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CONGENITAL CMV INFECTION AND CONNEXIN 26 MUTATIONS IN CHILDHOOD DEAFNESS – INTERVENTION WITH EARLY COCHLEAR IMPLANTATION

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av
Eva Karltorp
Leg Läkare

Huvudhandledare:
Professor Sten Hellström
Karolinska Institutet, Institutionen för Klinisk Vetenskap, Intervention och Teknik

Bihandledare:
Professor Ulf Rosenhall
Karolinska Institutet, Institutionen för Klinisk Vetenskap, Intervention och Teknik

Bihandledare:
Docent Ilona Lewensohn-Fuchs
Karolinska Institutet, Institutionen för laboratoriemedicin, Avd för klinisk mikrobiologi

Fakultetsopponent:
Professor Stefano Berrittini
Pisa Universitet
Dept of Neuroscience

Betygsnämnd:
Professor Helge Rask Andersen
Uppsala Universitet, Institutionen för kirurgiska vetenskaper, Enheten för ÖNH sjukdomar

Professor Birgitta Sahlén
Lunds Universitet
Institutionen för kliniska vetenskaper, Logopedi, foniatri och audiologi

Professor Hugo Lagercrantz
Karolinska Institutet, Institutionen för kvinnor och barns hälsa

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From DEPARTMENT OF CLINICAL SCIENCE,
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To my wonderful family
and to Elsa

ABSTRACT

Hearing impairment (HI) is a common disability, which affects a significant proportion of the population. Early in life, however, the risk of acquiring a HI is low, with 0.2 % of all newborns having a permanent HI, and of these, 0.04 % have a severe or profound HI. Even if there are only a few children born with a permanent HI, the consequences can be devastating for their speech perception and spoken language development. Normal hearing children, start to hear and differentiate sounds already in the fifth month of pregnancy, and thereafter, their speech and language acquisition is intensive during the first years of life. If, however, a child with a HI is to have a chance to catch up with normal hearing children, in terms of spoken language acquisition, it is important to provide the child with the best possible auditory input at the earliest opportunity.

The two most common reasons for permanent childhood HI are congenital cytomegalovirus (cCMV) infection and Connexin 26 (Cx26) mutations. cCMV infection might give the child other disabilities, such as cognitive delay, cerebral palsy and visual impairment, in addition to the HI. For children with Cx26 mutations, additional disabilities are less common.

The aim of this thesis was to study the results after CI intervention in children with permanent HI, and especially, to examine the effect of implantation in infants. Moreover, the aim was to study children with cCMV infection and Cx26 mutations and to describe the additionally disabilities arising from a cCMV infection.

In the first study, 90 children with a variety of HIs, which were of unknown etiology and non-syndromic, were tested for cCMV infection. The dried blood spot (DBS) sample, taken in the newborn period, was analysed for CVM DNA. Of the 90 children, 18 (20%) tested positive for cCMV infection.

In the second study, 79 children, of whom the majority had severe to profound, non-syndromic HI, were tested for Cx26 mutations. Twenty-four of the 79 children (30 %) had two pathological Cx26 mutations.

In the third study, 26 children with a HI caused by cCMV infection and 13 children with a HI caused by Cx26 mutations were examined by a multidisciplinary team, with the intention of investigating how frequently additional disabilities were present. Among the children with cCMV infection, there were a high number of children with disturbed balance and in addition neurodevelopmental disabilities and feeding problems were also found. Many of these additional disabilities have not previously been associated with a cCMV infection. In the Cx26 group, such additional problems were not found.

In the fourth study, a cohort of 137 children with CIs, operated between 2002 and 2011 was described. When children were operated on before nine months of age, no language delay was apparent when compared with data for normal hearing children. Additionally, their speech intelligibility was rated high sooner than for children who received their implants at a later age. The children who received implants between 9 and 11 months of age, caught up with the children operated on before they were nine months old, within two to three years. When their vocabulary was tested, the children with implants introduced at 12-17 months of age, caught up at early school-age. Those implanted later, when 18 months old or more, did not, however, catch up with the children who had received implants when younger.

In conclusion, early CI intervention is of great importance for children born with profound HI, if the aim is to acquire age-equivalent spoken language development. In addition, knowledge about the child's etiology is important for an appropriate early and correct HI diagnosis, and to identify possible additional disabilities. Based on this broader knowledge about the child with a HI, it will be possible to give the child and family tailored support.

LIST OF PUBLICATIONS

I. Karltorp E, Hellström S, Lewensohn-Fuchs I, Carlsson-Hansén E, Carlsson P-I, Engman M-L. Congenital CMV infection - a common cause of hearing loss of unknown aetiology. Acta Paediatr. 2012 Aug;101(8):e357-62

II. Carlsson P-I, Karltorp E, Carlsson-Hansén E, Åhlman H, Möller C, VonDöbeln U. GJB2 (Connexin 26) gene mutations among hearing-impaired persons in a Swedish cohort. Acta Otolaryngol. 2012 Dec;132(12):1301-5.

III. Karltorp E, Löfkvist U, Lewensohn-Fuchs I, Lindström K, Eriksson Westblad M, Teär Fahnehjelm K, Verrecchia L, Engman M-L. Impaired balance and neurodevelopmental disabilities in cochlear implanted children with cytomegalovirus-related hearing-loss. Submitted.

IV. Karltorp E, Eklöf M, Freijd A, Östlund E, Asp F, Smeds H, Hellström S, Löfkvist U. Cochlear implantation before nine months of age is beneficial for the outcome of spoken language – a longitudinal study. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ABR	Auditory brainstem response
ADHD	Attention deficit hyperactivity disorder
AR	Asymmetry ratio
ASD	Autism spectrum disorder
ASSR	Auditory steady state response
BNT	Boston naming test
cCMV	Congenital cytomegalovirus
CI	Cochlear implant
CIC	Cochlear implant clinic
CT	Computer tomography
Cx26	Connexin 26
DBS	Dried blood spots
fPB	Phonemically balanced words, female voice
FTF	Five to fifteen questionnaire
GJB2	Gap junction beta 2 gene
HI	Hearing impairment
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LI	Language impairment
M ABC-2	Movement ABC-2
mPB	Phonemically balanced words, male voice
MRI	Magnetic resonance imaging
PCC	Percentage consonants correctly produced
PCR	Polymerase chain reaction
PPVT-3	Peabody picture vocabulary test
RDLS III	Reynell developmental language test
SIR-2	Speech intelligibility rating scale
VEMP	Evoked myogenic potentials
vHIT	Video head impulse test
VRA	Visual reinforced audiometry
VOR	Vestibular ocular reflex
35delG	*GJB2* mutation

INTRODUKTION

The overall purpose of the work conducted for this thesis was to examine the possibility of restoring hearing with cochlear implants (CIs) in infants and young children and, especially, to study the effect of age at implantation. In addition, the two most common causes of early childhood hearing impairment, congenital cytomegalovirus (cCMV) infection and Connexin 26 (Cx26) mutations, have been explored.

1. Background

Hearing impairment

Hearing impairment (HI) is a common disability, affecting at least 10 % of the Swedish population. A HI might be anything from mild/unilateral hearing loss, to severe or profound HI, affecting both ears. As one might anticipate, the more pronounced the HI, the harder it is for a person to compensate for their HI.

Early in life, the risk of acquiring a HI is low in Sweden, with 0.2 % of all newborns having a permanent HI, and of these, 0.04 % have a severe or profound bilateral HI. The older a person gets, the higher the risk of acquiring a permanent HI. In a typical Swedish population of 80-year olds, at least 50 % have a HI that affects their ability to communicate, and, therefore, has an impact on their quality of life. A person with single sided HI or deafness will have an impaired sound localization ability and will have problems hearing in noisy environments, even if their hearing is normal on the contralateral ear.

