COCHLEAR IMPLANTATION IN DEAF CHILDREN WITH COMPLEX NEEDS

A Descriptive Study on Cochlear Implantation in Children with CHARGE Syndrome, Congenital Cytomegalovirus Infection or Kabuki Syndrome

Annemarie Vesseur

ISBN
978-94-92896-33-9

Design/lay-out
Promotie In Zicht, Arnhem

Cover design
Leonoor Vesseur

Print
Ipskamp Printing, Enschede

Cochlear Implantation in Deaf Children with Complex Needs

A Descriptive Study on Cochlear Implantation in Children with CHARGE Syndrome, Congenital Cytomegalovirus Infection or Kabuki Syndrome

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op donderdag 5 juli 2018
om 10.30 uur precies

door

Annemarie Christine Vesseur
geboren op 2 april 1984
te Rotterdam

Promotoren
Prof. dr. ir. A.F.M. Snik
Prof. dr. E.A.M. Mylanus (Universiteit Gent, België)
Prof. dr. C.M.A. van Ravenswaaij (Rijksuniversiteit Groningen)

Manuscriptcommissie
Prof. dr. I. Dhooge (Universiteit Gent, België)
Prof. dr. M.A.A.P. Willemsen
Prof. dr. H.E.T. Knoors

voor pappa en mamma

Contents

1

General Introduction

In 1990 at the conclusion of a multicentre trial, the US Food and Drug Administration (FDA) approved cochlear implantation in children with severe to profound hearing loss. The FDA had approved cochlear implantation in adults six years earlier. The first cochlear implantation in a child in the Netherlands occurred in 1987 at the Radboud University Medical Centre Nijmegen. Ten years of research and reports to the National Health Council (for example Cochleaire Implantatie bij kinderen, Eindverslag Ontwikkelingsgeneeskundeproject 1993 – 1996) were required before general reimbursement of cochlear implantation for adults and children was approved.

The initial eligibility criteria for children were quite strict and, for example, residual hearing, developmental delays, and anatomical malformations of the cochlea and the cochlear nerve were considered exclusion criteria. As research highlighted the beneficial outcome of rehabilitation of deaf children with cochlear implants in terms of audition, speech and language development and social and emotional development, the age at implantation gradually decreased to below 12-months of age. In general, evidence indicates implantation at a very young age results in improved hearing performance [1] and improved language and reading capacities [2] compared to children who are implanted at a later age. Over time, increasing numbers of children with developmental delays have joined the cochlear implant program. In many cases this was done knowingly but in many cases the developmental delay was not apparent until some years after cochlear implantation.

In due course, our clinical team gained considerable experience in the area of cochlear implantation in children with developmental delays [1]. There are two well-recognized groups of children who can have severe to profound hearing loss with or without intellectual disabilities: children with CHARGE syndrome and children with congenital cytomegalovirus (cCMV) infection. Children with cCMV infection are frequently included in the paediatric cochlear implant program at our medical centre. To counsel parents on possible outcomes of cochlear implantation in terms of hearing performance or quality of life, more information was required on the benefit of cochlear implantation in these children. Thus, an important goal of this thesis was to obtain performance and subjective data through evaluative, retrospective and cross-sectional research in children with severe to profound hearing loss and developmental delays. In this thesis we focus on CHARGE syndrome, cCMV infection and Kabuki syndrome.

Children with CHARGE syndrome, cCMV or Kabuki syndrome with severe to profound hearing loss present particular challenges for a cochlear implant team related to the combination of impaired cognition and anatomical variety seen in these children. This variety can be observed at the level of external auditory meatus, middle ear cavity, cochleovestibular system and cochlear nerve.

Anatomy and physiology of the ear

To appreciate the function and the impact of positioning of the cochlear implant, it is important to understand the anatomy of the auditory system. Similarly, to appreciate the challenges of cochlear implantation in a malformed middle ear cavity and compromised cochleovestibular system, it is necessary to discuss the anatomy of the facial nerve, particularly the facial nerve's pathway as it relates to the middle ear and mastoid [2].

The ear is imbedded in the petrosal bone and comprises three parts: the external part, the middle ear and the inner ear *(Figure 1)*. The external part consists of the pinna and external auditory meatus. The pinna contributes to spectral cues when it collects sound waves, which are conducted to the external auditory meatus. The auditory meatus ends at the tympanic membrane. The tympanic membrane, tympanic cavity, Eustachian tube and the middle ear ossicles and their ligaments are anatomical structures of the middle ear. The facial nerve travels from the brainstem into the internal auditory canal and runs parallel to the cochleovestibular nerve. The route of the facial nerve in the middle ear is initially horizontal and superior to the oval window and is followed by a vertical segment just posterior of the round window of the cochlea. Its close proximity to the cochlear windows, especially the round window, has implications for cochlear implant surgery.

Figure 1 The ear

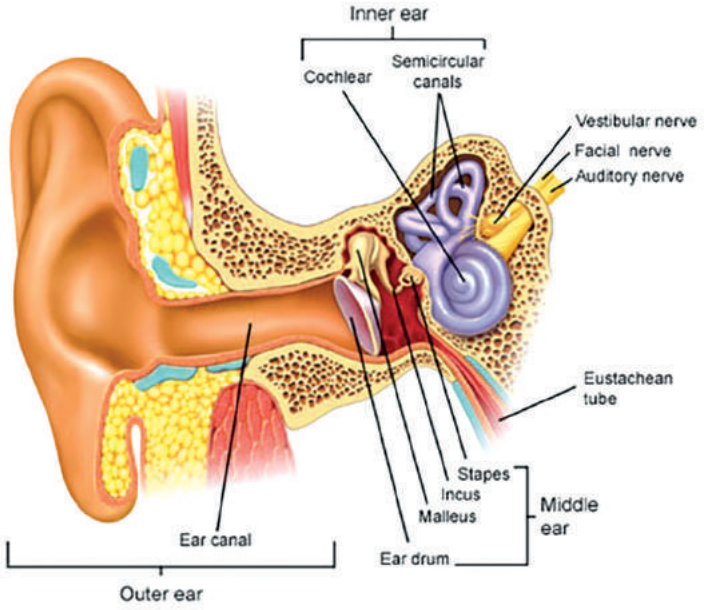


Image courtesy of Virtual Medical Centre

Sound waves cause the tympanic membrane to vibrate and, in turn, move the malleus, incus and stapes. These three structures are referred to as the ossicular chain and this chain stimulates the intracochlear fluid via the oval window. The inner ear comprises the cochlea, labyrinth and inner ear canal. The cochlea is a spiral channel with approximately 2.5 turns and consists of three ducts: the scala tympani (tympanic duct), scala media (cochlear duct) and scala vestibuli (vestibular duct) *(Figure 2)*. The labyrinth, consisting of the vestibulum and semicircular canals, is the organ that controls balance. At the level of the footplate of the stapes, sound waves travel through the fluid-containing ducts of the cochlea and deflect the basilar membrane between the scala tympani and scala media as "a travelling wave". The differential stiffness of the basilar membrane means high-frequency sounds affect the membrane close to the oval window whereas low-frequency sounds affect the membrane more apical to the oval window. This organisational frequency structure, or principle, is referred to as 'tonotopic organization'.

Figure 2 The cochlea

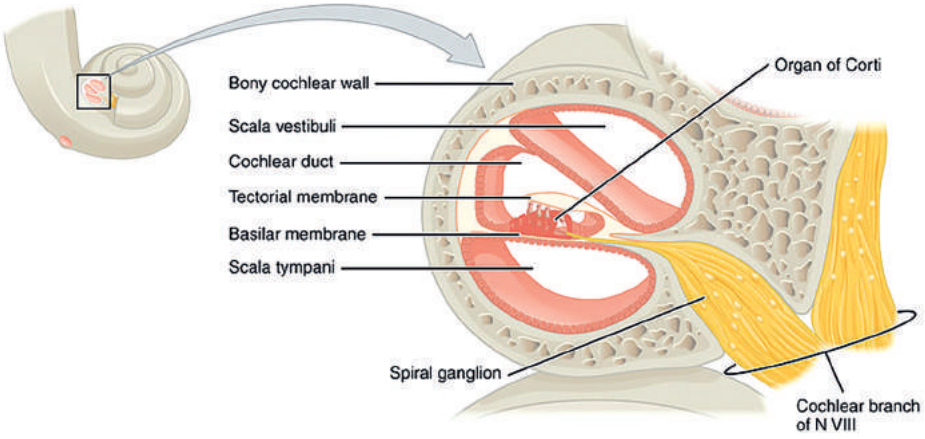
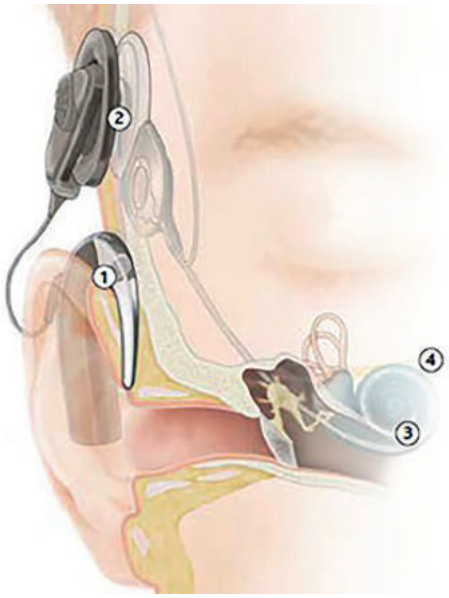


Image courtesy of Virtual Medical Centre

The basilar membrane contains the sensory organ, also referred to as the organ of Corti *(Figure 2)*. This organ comprises the inner and outer hair cells, of which the stereocilia are connected to a stiff tectorial membrane. This membrane makes the hair cells susceptible to movements of the basilar membrane. Stimulation of the sterocilia of the inner hair cells elicits an action potential of the dendrites of the cochlear nerve. From there on, action potentials are conducted to the central auditory system: the brainstem and auditory cortex.

Figure 3 Cochlear implant



1. Microphone; 2. Coil; 3. Electrode; 4 Cochlea.

Image courtesy of Virtual Medical Centre

Hearing loss in children

Dysfunction of the outer ear, middle ear or cochlea can cause hearing loss. Inefficient airborne sound transmission by the external or middle ear causes a so-called 'conductive hearing loss'. Conductive hearing loss may be congenital (e.g. anatomical anomaly of the external auditory meatus and/or the middle ear) or secondary to ear disease or trauma. Dysfunction of the cochlea or neural pathway to the brain causes a 'sensorineural hearing loss'. Cochlear dysfunction can be due to genetic abnormalities of the inner ear and is common in CHARGE, Branchio-oto-renal, Pendred, Waardenburg and Noonan syndromes. Sensorineural hearing loss can also be secondary to congenital infections (e.g. cytomegalovirus or Rubella) or to injury and medications that are toxic to the auditory system. A combination of sensorineural hearing loss and conductive hearing loss is termed 'mixed hearing loss'.

Cochlear implant

Conventional hearing aids are an effective solution for children with a mild to severe hearing loss. For children with severe to profound hearing loss or 'deafness', conventional

hearing aids are no longer effective. In the 1970s and 1980s, a device termed a 'cochlear implant' (CI) was developed. A CI is a semi-implantable device designed to electrically stimulate the auditory nerve endings in the cochlea. Over time, the initial single-electrode/single channel CI system evolved to a multiple-electrode/multiple channel CI system. These multiple-electrode systems have sophisticated speech-coding algorithms that are continually developed and refined.

The CI system consists of two parts: an external part and an internal part *(Figure 3)*. The external part contains the microphone, speech processor and battery compartment. The external part communicates transcutaneously with the internal part via electromagnetic induction. The internal part comprises a receiving antenna (coil) and a chip. The chip decodes the electromagnetic signal into electrical pulses that are conducted through the electrical leads to the electrode array. This array is surgically placed in the scala tympani and it directly stimulates the cochlear nerve (spiral ganglia and dendrites).

There are several surgical approaches to implanting the internal part of the CI. The technique used at our centre requires cortical mastoidectomy and posterior tympanotomy. The proximity of vascular structures, the facial nerve, chorda tympani and ossicular chain necessitates careful surgery to avoid complications during this elective surgical procedure.

Indication criteria

Cochlear implantation has become a regular treatment option for children and adults with severe or profound sensorineural hearing loss who cannot be treated with conventional hearing aids. Research indicates that in general, children who are born deaf, without co-morbidities and are implanted at a young age with a CI go on to develop age-appropriate speech and language skills. Based on these positive results with CI in children with isolated deafness, the criteria for implantation have gradually become more flexible and, for example, allowing children with cognitive delay to undergo implantation [3].

Whether a child profits from the CI depends on implant-related factors, environmental factors and several individual factors. Major concerns are the anatomy of the ear, for safe and effective surgery, proper fitting of the device enabling proper processing of auditory signals and, finally, the social, emotional and cognitive abilities and capabilities of the children.

CHARGE syndrome, cCMV infection and Kabuki syndrome are complex in nature and children with these syndromes can have (severe to profound) hearing loss. Children with the above syndromes or infection can be eligible for cochlear implantation, but the complexity of these syndromes makes it difficult to predict the success of CI.

CHARGE syndrome

In 1979, Hall noted that choanal atresia could be accompanied by a specific set of multiple anomalies [4]. In the same year, Hittner reported ten patients with the combination of coloboma, heart defect, external ear abnormalities, hearing loss and developmental delay.

In 1981, Pagon et al. used the acronym "CHARGE" to describe the association of Coloboma, Heart disease, Atresia of the choanae, Retarded growth and development and/or CNS anomalies, Genital hypoplasia, and Ear anomalies and/or deafness [5]. Blake revised this definition in 1998 into major and minor characteristics [6]. In 2005, Verloes suggested the following CHARGE diagnostic criteria: coloboma, atresia of choanae and hypoplastic semicircular canals as majors signs; Rhombencephalic dysfunction, hypothalamo-hypophyseal dysfunction, abnormal middle or external ear, malformation of mediastinal organs and intellectual disability were considered as minor signs [7]. Cranial nerve dysfunction of multiple nerves, including the acoustic and facial nerves, is seen in the majority of patients. In 2004, the causative gene was identified as *CHD7* on chromosome 8q12 [8] and the name changed to CHARGE syndrome (MIM, Mendelian Inheritance in Man, 214800).

The presentation of the syndrome is diverse with most children showing a variable combination of multiple congenital anomalies. Hearing loss and cognitive delays are frequently described in CHARGE syndrome [9, 10]. Hearing loss, present in 80–100% of the patients, is one of the most common characteristics and can be due to anatomical anomalies of the middle or inner ear, to aplasia or hypoplasia of the cochlear nerve, or to middle ear disease. As a consequence, hearing in children with CHARGE syndrome can range from normal to profound hearing loss [6, 9, 11]. As one of the minor characteristics, delayed cognitive abilities are also often described in children with CHARGE syndrome. The delay in cognitive development varies and is rarely expressed in "Intelligence Quotient" (IQ). Instead, cognition is expressed in relation to developmental age, abilities and educational level. Between 50% and 75% of children with CHARGE syndrome have below average intellectual development [12-16]. Language delays have been described [16] but little is known about language development in this group of children.

Children with CHARGE syndrome who have a profound to severe hearing loss could benefit from cochlear implantation as studies have reported children with CHARGE syndrome were more responsive and receptive after implantation than before implantation [17-20]. However, cochlear implantation in this group is not without challenges. One of the features seen in CHARGE syndrome is deficiency of the cochlear nerve [21] and the surgical procedure may be complicated by anatomical anomalies of the petrosal bone and facial nerve abnormalities [20]. In addition, development of speech and language after implantation may be difficult because of cognitive or physical impairments [17-20].

Congenital cytomegalovirus infection

Congenital cytomegalovirus infection is a common condition. In Western Europe and the USA, the prevalence is approximately 1%. The minority (10%) of these infants shows symptoms such as jaundice, hepatosplenomegaly, petechiae, microcephaly and chorioretinitis at birth. The remaining infants (90%) are asymptomatic. Infants symptomatic at birth have greater neurological sequelae, sensorineural hearing loss and visual abnormalities than asymptomatic children. The neurological sequelae consist of intellectual disability

and neurological abnormalities (hypotonia, spasticity, delayed motor development and seizures) [22, 23].

Diagnosis of cCMV infection is established either by isolation of the virus in urine, blood or saliva of the newborn or by identifying CMV-specific IgM in cord blood or in the infant's blood. In retrospective, diagnosis can be confirmed by PCR (polymerase chain reaction) on the dried blood spot on the Guthrie card.

For some individuals, cCMV infection can be indicated after brain imaging. Different intracerebral abnormalities are described in the literature. In children with an asymptomatic infection, the abnormalities are milder and occur less often than in symptomatic children [24]. The anomalies generally seen are intracerebral calcifications, ventriculomegaly, white matter abnormalities, neuronal migrations disorders and encephalopathy [25, 26]. Children with intracerebral anomalies have a greater chance to develop sensorineural hearing loss, neurological problems (motor and cognitive delays) and visual disturbances [25, 27-29].

Children with an asymptomatic infection have a 15-25% chance of developing hearing loss in the first few years of life; Children with a symptomatic infection have a 60% chance of developing hearing loss. The hearing loss is sensorineural, ranges from a mild to profound hearing loss and the severity of the hearing loss may fluctuate over time [30]. Symptomatic and asymptomatic children with profound or severe hearing loss are eligible for cochlear implantation. The results of cochlear implantation in these groups vary but the majority of studies report two findings: (1) asymptomatic children with a CI perform equal to or better than peers with idiopathic hearing loss with a CI [31, 32] and (2) children with symptomatic cCMV can achieve substantial auditory and language skills but lag behind asymptomatic peers or peers with idiopathic hearing loss with a CI. This last finding has been attributed to poor attention control, cognitive disabilities, autistic spectrum disorders or central nervous system impairment [33-37].

Kabuki Syndrome

Kabuki syndrome, first described by Niikawa et al. in 1981, has characteristics such as a distinctive facial features, cognitive disabilities, postnatal growth deficiency, dermatoglyphic abnormalities and skeletal anomalies [38]. Hearing loss is one of the associated anomalies in Kabuki syndrome and is observed in 65% of cases [39]. The hearing loss can be conductive, sensorineural or of mixed origin. Anomalies of the middle ear and inner ear have been described [40, 41]. To the best of the authors knowledge, there are no published studies of cochlear implantation in children with Kabuki syndrome.

Aims of the study

The aim of this thesis is to describe the challenges and benefits of cochlear implantation in children with complex needs. With the expansion to the eligibility criteria for implantation, cochlear implantation is now possible for children with co-morbidities including cognitive delay in addition to a hearing loss. The difficulty becomes how to adequately prepare

parents and caregivers on possible outcomes when there is a lack of research investigating CI use in these cohorts. Because, the more complex the disorder, the more difficult to counsel the parents on the possible outcome. In this thesis, CI use is investigated in children with hearing loss due to three aetiologies: children with CHARGE syndrome, children with severe to profound hearing loss as a result of cCMV infection and a child with Kabuki syndrome.

A second aim is to identify predictive factors for performance outcome and quality of life with a CI that could be evaluated during the pre-implantation assessment. Identification of predictive factors would greatly assist with preparing parents and caregivers for possible CI outcomes.

Multiple factors should be considered when considering CI in children with CHARGE syndrome. *Chapter 2* focuses on several factors, such as anomalies of the petrosal bone, which can be challenging in CI surgery. Such anomalies of the temporal bone are described in Section *2.1.* For optimal planning of the CI procedure, the potential impact of anomalies we found, needs to be considered by the surgical team. For reference purposes, developmental norms of children with CHARGE syndrome without severe to profound hearing loss were acquired. In *Section 2.2* we describe the relationship of either hearing loss or cognitive abilities on language development in CHARGE syndrome. *Section 2.3* provides an overview of the challenges and benefits encountered in cochlear implant surgery in CHARGE syndrome. Based on this overview, a suggested guideline is presented. *Section 2.4* presents a case report that highlights the diagnostic dilemma of when to implant and when to refrain from cochlear implantation in cases of cochlear nerve deficiency.

Chapter 3 focuses on cochlear implantation in children with severe to profound hearing loss as a result of cCMV infection. *Section 3.1* focuses on the prevalence of cCMV infections among CI recipients with prelingual deafness and the pathophysiology of cCMV and severe to profound hearing loss. In children with cochlear implant, benefit is not necessarily best expressed in improvement of speech and language abilities; rather it can be expressed in terms of changes to quality of life. *Section 3.2* presents the outcomes of this quality of life investigation.

Chapter 4 describes the challenges of cochlear implantation in a child with Kabuki syndrome.

Chapter 5 presents the final conclusions and general discussion and is followed by a thesis summary written in English and in Dutch.

References

1. Hoffer, M.M.R., et al., *Cochleaire implantatie bij meervoudig gehandicapte kinderen: kwaliteit van leven en taalbegrip.* Stem-, Spraak- en Taalpathologie, 2006. **14**(2): p. 143-160.
2. Mylanus, E.A., L.J. Rotteveel, and R.L. Leeuw, *Congenital malformation of the inner ear and pediatric cochlear implantation.* Otol Neurotol, 2004. **25**(3): p. 308-17.
3. Wakil, N., et al., *Long-term outcome after cochlear implantation in children with additional developmental disabilities.* Int J Audiol, 2014. **53**(9): p. 587-94.
4. Hall, B.D., *Choanal atresia and associated multiple anomalies.* J Pediatr, 1979. **95**(3): p. 395-8.
5. Pagon, R.A., et al., *Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association.* J Pediatr, 1981. **99**(2): p. 223-7.
6. Blake, K.D., et al., *CHARGE association: an update and review for the primary pediatrician.* Clin Pediatr (Phila), 1998. **37**(3): p. 159-73.
7. Verloes, A., *Updated diagnostic criteria for CHARGE syndrome: a proposal.* Am J Med Genet Part A, 2005. **133A**(3): p. 306-8.
8. Vissers, L.E., et al., *Mutations in a new member of the chromodomain gene family cause CHARGE syndrome.* Nat Genet, 2004. **36**(9): p. 955-7.
9. Shah, U.K., et al., *Otologic management in children with the CHARGE association.* Int J Pediatr Otorhinolaryngol, 1998. **44**(2): p. 139-47.
10. Tellier, A.L., et al., *CHARGE syndrome: report of 47 cases and review.* Am J Med Genet, 1998. **76**(5): p. 402-9.
11. Dhooge, I., et al., *Otological manifestations of CHARGE association.* Ann Otol Rhinol Laryngol, 1998. **107**(11 Pt 1): p. 935-41.
12. Davenport, S.L., M.A. Hefner, and J.W. Thelin, *CHARGE syndrome. Part I. External ear anomalies.* Int J Pediatr Otorhinolaryngol, 1986. **12**(2): p. 137-43.
13. Blake, K.D., et al., *Who's in CHARGE? Multidisciplinary management of patients with CHARGE association.* Arch. Dis. Child., 1990. **65**(2): p. 217-23.
14. Harvey, A.S., P.M. Leaper, and A. Bankier, *CHARGE association: clinical manifestations and developmental outcome.* Am J Med Genet Part A, 1991. **39**(1): p. 48-55.
15. Raqbi, F., et al., *Early prognostic factors for intellectual outcome in CHARGE syndrome.* Dev Med Child Neurol, 2003. **45**(7): p. 483-8.
16. Dammeyer, J., *Development and characteristics of children with Usher syndrome and CHARGE syndrome.* Int J Pediatr Otorhinolaryngol, 2012. **76**(9): p. 1292-6.
17. Bauer, P.W., et al., *Cochlear implantation in children with CHARGE association.* Arch Otolaryngol Head Neck Surg, 2002. **128**(9): p. 1013-7.
18. Lanson, B.G., et al., *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes.* Laryngoscope, 2007. **117**(7): p. 1260-6.
19. Ricci, G., et al., *Cochlear implantation in children with "CHARGE syndrome": surgical options and outcomes.* Eur Arch Otorhinolaryngol, 2014. **271**(3): p. 489-93.
20. Birman, C.S., et al., *CHARGE syndrome and Cochlear implantation: Difficulties and outcomes in the paediatric population.* Int J Pediatr Otorhinolaryngol, 2015.
21. Holcomb, M.A., Z. Rumboldt, and D.R. White, *Cochlear nerve deficiency in children with CHARGE syndrome.* Laryngoscope, 2013. **123**(3): p. 793-6.
22. Madden, C., et al., *Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss*, in *Int J Pediatr Otorhinolaryngol*. 2005. p. 1191-8.
23. Malm, G. and M. Engman, *Congenital cytomegalovirus infections*, in *Semin Fetal Neonatal Med*. 2007. p. 154-9.
24. van der Voorn, J., et al., *Quantitative MR imaging and spectroscopy in congenital cytomegalovirus infection and periventricular leukomalacia suggests a comparable neuropathological substrate of the cerebral white matter lesions*, in *Neuropediatrics*. 2009. p. 168-73.
25. Noyola, D., et al., *Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection*, in *J Pediatr*. 2001. p. 325-31.
26. van der Knaap, M., et al., *Pattern of white matter abnormalities at MR imaging: use of polymerase chain reaction testing of Guthrie cards to link pattern with congenital cytomegalovirus infection*, in *Radiology*. 2004. p. 529-36.

27. Boppana, S., et al., *Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection*, in *Pediatrics*. 1997. p. 409-14.
28. Haginoya, K., et al., *Abnormal white matter lesions with sensorineural hearing loss caused by congenital cytomegalovirus infection: retrospective diagnosis by PCR using Guthrie cards*, in *Brain Dev.* 2002. p. 710-4.
29. Rivera, L., et al., *Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection*, in *Pediatrics*. 2002. p. 762-7.
30. Fowler, K., et al., *Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection*, in *J Pediatr.* 1997. p. 624-30.
31. Iwasaki, S., et al., *Cochlear implant in children with asymptomatic congenital cytomegalovirus infection*, in *Audiol Neurootol.* 2009. p. 146-52.
32. Philips, B., et al., *Cochlear implants in children deafened by congenital cytomegalovirus and matched Connexin 26 peers.* Int J Pediatr Otorhinolaryngol, 2014. **78**(3): p. 410-5.
33. Malik, V., et al., *Outcome of cochlear implantation in asymptomatic congenital cytomegalovirus deafened children.* Laryngoscope, 2011. **121**(8): p. 1780-4.
34. Yamazaki, H., et al., *Cochlear implantation in children with congenital cytomegalovirus infection accompanied by psycho-neurological disorders.* Acta Otolaryngol, 2012. **132**(4): p. 420-7.
35. Yoshida, H., et al., *Cochlear implantation in children with congenital cytomegalovirus infection*, in *Otol Neurotol.* 2009. p. 725-30.
36. Ciorba, A., et al., *Rehabilitation and outcome of severe profound deafness in a group of 16 infants affected by congenital cytomegalovirus infection*, in *Eur Arch Otorhinolaryngol.* 2009. p. 1539-46.
37. Ramirez Inscoe, J. and T. Nikolopoulos, *Cochlear implantation in children deafened by cytomegalovirus: speech perception and speech intelligibility outcomes*, in *Otol Neurotol.* 2004. p. 479-82.
38. Niikawa, N., et al., *Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients.* Am J Med Genet, 1988. **31**(3): p. 565-89.
39. Barozzi, S., et al., *Audiological and vestibular findings in the Kabuki syndrome.* Am J Med Genet A, 2009. **149a**(2): p. 171-6.
40. Say, B., et al., *Kabuki make-up syndrome and hearing impairment, abstract.* Clin Dysmorphol, 1993. **2**(1): p. 68-70.
41. Igawa, H.H., et al., *Inner ear abnormalities in Kabuki make-up syndrome: report of three cases, abstract.* Am J Med Genet, 2000. **92**(2): p. 87-9.

2

CHARGE Syndrome

2.1

CT findings of the temporal bone in CHARGE syndrome: aspects of importance in cochlear implant surgery

Published as
CT Findings of the Temporal Bone in CHARGE Syndrome: Aspects of Importance in Cochlear Implant Surgery Vesseur AC, Verbist BM, Westerlaan HE, Kloostra FJ, Admiraal RJ, van Ravenswaaij-Arts CM, Free RH, Mylanus EA. *Eur Arch Otorhinolaryngol. 2016 Dec; 273(12):4225-4240. Epub 2016 Jun 20.*

Abstract

Objectives

To provide an overview of anomalies of the temporal bone in CHARGE syndrome relevant to cochlear implantation (CI), anatomical structures of the temporal bone and the respective genotypes were analysed.

Materials and Methods

In this retrospective study, 42 CTs of the temporal bone of 42 patients with CHARGE syndrome were reviewed in consensus by two head-and-neck radiologists and two otological surgeons. Anatomical structures of the temporal bone were evaluated and correlated with genetic data.

Results

Abnormalities that might affect CI surgery were seen, such as a vascular structure, a petrosquamosal sinus (13%), an underdeveloped mastoid (8%) and an aberrant course of the facial nerve crossing the round window (9%) and/or the promontory (18%). The appearance of the inner ear varied widely: in 77% of patients all semicircular canals were absent and the cochlea varied from normal to hypoplastic. A stenotic cochlear aperture was observed in 37%. The middle ear was often affected with a stenotic round (14%) or oval window (71%). More anomalies were observed in patients with truncating mutations than with non-truncating mutations.

Conclusion

Temporal bone findings in CHARGE syndrome vary widely. Vascular variants, aberrant route of the facial nerve, an underdeveloped mastoid, aplasia of the semicircular canals, and stenotic round window may complicate cochlear implantation.

Introduction

The criteria for the clinical diagnosis of CHARGE syndrome (MIM, Mendelian Inheritance in Man, 214800), have been defined by Blake et al. and Verloes [1][2]. CHARGE syndrome is an acronym of Coloboma, Heart disease, choanal Atresia, Retardation, Genital hypoplasia and Ear anomalies. Organ involvement and severity is highly variable amongst affected patients. A major criterion includes the condition of the temporal bone, which may be hypoplastic or show an absence of the semicircular canals, according to Verloes. Anomalies are seen in the external, middle and inner ear, such as the typically low-set, cup-shaped ears, ossicular malformations, an aberrant course of the facial nerve, hypoplastic internal auditory canal, and an abnormally developed cochlea. Some of these malformations can cause hearing loss: 60-90% of patients with CHARGE syndrome have moderate to severe hearing loss due to conductive, sensorineural or mixed defects. In most patients, hearing loss can be partially compensated with hearing aids. When hearing aids do not have the desired outcome due to the presence of profound to severe hearing loss, cochlear implantation may be considered. If cognitive disabilities, developmental and behavioural problems do not preclude cochlear implantation, a thorough assessment of the temporal bone anatomy is necessary. Anatomical alterations pose additional surgical risks during the implantation, by hampering the surgical approach to the cochlea or the insertion of the electrode array into the cochlea, and they may influence the surgical results in terms of speech perception.

In 2004, the causative gene for CHARGE syndrome was identified as *CHD7* on chromosome 8q12.1 [3]. Since then, 528 different mutations of the gene have been described, but no clear genotype-phenotype correlation could be recognized (www.CHD7.org) [4]. In the *CHD7* mutation positive patients, the most common clinical findings were temporal bone anomalies (98%), external ear malformations (91%), and hearing loss (89%) [5].

The main goal of this retrospective study was to analyse the presence of the anomalies of the temporal bone in patients with CHARGE syndrome and their potential impact on cochlear implant surgery planning. The secondary goal was to study possible genotype-phenotype correlations.

Materials and Methods

We collected analogue and digital CT studies of the temporal bone of patients attending the Dutch CHARGE centre of expertise (University Medical Centre Groningen, the Netherlands), after obtaining written informed consent from all patients or their legal representatives.

All patients had molecularly confirmed CHARGE syndrome, or clinically typical CHARGE syndrome according to the Blake or Verloes criteria (table 1, 4) except for one patient with atypical CHARGE syndrome (patient 12), because the parents did not wish further investigation [1; 2].

The patients were investigated in different time periods and in different Dutch hospitals, so the scans were made with different scanner types and variable scan parameters.

We evaluated CTs of 84 ears of 42 patients (22 male, 20 female) with CHARGE syndrome (29 digital and 13 analogue scans). The scans were performed between 1996-2010. The mean age of the patients at the time of scanning was 6.4 years, median 2.5 years (SD 9.8; min 0, max 47 years).

Table 1 Characteristics of CHARGE syndrome

1a. Major and minor signs of CHARGE syndrome[2]

Major Signs
Coloboma (iris or choroid, with or without microphthalmia)
Atresia of choanae
Hypoplastic semicircular canals
Minor signs
Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies and neurosensory deafness)
Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin deficiencies)
Abnormal middle or external ear
Malformation of mediastinal organs (heart, oesophagus)
Intellectual disability

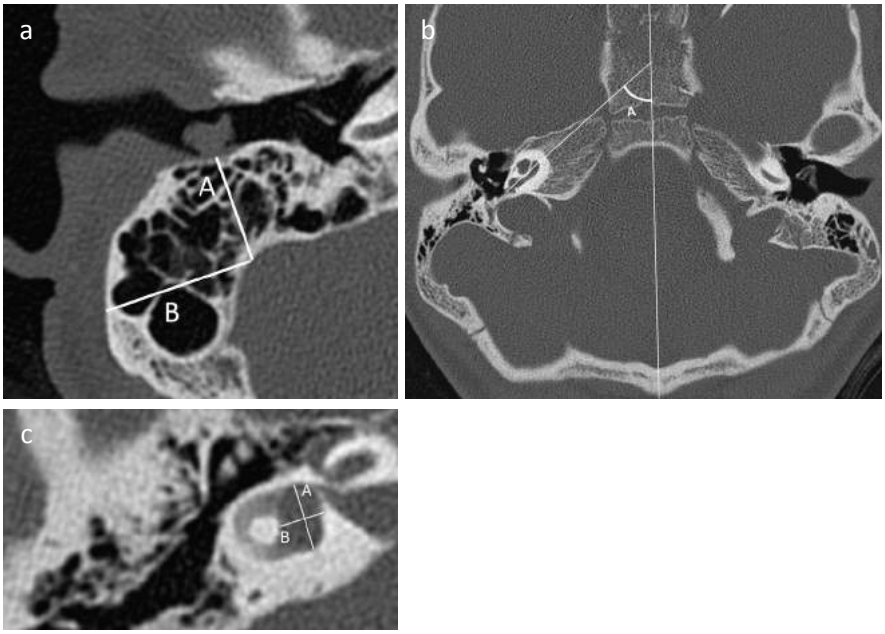
1b. Definition of typical, atypical, and partial CHARGE syndrome[2]

Typical CHARGE syndrome
3 major signs
2/3 major signs + 2/5 minor signs
Partial/incomplete CHARGE
2/3 major signs + 1/5 minor signs
Atypical CHARGE
2/3 major signs + 0/5 minor signs
1/3 major signs + 3/5 minors signs

Imaging analysis

All imaging studies were evaluated by four observers (two head-and-neck radiologists with 13 and seven years of experience and two otorhinolaryngologists with ten and 15 years of experience), who then met to reach a consensus opinion. The reviewers had no access to patients' names nor their clinical information. Each ear was evaluated separately, in axial and coronal planes, if available. The anatomic structures and normative measures determined are presented in *appendix A* and *figure 1*.

Figure 1 Measurements in axial CT images



1a. Mastoid size A: Anterior-posterior (AP) size, measured in the middle of the external meatus (cranial/caudal) as the minimal distance from the external meatus to sigmoid sinus B: Lateral-medial (LM) size, distance between outer cortex and sigmoid sinus, measured perpendicular to A; **1b.** Angle cochlear basal turn; **1c.** Vestibulum size A: Longitudinal extension, B: Transversal diameter (right ear)

All the scans were analysed as extensively as possible, using a standardized form (*appendix B*) compiled specifically for this study. Items that could not be analysed, e.g. due to a missing coronal plane or to slice thickness, were scored as 'unable to identify' (UTI).

The digital scans were analysed on a viewing station (IMPAX, Apache Software Foundation, Version 2.0, January 2004). Measurements were obtained in millimetre (to two decimal places) with electronic calipers provided by the pacs-system. Analogue films were evaluated on an illuminated view box and measurements were performed with an analogue ruler. If a structure could not be properly assessed, it was scored as 'unable to identify' (UTI).

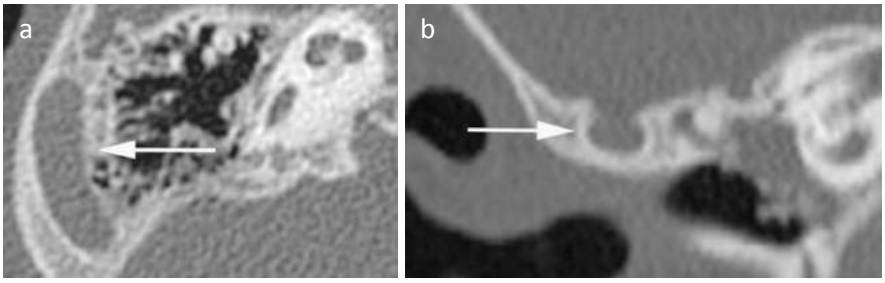
SPSS 20 was used to collect all data and perform statistical analyses. We used the X^2-test to test for significant correlations.

CHD7 analysis

The results of *CHD7* analysis were already known for all but one (patient 12) patients. The analyses were performed on DNA isolated from peripheral blood cells according to standard procedures. The 37 coding exons of *CHD7* (exons 2–38, RefSeq NM_017780.02) and their flanking intron sequences were amplified by PCR and sequenced as described earlier[3]. If no mutations were identified, *CHD7* was screened for whole exon deletions and duplications by multiplex ligation-dependent probe amplification (MLPA) using a commercially available set of probes: the SALSA P201 kit (MRC-Holland, Amsterdam, the Netherlands; http://www.mrc-holland.com) [6].

Nonsense and frameshift mutations and whole-gene or whole-exome deletions were categorised as truncating mutations, while missense and splice site mutations were categorised as non-truncating.

Figure 2 Petrosquamosal sinus



Axial (**a**) and coronal (**b**) CT image of a right ear showing this emissary vein coursing along the lateral superior surface of the temporal bone. The petrosquamosal sinus originates at the transverse sinus and drains either into the retromandibular vein or the pterygoid venous plexus.

Results

Mastoid and vascular structures (tables 2,3)

The first part of a cochlear implantation, the mastoidectomy, can be challenging in an underdeveloped mastoid. The AP-size (anterior-posterior) and the LM-size (lateral-medial) of the mastoid could not be measured in 21 ears (25%), because of a hardly developed mastoid or moderate quality of the scan. These patients were particularly young (median age 5 years, mean 8.5 years, 22% < 1-year old). In 25 ears (29.8%), an emissary vein with a diameter larger than 1 mm was present *(figure 2a,b)*.

Table 2 Ear structure observations

Structure on CT	Normal	Abnormal	UTI
Pneumatisation mastoid	Good	No cells	UTI
	73 (87%)	7 (8%)	4 (5%)
Middle ear cavity size	Normal	Small/large	UTI
	84 (100%)	0	0
Jugular bulb	Normal	High	UTI
	59 (70%)	23 (27%)	2 (2%)
Emissary veins	Total	>1mm	PSS
	28 (33%)	25 (30%)	11 (13%)
Windows	Present	Absent/stenotic	UTI
Oval	22 (26%)	60 (71%)	2 (2%)
Round	70 (83%)	12 (14%)	2 (2%)
Ossicles	Normal	Dysplastic	UTI
Malleus	83 (99%)	1 (1%)	0
Incus	75 (89%)	9 (11%)	0
Stapes	27 (32%)	42 (50%)	13 (15%)
Facial nerve	Normal	Aberrant course	UTI
Tympanic	54 (64%)	24 (29%)	6 (7%)
Mastoid	70 (83%)	6 (7%)	8 (10%)
Vestibular aqueduct	Normal	Aberrant course	UTI
	12 (14%)	57 (68%)	12 (14%)
Cochlear apertura	Normal	Stenotic	UTI
	51 (61%)	31 (37%)	2 (2,4%)
SCC	Normal	Aplastic	Dysplastic
	2 (2%)	65 (77%)	17 (20%)

Number of ears: 84; UTI unable to identify; PPS persistent petrosquamosal sinus; SCC semicircular canals.

