous changes, cerebral calcification, seizures, microcephaly, and hydrocephalus. 2) Children with an *asymptomatic CMV infection* (90%), which may show a little development delay.

SNHL reportedly occurs in 20–65% of children with symptomatic infection at birth and in 15–25% of children with asymptomatic infection [1,2,4,5]. In both cases the deafness may be progressive or late-onset, requiring close audiological monitoring [1,5].

Children with symptomatic CMV infection present a higher risk of neurologic and cognitive deficits associated with their SNHL and often have a worse prognosis than those with asymptomatic CMV infection [6]. Imaging of the central nervous system performed at birth may predict the cognitive and motor deficits, but they cannot always predict a hearing loss or its severity [1].

Suggesting cochlear implantation in children with a congenital CMV infection has been questioned by some authors [7] because of highly divergent results in this group of children. Outcomes are generally inferior to the results expected for children who have a profound hearing loss due to other aetiologies. This can perhaps be explained by the higher incidence of motor and cognitive deficits (as well as central auditory changes) which interfere with acquiring spoken language. Furthermore, attention deficits noticed in many such children may interfere with their education and rehabilitation after implantation. On the other hand, some reports [8,9] have suggested that cochlear implantation can improve quality of life, even if progress is slower or less complete than in congenitally deaf children not infected with CMV.

This study aims to describe the results of children with deafness from CMV infection rehabilitated with a cochlear implant and compares them to those children with genetic hearing loss caused by GJB2 mutation (connexin 26).

Material and methods

In Portugal every newborn is screened at birth for SNHL using otoacoustic emissions. Women are screened for CMV infection/seroconversion during pregnancy; of those who test positive the newborns are also tested. In our study, diagnosis of congenital CMV infection was confirmed in every child by isolation of the virus in urine (PCR or culture) or by measurement of levels of IgM CMV in the first 3 weeks of life.

We evaluated 11 children with profound SNHL caused by confirmed congenital CMV infection and rehabilitated with CI in our institution. Hearing thresholds were determined with brainstem evoked potentials performed under general aesthesia and/or behavioural audiometry. We collected data on clinical history, diagnosis of deafness, associated pathologies, image data, age of implantation, implanted ear, and period of usage. The performance of these 11 children was compared to the results of 61 children who had genetic deafness by GJB2 mutation and implanted in our institution, matched according to the age of implantation.

In order to compare performance, children were divided into 3 groups according to age of implantation: <2 years, 2–3 years, and >3 years. Hearing thresholds with CI were determined and the following tests applied: speech intelligibility rating (SIR), categories of auditory performance (CAP), vocal characteristics evaluation grid (VCEG), meaningful auditory integration scale (MAIS), and meaningful use of speech scale (MUSS). We used the two-sample Kolmogorov–Smirnov test and the Kruskal-Wallis test to compare results (significant p value <0.05) using the SPSS 9.0 program.

Results

Clinical descriptions of the 11 children (8 male and 3 female) with CMV infection is presented in Table 1. The age of implantation ranged between 1 year 3 months and 12 years; the length of CI use varied between 3 months and 12 years and 2 months. Of the 11 children, 9 showed a symptomatic infection and the most common effect was motor disability/ataxia. Two children had seizures in the first months of life. In 7 children, MRI images showed white matter lesions in T2 (typical of CMV infection). There were also signs of hydrocephalus, cerebral cysts, and areas with retarded myelination.

CT scans did not show any characteristic changes from CMV infection, but they were very important for evaluating cochlear permeability and, subsequently, in the clinical decision about which ear to implant.

The genetic mutations of children in the GJB2 group are described in Table 2. These children did not have any comorbidities associated with their deafness.

There were no significant differences in CI hearing thresholds between the CMV group and the GJB2 group (Figure 1), although the mean thresholds are consistently lower for the CMV group.

To compare the CMV and GJB2 groups in more detail, the children were divided into three groups according to the age of implantation: <2 years old (4 and 7 children, respectively), 2–3 years (3 and 33children), and >3 years old (4 and 21 children). Because there was such a small number of subjects in each CMV subgroup, the associated error bars were large and in general there were no significant statistical differences between the SIR or VCEG tests or in the MAIS and MUSS questionnaires (Figures 2 and 3). There appeared to be a significant difference in the CAP test (p=0.049) where the GJB2 group had superior results.

