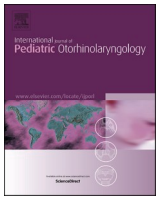
International Journal of Pediatric Otorhinolaryngology 138 (2020) 110364

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl



Outcome of cochlear implantation in children with congenital Cytomegalovirus infection: A retrospective case control study

Virginia Corazzi, Andrea Ciorba *, Chiara Bianchini, Monica Rosignoli, Laura Negossi, Federica Minazzi, Michela Borin, Nicola Malagutti, Francesco Stomeo, Stefano Pelucchi

ENT & Audiology Department, University Hospital of Ferrara, Via A. Moro 8, Loc Cona, Ferrara, 44124, Italy

ARTICLE INFO

Keywords:
Congenital Cytomegalovirus infection
cCMV
Profound sensorineural hearing loss
SNHL
Cochlear implant

ABSTRACT

Introduction: To date, cCMV represents the most frequent non-genetic congenital cause of permanent sensorineural hearing loss (SNHL) in childhood and the leading infectious cause of developmental and neurologic disabilities. The aim of this paper is to describe the outcome of cochlear implantation in children affected by severe-to-profound sensorineural hearing loss, due to a symptomatic or asymptomatic cCMV infection, particularly comparing their performance results to that of matched mutated Connexin 26 (Cx26) implanted patients.
Methods: Retrospective case control study. The clinical data of symptomatic cCMV and asymptomatic cCMV patients were collected and compared to those of Cx26 patients matched for age and pre-CI (cochlear implant) linguistic category; all subjects were affected by bilateral severe-to-profound SNHL and were treated by CI and speech therapy rehabilitation. The Speech Perception Category, the language stage and the linguistic level scores, at 6 months, 1 year, and 3–4 years after CI of the three groups (symptomatic cCMV, asymptomatic cCMV and Cx26 mutation) were collected and compared.
Results: Statistical analysis did not show any significant difference in pre-CI perception category and linguistic level among the three groups; the symptomatic cCMV group showed a statistically worse performance of the language stage over time ($p = 0.017$).
Conclusions: Our data support that children affected by cCMV have improved language abilities over time, although the symptomatic cCMV group achieved a lower language stage 3–4 years after CI compared to the asymptomatic cCMV and Cx26 mutation groups. Nonetheless, to date, CI supported by speech therapy can be considered an effective intervention for children affected by cCMV-related severe-to-profound hearing loss.

1. Introduction

To date, Cytomegalovirus (CMV) represents the most common congenital infection worldwide. Congenital CMV infection (cCMV) is reported to be the leading cause of permanent non-genetic sensorineural hearing loss (SNHL) in children and the most frequent infectious cause of neurological disorders [1,2]. cCMV has been defined as "the elephant in our living room" [3], as it still represents one of the major current public health issues. The cCMV incidence in developed countries is reported to be 0.3–2.3% of all born alive babies [4].

cCMV is classified into two categories: i) symptomatic and ii) asymptomatic, depending on its clinical manifestation at birth; according to the European Consensus Statement [5] and to Rawlinson [6], the symptomatic form is identifiable by the clinical features at birth, while the asymptomatic infection is identifiable only through screening or other investigations (such as newborn hearing screening and magnetic resonance imaging), as affected infants show no apparent clinical signs of cCMV.

Most frequently, cCMV is present as asymptomatic at birth (about 90%), although up to 15% of cases are at risk of developing long-term permanent neurological (cerebral anomalies such as leukomalacia, ventriculomegaly, and calcifications) and, more frequently, audiological sequelae [7,8]. Only 10% of newborns affected by cCMV are symptomatic [7,9]; among symptomatic infants, 70–80% of cases present severe neurological sequelae, mainly psychomotor developmental defects including SNHL [7,10–12]. Petechiae, purpura, jaundice, hepatosplenomegaly, hepatitis, ascites may also occur [12,13]. Intrauterine growth restriction (IUGR) and low birth weight can be present in about 50% of symptomatic newborns [7].

The aim of the present paper is to describe the outcome of cochlear

* Corresponding author.
E-mail address: andrea.ciorba@unife.it (A. Ciorba).

https://doi.org/10.1016/j.ijporl.2020.110364
Received 3 May 2020; Received in revised form 3 September 2020; Accepted 3 September 2020
Available online 9 September 2020

implantation in children affected by severe-to-profound sensorineural hearing loss, due to symptomatic and asymptomatic cCMV infection, particularly comparing their performance results to that of matched implanted patients with SNHL due to Connexin 26 (Cx26) gene mutation. Unlike cCMV, SNHL caused by Cx26 gene defect is a condition with a low risk of comorbidity and associated disability, and data from literature show excellent post-CI linguistic outcomes [14].