Table 3 Ear structure measurements

Structure	Mean (mm)	Median (mm)	SD (mm)	Max (mm)	Min (mm)	UTI (ears)
Mastoid						
AP-size	10.6	11.0	3.2	19.4	5.0	21
LM-size	7.9	7.0	6.2	40.0	1.2	22
Vestibulum						
length	4.7	4.7	1.0	9.0	2.9	0
width	2.3	2.3	0.6	5.0	1.0	1.0
VA diameter[1]						
	0.7	0.6	0.3	1.9	0.1	11
IAC						
	3.6	3.5	0.9	7.0	2.0	0

Number of ears: 84; [1] only digital scans (n= 58); AP anterior-posterior; LM lateral-medial; VA vestibular aqueduct; IAC internal auditory canal; SD standard deviation; UTI: unable to identify

Middle ear (windows/ossicles/facial nerve) (tables 2, 3)

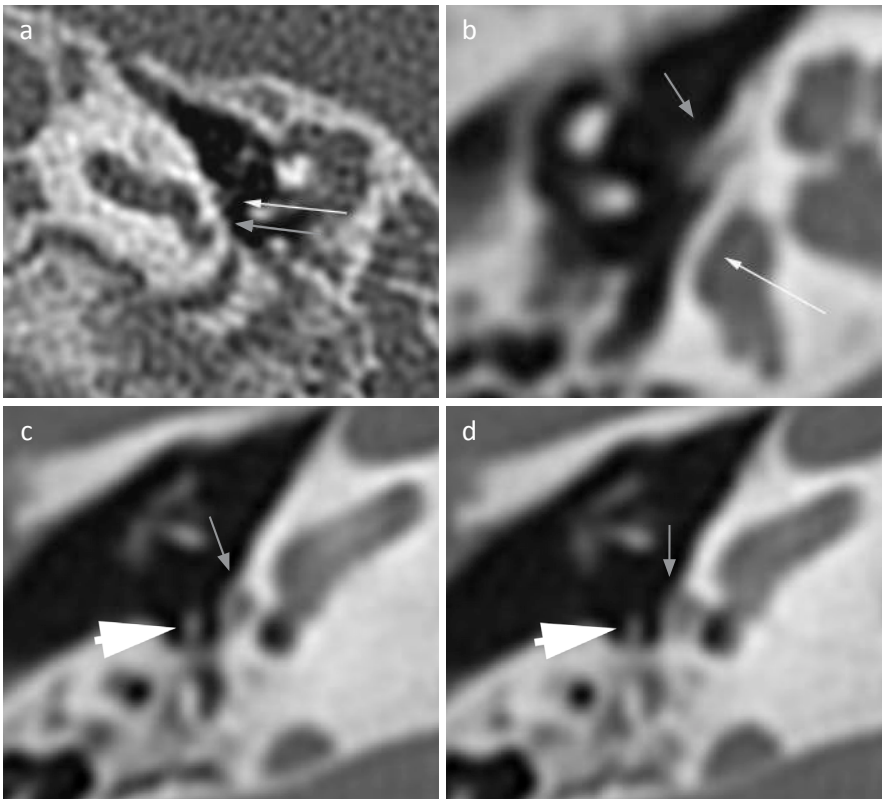
Middle ear anomalies can be a challenge in preparing and making the cochleostomy. The size of the middle ear cavity was within normal limits in all patients and thus will not pose a problem in surgery. Overall, there was an aberrant course of the tympanic part of the facial nerve crossing the promontory in 16 ears (19.0% of the total number of ears) and in eight ears also the round window (9.5% of the total number of ears). The aberrant mastoidal portion of the facial nerve seemed to run more medially than normal in four ears. The windows and ossicles were difficult to assess due either to otitis media or to the moderate quality of the scan in 20 patients (23.8%).

In 43 ears (51.2%) with a stenotic oval window, the stapes was not identifiable or dysplastic, either presenting as a monopod stapes (one ear), or displaced on the promontory or into the middle ear cavity (six ears) *(figure 3)*.

Cochleovestibular system (tables 5, 6)

Abnormalities of the cochlea can complicate the insertion of the electrode array. *Table 5* shows the distribution of cochlear type, omitting patient 12 (who had no mutation found *(table 4)* and normal cochleas), and patient 30 (who had an 'unknown variant' missense mutation (*table 4)*, one normal cochlea and one cochlear hypoplasia type IV). In 32 (38.1%) ears, an abnormal cochlea was seen. The ears with an incomplete partition type II (IPII) deformity of the cochlea did not show an enlarged vestibular aqueduct or dilated vestibulum. In 22 (26.2%) ears, the cochlea appeared abnormal, but the type of dysplasia could not be determined according to Sennaroglu's classification (*Figure 4a,b,c*). In these cochleae, the second turn seemed not to have developed fully, but the apex and basal

Figure 3 Examples of window stenosis

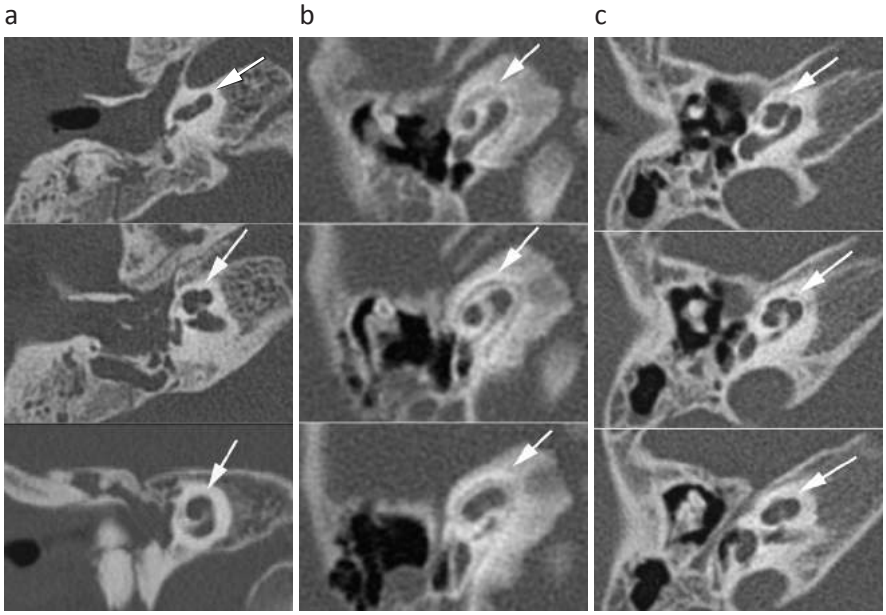


3a. Axial CT image showing stenosis of the round window niche (grey arrow) in a left ear. Note also dysplastic stapes on the promontory (white arrow); **3b-d.** Axial CT images showing atresia of the oval window (thin arrow), aberrant course of the facial nerve crossing the round window (arrowhead) and a dysplastic stapes positioned at the sinus tympani (thick arrow). Note aplasia of the semicircular canals.

turn were normal, with normal presence of interscalar septae and spiral osseous lamina, and in all but two of them the modiolus was normal. We will refer to this as hypoplasia type IV.

The angle of the basal turn was only measured on the digital scans; the mean was 57 degrees (SD 6.3), with a range from 43.5 degrees to 78.6 degrees. The mean age of this group was 3.7 years.

Figure 4 Range of abnormalities of the cochlea seen in axial CT images

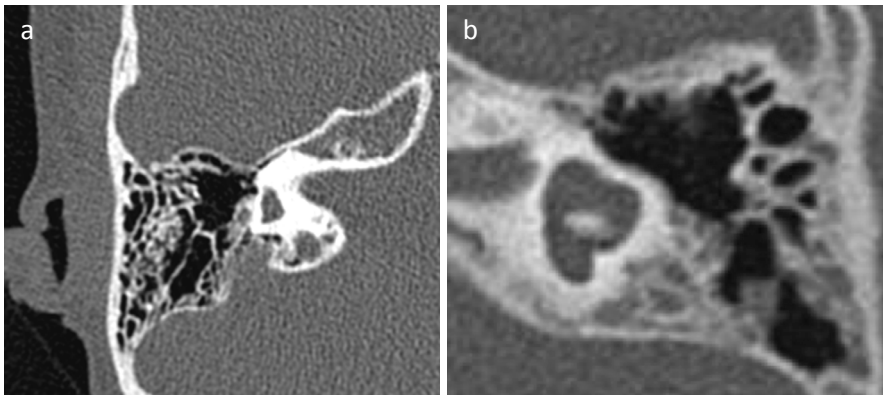


4a. Incomplete partitioning type II: normal development of the basal turn, but fusion of the second and apical turn seen in axial and coronal planes; **4b.** Hypoplasia type III: cochlea with less than 2 turns; **4c.** Cochlea type 'IV': the basal, second and apical turns are present, but the second turn seems shortened, giving the cochlea an asymmetric, flattened appearance.

Table 6 shows the distribution of SCC malformations excluding patient 12 (no mutation found and dysplasia of LSCC bilaterally) and patient 30 (UV missense mutation and total aplasia of SCC bilaterally). Aplasia of all SCCs was seen in 65 ears (77.3%), while dysplasia of one or all SCCs was seen in 17 ears (20.2%) and ranged from the strongly reduced development of one canal, like a bud, to just one affected canal (while the other two were present and normal) (*figure 5a,b*). In ears with a solitary canal aplasia or dysplasia, it was the lateral semicircular canal that was most often affected. If the superior semicircular canal was dysplastic, the lateral and posterior semicircular canals were absent.

Generally, the vestibulum was smaller than normal, both in length and width. The aberrant vestibular aqueducts had a course mainly in a perpendicular line from the vestibulum to the posterior fossa. If SCCs were absent, the aqueduct showed a more medial course than when they were severe or mild dysplastic. We found one ear with a large vestibular aqueduct (1.9mm diameter), but normally developed cochlea.

Figure 5 Range of abnormalities of the vestibular system seen in axial CT images



5a. Aplasia of the semicircular canals; **5b.** Dysplasia of the vestibule and semicircular canals in a left ear, with a malformed vestibule, shortened and dilated horizontal semicircular canal with small bony island, incomplete formation and dilatation of the posterior semicircular canal.

Table 5 Distribution of cochlear types for different types of mutations

Cochlear type	Normal	IPII[1]	Hypoplasia type III	Hypoplasia type IV
Total	49 (61.2%)	7 (8.3%)	3 (3.8%)	21 (26.3%)
Truncating mutations	27 (33.8%)	6 (7.5%)	3 (3.8%)	14 (17.5%)
Non-truncating mutations	22 (27.5%)	1 (1.3%)	0	7 (8.8%)

Number of ears: 80 (patients 12 and 30 excluded); IPII[1]: incomplete partition type II without enlarged vestibular aqueduct or dilated vestibulum; $P = 0.194$ (X^2)

Table 6 Distribution of semicircular canal malformations for different types of mutations

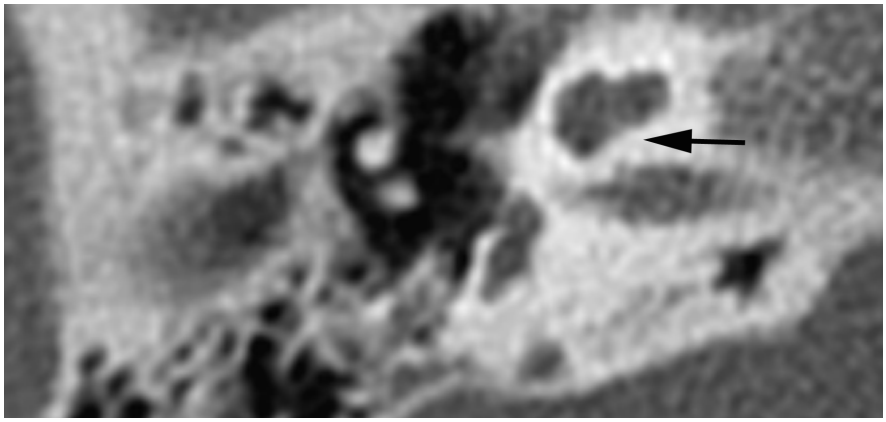
Defect	SCC normal	PSCC dysplasia	SSCC dysplasia	PSCC + LSCC dysplasia	SCCC +LSCCC dysplasia	All aplastic	All dysplastic
Total	2 (2.5%)	4 (5.0%)	5 (6.3%)	1 (1.3%)	2 (2.5%)	63 (78.8%)	3 (3.8%)
Truncating	0	0	3 (3.8%)	0	0	46 (57.5%)	1 (1.3%)
Non-truncating	2 (2.5%)	4 (5.0%)	2 (2.5%)	1 (1.3%)	2 (2.5%)	17 (21.3%)	2 (2.5%)

Number of ears: 80 (patients 12 and 30 excluded); SCC semicircular canals; PSCC posterior semicircular canal; SSCC superior semicircular canal; LSCC lateral semicircular canal; $P = 0.004$ (X^2)

Cochlear aperture and inner ear (table 2)

In 13 of 31 ears with a stenotic aperture, the cochlea was abnormal (one incomplete partitioning type II, three hypoplasia type III, and nine type IV) (*table 2, figure 6*).

Figure 6 Cochlear aperture – axial CT image shows a lacking cochlear aperture



Surgical challenges

Table 7 summarizes the observed anomalies expecting to be challenging in cochlear implant surgery. Figure 7 illustrates the differences in mastoid size between an ear with a small mastoid and an ear with a wide mastoid (AP-size).

Phenotypes

No typical CHARGE phenotype of the temporal bone, i.e. a constant combination of several anomalies, could be determined. Some combinations of anomalies which were often seen are presented in *table 8*. More than two-thirds of the patients (68%) had an aberrant course of the vestibular aqueduct, and more than two-thirds (77%) had aplasia of the SCC.

Table 7 Surgical challenges in cochlear implantation

Surgical step	Structure on CT	Anomaly	Surgical challenge
Mastoidectomy	Mastoid	Underdeveloped	Reduced access to the middle ear
	Vascular structures	Large emissary vein	Unexpected bleeding
		PSS	Bleeding, reduced mastoid size
	Semicircular canals	Aplasia	Loss of landmark
Post. tympanotomy	Facial nerve	More medial route	Facilitates entrance to the middle ear
Cochleostomy	Ossicles	Dysplasia	Obstructed vision by the incus
	Facial nerve	Aberrant route	Impedes cochleostomy
	Windows	Round window stenosis	Choosing optimal side for cochleostomy
	Jugular bulb	High	Preparing cochleostomy
Insertion	Cochlea	Aplasia	Insertion

Post.: posterior; PSS: petrosquamosal sinus

Figure 7 Mastoid size - axial CT images of a small mastoid (**a**) and a wide mastoid (**b**); both ears had a grommet in situ.

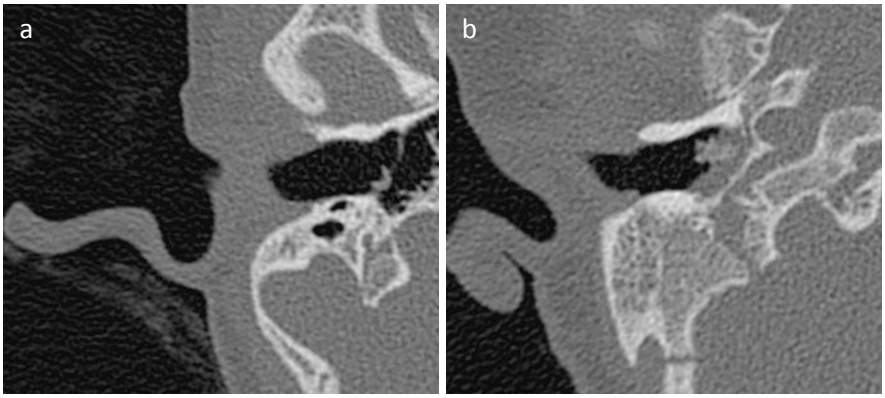


Table 8 Combinations of anomalies often seen

Anomaly	In combination with	Number of patients (percentage of all patients)
Absent RW	Absent OW	12 (14.3%)
Stenotic OW	Dysplastic stapes	23 (27.3%)
Aberrant tympanic portion facial nerve	Dysplastic stapes	24 (28.6%)
Total SCC hypoplasia	OW stenosis	21 (25.0%)
Aberrant VA	SCC hypoplasia with SCA SCC hypoplasia without SCA	14 (16.7%) 14 (16.7%)

OW: oval window; RW: round window; SCC: semicircular canals; SCA: stenotic cochlear aperture; VA: vestibular aqueduct

Genotypes (table 4)

The results of *CHD7* analysis were available for all 42 patients. We had 25 patients (50 ears, 59.5% of 84 ears) with a truncating mutation (of which were 56% nonsense, 20% frameshift, 4% deletions) and 15 patients (30 ears, 35.7% of 84 ears) with a non-truncating mutation (47% missense, 53% splice site). In one patient an unclassified *CHD7* variant was detected (UV-missense) and in another patient no *CHD7* mutation was found. Remarkably, 12/42 patients did not fully comply with the clinical diagnostic criteria [2]. Of these 12 patients, eight had a non-truncating mutation, in one patient no mutation was found, and in another only an unclassified variant could be detected in *CHD7*. Thus, only 2/12 atypical patients (16.7%) had a truncating mutation. In contrast, truncating mutations were found in 23/30 patients (76.7%) who had clinically typical CHARGE syndrome.

Because no constant combination of anomalies could be identified, no correlation could be made between phenotype and genotype. Nevertheless, of the surgical challenging anomalies, SCC aplasia (*table 6)* and oval window atresia (truncating 72%, P=0.001) were found more frequently in patients with truncating mutations than in those with non-truncating mutations (P<0.05) (chi-squared test). Cochlear anomalies (*table 5)*, petrosquamosal sinus (73% truncating, P=0.679) and an aberrant course of the tympanic portion of the facial nerve (67% truncating, P=0.602) were also found more frequently in patients with truncating mutations than in those with non-truncating mutations, but these results were not significant (chi-squared test).

The patient without anomalies of the SCC, cochlea and windows, had a non-truncating mutation. In contrast, in the group with truncating mutations, there were no patients without anomalies of at least one of these structures.

Table 4 Mutations

Patient no.	Mutation	Mutation type	Blake/Verloes criteria
1	nonsense	truncating	positive
2	missense	non-truncating	negative
3	nonsense	truncating	positive
4	nonsense	truncating	positive
5	splice-site	non-truncating	negative
6	splice-site	non-truncating	positive
7	nonsense	truncating	positive
8	missense	non-truncating	positive
9	splice-site	non-truncating	atypical
10	splice-site	non-truncating	atypical
11	missense	non-truncating	atypical
12	no mutation		atypical
13	missense	non-truncating	negative
14	frameshift	truncating	positive
15	frameshift	truncating	positive
16	nonsense	truncating	positive
17	nonsense	truncating	positive
18	missense	non-truncating	positive
19	nonsense	truncating	positive
20	frameshift	truncating	positive
21	splice-site	non-truncating	negative
22	nonsense	truncating	positive
23	splice-site	non-truncating	positive
24	nonsense	truncating	positive
25	frameshift	truncating	positive
26	frameshift	truncating	positive
27	frameshift	truncating	positive
28	missense	non-truncating	positive
29	frameshift	truncating	positive
30	UV missense		atypical
31	frameshift	truncating	partial
32	nonsense	truncating	positive

Table 4 Continued

Patient no.	Mutation	Mutation type	Blake/Verloes criteria
33	splice-site	non-truncating	Positive
34	missense	non-truncating	positive
35	splice site	non-truncating	Atypical
36	nonsense	truncating	Positive
37	nonsense	truncating	Positive
38	frameshift	truncating	Positive
39	nonsense	truncating	Positive
40	frameshift	truncating	Positive
41	nonsense	truncating	Atypical
42	deletion	truncating	Positive

UV: unknown variant

Discussion

Analysis of available imaging material and genetic information of the Dutch cohort of patients with CHARGE syndrome revealed a great variability in anomalies of the temporal bone with possible implications for cochlear implantation. More anomalies were found in patients with truncating *CHD7* mutations than in those with non-truncating mutations. A shortcoming of this study is the variability in image quality leading to missing values of several fine anatomical structures (the imaging data were collected from different hospitals). Nevertheless, we were able to analyse the temporal bone and the anomalies, and to assess the potential impact on plans for cochlear implant surgery.

Temporal bone anomalies detected by CT are important when planning an operation. Vascular variations, missing anatomical landmarks such as the lateral semicircular canal or the vestibular system, an aberrant course of the facial nerve, or stenosis of the round window may hamper safe surgical access to the round window. Given our findings, when planning CI or ear surgery, care must be taken with regard to the reduced development of the mastoid, leading to a smaller access to the middle ear, especially in young children. In these cases, an endaural approach instead of a mastoidectomy [7], or a temporary intra-operative removal or anterior displacement of the posterior wall of the outer ear canal could be considered. Vascular anomalies could also complicate a mastoidectomy, since these may cause uncontrollable bleeding during surgery or postoperative thrombosis of the sigmoid sinus [8-10]. In our group of CHARGE patients, large emissary veins and a persistent petrosquamosal sinus were often present. Whereas emissary veins through the temporal squama are a common anatomical variant [11; 12] and easily dealt with during

surgery, a persistent petrosquamosal sinus is rare in the general population (Koesling et al. [11] estimated this at 1%). However, several authors have reported it to be present in 11–89% of CHARGE patients [9; 13-15]. The highest incidence was described by Giesemann et al. in 2011, in patients who all had aplasia of the SCCs. In our patient population, which included patients with partially and fully developed vestibular systems, a persistent petrosquamosal sinus was seen in 13%. The persistent petrosquamosal sinus can impede the surgical approach, this can be a reason to choose the contra lateral ear for CI.

SCC aplasia is a hallmark of CHARGE syndrome. *CHD7* is highly expressed in the developing ear and is required for development of the SCCs. Delayed fusion and altered gene expression contribute to SCC defects in *CHD7*-deficient mice [16]. Currently, the presence of SCC abnormalities is considered an important indication for performing sequencing of the *CHD7* gene and diagnosis [17]. In our study, we found that normal SCC were present in only one patient. However, during mastoidectomy, the lateral SCC serves as an important anatomical landmark, so the appearance of the SCCs, ranging from complete absence of all canals to normal development, should be meticulously described [7; 13]. In case of a lateral SCC aplasia, the tegmen serves as an paramount marker to direct the surgeon towards the antrum. Anomalies of the SCCs were associated with hypoplasia of the vestibule and a shortened vestibular aqueduct coursing straight to the posterior fossa. This confirms what was reported by Morimoto et al.: 'An aberrant course of the vestibular aqueduct is hypothesized to be the result of semicircular aplasia and the associated displacement of normal surrounding structures' [9].

The facial nerve is another structure at risk during cochlear implantation. As described in the literature, the facial nerve often showed an aberrant course in its tympanic or mastoidal portion [9; 13; 18]. The more medial course of the mastoidal portion of the facial nerve allows a surgeon to create a wider entrance to the middle ear (through a posterior tympanotomy). However, the aberrant course of the tympanic segment of the facial nerve, in particular when it covers the round window, may complicate creating the cochleostomy for intracochlear insertion of the cochlear implant. The aberrant facial nerve may be at risk of injury during cochleostomy [19] or may even be a reason to abort the implantation [20]. The association we observed of an aberrant course of the facial nerve with dysplastic stapes and absence of the oval window was described by Zeifer et al. in different aetiologies without CHARGE syndrome [21].

Absence or stenosis of the oval window was present in more than two-thirds of our patients and is a well-known feature in CHARGE syndrome [9; 13; 22; 23]. Stenosis or absence of the round window was seen less often (as confirmed in the literature). Yet this poses an additional challenge for the surgeon in choosing the optimal site for a cochleostomy.

The size and shape of the cochlea will influence the choice of CI-type. According to the literature, the cochlea is dysplastic in between 20-100% of the ears described in patients with CHARGE syndrome [9; 18; 24; 25]. The anomalies vary from a fused second

and apical turn to a cochlea with 1.5 turns [26-28]. We describe several cases with a shortened cochlea despite the presence of a basal, second and apical turn (referred to as hypoplasia type IV). To the best of our knowledge, this cochlear appearance has not been described in CHARGE syndrome before, but it appears to be consistent with the description of cochlear hypoplasia type IV in a recently published study by Sennaroglu [29] or may be comparable with the flattened cochlea observed by Elmaleh et al. [30] in patients with Waardenburg syndrome. However, the other temporal bone anomalies described in Waardenburg syndrome, besides SCC aplasia and the flattened cochlea, differ from our findings.

Both this cochlear anomaly, as well as the IPII and hypoplasia type III found in this study, should not cause any problems for the insertion of an electrode array as opposed to more severe malformations [31; 32]. The successful outcome of a cochlear implantation also depends on the presence of the cochleovestibular nerve.

In our phenotype-genotype analysis we showed that total aplasia of the SCC and oval window aplasia is more common in patients with truncating mutations than in those with non-truncating mutations– in agreement with the results of Corsten-Janssen et al., showing more anomalies in patients with truncating mutations [33]. Remarkably, the distribution of mutations present in our cohort differs from that reported for large cohorts in the literature. Our percentage of patients with non-truncating mutations (splice-site and missense) was relatively high with 35.7% in comparison to Zentner et al. [5] and to Janssen et al. [4] who reported 23% and 20% of patients with non-truncating mutations, respectively. This discrepancy might be because a CT is often used in mildly affected patients to check the semicircular canals and to provide further proof for the clinical diagnosis. Our cohort might be enriched with more mildly affected patients (12/42), and thus of missense mutations.

In general, we conclude that temporal bone findings in patients with CHARGE syndrome vary widely and should therefore be studied meticulously before performing any surgery. Imaging may exclude patients from cochlear implantation or reveal an aberrant course of the facial nerve , vascular and middle ear abnormalities that could complicate CI surgery. Such information is valuable and should be combined with records on the developmental and behavioural problems that are also common in CHARGE syndrome. Moreover, patients with CHARGE syndrome often have post-surgical complications due to their neurological and anatomical abnormalities [34]. A balance between the benefit of CI, the surgical procedure's chance of success, and the anaesthetic risks should be sought by a multi-disciplinary team working with the patient and his/her family.

Acknowledgements

We thank parents of patients for giving the permission to use their data. We thank Jackie Senior for editing the manuscript.

References

1 Blake KD, Davenport SL, Hall BD et al (1998) CHARGE association: an update and review for the primary pediatrician. Clin Pediatr (Phila) 37:159-173

2 Verloes A (2005) Updated diagnostic criteria for CHARGE syndrome: a proposal. Am J Med Genet A 133A: 306-308

3 Jongmans MC, Admiraal RJ, van der Donk KP et al (2006) CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. J Med Genet 43:306-314

4 Janssen N, Bergman JE, Swertz MA et al (2012) Mutation update on the CHD7 gene involved in CHARGE syndrome. Hum Mutat 33:1149-1160

5 Zentner GE, Layman WS, Martin DM, Scacheri PC (2010) Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. Am J Med Genet A 152A:674-686

6 Bergman JE, de Wijs I, Jongmans MC, Admiraal RJ, Hoefsloot LH, van Ravenswaaij-Arts CM (2008) Exon copy number alterations of the CHD7 gene are not a major cause of CHARGE and CHARGE-like syndrome. Eur J Med Genet 51:417-425

7 Stjernholm C (2003) Aspects of temporal bone anatomy and pathology in conjunction with cochlear implant surgery. Acta Radiol Suppl 430:2-15

8 Marsot-Dupuch K, Gayet-Delacroix M, Elmaleh-Berges M, Bonneville F, Lasjaunias P (2001) The petrosquamosal sinus: CT and MR findings of a rare emissary vein. AJNR Am J Neuroradiol 22:1186-1193

9 Morimoto AK, Wiggins RH, 3rd, Hudgins PA et al (2006) Absent semicircular canals in CHARGE syndrome: radiologic spectrum of findings. AJNR Am J Neuroradiol 27:1663-1671

10 An YH, Wee JH, Han KH, Kim YH (2011) Two cases of petrosquamosal sinus in the temporal bone presented as perioperative finding. Laryngoscope 121:381-384

11 Koesling S, Kunkel P, Schul T (2005) Vascular anomalies, sutures and small canals of the temporal bone on axial CT. Eur J Radiol 54:335-343

12 Louis RG, Jr., Loukas M, Wartmann CT et al (2009) Clinical anatomy of the mastoid and occipital emissary veins in a large series. Surg Radiol Anat 31:139-144

13 Satar B, Mukherji SK, Telian SA (2003) Congenital aplasia of the semicircular canals. Otol Neurotol 24:437-446

14 Giesemann AM, Goetz GF, Neuburger J, Lenarz T, Lanfermann H (2011) Persistent petrosquamosal sinus: high incidence in cases of complete aplasia of the semicircular canals. Radiology 259:825-833

15 Friedmann DR, Amoils M, Germiller JA et al (2012) Venous malformations of the temporal bone are a common feature in CHARGE syndrome. Laryngoscope 122:895-900

16 Hurd EA, Micucci JA, Reamer EN, Martin DM (2012) Delayed fusion and altered gene expression contribute to semicircular canal defects in Chd7 deficient mice. Mech Dev 129:308-323

17 Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM (2011) CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. J Med Genet 48:334-342

18 Lanson BG, Green JE, Roland JT, Jr., Lalwani AK, Waltzman SB (2007) Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes. Laryngoscope 117:1260-1266

19 Ahn JH, Lee KS (2013) Outcomes of cochlear implantation in children with CHARGE syndrome. Acta Otolaryngol 133:1148-1153

20 Bauer PW, Wippold FJ, 2nd, Goldin J, Lusk RP (2002) Cochlear implantation in children with CHARGE association. Arch Otolaryngol Head Neck Surg 128:1013-1017

21 Zeifer B, Sabini P, Sonne J (2000) Congenital absence of the oval window: radiologic diagnosis and associated anomalies. AJNR Am J Neuroradiol 21:322-327

22 Admiraal RJ, Joosten FB, Huygen PL (1998) Temporal bone CT findings in the CHARGE association. Int J Pediatr Otorhinolaryngol 45:151-162

23 Arndt S, Beck R, Schild C, Grauvogel TD, Laszig R, Aschendorff A (2010) Management of cochlear implantation in patients with malformations. Clin Otolaryngol 35:220-227

24 Holcomb MA, Rumboldt Z, White DR (2013) Cochlear nerve deficiency in children with CHARGE syndrome. Laryngoscope 123:793-796

25 Song MH, Cho HJ, Lee HK et al (2011) CHD7 mutational analysis and clinical considerations for auditory rehabilitation in deaf patients with CHARGE syndrome. PLoS One 6:e24511

26 Guyot JP, Gacek RR, DiRaddo P (1987) The temporal bone anomaly in CHARGE association. Arch Otolaryngol Head Neck Surg 113:321-324
27 Glueckert R, Rask-Andersen H, Sergi C et al (2010) Histology and synchrotron radiation-based microtomography of the inner ear in a molecularly confirmed case of CHARGE syndrome. Am J Med Genet A 152A:665-673
28 Haginomori S, Sando I, Miura M, Casselbrant ML (2002) Temporal bone histopathology in CHARGE association. Ann Otol Rhinol Laryngol 111:397-401
29 Sennaroglu L, Yucel E, Sennaroglu G, Ozgen B (November 2015) Management of Children with Inner Ear Malformations In: Publishers JM, (ed) Sataloff's Comprehensive Textbook of Otolaryngology: Head & Neck Surgery (Pediatric Otolaryngology), pp 91-106
30 Elmaleh-Berges M, Baumann C, Noel-Petroff N et al (2013) Spectrum of temporal bone abnormalities in patients with Waardenburg syndrome and SOX10 mutations. AJNR Am J Neuroradiol 34:1257-1263
31 Mylanus EA, Rotteveel LJ, Leeuw RL (2004) Congenital malformation of the inner ear and pediatric cochlear implantation. Otol Neurotol 25:308-317
32 Sennaroglu L (2010) Cochlear implantation in inner ear malformations--a review article. Cochlear Implants Int 11:4-41
33 Bergman JE, Janssen N, van der Sloot AM et al (2012) A novel classification system to predict the pathogenic effects of CHD7 missense variants in CHARGE syndrome. Hum Mutat 33:1251-1260
34 Blake K, MacCuspie J, Hartshorne TS, Roy M, Davenport SL, Corsten G (2009) Postoperative airway events of individuals with CHARGE syndrome. Int J Pediatr Otorhinolaryngol 73:219-226

Appendix A Radiologic criteria for the os petrosum in patients with CHARGE syndrome

Mastoid and vascular structures	
Mastoid	Observation: pneumatisation of one or more cells Measurement: AP size: minimal distance from external meatus wall to sigmoid sinus taken at the middle of the meatus in the axial plane. Measurement: LM size: minimal distance from cortex to sinus at the most anterior border of the sinus perpendicular to the mastoid AP size.
Emissary veins	Observation: emissary veins through temporal squama, persistent petrosquamosal sinus [13] Measurement: >1 mm and <1 mm
Jugular bulb	Observation: high if at the level or cranial of the round window in axial plane
Middle ear	
Ossicles	Observation: dysplasia
Windows	Observation: stenotic
Facial nerve	Observation: normal with present SCC: in transverse plane caudal of the LSCC and lateral and superior of the oval window. In coronal plane lateral and medial of the SCC. Normal with absent SCC: coronal plane cranial of the oval window, posterior of the axis of the basal turn of the cochlea at the level of the anterior rim of the round window.
Cochlear vestibular system	
Cochlea	Measurement: angle basal turn and midline skull (54.6 degrees (range 46.8–63.8 degrees; standard deviation, 3.5) [24] Observation: dysplasia [31] with separate judgment of modiolus.
SCC	Absent, dysplastic, normal
Vestibulum	Measurement length: maximum longitudinal extension, width maximum transversal diameter, perpendicular to the length.[22] (normal (6.18-6.42) x (3.44-3.59) mm, *interval*)
Vestibular aqueduct	Measurement: diameter at midpoint (normal 1.5-2 mm) Observation: course
IAC	Measurement: Midline in axial plane(normal 2-8 mm)
Cochlear aperture	Observation: present or bony stenosis
Nerves in IAC	Observation on MRI: normal, hypoplastic or aplastic

AP anterior-posterior; LM lateral-medial; SCC semicircular canal; LSCC lateral semicircular canal; IAC internal auditory canal

Appendix B Radiologic set of criteria for CT scan

Name Observer	
Date	
ID scan	
Quality Image	☐ good ☐ moderate ☐ bad

Item	**AD**	**AS**
Cochlea – **External contours:** 2.5 turn?	☐ yes ☐ no ☐ unable to identify	☐ yes ☐ no ☐ unable to identify
Cochlea internal: Interscalar septa present?	☐ yes ☐ no ☐ unable to identify	☐ yes ☐ no ☐ unable to identify
Modiolus	☐ present ☐ absent ☐ unable to identify	☐ present ☐ absent ☐ unable to identify
Angle of basal turn		
Cochlear aperture: Is an aperture visible?	☐ yes ☐ no ☐ unable to identify	☐ yes ☐ no ☐ unable to identify
Internal Auditory Canal (mm)		
Notes Cochlea		
PSCC	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify
SSCC	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify
LSCC	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify	☐ normal ☐ aplastic ☐ dysplastic/hypoplastic ☐ unable to identify
SCC – NOTES		

Appendix B Continued

Item	AD	AS
Vestibulum Length (mm)		
Vestibulum width (mm)		
Vestibular Aqueduct Diameter (mm)		
Vestibular Aqueduct Course	☐ normal ☐ aberrant ☐ unable to identify	☐ normal ☐ aberrant ☐ unable to identify
Vestibular aqueduct – NOTES		
Oval window	☐ present ☐ absent/stenotic ☐ unable to identify	☐ present ☐ absent/stenotic ☐ unable to identify
Round window	☐ present ☐ absent/stenotic ☐ unable to identify	☐ present ☐ absent/stenotic ☐ unable to identify
Windows – NOTES		
Stapes	☐ normal ☐ dysplastic ☐ unable to identify	☐ normal ☐ dysplastic ☐ unable to identify
Incus	☐ normal ☐ dysplastic ☐ unable to identify	☐ normal ☐ dysplastic ☐ unable to identify
Malleus	☐ normal ☐ dysplastic ☐ unable to identify	☐ normal ☐ dysplastic ☐ unable to identify
Ossicles – NOTES		
Facial nerve tympanic segment	☐ Normal ☐ aberrant ☐ unable to identify	☐ Normal ☐ aberrant ☐ unable to identify
Facial nerve tympanic segment – NOTES		
Facial nerve mastoid segment	☐ Normal ☐ aberrant ☐ unable to identify	☐ Normal ☐ aberrant ☐ unable to identify
Facial nerve mastoid segment – NOTES		

Appendix B Continued

Item	AD	AS
Mastoid AP-size (mm)		
Mastoid LM-size (mm)		
Mastoid pneumatisation?	☐ yes ☐ no ☐ unable to identify	☐ yes ☐ no ☐ unable to identify
Jugular Bulb	☐ normal ☐ high ☐ unable to identify	☐ normal ☐ high ☐ unable to identify
Emissary veins	☐ absent ☐ <1 mm ☐ >1 mm ☐ unable to identify	☐ absent ☐ <1 mm ☐ >1 mm ☐ unable to identify
Petrosquameuse sinus	☐ absent ☐ present ☐ unable to identify	☐ absent ☐ present ☐ unable to identify
Vascular structures NOTES		
NOTES overall		

PSCC posterior semicircular canal; SSCC superior semicircular canal; LSCC lateral semicircular canal; SCC semicircular canal; AP anterior-posterior; LM lateral-medial

2.2

Influence of hearing loss and cognitive abilities on language development in CHARGE syndrome

Published as:
Influence of Hearing Loss and Cognitive Abilities on Language Development in CHARGE Syndrome Vesseur AC, Langereis MC, Free RH, Snik AFM, van Ravenswaaij-Arts CM, Mylanus EAM *Am J Med Genet A. 2016 Aug;170(8):2022-30. Epub 2016 May 4.*

Abstract

Objectives

Hearing loss and cognitive delay are frequently occurring features in CHARGE syndrome that may contribute to impaired language development. However, not much is known about language development in patients with CHARGE syndrome.

Materials and Methods

In this retrospective study, hearing loss, cognitive abilities and language development are described in 50 patients with CHARGE syndrome. After informed consent was given, data were collected from local medical files.

Results

Most patients (38.3%; 18/47 patients) had moderate hearing loss (41-70dB) and 58.5% (24/41 patients) had an IQ below 70. The mean language quotients of the receptive and expressive language were more than one standard deviation below the norm. Both hearing loss and cognitive delay had an influence on language development. Language and cognitive data were not available for all patients, which may have resulted in a pre-selection of patients with a delay.

Conclusion

In conclusion, while hearing thresholds, cognitive abilities and language development vary widely in CHARGE syndrome, they are mostly below average. Hearing loss and cognitive delay have a significant influence on language development in children with CHARGE syndrome. To improve our knowledge about and the quality of care we can provide to CHARGE patients, hearing and developmental tests should be performed regularly in order to differentiate between the contributions of hearing loss and cognitive delay to delays in language development, and to provide adequate hearing amplification in the case of hearing loss.

Introduction

Hall was the first to note that choanal atresia could be accompanied by a specific set of multiple anomalies [1]. In 1981, Pagon et al. first used the acronym 'CHARGE' to describe the association of Coloboma, Heart disease, Atresia of the choanae, Retarded growth and development and/or CNS anomalies, Genital hypoplasia, and Ear anomalies and/or deafness [2]. Because of increased knowledge about the syndrome, Blake revised this definition in 1998 into major and minor characteristics [3]. The major characteristics, which are the features that occur commonly in the then-called CHARGE *association* but rarely in other conditions, include coloboma, choanal atresia, cranial nerve involvement and ear abnormalities. The minor characteristics, which occur less frequently or are less specific, include cardiovascular malformations, genital hypoplasia, cleft lip/palate, tracheoesophageal fistula, distinctive CHARGE face, growth deficiency and developmental delay. In 2005, Verloes suggested changes to the diagnostic criteria, as shown in *table 1 a, b* [4]. In 2004, the causative gene was identified as *CHD7* on chromosome 8q12.1 [5] and the name changed to CHARGE *syndrome* (MIM, Mendelian Inheritance in Man, 214800).

The presentation of the syndrome can be very diverse, with most patients showing a variable combination of multiple congenital anomalies. Hearing loss and cognitive delays are frequently described in CHARGE syndrome [6, 7]. Hearing loss, present in 80-100% of the patients, is the most common characteristic and can be due to anatomical anomalies of the middle or inner ear, to aplasia or hypoplasia of the cochlear nerve, or to middle ear disease. As a consequence, hearing in CHARGE syndrome can range from normal to profound deafness [3, 6, 8]. As one of the minor characteristics, delayed cognitive abilities are also often described in CHARGE syndrome. The delay in cognitive development varies and is rarely expressed in 'Intelligence Quotient' (IQ), but is based instead on developmental age, abilities and educational level. More than 50%, and possibly up to 75%, of patients have an intellectual development below average [9-13]. Little is known about language development in this group of patients, but language delays have been described [13]. One might argue that intellectual disability and hearing loss, or the combined presence of both, may have a strong influence on language development. Thus language development needs special attention in this vulnerable group of children with CHARGE syndrome, a finding further supported by Thelin, who found that parents rank hearing loss as the factor with the largest effect on the ability of their child to communicate [14].

The aim of this study is twofold. Firstly, we aim to improve our knowledge of hearing loss, cognitive ability and language development in a large group of patients with CHARGE syndrome. Secondly, we want to establish an indicative dataset for a group of patients with multiple needs by analyzing the relationship of both hearing loss and cognitive abilities with language development.

Patients and methods

In this retrospective study, the data of patients registered at the Dutch CHARGE centre of expertise (University Medical Centre Groningen, the Netherlands) were used after written informed consent was obtained from patients or their legal representatives.

Patients who received a cochlear implant (CI) were excluded because the language development of patients with CI is the topic of a separate study. Data from the present study can be used as reference data for the evaluation of the results of language development in patients with CHARGE syndrome and CI.