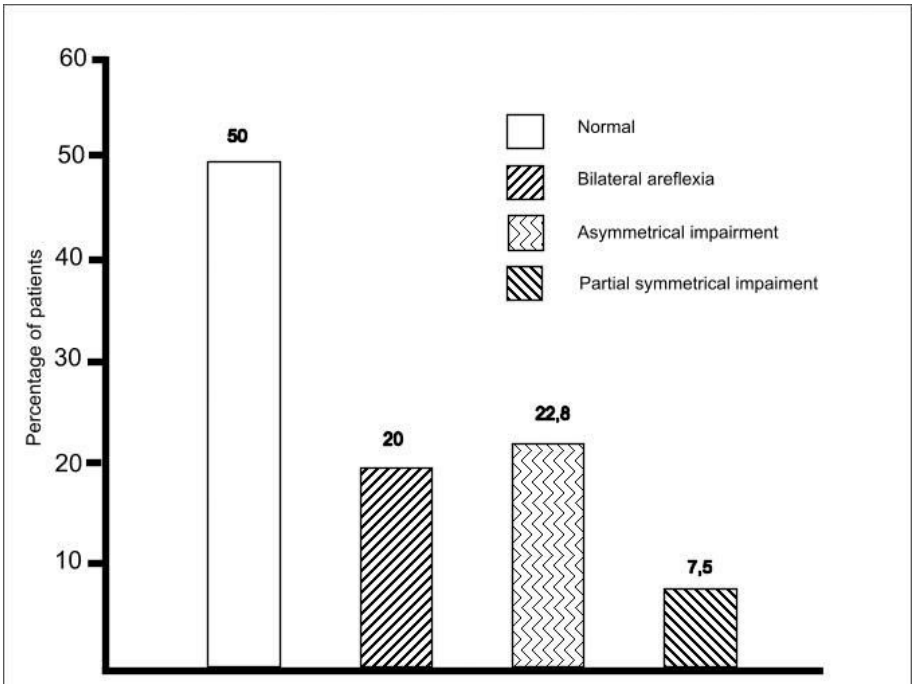
In almost all cases of permanent HI, the hair cells in the sense organ inside the cochlea are damaged, but in rare cases the reason for the HI is an ossified, malformed or even absent cochlea, and/or a thin or absent hearing nerve.

Balance disability among children with HI

The vestibular receptors, consisting of vestibular canals and otolith organs in the inner ears, contribute to postural control and gaze stabilization. As the vestibular receptors and the cochlea are closely located, it is not surprising that many children with HIs also have vestibular loss. Studies of children with, for example bilateral, profound HI of unknown etiology, showed that only 50 % had normal, symmetrical vestibular function. Of the children with vestibular dysfunction, 20 % had a total, bilateral loss and more than 20 % had an asymmetrical impairment. The vestibular dysfunction gives rise to impairment in the children's motor development, balance and reading abilities, issues for which the children in the investigation needed to receive appropriate interventions.

As for HI, the more pronounced the vestibular loss, the harder it is for the patient with vestibular loss to compensate. However, one difference with vestibular function compared to hearing function, is that a normal vestibular function on just one side, is sufficient to enable the affected child to attain normal balance in daily life.

Vestibular impairments among children with profound HI



With permission from the author, Dr Wiener-Vacher, Paris

Brain plasticity

Even if relatively few children are born with a permanent HI, the consequence of an early HI is devastating where the children's speech perception and spoken language development are concerned. It is in the brain's auditory domains that sounds, transferred from the sensory organ in the cochlea, are perceived and interpreted[1]. The brain has developed to learn to interpret sounds early on in life and, in the brain of a normal hearing child, this auditory developmental phase is thought to be as short as three years, then it declines. The hearing process already starts before birth, as the unborn child hears and starts to differentiate sounds from the fifth month of pregnancy onwards[2, 3]. With this in mind, it is easy to draw the conclusion that these early months and years of the infants' hearing development are of the utmost importance[4-6]. It is, thus, necessary to give the infant with a HI the best possible auditory input at the earliest opportunity to enhance the child's acquisition of spoken language[1].

In contrast, for a person who has learnt to hear and talk through audition, and then loses the hearing ability later in life, the memory of sounds and language is imprinted in the brain. Thus, a person with this background can benefit from a CI intervention decades after the actual hearing loss. Adolescents and adults with acquired hearing loss have a much longer time span during which they can receive help to restore their hearing, compared to an infant born with a profound HI.

Neonatal hearing screening

Universal neonatal hearing screening started in 1989 in Rhode Island[7, 8], followed by Hawaii[9], both in US, and gradually, thereafter, the screening spread to all developed countries. In Sweden, the university hospital in Linköping started a newborn hearing screening program in 1995[10], and this was the first such program in Sweden. In 1998, Karolinska University Hospital, Huddinge, also started to screen newborn babies[11]; the other hospitals in Sweden followed. Since 2006, hearing screening is offered to all newborns in Sweden.

The neonatal hearing screening has been shown to be an excellent tool with which to identify children with a HI during the first weeks of life[8].

Further hearing assessments

The hearing screening of a newborn will only reveal if the child has normal hearing or not. Hereafter an assessment of the permanent hearing-impaired child has to take place with the aim of finding out if the HI is mild, moderate or severe. Moreover, one has to determine if the impairment is symmetric or asymmetric. Electrophysiology tests, with click-evoked auditory brainstem response (ABR) and auditory steady state response (ASSR), both of which are tested when the child is sleeping, are used. Together with behavior testing with visual reinforcement audiometry (VRA), used when the child is awake, one often gets a full picture of the child's HI. Even so, in some cases it can be hard to be sure of the degree of the child's HI. Audiological tests, paired with knowledge of the etiology of the HI, will raise the certainty of the level of the child's hearing loss. Thus, a known etiology, such as a cCMV infection, Cx26 mutations or another recognized cause, will add certainty to the HI diagnosis and, therefore, be an important tool in the diagnostic work.

Early hearing aid fitting

In 1998, Yoshinaga-Ithano et al[12], showed that the results were better if the child was fitted with a HA before six months of age, compared to children fitted after six months of age. At that time, fitting a HA at the age of six months was thought to be very early. However, this was in line with the scientific hypothesis that there is a critical period when language acquisition has to take place. Referring to the results of Yoshinaga's study, audiologists in many places around the world, started to fit HAs on younger and younger children. In Stockholm, the first child younger than six months of age was fitted with a HA in 1999. Soon, though, it became a standard procedure to fit a HA on children below six months of age. To accomplish this early HA fitting for the majority of children with HI, neonatal hearing screening was a necessity.

Cochlear implants; technology, operations and surgical complications

A CI is an implanted device that gives a person with profound HI/deafness the possibility to hear. The device consists of two parts; one implanted part with a receiver connected to an electrode, which is placed inside the cochlea, and an external part worn behind the ear.

The first CI operation in an adult with an early, single channeled CI technology was performed in US 1971[13]. The first child was operated on 1975. Two other research groups, one in Vienna, Austria[14] and one in Melbourne Australia[15], worked on multi-channeled devices. The first operations to implant these multi-channeled devices, took place in 1977 and 1978 respectively. In the following years, a remarkable development in the CI

technology was seen, giving the persons operated on with the more modern CI technology better possibility of achieving higher levels of speech perception.

The first CI operation of a Swedish adult was performed in 1984, and in 1990 the first Swedish child was operated on. At present, in November 2013, approximately 2600 Swedish persons have received and use CIs, amongst whom 830 (30 %) implanttations were performed in childhood.

The rate of major surgical complications, such as wound infections, is very low for both pediatric and adult CI surgery, and in most reports are around 2 % of the cases[16].

Criteria for pediatric CI intervention

At the advent of pediatric cochlear implantation the criteria for receiving a CI was a bilateral, profound HI. The vast majority of the children worldwide received a CI in only one ear. In Sweden, there was a shift towards bilateral implants for children around 2004, and, since then, almost all Swedish children receive bilateral implants, if their HI is profound in both ears.

The bilateral approach also changed the criteria for children with an asymmetric HI. In Stockholm, children with a moderate HI on one ear and a profound HI on the other ear, have been offered a CI on the ear with profound HI since 2005. Furthermore, since 2008, children with normal or close to normal hearing for the low frequencies and a severe high-frequency hearing loss, have been offered a CI. For these operations, a soft, short electrode designed to preserve the natural hearing in the low frequencies is used.

In summary, the changing criteria for pediatric CI intervention, has led to the possibility to help a much larger group of children and teenagers with HIs to acquire a better speech perception and spoken language development.