Table 1. Clinical characteristics of 11 children with CMV infection

	Sex	Birthdate	Implanted ear	Age at implantation	CI use	Other diseases	Ear imaging studies
1	M	18.01.2010	Right	1 Y 3 M	1 Y e 9 M	Seizures at the age of 4 months	CT – normal MRI – braquychephaly, mild hydrocephalus, white matter lesions, subependymal cysts, normal labyrinth
2	M	05.12.2007	Right	2 Y e 4 M	2 Y e 9 M		CT – normal MRI – macrocranium, mild cortical athrophy, reduced permeability of the posterior semicircular channel
3	F	27.08.2010	Right	1 Y e 6 M	11 M	Secondary pseudohypoal-dosteronism with severe hyponatremia, atrial septal defect, autoimmune intestinal disease	CT – normal MRI – normal
4	M	18.11.1999	Right	3 Y e 4 M	9 Y e 10 M	Neonatal asphyxia Motor development delay/Ataxia Microcephaly	CT– normal MRI – normal
5	M	23.02.2011	Left	1 Y e 7 M	3 M	Hypotonia	CT – normal MRI – mild cortical atrophy; hyperintense areas of the white matter in T2
6	M	28.10.2008	Bilateral	RE – 1 Y e 3 M LE – 2 Y e 7 M	OD – 3 Y OE – 1 Y e 8 M	Disturbances in interpersonal relationships; Delayed motor development	CT – normal MRI – microcyst of the white matter; frontal cyst; lateral ventriculum enlargement; dilation of the temporal horns; external hidrocephaly; thin cochlear and facial nerves (left)
7	F	16.02.2005	Right	5 Y e 6 M	2 Y e 5 M	Language delay – fluctuating deafness	CT – decreased permeability of the left cochlear basal turn MRI – hyperintense areas of the white matter
8	F	22.02.2001	Left	12 Y	11 M	Suspected epilepsy	CT – polymicrogyria MRI – polymicrogyria; malformation of the cortical development (fronto-insular, temporal and parietal), hyperintense areas of the white matter
9	M	12.05.2001	Right	5 Y e 4 M	7 Y e 4 M	Ataxia	CT – normal MRI – braquicephaly
10	M	12.06.2008	Right	2 Y e 3 M	2 Y e 4 M		CT – normal MRI – hyperintense areas of the white matter
11	M	17.12.1997	Left	2 Y e 11 M	12 Y e 2 M	Epilepsy Delayed motor development (axial hypotonia)	CT – mild bilateral internal acoustic meatus enlargement MRI – hyperintense areas of the white matter in T2, accentuation of the central sulcus, areas of delayed myelination

Discussion

Studies by Ramirez and al. [10], Ciorba et al. [1], Malik et al. [2], and Viccaro et al. [11] have shown that CI rehabilitation in children with CMV infection is not as good as that in the standard paediatric population. These findings motivated us to evaluate a paediatric population with congenital CMV infection after they were rehabilitated with a CI in our institution.

Children with GJB2 mutation were chosen as a matching group as their SNHL is caused by inner ear changes

Table 2. Genetic mutations of children in the GJB2 group

Mutation	Occurrence (percent)	
+/A40A	1	(1.6%)
35delG/E47X	1	(1.6%)
35delG/GJB6 (del1854)	1	(1.6%)
35delG/GJB6 (delD13S1830)	1	(1.6%)
35delG/35delG	39	(63.9%)
+/G130A	1	(1.6%)
35delG/R184W	1	(1.6%)
E47X/E47X	2	(3.3%)
+/V371	1	(1.6%)
+/N206S	1	(1.6%)
Not classified (out of institution)	12	(19.7%)
Total	**61**	**(100.0%)**

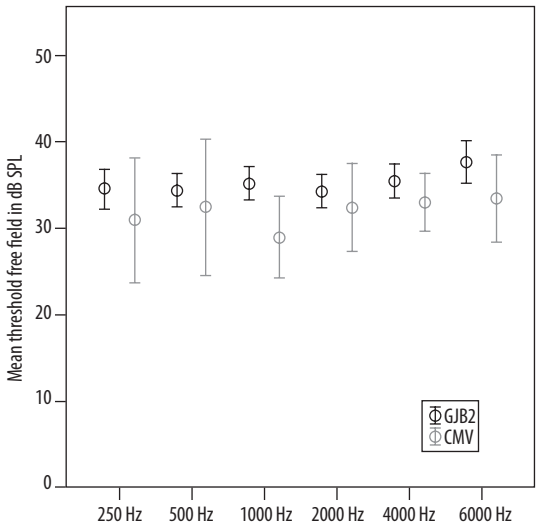

Figure 1. CI hearing thresholds in the CMV group (grey) and GJB2 group (black). The error bars show 95% confidence intervals. Although there are no statistically significant differences between the populations, the mean thresholds are consistently lower for the CMV group