Table 1 Characteristics of CHARGE syndrome

1a. Major and minor signs of CHARGE syndrome [4]

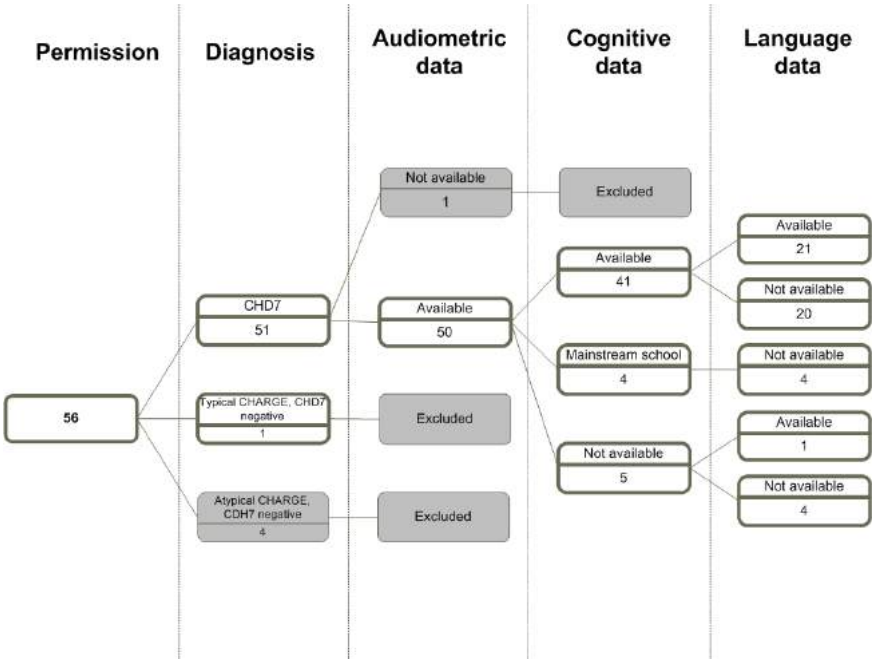
Major signs
Coloboma (iris or choroid, with or without microphthalmia)
Atresia of choanae
Hypoplastic semicircular canals
Minor signs
Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies and neurosensory deafness)
Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin deficiencies)
Abnormal middle or external ear
Malformation of mediastinal organs (heart, esophagus)
Intellectual Disability

1b. Definition of typical, atypical, and partial CHARGE syndrome [4]

Typical CHARGE syndrome
3 major signs
2/3 major signs + 2/5 minor signs
Partial/incomplete CHARGE
2/3 major signs + 1/5 minor signs
Atypical CHARGE
2/3 major signs + 0/5 minor signs
1/3 major signs + 3/5 minors signs

In total 56 patients (or their legal representatives) gave permission for the use of their data. Fifty-one patients had molecularly confirmed CHARGE syndrome (*CHD7 mutation*). The patients were classified according to Verloes' criteria (*table 1)* [4]. Five patients who had no molecular confirmation were excluded. One other patient was excluded because of a lack of audiometric, cognitive and language data. For all 50 patients included, audiometric data were available. For 41 of these patients, cognitive data were available and for 22 patients language data were available (*figure 1*). The study group was divided into two groups: *group A* without language developmental data and *group B* with available language data. Data were obtained from medical records available in hospitals, Audiologic Centres and institutes for children with hearing problems and intellectual disability.

Figure 1 Patient selection



The numbers are the absolute numbers of patients. White: patients described in the study; light grey: excluded patients.

Audiometric data

For 45 patients a tone audiogram was available (headphone or free-field). Per patient, between one and eight tests were available (mean 3, median 2). The average hearing loss at 0.5, 1 and 2 kHz (Pure Tone Average or PTA) of all available tests of the best ear was used. In five cases, only the objectively obtained hearing thresholds (Brainstem Evoked Response or BER) had been carried out; in these cases, the BER thresholds were used for the analysis. On the basis of the PTA or the BER thresholds, patients were categorized as normal hearing: threshold 0-20 dB; mild hearing loss: 21-40 dB; moderate hearing loss: 41-70 dB; severe hearing loss: 71-90 dB; or profound hearing loss: >90 dB. For the analysis, 'functional hearing thresholds' were used, including the 'aided PTA' in patients using hearing aids and the 'unaided PTA' in patients who did not use hearing aids. The patients using hearing aids were excluded from the analysis if the aided thresholds were unknown. Speech perception was measured by the NVA lists, a standardized Dutch monosyllable test [15].

Cognitive ability tests

Cognitive data were available for 41 patients. The cognitive ability tests used in our cohort were validated intelligence tests in which the use of spoken or written language is not necessary. These tests are especially suitable for children and adults with language disabilities, like hearing impaired patients, or patients with autism or intellectual disability. The standardized tests used included the Dutch version of the Bayley Scales of Infant Development (BSID-NL-II) [16] and the Dutch version of the Wechsler Intelligence Scale for Children Revised and Third edition (WISC-RN and WISC-III-NL)[17, 18].

When longitudinal data were available, data from the most recent evaluation were used. Based on the non-verbal-IQ outcome or the developmental age, we categorized the patients into low IQ <70, subnormal IQ 70-85, normal IQ 86-115, and above average IQ >115. The developmental age was scaled in retrospect by psychologists skilled in assessing hearing impaired children using an informal procedure. In patients without available cognitive data, the school type was used in the descriptive analysis.

Both audiometric and cognitive data were categorized to observe the distribution among the patients and to filter small measurement differences.

Language development tests

Standardized age- and capacity-related tests were used, this was generally the Dutch version of the Reynell Developmental Language Scales [19], but any other standardized test was used if available. All tests are well validated and with available norms. Scores of these tests can be expressed as a standard score, percentile or an age-equivalent score. In case of longitudinal data, the data of the most recent evaluation of each patient were used. Both receptive and expressive language subtests were used. We express the language development in Language Quotient (LQ = age equivalent/chronological age*100).

Statistical analysis

SPSS 20 was used to collect all data and perform statistics. We made use of the Spearmans' correlation test to test for significant correlations.

Results

The study group consisted of 50 patients, 32 male and 18 female. Of all patients, 33 patients had typical CHARGE syndrome, four patients had atypical CHARGE syndrome, one patient had partial CHARGE syndrome and six did not meet the criteria. For six other patients it was not possible to score them for the Verloes criteria[4].

Audiometric data

Audiometric data were available for all 50 patients. The mean age at the most recent audiometric test was 10.9 years (median 9; minimum 5 months; maximum 48 years, SD 10.4). *Table 2* shows the hearing threshold classification of the best ear. For three patients, only aided thresholds were retrievable, meaning they could not be included in the unaided threshold classification. For eight patients, no aided thresholds were available. The majority (83.0%) of the patients had hearing loss and were equally divided among the various categories (between 10.6 and 19.2%), with the exception of the group of patients with moderate hearing loss, who make up 38.3%. Of the total study group, 29 patients used hearing aids (including three bone-anchored hearing aid users), which resulted in better hearing thresholds that we further refer to as "functional hearing thresholds". Ten patients wore no device due to refusal, recurrent infections (with moderate/severe hearing loss) or poor auditory responses. In four patients with poor auditory responses, CI had been considered but rejected because of cochlear nerve hypo-/ aplasia or surgical risks.

Cognitive abilities

Cognitive developmental tests were available for 41 patients. *Table 3* shows the distribution of cognitive levels within the group. The mean age of the patients at the time of the cognitive developmental tests was 10.5 years (median 9; minimum 1; maximum 56 years; SD 9.7). The majority of the patients (58.5%) had an IQ below 70. Nine patients were excluded from *table 3*: for the four patients who attended mainstream schools, no cognitive tests were conducted; for five other patients, no cognitive development tests were available and the school type was unknown.

Group A (patients without data on language development)

For 28 patients, no language development data were available. Their characteristics are shown in *table 4*. Four patients for whom only audiometric data were available were

Table 2 Hearing thresholds

Category hearing threshold	Unaided N	%	Functional N	%
Normal (0-20dB)	8	16.6	9	20.9
Mild (21-40dB)	6	12.5	13	30.2
Moderate (41-70dB)	18	37.5	13	30.2
Severe (71-90dB)	9	18.8	3	7.0
Deaf (>90dB)	7	14.6	5	11.7
Total	**48**	**100**	**43**	**100**
No unaided/aided data available	*3*[1]		*8*[2]	

N: number of patients; [1] aided, no unaided data; [2] aided, but no aided data available.

Table 3 Cognitive abilities

IQ	N	%
Above average (IQ>115)	0	0
Normal (IQ=86-115)	10	23.8
Subnormal (IQ70-85)	8	19.0
Low (IQ<70)	24	57.2
Total	**42**	**100**
No data available	*9*	

N: number of patients, IQ: Intelligence Quotient.

excluded from this table. Five patients attended or have attended mainstream schools in childhood and no language development tests had been conducted with them, but we assumed that they communicated in spoken language. All five patients had a *CHD7* mutation, but none fulfilled the CHARGE criteria according to Verloes [4].

In ten patients, no language tests were performed because they had very limited spoken language levels. They had insufficient communication skills and communicated with pictograms, signal behavior and finger spelling. All of these patients had an IQ below 70 and moderate to severe functional hearing thresholds. All ten patients fulfilled the CHARGE criteria according to Verloes [4].

For nine patients, there was no information available on language development or educational level. The cognitive abilities of these patients range from normal to low. Of these nine patients, one patient (ID 51), did not meet the Verloes' criteria [4], for one patient (ID 22) this was unknown and one had atypical CHARGE syndrome (ID 6).

Table 4 Characteristics of Group A (patients without language developmental tests)

ID	Cognitive ability	Functional hearing threshold	Speech perception	Language development	Comments
26	Normal	Normal	100% 50dB	Mainstream school	
6	Normal	Moderate*	85% 80dB aided	No info	HA
22	Normal	Moderate	50% 65dB	No info	HA
51	Normal	Moderate*	95% 55dB aided	No info	
4	Subnormal	Mild		No info	
14	Subnormal	Moderate		No info	HA
49	Subnormal	Normal		No info	
28	Subnormal	Deaf		No info	No HA
8	Low	Moderate		Very limited	HA not accepted
24	Low	Moderate		Very limited	HA
25	Low	Moderate		Very limited	BAHA
29	Low	Severe		Very limited	No HA, because poor auditory performance
31	Low	Severe		Very limited	Started with CI evaluation
36	Low	Deaf		Very limited	NvIII aplasia
37	Low	Deaf		Very limited	HA
43	Low	Deaf		Very limited	No HA because recurrent otitis
45	Low	Deaf		Very limited	Parents canceled CI
52	Low	Severe		Very limited	HA
42	Low	Deaf		No info	nVIII hypoplasia
34	Low	Mild		No info	BAHA
39	No test	Mild		Mainstream school	
48	No test	Normal	100% 55dB	Mainstream school	
50	No test	Normal		Mainstream school	
18	No test	Normal		Mainstream school	

Number of patients: 24; HA: hearing aid; BAHA: bone anchored hearing aid; * aided but no data; 4 patients excluded with only audiometry available.

Group B (language data)

Table 5 presents *group B*, comprising the 22 patients with complete records, except for three patients (ID 17, 23 and 54) using hearing aids, but without known aided thresholds, and one patient (ID15) whose cognitive abilities are unknown. At the most recent evaluation of the language development, the age of the patients varied between one and

Table 5 Characteristics and language data of group B

ID	Cognitive ability	Functional hearing threshold	Receptive language			Expressive language			Maximal speech perception			
			CA in months (years)	LA in months	LQ	CA in months (years)	LA in months	LQ	Max in %	dB	Max in % with HA	dB with HA
2	Normal	Mild*	31 (2)	24	79							
3	Normal	Moderate*	39 (3)	23	59	39	22	56				
5	Normal	Normal	44 (3)	44	100	44	42	95	100	65		
7	Low	Moderate*	23 (1)	12	52	23	12	52				
10	Low	Mild	302 (25)	18	6							
12	Subnormal	Severe*	274 (22)	34	12							
15	Unknown	Moderate*	14 (1)	12	86	14	15	107				
16	Low	Moderate*	34 (2)	25	74							
17	Low	Moderate [1]	124 (10)	90	73	97	29	30	90	110	90	75
19	Normal	Moderate*	30 (2)	14	47	30	14	47				
20	Low	Moderate*	171 (14)	27	16							
23	Low	Moderate[1]	60 (5)	30	50				95	90	100	70
27	Normal	Severe*	37 (3)	26	70							
30	Subnormal	Normal	62 (5)	69	111	63	56	89				
35	Subnormal	Normal	54 (4)	43	80	39	38	97				
38	Normal	Mild*	42 (3)	33	79	42	30	71	95	75		
40	Subnormal	Mild	39 (3)	32	83	39	39	77	100	60		
41	Subnormal	Mild	39 (3)	34	87	39	34	87	100	65		
44	Low	Moderate*	113 (9)	21	19							
55	Low	Moderate*	194 (16)	87	45				100	75		
53	Low	Mild	65 (7)	42	65	65	44	67				
54	Low	Moderate[1]	96 (5)	57	59	97	57	59			100	65
57	Low	Mild *	127 (12)	55	43	127	66	52	70		96	

N: 23; CA: calendar age; LA: language age; LQ: language quotient; HA: hearing aid; dB: decibel; *: aided thresholds; 1: aided, no aided thresholds available

25 years, with a mean of 7.1 years (median 4.5; SD 6.7). In one patient, the receptive language age was age adequate; this patient had no hearing loss and normal cognitive abilities. One patient achieved better scores than expected for his age with subnormal cognitive abilities (IQ 75-85). The remaining patients scored below the age equivalent scores.

The mean receptive language quotient of the 22 patients was 59.7 and the median was 62.0 (SD 28.47). Both the mean and the median were close to two standard deviations below the norm (85). The mean and median of the expressive language quotient (14 patients) were also more than one standard deviation below the norm, with 70.5 and 69.2 (SD 22.5), respectively. Cognitive abilities in this subgroup were normal in 22.7% of patients (5/22), subnormal in 22.7% (5/22) and low in 50% (11/22). The functional hearing thresholds varied from normal to deaf, with 50% of patients (11/22) showing moderate hearing loss. Patients with restricted spoken language scores used other modes of communication like sign language or sign-supported spoken language.

Two patients had 'atypical CHARGE' (ID 3, 23), three did not fulfill the Verloes criteria (ID 5, 54, 57) and one patient could not be scored (ID 20).

Relationship between hearing loss, cognitive abilities and language development

Of the 22 patients in *group B,* four patients were excluded: three because of unknown aided thresholds, and one because of missing cognitive abilities. In the remaining 18 patients, the following significant correlations were found: between receptive language quotient and degree of functional hearing loss (Spearman p 0.006, r^2 -0.622); between receptive language quotient and cognitive abilities (p 0.038, r^2 0.493); and between expressive language quotient and degree of functional hearing loss (p 0.001, r^2 -0.845). No significant correlation was found between expressive language quotient and cognitive abilities (p 0.651, r^2 0.154), and between cognitive abilities and hearing loss (p 0.310, r^2 -0.246). *Figure 2* and *figure 3* show that the receptive language quotient and the expressive language quotient decrease with an increase of functional hearing thresholds in patients with normal or subnormal cognitive abilities.

Figure 2 Receptive language quotient

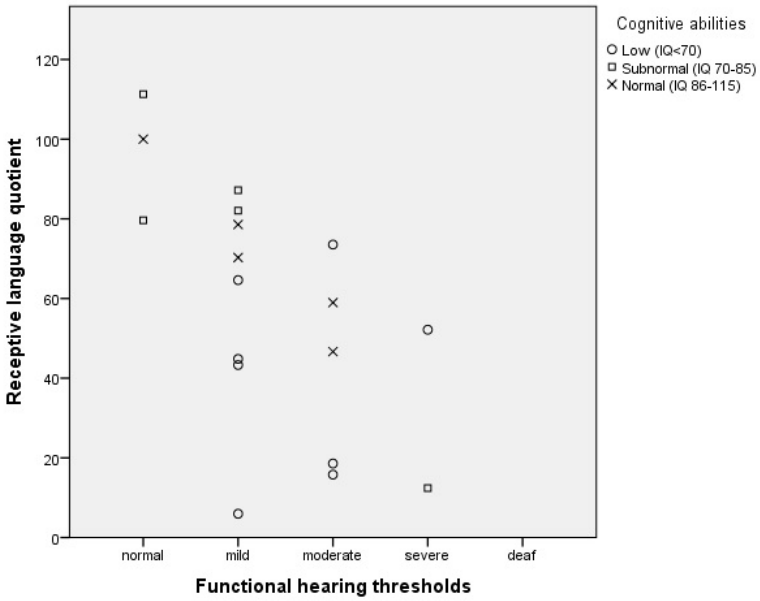
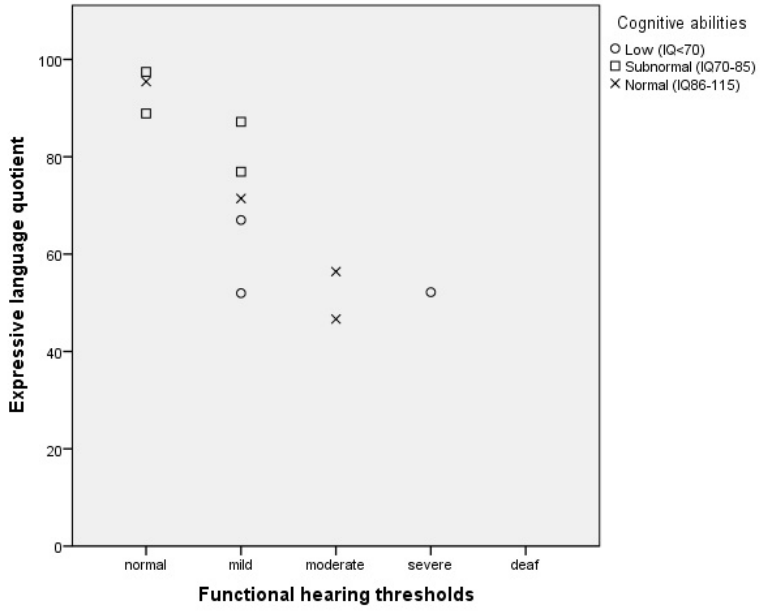


Figure 3 Expressive language quotient



Discussion

The present study gives an overview of hearing loss, cognitive abilities and language development of a cohort of Dutch patients with CHARGE syndrome. Large variability is shown, but the majority of the patients had moderate hearing loss and cognitive abilities were below average in slightly over half of the patients. Both hearing thresholds and cognitive abilities influenced language development, resulting in delayed language development.

The range in hearing loss in the whole study group (60-90% had moderate to total hearing loss) corresponds with that reported for CHARGE syndrome in the literature [6, 10, 20]. Some patients had unaided hearing loss because of recurrent otitis media, refusal of hearing aids or fitting problems because of the shape of the auricle or poor auditory responses. Alternatives to conventional hearing aids, like a bone anchored hearing aid and CI, were considered in these patients. These difficulties in adequate hearing amplification were also described by Thelin and Fussner [14] and show that it can be challenging to give the optimal therapy in children with CHARGE syndrome. Based on our results, we emphasize the importance of early screening and follow up of the hearing thresholds in order to begin adequate hearing revalidation as soon as possible because hearing loss has a big impact on language development.

Comparing the outcome of cognitive abilities with the literature is difficult because of the different tests and the different definitions of levels of cognitive ability that were used. The distribution of patients with subnormal or low cognitive abilities in our study (78%) is slightly higher compared with results from other studies [9, 11, 21], possibly due to our exclusion, of patients attending mainstream schools with an assumed average cognitive abilities. Factors like behavioral problems (autism, obsessive-compulsive disorders, tics, attention deficits disorders) frequently described in CHARGE syndrome [22-24] were not intensively studied in the present study, but could influence development, making this a topic for further research.

In ten patients, no language developmental data could be gathered because their receptive language was highly delayed due to their cognitive delay. These patients suffered from severe hearing loss and severe cognitive developmental delays. For the five patients with mild or no hearing loss who had attended mainstream schools, we assume they had normal language development because of the educational level of mainstream schools. A possible explanation for this is that developmental tests are normally not applied at mainstream schools.

To the best of our knowledge, the language development in a cohort of patients with CHARGE syndrome has not been previously described in this detail. In *group B* the majority had language development and cognitive abilities more than one standard deviation below the norm, suggesting that IQ and LQ are broadly similar, confirmed by the significant correlation of cognitive abilities and receptive language quotient. This is in line with Santoro et al. who showed that cognitive developmental delay has a significant impact

on communication, even if the expressive communication skills are preserved [25]. No significant correlation of cognitive abilities and expressive language quotient was found. Particularly patients with lower cognitive abilities did not show expressive language quotients and could not be included in the calculations, probably causing a bias. In this study we also show that patients with CHARGE syndrome with lower functional hearing thresholds reach lower levels of language development.

A shortcoming of this study is the variability in data sources. Data were collected from different professionals and institutions, leading to missing language and cognitive developmental testing data. Despite these problems, enough data were gathered to give an impression of the hearing loss, cognitive development and language development and to do an analysis of the impact of hearing loss and cognitive development on language development in CHARGE syndrome in, as far as we know, the largest group of CHARGE patients in which this has been described.

The tests described in the *group B* patients were probably conducted for a specific reason such as a delay in cognition and/or language development, that made knowledge about the patient's development necessary for, for instance, educational advice. Reasons for non-availability of the tests could be: patient unable to perform the test, patient performing at average levels with no reason to be tested, or tests had been conducted but were no longer available. In addition, patients with CI were omitted from the descriptive analysis. It is possible that the group with available cognitive (and language) data represented a pre-selection of patients with a developmental delay by excluding those too well-performing to have tests done and those too poor-performing to participate in language tests. If this was the case, the results of this study may not reflect the entire population of patients with CHARGE syndrome, but are biased towards to the more moderate group. In the future this could be resolved by performing a standard language and cognitive developmental test with every CHARGE syndrome patient. Although some parents of patients think the abilities of their children are underestimated by most standard tests [14], a standardized collection of data is still needed to analyse the properties of CHARGE syndrome and to improve care for these patients.

In general we can conclude that the auditory abilities, cognitive abilities and language development in CHARGE syndrome vary widely, but are mainly below average. Therefore, these children should be tested regularly with respect to auditory and cognitive development in order to be able to differentiate between the contributions of hearing loss and cognitive delay to delays in language development. This is especially critical for hearing loss because it has great impact on language development and adequate amplification is therefore important.

Acknowledgements

We thank parents of patients for giving the permission to use their data. We thank Kate McIntyre for editing the manuscript.

References

1. Hall, B.D., *Choanal atresia and associated multiple anomalies.* J Pediatr, 1979. **95**(3): p. 395-8.
2. Pagon, R.A., et al., *Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association.* J Pediatr, 1981. **99**(2): p. 223-7.
3. Blake, K.D., et al., *CHARGE association: an update and review for the primary pediatrician.* Clin Pediatr (Phila), 1998. **37**(3): p. 159-73.
4. Verloes, A., *Updated diagnostic criteria for CHARGE syndrome: a proposal.* Am J Med Genet Part A, 2005. **133A**(3): p. 306-8.
5. Vissers, L.E., et al., *Mutations in a new member of the chromodomain gene family cause CHARGE syndrome.* Nat Genet, 2004. **36**(9): p. 955-7.
6. Shah, U.K., et al., *Otologic management in children with the CHARGE association.* Int J Pediatr Otorhinolaryngol, 1998. **44**(2): p. 139-47.
7. Tellier, A.L., et al., *CHARGE syndrome: report of 47 cases and review.* Am J Med Genet, 1998. **76**(5): p. 402-9.
8. Dhooge, I., et al., *Otological manifestations of CHARGE association.* Ann Otol Rhinol Laryngol, 1998. **107**(11 Pt 1): p. 935-41.
9. Blake, K.D., et al., *Who's in CHARGE? Multidisciplinary management of patients with CHARGE association.* Arch. Dis. Child., 1990. **65**(2): p. 217-23.
10. Davenport, S.L., M.A. Hefner, and J.W. Thelin, *CHARGE syndrome. Part I. External ear anomalies.* Int J Pediatr Otorhinolaryngol, 1986. **12**(2): p. 137-43.
11. Harvey, A.S., P.M. Leaper, and A. Bankier, *CHARGE association: clinical manifestations and developmental outcome.* Am J Med Genet Part A, 1991. **39**(1): p. 48-55.
12. Raqbi, F., et al., *Early prognostic factors for intellectual outcome in CHARGE syndrome.* Dev Med Child Neurol, 2003. **45**(7): p. 483-8.
13. Dammeyer, J., *Development and characteristics of children with Usher syndrome and CHARGE syndrome.* Int J Pediatr Otorhinolaryngol, 2012. **76**(9): p. 1292-6.
14. Thelin, J.W. and J.C. Fussner, *Factors related to the development of communication in CHARGE syndrome.* Am J Med Genet Part A, 2005. **133A**(3): p. 282-90.
15. Bosman, A.J., *Speech perception by the hearing impaired.* 1989, University of Utrecht: Utrecht. p. 200.
16. Bayley, N., *Bayley Scales of Infant Development Manual.*, in *San Antonio: The Psychological Corporation.* 1993.
17. Bruyn, E.d., G.v.d. Steenen, and P.P.v. Haasen, *Wechsler Intelligence Scale for Children-Revided (WISC-R), Nederlandstalige uitgave en verantwoording.* 1986, Lisse: Swets & Zeitlinger.
18. Kort, W., et al., *WISC-III NL Wechsler Intelligence Scale for Children. Derde Editie NL. Handleiding en Verantwoording.*, H.T.P.N.I.v. Psychologen, Editor. 2005: Amsterdam.
19. Reynell, J.K. and C.P. Gruber, *Reynell Developmental Language Scales*, W.P. Services, Editor. 1990: Los Angeles.
20. Jongmans, M.C., et al., *CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene.* J Med Genet, 2006. **43**(4): p. 306-14.
21. Lasserre, E., L. Vaivre-Douret, and V. Abadie, *Psychomotor and cognitive impairments of children with CHARGE syndrome: common and variable features.* Child Neuropsychol, 2013. **19**(5): p. 449-65.
22. Hartshorne, T.S., M.A. Hefner, and S.L. Davenport, *Behavior in CHARGE syndrome: introduction to the special topic.* Am J Med Genet Part A, 2005. **133A**(3): p. 228-31.
23. Bernstein, V. and L.S. Denno, *Repetitive behaviors in CHARGE syndrome: differential diagnosis and treatment options.* Am J Med Genet Part A, 2005. **133A**(3): p. 232-9.
24. Smith, I.M., et al., *Behavioral profiles and symptoms of autism in CHARGE syndrome: preliminary Canadian epidemiological data.* Am J Med Genet Part A, 2005. **133A**(3): p. 248-56.
25. Santoro, L., et al., *Cognitive-motor profile, clinical characteristics and diagnosis of CHARGE syndrome: an Italian experience.* Am J Med Genet A, 2014. **164a**(12): p. 3042-51.

2.3

Suggestions for a guideline for cochlear implantation in CHARGE syndrome

Published as**:**

Suggestions for a Guideline for Cochlear Implantation in CHARGE Syndrome. Vesseur AC, Verbist BM, Westerlaan HE, Kloostra FJ, Admiraal RJ, van Ravenswaaij-Arts CM, Free RH, Mylanus EA.*Otol Neurotol. 2016 Oct;37(9):1275-83.*

Abstract

Objectives

Identifying aspects for establishing cochlear implantation guidelines for patients with CHARGE syndrome .

Material and Methods

In this explorative retrospective study, the challenges and benefits of cochlear implantation were described of ten patients with CHARGE syndrome. They received a cochlear implant between 2002 and 2012 in one of the cochlear implant centres of tertiary referral centres in the Netherlands. Imaging and surgical findings, language development and Quality-of-life (QoL), were compared with two control groups: (1) 34 non-syndromic CI-users and (2) 13 patients with CHARGE syndrome without CI because of sufficient hearing.

Results

Subjective and objective audiometry and MRI were necessary to confirm the presence of the cochlear nerve. Surgery in CHARGE syndrome was challenging due to enlarged emissary veins, semi-circular-canal aplasia, aberrant facial nerve and dysplastic cochlear windows, making CT indispensable in surgical preparations. No major intra-operative complications occurred. Despite additional handicaps, all patients showed auditory benefit and improvement in disease-specific QoL. Patients implanted at a relatively young age (≤37 months) followed by a long period of CI-use (>five years) and with minor additional problems, developed spoken language at a basic level comparable to that of the control group of CHARGE syndrome patients.

Conclusion

A CI should be considered in all patients with CHARGE syndrome and severe sensorineural hearing loss. A careful work-up is required, comprising CT, MRI, objective and subjective audiometry and assessment by a specialized multidisciplinary team. Cochlear implantation in CHARGE syndrome might be complicated by syndrome-related temporal-bone anatomy, and the outcome of the CI is more individually determined. Early implantation should be aimed for.

Introduction

Cochlear implants (CI) have become instrumental in the treatment of children and adults with severe or profound sensorineural hearing loss. Based on the positive results with CI in patients with isolated deafness, the criteria for implantation have gradually become less strict, allowing patients with additional handicaps, including patients with cognitive delay, to undergo implantation [1].

Patients with CHARGE syndrome fall within the group of patients with complex needs. Their major features are ocular coloboma, choanal atresia, heart defects and aplasia of the semicircular canals (SCC) [2]. Hearing loss is one of the most common features seen in CHARGE syndrome and is present in 60-90% of patients [3, 4]. CI can be a solution in these patients if conventional hearing aids or bone-anchored hearing aids do not provide them with optimal hearing abilities [5-10].

Cochlear implantation in CHARGE syndrome is not without challenges. One of the features seen in CHARGE syndrome is deficiency of the cochlear nerve [11]. The surgical procedure may be complicated by anatomical anomalies of the petrosal bone including a narrow mastoid, an aberrant course of the facial nerve, absent SCC, absent or covered cochlear windows and/or a dysplastic cochlea [9]. In addition, development of speech and language after implantation may be difficult because of cognitive disabilities or physical handicaps [6-10]. Despite the reduced development of speech and language, most CHARGE patients with cognitive disabilities showed more responsiveness and receptiveness to the world around them after implantation [6-10].

The aim of this study is to identify factors to be considered when establishing cochlear implantation guidelines for patients with CHARGE syndrome by giving an overview of the challenges and benefits encountered with cochlear implantation in these patients. We describe the pre-operative imaging, surgical findings and the results of spoken language development and quality-of-life (QoL) after implantation. Our results are compared with those of non-syndromic patients with CI and with those of patients with CHARGE syndrome with normal hearing or successfully fitted with conventional hearing aids.

Patients and Methods

Participants

In this exploratory retrospective study, the databases of contributing CI-centres in the Netherlands were searched for data from patients with CHARGE syndrome who received a CI. One patient was implanted in Belgium. Ten patients were included who underwent implantation between 2002 and 2012. All ten patients had molecularly confirmed CHARGE syndrome and clinically typical CHARGE syndrome according to the Verloes criteria [2].

All patients were pre-operatively assessed by a multidisciplinary team consisting of an otologic surgeon, an audiologist, a speech therapist and a psychologist. The radiological and medical data of the ten patients were reviewed and analysed after informed consent was obtained from the patients and/or their parents according to Dutch legislation.

Language data and QoL data of the study group were compared with data that was already available for a control group of patients with unilateral CI and without co-morbidity who were implanted at the Radboud University Medical Centre Nijmegen. This control group consists of 34 prelingual deaf patients with an IQ above 85. The etiology of hearing loss in these patients is genetic/hereditary (14 patients) or unknown (20 patients). Patients with hearing loss caused by meningitis or a syndrome were excluded. This group is hereafter referred to as 'non-syndromic CI-users'.

Language development in our study cohort is also compared with a second control group consisting of 13 patients with CHARGE syndrome with adequate hearing, with or without hearing aids, and with an IQ below 85. These patients have been described in more detail in a previously published paper [12].

Imaging

All patients had a pre-operative CT of the petrosal bone, and all but one patient had a MRI of the inner ear. The radiologic data of nine patients have been described previously [13].

Cognitive data

Non-verbal IQs were obtained by validated tests suitable to the ages and abilities of the patients using the Dutch versions of either the Bayley Scales of Infant Development (BSID-NL-II[14]), the Snijders Oomen non-verbal intelligence test (SON-R [15]) or the Kent Infant Development Scale (KID-N[16]).

Audiological data

Objective hearing thresholds were obtained pre-operatively by Brainstem Evoked Response Audiometry (BERA). Pure tone audiometry and speech perception tests were done pre-implantation and at 12, 24, 36, 60 months and ten years post-implantation. Speech perception was measured by the NVA-test, a standardized Dutch monosyllable test [17]. The communication mode was observed at the evaluation moments and classified as body- or sign language or spoken language with or without sign support.

Language development

Language data were collected at the same standard evaluation moments as the audiological tests. Depending on the age and abilities of the patients, the following tests were conducted: the NNST (Dutch Non-speech Test) [18], the Reynell test [19], the *Taaltest voor Kinderen* [20] (Dutch language test), the Peabody Picture Vocabulary [21] and the Schlichting test [22]. For each test, the 'language age' was used as the outcome variable.

Quality of Life

Three standardized parent-proxy questionnaires were used to evaluate the QoL. The questionnaires were completed using a 5-point Lickert scale. The Glasgow Children's Benefit Inventory (GCBI [23]) is a disease-specific QoL-questionnaire developed for different interventions in otorhinolaryngology. The Nijmegen Cochlear Implant Questionnaire (NCIQ [24]) is a disease-specific questionnaire for CI-users. The PedsQL [25] measures general health-related-QoL in children and adolescents.

Data analysis

SPSS 20.0 was used for statistical analysis. Descriptive statistics were used to define the baseline characteristics. The effect of CI on QoL was statistically analysed using multiple linear regression.

Results

Patient characteristics

Table 1 shows the characteristics of the study group. All patients were congenitally deaf and had cognitive abilities below average (IQ<85). Patient 4 was known to have autistic-like behavior, while no behavioral problems were reported in the other patients. For patient 3 and 6, only psychological observation was available, no cognitive test results. Six patients had coloboma, causing limited vision in three patients (5, 6 and 8), while patient 7 was suspected to have a limited vision but could not be tested. With the exception of patient 6, all patients had repeated major surgery prior to cochlear implantation (choanal, cardiac or cleft lip/palate surgery) compared to the control group in which 11 of 34 patients had only minor surgery (grommets and/or adenotomy).

The implantation age of the study group ranges from 16 months-20 years and the follow up period varied from 24-120 months post-implantation (*table 2*). The implantation age of the non-syndromic CI-users ranges from nine months-15 years and follow up period from 24-120 months post-implantation. The implantation age, years of CI-use and CI-use in hours per day (based on subjective information) of our CHARGE study group did not differ significantly from the non-syndromic CI-user control group (Mann-Whitney U test). The majority (43%; 6/13 patients) of the CHARGE patients without CI had aided mild hearing thresholds (21-40dB) and a mean age of 9;7 years (range 1;11-25;02).

BERA and MRI findings

Table 2 shows BERA en MRI findings of the implanted ear. We found in three patients (1, 4 and 6) reliable responses while using hearing aids and during subjective audiometry, without responses with BERA and with no confirmation of presence of the cochlear nerve on MRI. The cochlear nerve was not identifiable on MRI possibly due to absence of the

Table 1 Patient characteristics

Patient No.	Sex	*CDH7 mutation*	Criteria (Verloes)	Test	Test age (months)	Cognition (IQ)	MAJOR			MINOR				
							Col	CA	CND	genital	CV	RG	cleft	TF
1	M	+	+	BSID-II-NL	12	70-85	n	y	y	y	y	n	n	n
2	M	+	+	BSID-II-NL	22	70-85	y	n	n	n	n	y	y	n
3	F	+	+			No test	n	n	n	y	y	y	n	n
4	M	+	+	SON-R 2,5-7	67	70-85	y	y	y	y	y	n	n	n
5	F	+	+	SON-R 2,5-7	74	<70	y	n	n	unknown	y	y	n	y
6	F	+	+			No test*	y	n	n	y	n	y	n	n
7	F	+	+	BSID-II-NL	7	<70	y	n	n	unknown	y	y	y	n
8	F	+	+	SON-R 2,5-7	82	<70	y	n	n	y	y	n	y	n
9	M	+	+	BSID-II-NL	37	<70	n	y	n	y	y	n	n	n
10	M	+	+	Kid-N	20	<70	n	n	n	y	y	n	y	n

CA: choanal atresia; cleft: cleft lip and palate; CND: cranial nerve dysfunction other than sensorineural hearing loss; Col: coloboma; CV: cardiovascular anomalies; F: female; M: male; n: no; genital: genital hypoplasia; RG: retarded growth; TF: tracheoesophageal fistula; y: yes

* estimated IQ 70-85 based on educational level

Table 2 Implantation

Patient No.	Age at implantation (months)	Implant type	Side	Insertion	Response on NRT	Time since CI (months)	Hearing aid contra-lateral
1	16	CI24RE	AS	Full	Yes	60	No
2	25	Nucleus freedom	AS	Full	Partial	60	Yes
3	37	Nucleus contour	AD	Full	NC	120	No
4	68	Nucleus contour advanced soft tip	AS	Full	No	60	No
5	79	Nucleus 24 contour	AD	Full	Yes	120	No
6	249	Nucleus freedom	AS	Full	Partial	60	No
7	99	Nucleus 24 contour	AD	Full	Yes	60	No
8	31	HiRes90k	AS	Full	NC	60	No
9	49	Nucleus freedom	AS	Full	Yes	24	Yes
10	17	Nucleus freedom	AD	Full	Yes	36	No

NRT: neural response telemetry; NC: not conducted

nerve, a poor quality of scan or blurry images due to movement artefacts. The other patients had responses with BERA and/or a present cochlear nerve on MRI.

CT and intra-operative findings (table 3)

All patients underwent a retro-auricular approach with a cortical mastoidectomy. The mastoidectomy was anticipated to be more complicated because of absence of the lateral SCC, which is an important landmark in ear surgery. The incus was identified in all patients and dysplastic in three patients. In four patients, the incus was removed to improve the view on the promontory. In one patient, a defect of the tegmen was found with an exposed middle fossa dura.

As shown in *table 3,* there were subtle differences between the pre-operative CT and the intra-operative findings, mainly concerning the round window, the stapes or the route of the facial nerve. The oval window was often diagnosed as aplastic on CT. As a result of the absent lateral semicircular canal, the facial nerve seems to have a more inferior course at the oval window region and a more anterior course in its vertical segment, in some cases coinciding with aplasia of the oval window, and, if present, a stapes only connected to the incus. Finding the round window as a landmark for use in performing the cochleostomy was often challenging. If the facial nerve covered the round window, the cochleostomy was placed anterior of the (supposed) round window. In patient 8, the cochleostomy was drilled through the posterior tympanotomy as well as transmeatal (after lifting the tympanic membrane) because the lumen of the scala tympani could not

Table 3 CT and intra-operative findings

Patient No.	Cochlea		Oval window		Round window	
	CT	Insertion	CT	Surgery	CT	Surgery
1	type IV[3]	full	aplasia	dysplastic: slitshaped	N	aplasia
2	N	full	aplasia	ND	N	covered by nVII
3	type IV[3]	full	aplasia	rudimentary	N	rudimentary
4	IPII[2]	full	aplasia	rudimentary	N	rudimentary covered by nVII
5	N	full	aplasia	ND	N	N
6	N	full	N	ND	N	More posteriorly
7	type IV[3]	full	aplasia	ND	N	ND
8	type IV[3]	full	aplasia	ND	aplasia	aplasia
9	N	full	aplasia	aplasia	N	N
10	N	full	aplasia	covered by nVII	N	covered by nVII

EV: emissary vein; HB: high riding jugular bulb; N: normal; ND: not described; OW: oval window; PSS: petrosquamosal sinus; RW: round window; [1] mastoidal and tympanic facial nerve; [2] incomplete partitioned type II (28); [3] Type IV: shortened cochlea

be found directly. Twice, a per-operative CT was performed in this patient to confirm the right location and direction of the cochleostomy and position of the electrode. The electrode was fully inserted, but the CT showed buckling of the basal part of the electrode array. In all other patients, full insertion of the electrode was achieved despite five dysplastic cochleas on CT. In patient 2, the scala tympani had to be drilled out because of a narrow proximal scala tympani.

Complications

During surgery, the main complication was bleeding from (enlarged) emissary veins. In four patients, excessive bleeding occurred while lifting the periosteum. Hemostasis was achieved with bone wax or absorbable hemostat. In patient 5, a wound drain had to be left in situ and postsurgical supplementation with ferrous fumarate was necessary for six weeks because of anemia (Hb 5.8mmol/L). In patient 8, there was a temporary pre-operative desaturation to 47%, possibly caused by bronchospasm with dislocation of the tube. The patient recovered after two re-intubations, and intensive care was needed post-operatively because of pneumonia from which the patient recovered completely.

Stapes		nVII[1]		Vascular	
CT	**Surgery**	**CT**	**Surgery**	**CT**	**Surgery**
dysplastic	fusion of crurae, no contact with footplate	N	more anterior, near RW	none	N
dysplastic	N	N	N	large EV	bleeding
dysplastic	monopodal, no contact with footplate	N	N	EV, HB	N
dysplastic	no stapes	aberrant	over RW and OW	EV, PSS	N
dysplastic	surrounded by mucosa	N	N	none	bleeding
N	ND	N	N	none	N
dysplastic	N	N	not identified	EV	bleeding
dysplastic	ND	aberrant	not identified, thickened mucosa	EV	N
N	no contact with footplate, crurae pointed at nVII	N	inferior of OW	none	bleeding
dysplastic	rudimentary	aberrant	over RW and OW, mastoidal portion: siphon like	none	N

Patient 1 had a temporary worsening of his pre-existing unilateral facial paresis but recovered quickly without treatment. Patient 10 suffered from mastoiditis at the implanted ear two years after implantation. A mastoidectomy was performed with drainage of the purulence (caused by *streptococcus intermedius*), but the electrode and receiver seemed unaffected and were left *in situ*. Gentamycin sponges were left behind and removed after five days during a re-mastoidectomy because of the suspicion of mastoiditis, but appeared to be edema. Systemic antibiotics were applied for one week, resulting in a good recovery.

