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AUDIOLOGY

Outcomes of long-term audiological rehabilitation in CHARGE syndrome

Sindrome di CHARGE: risultati a lungo termine della riabilitazione audiologica

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SUMMARY

The aim of this paper is to assess the long-term audiological features and outcomes of hearing rehabilitation in a large group of individuals with CHARGE Syndrome. The study has been conducted retrospectively, on a paediatric patient database, at the Audiology Department of the University Hospitals of Ferrara and Padua. The study sample included 31 children presenting with different degrees of hearing impairment associated with CHARGE syndrome. Hearing was assessed using auditory brainstem responses (ABRs) and/or electrocochleography, or conditioned audiometry (visual reinforcement audiometry [VRA] or play audiometry). Auditory-perceptual outcomes in terms of communication skills and expressive language were also recorded. The effects of hearing rehabilitation (with hearing aids or cochlear implants) in this group of children and language outcomes after rehabilitation were monitored during long-term follow-up. The outcomes of rehabilitation measures differed in relation to the heterogeneous and often severe disabilities associated with CHARGE syndrome, e.g. developmental delay, intellectual delay, visual impairment, thin 8th nerve with retrocochlear auditory dysfunction (as described in cases of auditory neuropathy/dyssynchrony). Oral expressive language was severely impaired in most cases, even after lengthy follow-up, suggesting the need for alternative augmentative communication modes. The early identification of sensorineural hearing loss, and carefully planned rehabilitation treatments, can be of some benefit in children with CHARGE syndrome.

KEY WORDS: CHARGE syndrome • Inner ear • Hearing loss • Cochlear implants • Rehabilitation

RIASSUNTO

Obiettivo del presente lavoro è valutare i risultati della riabilitazione audiologica su un gruppo, numericamente consistente, di bambini affetti da sindrome di CHARGE. Lo studio è stato eseguito retrospettivamente, utilizzando il database dei pazienti pediatrici, presso l'Audiologia dell'Azienda Ospedaliero-Universitaria di Padova e di Ferrara. Sono stati individuati 31 bambini in totale, che hanno presentato diversi gradi di disabilità uditiva associata alla sindrome di CHARGE. La valutazione audiologica è stata eseguita utilizzando i potenziali evocati uditivi (ABR) e/o l'elettrococleografia, oppure le tecniche di audiometria infantile (VRA o play audiometry). Sono stati valutati anche i risultati percettivi, in termini di capacità di comunicazione e linguaggio espressivo. Sono quindi stati studiati gli effetti della riabilitazione uditiva (con apparecchio acustico o impianto cocleare) e in particolare lo sviluppo del linguaggio nel corso di un lungo follow-up. Gli esiti degli interventi riabilitativi sono risultati diversi in relazione alle eterogenee e spesso gravi disabilità associate alla sindrome di CHARGE (ad esempio, ritardo di sviluppo psico-fisico, gravi disturbi visivi concomitanti, disfunzioni uditive retrococleari per neuropatia uditiva/dissincronia associata). Anche dopo lungo follow-up, lo sviluppo del linguaggio è risultato gravemente compromesso nella maggior parte dei casi, suggerendo quindi la necessità di sviluppare modalità di comunicazione alternative in questo gruppo di piccoli Pazienti. L'identificazione precoce della sordità neurosensoriale e l'accurata pianificazione di trattamenti riabilitativi mirati, è in ogni caso fondamentale nei bambini con sindrome di CHARGE.

PAROLE CHIAVE: *Sindrome di CHARGE • Orecchio interno • Ipoacusia neurosensoriale • Impianto cocleare • Riabilitazione*

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Introduction

The association of conditions was first described by Hall et al., in 1979, in 17 children with multiple congenital anomalies [1]. In the same year, Hittner reported this syndrome in 10 children with ocular colobomas and multiple congenital anomalies [2]. Hence the alternative name of Hall-Hittner syndrome [3]. Pagon et al. first adopted the acronym CHARGE in 1981 [4]. The syndrome comprises a cluster of conditions including: ocular coloboma (C); congenital heart defects (H); atresia of the choanae (A); retarded growth or development and/or central nervous system anomalies (R); genital hypoplasia (G); and ear anomalies, including deafness and vestibular dysfunction (E) [1].

