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Rehabilitation and outcome of severe profound deafness in a group of 16 infants affected by congenital cytomegalovirus infection

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Abstract The aim of the study was to characterize the audiological consequences of congenital cytomegalovirus infection (CMV) and to evaluate the outcome of rehabilitation with hearing aids and/or cochlear implant (CI), associated with an adequate speech–language therapy. A retrospective review of data was made from a total of 16 infants, affected by severe to profound hearing loss from congenital CMV infection, referred to a tertiary audiological center for rehabilitation. Audiological evaluation was performed using behavioral audiometry, auditory brainstem responses (ABR) and/or electrocochleography (ECochG). Of the 16 children (median age at diagnosis of hearing loss: 21.33 ± 0.7 months) with CMV hearing loss, 14 were affected by profound bilateral hearing loss and received a CI, while 2 were affected by bilateral severe hearing loss and received hearing aids. Cochlear implants can provide useful speech comprehension to patients with CMV-related deafness, even if language development is lower when compared to a group of Connexin (Cx) 26+ cochlear-implanted children (eight subjects), matched for age. Congenital CMV infection still represents a serious clinical condition, as well as an important cause of hearing loss in children. More studies have claimed to identify the pathophysiological mechanisms of damage and thus to ensure a better therapeutic approach. Nonetheless, in cases of CMV-deafened babies, the overall outcome of cochlear implantation is good.

Keywords Congenital CMV infection · Sensorineural hearing loss · Cochlear implants · CI outcome

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Introduction

Congenital cytomegalovirus (CMV) infection is a leading cause of neurological disease and hearing loss in children [1–5]. Today, CMV infection is considered as one of the principal non-genetic congenital causes of sensorineural hearing loss (SNHL) in developed countries [1, 2, 4–10], since rubella, measles and mumps have become rare due to vaccination [3, 11–13]. Even though central nervous system (CNS) manifestations at birth in infants with clinically congenital CMV infection predict cognitive and motor deficits, they do not always predict hearing loss [2, 7, 14].

The prevalence of congenital CMV infection varies widely among different populations (0.2–3.0%) in most European countries; in Sweden, it has been reported that it occurs in 35–40% of congenital SNHL [15–17].

Current estimates suggest that there are 30,000–40,000 infants born with congenital CMV infection annually in the USA, and of these approximately 8,000 children develop sensorineural hearing loss and/or permanent central nervous system defects [18–20]. Therefore, CMV is still one of the most common and important congenital infections in developed countries [21].

The authors present a retrospective study with the aim of describing the audiological rehabilitation and outcome of a group of CMV congenital infected babies, referred to the

Audiology Department of the University of Ferrara (Italy) for a third-level assessment and treatment.

Congenital CMV infection and hearing loss

Approximately 10% of congenitally infected infants have clinical evidence of the disease at birth. The symptomatic congenital form of CMV infection (also defined as cytomegalic inclusion disease, CID) may cause prematurity and low birth weight, as well as intrauterine growth retardation, hepatosplenomegaly, hematological abnormalities (particularly thrombocytopenia) and a variety of cutaneous manifestations, including petechiae and purpurae. The most significant manifestations of CID are those involving the central nervous system, including sensorineural hearing loss (it can be present in about 20–65% of children with CID) [5, 9, 21–24].

With regards to the asymptomatic congenital CMV-infected infants, even if most children appear clinically normal at birth, they may have subtle growth retardation compared to uninfected infants. Moreover, these infants are also at risk for neurodevelopmental and audiological sequelae. It has been reported that approximately 15–25% of these infants can develop unilateral or bilateral SNHL [5, 22–24].

For both groups (symptomatic and asymptomatic infants), several authors noticed that SNHL becomes more severe after the 1st year of life [1, 15], with a further deterioration within the first 4 years of life (progressive SNHL) [9, 16, 17].

Congenital CMV-infected children and cochlear implants

So far, there have only been two studies in literature that have specifically explored the efficacy of cochlear implants in CMV-deafened babies [25, 26]. The suitability for cochlear implantation has been questioned for children deafened by CMV, because of the high incidence of motor–cognitive and central auditory disorders that may interfere with the acquisition of the spoken language. Moreover, attention disorders observed in many children deafened by CMV could affect the educational management and the rehabilitation of these children after implantation. However, in both the studies mentioned above, the reported average linguistic outcome after cochlear implantation was positive [25, 26].

Patients and methods

A retrospective study of the pediatric patient database at the Audiology Department of the University Hospital of Ferrara was performed. Between January 1990 and December 2004, 16 patients with CMV-related hearing loss were assessed for tertiary-level audiological evaluation and rehabilitation.