Use of the CI

The number of hours of CI-use per patient was variable. Eight patients used their CI during most of the day, as indicated at their last follow up. Patient 5 stopped using the CI after ten years due to epileptic seizures and limited auditory benefit. Patient 10 did not use his CI frequently because of recurrent airway infections and related hospital admissions with his revalidation being focused on physical recovery.

Table 4 Speech perception at most recent follow up

Patient No.	Time since CI (months)	Age at evaluation (months)	Speech perception
1	60	76	Could not be tested but could discriminate and identify sounds
2	60	85	62% NVA test
3	120	157	78% NVA test
4	60	128	75% NVA test
5	120	199	No speech perception but enjoyed music
6	24	273	Discrimination of vocals 90%, consonants 50%
7	60	159	Could discriminate four sounds
8	24	55	Could not be tested but could identify sounds
9	24	73	Could not be tested but could discriminate and identify sounds
10	24	41	Could not be tested but enjoyed music

CI: Cochlear implant; NVA test: Dutch speech perception test
Test was carried out in standardized conditions using the pre-recorded test or live voice if it was difficult to hold the attention of the patient. The test results obtained with the most optimal hearing amplification were used (i.e. with CI and, if used, a contra-lateral hearing aid). In patient 6 and 8 no speech perception tests were conducted at more recent follow up moments, while their last evaluation moment was 60 months post-implantation

Auditory

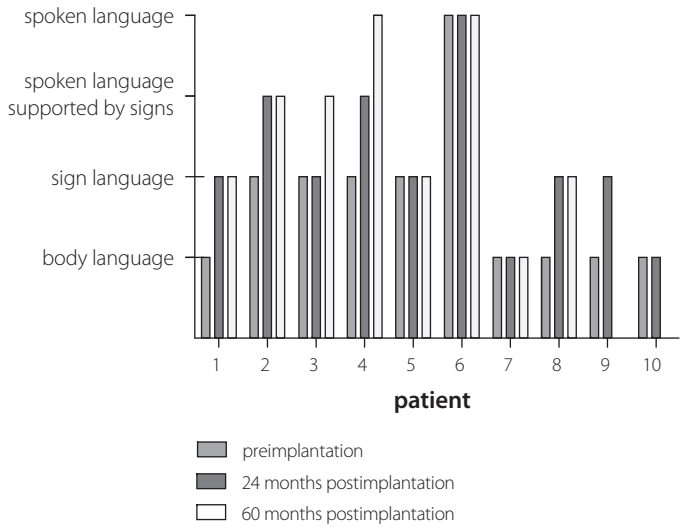
All patients had hearing thresholds with their CI between 25-40dB at the implanted ear, except patients 5 and 8 who had unfavorable hearing thresholds of 60dB at the implanted ear. *Table 4* shows the speech perception scores at the most recent follow up. Three patients (2, 3 and 4) showed speech perception scores of more than 60%, and one patient (6) could discriminate 90% of the vocals and 50% of the consonants. These four patients were tested after 60 or 120 months. In the other six patients, speech perception could not be measured with standard tests, but with the CI these patients could detect sounds adequately. Typically, these patients have been tested after a shorter follow up period (24-60 months) than patients with measurable speech perception, except patient 5. No speech perception tests were conducted at the more recent follow up visits in patients 6, who already had satisfying scores, and patient 8, who was not able to perform speech perception measurements even after a long period of CI-use, which was consistent with the restricted audibility of this patient.

Communication mode

The main communication mode is shown in *figure 1* as well as the changes in spoken communication mode over time in six patients. In the other four patients, no change in communication mode was observed. Patient 5 had restricted hearing abilities. Patient 6

was 19 years old at implantation and already using spoken language with lip-reading before implantation. Patient 7 had very limited cognitive development. Patient 10 did not use the CI frequently.

Figure 1 Communication mode of the study group at 0, 24 and 60 months post implantation

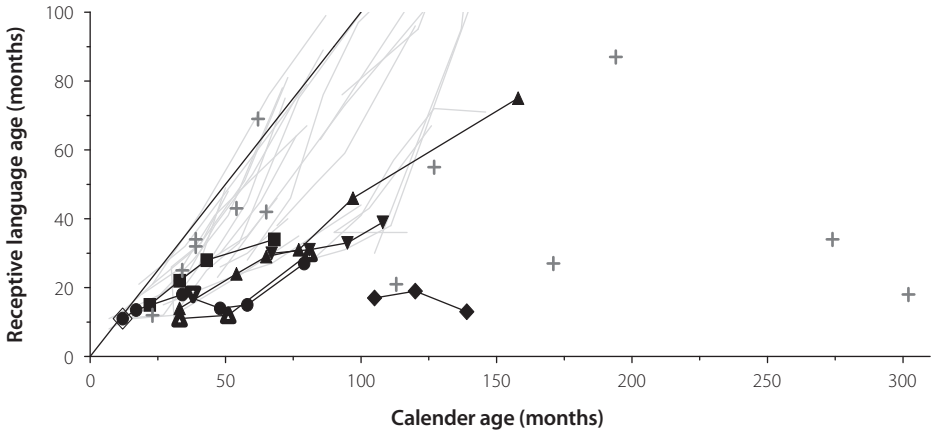


Language development

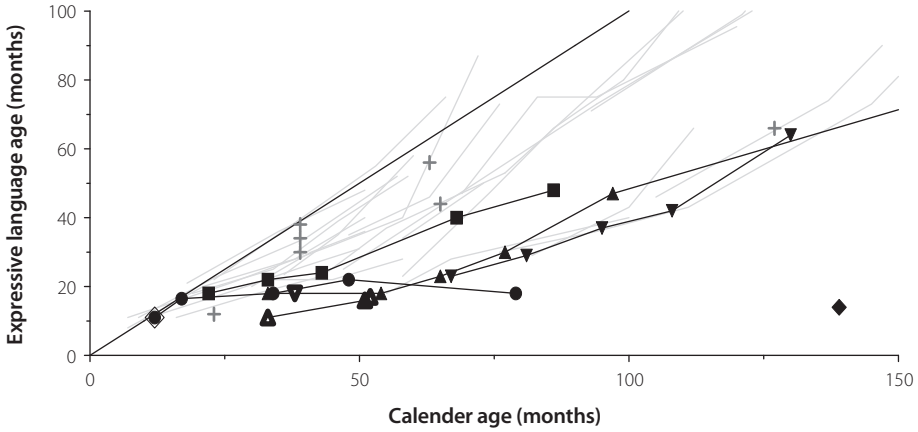
Figure 2a and 2b show the receptive language and expressive language age of eight of the ten patients with CHARGE syndrome and CI over time (see *Supplement 1* for individual data). The data are plotted against the language development of the non-syndromic CI-users (grey lines, see *Supplement 2* for individual data) and the cross-sectional data of receptive and expressive language of the control group with CHARGE syndrome and adequate hearing (see *Supplement 3* for individual data). The language age of the study patients developed more slowly than in the non-syndromic control group but seems comparable with the control group of CHARGE patients without CI. The patients in the study group with measurable speech perception scores (patients 2, 3 and 4) showed the largest improvement in language development. In patient 8, the tests were conducted supported by signs. Patient 6 was too old for the language developmental test. Patient 7, 9 and 10 had poor language abilities and therefore conducting a standard test reliably was not possible.

Figure 2 Language development

2a. Receptive language development



2b. Expressive language development



Longitudinal data of the study group (without patient 6 and 7; patient 8 supported by signs) and non-syndromic control group, plotted against cross-sectional data of the control group 'CHARGE without CI'.
Longitudinal: ● patient 1; ■ patient 2; ▲ patient 3; ▼ patient 4; ◆ patient 5; △ patient 8; ▽ patient 9; ◇ patient 10; — age adequate; — non-syndromic patients with CI;
Cross-sectional: + CHARGE without CI (figure 2a 13 patients, figure 2b 7 patients)
For detailed (individual) data see Supplement 1, 2, 3

Quality of life

The QoL of the patients with CHARGE syndrome and CI is compared with the control group of non-syndromic CI-users *(*see *Supplement 4* for detailed data*)*. The parents of five patients (with varying performances) of the study group completed the questionnaires (patients 1, 3, 5, 7 and 9). The parents of the other five patients did not respond or choose not to fill in the questionnaires. In all questionnaires, the absolute scores were lower in the patients with CHARGE syndrome than in the control group. In all domains of the questionnaires the scores were higher than zero for all patients of the study group, showing a positive effect of the CI on QoL. No statistical differences were found on the domains of the GCBI between the study group and the control group. The study group only showed statistically significant lower scores than the control group on the 'sound perception basic' ($p<0.05$), 'sound perception advanced' ($p<0.0001$), and 'speech production' ($p<0.005$) subdomains of the NCIQ. Statistically significant lower scores were found on the total PedsQL score ($p<0.001$), on the 'psychosocial' domain ($p<0.005$), the 'emotional' ($p<0.005$) and the 'social' ($p<0.0001$) subdomains of the study group in comparison with the control group. Some parents added positive comments about the changes they observed in their children post implantation to the questionnaires. For example, one patient understood conversations not directly addressed to her despite her limited vision (patient 7) while another made more sounds and responded to hearing his name called when using the CI (patient 9).

Discussion

This study shows the challenges and benefits of cochlear implantation in CHARGE patients. The assessment phase is complicated because of the complexity of the syndrome and the possibility of cochlear nerve aplasia. The surgical procedure of implantation is challenging in this syndrome because of widely variable temporal bone findings. However, all patients with CHARGE syndrome and severe sensorineural hearing loss show some benefit from cochlear implantation in terms of auditory functioning, language development and/or QoL. Based on the results of this study, and on the discussion below, we have developed a proposal for guidelines to be used when considering CI for CHARGE patients.

The presentation of CHARGE syndrome can be vary divers, with a variable combination of multiple anomalies [2]. A multidisciplinary team, familiar with the syndrome specific problems, should be involved in the assessment of mental and physical health status (*table 5)*.

One of the features seen in CHARGE syndrome is deficiency of the cochlear nerve [11]. MRI findings of the cochlear nerve do not always correlate with the BERA results or with the auditory benefits of CI. In three patients in the study group, both the outcome of the MRI and the BERA could not rule out an aplasia of the cochlear nerve. The decision

Table 5 Guideline suggestion

1.	**Target Group**
Molecularly confirmed CHARGE syndrome or clinically typical CHARGE syndrome (Verloes [2]) and severe to profound hearing loss and no benefit of hearing aids	
2.	**Assessment phase**
2.1	Assessment by a multidisciplinary team consisting of o Otologic surgeon With experience of surgery of abnormal anatomy of the petrosal bone o Speech therapists To evaluate the communicative skills and intentions o Psychologists familiar with patients with complex needs To evaluate the cognitive abilities
2.2	A positive result in at least one of the following examinations o BERA o Subjective audiometry o MRI: to identify the presence of the cochlear nerve
2.3	Contra-indications o Cochlear nerve aplasia (no response on BERA, no reaction with hearing aids and no cochlear nerve on MRI) o Poor general (physical/mental) health status
3.	**Pre-implantation phase**
3.1	CT: imaging the surgical route and challenging anomalies Radiologic report should contain at least: o development of mastoid and presence of venous anomalies o route of the facial nerve o anatomy of semicircular canals o description of the location and aspect of the windows o anatomy of the cochlea
3.2	Pre-anesthesia assessment o Pediatric cardiologist Congenital heart defects are present in 74% of patients with CHARGE syndrome [28] o Pediatrician To evaluate the general health status o Pediatric anesthetist Be aware of micrognatia and laryngomalacia. Consider discussing tracheotomy (26).
3.3	Counseling of parents including the risks and possibility of failure due to, e.g., unforeseen nVIII aplasia
4.	**Surgical phase**
4.1	Choice for side of implantation Depends on presence of petrosquamosal sinus, large emissary veins, route of the facial nerve, development of the mastoid, presence cochlear nerve and development of the cochlea

Table 5 Continued

4.	**Surgical phase**
4.2	Surgical steps o Facial nerve monitoring o Facial nerve stimulation o Consider using a navigation system o Mastoidectomy: use the tegmen as a guide to the antrum o Posterior tympanotomy: facilitated by the more medial route of the facial nerve but may require removal of the incus to extend vision in the middle ear. o Cochleostomy: consider a combined approach (transmastoidal and transtympanic) in cases where nVII is blocking the RW
4.3	Complications: bleeding from emissary veins, gusher, incomplete insertion of the electrode. Anesthetic complications (airway management).
4.4	Prolonged post-anesthesia surveillance [27] Risk of postoperative airway dysfunction through post-intubation arytenoid dislocation
5.	**Rehabilitation phase**
5.1	Outcomes are variable from signal function to open speech perception and spoken language, depending on individual variables and implantation age
5.2	Improvement in disease specific quality of life
5.3	The post-operative auditory rehabilitation should be tailored to the individual patient's needs

BERA: brainstem evoked response audiometry; nVII: facial nerve; RW: round window; SCC: semicircular canal

to implant was based on responses on subjective audiometry and led to satisfying outcomes for all three patients. Therefore we always recommend performing MRI, BERA and subjective audiometry to establish the presence of the cochlear nerve in CHARGE patients.

Surgery and anesthesia could result in respiratory complications in CHARGE syndrome, which we also experienced in one patient [26-28]. Micrognatia, laryngomalacia and postintubational arythenoid dislocation may compromise the airway. These issues need to be discussed during the pre-operative counseling, including the performance of a tracheotomy if needed.

In the temporal bone of patients with CHARGE syndrome the high percentage of aberrant vascular structures like PSS [29] is specific to the syndrome. These structures can cause surgical problems. An aplastic lateral SCC, an inferior-anterior displacement of the facial nerve at the second genu, an aplastic oval window and an aplastic round window are frequently seen in CHARGE syndrome. We advise the detection and localization of these structures, before implantation and the incorporation of this knowledge into surgical planning. Per-operatively, a navigation system may be of value [9]. As we demonstrated, the presence of an aberrant facial nerve may complicate the creation of the cochleostomy but does allow full insertion of the electrode. More space and a better view of the facial

nerve may be achieved by removal of the incus. The surgeon should use facial monitoring and stimulation to diminish the risk of the facial nerve injury. A transtympanic route can also be added to the transmastoidal and posterior tympanotomy in order to perform the cochleostomy to the scala tympani anterior to the facial nerve. The electrode may then be routed through the posterior tympanotomy prior to insertion or through a temporary slit in the external meatal wall post insertion.

Cochlear malformations, like incomplete partition or cochlear hypoplasia are present in patients with in CHARGE syndrome. Nevertheless, in all our patients, a standard electrode could be deployed. More severe malformations might necessitate a different choice of electrode. We did not observe the perilymfe gushers described in patients with CHARGE syndrome by other authors [6, 7, 30].

Despite their cognitive disabilities and additional handicaps, all patients showed auditory profit that ranged from enjoying music up to speech perception scores of 78%. Seven of the ten patients changed their communication mode, with five tested patients showing increased spoken language abilities. General health status influenced CI-use, and possibly language development, in two patients including one non-user. In five patients, an increase of spoken language abilities was observed. These were all patients who received their implants at relatively young ages (≤37 months) and who had used their CI for a relatively long period of time (60 and 120 months). These patients had relatively higher IQ's (70-85) and were using sign-language pre-operatively. The non-syndromic CI-users performed better than the patients with CHARGE syndrome and CI, but the performance of tested CHARGE patients with CI is quite similar to that of CHARGE patients without CI. Thus, overall, the performances with CI are quite satisfactory for a complex multi-impairment syndrome, however three patients did not show spoken language. Despite one non-user (after ten years), no negative effects of the CI were identified. Although based on only five patients (with different performance), the results of the QoL-questionnaires support an improved disease-specific QoL after implantation, and without significant differences when compared with the non-syndromic CI-users. The general health-related-QoL is significantly lower in comparison with non-syndromic CI-users, possibly due to the additional handicaps and restricted cognitive abilities.

This study was performed retrospectively and describes a small study population, which is a logical consequence of the low incidence of this syndrome (1:15,000-1:17,000 in the Netherlands [31]). As far as we know, this is the first study to compare language development in CHARGE patients with CI with 'general' language development in CHARGE syndrome. However, due to the retrospective study design, the development of our patients could not be compared with that in patients with CHARGE syndrome who had received negative advice for CI. Reasons not to implant a patient with CHARGE syndrome could be cochlear nerve aplasia, low cognitive abilities, autism or poor general health status. This may have produced a positive bias in our results because more seriously affected patients could not be part of the study.

Based on these challenges and benefits, and taking into account the considerations described above, we have composed the guidelines presented in *table 5*. These guidelines are necessary because, as we have shown, CI in CHARGE syndrome is complicated by the syndrome-related temporal bone anatomy and additional features. Nonetheless, given their improved performance and QoL, CI should be considered in patients with CHARGE syndrome and severe sensorineural hearing loss. The outcome of the CI seems to be more individually determined. However, the goal for these patients should be early implantation. We invite other groups to use and comment on our guideline in order to reach best practice for children with CHARGE syndrome and severe hearing loss.

References

1. Wakil, N., et al., *Long-term outcome after cochlear implantation in children with additional developmental disabilities*. Int J Audiol, 2014. **53**(9): p. 587-94.
2. Verloes, A., *Updated diagnostic criteria for CHARGE syndrome: a proposal.* Am J Med Genet A, 2005. **133A**(3): p. 306-8.
3. Jongmans, M.C., et al., *CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene.* J Med Genet, 2006. **43**(4): p. 306-14.
4. Dammeyer, J., *Development and characteristics of children with Usher syndrome and CHARGE syndrome.* Int J Pediatr Otorhinolaryngol, 2012. **76**(9): p. 1292-6.
5. Shah, U.K., et al., *Otologic management in children with the CHARGE association.* Int J Pediatr Otorhinolaryngol, 1998. **44**(2): p. 139-47.
6. Bauer, P.W., et al., *Cochlear implantation in children with CHARGE association.* Arch Otolaryngol Head Neck Surg, 2002. **128**(9): p. 1013-7.
7. Lanson, B.G., et al., *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes.* Laryngoscope, 2007. **117**(7): p. 1260-6.
8. Ricci, G., et al., *Cochlear implantation in children with "CHARGE syndrome": surgical options and outcomes.* Eur Arch Otorhinolaryngol, 2013.
9. Birman, C.S., et al., *CHARGE syndrome and Cochlear implantation: Difficulties and outcomes in the paediatric population.* Int J Pediatr Otorhinolaryngol, 2015.
10. Ricci, G., et al., *Cochlear implantation in children with "CHARGE syndrome": surgical options and outcomes.* Eur Arch Otorhinolaryngol, 2014. **271**(3): p. 489-93.
11. Holcomb, M.A., Z. Rumboldt, and D.R. White, *Cochlear nerve deficiency in children with CHARGE syndrome.* Laryngoscope, 2013. **123**(3): p. 793-6.
12. Vesseur, A., et al., *Influence of hearing loss and cognitive abilities on language development in CHARGE Syndrome.* Am J Med Genet A, 2016.
13. Vesseur A.C., et al., *CT Findings of the Temporal Bone in CHARGE Syndrome: Aspects of Importance in Cochlear Implant Surgery* Eur Arch Otorhinolaryngol (in press), 2016.
14. Bayley, N., *Bayley Scales of Infant Development Manual.* 1993, The Psychological Corporation: San Antonio.
15. Tellegen, P.J., et al., *Snijder-Oomen Niet-verbale intelligentietest SON-R 2½5-7. Verantwoording en handleiding.* 1998, Hogreve uitgevers.: Amsterdam, The Netherlands.
16. Scheider, M.J., G.M.P. Loots, and J. Reuter, *Kent Infant Development Scale. Nederlandse bewerking. Handleiding.* 1990, Swets en Zeitlinger: Lisse, The Netherlands.
17. Bosman, A.J., *Speech perception by the hearing impaired.* 1989.
18. Zink, I. and D. Lembrechts, *NNST Nederlandstalige Nonspeech Test.* 2000, Uitgeverij Acco: The Netherlands.
19. Eldik, M.C.M., et al., *Handleiding Reynell Test voor Taalbegrip.* 1997, Berkhout BV: Nijmegen, The Netherlands
20. Bon, W.H.J.v. and J.G. Hoekstra, *TvK (Taaltest voor Kinderen).* 1992, Pearson Assessment and Information B.V. .
21. Dunn, L.M. and L.M. Dunn, *Peabody Picture Vocabulary Test-III-NL (PPVT-III-NL).* 2005, Pearson Assessment and Information B.V.
22. Schlichting, L. and H. Spelberg, *Schlichting Test voor Taalbergip.* 2010, Bohn Stafleu van Loghum: The Netherlands.
23. Kubba, H., I.R. Swan, and S. Gatehouse, *The Glasgow Children's Benefit Inventory: a new instrument for assessing health-related benefit after an intervention.* Ann Otol Rhinol Laryngol, 2004. **113**(12): p. 980-6.
24. Hinderink, J.B., P.F. Krabbe, and P. Van Den Broek, *Development and application of a health-related quality-of-life instrument for adults with cochlear implants: the Nijmegen cochlear implant questionnaire.* Otolaryngol Head Neck Surg, 2000. **123**(6): p. 756-65.
25. Varni, J.W., M. Seid, and P.S. Kurtin, *PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations.* Med Care, 2001. **39**(8): p. 800-12.
26. Stack, C.G. and R.K. Wyse, *Incidence and management of airway problems in the CHARGE Association.* Anaesthesia, 1991. **46**(7): p. 582-5.
27. Chowdhury, F., et al., *Postintubation arytenoid dislocation/subluxation in CHARGE infants.* Paediatr Anaesth, 2014. **24**(2): p. 225-7.
28. Corsten-Janssen, N., et al., *The cardiac phenotype in patients with a CHD7 mutation.* Circ Cardiovasc Genet, 2013. **6**(3): p. 248-54.

29. Giesemann, A.M., et al., *Persistent petrosquamosal sinus: high incidence in cases of complete aplasia of the semicircular canals.* Radiology, 2011. **259**(3): p. 825-33.
30. Arndt, S., et al., *Management of cochlear implantation in patients with malformations.* Clin Otolaryngol, 2010. **35**(3): p. 220-7.
31. Janssen, N., et al., *Mutation update on the CHD7 gene involved in CHARGE syndrome.* Hum Mutat, 2012. **33**(8): p. 1149-60.

Supplement 1

Receptive language study group

	Follow up (months)																				
	0	0	0	6	6	6	12	12	12	24	24	24	36	36	36	60	60	60	120	120	120
NR	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**
1	N	12	11	N	17	13,5	N	34	18	N	48	14	R	58	15	R	79	27			
2	N	22	15	N	33	22	R	43	28				R	68	34	R	86				
3	N	33	14				R	54	24	R	65	29	R	77	31	R	97	46	P	158	75
4	R	67	30				R	81	31	R	95	33	R	108	39						
5										R	105	17	R	120	19	R	139	13			
6																					
7																					
8				N	33	11	N	51	12							R	81	30			
9	N	38	18																		
10	N	12	11																		

age in months; LA: language age in months; N: NNST; P: Peabody; R: Reynell

Expressive language study group

	Follow up																	
	0	**0**	**0**	**6**	**6**	**6**	**12**	**12**	**12**	**24**	**24**	**24**	**36**	**36**	**36**	**60**	**60**	**60**
NR	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**	**TEST**	**Age**	**LA**
1	N	12	11	N	17	16,50	N	34	18	N	48	22				S	79	18
2	N	22	18	N	33	22	S	43	24				S	68	40	S	86	48
3	N	33	18				S	54	18	S	65	23	S	77	30	S	97	47
4	S	67	23				S	81	29	S	95	37	S	108	42			
5																S	139	14
6																		
7																		
8				N	33	11	N	51	16	N	52	17						
9	N	38	18															
10	N	12	11															

age in months; LA: language age in months; ; N: NNST; S: Schlichting

Supplement 2

Receptive language control group (non-syndromic)

	Follow up (months)																	
	0	**0**	**0**	**12**	**12**	**12**	**24**	**24**	**24**	**36**	**36**	**36**	**60**	**60**	**60**	**120**	**120**	**120**
ID	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**
D1	N	23	21	R	41	42	R	53	58	R	66	76	P	87	99			
D2	R	48	30	R	63	45	R	76	64									
D3	R	82	28	R	100	41	T	112	57	P	127	72	P	146	71			
D4	T	85	63							P	126	112						
D5	R	76	27	R	94	31	R	111	38				T	145	112	P	206	171
D6	T	93	76	T	121	95				T	134	121				T	218	218
D7													P	246	93			
D8																		
D9	R	33	13				R	54	23	P	77	35						
D10	R	58	28	R	74	46	T	86	76	T	99	97	T	120	113			
D11	N	7	11	R	26	18	R	45	29	R	58	45	P	72	75			
D12	R	31	11	R	30	26	R	41	33	R	51	48						
D13	R	27	15				R	55	24	R	67	27	R	100	44			
D14																		
D15																		
D16				R	69	38	R	83	50	R	94	59	T	120	96			
D17																		
D18										R	80	39						
D19																		
D20				R	117	36	R	90	36	R	103	43	R	126	67			
D21	R	133	33															
D22	R	47	23				T	94	73				T	125	102			
D23				R	48	26	R	58	30	R	73	40						
D24										R	133	31						
D25										R	175	41						
D26	R	105	30				T	137	95	T	147	161						
D27	N	18	21	R	35	32							P	80	79			
D28	N	32	22				R	58	35	P	69	46						
D29	N	7	8	R	21	14	R	38	28	R	51	41	P	71	78			
D30	N	11	11	N	27	12	R	40	26	P	50	49						
D31	N	9	11	R	23	21	R	40	32	P	57	51	P	73	81			
D32	N	19	18	R	34	26	R	46	41	R	59	51	P	80	67			
D33				R	36	24	R	46	38	R	60	53	P	86	89			
D34	N	16	11	N	31	12	R	43	25	R	55	33	T	77	75	P	141	144

Age: in months; LA: language age in months; N: NNST; P: Peabody; R: Reynell; T: tvk (taaltest voor kinderen, Dutch Language test)

Expressive language control group (non-syndromic)

	Follow up (Months)																	
	0	**0**	**0**	**12**	**12**	**12**	**24**	**24**	**24**	**36**	**36**	**36**	**60**	**60**	**60**	**120**	**120**	**120**
ID	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**	**Test**	**Age**	**LA**
D1	N	23	22				S	53	55	S	66	75						
D2	S	48	35	S	63	46	S	76	73									
D3	S	82	29	S	100	43	T	112	66									
D4				T	101	61												
D5	S	76	30	S	94	36	S	111	43				T	145	73	P	206	171
D6	T	93	71	T	121	99				T	134	121						
D7																		
D8																		
D9							S	54	20									
D10	S	58	23	S	74	47	T	86	66	T	99	80	T	120	121			
D11	N	7	11	S	26	21	S	45	32	S	58	40	P	72	87			
D12				S	30	20	S	41	30	S	51	36						
D13							S	55	18	S	67	28	S	100	40			
D14																		
D15																		
D16				S	69	47	S	83	75	T	94	75	T	120	95,5			
D17																		
D18										S	80	39						
D19																		
D20																		
D21																		
D22	S	47	25				T	94	73				T	125	102			
D23							S	58	34	S	73	50						
D24										S	133	44						
D25										S	175	34						
D26	S	105	46				T	137	74	T	147	90						
D27	N	18	21	S	35	36	S	51	48									
D28	N	32	22	S	45	22	S	58	28									
D29	N	7	8	S	21	20	S	38	28	S	51	40						
D30	N	11	11	N	27	19	S	40	26	S	50	31						
D31	N	9	11	S	23	22,5	S	40	34	S	57	52						
D32	N	19	18	S	34	25	S	46	39	S	59	52						
D33				S	36	23,5	S	46	35	S	60	58						
D34	N	16	11	N	31	18	S	43	23	S	55	37	T	77	53	P	141	144

Age: in months; LA: language age in months; N: NNST; P: Peabody; R: Reynell; S: Schlichting; T: tvk (taaltest voor kinderen, Dutch Language test)

Supplement 3

Patient characteristics and language age control group (patient with CHARGE syndrome without CI)

NR	IQ	Hearing loss	Test	Receptive test age	Receptive language age	Test	Expressive test age	Expressive language age
c7	<70	severe	NNST	23	12	NNST	23	12
c10	<70	mild	Reynell	302	18			
c12	70-85	severe	Peabody	274	34			
c16	<70	moderate	Reynell	34	25			
c20	<70	moderate	Peabody	171	27			
c30	70-85	normal	Reynell	62	69	Schlichting	63	56
c35	70-85	normal	Reynell	54	43	Schlichting	39	38
c40	70-85	mild	Reynell	39	32	Schlichting	39	30
c41	70-85	mild	Reynell	39	34	Schlichting	39	34
c44	<70	moderate	Reynell	113	21			
c53	<70	mild	Reynell	65	42		65	44
c55	<70	mild	TVK	194	87	TVK		
c57	<70	mild	Peabody	127	55	Peabody	127	66

TVK: taaltest voor kinderen (Dutch language test)

Supplement 4

Results of the step-wise regression analysis of the GCBI scores. CHARGE syndrome versus control group (non-syndromic)

GCBI	Total	Emotion	Physical	Learning	Vitality
(Constant)	33.897	34.040	19.376	46.122	32.797
Diagnosis	7.838	6.585	13.659	8.043	5.953

B-values: regression coefficients of the regression model of the total GCBI score and the different subdomain scores.

Results of the step-wise regression analysis of the PedsQL scores. CHARGE versus control group (non-syndromic).

PedsQL	Total	Physical	Psychosocial	Emotional	Social	School
(Constant)	88.784	94.974	85.357	78.850	82.099	88.116
Diagnosis	-26.828**	-7.474	-22.580*	-23.850*	-30.991**	-13.116
IQ 71-85[a]		-81.250				
CI use: 4-6 hours/day[b]		81.250				
CI use: 12-16 hours/day[c]					10.837	
CI use: >16 hours/day[d]	-21.744	-15.954	-24.712		-29.599	-26.451

*p<0.005, **p<0.001

B-values: regression coefficients of the regression model of the total PedsQL score and the different subdomain scores.

[a] B-values of the IQ 71-85 group compared with the other IQ subgroups.

[b] B-values of the CI use 4-6 hours/day group compared with the other CI use subgroups.

[c] B-values of the CI use 12-16 hours/day group compared with the other CI use subgroups.

[d] B-values of the CI use >16 hours/day group compared with the other CI use subgroups.

Results of the step-wise regression analysis of the NCIQ scores. CHARGE syndrome versus control group (non-syndromic).

NCIQ	Physical			Psychological	Social	
	Sound perception basic	Sound perception advanced	Speech production	Self esteem	Activity limitations	Social interactions
(Constant)	70.001	91.794	59.006	83.791	87.059	84.693
Diagnosis	-16.464*	-28.461***	-21.613**	-11.931	-1.504	-7.193
IQ 71-85[a]					-25.555	-25.000
IQ above average[b]		-10.597				
CI use: 4-6 hours/day[c]		-38.333				
CI use: 6-9 hours/day[d]		-30.146		-21.791		
CI use: 12-16 hours/day[e]	12.914		15.477			
CI use: >16 hours/day[f]					-16.879	

*p<0.05, **p<0.005, ***p<0.001

B-values: regression coefficients of the regression model of the NCIQ subdomain scores.

[a] B-values of the IQ 71-85 group compared with the other IQ subgroups.

[b] B-values of the IQ above average group compared with the other IQ subgroups.

[c] B-values of the CI use 4- 6 hours/day group compared with the other CI use subgroups.

[d] B-values of the CI use 6-9 hours/day group compared with the other CI use subgroups.

[e] B-values of the CI use 12-16 hours/day group compared with the other CI use subgroups.

[f] B-values of the CI use >16 hours/day group compared with the other CI use subgroups.

2.4

Hearing restoration in cochlear nerve deficiency: the choice between cochlear implant or auditory brainstem implant

Published as:
Hearing Restoration in Cochlear Nerve Deficiency: The choice between Cochlear Implant or Auditory Brainstem Implant, a meta-analysis. Vesseur AC, Free RH, Snels C, Dekker F, Mylanus EA, Verbist BM, Frijns J *Otology & Neurotology 2018 Apr:39(4):428-437*

Abstract

Objectives

To answer the dilemma clinician's face when deciding between cochlear implant (CI) and auditory brainstem implant (ABI) treatment options in patients with cochlear nerve deficiency (CND).

Material and Methods

In this study, a case study is supplemented with literature review and meta-analysis. The case study describes a child with CHARGE syndrome and congenital deafness. The child received an ABI as there was no benefit after bilateral cochlear implantation. Speech and language development and quality of life were the main outcome measurements.

Results

In one ear the cochleovestibular nerve was present on MRI without preoperative ABR responses. In the contra lateral ear the nerve could not be identified, despite present ABR responses. Nevertheless, there was no positive outcome with CI. The patient had positive changes to speech and language and quality of life with ABI.

Of the 108 cases of patients with CND and CI identified in the literature review, 25% attained open-set speech perception, 34% attained closed-set speech perception and 41% detected sounds or less. The aspect of the cochlear nerve on MRI was a useful predictor of success, with cochlear nerve aplasia on MRI associated with a smaller chance of a positive outcome post cochlear implantation compared to patients with cochlear nerve hypoplasia.

Conclusions

Although patients with (apparent) cochlear nerve aplasia are less likely to benefit from CI, CI prior to ABI is supported as some patients attain closed or open-set levels of speech perception after cochlear implantation.

Introduction

Cochlear implantation is a well-established surgical treatment to restore hearing in patients with a severe to profound hearing loss. This procedure can result in improved auditory skills, especially when performed early in children with congenital deafness. However, in some children a cochlear implant (CI) has no or minimal effect on speech and language development. One reason for this variation in CI outcomes is cochlear nerve deficiency (CND) [1-16]. CND is caused by inadequate development of the cochlear nerve and the nerve is partially developed (termed hypoplasia) or is absent (termed aplasia). An alternative treatment for patients with CND and no effect of cochlear implantation is an auditory brainstem implant (ABI), although the likelihood of ABI success is difficult to predict, and generally worse than with CI [17].

During the pre-operative screening stage for a child with CND, it is important to consider the likely outcome of cochlear implantation and whether an ABI or a CI will provide the child with the best outcome. Various pre-operative diagnostic tools are used to diagnose CND. Observing the small diameter of the internal auditory canal (IAC) and/or bony cochlear nerve canal (BCNC, synonymous with cochlear aperture) on CT could indicate CND [18,19], however, a normal IAC diameter is not a reliable marker for a normally developed cochlear nerve [20]. The aspect of the cochleovestibular nerve (CVN) and cochlear branch can be assessed on MRI [18,21]. Imaging in combination with auditory tests such as (aided) hearing thresholds, (electrically evoked) auditory brainstem responses ((e)ABRs) and oto-acoustic emissions (OAEs) have a prognostic value [21,22] but the presence of the CVN must be considered when there is no CVN visible (MRI) or measurable (audiometric tests) on pre-operative evaluations [23].

Hearing loss due to CND is frequently seen in patients with CHARGE syndrome [24]. The major features of CHARGE syndrome are choanal atresia, and malformations of the heart, the inner ear and the eye [25]. Most children with CHARGE syndrome (with or without CND) who have undergone cochlear implantation achieve varying but limited levels of auditory benefit, after implantation [26,27].

The aim of this study was to answer to the question: When should CI and when should ABI be considered the primary treatment option for children with CND? To illustrate this dilemma, we present a case study of a child with CHARGE syndrome who had no benefit from bilateral cochlear implantation and required an ABI for hearing restoration. During case evaluation several steps in the decision process were questioned. This was the motivation for a literature review and meta-analysis on this topic to provide an evidence-based therapeutic strategy in future cases.

Material and Methods

Case study

After the parents of the child in this case study provided written informed consent, the child's medical, audiological, radiological and surgical data were gathered and reviewed by the authors. The child had CHARGE syndrome and one of the characteristics included a profound sensorineural hearing loss (see *table 2 for full list of characteristics).* She had undergone sequential bilateral cochlear implantation but both were without benefit. After consideration of the treatment options, an ABI was recommended.

Postoperative ABI evaluations included pure-tone audiometry, the Dutch version of the Speech Intelligibility Rating (SIR-NL)[28], the Categories of Auditory Performance (CAP) [29], the Infant-Toddler Meaningful Integration Scale (IT-MAIS) [30] and the Meaningful Use of Speech Scale (MUSS) [31].

Three quality of life (QoL) questionnaires were used to measure the QoL after ABI: the Glasgow Children's Benefit Inventory (GCBI) [32], the Nijmegen Cochlear Implant Questionnaire (NCIQ) [33] and the Paediatrics Quality of Life Measurement (PedsQL) [34]. The GCBI is designed to measure changes in QoL after an intervention and the PedsQL measures general health-related QoL. The NCIQ is a disease-specific health-related QoL tool developed for use in CI. Although the NCIQ has not been validated for patients with an ABI, the results might give an indication in these patients.

Literature review

This literature review was performed considering the MOOSE criteria [35]. The criteria were adhered to where possible. We searched PubMed database and the Cochrane Database of Systematic Reviews for studies published, in the English language, with the following search terms: cochlear nerve AND/OR deficiency, CI, ABI, magnetic resonance imaging (MRI) and computed tomography (CT). The time period was not specified. This search resulted in 618 identified papers. The primary author reviewed all titles and abstracts. The full article was reviewed if inclusion or exclusion criteria could not be decided based on title and abstract alone. An additional search was performed on the reference lists of the included studies. Studies with information in the title and abstract indicating the paper focussed on surgery, animals, unilateral hearing loss, general anomalies, vestibular anomalies and questionnaire studies were excluded (n=550). All papers with a detailed (per patient) description of the results of cochlear implantation in patients with CND on MRI were retained (n=15), no assessments of confounding, heterogeneity and study quality were performed. The presented case study is not included in meta-analysis.

Demographics

An overview of the 15 selected studies is listed in *Table 1.* Walton et al. [4] and Jeong et al. [12] described numerous patients with auditory neuropathy. In these two papers,

Table 1 Overview of papers included in literature review listed by publication year.

First author	Publication year	Number of patients	Patient selection	Aetiology, cognitive development	Mean implantation age (months)	SD implantation age (months)
Govaerts (2)	2003	4	CND with CI	1 considered CD (sounds)	60	49
Zanetti (3)	2006	1	CND with CI		29	
Walton (4)	2008	15	CND with CI selected from a group with auditory neuropathy and CI	Different aetiologies, 1 CD (sounds)	44	
Oker (5)	2009	2	CND with CI	1 CHARGE (closed set)	25	12
Kang (6)	2010	6	CND with CI	No info	19	9
Warren (7)	2010	3	CND with CI	Different aetiologies	34	13
Kutz (8)	2011	9	CND with CI	No info	61	43
Zhang (10)	2012	9	CND with CI	2 CD (open set)	26	13
Young (9)	2012	10	CND with CI	Different aetiologies	31	15
He (11)	2012	7	CND with CI with 3 non-CND controls*	No info	55	33
Jeong (12)	2013	5	CND with CI selected group from auditory neuropathy	No info	60	43
Vincenti (13)	2014	5	CND with CI	Different aetiologies, 1 CD (closed set)	26	7
Wu (14)	2015	15	Selected from a group of patients with CND, with and without CI	No info	58	34
Birman (15)	2015	7	CND with CI selected from a group of patients with CHARGE syndrome		20	14
Chao (16)	2016	10	CND with CI	No co-morbidities	62	42

* controls were not described in this study; No: number, SD: standard deviation; CD cognitive delay; CI: cochlear implant; CND: cochlear nerve deficiency

the information included in this literature review was restricted to the subset of patients with CND. In the remaining 13 studies, only the cases that identified an aplastic or hypoplastic cochlear nerve on MRI were included.

Patients underwent MRI with field strength 1.5 Tesla in all studies except Kang et al. [6], which used 3 Tesla. All studies included axial T2-weighted images that were reconstructed in a coronal oblique plane for assessment of the cochlear nerve (0.7-1mm slice thickness, or not reported). In those studies were CT technique was specified, high-resolution CT (HRCT) was performed, using a bone algorithm technique. Images were acquired with slice thickness of 0.7-1mm with targeted magnified reconstruction. The definitions used by the authors to assess the cochlear nerve, CVN, BCNC and IAC are listed in *supplement 1*.

Each included paper reported the outcome of cochlear implantation per individual patient. Based on the conducted tests, the patients were categorized in either 'open-set', 'closed-set' or 'sounds' (see *supplement 2*). If these test results were not available (34 of the 108 patients), patients were categorized based on the description of the results.

The following pre-operative (diagnostic) data were included in the analysis: age at implantation, hearing thresholds, aided hearing thresholds, ABR thresholds, pre-operative eABR responses, presence and size of the IAC and BCNC on CT, and presence and size of the cochlear nerve and CVN on MRI.

Statistical analysis

SPSS statistics 22 (IBM Corp, Armonk, NY) was used for statistical analyses. Descriptive statistics were used to define baseline characteristics. Continuous data was normally distributed and univariate analyses were performed using Fisher exact-tests and independent sample *t*-tests. The 'relative risk' (RR) indicates the probability of a patient to have 'open set' divided by the probability to have 'closed set' speech perception after implantation, based on the outcomes of the pre-operative diagnostic tools. This relative risk with its 95% Confidence Interval (CI) is used to identify indicators of future success.