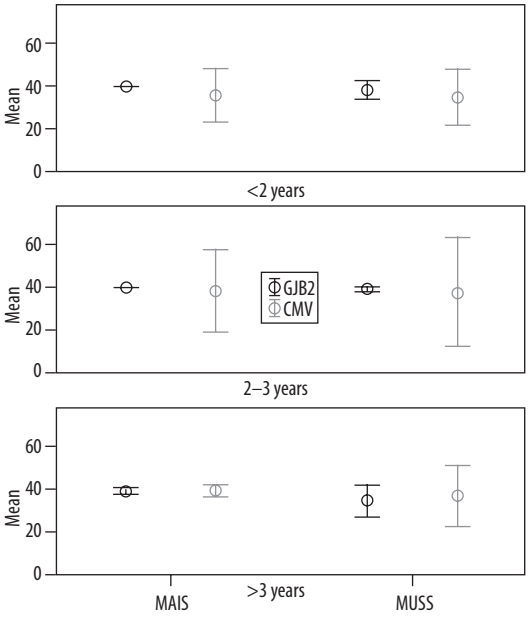

Figure 2. Results of MAIS and MUSS questionnaires in the CMV group (grey) and GJB2 group (black). Error bars show 95% CI. There are no statistically significant differences between the groups

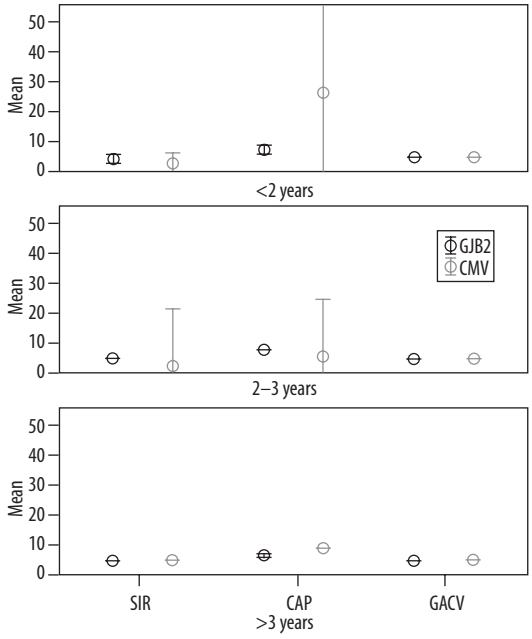

Figure 3. Results of SIR, CAP, and VCEG tests in the CMV group (grey) and the GJB2 group (black). There are no statistically significant difference between the groups

without any other associated deficits. We expected this group to show the best results from CI rehabilitation.

There were no significant statistical differences in almost all the tests. There was a higher dispersion in the results obtained in the CMV group which can be explained by the limited number of subjects in this group. This finding can be related to changes in the central nervous system of those in the CMV infection group. However, we did not see any relation between MRI alterations and performance with a CI, and so this cannot be considered a prognostic indicator in these children.

The better results showed by the GJB2 group in the CAP test (p=0.049) may again be explained by the cognitive deficits shown by some children with CMV infection, deficits which interfere with sound perception. Over time, this difference may not persist because children with CMV infection may take longer to achieve the same results as

other children, as described by other authors [8,9]. However, we again note that there was no statistical difference in the SIR or VCEG tests, so cognitive deficits apparently did not interfere with the acquisition of spoken language.

Our results are comparable to those published by Matsui et al. [12] in a comparative study between children with asymptomatic CMV infection and children with a GJB2 mutation; they found that the results obtained from children with CMV infection were practically the same as those of children with GJB2 mutation. These authors concluded that, although children with developmental changes show a worse performance, a CI cannot be counterindicated.

Another two studies with results in favour of a cochlear implant were published by Lee et al. [8] and Yoshida et al. [9] In the first publication, 13 children with CMV infection and rehabilitated with a CI were studied, and it was verified that the results obtained were within that expected for the general paediatric population. In the second, children with CMV infection were compared with those with deafness resulting from other aetiologies. In the first 12 months there was worse oral production in the group with CMV; after that there was a good progression (similar to that of children with hearing loss from other aetiologies). These authors concluded that the long term results were satisfactory.

Limitations of the study

The main limitation of the present study is the small sample size of deaf children with a congenital CMV infection which did not allow statistical significance to be reached.

The variability of age of implantation in children with CMV (3 children implanted after 3 years of age) was due to the progressive nature of the deafness associated with this type of infection. Since age of implantation is a major prognostic factor in the success of a CI, to minimize bias children were matched according to the age of implantation.

Conclusions

Children with a SNHL caused by congenital CMV infection display a great variety of clinical presentations, audiometric profiles, and need for educational support. Given that the outcome is quite unpredictable, early diagnosis and prompt therapeutic intervention are vital to give the best chances of providing sound perception, language acquisition, and cognitive development. In our study, a timely diagnosis in each case gave the cochlear implant team a good basis for undertaking the best strategy.

Some studies have achieved less favourable results than those attained here, and this might be attributed to the inherent cognitive and motor deficits which occur in children with profound hearing loss caused by CMV infection; in such cases CI rehabilitation is always going to be less successful when compared to the general paediatric population.

The present study has found that the CMV group demonstrated worse results in the CAP test and a wider dispersion of results in the other tests. However, this group of children attained results comparable to the children with profound hearing loss without any other deficits, and have thus benefited from receiving a cochlear implant.

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