Original Article

The Correlation of Congenital CMV Infection and the Outcome of Cochlear Implantation

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OBJECTIVES: Cytomegalovirus (CMV) infection is the most common intrauterine viral infection, affecting approximately 0.5-2.5% of all live births in the world. The majority of patients are asymptomatic at birth, but several clinical consequences are related to this infection, including neuro-sensory hearing loss. The cochlear implant is the treatment of choice when the hearing loss is severe to profound. Compare the audiological evolution after cochlear implant surgery in a group of children born with congenital CMV infection compared to a control group of children born with a genetic cause of congenital hearing loss. Determine prognostic factors predicting the outcome of patients with congenital hearing loss secondary to CMV infection following cochlear implantation.

METHODS: Our retrospective study aimed at the analysis of 48 patients with cochlear implants, 25 patients with congenital CMV, and 23 patients in the control group with cochlear cause of hearing loss, who were matched for gender, age of onset, and type of hearing loss. Primary outcomes are auditory evolution with the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) and the multimedia audiologic test (MAT). Secondary outcomes are evaluation of prognostic factors for the CMV group, like MRI severity sign, antiviral treatment, and neuropsychological disorder.

RESULTS: For the MAT, the results are 73.9% in the CMV group and 81.6% in the control group ($P = .03$). For the IT-MAIS, the results are 29.3/40 in the CMV group and 29.2/40 in the control group ($P = .96$). In the CMV group, the children treated with antiviral treatment have IT-MAIS difference of 28.5/40 compared to 23.2/40 for the children without antiviral treatment ($P = .03$). We found a little trend in the correlation between auditory results and the presence of neuropsychological disorders, but there are no statistically significant results.

CONCLUSION: The results of the audiological tests in the CMV group allow an adequate functioning, even if lower than in the control group. There are benefits of implantation in patients with CMV, and audiological results are still satisfactory for proper functioning. CMV patients enjoy superior results in terms of hearing, with antiviral treatment.

KEYWORDS: Cochlear implants, cochlear implantation, cytomegalovirus, CMV, congenital, hearing loss, deafness, antiviral treatment

INTRODUCTION

Cytomegalovirus (CMV) infection is the most common intrauterine viral infection.[1] About 90% of children with congenital infection are asymptomatic after birth. However, later complications such as hearing loss, mental retardation, delayed psychomotor development, learning disabilities, and expressive speech delays are reported in more than 90% of them.[2,3] In this group, hearing loss will be detected in 13-24% of patients.[4,5] For the rest, 10% of infected patients have severe and obvious symptoms at birth that are related to CMV infection.[2] In this group, hearing loss will be detected in 50% of patients and 66% will develop progressive hearing loss.[6] The earlier the infection is acquired, the more the manifestations are numerous and significant.[7,8] For hearing loss, the hypothesis is that the CMV infection acts directly on the otic capsule. The CMV antigen was found in the organ of Corti, the auditory nerve, the semicircular canals, the perilymph, and the cochlear duct of patients infected with CMV.[9] Cochlear implantation is an effective but variable treatment for these patients. Several factors influence the rehabilitation of the cochlear implant, including neuropsychological disorders.[10] The company's overall cost for services to patients with congenital CMV infection is estimated to be $1.9 billion per year, making it a critical issue.[11] The literature is rather controversial on the usefulness of cochlear implantation and prognostic factors in patients with hearing loss secondary to CMV infection. The present study will attempt

to determine the actual results of cochlear implantation in these patients in addition to determining the prognostic factors that can predict these results.[12-15]

MATERIALS AND METHODS

The study was made from the database of the Quebec Cochlear Implant Program and accepted by the ethics committee of our institution (Ethics committee approval number 2019-4180).

The objectives of the study are to compare the audiological evolution after cochlear implant surgery in a group of children born with congenital CMV infection compared to a control group of children born with a genetic cause of congenital hearing loss, and to determine prognostic factors predicting the outcome of patients with congenital hearing loss secondary to CMV infection following cochlear implantation.