Results

Case study

Characteristics

Our patient is a 10-month old girl who was diagnosed with (atypical) CHARGE syndrome at the age of 10 months. The diagnosis 'CHARGE syndrome' was confirmed by the mutation (8077-1G>A) in the *CHD7* gene. *Table 2* lists the characteristics of the patient. She was born without complications to Dutch-speaking parents after 41 weeks of gestation and had an APGAR score of 10. At age three months, the child was diagnosed with congenital severe sensorineural hearing loss and was fitted with hearing aids. Her parents reported the child responded to sounds when wearing the hearing aids, however

the child demonstrated neither effective hearing nor signs of oral language development. Neurodevelopmental assessment at age three years and five months reported below average developmental abilities and a non-verbal IQ of 69.

Table 2 Characteristics of a patient with CHARGE syndrome

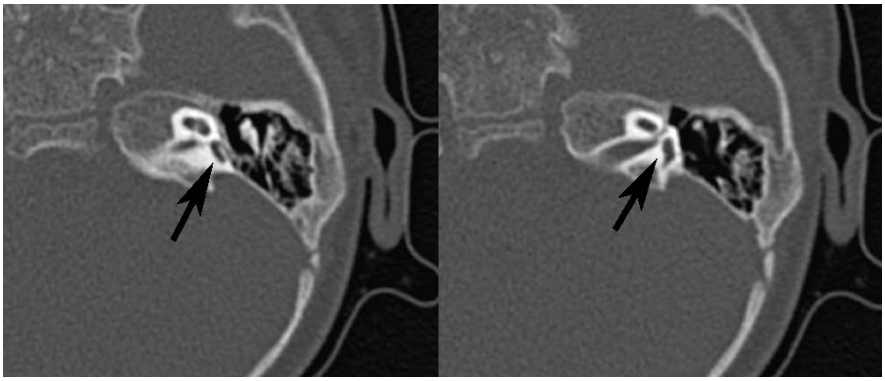
C	Hypermetropia
H	Atrial septal defect, ventricle septal defect, small open ductus arteriosus
A	No choanal atresia
R	Cognitive disability (subnormal), facial nerve palsy
G	No genital hypoplasia
E	Congenital deafness, severe dysplastic vestibular canals, low ear implant

Pre-operative evaluation

Repeated ABR showed no responses to stimuli on the right ear and variable results to stimuli on the left ear, namely atypical responses at 75dB HL and 90dB HL at 3kHz.

Pre-operative MRI indicated the right cochlear nerve was present but the left cochlear nerve could not be identified. The IAC was bilaterally hypoplastic. CT showed bilateral hypoplasia type III [36] of the cochlea and dysplasia of the semicircular canals (see *Figure 1a*). The BCNC was not described separately, but the report mentioned a remarkably sclerotic boundary of the cochlea on both sides.

Figure 1a



Hypoplastic vestibulum and aplastic semicircular canals (black arrow) (CT, slice thickness of 0.75mm)

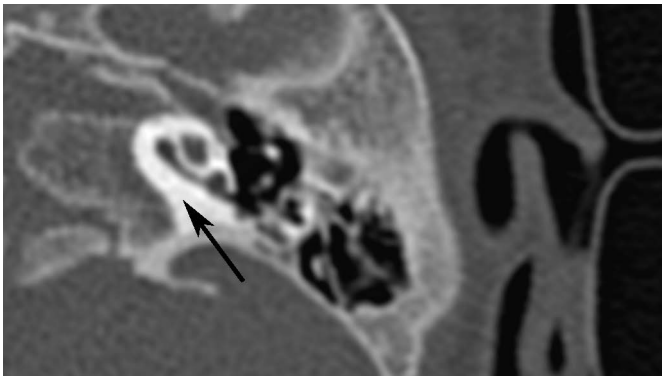
Cochlear implantation

The patient received a CI (Nucleus Freedom) in the right ear at age one year and two months because of lack of effective hearing using hearing aids. The right ear was selected as this was the side with a cochlear nerve (confirmed on MRI) but had no measurable responses to pre-operative ABR. The procedure was performed via a transmastoidal approach with cochleostomy. There were no complications during surgery and post-operative CT confirmed full insertion was achieved. During surgery, impedance measurements were good, but no neural response telemetry (NRT) responses were observed. A year after implantation, the child did not demonstrate reliable responses to sounds when using the CI in combination with a contralateral hearing aid. The patient communicated with sign language only.

Subsequently, it was decided to implant the contralateral (left) ear with the same device as the first at the age of three years and one month because of the absence of auditory benefit of the first CI. There was an assumed presence of the cochlear nerve on the left side because of the varying ABR responses measured. There were no complications during the second CI surgery and impedance measurements and intra-operative NRT responses were obtained over all electrodes.

At follow-up 13 months after the second implantation, no responses, auditory benefit or oral speech and language development were observed. At age four years and three months, three years and one month after the first CI and 13 months after the second CI, the child was referred to the Leiden University Medical Centre for ABI.

Figure 1b

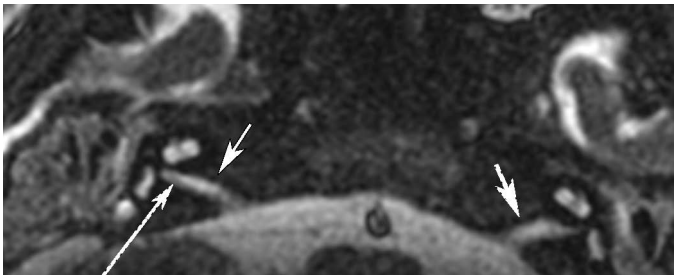


Stenotic cochlear aperture/bony cochlear nerve canal left (black arrow) (CT, slice thickness of 0.75mm)

Auditory brainstem implant

Re-evaluation of the pre-operative CT and MRI indicated bilateral stenotic BCNC *(see Figure 1b)* without a visible cochlear nerve in both IACs *(see Figure 1c)*. A thin CVN was identified on the right side at the cerebellopontine cistern.

Figure 1c



Bilateral small internal auditory canal and absent nerve (big white arrowhead; thin white arrow is the right facial nerve) (MRI, 1.5 Tesla, slice thickness of 0.3mm)

At age of four years and six months, in a single surgical session the receiver-stimulator of the right CI was removed (array was left in the cochlea) and the ABI (MedEl, Synchrony pin) was inserted into the right side. The right side was selected as ABI site because the presence of the thin CVN in the cerebellopontine cistern indicated potential of a well-developed cochlear nucleus. The ABI was implanted via a retrosigmoidal craniotomy approach. After opening the dura, the lateral recess of the fourth ventricle was located by tracking the vagal and accessory nerves and identifying the facial nerve. The final electrode paddle was placed after good bipolar eABR responses with the test electrodes. Good responses of all twelve final electrodes were found on monopolar and bipolar stimulation. The surgery was without complications.

Performance with ABI

In the first months, five electrodes were switched off because of non-auditory stimulation or limited auditory responses. Nine months after surgery, responses were observed with seven active electrodes on warble sounds at 45-50dB HL at 500Hz-1-2-4 kHz and 30-40dB HL two years after surgery *(Figure 2)*. The child used the ABI almost every day, responded to her name and to sounds and was sometimes vocalizing while communicating in sign language. Results of the IT-MAIS, the SIR-NL, CAP-NL and MUSS-NL are listed in *Table 3*. Formal testing indicated that language production was barely present and the child's ability to identify words was limited.

Figure 2 Post ABI audiometry

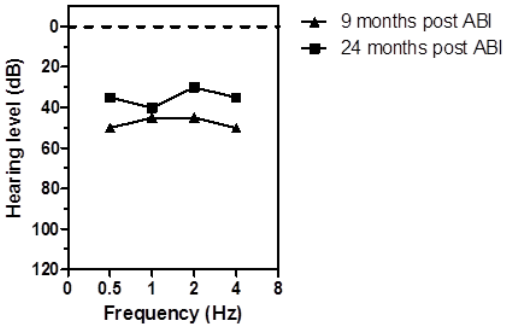


Table 3 ABI results of the case report

Months after ABI implantation	IT-MAIS	SIR-NL	CAP-NL	MUSS-NL
2	2/40	-	-	-
3	7/40	-	-	-
9	20/40	1/5	3/7	9/40
24	19/40	2/5	3/7	8/40

ABI: auditory brainstem implant; CAP: Categories of Auditory Performance; MUSS: Meaningful Use of Speech Scale; IT-MAIS: Infant-Toddler Meaningful Integration Scale; SIR: Speech Intelligibility Rating.

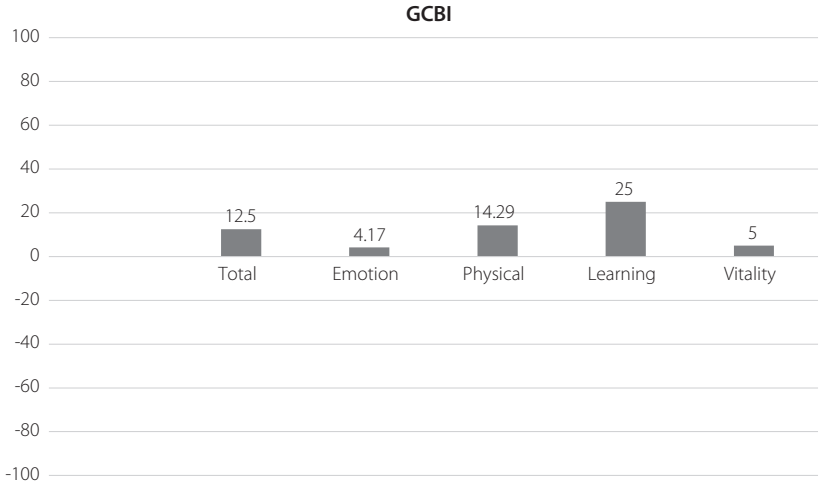
Quality of life

The child's parents completed QoL-questionnaires 14 months after ABI surgery when the child was aged five years and eight months. The results of the GCBI, NCIQ and PedsQL questionnaires are displayed in *Figure 3*. The GCBI results indicated improved QoL post ABI and PedsQL results indicated that the patient had a high general QoL.

Literature review

Figure 4 illustrates widely varying CI outcomes in patients with CND. Of the total number of patients (n=108), 27 (25%) attained 'open-set' speech perception, 37 (34%) attained 'closed-set' speech perception and 44 (41%) attained sound detection only. The influence co-morbidity and cognitive delay on the outcome of CI could not be assessed, because the published studies lacked detailed patient information.

Figure 3 Quality of life



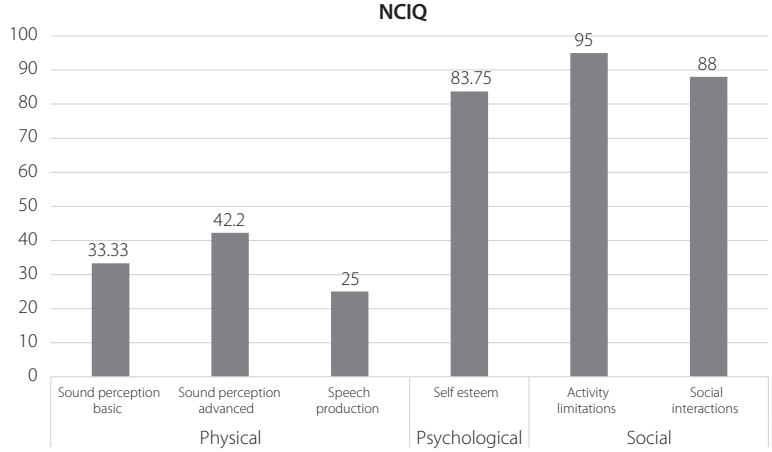


Figure 3 Continued

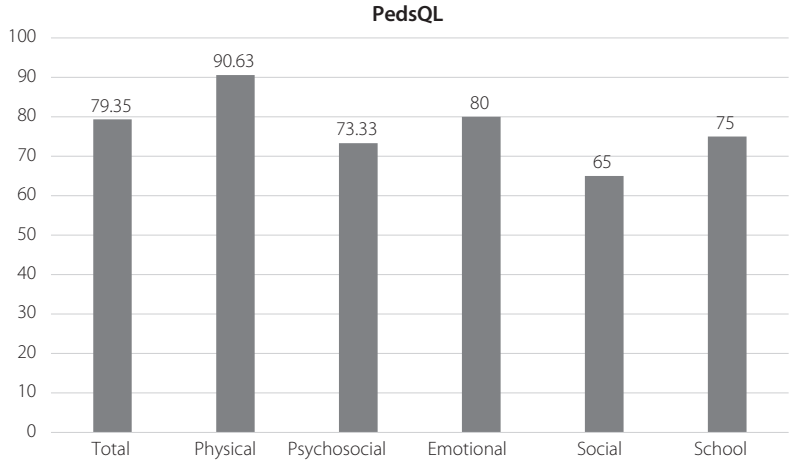
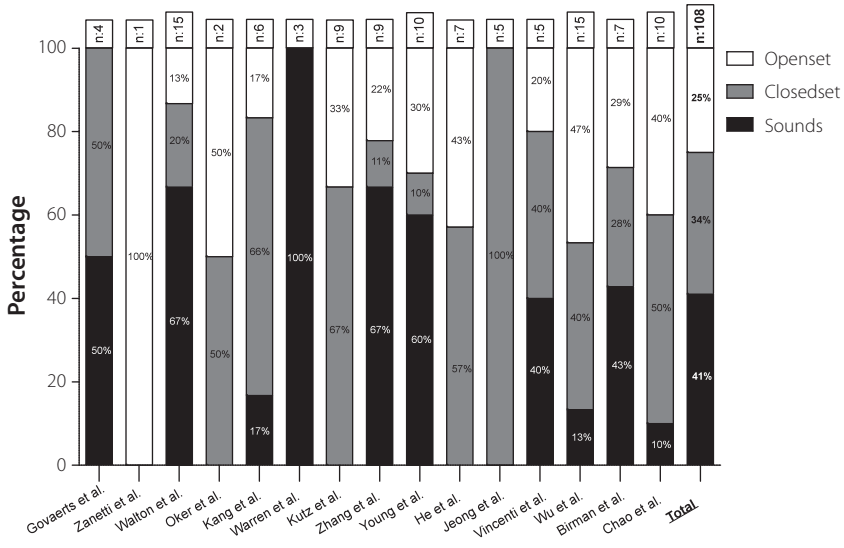


Figure 4 Literature review results, presented by publication year



The patients with 'open-set' and 'closed-set' speech perception were pooled for further analysis. The outcomes of 64 patients (59%) of this so-called 'speech perception group', were compared to the 44 (41%) patients who could detect sounds, called the 'sound perception group'. *Table 3a* lists the results of the analyses of the different diagnostic tools, used in pre-operative screening for CI. The outcomes of the pre-operative diagnostic tools were tested whether the scores differed between the two groups, to be able to identify indicators of future success. The age at implantation had a wide distribution, and is not significantly different between the two groups (independent sample *t*-test). More patients with an aplastic cochlear nerve on MRI fell within the 'sound perception group' compared to patients with a hypoplastic cochlear nerve on MRI (Fisher exact-test, $p<0.05$). The outcome of the other pre-operative tests were not different between the two groups ($p>0.05$). A normal CVN on MRI could not be proven to be a valid predictor of success (speech perception) with cochlear implantation, as the relative risk for success ranged between 0.38 and 4.68 (*Table 4a)*.

Table 4b lists the relationship between the aspect of the BCNC and the cochlear nerve on MRI. More patients with a normal BCNC had a hypoplastic cochlear nerve than patients with an absent BCNC ($p<0.05$). Note that four patients with a normal BCNC had an aplastic cochlear nerve and one patient was without BCNC and had a hypoplastic cochlear nerve.

Table 4a Potential predictors of outcome of CI

Potention predictors	Values	Sound perception	Speech perception	RR	RR 95%-CI	*p*-value RR
Implantation age (months) (n = 93)	Mean age	42.9 (SD 34.5)	44.5 (SD 32.8)			0.82†
Cochlear nerve (n: 91)	Aplastic	30	32	1		
	Hypoplastic	7	22	2	1.00-4.01	0.04*∫
	Total	*37*	*54*			
Cochleovestibular nerve (n:40)	Abnormal/absent	3	6	1		
	Hypoplastic	8	7	0.63	0.22-1.77	0.42∫
	Normal	4	12	1.33	0.38-4.68	0.67∫
	Total	*15*	*25*			
Internal auditory canal (n: 62)	Small	18	23	1		
	Normal	9	12	1.02	0.56-1.87	1∫
	Total	*27*	*35*			
Bony cochlear nerve canal (n:51)	Absent	8	11	1		
	Small	7	16	1.38	0.61-3.12	0.52∫
	Normal	3	6	1.26	0.44-3.66	1∫
	Total	*18*	*33*			
OAE (n: 45)	Absent	12	31	1		
	Present	1	1	0.56	0.13-2.41	0.50∫
	Total	*13*	*32*			
ABR (n: 59)	No response	13	36	1		
	Abnormal/absent	0	5	-1	-1-1	
	Some response	1	4	1.36	0.22-8.14	1∫
	Response	0	0			
	Total	*14*	*45*			
Hearing thresholds (N: 17)	No response	1	0			
	Response	7	9	-		
	Total	*8*	*9*			
Aided hearing thresholds (n: 52)	No response	7	4	1		
	Vibrotactil	4	1	0.80	0.43-1.49	1∫
	Response	13	23	1.75	0.95-3.29	0.16∫
	Total	*24*	*28*			
eABR (N: 37)	No response	6	2	1		
	Abnormal/absent	10	5	1.13	0.66-1.92	1∫
	Some response	1	3	2.67	0.47-15.11	0.26∫
	Response	4	6	1.88	0.79-4.42	0.19∫
	Total	*21*	*16*			

* statistically significant result; †: independent sample t-test; ∫: 2-tailed Fisher Exact; ABR: auditory brainstem response; CI: confidence interval; eABR: electrical ABR; OAE: oto-acoustic emissions; RR relative risk;

Table 4b Presence of bony cochlear nerve and cochlear nerve on MRI

Bony cochlear nerve canal	Cochlear nerve on MRI		RR	95%- CI	*p*-value RR
	Aplastic	Hypoplastic			
Absent	17	1	1		
Small	13	6	1.38	1.00-1.91	0.09[ʃ]
Normal	4	5	2.12	1.01-4.45	0.01[ʃ]
Total	*34*	*12*			

BCNC: bony cochlear nerve canal; CI: confidence interval; ʃ: 2-tailed Fisher Exact; RR relative risk

Discussion

This study highlights the dilemma of cochlear implantation in patients with CND: Which pre-operative variables in patients with CND can indicate successful CI outcome. The case study highlighted that neither the presence of the CVN on MRI without pre-operative ABR responses on the same side nor lack of indication of the nerve on MRI but with ABR responses on the contralateral side lead to a positive hearing outcome post cochlear implantation. An ABI was a successful alternative treatment.

The review of literature indicated a variety of results of cochlear implantation in patients with CND: 25% of the patients attained open-set speech perception, 34% attained closed-set speech perception and 41% could detect sounds or less. The appearance of the cochlear nerve and presence of CVN on MRI, the diameter of the IAC and BCNC on CT, (e) ABR, (aided and unaided) pure tone audiometry and OAEs were the variables included in our analyses to identify differences between the groups in terms of CI success in patients with CND.

We found that patients with cochlear nerve aplasia on MRI had a smaller chance of attaining a good outcome of cochlear implantation than patients with cochlear nerve hypoplasia. This finding corroborates the findings presented in smaller cohorts reported in Kutz et al., Wu et al. and Birman et al. [8,14,22]. Note there were exceptions to this finding. None of the other investigated variables supported differences between the groups. This supports the notion that current imaging and audiometric testing limit the ability to identify predictors of CI success.

Because our results are not statistically significant, our study can not support the hypothesis that a normally developed CVN leads to better CI outcomes than an absent or abnormal CVN (one, two or three nerves in IAC) [21]. MRI is indispensible in the pre-operative cochlear implantation work-up. Nevertheless, it may be difficult to assess the nerves on current MRI, supported by the findings of Song et al. [23]. Song described a high correlation between the MRI assessment with the surgical findings regarding presence or

absence of the CVN, although one very thin CVN identified during ABI surgery was missed on MRI. However, the cochlear nerve itself could still be absent.

The studies in our literature review used clinical MRI field strengths of 1.5 or 3 Tesla and similar sequences and image resolution and there were no major changes in these settings over time. Further development of these settings and sequences may be helpful in diagnosing CND. Techniques such as high-resolution three-dimensional variable flip-angle turbo spin-echo sequence in combination with a surface coil [37], diffusion kurtosis imaging [38] or ultra high field imaging [39] could improve sensitivity of MRI to detect cochlear nerve fibres. The development of non-invasive diagnostic tools allowing investigation of the function of the auditory pathway, such as functional diffusion imaging techniques or functional MRI, would improve the identification of optimal therapeutic strategies.

In agreement with the findings of our literature review, multiple authors [19,20,40] reported that a narrow IAC or BCNC suggests a compromised auditory nerve. Nevertheless, the diameter of the IAC of BCNC does not always correlate with the presence or absence of the cochlear nerve.

Given that imaging does not provide answer to the CND dilemma, perhaps audiometric results or the combination of imaging with the audiometric results could provide better guidance. Of the studies identified in the literature review, ABR was used as a pre-operative diagnostic tool in 55% of the patients but none of these patients had normal responses and, thus, ABR could not be used as a predictive tool.

According to Kim et al. and Birman et al. [22,41], pre-operative extra-cochlear ABR could be more accurate to diagnose CND than ABR because of effective electric stimulation of the auditory pathway. Although pre-operative eABR was used in some of the reviewed studies [4,7,10,12,15], our analyses showed it could not predict the outcome of cochlear implantation. Yamazaki et al. [21] suggested that eABR testing during surgery in combination with the MRI findings is useful to predict postoperative auditory perception with CI, but precise discrimination between patients with poor, moderate or good outcomes might be difficult when either eABR or MRI is used alone. The disadvantage of the eABR during surgery with stimuli provided by the electrode is that cochlear implantation must be performed in order to perform eABR as the predictive (diagnostic) tool. Nevertheless a negative eABR could be used as an indicator for ABI after cochlear implantation.

Although positive results on implantation would be expected in patients with pre-operative responses on pure tone audiometry (aided or unaided), this was not supported by our meta-analysis. This might be due to the small numbers of patients.

We have considered the MOOSE criteria [35] and have tried to conform the manuscript as much as possible. Nevertheless, because of the scarce literature and several case studies we could not meet all criteria. In addition to the anatomy and physiology of the ear, factors such as co-morbidities, cognitive disability or age at implantation have significant impacts on the outcome with CI [22] and with ABI [42,43]. Our review provides little insight into the

aetiology of the CND or associated syndromes and cognition. No more than three studies described the presence of cognitive disabilities. We combined various definitions *(see SDC 2)* to categorize the outcomes of the diagnostics tools to allow us to analyse the studies together. Using these combinations caused some overlap in definitions, which could have biased our results. We (and the reviewed studies) focused on the cochlear (vestibular) nerve and disregarded other inner ear anomalies, despite the possibility that CND could be associated with other inner ear malformations (e.g. cochlear dysplasia or vestibular dysplasia). Inner ear anomalies could negatively influence the outcome of cochlear implantation [44]. This possible negative influence is not included in our meta-analysis. Despite the relatively large number of patients included in the meta-analysis (n=108), it remains a small sample and, as such, lacks statistical power. Multivariate analysis was not used because of the small sample size and the various pre-operative diagnostic tools across the studies.

ABI could be an alternative treatment for cochlear implantation in patients with CND. Although outcomes are generally worse for patients with an ABI than patients with a CI [17,45,46], with results in terms of vocalisation and alertness to sounds [47] and pattern perception [48]. However, open-set speech recognition [43,45] have been reported in children with ABI, especially for those without additional disabilities [43]. At this stage only short-term results are available for the case study, but the short-term results showed increased performance with ABI than with CIs. It is likely the results were negatively influenced by the relatively late age of ABI implantation (4;06 years) and the child's cognitive disability. Nevertheless, the child showed positive effect of ABI with positive scores on the GCBI. The PedsQL showed a good general quality of life with a total score above 65.4 (lower scores have an at-risk status for an impaired HR-QoL status) [34]. The NCIQ showed low scores on the physical domains in comparison to the scores on these domains in patients with CHARGE syndrome and CI [26]. However, the scores on the psychosocial and social domains were quite comparable [26]. The NCIQ results cannot be compared to normative data because normative data are not available.

Based on the results of the meta-analysis and with the knowledge of the poor bilateral CI results in this case study, opting to initial treatment using CI on the right side would still have been the likely therapeutic decision; the presence of the CVN in cerebello-pontine angle segment on the right side indicates that a cochlear nerve would be present but was too hypoplastic to observe on MRI. Studies showing good results of CI in seemingly cochlear nerve aplasia on MRI, cochlear implantation prior to ABI is advisable possibly in conjunction with eABR measurements during surgery. However, when there is no response with CI within several months, we believe the preferred course of action should be to proceed to ABI surgery on the same side and to avoid cochlear implantation on the left side. We base this decision on the limited chances for success of second implantation in this case and the desire to limit any further delay in auditory input, which negatively influences the potential for speech and language development.

Conclusion

Based on this case study and literature review meta-analysis, no compelling contraindications were identified for cochlear implantation in patients with CND. Although children with (apparent) cochlear nerve aplasia have decreased chances of successful implantation, there are examples of children described with cochlear aplasia on MRI who attain closed-set or open-set levels of speech perception months to years after implantation. When there is no success with this first CI, we recommend the treating team consider proceeding to an ABI rather than attempt a second CI and risk further delay in auditory input.

References

1. Noij KS, Kozin ED, Sethi Ret al. Systematic Review of Nontumor Pediatric Auditory Brainstem Implant Outcomes. *Otolaryngol Head Neck Surg* 2015;153:739-50.
2. Govaerts PJ, Casselman J, Daemers Ket al. Cochlear implants in aplasia and hypoplasia of the cochleovestibular nerve. *Otol Neurotol* 2003;24:887-91.
3. Zanetti D, Guida M, Barezzani MGet al. Favorable outcome of cochlear implant in VIIIth nerve deficiency. *Otol Neurotol* 2006;27:815-23.
4. Walton J, Gibson WP, Sanli Het al. Predicting cochlear implant outcomes in children with auditory neuropathy. *Otol Neurotol* 2008;29:302-9.
5. Oker N, Loundon N, Marlin Set al. Bilateral implantation in children with cochleovestibular nerve hypoplasia. *Int J Pediatr Otorhinolaryngol* 2009;73:1470-3.
6. Kang WS, Lee JH, Lee HNet al. Cochlear implantations in young children with cochlear nerve deficiency diagnosed by MRI. *Otolaryngol Head Neck Surg* 2010;143:101-8.
7. Warren FM, 3rd, Wiggins RH, 3rd, Pitt Cet al. Apparent cochlear nerve aplasia: to implant or not to implant? *Otol Neurotol* 2010;31:1088-94.
8. Kutz JW, Jr., Lee KH, Isaacson Bet al. Cochlear implantation in children with cochlear nerve absence or deficiency. *Otol Neurotol* 2011;32:956-61.
9. Young NM, Kim FM, Ryan MEet al. Pediatric cochlear implantation of children with eighth nerve deficiency. *Int J Pediatr Otorhinolaryngol* 2012;76:1442-8.
10. Zhang Z, Li Y, Hu Let al. Cochlear implantation in children with cochlear nerve deficiency: a report of nine cases. *Int J Pediatr Otorhinolaryngol* 2012;76:1188-95.
11. He S, Grose J, Hang AXet al. Cochlear implant-evoked cortical activation in children with cochlear nerve deficiency. *Otol Neurotol* 2012;33:1188-96.
12. Jeong SW, Kim LS. Auditory neuropathy spectrum disorder: predictive value of radiologic studies and electrophysiologic tests on cochlear implant outcomes and its radiologic classification. *Acta Otolaryngol* 2013;133:714-21.
13. Vincenti V, Ormitti F, Ventura Eet al. Cochlear implantation in children with cochlear nerve deficiency. *Int J Pediatr Otorhinolaryngol* 2014;78:912-7.
14. Wu CM, Lee LA, Chen CKet al. Impact of cochlear nerve deficiency determined using 3-dimensional magnetic resonance imaging on hearing outcome in children with cochlear implants. *Otol Neurotol* 2015;36:14-21.
15. Birman CS, Brew JA, Gibson WPet al. CHARGE syndrome and Cochlear implantation: difficulties and outcomes in the paediatric population. *Int J Pediatr Otorhinolaryngol* 2015;79:487-92.
16. Chao X, Luo J, Fan Zet al. Usefulness of radiological findings for predicting cochlear implantation outcomes in children with cochlear nerve deficiency: a pilot study. *Acta Otolaryngol* 2016:1-10.
17. Colletti L, Colletti G, Mandala Met al. The Therapeutic Dilemma of Cochlear Nerve Deficiency: Cochlear or Brainstem Implantation? *Otolaryngol Head Neck Surg* 2014;151:308-14.
18. Glastonbury CM, Davidson HC, Harnsberger HRet al. Imaging findings of cochlear nerve deficiency. *AJNR Am J Neuroradiol* 2002;23:635-43.
19. Casselman JW, Offeciers FE, Govaerts PJet al. Aplasia and hypoplasia of the vestibulocochlear nerve: diagnosis with MR imaging. *Radiology* 1997;202:773-81.
20. Adunka OF, Jewells V, Buchman CA. Value of computed tomography in the evaluation of children with cochlear nerve deficiency. *Otol Neurotol* 2007;28:597-604.
21. Yamazaki H, Leigh J, Briggs Ret al. Usefulness of MRI and EABR Testing for Predicting CI Outcomes Immediately After Cochlear Implantation in Cases With Cochlear Nerve Deficiency. *Otol Neurotol* 2015;36:977-84.
22. Birman CS, Powell HR, Gibson WPet al. Cochlear Implant Outcomes in Cochlea Nerve Aplasia and Hypoplasia. *Otol Neurotol* 2016;37:438-45.
23. Song MH, Kim SC, Kim Jet al. The cochleovestibular nerve identified during auditory brainstem implantation in patients with narrow internal auditory canals: can preoperative evaluation predict cochleovestibular nerve deficiency? *Laryngoscope* 2011;121:1773-9.
24. Holcomb MA, Rumboldt Z, White DR. Cochlear nerve deficiency in children with CHARGE syndrome. *Laryngoscope* 2013;123:793-6.

25. Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A* 2005;133a:306-8.
26. Vesseur A, Free R, Langereis Met al. Suggestions for a Guideline for Cochlear Implantation in CHARGE Syndrome. *Otol Neurotol* 2016;37:1275-83.
27. Arndt S, Laszig R, Beck Ret al. Spectrum of hearing disorders and their management in children with CHARGE syndrome. *Otol Neurotol* 2010;31:67-73.
28. Allen C, Nikolopoulos TP, Dyar Det al. Reliability of a rating scale for measuring speech intelligibility after pediatric cochlear implantation. *Otol Neurotol* 2001;22:631-3.
29. Archbold S, Lutman ME, Marshall DH. Categories of Auditory Performance. *Ann Otol Rhinol Laryngol Suppl* 1995;166:312-4.
30. Zimmerman-Phillips S, Robbins A, Berger M. Infant-Toddler Meaningful Auditory Integration Scale. Sylmar, Calif: Advanced Bionics Corp, 2001.
31. Robbins AM, Osberger MJ. Meaningful Use of Speech Scale (MUSS). Indianopolis: Indiana University School of Medicine, 1990.
32. Kubba H, Swan IR, Gatehouse S. The Glasgow Children's Benefit Inventory: a new instrument for assessing health-related benefit after an intervention. *Ann Otol Rhinol Laryngol* 2004;113:980-6.
33. Hinderink JB, Krabbe PF, Van Den Broek P. Development and application of a health-related quality-of-life instrument for adults with cochlear implants: the Nijmegen cochlear implant questionnaire. *Otolaryngol Head Neck Surg* 2000;123:756-65.
34. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;39:800-12.
35. Stroup DF, Berlin JA, Morton SCet al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000;283:2008-12.
36. Sennaroglu L, Yucel E, Sennaroglu Get al. Management of Children with Inner Ear Malformations In: Hartnick RTSCJ, ed. *Sataloff's Comprehensive Textbook of Otolaryngology: Head & Neck Surgery (Pediatric Otolaryngology)* Jp Medical Publishers, 2015:91-106.
37. Giesemann AM, Raab P, Lyutenski Set al. Improved imaging of cochlear nerve hypoplasia using a 3-Tesla variable flip-angle turbo spin-echo sequence and a 7-cm surface coil. *Laryngoscope* 2014;124:751-4.
38. Chinnadurai V, Sreedhar CM, Khushu S. Assessment of cochlear nerve deficiency and its effect on normal maturation of auditory tract by diffusion kurtosis imaging and diffusion tensor imaging: A correlational approach. *Magn Reson Imaging* 2016;34:1305-13.
39. van der Jagt MA, Brink WM, Versluis MJet al. Visualization of human inner ear anatomy with high-resolution MR imaging at 7T: initial clinical assessment. *AJNR Am J Neuroradiol* 2015;36:378-83.
40. Papsin BC. Cochlear implantation in children with anomalous cochleovestibular anatomy. *Laryngoscope* 2005;115:1-26.
41. Kim AH, Kileny PR, Arts HAet al. Role of electrically evoked auditory brainstem response in cochlear implantation of children with inner ear malformations. *Otol Neurotol* 2008;29:626-34.
42. Wakil N, Fitzpatrick EM, Olds Jet al. Long-term outcome after cochlear implantation in children with additional developmental disabilities. *Int J Audiol* 2014;53:587-94.
43. Colletti L, Shannon RV, Colletti V. The development of auditory perception in children after auditory brainstem implantation. *Audiol Neurootol* 2014;19:386-94.
44. Isaiah A, Lee D, Lenes-Voit Fet al. Clinical outcomes following cochlear implantation in children with inner ear anomalies. *Int J Pediatr Otorhinolaryngol* 2017;93:1-6.
45. Sennaroglu L, Sennaroglu G, Yucel Eet al. Long-term Results of ABI in Children With Severe Inner Ear Malformations. *Otol Neurotol* 2016;37:865-72.
46. Merkus P, Di Lella F, Di Trapani Get al. Indications and contraindications of auditory brainstem implants: systematic review and illustrative cases. *Eur Arch Otorhinolaryngol* 2014;271:3-13.
47. Puram SV, Barber SR, Kozin EDet al. Outcomes following Pediatric Auditory Brainstem Implant Surgery: Early Experiences in a North American Center. *Otolaryngol Head Neck Surg* 2016;155:133-8.
48. Wilkinson EP, Eisenberg LS, Krieger MDet al. Initial Results of a Safety and Feasibility Study of Auditory Brainstem Implantation in Congenitally Deaf Children. *Otol Neurotol* 2016.

Supplement 1

Definitions

	Cochlear nerve at midpoint IAC	Cochleovestibular nerve at CPA	Bony cochlear nerve canal	Stenotic IAC
Normal	- >nVII (4,16) - Present	- ≥ 2 times nVII (8) - >nVII (21)	- >1.5mm (16) - >1.4mm (8,12,20,21) - >1mm (9)	>3mm (4,16)
Small/deficient	- <nVII (4,9,16) - <1 mm (9)	- <1.5mm (9) - less than 1.5 times nVII (9)	- <1.5mm - <1.4mm - <1mm	2-3mm (4,6,9,20)
Absent	Not seen on all images (4,6,7)	- Not seen on all images - One, two or three nerves in IAC (22)		<2mm (4)

CPA: cerebellopontine angle; IAC: internal auditory canal

Supplement 2

Outcome categories

Category	Tests scores		
	MSPS	CAP	SPC
Open-set	5-7	5-7	6 and 7
Closed-set	3 and 4	3 and 4	3-5
Sounds	1 and 2	1 and 2	0-2

CAP: category auditory perception; MSPS: Melbourne speech perception test; SPC: speech perception category

3

Cochlear Implantation in Patients Deafened by Congenital Cytomegalovirus

3.1

Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness

Published as:
Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness de Vries JJC, Vesseur AC, Rotteveel LJC, Korver AMH, Rusman LG, Wessels E, Kroes ACM, Mylanus EAM, Oudesluys-Murphy AM, Frijns JHM, Vossen ACTM *J Clin Virol 56(2): 113-117.*

Abstract

Objectives

Congenital cytomegalovirus (CMV) infection is the leading cause of non-genetic congenital hearing loss. The contribution of congenital CMV to prelingual deafness and the pathophysiology is largely unknown. The aim of this study is 1) to analyse the prevalence of congenital CMV among cochlear implant (CI) recipients with prelingual deafness. 2) To genotype CMV present in dried blood spots (DBS) and in the inner ear years after birth.

Material and Methods

Children and adults with prelingual deafness who received a CI in 2010-2011 were included prospectively. Perilymphatic fluids were collected during CI surgery and, in the pediatric cases, DBS were retrieved for CMV DNA detection. Furthermore, a cohort of children with prelingual deafness who received a CI between 2003 and 2008 were included retrospectively. CMV detection in DBS and perilymph was followed by gB and gH genotyping.

Results

Sixtyseven pediatric CI recipients were included. Seventy DBS were tested for CMV DNA, resulting in a prevalence of congenital CMV of 14% (10/70). Perilymphatic fluid was available from 29 pediatric CI recipients. One perilymph fluid, of a 21-month old girl with congenital CMV, asymptomatic at birth, was CMV DNA positive. The CMV strain in the perilymph was genotypically identical to the strain present in her DBS (gB1/gH2). Perilymph samples from 21 adult CI recipients were CMV DNA negative.

Conclusions

Our study stresses the important contribution of congenital CMV among pediatric CI recipients. Furthermore, our genotyping data support the hypothesis that CMV-related hearing loss is associated with ongoing viral replication in the inner ear up to years after birth.

Background

Congenital cytomegalovirus (cCMV) affects approximately 1 in 200 newborns and is the leading cause of non-genetic childhood sensorineural hearing loss [1]. Hearing loss can be detected at birth in approximately 10% of children with symptomatic cCMV. Since the hearing loss is of late-onset character in approximately half of the cases [2], an additional 10% of the infected children will develop hearing loss in the years after birth [3].

Bilateral hearing loss has been reported to be attributable to cCMV in 15-40% of cases [4-7], depending on the studied population. We previously found 8% cCMV infections among children with hearing loss of >40dB at the age of 3-5 years in the Netherlands [8]. However, the exact prevalence of cCMV among children with cochlear implant (CI) is unknown.

The pathophysiology of CMV-related hearing loss has been studied in animal models. Data from mouse [9] and guinea pig [10] models show the presence of CMV in the inner ear predominantly in the coclear perilymphatic epithelial cells of the scala tympani and the auditory nerve spiral ganglion cells [11]. Besides a direct viral effect, inflammation may play a role in cochlear hair cell death causing hearing loss [9]. Some authors have tried to detect CMV in the inner ear during autopsy of congenitally infected fetuses [12] or newborns [13, 14]. Data on CMV detection in the inner ear of living children are limited.

Objectives

The aim of this study was to analyse the prevalence of cCMV infections among CI recipients with prelingual deafness. Therefore, we retrospectively diagnosed cCMV in a cohort of pediatric and adult CI recipients with prelingual deafness using dried blood spots (DBS). Furthermore, we analysed perilymphatic fluid, which is routinely exposed during CI surgery, for the presence of CMV DNA (including CMV gB/gH genotypes), in an attempt to gain insight into the pathophysiology.

Study design

Study population

Pediatric CI recipients

The pediatric study population consisted of profoundly deaf children who received a unilateral CI from October 2010 to December 2011 in the Leiden University Medical Centre (LUMC), and from February to December 2011 in the Radboud University Medical Centre Nijmegen (UMCN). These children were included prospectively (n=31). Blood and perilymphatic fluid were collected during CI surgery and DBSs were retrieved to diagnose cCMV infection retrospectively. Because of the limited national storage duration of DBS, the inclusion was limited to children up to the age of 6 years.

Furthermore, a cohort of profoundly deaf children who received a CI from 2003 to 2008 at the age of 0-5 years were included retrospectively (n=45). These children were part of the previously published DECIBEL study, which included infants with permanent bilateral hearing impairment (≥40 dB in the better ear) at the age of 3 to 5 years [8]. DBS were retrieved from these children. Since these children were retrospectively included, no blood and perilymphatic fluid samples were available.

Adult CI recipients

The adult study population consisted of patients with profound prelingual deafness who received a unilateral CI from April to December 2011 in the LUMC (n=21). These adults were included prospectively and perilymphatic fluid and blood samples at the time of CI surgery were collected. No DBS could be retrieved from these adults because the national storage duration of DBS is limited to 6 years.

Written (parental) informed consent was given. The study was approved by the Medical Ethics Committee (CME) of the LUMC, the Netherlands.

Specimen processing

Blood samples

EDTA-anticoagulated blood samples were drawn during CI surgery from the prospectively included pediatric and adult CI recipients. IgG anti-CMV antibodies were measured in plasma using an automated chemiluminescent microparticle immunoassay (Architect, Abbott Laboratories, Abbott Park, IL). A CMV antibody level ≥6 AU/ml was considered to be positive.