Their clinical notes were reviewed for additional clinical information including clinical history, neonatal and past medical history, imaging data as well as laboratory and clinical examination findings.

The audiological assessment was set using behavioral audiometry, auditory brainstem responses and electrocochleography. An EM 12 Mercury apparatus was used for the electrophysiological threshold identification.

We defined mild hearing loss as a loss of 45 dB, moderate loss as a loss of 46–70 dB, severe loss as a loss of 71–90 and profound hearing loss as a loss > 90 dB, according to ASHA protocols.

Only infants affected by bilateral severe to profound SNHL were included in the study. Children were determined to have asymptomatic congenital CMV infection if they had any of the following: prenatally within the mother's serum, assessment of CMV-specific IgG and IgM using ELISA technique; postnatally, evaluation of CMV antigenemia by polymerase chain reaction (PCR) in blood and urinary specimens, plus serological testing for the CMV-specific IgG and IgM levels [27].

Children were determined to have symptomatic congenital CMV infection if they had any of the following signs or symptoms during the newborn pre-perinatal period: significant intrauterine growth retardation; microcephaly; chorioretinitis; petechiae; hepatoslenomegaly; intracranial calcification; hydrocephalus; severe liver dysfunction; direct hyper-bilirubinemia (also see Table 1). The diagnosis was confirmed by assessment of CMV-specific IgG and IgM using ELISA technique prenatally within the mother's serum and/or by amniocentesis, and/or postnatally by evaluation of CMV antigenemia plus serological tests [27].

Patients' speech perception scores were translated into a common outcome parameter, the Speech Perception

Table 1 Clinical diagnostic features in children with symptomatic congenital CMV infection (modified from Rivera LB et al. [2])

Intrauterine growth retardation
Prematurity <37 weeks gestation and low birth weight
Petechiae
Jaundice and hyper-bilirubinemia
Hepatosplenomegaly and severe liver dysfunction
Microcephaly
Seizures
Chorioretinitis
Intracranial calcification
Hydrocephalus

Table 2 Symptomatic and asymptomatic newborns affected by congenital CMV infection, sub-groups A and B

Patient	Birth date	IC/prosth date	RMN modification	Weight at birth	Neonatal stress	Clinical signs	Visual impairment	Cognitive impairment[a]	Motor impairment	Seizures
Symptomatic CMV infection, sub-group A										
1	23/3/04	12/4/06	Yes	2,765	No	Thrombocytopenia	Normal	0	Slight	No
2	9/4/96	4/4/01	Yes	2,500	Yes	Thrombocytopenia and hepatosplenomegaly	Normal	2	Spastic tetraparesis	EEG alterations
3	26/8/03	17/5/07	Yes	1,500	No	Hydrocephalus	Normal	0	Slight	No
4	26/8/00	4/6/02	Yes	2,580	No	No	Normal	1	No	No
5	13/5/98	6/3/02	Yes	1,615	No	Growth delay	Normal	0	No	No
6	6/6/90	30/6/04	Yes	2,500	Yes	Microcephalus	Left eye	1	Right side	Yes
7	5/5/02	20/5/06	Yes	1,510	Yes	Seizures	Light	3	Tetraparesis	EEG alterations
8	19/12/00	21/4/04	Yes	2,800	No	Seizures; left hemiplegia	Normal	0	Slight left	Yes
9	22/10/95	21/11/02	Yes	NA	No	Microcephalus	Left eye	3	Slight	
10	18/8/06	6 months	Yes	1,750	Yes	Petecchiae, coloboma	Normal	0	Slight	No
11	6/12/89	15 months	Yes	1,780	Yes	Intrauterin growth delay	Normal	3	Slight	Yes
12	2/5/96	10 months	Yes	2,550	No	Seizures; left hemiplegia	Normal	0	Slight	EEG alterations
Asymptomatic CMV infection, sub-group B										
1	27/3/03	9/12/04	Yes	2,800	No	No	No	0	No	No
2	1/10/01	31/3/04	Yes	NA	No	No	No	0	No	No
3	9/1/90	25/5/06	Yes	NA	No	No	No	0	No	No
4	1/1/01	13/7/04	Yes	2,900	No	No	No	0	No	No

[a] Mental retardation scale (nonverbal IQ) according to DSM IV criteria. 0 Normal (QI > 70), 1 moderate (QI 50–70), 2 middle (QI 35–50), 3 severe (QI 20–35), 4 profound (QI < 20)

Categories according to the Geers and Moog Scale [28], in order to compare subjects across different ages and varying degrees of speech development. Six levels of speech perception were then used: 0 = no detection of speech sounds; 1 = simple detection; 2 = pattern perception; 3 = inconsistent closed set word recognition; 4 = consistent closed set word recognition; 5 = open set word recognition; 6 = open set word recognition, exceeding performance with old device.