2. Methods

The study was conducted retrospectively, reviewing the pediatric patient database at the Audiology Department of University Hospital of Ferrara (Italy). The study group included patients from a previous published database [15], and new patients, treated at our center, between January 2005 and December 2016. Therefore, the newly studied cohort is composed, in total, by 30 patients, affected by cCMV related bilateral severe-to-profound SNHL and treated by CI and speech therapy rehabilitation. cCMV patients were further divided into 2 groups: symptomatic cCMV and asymptomatic cCMV.

Data concerning medical history and the audiological assessment were reviewed; in particular, all clinical information were collected including neonatal and past medical history, imaging and laboratory data, clinical findings, as in our previous study [15].

The research protocol was conducted in compliance with the Helsinki Declaration (2008); the study was performed retrospectively through a case record review and therefore did not affect patient care in any way. However, all patients (and/or their parents) were informed about the project during their follow-up visits and provided their participation consent.

2.1. cCMV infection diagnostic criteria

The diagnostic criteria adopted for the cCMV infection were: i) CMV-DNA quantification through real-time PCR in amniotic fluid [16,17], ii) in urine, saliva and neonatal blood within the first 15–21 days of life, or, retrospectively, iii) in the Guthrie card [5,18]; iv) IgG and IgM research through ELISA (enzyme-linked immunosorbent assay) technique in the maternal serum during pregnancy and in neonatal serum [19,20]. Serological tests in mothers were considered diagnostic in cases of ascertained seroconversion during pregnancy and when a low avidity of IgG was found in cases of a maternal positivity for both IgM and IgG [19]. cCMV was considered symptomatic whenever one or more of the abovementioned diagnostic criteria were positive, and the patient showed one or more of the following signs or symptoms during the pre-natal or peri-natal period: IUGR (as a prenatal ultrasound finding), prematurity (<37 weeks of gestation), low birthweight, microcephaly, chorioretinitis, petechiae, hepatosplenomegaly, intracranial calcifications, hydrocephalus, severe liver failure, jaundice, direct hyperbilirubinemia, convulsions. cCMV was considered asymptomatic when the diagnosis was possible only on the basis of laboratory data or screening test (without detectable clinical signs). As a consequence, in the present study, infants with no signs or symptoms of cCMV infection other than hearing loss were considered asymptomatic.

2.2. Control group selection

We compared the cCMV implanted group with a group of implanted patients affected by bilateral severe-to-profound SNHL due to Cx26 gene mutations (homozygosity for the c.35delG mutation), matched by age and pre-CI linguistic category.

2.3. Speech perception and language assessment

Within the present study, speech perception was evaluated by using the Speech Perception Categories, according to the Geers and Moog Scale [21], in order to compare patients across different ages and diverse degrees of speech development (see Table 1). Language development was assessed using the Nottingham classification categories (language stage), and the classification adapted from Bates E et al. [22] (linguistic level) (see Table 1). In other available experiences, speech perception and language development were evaluated using different scales. For instance, Matsui et al. [23] adopted the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), the Meaningful Use of Speech Scale (MUSS), and the Test for Japanese Language Retardation Based on Sign-Significant Relations (S–S method); Philips et al. [24,25] adopted longitudinal scales, such as the Categories of Auditory Performance (CAP) for speech perception, and the Speech Intelligibility Rating (SIR) for production skills. We adopted the aforementioned scales, as they resulted reliable and practical, in our experience and in other studies [26–28].

Therefore, we have tested the hypothesis that all three groups (symptomatic cCMV; asymptomatic cCMV; Cx26 mutation) have increased the Speech Perception Category, the language stage and the linguistic level scores, following CI and speech therapy rehabilitation. The same four time periods described in our previous paper were considered, in order to standardize the results: pre-CI (time 1, T1), 6 months (time 2, T2), 1 year (time 3, T3), and 3–4 years (time 4, T4) after CI. In order to evaluate the functional outcomes, at least after 3 years after CI, we analyzed the pediatric patient database until December 2016. All implanted patients underwent a speech therapy rehabilitation, and were followed up at regular intervals for clinical, audiological, neurological and phoniatric evaluations. All patients of the studied cohort were using bilateral hearing aid amplification before receiving the CI.