Factors influencing outcome among children with CI

Many factors are known to influence the outcome for children with a CI[17, 18]. A long stream of variables are involved: the etiology of the child's hearing loss, the child's hearing level during the first months or years of life, the child's age at the time of the CI operation, the presence of additional disabilities, the parent-child interaction, the parental education level, the quality and quantity of spoken language, the communication mode and bilingualism, among others. Because of the existence of all these variables, results relating to the outcome reported for children with CIs need to be estimated with caution. In addition, owing to the many factors influencing outcome, having a large number of children participating in the study is a necessity, if one is to be able to draw any firm conclusions from the results.

Speech recognition with CI

Children using CIs generally achieve high speech recognition in quiet environments, although not at the same level as their normal-hearing peers. However, the speech recognition achieved by children with CI, opens up the possibilities for these children to develop spoken language primarily through listening.

In the presence of background noise, a condition which children experience in daily life, speech recognition for children with CIs is severely affected[19]. In an attempt to provide better hearing in noise, it is increasingly common to implant children bilaterally, as this offers a significant speech recognition benefit in the presence of noise. In both quiet and noisy listening conditions, the intersubject variability is high, which in part may relate to

factors such as cochlear malformations, cochlear ossification and the quality and thickness of the auditory nerve, however, these factors only account for a part of the variability.

The age at the time of implantation, at least if the child is operated on below three years of age, has not been a significant factor for affecting the speech perception[20].

Language development with CI

The result and outcome of CI intervention is primarily measured as the rate of the spoken language development of the child who has been operated on. In the western world, and possibly especially in Sweden, an extraordinary shift has occurred during the last 10 years: Among children with a CI, there was a low level of spoken language ability 10-15 years ago. However, nowadays children in a comparable situation have the possibility of achieving age equivalent spoken language abilities.

During the 1990s, when about 150 Swedish children had received an implant, the theoretical basis and habitation situation in Sweden was based on a bilingual approach; sign language provided the foundation and, later, spoken and written Swedish acquisition was tackled[21]. The CI operation was postponed to later in the child's life, and, thus, spoken language development started at a greater age. The mean age for a CI-operation for children born with profound HI at this time was as high as around three to four years of age, and most children receiving a CI attended preschools and schools where sign language was their main educational language. There were generally low expectations for the children's auditory-verbal development during this period.

However, at the beginning of the 21th century, the age at implantation was gradually lowered and parents started to ask for habilitation options supporting spoken language development. Auditory verbal therapy (AVT)[22] was introduced as a new habilitation option in Sweden in 2005, and around 50 professionals from all over Sweden have been educated in AVT practice up to now (2013). The change of focus in the habilitation system, and the increasingly younger age at the time of implantation have, together, altered the potential spoken language outcome for a considerable number of children with CI. Nowadays, the vast majority of children with CI, without additional disabilities, are able to communicate using spoken language if the CI intervention commences within the first 2.5 years of the child's life. If the CI intervention is started even earlier, before one year of age, the majority of this group of children will attain an age equivalent spoken language level. The mean age at the time of operation for the 16 children, without additional disabilities, who have been operated on so far during 2013 at the Cochlear Implant Clinic (CIC) in Stockholm, was 10.6 months. Thus there has been a huge shift towards earlier CI intervention since the 1990s.

The development after the first CI fitting is measured by using validated and commonly used spoken language tests. Examples of language abilities that are followed longitudinally are language understanding (Reynell III[23]), vocabulary (PPVT III[24] and BNT[25, 26]), output phonology (PCC[27]) and speech intelligibility (SIRI-II[28]). The results are used for comparison with norm data and with results for children with CIs from other countries.

2. Etiology of permanent childhood hearing impairment

Acquired hearing impairment

There is a long list of different etiologies underlying permanent HI in early childhood[8, 29, 30]. Furthermore, all through history, the etiological patterns have looked different[31].

Infections such as rubella[32] and syphilis[33] that lead to fetuses already having HI at birth were common in western countries 30 years ago. Today these prenatal infections are very rare owing to the treatment of syphilis and the use of an effective vaccination against rubella. Bacterial meningitis caused by Haemophilus influenza and Streptococcus Pneumoniae could lead to deafness – if the patient survived the infection. In this instance both children and adults can be infected, but the infection is most common among children below the age of two years. These infections are getting increasingly rare, thanks to effective vaccination programs spreading in the developed world. Nowadays, meningitis is very rare cause of deafness in Sweden. General vaccination, as a part of the Swedish child vaccination program, started in 1974 against rubella, 1993 against Haemophilus influenza, type B and 2009 against some species of Streptococcus Pneumoniae. In developing countries, without general vaccination programs, these infections still affect children and cause, deafness, other disabilities as well as death.

CMV infection, however, still remains without an efficient treatment or vaccination available, and it is the most common congenital infection in existence today, at least in developed countries. This infection will be more thoroughly discussed later.

Hearing problems related to all of the infections mentioned above could be categorized as causing acquired hearing loss. In this group of etiologies, also includes other causes affecting the fetus or young child, like asphyxia, hyperbilirubinemia or other pre-natal risk-factors, or postnatal risk-factors like chemotherapy or cholesteatoma.

Estimated prevalence of HI among four year old children

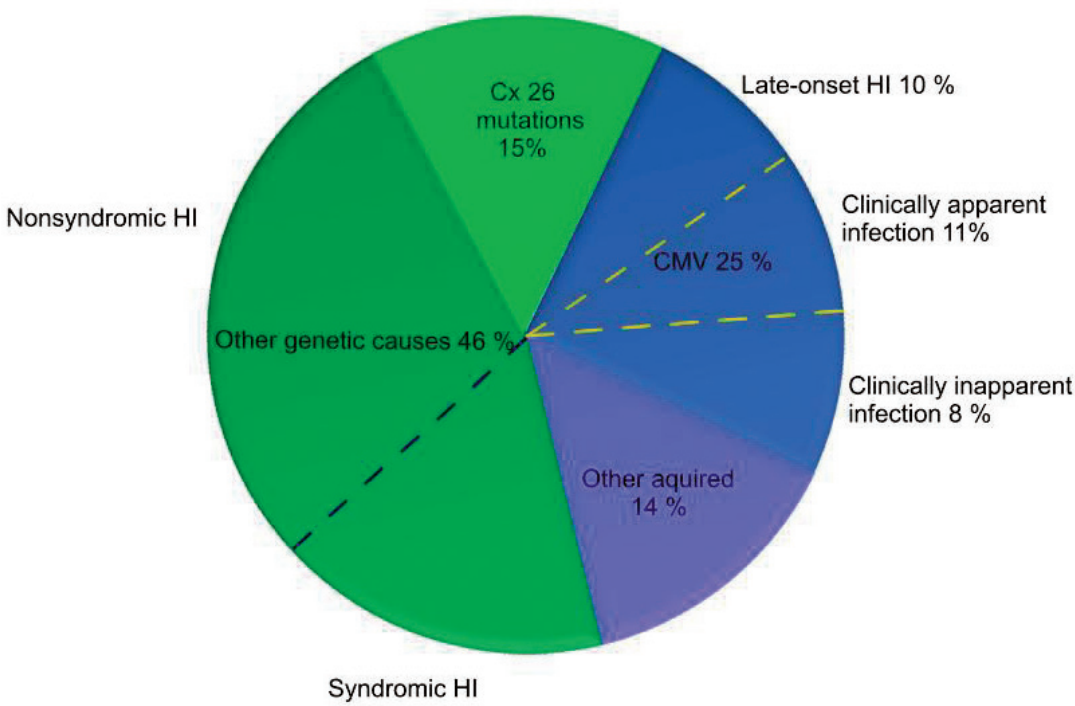


Chart adapted from Morton and Nance

Genetic hearing impairment

Other causes of early childhood HI are most probably attributable to genetic factors[8] and in the western world more than 50% of early onset HI is estimated to be genetic. Genetic HI can be classified as either syndromic or non-syndromic. Non-syndromic HI is a HI that is unrealted to other medical conditions. In contrast, syndromic HI occurs in connection with abnormalities in other parts of the body. At this time, the number of known genes causing non-syndromic HI is approaching 80, and in syndromic HI even greater number of genes have been identified.