The criteria for diagnosing CHARGE syndrome are listed in Table I. It has been suggested that diagnosis should be considered in any subject presenting with all four of the

Table I. Diagnostic criteria for CHARGE syndrome (from Blake KD et al., 2006 [10], mod.).

Major criteria	Minor criteria
Ocular coloboma	Cardiovascular malformations
Choanal atresia/stenosis	psychomotor retardation
Cranial nerve	Genital hypoplasia
Characteristic ear anomalies	Renal malformations
	Tracheoesophageal disease (i.e. atresia, laryngomalacia)
	Facial clefting
	Developmental delay, and short stature
	Hand dysmorphology
	Hypotonia

major criteria or with three of the major and three of the minor criteria [5 6]. Some of the features of CHARGE syndrome may be difficult to detect in the neonatal period, however, such a diagnosis needs to be kept in mind even for infants meeting one or two of the major and several of the minor criteria [5 6].

Concerning the syndrome's aetiopathogenesis, the majority of CHARGE cases identified so far have been classified as sporadic, but several genes may play a key part in this condition's pathogenesis. In 2005, a team from Radboud University (Nijmegen, Netherlands) using array-based comparative genomic hybridisation identified a small overlapping microdeletion at chromosome 8q12 in two patients with CHARGE syndrome. Therefore, the candidate CHD7 gene within this region was first identified and sequenced in 17 patients [7-9]. Although the CHARGE phenotype may be related to CHD7 gene mutations, there are still doubts concerning any genotype/phenotype correlation between the various features of CHARGE and different mutations in the CHD7 gene [10-12]. The use of genetic analysis as the sole tool for diagnosing this syndrome remains controversial [7 8 13].

External ear malformations have been described in association with CHARGE syndrome, including short and/or hypoplastic pinna with a minimal lobule, a hypoplastic helix or an anomalous concha [6]. Abnormalities have also been reported in the middle and inner ear [5 14 15], and hearing loss in CHARGE subjects may be conductive, sensorineural or mixed, ranging from mild to severe. Vestibular defects/malformations have also been described [16].

So far, only a few reports in the literature have focused on inner ear histopathology in CHARGE based on human autopsy studies. In 1986, Wright et al. [17] analysed the temporal bones of two infants who died soon after birth: the main findings were dysplastic ossicles, absence of the oval and round windows, cochleae that were normal in one case and short in the other, and varying degrees of hypoplasia of the vestibular sensory organs and nerves. In 1987, Guyot et al. [18] reported finding Mondini dysplasia of the pars inferior (cochlea and saccule) and absence of the pars superior (utricle and canals) in the temporal bone of a 7-month-old female with CHARGE syndrome. In 1993, Schuknecht [19] described two cases of CHARGE syndrome. In one, the external auditory canals, tympanic membranes, mallei and incudes were normal, but there was severe dysplasia of the stapes, and no oval windows and mesenchyme obliterating the round window niches. The other case revealed a one-turn cochlea on the right and a half-turn cochlea on the left. Both ears contained a few cochlear neurons in rudimentary modioli; saccules were present but hypoplastic, and the utricles and semicircular canals were lacking [19].

Other evidence come from radiological studies using temporal bone computerised tomography (CT) or magnetic resonance imaging (MRI). Amiel J et al. [20] reported that the main radiological features of CHARGE in their series were hypoplastic incus, Mondini defect and absence of semicircular canals. In 2003, Satar B et al. [21] studied 20 ears in CHARGE subjects and only 3 ears (15%) revealed a completely normal development of the cochlea in both the basal and upper turns; the others showed either mild hypoplasia of the upper turns (13 ears, 65%), or an incomplete partition typical of the classic Mondini deformity (4 ears, 20%). In 2006, Marimoto et al. [22] described 13 CHARGE patients who had cochlear atresia in 20 (77%) of 26 ears. Four of these ears were also assessed using MRI and were found to lack a cochlear nerve. Twenty-one (81%) of the 26 cochleae had some form of dysplasia. Six (23%) of the 26 round windows were aplastic, and 3 (12%) round windows were hypoplastic. Twenty-one (81%) of the 26 oval windows were atretic or aplastic. Fifteen (58%) of the 26 vestibules were hypoplastic or dysplastic. Five (19%) of the 26 vestibular aqueducts were enlarged. The semicircular canals were lacking in all these cases.