Dried blood spots

In the Netherlands, dried blood spots (DBS) are routinely collected from all newborns within a few days of birth for the nationwide metabolic and endocrine screening program. These are stored for a maximum of 6 years at the National Institute for Public Health and the Environment (RIVM, Bilthoven, the Netherlands). After parental informed consent, DBS were retrieved from pediatric CI recipients younger than 6 years of age.

DNA was extracted from the DBS using the QIAamp DNA Mini Kit following the protocol "Isolation of total DNA from FTA and Guthrie cards", as described previously[15].

Perilymphatic fluid

Study participants received standard care cochlear implantation including a mastoidectomy with facial recess approach into the middle ear. During cochleostomy, the scala tympani was entered with a 24 gauge needle attached to a 1 ml syringe, and the routinely exposed perilymphatic fluid was aspirated. The specimen (10-50 µl) was transferred to the laboratory within an hour, where the fluid was supplemented with phosphate buffered saline (PBS) to a total of 100 µl.

DNA was extracted from the perilymphatic fluid using the QIAamp DNA Blood Mini Kit following the protocol "Isolation of total DNA from Blood or Body Fluids (spin protocol)".

Real-time PCR

CMV DNA amplification

Amplification of a 126-bp fragment from the CMV immediate-early antigen region was performed using an internally controlled quantitative real-time PCR as described previously [15, 16]. Ten µl of DNA extract was used. Quantification was performed using a dilution series of titrated CMV (strain AD169; Advanced Biotechnologies Inc., Columbia, MD) as an external standard.

Beta-globin amplification

To control for the presence of human DNA in perilymphatic fluid, a 110-bp fragment of the housekeeping gene beta-globin was amplified by means of a monoplex real-time PCR. Ten µl of DNA extract of perilymphatic fluid was added to 40 µl PCR pre-mixture obtaining final concentrations of 0.5 µM forward beta-globin primer (5' AAG TGC TCG GTG CCT TTA GTG 3'), 0.5 µM reverse beta-globin primer (5' ACG TGC AGC TTG TCA CAG TG 3') , 0.2 µM beta-globin TaqMan probe (YAK- 5' TGG CCT GGC TCA CCT GGA CAA CCT 3' -BHQ-1), 4.5 mM $MgCl_2$, and 25 µl HotStar Master Mix (QIAGEN, Hilden, Germany). Template denaturation and activation of HotStar Taq DNA polymerase for 15 min at 95°C were followed by 50 cycles of denaturation at 95°C for 5 s, annealing at 55°C for 15 s, and extension at 72°C for 15 s. Real-time PCR was performed using a CFX96™ Real-Time PCR Detection System (Bio-Rad, Veenendaal, The Netherlands). Quantification was performed using a 10-fold dilution series of human genomic DNA (Promega Netherlands) (100 ng/µl to 0.1 pg/µl) as standard.

Genotyping of CMV

CMV envelope glycoproteins gB (UL55) and gH (UL75) genotypes were determined by means of two multiplex real-time PCR assays, as described previously[17].

Results

Pediatric CI recipients

Prevalence of cCMV

A total of 76 pediatric CI recipients were included in the study. Thirty-one patients were included prospectively and received a CI in the two university medical centres between 2010 and 2011 (LUMC: n=13, UMCN: n=18). The median age was 1 year (range 8 months - 8 years). Forty-five patients received a CI from 2003 to 2008 and were included retrospectively (DECIBEL-study [8], age range 3-5 years).

Blood samples were available from 29 of the 31 prospectively included patients (*Table* 1), of whom 52% (15/29) were CMV IgG seropositive. CMV IgG seronegativity excluded cCMV infection.

Table 1 CMV results of pediatric and adult CI recipients with pre- and perilingual deafness included in this study. CMV IgG serostatus at the age of CI surgery, CMV DNA detection in DBS (drawn at birth) and perilymphatic fluid (sampled during CI surgery) are shown.

CI recipients	CMV serostatus	CMV DNA positive	
		DBS	**Perilymfatic fluid**
Children	CMV IgG positive (n=15) (15/29=52%)	2/10	1*/14
	CMV IgG negative (n=14)	0/13	0/14
	CMV IgG NA (n=47)	8/47	0/1
	Total (n=76)	**10/70 (14%)**	**1/29**
Adults	CMV IgG positive (n=11) (11/20=55%)		0/11
	CMV IgG negative (n=9)		0/9
	CMV IgG NA (n=1)		0/1
	Total (n=21)	**NA**	**0/21**

* Also CMV positive DBS ; NA: not available

DBS of 70 out of 76 patients were available for CMV DNA detection. Thirteen of those were from CMV IgG seronegative patients and the other 57 DBS were from seropositive patients or from patients with unknown serostatus (no blood sample available from the 45 retrospectively included patients). Ten out of 70 tested DBS were CMV DNA positive (14%), demonstrating congenital infection.

CMV in perilymphatic fluid

Intraoperatively collected perilymphatic fluid was available for CMV DNA detection of 29 of the 31 prospectively included pediatric patients. The beta-globin PCR, which controlled the presence of human DNA, was positive in all but one perilymphatic fluids (median cycle threshold 31, range 27-37). The single child with the beta-globin negative perilymphatic fluid (implicating an insufficient amount of perilymphatic fluid sample for DNA detection) was also CMV seronegative, excluding cCMV infection.

Two of the perilymphatic fluid samples were from children with CMV positive DBSs, of whom one perilymph was CMV DNA positive (50%). The plasma sample (drawn during surgery) of the child with CMV positive perilymph was CMV DNA negative, which excluded capillary leakage of CMV into the perilymph.

Retrieval of clinical data revealed that the child was asymptomatic at birth and the hearing loss was detected in the first few weeks after birth. The MRI cerebrum showed white matter lesions. At the age of 2 years, no other neurological sequelae were apparent at physical examination.

All other perilymphatic fluid samples were CMV DNA negative.

Viral load and genotyping

Viral load and genotype results of the 7 pediatric CI recipients with CMV DNA positive DBS and/or perilymphatic fluid samples available (out of 10) for genotyping are shown in *table* 2. The median CMV DNA load in DBS was 4.0 (range <2.5 - 5.9) $\log_{10}$ copies/ml. All different gB and gH genotypes were detected in the DBSs and no clear association between viral load and genotype was seen.

Table 2 Viral load and genotype results of the pediatric CI recipients (n=7) with CMV DNA positive DBS and / or perilymphatic fluid samples available for genotyping.

Patient	DBS			Perilymphatic fluid		
	CMV DNA load (copies/ml whole blood)	Genotype		CMV DNA (Cycle threshold, Ct)	Genotype	
Prospectively included						
1	4.0 $\log_{10}$	gB1	gH1	**Negative**		
2	2.9 $\log_{10}$	gB1	gH1	**Positive (Ct 31)**	gB1	**gH2**
Retrospectively included						
3	4.9 $\log_{10}$	gB4	gH1	**NA**		
4	5.9 $\log_{10}$	gB3	gH2	**NA**		
5	5.3 $\log_{10}$	gB2	gH1	**NA**		
6	<2.5 $\log_{10}$	gB2	gH1	**NA**		
7	**3.6 $\log_{10}$**	**ND**	**ND**	**NA**		

DBS; dried blood spots, gB; glycoprotein B, gH; glycoprotein H, NA; not available, ND; not detected.

The CMV strain detected in the perilymph of the congenitally infected girl was genotypically identical to the strain present in her DBS (gB1/gH2).

Adult CI recipients

In total 21 adult CI recipients with profound pre- or perilingual deafness were included prospectively *(Table 1)*. They received a CI at the LUMC. The median age was 44 years (range 23 to 78 years).

Table 3 Literature reports on CMV DNA detection in perilymphatic fluid of CI patients

Reference, publication year	Number of CI recipients (age)	Population of patients (etiology)	Number of patients of whom perilymph
Present study	76 (0-8 years)	Unselected	29
Di Nardo[22;23], 2009, 2011	4 (2-7 years)	Unselected	4
Bauer[21], 2005	6 (1-4 years)	Congenital CMV	6
Sugiura[24;25], 2003, 2004	15 (1-59 years)	Unselected	8

Literature reports on CMV DNA detection in perilymphatic fluid of CI patients. All reports included pediatric patients, none of the reports tested DBS. * CMV IgM seronegative

Eleven of 20 the adult recipients were CMV IgG seropositive (55%) at the age of CI surgery, demonstrating previous infection with CMV, either congenitally or postnatally acquired. Because DBS were not available from adult patients, this distinction could not be made.

Six out of 21 adult recipients had possible alternative causes for their deafness (meningitis, congenital malformation, and connexin 26 mutation). CMV IgG seroprevalence among the adult recipients with deafness of unknown cause was 70% (7/14, median age 44 years), demonstrating a higher percentage of congenitally or postnatally acquired CMV infections.

CMV in perilymphatic fluid

Perilymphatic fluid was available for CMV DNA detection for all 21 adult recipients. The beta-globin PCR was positive in all but one perilymphatic fluids (median cycle threshold 35, range 30-39). The single adult with the beta-globin negative perilymphatic fluid was also CMV seronegative, excluding cCMV infection.

None of the perilymphatic fluid samples were found to be CMV DNA positive.

Discussion

We found that one in seven pediatric CI recipients with prelingual deafness was congenitally infected with CMV, stressing the role of cCMV in this patient group. Our study is in line with smaller studies addressing the cCMV disease burden among deaf children [18] and provided valuable information in view of the large number of patients (n=76) analysed.

Furthermore, we are the first to report detection of a CMV strain in the inner ear of a patient at the age of 21 months that was genotypically identical to the strain present in this patients DBS drawn shortly after birth. The presence of CMV in the inner ear years after

Number of congenital CMV	CMV positive perilymph/ congenital CMV	Clinical symptoms at birth of patient with CMV-positive perilymph	Age at CMV positive perilymph
10	1/2 (50%)	Asymptomatic	21 months
1 congenital or postnatal*	1/unknown*	Asymptomatic	15-month
6	4/6 (67%)	Asymptomatic (n=3) and symptomatic (n=1)	12, 19, 48, and 54 months
3	2/3 (67%)	Symptomatic	2 and 3 years

birth has already led to the speculation that ongoing viral replication, probably combined with inflammation, is responsible for deterioration of hearing after birth. Our finding supports this theory, and the magnitude of this deterioration is underscored by the fact that this currently profoundly deaf toddler had normal hearing at birth. The hypothesis of ongoing viral replication was based on data of prolonged excretion of CMV in the urine of congenitally infected newborns (median duration of approximately 4 years [19]), and recent data on the efficacy of prolonged treatment (6 months)of cCMV infection [20]. Only three authors report having tried to retrieve CMV from the perilymph in a limited number of living patients (*Table 3*) [21-25]. The oldest age at which CMV DNA was reported to be detected in the inner ear of a patient was four-and-a-half years [21]. Our data combined with these previous reports detecting CMV in perilymph, suggest that a large part of congenitally infected children harbor CMV DNA at later ages (50-67%).

Our finding that no CMV DNA could be detected in perilymph from adult CI recipients could theoretically be explained by an absence of cCMV in this group. However, on the basis of available literature, it is likely that a proportion of adult CI recipients with prelingual deafness of unknown cause would have cCMV. The CMV seroprevalence in our cohort of adult CI recipients was highest (70%) when selecting for patients with deafness of unknown cause, demonstrating a larger proportion of congenital and/or postnatally acquired infections. Another possibility is that CMV remained present in perilymph for only a limited period. Larger series of adult patients with confirmed cCMV infection should be studied to test this hypothesis.

In agreement with earlier studies by our and other groups attempting genotyping CMV on DBS, a genotype could be assigned to approximately 75 to 80% of the DBS samples [17, 26, 27]. The main limitation for the detection of CMV DNA in DBS is the small amount of dried blood (50 µl per spot) available and has been shown to be a challenge [15, 26, 28-31]. Genotypes gB1 and gB3 have been reported to be the most prevalent

genotypes in congenitally infected infants[17, 32-36]. The association of specific genotypes with congenital disease has been addressed with controversial results and is limited to the association of genotype gN4 with long-term sequelae [37] and genotype gB3 being found more often among congenitally CMV-infected than in postnatally infected children [38]. In our analysis, no clear association between specific CMV gB and gH genotypes and CI recipients and/or viral load was observed. However, the numbers were limited.

In short, our data stress the role of cCMV among CI recipients with prelingual deafness. Evidence accumulates that the congenitally acquired CMV strain is harbored in the inner ear for many years, resulting in progressive damage with deterioration of hearing, potentially leading to profound deafness. Ongoing viral replication might be influenced by antiviral therapy, and future data will reveal the efficacy of prolonged and/or postponed antiviral treatment of cCMV infected newborns at risk for profound hearing impairment.

Acknowledgements

We thank Foekje Stelma (Dept. Medical Microbiology, UMCN, Nijmegen, the Netherlands), Bert Elvers (National Institute for Public Health and the Environment, Laboratory for Infectious Diseases and Perinatal Screening, Bilthoven, the Netherlands), Cindy de Boer-Dexel and other members of the CI teams at the LUMC and UMCN for their contribution to the study (inclusion of patients, collecting and transport of perilymph and blood samples and DBS).

References

1. Kenneson, A. and M.J. Cannon, *Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection.* Rev Med Virol, 2007. **17**(4): p. 253-76.
2. Fowler, K.B., et al., *Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed?* J Pediatr, 1999. **135**(1): p. 60-4.
3. Dollard, S.C., S.D. Grosse, and D.S. Ross, *New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection.* Rev Med Virol, 2007. **17**(5): p. 355-63.
4. Barbi, M., et al., *A wider role for congenital cytomegalovirus infection in sensorineural hearing loss.* Pediatr Infect Dis J, 2003. **22**(1): p. 39-42.
5. Foulon, I., et al., *A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection.* J Pediatr, 2008. **153**(1): p. 84-8.
6. Harris, S., et al., *Congenital cytomegalovirus infection and sensorineural hearing loss.* Ear Hear, 1984. **5**(6): p. 352-5.
7. Ogawa, H., et al., *Etiology of severe sensorineural hearing loss in children: independent impact of congenital cytomegalovirus infection and GJB2 mutations.* J Infect Dis, 2007. **195**(6): p. 782-8.
8. Korver, A.M., et al., *DECIBEL study: Congenital cytomegalovirus infection in young children with permanent bilateral hearing impairment in the Netherlands.* J Clin Virol, 2009. **46 Suppl 4**: p. S27-31.
9. Schachtele, S.J., et al., *Cytomegalovirus-induced sensorineural hearing loss with persistent cochlear inflammation in neonatal mice.* J Neurovirol, 2011. **17**(3): p. 201-11.
10. Katano, H., et al., *Pathogenesis of cytomegalovirus-associated labyrinthitis in a guinea pig model.* Microbes Infect, 2007. **9**(2): p. 183-91.
11. Woolf, N.K., et al., *Congenital cytomegalovirus labyrinthitis and sensorineural hearing loss in guinea pigs.* J Infect Dis, 1989. **160**(6): p. 929-37.
12. Teissier, N., et al., *Inner ear lesions in congenital cytomegalovirus infection of human fetuses.* Acta Neuropathol, 2011. **122**(6): p. 763-74.
13. Davis, G.L., et al., *Cytomegalovirus endolabyrinthitis.* Arch Pathol Lab Med, 1977. **101**(3): p. 118-21.
14. Davis, L.E., et al., *Recovery and probable persistence of cytomegalovirus in human inner ear fluid without cochlear damage.* Ann Otol Rhinol Laryngol, 1987. **96**(4): p. 380-3.
15. de Vries, J.J., et al., *Evaluation of DNA extraction methods for dried blood spots in the diagnosis of congenital cytomegalovirus infection.* J Clin Virol, 2009. **46 Suppl 4**: p. S37-42.
16. Kalpoe, J.S., et al., *Validation of clinical application of cytomegalovirus plasma DNA load measurement and definition of treatment criteria by analysis of correlation to antigen detection.* J Clin Microbiol, 2004. **42**(4): p. 1498-504.
17. de Vries, J.J., et al., *Rapid genotyping of cytomegalovirus in dried blood spots by multiplex real-time PCR assays targeting the envelope glycoprotein gB and gH genes.* J Clin Microbiol, 2012. **50**(2): p. 232-7.
18. Carron, J.D., *Indications for pediatric cochlear implantation at the University of Mississippi Medical Center.* J Miss State Med Assoc, 2007. **48**(11): p. 331-5.
19. Noyola, D.E., et al., *Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. Congenital CMV Longitudinal Study Group.* Pediatr Infect Dis J, 2000. **19**(6): p. 505-10.
20. Amir, J., D.G. Wolf, and I. Levy, *Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir.* Eur J Pediatr, 2010. **169**(9): p. 1061-7.
21. Bauer, P.W., et al., *Cytomegalovirus in the perilymphatic fluid.* Laryngoscope, 2005. **115**(2): p. 223-5.
22. Di Nardo, W., et al., *Multiple viral genome search in endolabyrinthic fluids of profoundly deaf patients: possible cytomegalovirus intracochlear reactivation.* Audiol Neurootol, 2009. **14**(5): p. 290-5.
23. Di Nardo, W., et al., *Cytomegalovirus DNA retrieval in the inner ear fluids of a congenitally deaf child one month after primary infection: a case report.* Laryngoscope, 2011. **121**(4): p. 828-30.
24. Sugiura, S., et al., *Detection of herpesvirus DNAs in perilymph obtained from patients with sensorineural hearing loss by real-time polymerase chain reaction.* Laryngoscope, 2004. **114**(12): p. 2235-8.
25. Sugiura, S., et al., *Detection of human cytomegalovirus DNA in perilymph of patients with sensorineural hearing loss using real-time PCR.* J Med Virol, 2003. **69**(1): p. 72-5.
26. Barbi, M., S. Binda, and S. Caroppo, *Diagnosis of congenital CMV infection via dried blood spots.* Rev Med Virol, 2006. **16**(6): p. 385-92.

27. Choi, K.Y., et al., *Detection of cytomegalovirus DNA in dried blood spots of Minnesota infants who do not pass newborn hearing screening.* Pediatr Infect Dis J, 2009. **28**(12): p. 1095-8.
28. Atkinson, C., et al., *Use of stored dried blood spots for retrospective diagnosis of congenital CMV.* J Med Virol, 2009. **81**(8): p. 1394-8.
29. Boppana, S.B., et al., *Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection.* Jama, 2010. **303**(14): p. 1375-82.
30. de Vries, J.J., A.C. Vossen, and A.C. Kroes, *Screening newborns for congenital cytomegalovirus infection.* Jama, 2010. **304**(4): p. 407; author reply 408.
31. Vauloup-Fellous, C., et al., *Evaluation of cytomegalovirus (CMV) DNA quantification in dried blood spots: retrospective study of CMV congenital infection.* J Clin Microbiol, 2007. **45**(11): p. 3804-6.
32. Barbi, M., et al., *CMV gB genotypes and outcome of vertical transmission: study on dried blood spots of congenitally infected babies.* J Clin Virol, 2001. **21**(1): p. 75-9.
33. Jin, H., X. Wang, and S. Li, *Human cytomegalovirus glycoprotein B genotype correlates with different symptoms of infected infants.* Intervirology, 2007. **50**(3): p. 219-23.
34. Lukacsi, A., et al., *Human cytomegalovirus gB genotype 1 is dominant in congenital infections in South Hungary.* J Med Virol, 2001. **65**(3): p. 537-42.
35. Yamamoto, A.Y., et al., *Human cytomegalovirus glycoprotein B genotypes in Brazilian mothers and their congenitally infected infants.* J Med Virol, 2007. **79**(8): p. 1164-8.
36. Yu, Z.S., et al., *Cytomegalovirus gB genotype and clinical features in Chinese infants with congenital infections.* Intervirology, 2006. **49**(5): p. 281-5.
37. Pignatelli, S., et al., *Cytomegalovirus gN genotypes distribution among congenitally infected newborns and their relationship with symptoms at birth and sequelae.* Clin Infect Dis, 2010. **51**(1): p. 33-41.
38. Yan, H., et al., *Genetic variations in the gB, UL144 and UL149 genes of human cytomegalovirus strains collected from congenitally and postnatally infected Japanese children.* Arch Virol, 2008. **153**(4): p. 667-74.

3.2

A case-control study: quality of life in children post cochlear implantation with congenital cytomegalovirus-related deafness

Submitted as:
A Case-control study: Quality of life in children post Cochlear Implantation with congenital Cytomegalovirus-related deafness Vesseur A.C., Snels C., Langereis MC, Snik A.F.M, Mylanus E.A.M. *November 2017 submitted to Clinical Otolaryngology*

Abstract

Objectives

To investigate health-related quality of life (QoL) in children with a profound hearing loss due to congenital cytomegalovirus (cCMV) infection and treated with a cochlear implant (CI). Results of standardized QoL questionnaires are compared with a matched control group of children without co-morbidities and with a CI.

Material and Methods

In this explorative retrospective case-control study, two groups of children with CIs were compared: 25 with co-morbidities as a result of cCMV and 37 without co-morbidities. The main outcome measures were medical data, non-verbal IQ, age at implantation, months of CI use and speech perception results were available for analysis. The Nijmegen Cochlear Implant Questionnaire (NCIQ) and the Pediatrics Quality of Life Measurement (PedsQL) were administered to measure (health-related) QoL.

Results

The NCIQ total score and all but one NCIQ sub-domain had more variable score distributions compared to the control group. Median NCIQ total scores and sub-domain scores indicate lower QoL for the study group compared to the control group. Only half of the children in the study group attained a PedsQL total score above 65.4 ("good QoL"). Within the study group, IQ, implantation (unilateral or bilateral), hours of daily CI use and speech perception were positively associated with QoL outcomes.

Conclusion

The QoL scores on the disease-specific and general health questionnaires were more variable and were generally lower than the control group's scores. Cognitive impairment, co-morbidity and low speech perception could influence QoL after implantation.

Introduction

Congenital cytomegalovirus (cCMV) can cause sensorineural hearing loss. cCMV is an intrauterine viral infection and has a prevalence of 0.2-2% in western counties. Of the children born with cCMV, 90% are asymptomatic. Symptomatic cCMV manifests as severe neurologic sequelae, including sensorineural hearing loss in 29% of cases. Before the age of five, approximately 15% of initially asymptomatic children develop long-term sequelae, including hearing loss and behavioral problems [1, 2].

Cochlear implantation in children with (symptomatic) cCMV infection and profound hearing loss can provide beneficial, but sometimes limited, performance outcomes. Speech perception is more severely impaired mainly in cCMV children with cognitive disabilities in comparison to children with CI without co-morbidities. The spoken language is impaired in the majority of the symptomatic cCMV children (with and without cognitive disabilities) and cochlear implant (CI) [3, 4]. Subjective outcome measures, such as (health-related) quality of life (QoL), are an important adjunct to traditional outcome measures especially in children with severe developmental disabilities. Children with CI due to cCMV-related deafness have attained improved QoL, based on individual reports from parents of the children [5].

The aim of this study is to compare the health-related QoL by means of standardized questionnaires in two groups of children who use a CI: those with cCMV infection and those without co-morbidities.

Patients and methods

Ethical considerations

An explorative, retrospective case-control study was performed. After approval of the study protocol by the ethic committee, the authors searched the CI databases of several academic hospitals in the Netherlands and identified children with cCMV-related deafness and were treated with CI. The control group was selected from records of previous studies from the Radboud University Medical Centre in Nijmegen of which the data of QoL questionnaires were available [6].

Study group

The parents of 31 children with cCMV infection were invited to participate in this study. The parents of 26 children responded to this invitation and provided informed consent and 25 children were included in the study group. Note one child was excluded because the child's age at implantation (14 years) was considered an outlier as age at implantation for the remainder of the group was below 8 years. The mean age at implantation for the 25 children in the study group was 2;6 years (SD 18 months).

The diagnosis 'cCMV infection' was based on PCR (polymerase chain reaction) on Guthrie card, or positive urine culture on CMV direct postpartum or increased CMV titre. Children were considered 'symptomatic' if one or more significant neonatal abnormality was identified, including congenital hearing loss, petechien, jaundice, hepatosplenomegaly, microcephaly, and/or fundoscopic abnormalities. The remaining children were considered 'asymptomatic' and had progressive hearing loss in the first years of life.

Control group

The control group consisted of 37 children with congenital severe or profound sensorineural hearing loss (hereditary or of unknown origin), had no other reported co-morbidities and who were implanted with a CI between 1996 and 2010. None of these children had a progressive hearing loss. Mean age at implantation was 3;5 years (SD 24 months). This would now be considered a relatively late implantation age for children with congenital severe of profound hearing loss and no co-morbidities.

Exclusion criteria were prematurity, congenital malformation of the middle or inner ear structures, and cognitive disability (IQ<85). Children were then matched with the study group for age at implantation and gender.

Data

Data for the following four variables were obtained from the records of the control and study groups: medical information (neonatal investigations) as described above, non-verbal IQ, age at time of unilateral or bilateral implantation, months of CI use at time of conducting the questionnaires (referred to as 'follow-up at Q') and speech perception test scores.

For both groups, the mean age at implantation was not different (*p=0.07, Chi squared test)*(see *Table 1*). The distribution of males and females was not different between the study group and the control group (p=0.44, Chi-squared test). The children in the study group were older than the children in the control group when the QoL questionnaires were completed. We discuss the implications of this later in this paper.

Cognitive abilities

The Dutch version of the Bayley Scales of Infant Development (BSID-NL-II) [7], the Snijders Oomen non-verbal intelligence test (SON-R) [8], or the Kent Infant Development Scale (KID-N) [9] was administered to obtain a child's performance IQ. Children were divided into four predetermined categories based on IQ scores: <70, 70-85, 86-115 and >115. There were no IQ data for 15 children in the control group because there was no indication of developmental delay.

Questionnaires

Two standardized parent-proxy questionnaires were used to evaluate QoL: a disease-specific health-related questionnaire, the Nijmegen Cochlear Implant Questionnaire (NCIQ) [10] and a generic health-related questionnaire, the Pediatrics Quality of Life Measurement (PedsQL) [11]. Electronic or hardcopies of these questionnaires were sent to parents of children, depending on the preference of the parents.

Parents of children in the control group had completed the questionnaire as part of the clinic's standard evaluation process. The questionnaires were completed on average three years post-implantation [6]. Parents of children in the study group received the questionnaires as part of this study on average of six years post-implantation. The results of the NCIQ, and PedsQL domains were computed following the guidelines of each questionnaire.

In addition to the above QoL questionnaires, parents also completed an in-house/non-validated general questionnaire. This questionnaire asked parents to estimate the number of hours per day that his/her child used the CI.

Speech perception

Speech perception was measured with the NVA test, a Dutch standardized open-set monosyllable test. Words were presented at conversational level (65dB SPL). The speech perception was conducted no more than one year after 'follow-up at Q'. Children who were too young to complete the NVA speech test, who had limited auditory functions or who had poor cognitive abilities completed a closed speech perception test. Speech perception tests were conducted with the CI in the optimal fitted condition (i.e. bilateral CI, unilateral bimodal or single CI).

Nijmegen Cochlear Implant Questionnaire [10]

The NCIQ contains 60 questions and covers three domains: physical, psychological, and social. Each domain can be subdivided. Per domain, scores can range from 0 to 100, where 0 indicates very low quality of life and 100 indicates very high quality of life. The NCIQ total score is the mean score of the six sub-domains [12]. The NCIQ has been used to evaluate cochlear implantation in children [13, 14].

Pediatrics Quality of Life Measurement [11]

Different versions of the questionnaire were used depending on the age of the child. The questionnaire consists of 23 questions, which are divided into four domains: physical functioning, emotional functioning, social functioning and school functioning. The total score ranges from 0 to 100 and a higher score indicates a better quality of life. A total score of 65.4 is considered a cut-off score and children with scores below this cut-off are considered at-risk of an impaired HR-QoL status [11]. The PedsQL has been used in studies of children with a CI [14-16].

Statistical analysis

Statistical analyses were completed using SPSS (statistics 22, IBM Corp, Armonk, NY). Descriptive statistics were used to compare baseline characteristics between the groups, including child gender, child age at questionnaire administration, child age at implantation, years of device use (unilateral or bilateral CI). Nonparametric tests (chi-squared test, Mann-Whitney U test) were used to test for differences between the study and control groups. Correlations were calculated using Spearman's rank order correlation coefficient.

Results

Characteristics

All but one child in the study group had symptomatic cCMV. Co-morbidities included cognitive disability, delayed motor development, visual impairment, epilepsy and eating disorder. The child with asymptomatic cCMV had a progressive hearing loss and no other reported co-morbidities. This child was implanted at 57 months.

All children were implanted in the period from 1996 to 2013 and all procedures followed standard protocols with complete insertion of the electrodes into the cochlea and no major complications.

Table 1 lists the general characteristics of the study group and control group. Although the control group was younger at age of 'diagnosis of deafness', mean age at diagnosis for both groups was below twelve months. More children with cCMV infection were implanted bilaterally compared to the control group (p=0.002; chi-squared test). 'Follow-up at Q' for all children in the control group was 8;6 years or less whereas it was below 14;8 years for the study group. To account for this difference we performed two analyses: one using all participants in the study group and a second analysis, referred to as the 'sub analysis' that excluded data of children in the study group with a follow-up over 8;6 years (in total seven children).

In the study group, for seven children, no open-set speech perception scores were available. At the time of data collection, five children had not completed any speech perception testing and two children had been tested just with a closed-set speech perception test (note that both children attained 100% closed-set scores). In the study group, one child was too young to complete the NVA test, but attained 83% correct score on a closed-set speech perception test). The open-set speech perception scores of the two groups did not significantly differ (Mann-Whitney-U test p= 0.07).

Table 1 Patient characteristics

	cCMV: 25	Controls: 37
Gender		
Female	14 (56%)	20 (54%)
Male	11 (44%)	17 (46%)
Mean age at diagnosis (deafness) (months)	8.7 (2-37)	6.3 (0-75)
IQ		
<70	4 (20%)	0
70-85	3 (15%)	0
86-115	13 (65%)	16 (73%)
>115	0	6 (27%)
Missing data	5	15
Implantation date (year)	1998-2013	1996-2010
Implantation		
Unilateral	15 (60%)	34 (92%)
Bilateral	10 (40%)	3 (8%)
Mean age at implantation	30.2 (11-64) months; 2;6 years	41.3 (9-87) months; 3;5 years
Follow-up at Q	81.2 (12-176) months 6;9 years	38.9 (9-102) months; 3;3 years
Mean age at Q	112.7 (30-233) months; 9;5 years	80.7 (26-162) months; 6;8 years
Daily CI use (hours)		
0-2	2 (9%)	0
2-6	0	0
6-9	1 (5%)	0
9-12	6 (27%)	11 (35%)
12-16	11(50%)	18 (58%)
>16	2 (9%)	2 (7%)
Missing data	3 (-)	6 (-)
Speech perception	65 (0-97)	84 (15-99)
Missing data	7*	1

Between brackets: percentage or range; Q: questionnaires; * two children too young to test, five missing

Questionnaires

NCIQ

Figure 1a displays the results from the NCIQ for the two groups. The NCIQ total score was more widespread in the study group compared to the control group (Mann-Whitney-U test). This distribution pattern is seen for all sub-domains ($p<0.05$) except 'speech production' ($p=0.18$). The median total NCIQ score and the medians of all but one sub-domain were lower in the study group compared to the control group.

Figure 1a Total score and domain scores of the total study group and total control group

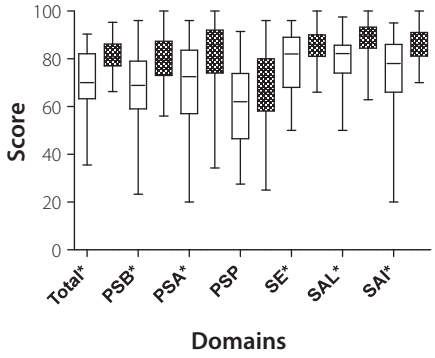
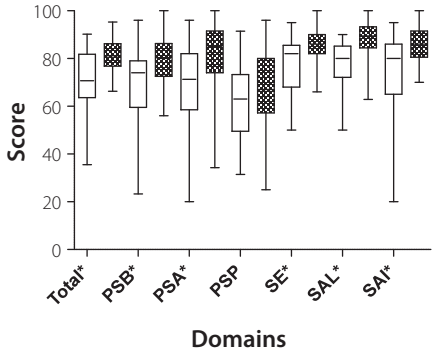


Figure 1b Total score and domain scores of the selected study group (follow-up at Q< 8;6 years) and total control group



Open boxes: study group; shaded/filled boxes: control group; boxes: 25-75%; horizontal line: median. PSA: Physical sound perception advanced; PSB: Physical sound perception basic; PSE: Psychological self-esteem; PSP: Physical Speech Production; SAL: Social activity limitations; SAI: Social interactions; SPS Physical speech production;
*** significant difference in distribution between study and control group.**

Figure 1b shows the result after excluding the 5 children with follow-up > 6.8 years. Little difference is seen between Figures 1a and 1b. The sub analysis showed that there was no statistical difference in outcome between the full group (n=27) and subgroup (n=20) (Man-Whitney-U test). The mean speech perception score of this subgroup was 68% and did not significantly differ with the mean speech perception score (84%) of the control group (Mann-Whitney-U test p=0.12).

PedsQL

Figure 2a displays the PedsQL results for the two groups. The scores for the study group were more widespread than the control group for the PedsQL total score and all sub-domains with the exception of *emotional* (p=0.19). The median total score and median sub-domain scores were lower in the study group than in the control group. Only half of the children in the study group attained a total PedsQL score above the 65.4 cut-off (86.5 in control group).

The sub analysis showed again that there was no statistical difference in distribution between the full group (n=27) and subgroup (n=20) (Man-Whitney-U test). However, when comparing *figures 2a* and *2b*, differences are obvious with regard to the minimum values. Apparently, excluding the seven patients who had completed QoL questionnaires more than 8;6 years after CI, resulted in excluding patients with the lowest scores on the PedsQL.

Correlations

Table 2 lists the results of the correlation analyses. There was a significant positive correlation within the study group between performance IQ and both the total score of the NCIQ and the PedsQL (p=0.001 and p=0.016, respectively). Within the study group, high daily CI use and bilateral implantation were both significantly associated with higher total NCIQ scores (p=0.04 and p=0.01 respectively). Bilateral implantation was significantly associated with higher total PedsQL scores (p=0.04). Speech perception scores and the NCIQ total score were positively correlated in both the study and the control groups.

Figure 2a Total score and domain scores of the total study group and total control group

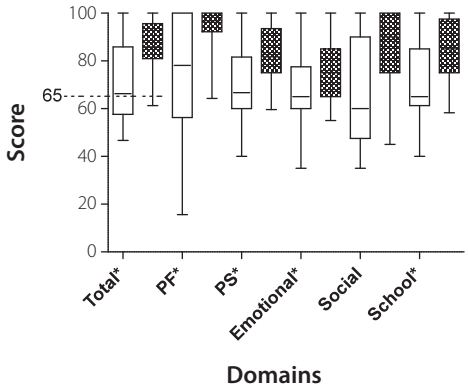
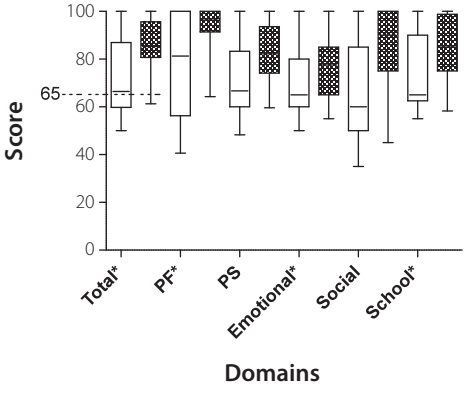


Figure 2b Total score and domain scores of the selected study group (follow-up at Q< 8;6 years) and total control group



Open boxes: study group; shaded/filled boxes: control group; boxes: 25-75%; horizontal line: median PF: physical functioning; PS: psychosocial health summery score (sum score of the items over the numbers of items answered in the Emotional, Social and School functioning sub-domains). Dotted line: cut off point
*** significant different in distribution between study and control group.**

Table 2 Correlations

Variables		Studygroup		Control group	
		Total NCIQ test	Total PedsQL	Total NCIQ test	Total PedsQL
IQ	**Correlation Coefficient**	.7**	.6*	.032	.242
	Sig. (2-tailed)	0,001	0,02	ns	ns
	N	20	17	22	22
Uni/bilateral	**Correlation Coefficient**	.5*	.2	.102	.334*
	Sig. (2-tailed)	0.01	ns	ns	0.04
	N	25	22	37	37
Implantation age (months)	**Correlation Coefficient**	-.3	-.3	-.331*	-.004
	Sig. (2-tailed)	ns	ns	0.05	ns
	N	25	22	37	37
Follow up at Q	**Correlation Coefficient**	-.3	-.4	-.105	-.176
	Sig. (2-tailed)	ns	ns	ns	ns
	N	24	21	37	37
CI use per dag (hours)	**Correlation Coefficient**	.5*	.3	.234	-.171
	Sig. (2-tailed)	0.04	ns	ns	ns
	N	22	19	31	31
Speech perception	**Correlation Coefficient**	.6**	.2	.378*	-.116
	Sig. (2-tailed)	0.008	ns	0.02	ns
	N	18	16	36	36

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). Shaded cells: significant correlations. Spearmans' rho.

CI: cochlear implant; IQ intelligence quotient; N number; NCIQ Nijmegen Cochlear Implant Questionnaire; ns: not significant; PedsQL Paediatrics Quality of Life Measurement; Q questionnaire; Sign: significant

Discussion

Synopsis of key findings

Children with cCMV-related deafness who use a CI have lower and more wide-spread disease-specific QoL scores and generic health-related QoL scores then deaf children without co-morbidities who use a CI. Interesting, in 50% of the patients in the study group in comparison to 86.5% of the patients in the control group, the total PedsQL showed scores above the cut-off value of 65.4 as introduced by Varni et al. [11]. This indicates that half the children in the study group had relatively good QoL. For the remaining children, scores below cut-off indicate that the parent/caregiver had concerns about the wellbeing of his/her child. For the NCIQ results such a cut-off score is not defined.

Comparison with other studies

The wider spread and lower median scores in almost all sub-domains in the study group for both QoL questionnaires might be explained by the co-morbidities and variable cognitive abilities of children in the study group. This idea is supported in the work by Zaidman et al. [17], who described lower health-related quality of life in people with developmental disabilities and our finding of correlation between cognition (IQ) and the NICQ total score. The spread in QoL outcomes might correspond to the various presentations of cCMV infection, varying from asymptomatic patients to patients with neurologic sequelae (intellectual disability and neurologic abnormalities [18, 19]).

Several published studies reported that social and emotional well-being is associated with speech perception and communication abilities [20, 21]. In agreement with those observations, we found a relationship between speech perception scores and total PedsQL score.

Strength and weakness of the study

The retrospective nature of the study is a limitation to the study design and resulted in heterogeneous groups that contained missing data. Nevertheless, this aspect played a role in either group. Age at implantation and the duration of CI use differed between the groups. As the study group was implanted at a later age and at a later period than the control group, this may explain the higher number of children with bilateral CIs in the study group.

The control group had a shorter duration from implantation to follow-up when QoL data was gathered (coded as 'follow-up at Q'). Excluding children in the study group with lengthy follow-up and repeating the analysis did not change any outcomes. We note, however, that excluding these subjects also resulted in removal of children with poor PedsQL scores. This suggests a (negative) effect of time of follow-up on the quality of life, what is not likely. It is speculated that other factor must have played a role like changing inclusion criteria over time.

For reasons not recorded in the children's medical records, speech perception results were not recorded for five children in the study group. If low auditory functioning was the reason speech perception testing was not performed, the average speech perception scores we used in our analysis are overestimated.

Sophisticated statistical analysis was not possible due to the relatively small sample sizes and the heterogeneity within the study group. Nonetheless these weaknesses, as far as we know, the present study comprises the largest group of patients with cCMV with a significant follow up, evaluated with one and the same test procedure.

Acknowledgement

The authors would like to thank the parents of the children who participated in this study. We also would like to thank the participating cochlear implant centres in Amsterdam (Amsterdam Medical Centre and VU Universal Medical Centre), in Leiden (Leiden University Medical Centre) and in Maastricht (Maastricht University Medical Centre) for providing data for this study.