In the near future, it will be possible to perform a broad genetic screening on all newly diagnosed children with a HI. Until then, only tests for the most common genes are carried out. As a consequence, today the molecular genetic background of hereditary HI is not widely available in the clinical setting.

More than 50% of recessive non-syndromic HI is caused by bi-allelic mutations in one single gene, *GBJ2*. The gene encodes the gap junction beta 2 proteins, Connexin 26 (Cx26), and the importance of this gene in congenital or early onset HI will be discussed separately.

2.1 Congenital cytomegalovirus (cCMV) infection

CMV has long been believed to be a harmless virus, except when it infects fetuses and individuals with a suppressed immune system. The supposed harmlessness of CMV might, however, not be true, as studies have shown that CMV can be involved in the pathogenesis of Alzheimer, cancer and autoimmune diseases, among others[34-36]. Even if only a part of these concerns will be proven to be correct, the harm that the CMV virus could do is large.

CMV is a beta-herpes virus: it is the largest virus within the group. One characteristic of CMV, as for the rest of the herpes virus-group, is that, once it has been introduced, the virus remains in the body for the rest of a person's life[37]. When a person gets the infection for the first time, it is called a primary infection[38]. After this event, the infection remains in the white blood cells of the infected person. Hereafter, the virus can reactivate at times when the person's immune system is suppressed, for example, during pregnancy or during an active HIV infection[39]. There is also a possibility to get infected by a new strain of CMV virus[40].

After infection with CMV, one has a period in which the CVM virus is shed through the urine, saliva, blood, milk and, for males, through semen[41]. The time period for shedding the virus might be many years, especially for toddlers. If the virus gets reactivated, a shorter or longer time of shedding occurs once again. Children with a congenital CMV infection have a particularly long shedding period. CMV is spread through close contact with body fluids and, as expected, the most common means of transmission is to get the infection from children of the pre-school age. The symptoms of a primary CMV infection are very meager in general, but a long period of unexplained fever or exhibition of the symptoms of a sinusitis might occur. The lack of specific symptoms means that the infection remains unidentified and is hard to map.

Most often, one acquires the infection early in life, and in developing countries the majority of the population have had a CMV infection before they reach adulthood. In the western world, fewer have been infected by the time that they are young adults, and the more urban the environment in which a person lives, the lower the chance that a person

will have been infected. For example, in Brazil, 99 % of first time mothers are carriers of CMV DNA[42], compared to 70 % in Sweden[38] and 50 % in London[43].

If a pregnant woman has a CMV infection, there might be transmission to the fetus by the placenta. If the infection is a primary infection, the risk of transmission to the fetus is much higher (30-50%), in comparison to the transmission risk associated with recurrent infections or an infection with a new strain (1-3 %). A prospective Swedish study from 1990[38], showed that 50 % of the children with a cCMV infection had mothers with primary CMV infections and the remaining 50 % of the children had mothers with recurrent infections or who had been infected with a new strain.

Congenital CMV infection is present in 0.3 – 5.0 % of all newborn children[39, 44, 45]. The difference in prevalence is mainly thought to be the result of differences in the prevalence of CMV among mothers. In Brazil, where almost all mothers are already infected with CMV and thus the vast majority of children born with cCMV attain the virus through reactivated infections or infections with a new strain, the incidence of cCMV infection among newborns is 2 %[42].

Symptomatic/asymptomatic cCMV infection

Ten to fifteen percent of newborns with a cCMV infection might have symptoms at birth, however, as the majority of children with a cCMV infection do not have any symptoms in the neonatal stage, the infection would not be discovered by the conventional check-ups made at this time of life. The neonatal symptoms are unspecific and thus often overlooked like the symptoms of cCMV infection. The neonate with cCMV infection might have petechiae, jaundice and hepatosplenomegali. Premature birth might occur and the infant might have a low birth weight owing to placental insufficiency. Other symptoms are seizure and hypotonia. In a few percentages of cases, a severe, life-threating disease will occur owing to pneumonitis.

Permanent disability

Only cCMV infection is believed to give rise to permanent disabilities, in contrast to infections acquired during birth or later in life.

Fifteen to twenty percent of children born with a cCMV infection are believed to have a permanent disability. Previously, it was believed that only primary CMV infections would lead to a permanent disability in the child. Now, however, it is well-known that reactivated infections, and infections with new strains of CMV, may also give rise to permanent disabilities. Children with a cCMV infection who have symptoms at birth have a greater risk of permanent disability.

The permanent disabilities known to be caused by cCMV infection are hearing loss, cognitive delay, autism, epilepsy, cerebral palsy and vision impairment. A child with permanent disabilities after a cCMV infection might have one or many of these disabilities.

There is great variation in the hearing loss attributable to a cCMV infection, covering mild and/or single-sided loss to bilateral profound deafness. The onset of the hearing loss varies too, from being present already at birth, to a debut of the hearing loss at 1-2 years of age and even up to 6-7 years of age. This is called late-onset HI, and it is often missed, as the child's hearing was normal at birth.

The hearing loss caused by cCMV infection is often progressive, and thus children with hearing loss due to cCMV infection need frequent follow-ups. The progressive hearing loss might be dramatic, from normal hearing at birth to profound HI at the age of one year.

Diagnosis: mother

The most reliable test to prove a primary maternal CMV infection is an IgG seroconversion. After the primary infection, IgG will be present for the life-time of the infected person. Thus, the first test should always be an IgG test of the mother, as a negative test rules out the possibility of a cCMV infection in the child.

A CMV-IgG avidity test could be used to date the time of infection. The binding capacity between IgG antibodies and antigen is measured with the CMV-IgG avidity test. A low avidity is seen if the infection is recent, as the binding capacity increases with time.

The determination of IgM antibodies is normally useful to detect recent primary infections. For CMV, the use of IgM is limited as IgM can last long after the primary infection and might also appear again after reactivation and reinfections with new strains. False positives may occur because of cross-reactions with other herpes viruses.

Diagnosis: child

The use of the polymerase chain reaction (PCR) technique has changed the possibility of diagnosing a cCMV infection. Earlier, viral cultures from urine or saliva were used, however this way of obtaining a diagnosis has two major drawbacks. The first is that one has to have a sample from the newborn child, taken within two weeks of birth if one is to be able to distinguish a congenital infection from an infection acquired after birth. The second is that it is time-consuming. In contrast, the PCR technique, where viral DNA is amplified, is fast and has a high sensitivity and specificity.

All body fluid contains CMV DNA in infected patient and the highest and most consistent amount is found in saliva and urine, which could therefore be the fluid of choice for CMV diagnosis. On the other hand, DBS samples are used in all developing countries and therefore provide a firm source information on CMV DNA. In Sweden, these DBS cards are stored from 1975 and onwards, which enables a retrospective cCMV diagnosis to be made.

IgG antibodies from the infant are difficult to evaluate, as maternal antibodies are transferred passively across the placenta. However, if IgG is negative, this rules out the possibility of a cCMV infection. As IgG is a highly specific, fast, low cost test, it is recommended as the initial test for the child. IgM antibodies do not pass the placenta, and thus, IgM antibodies in the blood of an infant, found in the first 2 - 3 weeks of life, would be diagnostic for a congenital infection. Unfortunately the sensitivity to CMV infection is low, only 70 %, and a risk of a false positive reaction is present.

Other assessment

Brain abnormalities might be detected with magnetic resonance imaging (MRI) and a Computer tomography (CT) scan. White matter abnormalities, ventricular enlargement, calcifications, cortical atrophy and parenchymal cysts among other pathological findings are typical of a cCMV infection. A child can present one or more of these, and anomalies of these kinds are present in the vast majority of children with permanent disabilities arising from cCMV infection, making neuroimaging an important diagnostic tool.

Ophthalmological assessment is also important, as visual impairment is present in approximately 20 % of children with permanent disabilities[46, 47].

Treatment

There are antiviral drugs to treat cCMV infection: Ganciclovir and Valganciclvir, however, the benefits of these treatments are still being debated. Nevertheless, more and more data is supporting treatment of the cCMV-infected child[39, 48].