Twenty-three (88%) of the 26 facial nerve canals had an anomalous course. Finally, in 2013, Holcomb MA et al. [23] reported that the cochlear nerves were absent or deficient in 13 of 14 ears with sensorineural hearing loss (SNHL) in a series of CHARGE cases.

In conclusion, the prevalence of inner ear anomalies in the CHARGE syndrome has been reported to be higher than 90% [24]; these can include cochlear hypoplasia, in-

complete cochlear partition, Mondini dysplasia, incomplete formation or absence of semicircular canals, utricle and saccule [10 25 26]. Also, the auditory nerve in CHARGE patients can be reduced in diameter or absent, and nerve anomaly can be asymmetric [10 25 26]. It is clear that a correct neuroradiological assessment of these patients is crucial, in particular for the implications regarding the choice of rehabilitative approach that can be provided.

Materials and methods

This retrospective study was conducted on the paediatric patient database, at the Audiology Department of the University Hospitals of Ferrara and Padua.

The study included a total of 31 patients meeting diagnostic criteria for CHARGE syndrome (Table I) and followed regularly from January 1993 to July 2014. Clinical records were examined to ascertain the details of diagnosis and manifestations of CHARGE syndrome, neonatal and subsequent medical history, imaging data, laboratory and clinical findings, auditory perception and communication skills.

The median age of our sample when hearing loss was diagnosed was 21.15 months, and audiological and communication assessment were adapted to each subject's age and stage of development. Auditory brainstem responses (ABRs) were recorded for all patients to ascertain their hearing threshold. An EM 12 Mercury apparatus was used to identify the electrophysiological threshold. Other tests performed in the diagnostic workup and/or during the follow-up included: pure tone testing, behavioural conditioned audiometry (BCA, play audiometry), DPOAE recording, tympanometry and study of stapedial reflexes. Electrocochleography was also performed in some cases. Cortical evoked potentials in hearing-aided and -unaided patients were also used, in accordance with the Australian Hearing Aided Cortical Evoked Potentials Protocols [27], to measure the benefit of any hearing aids, and in the event of suspected auditory neuropathy/dyssynchrony. Based on American Speech-Language-Hearing Association (ASHA) protocols, a loss of 45 dB was defined as mild hearing loss, loss of 46-70 dB as moderate hearing loss, loss of 71-90 dB as severe hearing loss, and loss > 90 dB as profound hearing loss. CT and MRI data were assessed and any malformations were noted.

All subjects were followed up regularly (including phoniatric assessments) except for two patients who were lost to follow-up and three who died. In particular, perceptual and expressive language skills were assessed (and the findings analysed) at presentation and at 6, 12 and more than 36 months after fitting hearing aids (HA) or cochlear implants (CI). The follow-up was longer than 10 years for 8 patients, between 9 and 5 years for another 6 cases and around 3 years in the remaining 10 children. Speech perception was scored with a commonly-used outcome measure, the Speech Perception Category [28] in order to compare subjects across different ages and varying degrees of speech development. Speech perception was stratified on 6 levels: 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 previous device).

Expressive language outcomes with rehabilitation (HA or CI) were reported using 6 categories corresponding to the major stages of expressive language development in normally-hearing and normally-developing children, ranging from voice production (category1) to the acquisition of connected discourse conforming to the adult model (category 6), through the stages of single word utterance, first combination of words and first sequences based on syntactic rules (See Legend 4, adapted from Bates E, 1987) [29]. Unconventional assessments were also performed in cases with severe additional disabilities. When standard tests for assessing communication skills were unreliable, interviews with parents and video-recordings were used instead. Parents were asked about behavioural changes observed in their child in response to environmental sounds and communicative interactions. In some cases, the PEACH questionnaire developed by Ching et al. was administered. A modified version of the video-analysis recording proposed by Tait [30] was sometimes used to note eye movements and mimicry in children with severe cognitive impairments, in addition to the information provided by their parents.