Our study is a retrospective case-controlled study of children born with congenital CMV infection and hearing loss compared with a group of patients with cochlear cause of hearing loss. We analyzed the cochlear implant database of the CHU de Quebec between 2008 and 2018 to form 2 groups according to the inclusion and exclusion criteria. To be eligible for the CMV group, a patient had to meet all of the following criteria: congenital CMV infection confirmed at birth by direct identification of CMV in saliva, blood, urine, or amniotic fluid, or by brain MRI confirming the presence of characteristic signs of congenital CMV. Patients followed-up in ENT and by the audiology team of the cochlear implant program before surgery for CMV-related profound hearing loss, and patients undergoing rehabilitation post-cochlear implantation for a period of at least 12 months after surgery. To be eligible for the control group, a patient had to meet all of the following criteria: patients with a genetic cause of congenital profound hearing loss with no evidence of CMV-related hearing loss, patients with surgery for unilateral or bilateral cochlear implants, and patients undergoing rehabilitation post-cochlear implant for a period of at least 12 months after surgery. The analysis was done with the results following the rehabilitation for the first implant because we consider that it is the most important. Several children subsequently received a second implant, which was not included in our analysis.

After the analysis of the database, we found 25 patients with a congenital CMV infection that met the inclusion criteria. We formed a control group of 23 patients with cochlear cause of congenital hearing loss, caused by connexin 26 for the majority. These patients are considered to have an excellent prognosis for cochlear implantation. The control group was matched with the CMV group for gender, age at implantation, and type of hearing loss.

Multiple variables were collected on patients included in the study, such as age at implantation, presence of hearing loss secondary to CMV infection, presence of biological comorbidity related to CMV, presence of neuropsychological comorbidity, severity of MRI findings in relation to CMV, treatment of congenital CMV with antivirals at diagnosis by the pediatric team, unilateral or bilateral cochlear implantation, evolution of hearing loss (progressive, profound at birth, or sudden), and type of CMV confirmation test (urinary PCR, blood, amniotic fluid, or MRI).

Primary outcomes are auditory evolution with the IT-MAIS test[16] and multimedia audiologic test (MAT)[17] before the surgery and 12 months after the surgery, and rehabilitation for the first implant. Secondary outcomes are evaluation of prognostic factors for the CMV group, like MRI severity findings, antiviral treatment, and neuropsychological disorder. The 2 tests used to evaluate the audiological evolution are used preoperatively and postoperatively for cochlear implantation surgery in our program and have been validated in the literature.[16,17] The IT-MAIS test is a structured parent interview on 3 spheres, regarding the child's vocal behavior, the response to sounds, and the meaning of sounds. It contains 10 questions with a score of 0 to 4 for a total score of 40. The MAT test is a computer test with recorded sentences with voices of men, women and children. It is a reflection of speech understanding more than hearing sounds. The result is described in percentage (%) for open-set word recognition.

Secondary outcomes included evaluation of prognostic factors for the CMV group like MRI severity findings, antiviral treatment, and neuropsychological disorder. We did a subgroup analysis for the CMV group to try to find a correlation between some prognostic factors mentioned above and the auditory results of CMV patients. We looked at the severity MRI findings reported by the radiologist (absent, mild, moderate, or severe) based on classification in the literature.[2] For the neuropsychological disorder, we analyzed the patient's previous medical record to determine the diagnoses. We classified neuropsychological disorders as absence, presence of one disease, or 2 or more diseases. The main diagnoses found were autism spectrum disorders, attention deficit hyperactivity disorder, and intellectual disability. For antiviral treatment, valganciclovir and acyclovir were used by the pediatric teams.

Statistical Analysis

The statistical analysis was performed by the Biostatistics Department of our institution. A Student's t-test was used to compare the hearing results between the 2 groups and the age at implantation. An Exact Pearson Chi-squared test was used to compare demographic data between groups. A Pearson correlation coefficient was used to verify the correlation between the age at implantation and the auditory results of the IT-MAIS and MAT. A Student's t-test or a one-way analysis of variance F-test was used to explore the association between auditory results and prognostic factors.