Prevention

Where prevention is concerned, a vaccine against CMV is the main goal, and many research groups around the world are working to produce such a vaccine. The problems hindering the production of an efficient CMV vaccine are, among others, the recurrent infections and the possibility of getting infected with a new strain of CMV. Lately, positive reports have been heard on progress made by vaccine researchers, raising expectations of a vaccine becoming available in a few years' time.

Until an efficient vaccine is available, the only thing a pregnant woman can do is to adopt hygienic measures as frequent hand washing after exposure to CMV-laden secretions, and to avoid intimate contact with young children.

2.2 Connexin 26 mutations

The first non-syndromic autosomal hearing loss gene to be cloned was *GJB2*[49]. This gene is involved in synthesizing of the gap junction beta 2 protein Cx26, which is a membrane protein that is essential for recycling K^+ ions back to the endolymph in the inner ear following hair cell stimulation[50]. Disruption of the potassium ion flow in the cochlea is considered to be the underlying pathophysiology in HI caused by bi-allelic mutations in the *GJB2* gene.

More than 50% of all autosomal recessive HIs in infants are attributable to mutations in the *GJB2* gene, but in addition a few dominant mutations have been found[51].

There are several known *GJB2* mutations, but the first described and the most common is 35delG. In 75% of cases, this mutation is found in at least one allele. A person with 35delG homozygote mutations will most probably present a more profound HI, than in a person with compound heterozygote mutations[52].

The carrier frequency of the 35delG mutation in Europe is 1-2%, with a tendency for higher prevalence in southern Europe compared to the northern countries.

When mutations in the *GBJ2* gene were first identified, only bilateral profound HIs were identified. However, a variability in the degree and configuration of HIs have been found among patient's with *GJB2* mutations.

Moreover, the children with GJB2 mutations were classified as non-syndromic, which, today is known to be only partly true[53]. Syndromatic mutations in the gene have been found, and in a study of Kenna et al[53], 18 % of the children were described to have other disabilities in addition to their HI.

3. Early cochlear implantation

Why early?

Towards the end of the 1990s trend towards performing CI operations in children at an earlier age emerged. Inspired by the good results from the early HA fitting, a few CI centers started to operate on children before12 months of age. The first publication, reporting on five children who received a CI at less than12 months of age came in 2004, from Antwerp, Belgium[54]. Later in the same year a group from Toronto, Canada[55]

described 25 children who had been operated on as infants. In 2005, four research groups from Italy[56], Germany[57] and US[58, 59] reported on another 63 children operated on before the age of 12 months. In subsequent years, studies from a long series of western countries were published, describing the benefits of early CI intervention[60]. From then and until now, studies including more than 300 children who were operated on at the age of 12 months or earlier have been reported[17, 20, 61].

Inspired by the German experiences, the CIS in Stockholm gradually lowered the age at which children received a CI. In 2002, the first child was operated on, at an age younger than 12 months. Since then, more than 70 infants have received an implant at the CIC. The children operated on in 2002 are now 12 years of age, and they still come for regular check-ups at the clinic. Thus, a long follow-up period is available for the first children who received an implant as an infant.

CI before 12 months of age

Yoshinaga et al[12], demonstrated the benefits associated with early HA fitting, comparing the difference between the fitting of a HA before and after six months of age. This shows that the auditory input is also of importance during the first months after birth. Taking this finding into consideration, it is feasible to assume that deaf/profoundly HI children, with even less auditory input than children with moderate HI, need and would benefit from implantation before six months of age.

A few studies have reported on children who were operated on before the age of six months. The largest study is from Verona in Italy[61], in which the case of 12 children who received implants from 2 – 6 months of age, are thoroughly described. The intervention took place without an increased level of complication being brought about by the children´s low age at the time of the operation. These children´s results, measured in terms of spoken language development, are equivalent to those of normal hearing children`s.

Early bilateral implantation

A growing number of investigations support early bilateral implantation[19, 62], mostly with the same motive as early HA fitting and early CI intervention; to utilize the brain plasticity and try to catch up with all the benefits the normal hearing children have from bilateral audition.

If the auditory/bilateral benefits were the only thing to be counted, most probably a simultaneous, bilateral CI-operation would be the best choice for a bilateral deaf/profoundly HI child. Furthermore, the family and child would benefit from the need for just one single surgical intervention. However, before making the decision about whether to perform simultaneous or sequential surgery, another aspects have to be considered: the child´s vestibular function. The knowledge that the vestibular function might be decreased as a result of the CI surgery is an issue that needs to be taken in account[63]. Even if the benefits of bilateral hearing are greater than the risk of vestibular loss, one should be aware of the downside when planning the surgical intervention. If the child, for example, has vestibular function in only one ear, it would be preferable to choose to implant the child sequentially, starting with the ear without vestibular function. Moreover, if the child has cochlear malformation, which is known to lead to a higher risk of vestibular deterioration, only sequential operations should be performed.

Safety

In many studies safety concerns related the CI operations in infants have been described, with only a few reports being found on complications[59, 61, 64]. The rate of complications has not been higher than for CI surgery in older children. However, it is of the utmost importance that pediatric anaesthesiologists with expertise in intervention on infants, are available when operating on such young patients.

AIMS OF THE THESIS

The aims of the thesis presented here were:

- to study the prevalence of cCMV infection in children with a HI of unknown etiology
- to study the various types of HI attributable to cCMV infection
- to study the prevalence of Cx26 mutations in children with a HI of unknown etiology
- to characterize the mutations found in the GJB2 gene in children with a HI of unknown etiology
- to evaluate potential comorbid conditions among children with a HI resulting from cCMV infection, in comparison with children with a HI of genetic origin (Cx26)
- to evaluate the effect on hearing and spoken language development in children receiving a CI at an early age
- to elucidate the risk of complications with early CI surgery

METHODS

Study groups

Study I and II

The children and teenagers who participated in Study I and II had HI of unknown etiology. They were patients and had their follow-ups either at the Department of Audiology, Karolinska University Hospital or at the Department of Audiology, Örebro University Hospital.

In the first study, in Cohort I, 100 children from the Stockholm area with unilateral or bilateral, permanent HI classified as being anywhere from mild to profound according to HEAR, were invited to participate. Of these, 44 children and their parents agreed to participate. The main reason for not accepting was probably that blood sampling was mandatory.

Initially, serum from each child was tested for the presence of CMV IgG antibodies. If antibodies were found, the DBS card, collected soon after birth, was examined to test for the presence of CMV DNA with a qualitative CMV DNA Polymerase Chain Reaction (PCR).

For Cohort II in Study I and Study II, students from Birgittaskolan were invited. Birgittaskolan is a special school for the deaf and hard of hearing in Örebro. The majority of the invited children had severe to profound HI. Fifty-three children, with unknown etiology were invited to participate in Study I, and 46 agreed. For Study II, another 33 children with a family history of HI were invited. All of them agreed, giving a total of 79 children.

In the 46 cases included in Study I, Cohort II, the DBS cards were analyzed for the presence of CMV DNA with quantitative CMV DNA PCR, without checking the CMV IgG status, thereby saving the students an extra visit to the hospital. The DBS cards of the 79 children in Study II were analyzed regarding Cx 26 mutations.

Study III

As of January 2012, thirty-one children and teenagers with HI due to cCMV infection had received a CI at the CIC. These 31 children (or their parents) were invited to the study and 26 agreed to participate. The children and teenagers were between 0-16 years of age.

Sixteen children with Cx26 mutation and who hade received a CI at the CIC, were also invited to participate in the study. Thirteen children, 1-13 years of age, accepted and composed the control group.

Each of the 26 children with cCMV infection and the 13 children with Cx26 mutations were assessed by a pediatrician, a neuropaediatrician, a speech and language pathologist, an ophthalmologist, an orthoptist, a physiotherapist and an otolaryngologist. Fifteen of the older children with cCMV infection were in addition invited for laboratory assessment of vestibular function at another time point, and 11 participated.

For background information on the children's HI, cognitive status, communication mode and school settings, se Table 1.