Results

The study population of 31 children with CHARGE syndrome included 16 girls and 15 boys (M/F ratio 0.93). All children were Caucasian and came from different Italian regions. The median age when hearing loss was diagnosed was 21.15 months. Table II shows the distribution of the major and minor diagnostic criteria in this sample of patients.

Hearing features and hearing rehabilitation

Fifteen of the 31 subjects had bilateral profound sensorineural hearing loss (SNHL); 10 had moderate to severe SNHL; 5 had moderate- to mild mixed hearing loss; and one had a normal hearing threshold but delayed perceptual development (Table III).

CIs were performed in 7 cases and 2 other patients were candidates for this surgery, while the other 8 children with bilateral profound SNHL were fitted with hearing aids. Air-conduction hearing aids were fitted in the children with moderate to severe SNHL as well as in those with a moderate and/or mixed hearing loss. One child only had

Table II. Prevalence of major and minor malformations in our sample of children with CHARGE syndrome.

MAJOR characteristics					MINOR characteristics				
Patient	Coloboma	Choanal atresia/ stenosis	Cranial nerve involvement	Ear anomalies	Cardiovascular malformations	Psychomotor retardation	Genital hypoplasia	Renal malformations	Tracheo-oesophageal disease
1	+		+	+	+			+	+
2	+		+	+	+		+		+
3		+	+	+	+	+			
4	+		+	+					
5	+		+	+	+	+			+
6	+		+	+	+	+		+	
7		+	+	+	+		+		+
8	+		+	+	+				
9	+		+	+		+			
10		+	+	+	+		+		
11	+		+	+	+				
12	+		+	+	+				
13	+		+	+	+	+			+
14		+	+	+		+			+
15	+		+	+	+	+			
16			+	+	+	+			+
17	+	+		+	+	+			
18	+	+			+	+			
19	+		+	+	+	+	+		
20				+	+		+		+
21	+		+	+		+	+		+
22	+	+	+	+	+	+	+		+
23		+	+	+	+	+			+
24	+	+		+	+	+	+	+	
25	+		+	+	+	+	+		+
26		+	+		+	+			
27		+	+	+				+	+
28	+	+	+	+	+	+			
29	+		+	+	+	+			+
30	+		+	+	+			+	
31	+			+		+			

a large air-bone gap and was successfully rehabilitated by means of a soft band bone conduction hearing aid.

Ear CT and Brain MRI findings

Twenty-one of the 31 subjects underwent high-resolution CT scanning and cerebral MRI under general anaesthesia to study their middle and inner ear, brainstem and brain. MRI alone was performed in another 6 patients. In the remaining 4 cases, the parents refused any neuroradiological investigations due to the risks related to general anaesthesia. Different types of ear malformation were identified, involving the cochlea (n = 19 ears), semicircular canals (n = 30), vestibule (n = 24), the internal auditory canal (n = 12), 8th nerve (n = 17), cochlear nerve (n =3) and facial nerve (n = 7).

There was also evidence of brain anomalies in 18 children, such other nerve hypoplasia and brainstem hypoplasia (the latter in only one case).

Psychomotor profile

Most of the children of the studied group presented some kind of delay in development of cognitive and motor abilities (Table II), mainly represented by a delayed postural control (i.e. difficulties in reaching the vertical position

Table III. CHARGE population: audiological features and rehabilitation (*referred to the better ear).

Patient	Hearing loss (*)	Type of rehabilitation	Communication mode
1	Sensorineural, profound	HA	Verb+sign
2	Sensorineural, profound	HA	(missing)
3	Sensorineural, profound	CI	Italian sign language
4	Sensorineural, moderate	HA	Italian sign language
5	Sensorineural, profound	HA	Very low communication skills
6	Sensorineural, profound	CI	Italian sign language
7	Sensorineural, profound	HA	(missing)
8	Sensorineural, moderate	HA	Verbal
9	Mixed, moderate	HA	Verbal
10	Sensorineural, moderate- severe	HA	(missing)
11	Mixed, mild	HA	Verbal
12	Mixed, mild	HA	(missing)
13	Sensorineural, profound	CI	Very low communication skills
14	Mixed, mild	HA	N/A
15	Mixed, mild	HA	Very low communication skills
16	Sensorineural, profound	CI	Verb+sign
17	Sensorineural, profound	CI	Verb+sign
18	Conductive, moderate	N/A	Verbal
19	Sensorineural, profound	HA	Verb+sign
20	Mixed, severe	HA	Verbal
21	Sensorineural, profound	HA	Very low communication skills
22	Sensorineural, profound	HA	Italian sign language
23	Mixed, moderate	HA	Verb+sign
24	Mixed, severe	HA	Very low communication skills
25	Sensorineural, profound	CI	Italian sign language
26	Mixed severe	HA	Very low communication skills
27	Normal	N/A	Very low communication skills
28	Sensorineural, profound	CI	Very low communication skills
29	Mixed, severe	HA	Italian sign language
30	Sensorineural, profound	HA	Very low communication skills
31	Mixed, moderate	HA	Verbal