2.4. Statistical analysis

Statistical analysis of the data was performed through descriptive tests by using SPSS statistical package (SPSS for Windows, Inc. Chicago, IL 60611). The non-parametric Kruskal-Wallis test was applied due to the unequal distribution of the data, mainly due to the small size of some groups; the presence of differences in speech perception, language stage, and linguistic level over time and among the groups was investigated. The differences between values were considered significant when $p <$

Table 1
Speech Perception Categories according to Geers and Moog Scale; Language Stage according to Nottingham Scale; Linguistic Level according to the classification adapted from Bates E et al. [20,21].

SCALES	CRITERIA
Speech Perception Category	
0	No detection of speech sounds
1	Simple detection
2	Pattern perception
3	Inconsistent closed set word recognition
4	Consistent closed sed word recognition
5	Open set word recognition
6	Open set word recognition, exceeding performance with old device
Language Stage (Nottingham Scale)	
Pre-verbal	No intentional verbal communication
Transitional	Use of words
Functional	Use of phrases and word sequences based on morphological and syntactic rules
Linguistic Level (Classification adapted from Bates et al)	
Absent	Voicing/babbling
Vocalizations	Vocalizations/CVC sequences to communicate intentionally
Words	First words/single word utterances that have communicative contents
Combinations	First words combinations/telegraphic utterances
Sentence Grammar	Combinations base on morphological and syntactic rules
Discourse Grammar	Connected discourse closely conforming to adult model

CVC: consonant-vowel-consonant.

0.05 (*) and highly significant when $p < 0.01$ (**).

3. Results

A total of 56 patients affected by bilateral severe-to-profound SNHL underwent CI, between 1990 and 2016, all native Italian speakers, and not exposed to multilingualism; of these, 30 patients were affected by cCMV (53.6%), while 26 were affected by Cx26 gene mutation (46.4%). In particular, among cCMV group, 22 were symptomatic, and 8 were asymptomatic (please see Table 2 and Table 3). In all cases, CI was performed in our department; electrodes have been fully inserted in all cases, and no postoperative complications were recorded in any case. There were no significant differences in pre-CI perception category ($p = 0.81$), language stage ($p = 0.30$), and linguistic level ($p = 0.44$) among asymptomatic cCMV, symptomatic cCMV and Cx26 mutation group, at the Kruskal-Wallis test. Furthermore, the three groups were found to be comparable also for mean age at implantation, as no significant difference was found at the analysis of variance ($p = 0.73$).

An overall progressive improvement over time (from T1 to T4) of all the parameters considered (speech perception, language stage and linguistic level) has been observed in each group (please see Figs. 1–3).

Table 2
Demographic data of the studied cohort.

Characteristic	Symptomatic cCMV (n = 22, 39.3%)	Asymptomatic cCMV (n = 8, 14.3%)	Cx26 mutation (n = 26, 46.4%)	p value
Gender				N/A
male	13 (59.1)	4 (50)	11 (42.3)	
female	9 (40.9)	4 (50)	15 (57.7)	
Mean age at the first hearing aid amplification (months)	13.4 ± 9.4	9.6 ± 2.6	15.4 ± 8.2	
Mean age at CI (months)	63.0 ± 63.9	45.9 ± 58.6	66.3 ± 60.9	0.73
Monoaural or bilateral stimulation				N/A
Bilateral CI	4 (18.2)	2 (25)	2 (7.8)	
Bimodal stimulation	18 (81.8)	6 (75)	24 (92.2)	
Pre-CI communication modality				N/A
Oral	16 (72.7)	8 (100)	23 (88.5)	
AAC/LIS	6 (27.3)	/	3 (11.5)	
Pre-CI perception category				0.81
0	7 (31.8)	3 (37.5)	9 (34.6)	
1	10 (45.5)	4 (50)	10 (38.5)	
2	5 (22.7)	1 (12.5)	3 (11.5)	
3	/	/	1 (3.8)	
4	/	/	2 (7.8)	
5	/	/	/	
6	/	/	1 (3.8)	
Pre-CI language stage				0.30
Preverbal	16 (72.7)	7 (87.5)	15 (57.7)	
transitional	4 (18.2)	/	6 (23.1)	
functional	2 (9.1)	1 (12.5)	5 (19.2)	
Pre-CI linguistic level				0.44
Absent	14 (63.6)	6 (75)	13 (50)	
vocalizations	2 (9.1)	1 (12.5)	2 (7.7)	
Words	2 (9.1)	/	2 (7.7)	
combinations	/	/	4 (15.4)	
sentence grammar	3 (13.6)	/	3 (11.5)	
discourse grammar	1 (4.6)	1 (12.5)	2 (7.7)	

CI = cochlear implant; AAC = augmentative and alternative communication; LIS = Italian Sign Language; SD = standard deviation; N/A = not available. Mean values have been reported as n±SD.