Language development, during the rehabilitative intervention (hearing aid or CI) was assessed using the Nottingham classification categories and the classification adapted from Bates E, O'Connel B, and Shore C, 1987 [29]. According to the Nottingham scale, three levels of speech development were then stratified: (1) pre-verbal = no intentional verbal communication, (2) periverbal = use of words, (3) functional = use of phrases and word sequences based on morphological and syntactic rules. According to the classification adapted from Bates E et al., six levels of speech development were also stratified: absent = voicing/babbling; voc = 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 based on morphological and syntactic rules; discourse grammar = connected discourse closely conforming to adult model. When necessary, also cognitive development was assessed by the use of DSM IV criteria.

All the CMV-infected infants were followed up clinically; audiological, neurological and phoniatric evaluations were repeated at regular intervals, and most of these patients were also managed by their local speech pathologist or deaf educator.

Finally, using statistical analysis, in order to evaluate the overall linguistic outcome after cochlear implant, we compared the CMV population with a group of Connexin (Cx) 26+ cochlear-implanted children (eight subjects), matched for age and pre-implant linguistic category.

For both groups, we tested the hypothesis that patients tend to increase their Speech Perception Category and Language Development scores, after CI (at 6 months, 1 and 3 years later or more). Hence four time periods were considered: pre-CI (time 1), 6 months (time 2), 1 year (time 3), 3 years or more (time 4). All pairwise comparisons were performed and adjusted for multiplicity using a Bonferroni correction. Since sample sizes are very small, exact permutation tests for paired samples were

Table 3 Perceptive score and linguistic outcome of the CMV affected subjects

Patient	Communication mode	Aided th. dB HL	Period of CI use	Auditory perceptive performance[a]	Major stages of language development[b]	Major stages of language development[c]
Symptomatic CMV infection, sub-group A						
1	Auditory–oral	75	Pre-CI	1	Pre-verbal	Absent
			6 months	3	Pre-verbal	Vocalization
			1 year	5	Transitional	Words
2	Augmentative altern communication	>130	Pre-CI	0	Pre-verbal	Absent
			6 months	1	Pre-verbal	Vocalization
			1 year	2	Pre-verbal	Vocalization
			3 years	3	Transitional	Words
			5 years	5	Transitional	Combinations
3	Auditory–oral	75	Pre-IC	1	Pre-verbal	Vocalization
			3 months	2	Pre-verbal	Vocalization
			6 months	2	Transitional	Words
4	Auditory–oral	80	Pre-IC	0	Pre-verbal	Vocalization
			6 months	2	Pre-verbal	Vocalization
			1 year	4	Transitional	Words
			3 years	5	Transitional	Combinations
			5 years	6	Functional	Sentence
5	Auditory–oral	55	Pre-IC	1	Transitional	Words
			6 months	2	Transitional	Words
			1 year	4	Transitional	Combinations
			2 years	5	Functional	Sentence
			5 years	6	Functional	Discourse
6	Augmentative altern communication	>130	Pre-CI	0	Transitional	Words
			6 months	2	Transitional	Words
			1 year	2	Transitional	Words
			2 years	3	Transitional	Words
			3 years	4	Transitional	Words
7	Augmentative altern communication	>130	Pre-CI	0	Pre-verbal	Absent
			6 months	1	Pre-verbal	Absent
			1 years	1	Pre-verbal	Absent
8	Auditory–oral	65	Pre-CI	1	Pre-verbal	Vocalization
			6 moths	3	Transitional	Words
			1 years	4	Transitional	Words
			2 years	5	Transitional	Combinations
			3 years	5	Transitional	Combinations
9	Augmentative altern communication	100	Pre-CI	0	Pre-verbal	Absent
			6 months	1	Pre-verbal	Vocalization
			1 year	2	Transitional	Words
			2 years	3	Transitional	Words
			4 years	5	Transitional	Combination
10	Auditory–oral	60	Pre-CI	1	Pre-verbal	Vocalization
11	Augmentative altern communication	>130	Before H.A.	0	Pre-verbal	Absent
			18 years	0	Pre-verbal	Absent
12	Auditory–oral	45	Before H.A.	0	Pre-verbal	Vocalization
			11 years	6	Verbal	Sentence