Table 1

Characteristics of tested children

CMV Case	Preschool / School-age	Sex	Neonatal hearing screening	Onset of HI (yr)	Type of HI	CI Op (yr)	Bilateral CI Op (yr)	PB	Cognitive status	Comm mode	School setting
1	S	F	0	0	3	1.8	7.9	86	1	1	1
2	S	F	0	1.5	2	1.8	1.8	60§	1	2	2
3	P	M	1	0	3	0.8	1.3	-	1	1	1
4	S	F	1	0	3	4.8	-	-	4	4	4
5	S	F	0	0	3	1.8	2.6	80	1	2	2
6	S	F	0	0.7	2	1.8	2.5	56	2	1	2
7	P	F	1	0	3	0.9	0.9	-	1	1	1
8	S	M	0	3	0	3.8	3.8	-	4	4	4
9	S	M	0	2	2	3.9	3.9	80§	1	1	2
10	S	M	0	0	3	1.9	3.7	76§	1	2	2
11	S	M	0	2	2	3.9	-	80§	1	1	1
12	S	M	0	0	3	1.5	2.5	82	1	1	1
13	S	M	0	1.5	2	3.3	5.9	48	1	1	1
14	P	F	1	1	2	1.9	2.6	-	3	4	4
15	S	M	1	0	3	0.8	1.2	44§	1	1	2
16	S	M	0	0	3	1.9	12	90	1	1	1
17	S	F	0	3	2	3.7	3.7	84§	1	1	1
18	P	M	1	1	1	1.2	1.2	-	3	4	4
19	P	F	1	0.5	0	1.3	2.3	-	1	1	1
20	P	F	1	0.5	1	2	3	56	1	1	1
21	S	F	1	1.5	2	2	5.9	56§	1	2	2
22	S	M	0	0	3	1.3	2.3	80	1	1	1
23	S	F	1	1	0	1.8	2	96	1	1	1
24	P	F	1	0	3	0.4	1	-	1	1	1
25	P	M	1	0.5	1	1.3	1.3	-	1	1	1
26	S	F	0	0	3	2.4	-	70	1	3	3
Mean				**0.8**		**2.1**	**3.3**				
Cx26 Case	Preschool / School-age	Sex	Neonatal hearing screening	Onset of HI (yr)	Type of HI	CI Op (yr)	Bilateral CI Op (yr)	PB	Cognitive status	Comm mode	School setting
1	P	M	1	0	3	0.8	0.8	-	1	1	1
2	P	M	1	0	3	0.7	1.6	-	2	2	2
3	P	M	1	0.5	2	1.9	19	-	2	2	2
4	P	M	1	0	3	0.8	0.8	-	1	1	1
5	S	M	0	0	3	1.8	2.3	64§	1	1	1
6	P	F	1	1	2	1.2	-	-	1	1	1
7	S	F	1	1	2	2.8	-	76§	1	1	1
8	S	F	1	0	3	0.9	2.2	76	1	1	1
9	S	F	0	1	2	1.6	1.6	58§	1	1	1
10	S	M	0	0	3	1.6	1.9	96§	1	1	1
11	S	F	0	1	2	5.5	-	76§	1	3	2
12	P	M	1	0	3	0.9	0.9	-	1	1	1
13	S	M	1	0	3	0.6	0.7	92§	1	2	2
Mean				**0.3**		**1.6**	**1.5**				

Preschool / School-age: P=Preschoolage 0-5yrs; S=Schoolage 6-19yrs
Neonatal hearing screening: 0=Not conducted; 1=Conducted
Type of HI (hearing impairment): 0=Bilat normal at birth; 1=One normal ear at birth; 2=Early bilat progressive; 3=Bilat severe HI at birth
CI Op= Cochlear implant operation
PB (Phonetically balanced words): latest performed test; §=Children PB
Cognitive status: 1=normal; 2=borderline/mild; 3=moderate; 4=Severe delay, globally
Comm mode (Communication mode): 1=Spoken language; 2: Mainly spoken language, but some signs; 3: Sign language first language, spoken language second language; 4: No or low language communication
School setting: 1=Regular school; 2= Special school for HI; 3= Special school, sign; 4= Special school, mentally disabled

Assessment of balance

A semistructured interview of the parents, including the history of pathological head movements (head tossing), was conducted by an otolaryngologist.

The balance of children in the age group 3–17 years was assessed by a physiotherapist using the motor screening instrument Movement ABC (M ABC-2).

During the vestibular evaluation the lateral semicircular canals were tested with caloric stimulations and video head impulse test (vHIT). The otolith organs were tested with evoked myogenic potentials (VEMP).

Assessment of neurodevelopmental dysfunction

Neurodevelopmental disabilities were evaluated through a semistructured interview of a parent, assessment of the child and review of records. The interview covered the neonatal period, heredity, developmental milestones and feeding issues. The parent questionnaire five to fifteen (FTF) [19], for the assessment of ADHD and comorbid conditions, was used if the child was 5-15 years of age.

Assessment of non-verbal cognitive and spoken language abilities

Non-verbal cognitive ability: All mentally intact children, 4-12 years of age, were assessed with the Ravens coloured matrices [20]. The Peabody Picture Vocabulary Test (PPVT-3) [21] was used to investigate *receptive vocabulary* in all children over 2.5 years of age who had been using the CI for least one year and who were not mentally delayed. *Speech intelligibility:* Spontaneous speech was rated on the Speech Intelligibility Rating Scale (SIR-2) [22].

Ocular assessment

The clinical investigation included tests of visual acuity, ocular alignment and fundoscopy.

Assessment of cCMV infection and Cx 26 mutations

CMV diagnosis: The child's blood was sampled to test for CMV IgG. If CMV IgG was positive, the child's DBS was analyzed for CMV DNA. The DBS is taken on all newborns in Sweden on day 2-5 for analysis of inborn errors of metabolism. After collection, the cards are stored at 4°C for the patient's lifetime. DBS cards, extraction procedures and quantitative CMV DNA PCR (TaqMan) have been described in detail earlier [23]. All children in the Cx26 group had their DBS analyzed. Conversely, all children with cCMV infection were tested for Cx26 mutations.

Study IV

Subjects

Between January 2002 and December 2011, 271 children between five months and 18 years of age, were implanted with CIs at the CIC. Of these children, all that were younger than 30 months of age at the time of the CI operation, and who had their clinical follow-ups at the CIC were included in the study presented here. In total, they composed a study group of 144 children. Certain children were excluded from the study because of severe global development delay that made it impossible to test their spoken language and hearing ability (n=2), because they were non users of CI (n=1), or because they were

very young and had not cooperated in a test situation so far (n=4). This resulted in a study group of 137 children.

The study group (n=137) was divided into five groups according to the child's age when their first cochlear implantation was performed: Age group 1, < 9 months of age (mean 8.1 months, n=20); Age group 2, 9-11 months (mean 10.4 months, n=31); Age group 3. 12-17 months (mean 15.2 months, n=33); Age group 4, 18-23 months (mean 21.2 months, n=30) and Age group 5, 24-29 months (mean 26.3 months, n=23).

The children were tested pre-implantation, afterwards, and thereafter longitudinally at follow-up visits at CIC at Karolinska University Hospital at six-month intervals until 4.5 years after the operation; thereafter the follow-ups were annual. The first implanted children included in this study underwent follow-ups for up to 11 years (mean 6.8 years) and 86 children (63%) were followed for more than 5 years (Figure 1).
The background data about the children is summarized in Table 1.

Preoperative audiology

Click-evoked auditory brainstem response (ABR) and behavior testing with visual reinforcement audiometry (VRA) were used for all children. In addition to these, auditory steady state responses (ASSR) have been used for an increasing number of cases in recent years.
With few exceptions, the children had a trial with a HA for at least two months prior to the CI surgery.

Preoperative radiology and surgical technique

A preoperative computer tomography (CT) scan was performed on all children. In cases of post-meningitis, congenital cytomegalovirus infections, delayed motor development and in the presence of a small internal auditory canal, magnetic resonance imaging (MRI) was also done.
A conventional post auricular transmastoidal approach was used in almost all cases.