RESULTS

A total of 48 patients were evaluated, 25 in the CMV group and 23 in the control group. All data for each patient is available in the appendix of the article. There is no statistically significant difference for sex, type of hearing loss, and age at implantation between the 2 groups (Table 1). There was no difference for the preoperative MAT test between the 2 groups (Table 2). The results of postoperative MAT were 73.9% for the CMV group and 81.6% for the control group ($P = .03$), and the results of the difference between the postoperative MAT and the preoperative MAT were 51.3% for the CMV group and 59.7% for the control group ($P = .04$). There was no difference for the preoperative IT-MAIS between the 2 groups (Table 2). The results of the postoperative IT-MAIS were 29.3 for the CMV group and 29.2 for the control group ($P = .96$). The difference between the postoperative IT-MAIS and the preoperative IT-MAIS was 26.3 for the CMV group and 23.7 for the control group ($P = .23$) (Tables 1 and 2).

Table 1. Demographic Characteristic

Variable	CMV group (25), N (%)	Control group (23), N (%)	P
Gender			
F	15 (60)	13 (56.5)	.99
M	10 (40)	10 (43.5)	-
Type of hearing loss			
Profound at birth	17 (68)	19 (82.6)	.32
Progressive	8 (32)	4 (17.4)	-
Age at implantation for the first implant (month)	30.2	23.6	.34

Table 2. Results of Audiologic Tests (MAT and IT-MAIS test)

Variable	Group	Mean (%)	95% CI	Median (%)	P
Preoperative MAT	CMV	22.6	18.1 ; 27.1	22.0	.81
	Control	21.9	17.8 ; 25.9	18.0	-
Postoperative MAT	CMV	73.9	69.1 ; 78.7	74.0	.03*
	Control	81.6	76.5 ; 86.6	84.0	-
MAT difference (Postop–Preop)	CMV	51.3	44.8 ; 57.8	58.0	.04*
	Control	59.7	54.6 ; 64.8	60.0	-

Variable	Group	Mean (/40)	95% CI	Median (/40)	P
Preoperative IT-MAIS	CMV	3.00	0.97 ; 5.03	2.0	.14
	Control	5.43	2.67 ; 8.20	3.0	-
Postoperative IT-MAIS	CMV	29.28	27.07 ; 31.49	31.0	.96
	Control	29.17	25.75 ; 32.60	33.0	-
IT-MAIS difference (Postop–Preop)	CMV	26.28	23.70 ; 28.86	28.0	.23
	Control	23.74	20.22 ; 27.26	26.0	-

*Statistically significant difference for a P value of less than .05

Patient characteristics for the type of CMV confirmation, neuro-psychological disorders, antiviral treatment, and MRI results are described in Table 3. The results of the association between MRI signs, neuropsychological disorders, antiviral treatment, and the hearing outcomes are shown in Tables 4, 5, and 6 respectively. There are no significant findings for MRI results and for neuro-psychological disorders. There is only slight correlation for neuropsychological disorders. For the antiviral treatment, we found a significant result between the IT-MAIS difference and antiviral treatment *(P = .03)*.

DISCUSSION

This study is among the largest series in literature on cochlear implantation in patients with congenital CMV. We analyzed 2 different audiological tests that are regularly used in our center. We found a better audiological result for the control group in the MAT test. In our center, we consider a result superior to 70% on the MAT test as a good result for adequate functioning in everyday life. We therefore believe that the CMV group with a result of 73.9%, even

Table 3. Characteristics of the Patients in the CMV Group

Variable	N (%)
CMV confirmation	
MRI	4 (16)
PCR	17 (68)
Urine	4 (16)
Neuropsychological disorder	
Absent	13 (52)
1 disease	5 (20)
2 or more diseases	7 (28)
Antiviral treatment	
No	11 (46)
Yes	13 (54)
MRI severity sign	
Absent	5 (20)
Mild	9 (36)
Moderate	7 (28)
Severe	4 (16)