References

1. van Zuylen, W.J., et al., *Congenital cytomegalovirus infection: Clinical presentation, epidemiology, diagnosis and prevention.* Obstet Med, 2014. **7**(4): p. 140-6.
2. Goderis, J., et al., *Hearing in Children with Congenital Cytomegalovirus Infection: Results of a Longitudinal Study.* J Pediatr, 2016. **172**: p. 110-115.e2.
3. Yamazaki, H., et al., *Cochlear implantation in children with congenital cytomegalovirus infection accompanied by psycho-neurological disorders.* Acta Otolaryngol, 2012. **132**(4): p. 420-7.
4. Philips, B., et al., *Cochlear implants in children deafened by congenital cytomegalovirus and matched Connexin 26 peers.* Int J Pediatr Otorhinolaryngol, 2014. **78**(3): p. 410-5.
5. Yoshida, H., et al., *Cochlear implantation in children with congenital cytomegalovirus infection.* Otol Neurotol, 2009. **30**(6): p. 725-30.
6. Damen, G.W., *Cochlear Implantation and Quality of Life Assessment*, in *Otorhinolaryngology*. 2007, Radboud University: Nijmegen.
7. Bayley, N., *Bayley Scales of Infant Development Manual.* 1993, The Psychological Corporation: San Antonio.
8. Tellegen, P.J., Laros, J.A., *SON-R 2½-7 Snijders-Oomen Niet-verbale intelligentietest III. Nederlands-Duitse normen 2010.* 2010.
9. Schneider, M.J., Loots, G.M.P., Reuter, J., *Kent Infant Development Scale. Nederlandse bewerking. Handleiding.* Lisse: Swets en Zeitlinger., 1990.
10. Hinderink, J.B., P.F. Krabbe, and P. Van Den Broek, *Development and application of a health-related quality-of-life instrument for adults with cochlear implants: the Nijmegen cochlear implant questionnaire.* Otolaryngol Head Neck Surg, 2000. **123**(6): p. 756-65.
11. Varni, J.W., et al., *The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity.* Ambulatory Pediatrics, 2003. **3**(6): p. 329-41.
12. Krabbe, P.F., *The Measurement of Health and Health Status*. 2016: Academic Press. 380.
13. Damen, G.W., et al., *Quality of life and cochlear implantation in Usher syndrome type I.* Laryngoscope, 2006. **116**(5): p. 723-8.
14. Sparreboom, M., A.F. Snik, and E.A. Mylanus, *Sequential bilateral cochlear implantation in children: quality of life.* Arch Otolaryngol Head Neck Surg, 2012. **138**(2): p. 134-41.
15. Damen, G.W.J.A., Hoffer M.M.R., Hoekstra C.C., Mylanus E.A.M., *Cochlear Implantation in Multihandicapped Children: Quality of Life and Language Comprehension. Dutch title: Cochleaire implantatie bij meervoudig gehandicapte kinderen: kwaliteit van leven en taalbegrip.* Stem-, Spraak- en Taalpathologie, 2006. **14**(2): p. 143-60.
16. Beijen, J.W., A.F. Snik, and E.A. Mylanus, *Sound localization ability of young children with bilateral cochlear implants.* Otol Neurotol, 2007. **28**(4): p. 479-85.
17. Zaidman-Zait, A., et al., *Health-Related Quality of Life Among Young Children With Cochlear Implants and Developmental Disabilities.* Ear Hear, 2017.
18. Madden, C., et al., *Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss*, in *Int J Pediatr Otorhinolaryngol*. 2005. p. 1191-8.
19. Malm, G. and M. Engman, *Congenital cytomegalovirus infections*, in *Semin Fetal Neonatal Med*. 2007. p. 154-9.
20. Percy-Smith, L., et al., *Factors that affect the social well-being of children with cochlear implants.* Cochlear Implants Int, 2008. **9**(4): p. 199-214.
21. Langereis, M. and A. Vermeulen, *School performance and wellbeing of children with CI in different communicative-educational environments.* Int J Pediatr Otorhinolaryngol, 2015. **79**(6): p. 834-9.

4

Cochlear Implantation in Kabuki Syndrome

Cochlear implantation in a patient with Kabuki syndrome

Published as:
Cochlear Implantation in a Patient with Kabuki Syndrome Vesseur AC, Cillessen E, Mylanus EAM *J Int Adv Otol* ***12****(1): 129-131*

Abstract

Criteria for cochlear implants are expanding and now include children with disabilities in addition to hearing loss, such as children with Kabuki Syndrome. This case report describes the language outcomes and changes in quality of life of a female child with KS after cochlear implantation. The subject had a profound progressive sensorineural hearing loss, cognitive impairments and other disabilities and communicated using vocalised sounds and Dutch Sign Language. After cochlear implantation at age 9;03, the patient displayed no progress in speech production and minimal progress in receptive language development but the subject had increased awareness of the world and an increase in quality of life.

Introduction

Hearing impairment is one of the characteristics of Kabuki Syndrome (KS) and is seen in up to 50% of cases. Otitis media, malformation of the ossicular chain or various structural anomalies of the inner ear [1-3] can cause conductive, sensorineural or mixed hearing loss [1, 4]. For patients with KS and a profound sensorineural hearing loss, a cochlear implant (CI) can be considered. CI placement, however, can be challenging because of the additional handicaps and the anomalies of the petrosal bone. To the best of our knowledge, there is no literature describing the application of CI in individuals with KS. The estimated prevalence of KS is 1/32,000[5].

One of the aims of this case study is to provide an overview of the challenges health professionals may face when considering CI in children with KS and provide an indication of the outcomes so health professionals and families can have realistic expectations of what changes to language development and quality of life are possible after implantation. The second aim of this report is to investigate whether these challenges are similar to those of other patients with a profound hearing loss in addition to another disability. We use postoperative speech and language scores and data as indices of CI outcome.

Table 1

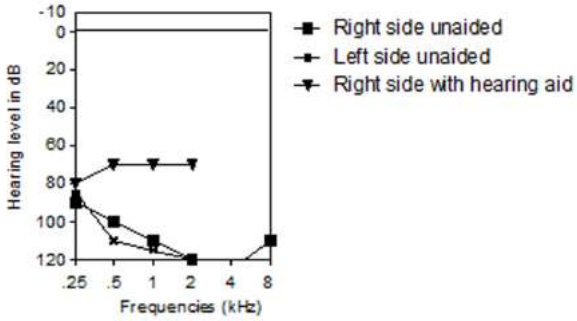
Clinical characteristics
Peculiar facial expression ("facies myopathica")
Thin upper lip
High-arched palate
Uvula bifida
Blue sclerae
Left-sided strabismus convergens and a Brown anomaly of the right eye
General muscular hypotonia
Hyper mobile joints in the extremities
Short fifth digit on left hand
Microcephaly (-3 SD)
Left sided congenital hip dysplasia with hip luxation
Cardiovascular anomalies: a slight pulmonary subvalvular stenosis, multiple septal defects and an atrial septal defect
Delayed physical growth and neurodevelopmental skills[1]

1. Sit up straight without aid at 13 months, walk at two years.

Case study

The female subject was born via a cesarean section (because of oligohydramnion and fetal distress) in the Netherlands in 2001. The child's mother was Cuban (Spanish speaking) and the father was Italian (Italian speaking). The parents communicated in Spanish and neither spoke Dutch fluently. At the age of one year, the subject was diagnosed with bilateral profound sensorineural hearing loss after brainstem evoked response audiometry (BERA) indicated auditory thresholds of 55 dB for the right ear (AD) and 80 dB for the left ear (AS). In the same year, the subject was diagnosed with KS by a pediatric neurologist (*Table 1*, a list of the subject's clinical features). From the ages of 1;6 to seven years, the subject predominately wore bilateral hearing aids only at day care. Audiological assessment at eight years of age revealed a progressive hearing loss (*Figure 1*). At this stage no signs of speech perception were observed.

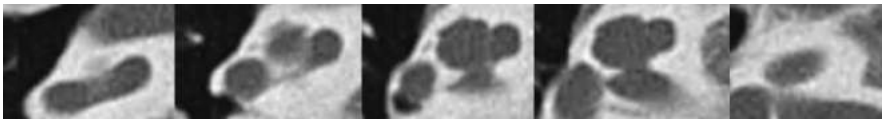
Figure 1 Pure tone audiometry before implantation



age: 8 years 7 months

CT showed bilateral enlarged vestibular aqueducts (EVA) Progressive hearing loss is common in people with EVA syndrome. Both left and right ossicular chains had a normal aspect, the mastoid appeared normal and no vascular anomalies were observed. The right modiolus was incomplete and the cochlea was classified as incomplete partition type II [6]. There was also evidence of dysplasia of the vestibulum and semicircular canals (*Figure 2)*. On subject's left side there was evidence of mild dysplasia of the semicirculair canals. These abnormalities within the vestibulocochlear system were confirmed using MRI (*Figure 3)*. The MRI also showed there were no anomalies of the facial nerves or vestibulocochlear nerves. A velocity step test indicated bilateral areflexia.

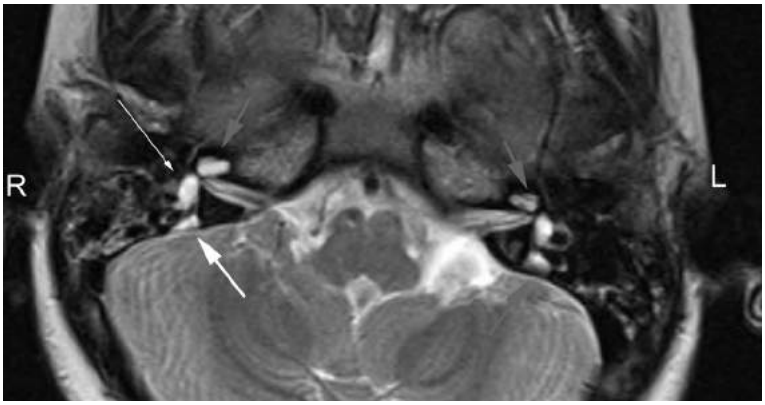
Figure 2 Cochlea



CT cochlea right side, incomplete partition type II

At the age of six the subject began attending a boarding school for deaf children with developmental disabilities and at the school she started learning Dutch Sign Language. At the age of 6;4, a Dutch version of the Non Speech Test (NNST; [7]), supported by sign language, indicated receptive and expressive language developments levels corresponding with a 21 month old hearing child. A cognitive assessment when the subject was seven showed an estimated non-verbal IQ of 54 (the Snijders-Oomen Nonverbal Intelligence Test; SON-R2,5-7 [8]).

Figure 3

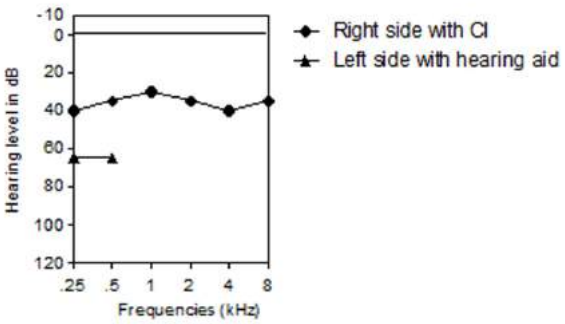


MRI T2; Grey arrows: cochlea; Small white arrow: relatively large vestibulum with dysplasia of the semicircular canals; Big white arrow: enlarged vestibular aqueduct

At the age of 9;6, the subject was implanted with a CI. The right side was selected because of its better preoperative hearing abilities and continued use of amplification compared to the left ear. The parents received extensive counseling that the outcome of CI may be low because of the subject's relatively high age for CI, her limited preoperative language skills and her intellectual disabilities.

The surgical procedure was performed via a cortical mastoidectomy and a posterior tympanotomy. During the cochleostomy, perilymph was released under slight pressure but no real gusher occurred. The cochleostomy was closed effectively with fascia and Tissucol. A Nucleus 22-electrode CI (Nucleus ® CI512 with contour advance electrode) was completely inserted. Intraoperative testing using stapes reflexes and neural response telemetry of all electrodes showed normal device functioning.

Figure 4 Pure tone audiometry after implantation



age: 10 years 9 months. No reaction with the hearing aid on the left side on frequencies of >0.5 kHz

One year after implantation, aided auditory thresholds (using headphones) were between 30 and 40 dB *(Figure 4)*. Language comprehension was tested using the Reynell Developmental Language Scales (RDLS)[9]. The subject performed at a developmental level of an 18 month-old. On the test she could correctly point to some objects on verbal request, but she needed additional sign language to understand more than single-word tasks. In terms of speech production, at this age she only produced isolated sounds.

At two and a half years postoperatively (age of 12 years), the subject's RDLS level had improved to an age equivalent of 23 months. When language was supported with sign language, the subject's language was at a level comparable to a three-year old hearing child. Perceptive speech and language skills continued to progress slowly over this time. At this stage, the subject was receiving frequent training with a speech therapist.

Discussion

The criteria for cochlear implantation continues to expand and children with plural disabilities are now eligible for CI. Although there are limited studies evaluating the use of CI on communication in children with plural disabilities, the results to date have been promising. We present this case study of a child with KS who had a profound hearing loss in addition to other impairments. The aim of our study was to contribute to the knowledge about the challenges of CI in patients with dual disabilities.

The subject was considered a candidate for CI because of her level of aided residual hearing in the right ear and her consistent use of a hearing aid throughout childhood. The expectations on the success of implantation to develop language skills were low given the petrosal bone anomalies, age at implantation, preoperative language abilities, intellectual disability and the use of more than one language in the home situation.

No intra-operative or postoperative complications occurred during implantation. Postoperatively, hearing and speech perception performance skills improved, but receptive and expressive language skills remained below average for the subject's chronological age. The subject required lip-reading and sign-language to supplement receptive language. In addition to improved language, the subject had improved recognition of environmental sounds, displayed stronger communicative skills.

The surgical procedure is challenging when the inner ear is malformed, however, the malformation observed in this subject was not regarded as a contraindication for cochlear implantation. No real gusher occurred during surgery, meanwhile research has shown that gusher does not influence postoperative speech perception performance [10]. Despite the incomplete partition of the cochlea, as seen on CT and MRI, there was sufficient cochlear lumen for an insertion of all electrodes.

The subject's intellectual disability and additional handicaps made it difficult to develop receptive and expressive language skills after implantation. Children with additional disabilities, including intellectual disabilities, generally have slower progress in language development compared to age-matched peers [11, 12]. The majority of children with KS have impairments across the areas of language, speech and oro-motor functions [13, 14]. Regardless of whether a child has a hearing loss only or has a disability in addition to the hearing loss, there is a relationship between increased age at implantation and poor performance [15]. In this case study, this means that despite the subject's residual hearing during her first years of life, her age at implantation meant she had experienced 9.5years with limited aural input.

KS and CHARGE syndrome have similar clinical features [16]. The challenges with CI described in this case study for a subject with KS are applicable to individuals with CHARGE syndrome who are eligible for CI. That is, both groups have handicaps in addition to the hearing loss and both groups have intellectual disabilities and anomalies of the petrosal bone [17]. Given the similarity between the groups and the lack of research on CI in KS,

studies investigating CI in individuals with CHARGE syndrome could aid clinical decision making when it comes to implantation in subjects with KS.

The heterogeneity of KS characteristics ensures it is difficult to generalize the results of individual cases. Whether a child with KS and a hearing impairment will benefit from cochlear implantation depends on each individual's profile. Although CI surgery and rehabilitation is challenging, our experience with the subject discussed in this case study indicates that CI in individuals with KS may assist language development.

Acknowlegdment

We thank parents and patient for giving the permission to use the data.

References

1. Peterson-Falzone, S.J., M. Golabi, and A.K. Lalwani, *Otolaryngologic manifestations of Kabuki syndrome.* Int J Pediatr Otorhinolaryngol, 1997. **38**(3): p. 227-36.
2. Igawa, H.H., et al., *Inner ear abnormalities in Kabuki make-up syndrome: report of three cases.* Am J Med Genet, 2000. **92**(2): p. 87-9.
3. Tekin, M., et al., *Niikawa-Kuroki (Kabuki) syndrome with congenital sensorineural deafness: evidence for a wide spectrum of inner ear abnormalities.* Int J Pediatr Otorhinolaryngol, 2006. **70**(5): p. 885-9.
4. Schrander-Stumpel, C.T., et al., *Kabuki syndrome: Clinical data in 20 patients, literature review, and further guidelines for preventive management.* Am J Med Genet A, 2005. **132a**(3): p. 234-43.
5. Niikawa, N., et al., *Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients.* Am J Med Genet, 1988. **31**(3): p. 565-89.
6. Sennaroglu, L. and I. Saatci, *A new classification for cochleovestibular malformations.* Laryngoscope, 2002. **112**(12): p. 2230-41.
7. I. Zink, D.L., *NNST Nederlandstalige Nonspeech Test.* 2000. **ISBN 9033446227**.
8. Tellegen, P.J., Laros, J.A., *SON-R 2½-7 Snijders-Oomen Niet-verbale intelligentietest III. Nederlands-Duitse normen 2010.* 2010.
9. Reynell J.K., G.C.P., *Reynell Developmental Language Scales.* 1990.
10. Adunka, O.F., et al., *Influence of an intraoperative perilymph gusher on cochlear implant performance in children with labyrinthine malformations.* Otol Neurotol, 2012. **33**(9): p. 1489-96.
11. Berrettini, S., et al., *Cochlear implantation in deaf children with associated disabilities: challenges and outcomes.* Int J Audiol, 2008. **47**(4): p. 199-208.
12. Waltzman, S.B., V. Scalchunes, and N.L. Cohen, *Performance of multiply handicapped children using cochlear implants.* Am J Otol, 2000. **21**(3): p. 329-35.
13. Morgan, A.T., et al., *Speech and language in a genotyped cohort of individuals with Kabuki syndrome.* Am J Med Genet A, 2015. **167**(7): p. 1483-92.
14. Defloor, T., et al., *Expressive language in children with Kabuki syndrome.* Am J Med Genet A, 2005. **132A**(3): p. 256-9.
15. Waltzman, S.B., J.T. Roland, Jr., and N.L. Cohen, *Delayed implantation in congenitally deaf children and adults.* Otol Neurotol, 2002. **23**(3): p. 333-40.
16. Verhagen, J.M., et al., *An unusual presentation of Kabuki syndrome: clinical overlap with CHARGE syndrome.* Eur J Med Genet, 2014. **57**(9): p. 510-2.
17. Lanson, B.G., et al., *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes.* Laryngoscope, 2007. **117**(7): p. 1260-6.

5

Closure

5.1

General Discussion

General Discussion

Cochlear implantation is a well-established method that enables children with profound to severe hearing loss to develop spoken language. The success of cochlear implantation in children with pre-lingual deafness without other co-morbidities has resulted in an expansion of the criteria for cochlear implantation. Amongst others, this expansion means that cochlear implantation is available for children who in addition to a hearing loss have another impairment, such as cognitive delay. It is, therefore, of utmost importance to identify the challenges and benefits of cochlear implantation in children with complex needs.

Surgery

This thesis focuses on the challenges of cochlear implantation in children with profound to severe hearing loss in addition to other co-morbidities. In children with CHARGE syndrome, cochlear implant surgery is challenging because of the presence of congenital anomalies in the temporal bone at the level of the middle ear, and inner ear. Most anomalies can be assessed on a CT, however in some cases anomalies can only be determined on MRI. The anomalies vary within the population (see Sections 2.1 and 2.3 for detailed information).

Reduced development of the mastoid, especially in young children, may impede the creation of a mastoidectomy and a sufficient exposure of the area where the posterior tympanotomy should be performed for a clear access to the round window niche. This situation may be further complicated if the facial nerve has an aberrant route, which is frequently found in these children. In cases with an aberrant facial route and reduced development of the mastoid, an endaural approach instead of mastoidectomy [1], or a temporary intra-operative removal or anterior displacement of the posterior wall of the outer ear canal should be considered. Mastoidectomy can also be hindered by vascular anomalies such as a large emissary vein or petrosquamos sinus. The petrosquamosal sinus is seen more often in CHARGE syndrome than in the general population [2]. Anomalies of the semicircular canals, a hallmark of CHARGE syndrome, can challenge surgery because it is an important landmark during mastoidectomy. Probably because of the partly or total absence of the semicircular canals, the route of the mastoid portion of the facial nerve is more medial compared to the general population, which provides a wider entrance to the middle ear. On the other hand, the aberrant route of the tympanic portion of the facial nerve may result in a position over the oval window, and a more anterior route of the vertical portion of the nerve over the round window, which complicates the cochleostomy. Identifying the round window is difficult on CT and during surgery. Removal of the incus may render more space and a better view. The surgeon may use a combined surgical approach using the abovementioned endaural route with the transmastoidal route. The posterior tympanotomy or the endaural route, after creating a tympanomeatal flap may be used to perform the cochleostomy to the scala tympani. In some cases, the cochleostomy may have to be performed anterior to the facial nerve, and the insertion of

the cochlear implant's electrode maybe executed working endaurally after passing the electrode array through the posterior tympanotomy. A recently published study described an osteoplastic approach via the posterior wall and an endaural approach in these cases with an aberrant route of the facial nerve [3]. Because of the difficulties localizing the round window and positioning and orientating the cochleostomy [4, 5], the use of a navigation system could be of value [5].

Anomalies of the cochlea vary from a fused second and apical turn to a cochlea with 1.5 turns. In Section 2.1, some of the children with CHARGE syndrome reported in our study, presented with an abnormal cochlea, shortened despite the presence of a basal, second and apical turn, which has not been described before in CHARGE syndrome. This cochlear type appears to be consistent with cochlear hypoplasia type IV as recently described by Sennaroglu [6]. The size and shape of the cochlea influences the choice of type of cochlear implant (CI) suitable for implantation. Despite the presence of cochlear anomalies in the children described in our studies, a standard electrode was implanted in all participants. All other anomalies observed in our children were in accordance with the anomalies described in the literature.

Cochlear nerve deficiency in the form of hypoplasticity or aplasticity is frequently observed in individuals with CHARGE syndrome [7] (see Sections 2.3 and 2.4 for details). This nerve deficiency is diagnosed on MRI. Because of the positive results of cochlear implantation reported in children with cochlear nerve deficiency, there is indirect evidence of the presence of functional nerve fibres. Measuring the diameter of the internal auditory canal and bony cochlear nerve could help to be more aware on cochlear nerve deficiency. However, these measurements cannot exclude the presence or absence of cochlear nerve fibres. Although there are exceptions, children with cochlear nerve aplasia as observed on MRI have a lower chance of successful cochlear implantation compared to children with cochlear nerve hypoplasia [8-12]. Other than visualization of the cochlear nerve on MRI, there is no pre-operative diagnostic alternative to indicate the presence of the cochlear nerve. This makes the pre-operative assessment phase very difficult. Despite this pre-operative difficulty, our results indicate that every patient with (apparent) cochlear nerve deficiency should be considered for cochlear implantation before an alternative treatment using an auditory brainstem implant is considered.

Complications

No major complications related to temporal bone anatomy were observed in our studies despite the aberrant facial nerve course often associated with CHARGE syndrome. An aberrant nerve course puts the facial nerve at risk of damage during cochlear implant surgery. The surgical techniques described above should be considered in the event the facial nerve deviates from its typical path. In all cases, it is advisable to use facial monitoring and to use the stimulus probe to diminish the risk of damaging the nerve.

In four of our children excessive bleeding occurred during surgery due to significant emissary veins. Adequate pre-operative assessment of the presence and position of aberrant vascular structures using CT may reduce the occurrence of preoperative haemorrhage, which in small children may lead to serious loss of blood volume. One may even consider implantation in the contra-lateral ear if emissary veins are identified.

In the general cochlear implant population, post-implantation infection is the most frequently reported complication in cochlear implantation [13]. Local infections a few years after surgery are described in this thesis and have been reported in CHARGE syndrome [4]. The incidence of post-operative infections in CHARGE syndrome is difficult to estimate, but may be higher than in the general population. Children with CHARGE syndrome may have a higher risk of persistent middle ear disease because of eustachian tube dysfunction due to choanal atresia [14]. Pre-existing middle ear disease may predispose children for post-implantation infections [15, 16]. In children with recurrent or chronic otitis media pre-implantation, staged surgery should be advised involving a mastoidectomy and tympanoplasty or a subtotal petrosectomy followed by cochlear implantation several months later to decrease the risk of post-implantation infections [17-20].

Although not described in the literature, the complications occurring during cochlear implantation in children with CHARGE syndrome can also occur in people with Kabuki syndrome. This is because of the overlap in anatomical anomalies associated with both syndromes. Although not studied in this thesis, cochlear implantation in children with congenital cytomegalovirus (cCMV) infection are likely to have similar risks for complications as in the general CI population as there are no cCMV-related anatomical anomalies of the petrosal bone [13].

In addition to post-surgical complications related to anatomy, anaesthesia-related complications have been observed in children with Kabuki syndrome and with CHARGE syndrome [21, 22]. Paediatric anaesthesiologists should be aware of the possibility of difficulties associated with tracheal intubation, cardiac lesions and respiratory problems. Prolonged post-anaesthetic observation is recommended after cochlear implant surgery.

Outcomes of cochlear implantation

Cochlear implantation in children with CHARGE syndrome is beneficial; our study has reported open speech perception scores up to 78%. The children with the best results were relatively young at age of implantation and had a relatively high IQ. In addition to speech recognition, speech and language development might be considered one of the primary outcomes of cochlear implantation in children. Owing to the variability in co-morbidities and its severity, such as in CHARGE syndrome, the speech and language development will be variable as well. As an example, Section 2.2 discusses the diversity of cognitive abilities, hearing loss and speech and language development in children with CHARGE syndrome with variable degrees of hearing loss (excluding the CI users). These data were used as a referential dataset.

As demonstrated in Section 2.3, the language development in deaf children with CHARGE syndrome using a CI is comparable to that of CHARGE children with hearing impairment, fitted with hearing aids. However, as illustrated in Section 2.4, cochlear implantation is not always successful. In Section 2.3 we suggested that cochlear implantation is contraindicated in deaf children when aplasia of the cochlear nerve is observed on MRI, no response on ABR is observed and the child does not respond to sounds while using well-fitted hearing aids. In this case, the CI team might consider an auditory brainstem implant (ABI). Owing to positive results of cochlear implantation in children with cochlear nerve deficiency and the reported relatively modest outcomes with ABI, a possible treatment modality might still be to implant such children with a CI before considering an ABI. This apparent contradiction shows the difficulty in the decisionmaking process in children with cochlear nerve deficiency. The suggestion to try CI before ABI, is based on a comprehensive literature search and statistical analyses of pre-operative assessment imaging, audiology measures and performance outcomes.

Similar to the other groups of children, hearing and speech perception improved after implantation in the patient with Kabuki syndrome. This progress was, however, slow and limited. The child's relatively high age at implantation, cognitive impairment and multilingual education likely impeded progress.

Cochlear implantation in children with cCMV is, overall, beneficial. Although significant improvements are reported [23-25] at group level, children with cCMV might not achieve the same levels of improvement as children without cCMV. In the literature, results have been reported varying from no benefit to accurate discrimination of speech sounds and common phrases without lip reading. Co-morbidities such as cognitive impairment, cerebral anomalies and psycho-neurological disorders affected the outcomes [23-25].
In addition to outcomes related to speech and language development, outcomes related to quality of life are an important marker of benefit, especially in children with multiple impairments and compromised development. In our studies, we compared the post-implantation quality of life of children with CHARGE syndrome and of children with cCMV infection with a control group. The control subjects concerned cochlear implant recipients without co-morbidities. In both the CHARGE and cCMV study groups lower scores on the disease-specific quality of life questionnaire (NCIQ) were observed in comparison with the control groups. However, the positive scores in the CHARGE group of the GCBI that assesses benefit of the treatment, indicated an increase in quality of life.

In 50% of the children with cCMV infection, the generic health-related quality of life score (PedsQL) was "acceptable" [26]; the lower score for the remainder of the group indicated the caregivers had concerns regarding their child's wellbeing. Both study groups scored significantly lower on the psychosocial domains of the generic quality of life questionnaire than the control group. Psychosocial wellbeing might be influenced by communicative abilities, and thus, by speech perception abilities [27, 28]. In general, the children with CHARGE syndrome and the children with symptomatic cCMV had lower

speech perception scores than the implanted children without co-morbidities. As discussed in Section 3.2, lower quality of life scores on the psychosocial domains may also have been linked to overall developmental delay. This is in accordance with Zaidman et al. [29] who reported lower health-related quality of life in children with developmental disabilities.

Limited improvement in generic quality of life for children with CHARGE syndrome or cCMV infection compared to control groups is not a contra-indication for cochlear implantation. This likely outcome should be discussed with caregivers during pre-implantation counselling. Continued monitoring of the speech abilities and quality of life is an important part of post-implantation rehabilitation and should play a role in the guidance of these children.

Factors influencing cochlear implantation outcomes

As described in Sections 2.3, 3.2 and 4.1, period of follow-up, cognitive abilities and other co-morbidities were associated with the outcomes. These conclusions are in line with published data [30-33]. In our studies age at implantation was relatively high compared to most CI studies in children without co-morbidities, published during the last decade. One explanation might be that in our study group, treatment for hearing loss occurred after medical treatment of potentially life-threatening co-morbidities. A second explanation could be that implantation can only occur after time consuming, careful assessment of the child's capacities and communicative needs. Coupled with this delayed development, caregivers may have a conservative attitude towards this group and may be reluctant to decide upon implantation before the developmental capacity of the child has been evaluated extensively.

Within the general CHARGE population, 78% of children present with IQ scores below normal levels (defined as IQ<85). Cognitive impairment is also observed in children with cCMV infection [34, 35] and Kabuki syndrome [36]. A relationship between cognitive development and communicative abilities has been reported [37] which is supported by the correlation between cognitive abilities and receptive language quotient, see Section 2.2. Determining individually the influence of cognitive development on the outcome of cochlear implantation is not simple owing to possible confounding variables related to co-morbidities as found in CHARGE syndrome, cCMV infection and Kabuki syndrome.
Two children in our group with CHARGE syndrome stopped using their CI due to serious general health problems. In addition to general health problems, co-morbidities such as visual defects, cranial nerve dysfunction and motor developmental delays might influence the outcome of cochlear implantation [38-40].

Study limitations

This thesis focuses on three specific patient groups. As CHARGE syndrome and Kabuki syndrome have a low incidence, the groups of children were rather limited in size. Although the incidence of cCMV is higher, the variability in comorbidities implies that it is

difficult to obtain a study group of sufficient size and homogeneity. The result of limited group sizes is poor statistical power. Despite the lack of statistical power, descriptive research remains valuable as it improves our knowledge, which is helpful when counselling parents and caregivers of the children.

The use of questionnaires to assess the benefit of cochlear implantation might also be viewed as a limitation. We used disease-specific and generic health-related quality of life questionnaires. The majority of the children in our studies were unable to complete questionnaires due to age or cognitive impairment and, therefore, questionnaires to be filled in by parents or caregivers were used. Published results concluded that parental proxy provides reliable information in studies comprising children with CI [41, 42] and that high levels of agreement were present between children who use a CI and their parents. In contrast, when responses of children with normal hearing are compared to his/her proxy completed quality of life questionnaires, the agreement is lower; an explanation for this discordance might be that children with a CI require more parental guidance than children with normal hearing [41]. This might lead to an increase in a parent's awareness of the child's wellbeing.

Future developments

Imaging is a vital component in the cochlear implantation assessment phase and the pre-operative implantation work-up. CT provides sufficient pre-operative information on a person's temporal bone anatomy. If the surgical team uses a per-operative navigation system, specialized sequences are required for the CT imaging. Many clinics use 'cone beam CT' for the pre-implantation work-up. The main benefit of cone beam CT is the lower radiation dosage. However, high-resolution CT of the temporal bone may also be achieved at low dose while achieving results of comparable image quality with cone-beam CT [43]. Future development of other MRI sequences could improve the detection of cochlear nerve fibres and could make the diagnosis of cochlear nerve deficiency more reliable. MRI techniques such as high-resolution three-dimensional variable flip-angle turbo spin-echo sequencing in combination with a surface coil and diffusion kurtosis imaging or ultra high field imaging could improve sensitivity of MRI to allow the user to detect cochlear nerve fibres.

In addition to image improvement, diagnostic tools require improvement to assist in determining the functionality of any nerve fibres. To date, audiometric tools (pure tone audiometry, ABR, and ABR with electric stimulation via a temporarily placed electrode in the round window niche) lack sensitivity to predict the functionality of the nerve fibres. Development of other non-invasive diagnostic tools, such as diffusion weight techniques or functional MRI, would allow us to investigate the activity within the auditory pathway.

Research on the pathophysiology and treatment of cCMV is an ongoing process. No standardized diagnostic and therapeutic strategies are used yet [44]. Further research is necessary to understand the pathophysiology and to be able to treat the disease. Until the detrimental result of a cCMV infection on hearing may become preventable or treatable, it is important to be able to predict the outcomes of cochlear implantation in these children.

To perform more powerful research in these specific groups of cochlear implant recipients, a possibility would be to combine outcomes of evaluation studies across implant centres. Especially if studies used similar outcome measures and used similar measurement protocols, study results could be pooled. Different speech and language tests can be compared across studies as long as the raw data can be compared to norms and expressed accordingly (e.g. quotient scores). By 2018 there will be a compulsory national registry of people with cochlear implants in the Netherlands. A national implant complication registry will be linked to the system. In the future, outcome data and user characteristics might be linked to this system and could be used for further research (as long as patient data remain protected).

Nowadays, cochlear implantation of children with special needs occur in all cochlear implant centres. This thesis describes the complex diagnostic work-up, surgery and aftercare in these children. Because of the variety of presentations of the diseases, it is important that expert teams assess and are involved in providing personalized health care for these children. Centralization would improve care, because of the expertise present and the presence of multidisciplinary professionals needed. The cochlear implant team should cooperate with recently recognized centres of expertise (CHARGE outpatient clinic University Medical Centre Groningen). This recommendation applies not only to the patient groups described in this thesis, but could apply to all children with a hearing loss as a result of a rare syndrome.

General conclusion

Children with CHARGE syndrome, cCMV infection and Kabuki syndrome present with anatomical anomalies, cognitive disabilities and other co-morbidities that pose a challenge for the team considering cochlear implantation. Despite these challenges, in general cochlear implantation in these children is beneficial. Nevertheless, the outcomes of cochlear implantation in terms of speech and language development and quality of life are lower than that of peers without co-morbidities who use a CI. The studies described in this thesis suggest that aside from medical/surgical issues, cognitive abilities rather than the disease itself is a significant factor in the outcome of cochlear implantation. Our results indicated no strict contra-indications for cochlear implantation and highlighted the importance of the multi-disciplinary team discussing all potential candidates on a case-by-case basis. This thesis might contribute to the knowledge on these syndromes and diseases and optimization of the care of children with complex diseases.

References

1. Stjernholm, C., *Aspects of temporal bone anatomy and pathology in conjunction with cochlear implant surgery.* Acta Radiol Suppl, 2003. **430**: p. 2-15.
2. Koesling, S., P. Kunkel, and T. Schul, *Vascular anomalies, sutures and small canals of the temporal bone on axial CT.* Eur J Radiol, 2005. **54**(3): p. 335-43.
3. Rah, Y.C., et al., *Cochlear Implantation in Patients With CHARGE Syndrome.* Ann Otol Rhinol Laryngol, 2016. **125**(11): p. 924-930.
4. Lanson, B.G., et al., *Cochlear implantation in Children with CHARGE syndrome: therapeutic decisions and outcomes.* Laryngoscope, 2007. **117**(7): p. 1260-6.
5. Birman, C.S., et al., *CHARGE syndrome and Cochlear implantation: Difficulties and outcomes in the paediatric population.* Int J Pediatr Otorhinolaryngol, 2015.
6. Sennaroglu, L., et al., *Management of Children with Inner Ear Malformations* in *Sataloff's Comprehensive Textbook of Otolaryngology: Head & Neck Surgery (Pediatric Otolaryngology),* J.M. Publishers, Editor. November 2015. p. 91-106.
7. Holcomb, M.A., Z. Rumboldt, and D.R. White, *Cochlear nerve deficiency in children with CHARGE syndrome.* Laryngoscope, 2013. **123**(3): p. 793-6.
8. Zhang, Z., et al., *Cochlear implantation in children with cochlear nerve deficiency: a report of nine cases.* Int J Pediatr Otorhinolaryngol, 2012. **76**(8): p. 1188-95.
9. Kang, W.S., et al., *Cochlear implantations in young children with cochlear nerve deficiency diagnosed by MRI.* Otolaryngol Head Neck Surg, 2010. **143**(1): p. 101-8.
10. Young, N.M., et al., *Pediatric cochlear implantation of children with eighth nerve deficiency.* Int J Pediatr Otorhinolaryngol, 2012. **76**(10): p. 1442-8.
11. Chao, X., et al., *Usefulness of radiological findings for predicting cochlear implantation outcomes in children with cochlear nerve deficiency: a pilot study.* Acta Otolaryngol, 2016: p. 1-10.
12. Wu, C.M., et al., *Impact of cochlear nerve deficiency determined using 3-dimensional magnetic resonance imaging on hearing outcome in children with cochlear implants.* Otol Neurotol, 2015. **36**(1): p. 14-21.
13. Jiang, Y., et al., *Analysis and Management of Complications in a Cohort of 1,065 Minimally Invasive Cochlear Implantations.* Otol Neurotol, 2017. **38**(3): p. 347-351.
14. Dhooge, I., et al., *Otological manifestations of CHARGE association.* Ann Otol Rhinol Laryngol, 1998. **107**(11 Pt 1): p. 935-41.
15. Fayad, J.N., et al., *Cochlear implantation in children with otitis media.* Laryngoscope, 2003. **113**(7): p. 1224-7.
16. Luntz, M., C.B. Teszler, and T. Shpak, *Cochlear implantation in children with otitis media: second stage of a long-term prospective study.* Int J Pediatr Otorhinolaryngol, 2004. **68**(3): p. 273-80.
17. Postelmans, J.T., et al., *Cochlear implantation in patients with chronic otitis media: 7 years' experience in Maastricht.* Eur Arch Otorhinolaryngol, 2009. **266**(8): p. 1159-65.
18. Jang, J.H., et al., *Long-term outcome of cochlear implant in patients with chronic otitis media: one-stage surgery is equivalent to two-stage surgery.* J Korean Med Sci, 2015. **30**(1): p. 82-7.
19. Wong, M.C., et al., *Cochlear implantation in patients with chronic suppurative otitis media.* Otol Neurotol, 2014. **35**(5): p. 810-4.
20. Free, R.H., et al., *The role of subtotal petrosectomy in cochlear implant surgery--a report of 32 cases and review on indications.* Otol Neurotol, 2013. **34**(6): p. 1033-40.
21. Atalay, Y.O., et al., *Anesthesia management in a patient with kabuki syndrome.* Med Arch, 2014. **68**(5): p. 359-60.
22. Stack, C.G. and R.K. Wyse, *Incidence and management of airway problems in the CHARGE Association.* Anaesthesia, 1991. **46**(7): p. 582-5.
23. Laccourreye, L., et al., *Speech perception, production and intelligibility in French-speaking children with profound hearing loss and early cochlear implantation after congenital cytomegalovirus infection.* Eur Ann Otorhinolaryngol Head Neck Dis, 2015.
24. Philips, B., et al., *Cochlear implants in children deafened by congenital cytomegalovirus and matched Connexin 26 peers.* Int J Pediatr Otorhinolaryngol, 2014. **78**(3): p. 410-5.
25. Yamazaki, H., et al., *Cochlear implantation in children with congenital cytomegalovirus infection accompanied by psycho-neurological disorders.* Acta Otolaryngol, 2012. **132**(4): p. 420-7.

26. Varni, J.W., et al., *The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity.* Ambulatory Pediatrics, 2003. **3**(6): p. 329-41.
27. Percy-Smith, L., et al., *Factors that affect the social well-being of children with cochlear implants.* Cochlear Implants Int, 2008. **9**(4): p. 199-214.
28. Langereis, M. and A. Vermeulen, *School performance and wellbeing of children with CI in different communicative-educational environments.* Int J Pediatr Otorhinolaryngol, 2015. **79**(6): p. 834-9.
29. Zaidman-Zait, A., et al., *Health-Related Quality of Life Among Young Children With Cochlear Implants and Developmental Disabilities.* Ear Hear, 2017.
30. Kirk, K.I., et al., *Effects of age at implantation in young children.* Ann Otol Rhinol Laryngol Suppl, 2002. **189**: p. 69-73.
31. Nikolopoulos, T.P., G.M. O'Donoghue, and S. Archbold, *Age at implantation: its importance in pediatric cochlear implantation.* Laryngoscope, 1999. **109**(4): p. 595-9.
32. Tobey, E.A., et al., *Influence of implantation age on school-age language performance in pediatric cochlear implant users.* Int J Audiol, 2013. **52**(4): p. 219-29.
33. Govaerts, P.J., et al., *Outcome of cochlear implantation at different ages from 0 to 6 years.* Otol Neurotol, 2002. **23**(6): p. 885-90.
34. Malm, G. and M. Engman, *Congenital cytomegalovirus infections*, in *Semin Fetal Neonatal Med*. 2007. p. 154-9.
35. Madden, C., et al., *Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss*, in *Int J Pediatr Otorhinolaryngol*. 2005. p. 1191-8.
36. Vaux, K.K., et al., *Developmental outcome in Kabuki syndrome.* Am J Med Genet A, 2005. **132a**(3): p. 263-4.
37. Santoro, L., et al., *Cognitive-motor profile, clinical characteristics and diagnosis of CHARGE syndrome: an Italian experience.* Am J Med Genet A, 2014. **164a**(12): p. 3042-51.
38. Meinzen-Derr, J., et al., *Language performance in children with cochlear implants and additional disabilities.* Laryngoscope, 2010. **120**(2): p. 405-13.
39. Birman, C.S., E.J. Elliott, and W.P. Gibson, *Pediatric cochlear implants: additional disabilities prevalence, risk factors, and effect on language outcomes.* Otol Neurotol, 2012. **33**(8): p. 1347-52.
40. Damen, G.W., et al., *Quality of life and cochlear implantation in Usher syndrome type I.* Laryngoscope, 2006. **116**(5): p. 723-8.
41. Duarte, I., et al., *Health-related quality of life in children and adolescents with cochlear implants: self and proxy reports.* Acta Otolaryngol, 2014. **134**(9): p. 881-9.
42. Meserole, R.L., et al., *Assessment of health-related quality of life 6 years after childhood cochlear implantation.* Qual Life Res, 2014. **23**(2): p. 719-31.
43. Theunisse, H.J., et al., *Cone-beam CT versus multi-slice CT systems for postoperative imaging of cochlear implantation--a phantom study on image quality and radiation exposure using human temporal bones.* Otol Neurotol, 2015. **36**(4): p. 592-9.
44. Rawlinson, W.D., et al., *Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy.* Lancet Infect Dis, 2017.