Fitting strategies, cochlear implant devices and bilateral considerations

The CI-fitting was performed by engineers and audiologists at the CIC, using both behavioral responses and electrophysiological information.
Of the 137 children, 117 had bilateral implants (85%). The children with one implant either still benefitted from a HA on the contralateral ear (n=13) or their second ear was not suitable for cochlear implantation for medical reasons (n=4). In a few cases, the families declined an operation on the second ear (n=3).

Most children (124) had implants from MedEl and 13 had implants from Cochlear Ltd. All bilaterally operated children had implants from the same company on both ears.

Assessment of complications

Throughout the study, the children were monitored in CIC for complications relating to the CI surgery, and for risks associated with the implant.

Speech perception post implantation

Monosyllabic speech recognition in quiet surroundings was measured in the sound field. The speech material consisted of phonemically balanced 25-item monosyllabic word lists with either a female (fPB)[19, 65], or a male voice (mPB). One list per child was presented at 65 dB SPL in a sound-treated room (fPB) or an audiometric test room (mPB). The children were instructed to repeat what they heard after each item, and scores were calculated as the

percentage of correctly repeated words. To get a fair comparison, the results we present regarding speech understanding are from tests done when the children were around eight years of age.

Assessment of spoken language abilities

The assessment tools were selected to allow us to describe both receptive and expressive spoken language abilities, and changes over time. The areas of spoken language specifically evaluated were language understanding, receptive and expressive vocabulary, output phonology and speech intelligibility.

Language understanding

The Reynell Developmental Language Scales (RDLS III)[23] are assessment tools developed for evaluation of spoken language understanding in children aged 0-6 years. In the current study only the comprehension scale of the RDLS III was used. Language understanding was assessed before cochlear implantation and at follow-up visits. The mean language growth rate and delay were calculated for children who were assessed two or more times with the RDLS III.

Receptive vocabulary

Receptive vocabulary was examined with a Swedish version of the Peabody Picture Vocabulary Test (PPVT III)[24]. The receptive vocabulary was first assessed 1.5 years post-implantation and then regularly, once a year. The mean language growth rate and delay were calculated for children who were assessed two or more times with the PPVT III.

Expressive vocabulary

Expressive vocabulary was assessed using a Swedish standardized version of the Boston Naming Test (BNT)[25, 26].

The results presented in this paper were collected from the child's most recent visit at CIC.

Output phonology

The Twelve-Word-Phonology Test (TWPT)[27, 66] was developed at the CIC, inspired by the short version of Phonemetest. In addition, it was used as a screening tool for output phonology, measuring the percentage of consonants correctly produced (PCC). The TWPT was assessed at follow-up visits conducted at 6, 12, 24, 36 and 48 months post-implantation.

Speech intelligibility

The Speech Intelligibility Rating Scales (SIR-1 and SIR-2)[28] were combined and are simply called SIR here. The scale was used to determine the intelligibility of the children's speech, and changes over time. In the present study SIR was rated before implantation and at follow-up visits at 6, 12, 24, 36 months and onwards until the individual child reached the top of the rating scale.

Ethical permission

All four studies were approved by the local ethics committee. Where participants were older than 15 years of age they gave their informed consent, otherwise the parents of the younger children did this on their child´s behalf.

RESULTS

Study I

Nine of the 44 children in Cohort I, equivalent to 20%, were CMV DNA positive (Table 1). HI in the CMV positive children covered a range of degrees and types. Three children of the four with severe HI were CMV DNA positive, in contrast to none of the 14 children with moderate HI. Three of another group of 14 children with unilateral HI were CMV DNA positive. The two children whose hearing loss was of late onset were both positive for CMV DNA.

In Cohort II, 9/46 children, roughly 20%, were positive for CMV DNA (Table 2). Eight of the nine hearing-impaired children who were found to be positive for CMV DNA had between 3×10^4 and 8×10^5 copies/mL whole blood, which is a relatively high number of copy.

Out of the 9 CMV-DNA positive children, three had Cx26 mutations.

Table Cohort I

Hearing loss PTA (dB HL)	**Number of patients n = 45**	**CMV DNA pos n = 9**
≥ 95 dB Profound	4	3
70 – 94 dB Severe	**3**	1
40 – 69 dB Moderate	14	0
20 – 39 dB Mild	10	2
unilateral	14	3

Table Cohort II

Table 2. The 9 participants (A – I) in Cohort II (n = 46), who are CMV DNA positive, in relation to viral copies and Cx26 mutations. The pure tone average (PTA) of hearing threshold levels in both left (L) and right (R) ears at 0.5, 1, 2 and 4 kHz are shown.

Subjects	**Hearing loss PTA (dB HL) L / R**	**Viral copy numbers per PCR reaction**	**Connexin mutations**	**Other known difficulties**
A	>100/>100	234	0	0
B	>100/>100	110	0	0
C	>100/>100	1	heteroC249	0
D	>100/>100	18	homo35delG	0
E	90 />100	464	homo35delG	0
F	>100/>100	115	0	0
G	93 / 95	107	0	motor delay
H	>100/>100	26	0	motor delay
I	>100/>100	14	0	prematurity, psychomotor delay

Study II

Of the 79 children included in the study, 28 (35%) had one or two pathological mutations or a mutation of unknown consequence in the *GJB2* gene. For 24 of the children, the mutation was 35delG, the most common Cx26 mutation, of which 22 children had the mutation on both alleles or in combination with another pathological mutation.

Result table Study II

Characteristic	n	%	Mutations
Homocygotes	19/79	24	c.35delG/c.35delG
	2/79		c.35delG/c.290insA
	1/79		c.35delG/c.269insT
Total compound heterozygotes	5/79	6	c.250G>C/c.427C>T
Heterocygotes	2/79	3	c.35delG
Total	26/79	33	

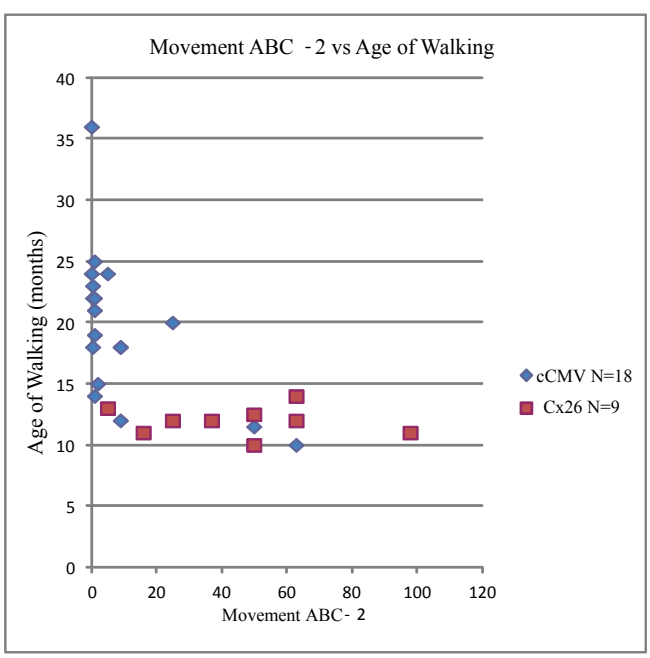
Study III

Symptomatic cCMV infection

Six of the 26 children with cCMV had symptoms such as petechiae, jaundice and hepatosplenomegaly, known to be associated with cCMV infection in the neonatal period.

Balance impairment

The children in the cCMV group had a late walking debut and learnt to walk significantly later than the control group.



In the cCMV group, 21 of the 25 children evaluated presented pathological head movements (head tossing), torticollis, muscle hypotonia or combinations of these three symptoms (Table 3). None of the control children with Cx26 had a history of head tossing, torticollis or muscular hypotonia (Table 3).