Table 4. Association Between MRI Sign and Hearing Outcomes

Variable	MRI Sign	Mean	P
Postoperative MAT (%)	Absence	73.4	.34
	Mild	75.9	-
	Moderate	67.9	-
	Severe	80.5	-
Postoperative IT-MAIS (/40)	Absence	26.6	.33
	Mild	28.1	-
	Moderate	25.1	-
	Severe	24.7	-

if less than the control group, will have adequate functioning, so it is advantageous to implant patients having hearing loss associated with congenital CMV. In addition, the results for the IT-MAIS test are comparable between the 2 groups, which supports this hypothesis.

As described above, the use of the IT-MAIS test allows the assessment of hearing and the response to sound. In addition, the use of the MAT test assesses speech understanding in a more complex and

Table 5. Association Between Neuropsychological Disorder and Hearing Outcomes

Variable	Neuropsychological Disorder	Mean	P
Postoperative MAT (%)	Absent	75.2	.78
	1 disease	73.6	-
	2 or more diseases	70.8	-
Postoperative IT-MAIS (/40)	Absent	30.1	.89
	1 disease	29.0	-
	2 or more diseases	28.8	-

Table 6. Association Between Antiviral Treatment and Hearing Outcomes

Variable	Antiviral Treatment	Mean	*P*
Postoperative MAT (%)	No	72.9	.72
	Yes	74.7	-
MAT difference (%)	No	47.6	.34
	Yes	53.9	-
Postoperative IT-MAIS (/40)	No	28.2	.41
	Yes	30.1	-
IT-MAIS difference (/40)	No	23.2	.03*
	Yes	28.5	-

*Statistically significant difference for a *P* value of less than .05

in-depth manner. This test is a good evaluation of the functioning of cochlear-implanted patients in social interactions. For us, the use of these 2 tests is complementary and allows the evaluation of the functioning of the patients in an optimal way. This allows us to assess patients in several psychosocial spheres. The IT-MAIS test is mainly used in young children while the MAT test can be used in all children but especially the older ones.

We can see a trend of an association between neuropsychological disorders and auditory results. A larger number of patients could have shown significant correlation.

On the other hand, we found an association with benefit for antiviral treatment between 2 antiviral treatments when diagnosing congenital CMV and auditory results. We believe that this association has not been well described in the literature before today. Further studies with a higher number of patients on this specific point should be made to clarify this association. Two antivirals were used in our study: valganciclovir and acyclovir in our study. The current literature favors valganciclovir for the treatment of CMV. In our study, acyclovir was mainly used in patients in the early years of the study when this evidence was not yet clear.

The literature is currently quite controversial on the indications of treatments in patients with congenital CMV. In some studies, deafness is a severity criterion of CMV, while in others it is not. The timing of treatment, the duration and the type of antiviral are also controversial in the literature. Further studies focusing on the use of antivirals for the treatment of patients with congenital deafness secondary to CMV are needed to assess the benefit of this treatment as well as to determine the best timing to initiate it.[18,19] There are some studies currently on the subject that assess antiviral treatment and hearing outcomes in patients with congenital CMV. We hope this will clarify the role of antivirals for deafness in patients with congenital CMV.

In our opinion, the strengths of the study are the number of patients, the analysis in which we compared the CMV group to a control group considered to have a good prognosis, and the use of 2 different audiological tests. The limitations of our study are obviously the usual limitations associated with a retrospective study. The 1-year follow-up is also a limitation but as the study is retrospective, after 1 year, the patients continue the follow-up in their regional center. A prospective study could be considered to confirm the results obtained.

CONCLUSION

There are benefits of the implantation in patients with CMV, giving audiological results satisfactory for proper functioning. The CMV group results showed adequate functioning even if lower than the control group. Antiviral treatment of congenital CMV appears to be an important prognostic factor for the auditory progression of patients with cochlear implantation. There are no clear guidelines on the subject, and this is rather controversial in the literature. Further studies will be needed to confirm this evidence.

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