Table 3 continued

Patient	Communication mode	Aided th. dB HL	Period of CI use	Auditory perceptive performance[a]	Major stages of language development[b]	Major stages of language development[c]
Asymptomatic CMV infection sub-group B						
1	Auditory–oral	65	Pre-CI	1	Pre-verbal	Vocalization
2	Auditory–oral	80	Pre-CI	0	Pre-verbal	Vocalization
			6 months	4	Transitional	Words
			1 year	5	Functional	Phrases
			3 years	6	Functional	Normal
3	Auditory–oral	55	Pre-CI	2	Functional	Normal
			6 months	4	Functional	Normal
			1 year	6	Functional	Normal
4	Auditory–oral	100	Pre-CI	0	Pre-verbal	Vocalization
			6 months	3	Transitional	Words
			1 year	5	Transitional	Words
			3 years	4	Transitional	Words

[a] Auditory perceptive performance [28]: 0 = no detection of speech sounds, 1 = simple detection, 2 = pattern perception, 3 = inconsistent closed set word recognition, 4 = consistent closed set word recognition, 5 = open set word recognition, 6 = open set word recognition, exceeding performance with old device

[b] Major stages of language development (Nottingham scale): pre-verbal transitional = transitional language/single word utterances or word sequences; functional = functional language/intelligible or unintelligible word sequences based on morphological and syntactic rules

[c] Major stages of language development: absent = voicing/babbling; vocalization = 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 based on morphological and syntactic rules; discourse grammar = connected discourse closely conforming to adult model

performed [30–32] using NPC test statistical software (http://www.salmasoluigi.it/biostat.htm). Nonparametric permutation tests were used to evaluate the possible significance in pre-post CI patients also with respect to the follow-up.

Results

The study population was composed of a total of 16 infants (six females and ten males, M/F = 1.66). All children were Caucasian, coming from different Italian regions; median age at diagnosis of hearing loss was 21.33 (±0.7) months.

Of the 16 children, 12 were affected by symptomatic CMV (Table 2), while the remaining 4 had an asymptomatic congenital CMV infection. Of the 12 cases with symptomatic congenital CMV infection (sub-group A, seven males and five females), 10 children presented with bilateral profound SNHL and the remaining 2 presented with bilateral severe SNHL (Table 2). In the sub-group A, the infection occurred during the first intrauterine trimester and all the patients presented with a concomitant severe CNS pathology at birth. All the ten babies affected by profound bilateral SNHL received a CI (three were implanted at other centers), while the remaining two babies with a bilateral severe SNHL received hearing aids (HA).

Among the four babies with asymptomatic congenital CMV infection (sub-group B; three males and one female), all had profound bilateral SNHL and had already received a CI. All infants (sub-groups A and B) were in clinical follow-up by a multidisciplinary team that included at least an audiologist, pediatric neuropsychiatrician, MD phoniatrician and speech–language pathologist.

Linguistic Categories (LC) were used to standardize the language outcomes following CI activation and rehabilitation. Particularly in the linguistic outcome of the CMV population, it was possible to observe that also children who had bilateral profound SNHL and some cognitive impairment (sub-group A) made some progress in the areas of speech perception and language development over time (Table 3). For those babies with asymptomatic CMV infection (sub-group B), speech perception and language development performances were in general relatively good (Table 3).

The overall linguistic outcome of the 14 babies (sub-group A + sub-group B), who received a cochlear implant (Table 3), was then compared to a group of Connexin (Cx) 26+ cochlear-implanted children (eight subjects), matched for age and pre-implant linguistic category (Table 4).

Table 4 Comparative linguistic outcome within a group of Cx 26+ cochlear-implanted subjects matched for age at CI