5.2

Summary

Introduction

Chapter 1 is a general introduction to cochlear implantation in deaf children and to the three syndromes studied in this thesis.

A cochlear implant (CI) is an electronic device that can restore hearing in deaf people. It consists of an electronic array implanted in the cochlea that directly stimulates the cochlear nerve fibres. Cochlear implantation has become a regular treatment option for children and adults with severe or profound sensorineural hearing loss who cannot be treated with conventional hearing aids. Based on positive results with CI in children with isolated deafness, the criteria for implantation have gradually become more flexible, for example now allowing children with cognitive delay to undergo implantation. CHARGE syndrome, congenital cytomegalovirus (cCMV) infection and Kabuki syndrome are all complex in nature, and children with these syndromes can have (severe to profound) hearing loss and cognitive delay in addition to other co-morbidities. These children could benefit from CI.

The criteria for the clinical diagnosis of CHARGE syndrome (MIM, Mendelian Inheritance in Man, 214800) have been defined by Blake et al. (1998) and Verloes (2005). CHARGE syndrome is an acronym of Coloboma, Heart disease, choanal Atresia, Retardation, Genital hypoplasia and Ear anomalies. In 2004, the causative gene was identified as *CHD7* on chromosome 8q12. Hearing loss, which is present in 80–100% of the children, is one of the most common characteristics and can be due to anatomical anomalies of the middle or inner ear, to aplasia or hypoplasia of the cochlear nerve, or to middle ear disease. As a consequence, hearing in children with CHARGE syndrome can range from normal to profound hearing loss.

Congenital CMV affects approximately 1 in 200 newborns and is the leading cause of non-genetic childhood sensorineural hearing loss. Hearing loss can be detected at birth in approximately 10% of children with symptomatic cCMV. Since the hearing loss has a late onset in approximately half of the individuals, an additional 10% of the infected children will develop hearing loss in the first years after birth.

Kabuki syndrome has characteristics such as distinctive facial features, cognitive disabilities, postnatal growth deficiency, dermatoglyphic abnormalities and skeletal anomalies. Hearing loss is one of the associated anomalies in Kabuki syndrome and is observed in 65% of cases.

CHARGE syndrome

Chapter 2 focuses on several factors in CHARGE syndrome that can be challenging in cochlear implantation. Temporal bone anatomy in patients with CHARGE syndrome varies widely as described in *section 2.1*. Analyses of CTs of the temporal bone have found vascular structures like petrosquamosal sinus and large emissary veins, an underdeveloped mastoid and an aberrant facial nerve crossing the round window and/or the promontory. These structures can make it challenging to perform the mastoidectomy and posteri-

or-tympanotomy. The cochleostomy can be difficult in patients with a stenotic round window (which is often seen in these patients). The appearance of the inner ear varies widely from partial to total absence of the semicircular canals and from normal to severely hypoplastic cochlea. More anomalies were observed in patients with truncating mutations than in those with non-truncating mutations in the *CHD7* gene.

The hearing loss, cognitive development and speech and language development of patients with CHARGE syndrome (without CI) is studied in *section 2.2*. Here we established an indicative dataset for a group of patients with multiple needs by analysing the relationship of hearing loss and cognitive abilities with language development. Data was analysed from 50 patients (age 5 months-48 years) known by 'the Dutch CHARGE centre of expertise' (University Medical Center Groningen, the Netherlands). The auditory abilities, cognitive abilities and language development in CHARGE syndrome vary widely, but they are mainly below average. The majority (83%) of the patients suffered from hearing loss and were almost equally divided among the various categories of hearing loss (mild, moderate, severe, deaf). Of the 41 patients for whom there was available cognitive data, the majority had an IQ below 70. The mean receptive language quotient (22 patients) was close to two standard deviations below the norm. The mean expressive language quotient (14 patients) was more than one standard deviation below the norm. Positive correlations were found between receptive language quotient and degree of functional hearing loss, between receptive language quotient and cognitive abilities, and between expressive language quotient and degree of functional hearing loss. Language and cognitive data were not available for all patients. It is possible that the group for whom data was available represent a pre-selection of patients with a developmental delay through exclusion of patients too well-performing to have tests done and of patients too poor-performing to participate in language tests. To avoid this pre-selection and improve the quality of care for CHARGE patients, hearing and developmental tests should be performed regularly to differentiate the contributions of hearing loss versus cognitive delay to delayed language development and to provide adequate hearing amplification in the case of hearing loss.

In *section 2.3* we evaluate data from ten children who received a CI between 2002 and 2012 to provide an overview of the challenges and benefits encountered in cochlear implant surgery in CHARGE syndrome. Imaging and surgical findings were analysed. Language development and Quality-of-life (QoL) in our group were compared to those of two control groups: (1) 34 non-syndromic CI-users and (2) 13 children with CHARGE syndrome but without CI because of sufficient hearing. Based on this section, we have developed a suggested guideline for cochlear implantation in CHARGE syndrome.

All children with CHARGE syndrome studied in this section were congenitally deaf and had cognitive abilities below average as well as other co-morbidities. In three children, pre-operative subjective and objective audiometry and MRI were necessary to confirm the presence of the cochlear nerve. In all children, surgery was challenging due to enlarged emissary veins, semi-circular canal aplasia, an aberrant facial nerve and dysplastic cochlear

windows, which made CT indispensable during the surgical preparations. No major intra-operative complications occurred. Despite additional handicaps, all patients showed auditory benefit and improvement in disease-specific QoL. The children with relatively long follow up who underwent implantation at a young age developed spoken language at a basic level comparable to that of the control group. Four children had speech perception scores between 60-90% after 60 to 120 months. In the other six children, speech perception could not be measured with standard tests, but with the CI these children could detect sounds adequately. General health status influenced CI-use, and possibly language development, in two patients including one non-user. Although the absolute scores on the QoL-test were lower in the children with CHARGE syndrome than in the control group, an improvement of disease-specific QoL after implantation was measured. Based on this evaluation, we conclude that a CI should be considered for all children with CHARGE syndrome and severe sensorineural hearing loss. A careful work-up is required —comprising CT, MRI, and objective and subjective audiometry— as is assessment by a specialized multidisciplinary team. Cochlear implantation in CHARGE syndrome might be complicated due to syndrome-related temporal-bone anatomy. The outcome of the CI is more individually determined. Early implantation should be aimed for.

As we discuss in *section 2.3*, the CI-team must be aware of cochlear nerve deficiency (CND) in patients with CHARGE syndrome. When CND is suggested, an auditory brainstem implant (ABI) could be an alternative treatment of CI. *Section 2.4* illustrates the dilemma faced when deciding between CI and ABI using a case report and literature review. We present a case study of a child with CHARGE syndrome who had no benefit from bilateral cochlear implantation and required an ABI for hearing rehabilitation. During the evaluation of this particular case, several steps in the decision process were questioned. The motivation for the literature review and meta-analysis on this topic was thus to provide an evidence-based therapeutic strategy for future cases.

In the case study, the MRI showed the presence of the cochleovestibular nerve in one ear, but there were no preoperative auditory brainstem responses. In the contralateral ear, the nerve could not be identified on MRI despite present auditory brainstem responses. Nevertheless, there was no positive outcome with bilateral CI. Therefore the decision was made to implant an ABI. With the ABI, the patient displayed benefit in terms of speech, language and QoL.

In the literature review, 108 cases of patients with CND and CI were identified. Of these patients, 25% attained open-set speech perception, 34% attained closed-set speech perception and 41% detected sounds or less. We studied which of the following variables could predict the effect of CI in patients with CND: the appearance of the cochlear nerve and presence of cochleovestibular nerve on MRI, the diameter of the internal auditory canal and bony cochlear nerve canal on CT, (electrically evoked) auditory brainstem response, (aided and unaided) pure tone audiometry and oto-acoustic-emissions. We found that patients with cochlear nerve aplasia on MRI had a smaller chance of attaining

a good outcome from cochlear implantation than patients with cochlear nerve hypoplasia, but there were exceptions to this finding. None of the other variables investigated could predict the outcome of cochlear implantation. This supports the idea that current imaging and audiometric testing limit our ability to identify predictors of CI success. ABI could be an alternative treatment for cochlear implantation in patients with CND, but outcomes are generally worse for patients with an ABI than patients with a CI. Based on these results, we concluded that the initial treatment in patients with (apparent) cochlear nerve aplasia is CI. When there is no success with a CI, we recommend considering proceeding to an ABI rather than attempting a second CI and risking further delay in auditory input.

Cochlear implantation in patients deafened by congenital cytomegalovirus infection

Chapter 3 focuses on cochlear implantation in patients with severe to profound hearing loss as a result of cCMV infection. cCMV is the leading cause of non-genetic congenital hearing loss. *Section 3.1* focuses on the prevalence of cCMV infections among CI recipients with prelingual deafness and the pathophysiology of cCMV and severe to profound hearing loss. For that purpose, cCMV was diagnosed retrospectively in a cohort of pediatric and adult CI recipients with prelingual deafness using dried blood spots (DBS). Furthermore, perilymphatic fluid, which is routinely exposed during CI surgery, was analysed for the presence of CMV DNA (including CMV gB/gH genotypes). A total of 76 pediatric recipients were included. Blood samples were available for 29 of the included patients, of whom 52% (15/29) were CMV IgG seropositive. CMV IgG seronegativity excluded cCMV infection. Seventy DBS were tested for CMV DNA, resulting in a prevalence of cCMV of 14% (10/70). Perilymphatic fluid was available from 29 pediatric CI recipients. One perilymphatic fluid, from a 21-month old girl with cCMV, was CMV DNA positive. The child was asymptomatic at birth and hearing loss was detected in the first few weeks after birth. The CMV strain in the perilymph was genotypically identical to the strain present in her DBS. Perilymph samples from 21 adult CI recipients were CMV DNA negative. These data stress the role of cCMV among CI recipients with prelingual deafness. Furthermore, the genotyping data support the hypothesis that CMV-related hearing loss is associated with on-going viral replication in the inner ear up to years after birth. On-going viral replication might be influenced by antiviral therapy, and future data should reveal the efficacy of prolonged and/or postponed antiviral treatment of cCMV-infected newborns at risk for profound hearing impairment.

In patients with CI, benefit is not necessarily optimally expressed in improvement of speech and language abilities, particularly in patients with cognitive disabilities. In these patients, benefit may better be expressed in terms of changes to QoL. *Section 3.2* investigates health-related QoL in children with a profound hearing loss due to cCMV infection and treated with a CI (25 children). Results of standardized QoL questionnaires were compared with a matched control group of children without co-morbidities and

with a CI (37 children). Medical data, non-verbal IQ, age at implantation, months of CI use and speech perception results were available for analysis. The Nijmegen Cochlear Implant Questionnaire (NCIQ) and the Pediatrics Quality of Life Measurement (PedsQL) were administered to measure (health-related) QoL. The NCIQ total score and all but one NCIQ sub-domain had more variable score distributions compared to the control group. Median NCIQ total scores and sub-domain scores indicate a lower QoL for the study group compared to the control group. Only half of the children in the study group attained a PedsQL total score above 65.4 ("good QoL"), as compared to 86.5% of the children in the control group. Within the study group, IQ, implantation (unilateral or bilateral), hours of daily CI use and speech perception were positively associated with QoL outcomes. In conclusion, the QoL scores on the disease-specific and general health questionnaires were more variable and generally lower than the control group's scores. Cognitive impairment, co-morbidity and low speech perception may have a negative influence on the improvement in QoL outcome after implantation.

Cochlear implantation in Kabuki syndrome

Chapter 4 describes the results of cochlear implantation in a child with hearing loss due to Kabuki syndrome. In addition to hearing loss, the child had cognitive impairment and other disabilities and communicated using vocalised sounds and Dutch Sign Language. Between the ages of one and a half years and seven years, the patient predominately wore bilateral hearing aids only at day-care. At eight years of age, progressive hearing loss was measured. After cochlear implantation at nine years of age, the patient displayed no progress in speech production and minimal progress in receptive language development, but she had increased awareness of the world and an increase in the outcome on the QoL assessment.

Discussion

In *Chapter 5* the previous chapters are discussed, and the challenges and benefits of cochlear implantation in children with complex needs are summarized. We conclude that children deafened by CHARGE syndrome, cCMV infection or Kabuki syndrome present challenging cases for the CI-team because of anatomical abnormalities, cognitive disabilities and other co-morbidities. However, even in the face of these challenges, cochlear implantation in these children is beneficial and no strict contra-indications are indicated. Nevertheless, the outcomes of cochlear implantation in terms of speech and language development and quality of life are lower than that of peers without co-morbidities who use a CI. The outcome of cochlear implantation is more determined by medical/surgical issues and cognitive abilities of the child than by the disease itself. It is therefore important that a multi-disciplinary team discusses all potential CI candidates on a case-by-case basis.

5.3

Nederlandse samenvatting

Introductie

Hoofdstuk 1 is een algemene introductie over cochleaire implantatie bij dove kinderen en over de drie syndromen welke worden beschreven in deze thesis.

Een cochleair implantaat (CI) is een elektronisch apparaat dat dove mensen weer kan laten horen. Het bestaat uit een in de cochlea geïmplanteerde elektrode die direct de cochleaire zenuwvezels stimuleert. Cochleaire implantatie is een standaard behandeloptie geworden voor kinderen en volwassenen met ernstig tot zeer ernstig sensorineuraal gehoorverlies, die onvoldoende horen met een conventioneel hoortoestel. Op basis van de positieve resultaten van CI bij kinderen met geïsoleerde doofheid zijn de implantatie-criteria geleidelijk uitgebreid. Inmiddels wordt de CI ook bij kinderen met cognitieve achterstand geïmplanteerd. Het CHARGE syndroom, congenitale cytomegalovirus (cCMV) infectie en Kabuki syndroom zijn complex. Kinderen met deze syndromen kunnen (ernstig tot zeer ernstig) gehoorverlies en een cognitieve achterstand hebben naast andere co-morbiditeiten. Ook deze kinderen zouden baat kunnen hebben bij een CI.

De criteria voor de klinische diagnose van het CHARGE syndroom (MIM, Mendelian Inheritance in Man, 214800) zijn gedefinieerd door Blake (1998) en Verloes (2005). Het CHARGE syndroom is een acroniem van Colobomen, Hartafwijkingen, choanaal Atresie, Retardatie, Genitale hypoplasie en Oor (ear) anomalieën. In 2004 werd het verantwoordelijke gen geïdentificeerd als *CHD7* op chromostoom 8q12. Gehoorverlies is een van de meest voorkomende karakteristieken, en komt voor bij 80-100% van de kinderen. Het gehoorverlies kan worden veroorzaakt door anatomische afwijkingen van zowel het binnenoor als middenoor, door aplasie of hypoplasie van de nervus cochlearis, of door middenoorpathologie zoals chronische otitis media met effusie. Dit leidt bij kinderen met het CHARGE syndroom tot gehoorverlies van verschillende aard en variërend van normaal tot zeer ernstig.

Congenitale CMV infectie komt voor bij 1 op de 200 geborenen en is de voornaamste oorzaak van niet-genetische pediatrisch sensorineuraal gehoorverlies. In ongeveer 10% van de kinderen met symptomatische cCMV infectie kan gehoorverlies reeds bij de neonatale screening worden vastgesteld. In de helft van de kinderen met gehoorverlies ontstaat het in de eerste jaren na de geboorte, wat leidt tot 10% extra kinderen met gehoorverlies.

Kabuki syndroom heeft karakteristieken zoals typische gezichtskenmerken, cognitieve achterstand, postnatale groei deficiëntie, afwijkingen aan de handen en skelet afwijkingen. Gehoorverlies is een van de geassocieerde anomalieën in Kabuki syndroom en geobserveerd in 65% van de kinderen.

CHARGE syndroom

Hoofdstuk 2 richt zich op verschillende factoren van het CHARGE syndroom die cochleaire implantatie kunnen bemoeilijken. Dat de anatomie van het os temporale sterk varieert in patiënten met CHARGE syndroom wordt beschreven in *sectie 2.1*. Analyse van CTs van het

os temporale toonde vasculaire structuren aan zoals een petrosquameuse sinus en grote vena emissaria, een onderontwikkeld mastoid en een afwijkend beloop van de nervus facialis over het ronde venster en/of promotorium. Deze structuren kunnen het maken van een mastoidectomie en posterieure-tympanotomie bemoeilijken. Het maken van de cochleostomie kan lastig zijn bij patiënten met een stenotisch ronde venster (wat vaak gezien wordt bij deze patiënten). Het aspect van het binnenoor varieert sterk van partiële tot totale afwezigheid van de semicirculaire kanalen en van een normale tot ernstig hypoplastische cochlea. Patiënten met truncerende mutaties vertoonden meer anomalieën dan de patiënt met niet-truncerende mutaties in het *CHD7* gen.

In *sectie 2.2* wordt het gehoorverlies, cognitieve ontwikkeling en spraak en taalontwikkeling van patiënten met CHARGE syndroom (zonder CI) bestudeerd. Door het analyseren van de relatie tussen gehoorverlies en cognitieve ontwikkeling met taalontwikkeling, hebben we een indicatieve dataset vastgesteld voor een groep patiënten met complexe problematiek. Van 50 patiënten (5 maanden-48 jaar oud) van 'het Nederlandse CHARGE expertise centrum' (Universitair Medisch Centrum Groningen, Nederland) is de data geanalyseerd. De auditieve mogelijkheden, cognitieve mogelijkheden en taalontwikkeling bij patiënten met het CHARGE syndroom variëren sterk, maar zijn over het algemeen onder gemiddeld. De meerderheid (83%) van de patiënten had gehoorverlies, nagenoeg verdeeld over de verschillende categorieën van gehoorverlies (mild, matig, ernstig, doof). Van de 41 patiënten waarvan de cognitieve data beschikbaar was, had de meerderheid een IQ lager dan 70. Het gemiddelde receptieve taalquotiënt (22 patiënten) was bijna twee standaard deviaties onder de norm. Het gemiddeld expressieve taalquotiënt (14 patiënten) was meer dan een standaard deviatie onder de norm. Zowel receptieve taalquotiënt en mate van het functioneel gehoorverlies als receptieve taalquotiënt en cognitieve mogelijkheden, als expressieve taalquotiënt en mate van functioneel gehoorverlies waren positief met elkaar gecorreleerd. Taal en cognitieve data waren niet van alle patiënten beschikbaar. Het is mogelijk dat de groep van wie de data beschikbaar was, een preselectie van patiënten was met een ontwikkelingsachterstand doordat er een exclusie is opgetreden van patiënten die zo goed presteerden dat er geen testen werden gedaan, of patiënten te slecht presteerden om mee te doen aan taaltesten. Om deze preselectie tegen te gaan en de kwaliteit van zorg rondom patiënten met het CHARGE syndroom te verbeteren, zouden hoor- en ontwikkelingstesten standaard moeten worden afgenomen om te kunnen differentiëren tussen de rol van het gehoorverlies versus cognitieve achterstand in de achterstand in taalontwikkeling. Hierdoor zal ook adequate hoortoestelaanpassing kunnen plaatsvinden bij patiënten met gehoorverlies.

In *sectie 2.3* wordt de data geëvalueerd van tien kinderen die een CI kregen tussen 2002 en 2012 om een overzicht te verkrijgen van de uitdagingen en voordelen van CI chirurgie bij CHARGE syndroom. Beeldvorming en chirurgische bevindingen werden geanalyseerd. Taalontwikkeling en kwaliteit van leven in onze groep werd vergeleken met twee controlegroepen: (1) 34 niet-syndromale CI-gebruikers en (2) 13 kinderen met

CHARGE syndroom, maar zonder CI vanwege voldoende gehoor. Op basis van deze studie hebben we een voorstel gedaan voor een richtlijn voor cochleaire implantatie bij het CHARGE syndroom.

Alle kinderen met CHARGE syndroom die in deze sectie werden beschreven waren congenitaal doof en hadden een beneden gemiddeld cognitieve ontwikkeling naast andere comorbiditeiten. In drie kinderen was zowel pre-operatief subjectieve audiometrie, objectieve audiometrie en MRI noodzakelijk om de aanwezigheid van de nervus cochlearis te bevestigen. In alle kinderen was de chirurgie uitdagend door vergrote vena emissaria, semi-circulaire kanaal aplasie, een aberrant verlopende nervus facialis en dysplastische cochleaire vensters, wat het gebruik van de CT bij de pre-operatieve voorbereidingen onmisbaar maakte. Er hebben zich geen grote intra-operatieve complicaties voorgedaan. Ondanks de bijkomende handicaps lieten alle patiënten auditief voordeel zien en verbetering van de ziekte specifieke kwaliteit van leven. De kinderen met relatief lange follow-up die op jonge leeftijd een CI kregen ontwikkelden gesproken taal op basisniveau in vergelijking met dat van de controlegroep. Vier kinderen hadden spraakverstaanscores tussen de 60-90% na 60 tot 120 maanden. In de andere zes kinderen, kon het spraakverstaan niet worden gemeten met standaard testen, maar de kinderen konden geluiden adequaat detecteren. Het CI-gebruik en mogelijk ook de taalontwikkeling werd beïnvloed door de algemene gezondheidstatus, inclusief een niet-gebruiker als gevolg. Ondanks dat de absolute scores op de kwaliteit van leven-test van de kinderen met CHARGE syndroom lager waren dan van de controlegroep, werd een toename van kwaliteit van leven na implantatie gemeten. Op basis van deze evaluatie kunnen we concluderen dat CI overwogen moet worden in alle kinderen met CHARGE syndroom en ernstig sensorineuraal gehoorverlies. Een zorgvuldige work-up is vereist – met CT, MRI en objectieve en subjectieve audiometrie - beoordeeld door een gespecialiseerd multidisciplinair team. Cochleaire implantatie bij CHARGE syndroom is mogelijk gecompliceerd door syndroom-gerelateerde anatomie van het os temporale. Maar de uitkomst van CI wordt meer door het individu bepaald. Implantatie op jonge leeftijd moet worden nagestreefd.

Zoals we in *sectie 2.3* beschrijven, moet het CI-team bewust zijn van een eventuele deficiëntie van de nervus cochlearis (CND) bij patiënten met het CHARGE syndroom. Als er sprake lijkt te zijn van CND is een auditory brainstem implant (ABI) een alternatieve behandeling voor een CI. *Sectie 2.4* illustreert aan de hand van een casusbespreking en literatuuroverzicht, het dilemma wat zich voordoet wanneer de keuze tussen een CI of ABI gemaakt moet worden. We presenteren een casus van een kind met het CHARGE syndroom dat geen baat had van bilaterale cochleaire implantatie en een ABI nodig had voor gehoorverbetering.

In deze casus was op MRI de nervus cochleovestibularis aanwezig in het ene oor, maar er waren geen pre-operatieve auditieve hersenstamresponsies. In het contralaterale oor kon de zenuw niet worden geïdentificeerd op de MRI, ook al waren hiervan wel auditieve hersenstamresponsies gemeten. Niettemin, was er geen reactie op geluid met

bilaterale CI. Daarom werd besloten over te gaan tot het implanteren van een ABI. Patiënt had baat van de ABI op het gebied van spraak, taal en kwaliteit van leven.

Tijdens de evaluatie van deze casus werden verschillende stappen in de besluitvorming voor cochleaire implantatie kritisch bezien. Een literatuuroverzicht en meta-analyse over dit onderwerp leidde tot een evidence-based behandelstrategie. In het literatuuroverzicht werden 108 patiënten met CND en CI geïdentificeerd. Van deze patiënten bereikte 25% open-set spraakverstaan, 35% bereikte gesloten-set spraakverstaan en 41% kon geluiden detecteren of minder. We bestudeerden welke van de volgende variabelen het effect van CI bij patiënten met CND kon voorspellen: het aspect van de nervus cochlearis en de waarneming van de nervus cochleovestibularis op MRI, de diameter van de inwendige gehoorgang en benige nervus cochlearis kanaal op CT, (electrische) auditieve hersenstamrepons, (geholpen en ongeholpen) toonaudiometrie en oto-acoustische emissies. We vonden dat patiënten waarbij de nervus cochlearis op MRI niet kon worden waargenomen, een kleinere kans hadden op goede uitkomst van cochleaire implantatie dan patiënten met hypoplasie van de cochleaire zenuw, maar er waren uitzonderingen op deze bevinding. Geen van de andere variabele die onderzocht zijn, konden de uitkomst van cochleaire implantatie voorspellen. Dit ondersteunt het idee dat de huidige beeldvorming en audiometrische testen ons vermogen om voorspellers van CI-succes te identificeren, beperken. ABI kan een alternatieve behandeling zijn van cochleaire implantie bij patiënten met CND, maar de uitkomsten zijn over het algemeen slechter dan van patiënten met CI. Gebaseerd op deze resultaten concluderen we dat de initiële behandeling van patiënten met (ogenschijnlijke) aplasie van de nervus cochlearis een CI is. Als er geen succes met CI wordt bereikt, adviseren we te overwegen door te gaan met een ABI, eerder dan een tweede CI en het risico op verder vertraging van auditieve input te voorkomen.

Cochleaire implantatie bij patiënten doof door congenitale cytomegalovirus infectie

Hoofdstuk 3 focust op cochleaire implantatie bij patiënten met ernstig tot zeer ernstig gehoorverlies door een cCMV infectie. cCMV is de meest voorkomende oorzaak van niet-genetisch congenitaal gehoorverlies. *Sectie 3.1* focust op de prevalentie van cCMV infecties bij CI ontvangers met prelinguale doofheid en de pathofysiologie van cCMV en ernstig tot zeer ernstig gehoorverlies.

Voor dat doel werd cCMV retrospectief gediagnosticeerd met behulp van de hielprikkaart in een cohort van kinderen en volwassenen met CI met prelinguale doofheid. Daarnaast werd perilymfatische vloeistof die standaard vrijkomt tijdens CI-chirurgie geanalyseerd op de aanwezigheid van CMV DNA (inclusief CMV gB/gH genotypes). In totaal werden 76 kinderen geincludeerd. Bloedmonsters waren beschikbaar van 29 van de geincludeerde patiënten waarvan 52% (15/29) CMV IgG seropositief waren. Indien CMV IgG seronegatief was, werd cCMV infectie als oorzaak van de doofheid verworpen.

Zeventig hielprikkaarten werden getest op CMV DNA, met als resultaat een prevalentie van cCMV van 14% (10/70). Perilymfe vloeistof was beschikbaar van 29 kinderen die een CI kregen. Van één patiënt, een 21 maanden oud meisje met cCMV, had CMV DNA positief perilymfe vloeistof. Het kind was asymptomatisch bij geboorte en het gehoorverlies werd gediagnosticeerd in de eerste weken na de geboorte. De CMV-stam in de perilymfe was genotypisch identiek aan de stam die aanwezig was in haar hielprikkaart. Perilymfe monsters van 21 volwassen CI ontvangers waren CMV DNA negatief. Deze data benadrukken de rol van cCMV bij CI ontvangers met pre-linguale doofheid. Daarnaast wordt door de genotypering de hypothese ondersteund dat CMV gerelateerde doofheid is geassocieerd met voortdurende virale replicatie in het binnenoor tot jaren na de geboorte. De voortdurende virale replicatie zou kunnen worden beïnvloed door antivirale therapie en uit toekomstige data zou de werkzaamheid moeten blijken van langdurige of uitgestelde antivirale behandeling van met cCMV geïnfecteerde pasgeborenen met een hoog risico op ernstig gehoorverlies.

Het voordeel van CI is niet altijd het best uitgedrukt in verbetering van spraaktaal-ontwikkeling, met name niet bij patiënten met cognitieve beperkingen. In deze patiënten is het voordeel soms beter uit te drukken in verandering van kwaliteit van leven. *Sectie 3.2* onderzoekt de gezondheidgerelateerde kwaliteit van leven in kinderen met zeer ernstig gehoorverlies door een cCMV infectie en behandeld met een CI (25 kinderen). Resultaten van de gestandaardiseerde kwaliteit van leven vragenlijsten werden vergelen met een controlegroep van kinderen zonder comorbiditeiten en een CI (37 kinderen). Medische data, niet-verbale IQ, leeftijd bij implantatie, aantal maanden CI gebruik en spraakverstaan resultaten werden gebruikt voor de analyses. De Nijmegen Cochlear Implant Questionnaire (NCIQ) en de Pediatrics Quality of Life Measurement (PedsQL) werden ingevuld om de (gezondheidsgerelateerde) kwaliteit van leven te meten. In de studiegroep werd voor de NCIQ totaalscore en voor alle subdomeinen van de NCIQ, op een subdomein na, een meer variabele score verdeling waargenomen in vergelijking met de controlegroep. De mediaan van de NCIQ totaalscore en subdomeinen duiden op een lagere kwaliteit van leven van de studiegroep in vergelijking met de controlegroep. Slechts de helft van de kinderen in de studiegroep behaalde een totaalscore op de PedsQL boven de 65,4 ('goede kwaliteit van leven'), in vergelijking met 86,5% van de kinderen in de controlegroep. Binnen de studiegroep waren IQ, implantatie (unilateraal of bilateraal), aantal uren van dagelijks CI gebruik en spraakverstaan positief geassocieerd met de kwaliteit van leven uitkomsten. Hieruit kunnen we concluderen dat uitkomsten van de ziektespecifieke en algemene gezondheid vragenlijsten meer gevarieerd en over het algemeen lager waren dan de uitkomsten van de controlegroep. Cognitieve beperkingen, comorbiditeit en laag niveau spraakverstaan, hebben mogelijke een negatieve invloed op de verbetering in kwaliteit van leven na implantatie.

Cochleaire implantatie bij Kabuki syndroom

Hoofdstuk 4 beschrijft de resultaten van cochleaire implantatie bij een kind met gehoorverlies door het Kabuki syndroom. Naast het gehoorverlies had patiënt cognitieve en andere beperkingen en communiceerde door middel van geluid en Nederlands gebarentaal. Tussen de leeftijd van anderhalf en zeven jaar droeg ze haar bilaterale hoortoestellen alleen op de dagopvang. Op acht jarige leeftijd werd een toename van gehoorverlies gemeten. Na cochleaire implantatie op negenjarige leeftijd vertoonde patiënt geen toename in spraakproductie en minimale verbetering in receptieve taalontwikkeling, maar er was een toename van bewustzijn van de wereld om haar heen en een verbetering in kwaliteit van leven.

Discussie

In *hoofdstuk 5* worden de voorgaande hoofdstukken bediscussieerd en zijn de uitdagingen en voordelen van cochleaire implantatie bij kinderen met complexe problematiek samengevat. We concluderen dat kinderen met doofheid door het CHARGE syndroom, cCMV infectie of Kabuki syndroom een uitdaging bieden voor het CI-team vanwege anatomische afwijkingen, cognitieve achterstand en andere comorbiditeiten. Maar zelfs in het licht van deze uitdagingen is cochleaire implantatie bij deze kinderen gunstig en zijn er geen strikte contra-indicaties indicaties aan te wijzen.

Desondanks zijn de uitkomsten van cochleaire implantatie in termen van spraak- en taalontwikkeling en kwaliteit van leven lager dan die van leeftijdsgenoten zonder comorbiditeiten die een CI gebruiken. Het resultaat van cochleaire implantatie wordt meer bepaald door medisch-chirurgische problemen en cognitieve vermogens van het kind dan door de ziekte zelf. Het is daarom belangrijk dat voor deze groep kinderen een gespecialiseerd multidisciplinair team alle potentiële CI-kandidaten van geval tot geval bespreekt, behandeld en een toegespitst zorgpad creëert.

5.4

Addendum

5.4.1 List of abbreviations

ABR:	auditory brainstem response
AP:	anterior-posterior
BCNC:	bony cochlear nerve canal
BER(A):	brainstem evoked response (audiometry)
cCMV:	congenital cytomegalovirus
CHARGE:	Coloboma, Heart disease, Atresia of the choanae, Retarded growth and development and/or CNS anomalies, Genital hypoplasia, and Ear anomalies
CI:	cochlear implant
CND:	cochlear nerve deficiency
CVN:	cochleovestibular nerve
CT:	computed tomography
dB:	decibel
DBS:	dried blood spots
IAC:	internal auditory canal
IP:	incomplete partition
IQ:	intelligence quotient
LM:	lateral-medial
LQ:	language quotient
MRI:	magnetic resonance imaging
OW:	oval window
PCR:	polymerase chain reaction
PPS:	persistent petrosquamosal sinus
PTA:	pure tone average
QoL:	quality of life
RW:	round window
SCC:	semicircular canal
SD:	standard deviation
UTI:	unable to identify
UV:	unknown-variant
VA:	vestibular aqueduct

5.4.2 Dankwoord

Het maken van een proefschrift doe je gelukkig niet alleen. Zonder de hulp van vele mensen was dit boekje niet tot stand gekomen. Een aantal van hen zou ik in het bijzonder willen bedanken.

Professor E.A.M. Mylanus, beste Emmanuel, er zijn maar weinig mensen met zo'n drukke agenda als jij. Ondanks deze drukte wist jij altijd een mogelijkheid te vinden voor overleg. Het is bewonderenswaardig hoeveel ballen jij in de lucht weet te houden en daarnaast een promotietraject weet te begeleiden. Fijn dat er naast de inhoudelijke zaken ook altijd aandacht was voor activiteiten buiten het ziekenhuis zoals hockey, fietsen en skiën. Dank voor je begeleiding!

Professor A. F.M. Snik, beste Ad, pas laat in het traject ben je bij mijn onderzoek betrokken geraakt, maar het was een groot voorrecht om met jou te mogen samenwerken. Jouw wetenschappelijke kennis, goede ideeën en (en soms vaderlijke) adviezen waren voor mij erg waardevol en heb ik erg gewaardeerd.

Professor C.M.A. van Ravenswaaij, beste Conny, jouw jarenlange ervaring in de wetenschap met name op het gebied van het CHARGE syndroom is van grote waarde geweest voor dit manuscript. Via jou heb ik veel data kunnen verkrijgen, maar ook jouw kritische blik heeft mij erg geholpen. Het was erg fijn met je samen te werken. Dank voor je goede adviezen en je begeleiding.

Dr. B. Verbist, beste Berit, met veel plezier kijk ik terug naar de uren die we in de 'badkamer' van de radiologie hebben doorgebracht. Ik heb veel van je geleerd en je bent onmisbaar geweest in de totstandkoming van enkele hoofdstukken. Dank voor je inzet en bijdrage aan mijn onderzoek en dank voor de gezelligheid tijdens het beoordelen van het de grote hoeveelheid scans.

Dr R.H. Free, beste Rolien, het was erg fijn om met jou samen te werken. Jouw inspanning bij het beoordelen van de scans, je ideeën en je motiverende mailtjes waren onmisbaar, heel veel dank voor het meedenken en je inzet.

Dr. M.C. Langereis, beste Margreet, ik kijk met plezier terug op onze samenwerking. Dank voor je eindeloos geduld om met mij door alle taaldata heen te werken, dank dat je ondanks je drukke agenda altijd tijd wist te maken voor overleg.

Leden van de manuscriptcommissie, professor. dr. I. Dhooge , professor dr. M.A.A.P. Willemsen, professor dr. H.E.T. Knoors hartelijk dank dat u het manuscript heeft willen lezen en beoordelen.

Drs. Snels, beste Chantal dank voor je hulp bij twee artikelen. Het was heel gezellig om samen te werken en het was fijn dat ik gebruik kon maken van jouw statistische vaardigheden.

Staf van de KNO Radboud. Dank voor de fijne en zeer goed opleiding. Bewonderenswaardig hoe jullie een veilige en motiverende leeromgeving weten te creëren, waarbij de gezelligheid niet vergeten wordt!

(oud-)AIOS van de KNO, dank voor alle gezelligheid in de afgelopen jaren. Fijn hoe je wordt opgenomen binnen de KNO-wereld en lief en leed met elkaar kan delen. En bijzonder dat je naast collega's ook goede vrienden kan zijn! De IMMG in het bijzonder!

Lieve oud-teamgenoten van dames 2/3 NMHC, dank voor de gezelligheid tijdens mijn Nijmeegse jaren. Zo fijn om naast het werken jullie als gezellige en sportieve uitlaatklep te hebben gehad!

Lieve paranimfen Eline en Nicole, dank dat jullie mij willen bijstaan! Eline, de jaren die wij samen op de researchgang hebben doorgebracht zal ik nooit vergeten, de kinderen-voor-kinderenliedjes, de grappen en het eindeloze kletsen waren een zeer aangename afleiding van het harde werken. Lieve Nicole, dank dat je altijd voor me klaar staat en dat ik alles met je kan bespreken. Ik bewonder je positieve instelling en gebruik vaak jou uitspraak: alles komt goed, uiteindelijk, altijd.

Lieve meisjes van JC Stout, bijzonder hoeveel we samen al meegemaakt hebben en hoeveel fantastische jaren we tot nu toe hebben beleefd! Door mijn verhuizing naar de andere kant van het land zagen we elkaar veel minder, maar de vriendschap is zeker niet minder geworden. Jullie hebben het af en toe zwaar met mij gehad, dank voor jullie luisterende oren en de afleiding in de afgelopen jaren.

Lieve pappa en mamma, Ernst Jan en Noor, dank voor jullie onvoorwaardelijke steun tijdens mijn promotietraject, maar ook in de rest van mijn leven. Dank dat jullie mij altijd hebben gestimuleerd om op ontdekking te gaan, door te zetten en dat jullie mij hebben geleerd door hard te werken ergens te komen. En Noor, heel veel dank dat ik gebruik heb kunnen maken van jouw vormgevende kwaliteiten, de kaft is prachtig!

Allerliefste Jasper, wat ben ik blij dat ik jou ben tegen gekomen, tegen al mijn verwachtingen in, een Brabander uit Nijmegen. De steun die jouw begrip, vertrouwen, liefde en gezelligheid mij hebben gegeven zijn niet in woorden uit te drukken, maar hebben een zeer grote rol gespeeld bij de totstandkoming van dit boekje, heel veel dank daarvoor! Daarnaast heb je gezorgd dat we heel veel leuke dingen samen deden als ik (wij) niet aan mijn promotie werkte. Die leuke dingen gaan we alleen nog maar meer doen…We gaan, samen met Thomas, nog een geweldig leven tegemoet! Ik hou van je!

5.4.3 Curriculum Vitae

Annemarie Vesseur, geboren op 2 april 1984, groeide op in Rotterdam. Vanaf haar tiende woonde ze in Zwolle, waar ze in 2002 haar diploma haalde aan het Gymnasium Celeanum. Ze studeerde geneeskunde aan de Universiteit Leiden. Tijdens haar studie was ze actief bij de Leidse studentenvereniging Minerva. Na haar studie startte ze in 2010 als arts-onderzoeker aan de afdeling KNO-heelkunde van het Radboud UMC, waar ze in 2011 begon aan de opleiding tot KNO-arts. Na haar opleiding in 2016 was ze werkzaam als KNO-arts in het Diakonessenhuis in Utrecht. Sinds april 2018 werkt ze in het Rijnstate in Arnhem.
Ze woont sinds 2015 samen met Jasper en zij hebben samen een zoon, Thomas.

5.4.4 List of Publications

Vesseur AC, Verbist BM, Westerlaan HE, Kloostra FJ, Admiraal RJ, van Ravenswaaij-Arts CM, Free RH, Mylanus EA. **CT findings of the temporal bone in CHARGE syndrome: aspects of importance in cochlear implant surgery.** Eur Arch Otorhinolaryngol. 2016 Dec;273(12):4225-4240. Epub 2016 Jun 20.

Vesseur A, Langereis M, Free R, Snik A, van Ravenswaaij-Arts C, Mylanus E. **Influence of hearing loss and cognitive abilities on language development in CHARGE Syndrome.** Am J Med Genet A. 2016 Aug;170(8):2022-30. Epub 2016 May 4.

Vesseur AC, Verbist BM, Westerlaan HE, Kloostra FJ, Admiraal RJ, van Ravenswaaij-Arts CM, Free RH, Mylanus EA. **Suggestions for a Guideline for Cochlear Implantation in CHARGE Syndrome.** Otol Neurotol. 2016 Oct;37(9):1275-83.

Vesseur A, Snels C, Mylanus E, Free R, Verbist B, Frijns J. **Hearing Restoration in Cochlear Nerve Deficiency: The choice between Cochlear Implant or Auditory Brainstem Implant**. Otology & Neurotology 2018 Apr:39(4):428-437

de Vries, J. J., A. Vesseur, L. J. Rotteveel, A. M. Korver, L. G. Rusman, E. Wessels, A. C. Kroes, E. A. Mylanus, A. M. Oudesluys-Murphy, J. H. Frijns and A. C. Vossen (2013). **Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness.** J Clin Virol **56**(2): 113-117.

Vesseur A, Snels C, Langereis M, Snik A, Mylanus E. **A Case-control study: Quality of life in children post Cochlear Implantation with congenital Cytomegalovirus-related deafness.** Submitted to Clinical Otolaryngology

Vesseur A, Cillessen E, and Mylanus E (2016). **Cochlear Implantation in a Patient with Kabuki Syndrome.** J Int Adv Otol **12**(1): 129-131.