Table 3
Clinical features of the symptomatic cCMV group (IUGR = Intrauterine Growth Restriction; CNS = central nervous system).

Clinical, laboratory, imaging characteristics	Mean	N	%
Prematurity		5	22.7
Birth weight (g)	2196 ± 505		
IUGR		3	13.6
Petechiae		2	9.1
Hepatosplenomegaly		2	9.1
Thrombocytopenia		3	13.6
Direct hyperbilirubinemia		2	9.1
Microcephaly		4	18.2
CNS abnormalities at neuroimaging		14	63.3
Convulsions		6	27.3
Chorioretinitis		4	18.2
Posturomotor deficit		14	63.3
Cognitive impairment		7	31.8

In order to highlight any differences in the functional outcomes after cochlear implantation among groups, perceptive categories, language stages, and linguistic levels at T2, T3, and T4 were all compared (please see Figs. 1–3). At the Kruskal-Wallis test, there were no significant differences ($p > 0.05$), except for the language stage at T4 ($p = 0.017$*), due to the significantly worse performance in the symptomatic cCMV group (Fig. 3). Finally, by using a post-hoc comparison for the language stage among pairs of groups by LSD (Least Significance Difference) procedure, a highly significant difference ($p = 0.006$**) was assessed only between the symptomatic cCMV group and the Cx26 mutation group.

4. Discussion

SNHL in infants with cCMV has always represented a major public health problem, since an unrecognized or misdiagnosed hearing defect can have a severe impact on language development and learning skills. In the present paper, we aimed to evaluate the outcome of cochlear implantation in children affected by bilateral severe-to-profound SNHL due to symptomatic and asymptomatic cCMV infection, comparing the post-CI performances to a matched group of implanted children affected by Cx26 mutation-related bilateral severe-to-profound SNHL.

In the current literature, there are not uniform data related to the post-CI functional outcomes of cCMV and Cx26 mutation populations; there is evidence that both populations can achieve similar outcomes; nonetheless, a worse performance for cCMV patients has also been reported [23–25,29].

Considering the present data, it has been possible to observe an overall progressive improvement over time (from T1 to T4) both of the perceptive level and of the overall language development (considering both language stage and linguistic level), in the three studied groups. In particular, no statistically significant difference was found between cCMV group and Cx26 mutation group at T1, T2, and T3, underlining that children with cCMV can reach post-CI functional outcomes fully

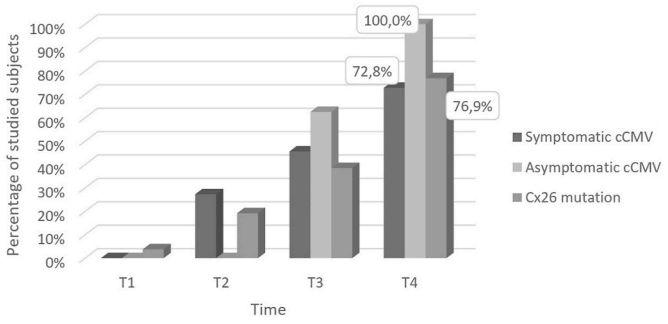


Fig. 1. Evaluation of the 6th perception category development, over time, for each of the three studied groups.

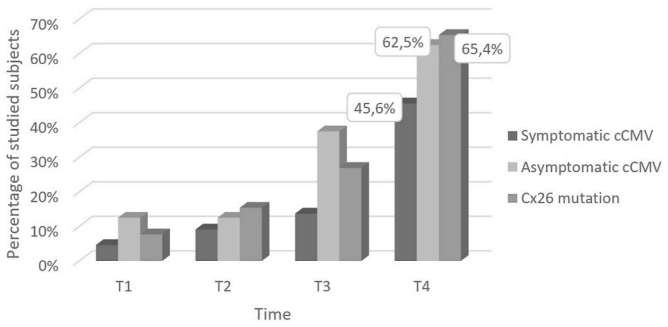


Fig. 2. Evaluation of the discourse grammar linguistic level development, over time, for each of the three studied groups.