or walking) or fine movements (i.e. grabbing or holding), light to moderate cognitive deficits, attention deficit or behavioural disorders. However, none of the children presented a severe cognitive delay, and 11/31 children had a satisfactory intellectual outcome (but always requiring special educational programs adapted to their age, hearing and language impairment, vision loss and to other disabilities).

Speech perception and expressive language development

Our data on speech perception and expressive language outcomes after rehabilitation (with CI and/or HA) were not homogeneous, due mainly to the different associated disabilities, such as developmental delay, intellectual delay and visual impairment (Table IV), and in light of the high mortality rate. Among the 7 children treated with CI, one did not benefit from the device, not even in the detection of loud sounds, probably due to a severe functional impairment of a thin 8th nerve. The other implanted children experienced a slow but consistent improvement in their perceptual abilities, achieving verbal word discrimination after a year or more of using the device. The majority of these patients developed delayed language skills (in comparison to deaf children of the same age treated with CIs). A similar trend was seen among the children with moderate to severe hearing impairments who were fitted with HA, so the results were analysed without distinguishing between the children with CIs and HAs.

Long-term follow-up after rehabilitation (at least 3 years) was available for all cases except the 3 children who died

Table IV. Perception scores and expressive language outcomes in children with CHARGE syndrome.

Patient	Perceptive category				Language development				
	Pre CI/HA	After 6 months	After 1 year	After 3 years or more	Pre CI/HA	After 6 months	After 1 year	After 3 years or more	Italian sign language development
1	1	3	5	5	1	2	3	3	+
2	N/A				N/A				
3	0	1	3	3	1	2	2	3	+
4	3	3	3	3	2	2	2	2	+
5	0	1	1	1	1	1	1	1	
6	0	1	3	3	N/A	1	2	2	+
7	0	1			1	2			
8	0	1	4	3	4	4	4	4	
9	2				2				
10	N/A				N/A				
11	6				6				
12	0	1			1	2			+
13	0	0			2	2			+
14	4	4	4	4	2	2	2	2	
15	N/A				N/A				
16	0	2	3	4	1	2	3	4	+
17	1	2	2		1	2	2		+
18	NO HA 5				6				
19	1	1	2	2	3	3	3	3	+
20	3	4	5	5	3	3	5	6	
21	0	1			1	1			
22	0	0 CAND CI			1	2			+
23	3	4	4		1	2	2		
24	0	0	0		1	1	1		
25	0	1	1		1	2	2		+
26	0	1	1		1	2	2		
27	NO HA 2				1				
28	0	1			1	1	1		
29	0	1	2	4	1	2	3	3	+
30	0	0 CAND CI							
31	4	5	6	6	5	5	5	6	

AUDITORY PERCEPTIVE PERFORMANCE (Geers, Moog, 1987 mod. [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)

MAJOR STAGES OF LANGUAGE DEVELOPMENT (Bates, O'Connel, Shore, 1987 mod. [29]).
1 = absent = voicing/babbling
2 = voc =vocalisations/CVC sequences to communicate intentionally
3 = words = first words/single word utterances that have communicative contents
4 = combinations = first words combinations/telegraphic utterances
5 = sentence grammar = combinations based on morphological and syntactic rules
6 = discourse grammar = connected discourse closely conformed to adult model

in early infancy and the 2 lost to follow-up. A slow improvement in auditory skills was recorded in three of the 26 cases followed up at length (who had complex needs and additional disabilities). Auditory-verbal communication as a single mode was only achieved in a few cases, while most patients used both signed and oral languages. One in three children developed some limited intentional communication activities, in addition to intentional vocalising or gestures. Almost all parents of these poorly-performing children nonetheless reported a significant improvement in their child's responsiveness to environmental sounds, and in their perception of their child's

quality of life following hearing rehabilitation, despite their lack of verbal production.