Patient	Birth date	CI date	CI age (years)	Cognitive Status[a]	Communication mode	Aided th. dB HL	Period of CI use	Auditory perceptive performance[b]	Major stages of language development[c]	Major stages of language development[d]
1	13/9/95	21/9/98	3	Normal	Auditory–oral	75	Pre-CI	1	Transitional	Combinations
							6 months	3	Transitional	Combinations
							1 year	5	Functional	Sentences
							5 years	6	Functional	Discourse
2	24/7/93	8/4/99	5	Normal	Auditory–oral	70	Pre-CI	1	Functional	Sentences
							6 months	2	Functional	Sentences
							1 year	4	Functional	Sentences
							5 years	6	Functional	Discourse
3	31/7/92	20/1/00	7	Normal	Auditory–oral	90	Pre-CI	0	Transitional	Words
							6 months	1	Transitional	Combinations
							1 year	2	Functional	Sentences
							5 years	5	Functional	Discourse
4	9/10/96	19/1/00	3	Normal	Auditory–oral	80	Pre-IC	1	Pre-verbal	Vocalization
							6 months	2	Transitional	Words
							1 year	4	Transitional	Combinations
							3 years	5	Functional	Sentences
							5 years	6	Functional	Discourse
5	17/12/95	11/5/00	4	Normal	Auditory–oral	70	Pre-CI	1	Transitional	Combinations
							6 months	3	Transitional	Combinations
							1 year	5	Functional	Sentence
							2 years	5	Functional	Discourse
							5 years	6	Functional	Discourse
6	15/4/98	8/11/00	2	Normal	Auditory–oral	70	Pre-CI	0	Transitional	Words
							6 months	3	Transitional	Combinations
							1 year	3	Transitional	Combinations
							2 years	5	Functional	Sentences
							3 years	6	Functional	Discourse
7	20/6/98	22/11/00	2	Normal	Auditory–oral	80	Pre-CI	0	Pre-verbal	Vocalization
							6 months	1	Pre-verbal	Vocalization
							1 year	4	Transitional	Words
							3 years	5	Functional	Sentences
							5 years	6	Functional	Discourse

[a] Mental retardation scale (nonverbal IQ) according to DSM IV criteria. 0 Normal (QI > 70), 1 moderate (QI 50–70), 2 middle (QI 35–50), 3 severe (QI 20–35), 4 profound (QI < 20)

[b] Auditory perceptive performance [28]: 0 = no detection of speech sounds, 1 = simple detection, 2 = pattern perception, 3 = inconsistent closed set word recognition, 4 = consistent closed set word recognition, 5 = open set word recognition, 6 = open set word recognition, exceeding performance with old device

[c] Major stages of language development (Nottingham scale): pre-verbal transitional = transitional language/single word utterances or word sequences; functional = functional language/intelligible or unintelligible word sequences based on morphological and syntactic rules

[d] Major stages of language development: absent = voicing/babbling; vocalization = 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 based on morphological and syntactic rules; discourse grammar = connected discourse, closely conforming to adult model

Since the 1st year, the speech perception score as well as the language development score results improved statistically in both groups of patients (CMV and Cx26+); nonetheless, the language development score improvement of the CMV group was weaker in terms of *p*-value (significant at 10%), when compared with the progression of the speech perception score (significant at 5%). These results indicate that both groups progressed over time on the outcome measures, but the group with hearing loss due to Connexin 26 progressed faster, as this group did not have any concomitant cognitive impairment.

Discussion and conclusion

Children with sensorineural hearing loss from congenital CMV infection vary widely in their clinical features, audiometric outcomes and eventual need of educational support (3, 24). Early hearing rehabilitation of these infants, either with hearing aids or cochlear implants, is necessary to ensure appropriate perception skills as well as language and cognitive function development [3, 24]. Follow-up should be organized in order to: (1) provide additional information regarding speech perception and language development, as well as school performance; (2) avoid missing diagnosis of ''later'' onset and/or progression of hearing loss [3].

With regard to our case series, the correct and timely diagnosis of congenital CMV infection allowed the medical team to assess the appropriate level of intervention during the neonatal period. A significant improvement in the perception score after cochlear implantation or prosthesization was observed in most of the cases. The linguistic outcome also improved globally in both groups, though in CMV patients, the overall language development score was lower, possibly due to CNS impairment.

So far, there are only a few studies in literature regarding the outcome of CI in congenital CMV-infected babies [2, 25, 33]. Published data have shown that only early cochlear implantation associated with comprehensive rehabilitation can provide good speech perception also in CMV-infected infants.

In this retrospective study, we have shown that children with CMV-related deafness can achieve substantial auditory and language skills following cochlear implantation and rehabilitation. These progresses are faster over time, especially for those with asymptomatic CMV infection. From the analyses performed in our study, it is possible to get two main information: (1) using cochlear implant, children with symptomatic CMV infection, who have profound hearing loss and some cognitive impairment, can make some progress in the areas of speech perception and language development over time; (2) the difference in the linguistic outcome between the CMV and Connexin 26+ groups can mainly be attributed to the possible CNS impairment of the CMV subjects.

Thus, early hearing rehabilitation of children with CMV-related deafness can successfully increase access to oral language, even in the presence of other CNS abnormalities. Longitudinal follow-up of these children can provide additional functional outcome data regarding speech perception, language development and school performance. This data can be correlated with factors such as age at implantation, duration of deafness and the presence of motor or cognitive delay to assess the long-term benefits of cochlear implantation in these patients.

Further research is needed to identify features that may influence the cochlear implant outcome within this specific sub-population.

Conflict of interest statement None.

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