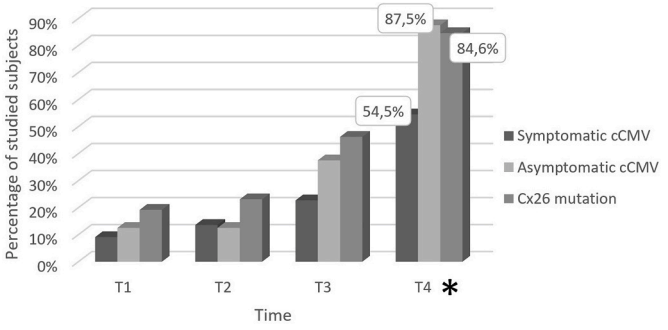


Fig. 3. Evaluation of the functional language development, over time, for each of the three studied groups.

comparable with those affected by Cx26 mutation. According to our results, at 3–4 years after CI, all asymptomatic cCMV patients reached the sixth perceptual category (the most advanced); about 90% developed a functional language and about 60% produced combined sentences conforming to the adult model. In the symptomatic cCMV group, about 75% of patients reached the sixth perceptual category, about 55% developed a functional language, and just less than half produced a grammatical level of speech in accordance with the adult model. As shown in Table 3, a significant percentage of symptomatic subjects was presenting microcephaly, CNS abnormalities at neuroimaging, convulsions, and cognitive impairment; as already stated in the literature, these clinical features can be considered possible causes of the reduced post-CI improvement rate in the symptomatic group [23]. These data are consistent with current literature, since patients with symptomatic cCMV, sometimes with associated cognitive deficits, show a reduced post-CI improvement rate compared to asymptomatic cCMV patients [30,31]. Concerning the achievement of the functional stage of language at T4: symptomatic cCMV patients significantly performed worse compared to asymptomatic cCMV and Cx26 mutation groups. About 30% of patients with symptomatic cCMV had a pre-CI AAC (augmentative and alternative communication), LIS (Italian Sign Language) communication modality, or a combination of these two modalities, unlike Cx26 mutation (about 11% showed a pre-CI AAC/LIS communication modalities) and asymptomatic cCMV (all patients showed an oral communication modality) groups (see Table 2). Patients affected by symptomatic cCMV presented different communication abilities at baseline compared to the other groups, probably due to different neurodevelopmental, psychomotor, or cognitive disorders (as reported in Table 3) affecting the adaptation to alternative communication modalities, even after cochlear implantation and speech therapy rehabilitation [32]. About 36% of patients with symptomatic cCMV presented a transitional language stage at T4, using words even if in a persisting AAC modality. All asymptomatic cCMV patients of our studied cohort presented an oral communication in the pre-CI period, probably due to early application of hearing aids and to the absence of neurodevelopment comorbidities. These facts, in association to the earlier mean age at CI intervention (see Table 2), allow asymptomatic cCMV patients to develop effective communication skills. The overall variability of post-CI results present in the current literature could be related to the different clinical severity of cCMV; in fact, asymptomatic cCMV patients show faster progress than patients with symptomatic cCMV [29].

Furthermore, data reported in Table 2 show that a high percentage of patients in each group has received a unilateral implantation, consequently presenting a bimodal stimulation. This fact can be explained since the majority of the patients underwent cochlear implantation several years ago, while the most recent cases received a bilateral CI, more often simultaneously.

Nowadays, cochlear implants (and, when indicated, bilateral and simultaneous) supported by speech therapy rehabilitation are recognized as an effective auditory rehabilitation strategy in case of cCMV related severe-to-profound SNHL.

5. Conclusion

Considering the data of the present study, it is possible to observe an overall improvement in language skills for both cCMV, symptomatic and asymptomatic, as well as for Cx26 mutation patients, although the symptomatic cCMV group achieved a lower language stage 3–4 years after CI compared to asymptomatic cCMV and Cx26 mutation groups, probably due to the associated neurodevelopmental comorbidities. Also in our opinion, CI supported by speech therapy can be considered an effective treatment for children affected by cCMV-related severe-to-profound hearing loss, as also supported by other Authors [24,25,30,33–35].

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

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