Discussion

It is well known that it is important for a child's development to diagnose and treat any sensory deficits as early as possible. Particularly in subjects with CHARGE syndrome, the combination of visual and auditory impairments with central nervous system anomalies makes audiological/otological intervention essential. Although the anomalies associated with CHARGE are numerous, an increasing number of reports has shown that audiological rehabilitation, and particularly cochlear implantation, may be a feasible rehabilitation method [30-33], and should be considered early because of the children's other communication problems [34], also calculating the risk of unsuccessful stimulation related to a thin 8th nerve and a prognosis of poor cognitive development.

The true incidence of CHARGE syndrome is still not known, but estimates have been in the range of 0.1-1.2/10,000 live births [35]. An epidemiological study of patients with CHARGE syndrome conducted as part of the Canadian Paediatric Surveillance Programme (CPSP) from September 2001-2004 estimated the incidence of this syndrome at 1:8,500 live births [35 36], so the incidence reported internationally may be underestimated [37].

As for the incidence of ear anomalies and hearing loss in CHARGE syndrome subjects, this has been described in 80-100% of reported cases [10], with a prevalence of severe- or profound hearing loss of approximately 50% in series of CHARGE cases [10]. The most frequent inner ear anomalies in patients with CHARGE are cochlear dysplasia, aplasia of the semicircular canals [20 34] (as in our series) and 8th nerve anomalies/dysfunction. High-resolution CT is therefore mandatory, particularly before considering cochlear implantation, to detect anomalies in the middle and/or inner ear and identify any atypical routing of the facial nerve. Obtaining information on the state of the internal auditory canal is also important, as this may provide evidence of aplasia/hypoplasia of the auditory nerve. Patients with CHARGE syndrome should always undergo MRI to assess the 8th nerve [34]. In the series presented here, the cochlear nerve was missing in 3 patients, and many others showed hypoplasia of the vestibulocochlear nerve.

The outcome after hearing rehabilitation (with CIs and HAs) in patients with CHARGE syndrome varies due to the differing extent of other disabilities (e.g. developmental delay and visual impairment). Most of the patients in our series showed some improvement in responsiveness once they were using HAs or had a CI. Open speech comprehension was only seen in one of the four cases. There are few reports in the literature on the outcome of treatment with CIs in CHARGE patients. Lanson BG (2007), Bauer PW (2002) Arndt S (2010), Ahn (2013), Cardoso (2013) and Birman (2015) all demonstrated that CI is a feasible option for such patients, even though variations in temporal bone anatomy can lead to higher surgical risks [34-45]. There is a general consensus that early audiological intervention is important in children with dual/multiple sensory impairments to facilitate their optimal development and enable at least minimal communication [5 34-39 46], but to the best of our knowledge there are still no publications on the long-term results achieved with CIs in children with CHARGE syndrome.

As for any improved communication and perception in our CHARGE patients, prognosis in terms of the effects of rehabilitation should be considered with caution because most of our cases were complicated by cognitive impairments, developmental disorders, or severe physical diseases (respiratory and cardiac insufficiency, severe dysphagia), which compounded the severity of their hearing impairments. Such additional handicaps interfere with the comprehension and production of speech and undermine any benefits achieved thanks to appropriate hearing rehabilitation. Severe physical diseases also mean lengthy hospital stays and other concerns for the child's health and life. Although the auditory-processing and language development in these children is limited by their cognitive and/or physical disorders, careful planning of their hearing rehabilitation (including CI) may offer auditory benefits and some improvements in their communication skills (as seen in our sample). The functional (hearing) prognosis for this particular category of patients should therefore be formulated after carefully weighting patients' auditory and non-auditory factors. A multimodal communication approach (also including sign language) should be planned in advance, tailored to each case and fine-tuned over the course of time.

Conclusions

In conclusion, it is common knowledge that early diagnosis and treatment of sensory deficits is crucial [41]. In the case of CHARGE syndrome, the concomitant presence of characteristic developmental features as well as neuropsychological impairments should be borne in mind in order to plan personalised rehabilitation.

References

1 Hall BD. *Choanal atresia and associated multiple anomalies*. J Pediat 1979;95:395-8.

2 Hittner H, Hirsch N, Kreh G, et al. *Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation: a syndrome*. J Pediatr Ophthalmol Strabismus 1979;16:122-8.

3 Graham JM Jr. *A recognizable syndrome within CHARGE association: Hall-Hittner syndrome*. Am J Med Genet 2001;99:120-3.

4 Pagon RA, Graham JM Jr, Zonana J, et al. *Coloboma, con-*

genital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 1981;99:223-7.

[5] Blake KD, Davenport SLH, Hall BD, et al. *CHARGE association: an update and review for the primary pediatrician*. Clin Pediatr (Phila) 1998;37:159-73.

[6] Davenport SLH, Hefner MA, Mitchell JA. *The spectrum of clinical features in CHARGE syndrome*. Clin Genet 1986;29:298-310.

[7] Jongmans M, Admiraa R, van der Donk K, et al. *CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene*. J Med Genet 2005;43:306-14.

[8] Sanlaville D, Etchevers HC, Gonzales M, et al. *Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development*. J Med Genet 2005;43:211-317.

[9] Lalani SR, Safiullah AM, Fernbach SD, et al. *Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation*. Am J Hum Genet 2006;78:303-14.

[10] Blake KD, Prasad C. *CHARGE Syndrome*. Orphanet J Rare Dis 2006;1:34.

[11] Aramaki M, Udaka T, Kosaki R, et al. *Phenotypic spectrum of CHARGE syndrome with CHD7 mutations*. J Pediatr 2006;148:410-4.

[12] Husu E, Hove HD, Farholt S, et al. *Phenotype in 18 Danish subjects with genetically verified CHARGE syndrome*. Clin Genet 2013;83:125-34.

[13] Delahaye A, Sznajer Y, Lyonnet S, et al. *Familial CHARGE syndrome because of CHD7 mutation: clinical intra- and interfamilial variability*. Clin Genet 2007;72:112-21.

[14] Tellier AL, Cormier-Daire V, Abadie V, et al. *CHARGE syndrome: report of 47 cases and review*. Am J Med Genet 1998;76:402-9.

[15] Peterson LE, McPherson JD, Gibbs RA, et al. *Spectrum of CHD7 Mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation*. Am J Hum Genet 2006;78:303-14.

[16] Edwards BM, Kileny PR, Van Riper LA. *CHARGE syndrome: a window of opportunity for audiologic intervention*. Pediatrics 2002;110:119-26.

[17] Wright CG, Brown OE, Meyerhoff WL, et al. *Auditory and temporal bone abnormalities in CHARGE association*. Ann Otol Rhinol Laryngol 1986;95:480-6.

[18] Guyot JP, Gacek RR, DiRaddo P. *The temporal bone anomaly in CHARGE association*. Arch Otolaryngol 1987;113:321-4.

[19] Schuknecht HF. *Developmental defects*. In: Pathology of the Ear. Second Edition. Philadelphia: Lea & Febiger; 1993. pp. 141-2.

[20] Amiel J, Attiee-Bitach T, Marianowski R, et al. *Temporal bone anomaly proposed as a major criterion for diagnosis of CHARGE syndrome*. Am J Med Genet 2001;99:124-7.

[21] Satar B., *Mukherjei SK, Telian SA*. *Congenital aplasia of the semicircular canals.* Otol Neurotol 2003;24:437-46.

[22] Morimoto AK, Wiggins RH 3rd, Hudgins PA, et al. *Absent semicircular canals in CHARGE syndrome: radiologic spectrum of findings*. AJNR Am J Neuroradiol 2006;27:1663-71.

[23] Holcomb MA, Rumboldt Z, White DR. *Cochlear nerve deficiency in children with CHARGE syndrome*. Laryngoscope 2013;123:793-6.

[24] Sanlaville D, Verloes A. *CHARGE syndrome: an update*. Eur J Hum Gen 2007;15:389-99.

[25] Thelin JW, Krivenki SE. *Audiologic Issues in CHARGE Syndrome*. American Speech-Language-Hearing Association (ASHA). http://www.asha.org/aud/articles/CHARGESyndrome/

[26] Hsu P, Ma A, Wilson M, et al. *CHARGE syndrome: a review*. J Paediatr Child Health 2014;50:504-11.

[27] Chang HW, Dillon H, Carter L, et al. *The relationship between cortical auditory evoked potential (CAEP) detection and estimated audibility in infants with sensorineural hearing loss*. Int J Audiol 2012;51:663-70.

[28] Geers AE, Moog JS. *Predicting spoken language acquisition of profoundly hearing-impaired children*. J. Speech Hear Disord 1987;52:84-94.

[29] Bates E, O'Connel B, Shore C. *Language and communication in infancy*. In: Osofsky J (Ed.). *Handbook on Infant Development.* New York: Wiley; 1987. pp. 149-203.

[30] Tait ME, Nikolopoulos TP, Wells P, et al. *The use and reliability of Tait video analysis in assessing preverbal language skills in profoundly deaf and normally hearing children under 12 months of age*. Int J Pediatr Otorhinolaryngol 2007;71:1377-82.

[31] Woolley AL, Jenison V, Stroer BS, et al. *Cochlear implantation in children with inner ear malformations*. Ann Otol Rhinol Laryngol 1998;107:492-500.

[32] Papsin BC. *Cochlear implantation in children with anomalous cochleovestibular anatomy*. Laryngoscope 2005;115(1 Pt 2 Suppl 106):1-26.

[33] Lanson BG, Green JE, Roland JT Jr, et al. *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes*. Laryngoscope 2007;117:1260-6.

[34] Arndt S, Laszig R, Beck R, et al. *Spectrum of hearing disorders and their management in children with CHARGE syndrome*. Otol Neurotol 2010;31:67-73.

[35] Blake KD, Issekutz KA, Smith IM, et al. *The incidence and prevalence of CHARGE syndrome*. The CPSP Annual Report 2002 and 2003. http://www.CPS.ca.

[36] Issekutz KA, Smith IM, Prasad C, et al. *An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study*. Am J Med Genet A 2005;133:309-17.

[37] Ahn JH, Lee KS. *Outcomes of cochlear implantation in children with CHARGE syndrome*. Acta Otolaryngol 2013;133:1148-53.

[38] Ricci G, Trabalzini F, Faralli M, et al. *Cochlear implantation in children with "CHARGE syndrome": surgical options and outcomes*. Eur Arch Otorhinolaryngol 2014;271:489-93.

[39] Southwell KE, Bird PA, Murray DP. *Cochlear implantation in children with CHARGE syndrome*. Cochlear Implants Int 2010;11:241.

[40] Harris J, Robert E, Kallen B. *Epidemiology of choanal atresia with special reference to the CHARGE association*. Pediatrics 1997;99:363-7.

[41] Searle C, Graham JM, Prasad C, et al. *CHARGE syndrome from birth to adulthood: an individual reported from 0 to 33 years*. Am J Med Genet A 2005;133A:344-9.

[42] Bauer PW, Wippold FJ 2nd, Goldin J, et al. *Cochlear implantation in children with CHARGE association*. Arch Otolaryngol Head Neck Surg 2002;128:1013-7.

[43] Lanson BG, Green JE, Roland JT Jr, et al. *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes*. Laryngoscope 2007;117:1260-6.

[44] Birman CS, Brew JA, Gibson WP, et al. *CHARGE syndrome and Cochlear implantation: difficulties and outcomes in the paediatric population*. Int J Pediatr Otorhinolaryngol 2015;79:487-92.

[45] Cardoso CC, Sales de Meneses M, Silva IM, et al. *Cochlear implants in children diagnosed with CHARGE syndrome*. Int Arch Otorhinolaryngol 2013;17:424-8.

[46] Santoro L, Ficcadenti A, Zallocco F, et al. *Cognitive-motor profile, clinical characteristics and diagnosis of CHARGE syndrome: an Italian experience*. Am J Med Genet A 2014;164:3042-51.

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