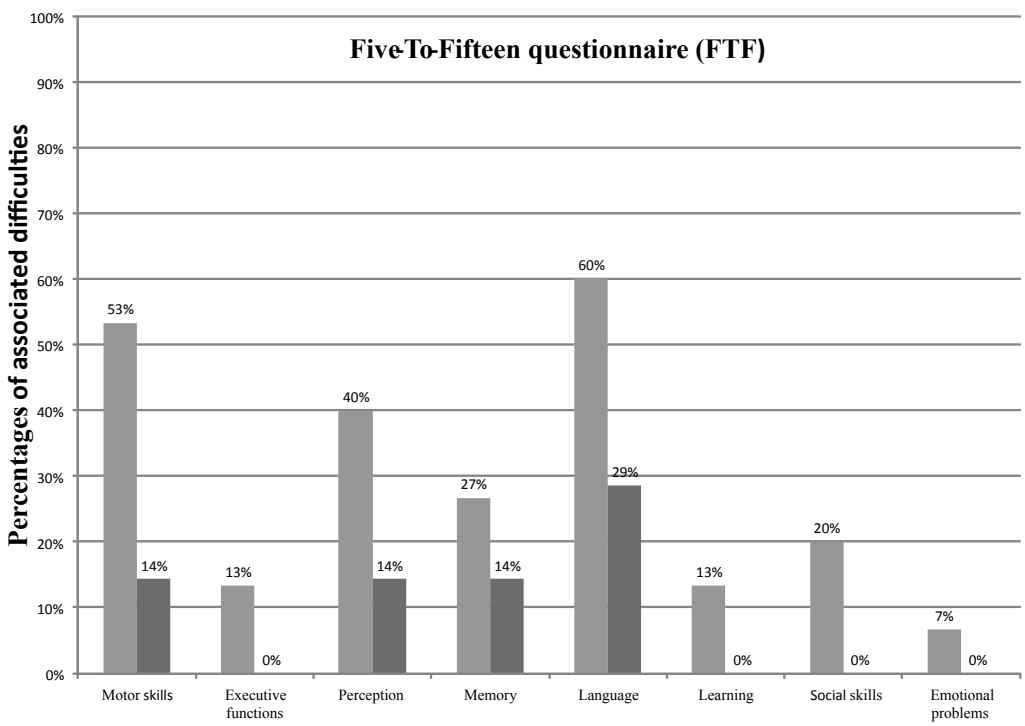
Eighteen of the children in the cCMV group and nine in the Cx26 group were in the right age span to be tested with the motor screening instrument M ABC. On the "static and dynamic balance" part of the test, 3/18 children with cCMV infection reached normal values. The mean percentile for the cCMV group was 9.9 compared to 45.2 for the Cx26 group ($p<0.01$) (Table 3).

Eleven children with cCMV infection, 7-16 years of age, underwent vestibular testing. The caloric test result (n=10) was normal in only one child, whereas five had unilateral weakness, one bilateral hyporeflexia and three bilateral areflexia (Table 3). There was good correlation concerning the side difference in vestibular function between VEMP evoked by vibrations, the refixation rate at vHIT and caloric responses.

Neurodevelopmental dysfunction

Four children in the cCMV group had ASD and two had ADHD. In addition, two children were under investigation for ADHD. In the control group no children had neurodevelopmental disabilities diagnosed.

Fifteen children in the cCMV group, without known mental retardation, and seven in the Cx26 group, were between 5 and 15 years of age and were screened with the parent questionnaire FTF. The children in the cCMV group tended to have more pronounced difficulties in all the areas tested.



Non-verbal cognitive and spoken language abilities

No significant differences were found between the study group and the controls when non-verbal cognitive and spoken language abilities were measured. However, two children with cCMV infection had language impairment (LI) and five had a history of speech-related oral motor problems in early childhood. One child with Cx26 had oral motor deficit problems.

Of the 26 children with cCMV infection, all but two had an obvious lack of impulse control during the language assessment, whereas none of the children in the control group showed this behavior.

Feeding issues

From 12/26 of the families with cCMV infected children, the parents reported feeding difficulties. These problems either lasted only during the first years of life (n=4), or throughout the preschool period (n=8). In the Cx26 group there were no feeding problems reported (Table 3).

Visual impairment

Twenty percent of the children with cCMV infection had ocular pathology, mainly chorioretinal scars. The severe visual impairment affected only one eye.

Table 3, Results Study III

Table 3

Results

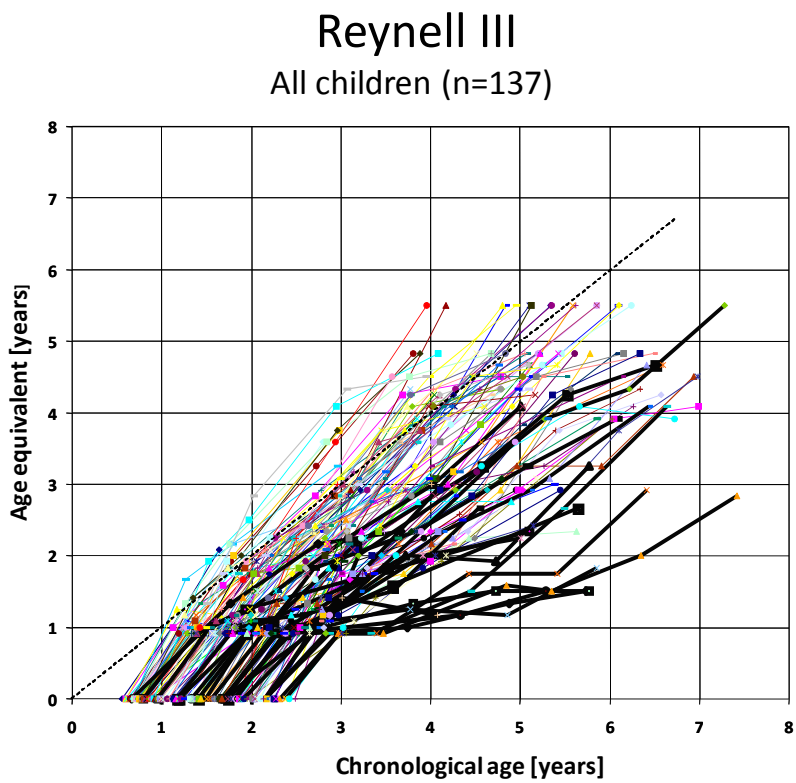
CMV Case	Neo Sympt	Path head move	Age of walking (mo)	Movement ABC-2 *n* = 18	Vestibular function *n* = 11	Feeding issues	Raven *n* = 13	PPVT-3 *n* = 20	SIR-2	DBS copy number	Cx26 mutations	MRI *n* = 12	Visual function
1	0	0	12	50	1	0	-	135	5	$7.6 \cdot 10^6$	0	-	1
2	1	3	14	1	2	1	75	69	4	$3.0 \cdot 10^6$	0	1	2
3	1	2	19	-	-	0	-	12	2	$8.3 \cdot 10^6$	1	1	1
4	1	5	Nw	-	-	4	-	-	0	NA	0	3	1
5	0	6	20	25	1	0	75	164	5	$1.0 \cdot 10^4$	0	-	1
6	0	2	15	2	-	0	25	75	5	$6.5 \cdot 10^5$	0	-	1
7	0	2	18§	-	-	0	-	28	3	$3.4 \cdot 10^5$	0	1	1
8	0	5	36	0.1	-	3	-	-	1	$>20 \cdot 10^6$	0	-	1
9	1	6	19	1	1	1	50	172	4	$4.5 \cdot 10^4$	0	-	1
10	0	4	24	0.1	2	0	10	179	5	$10 \cdot 10^6$	0	2	1
11	1	3	25	1	-	0	90	128	5	$3.2 \cdot 10^5$	0	2	2
12	0	5	21	1	-	1	10	136	5	$9.7 \cdot 10^6$	0	-	1
13	0	3	22	0.5	-	3	-	180	5	$1.7 \cdot 10^6$	0	-	2
14	0	3	24	-	3	3	-	-	1	$3.6 \cdot 10^4$	0	-	1
15	0	3	18	9	-	0	5	98	3	$7.5 \cdot 10^5$	0	1	2
16	0	0	10	63	-	0	-	134	5	NA	0	-	1
17	1	5	23	0.5	1	4	75	138	5	$>50 \cdot 10^6$	0	-	1
18	0	3	18	-	-	0	-	-	1	$>30 \cdot 10^6$	0	1	1
19	0	3	12§	-	0	3	-	12	2	$2.1 \cdot 10^5$	0	-	1
20	0	0	12§	9	3‡	0	25	37	3	$3.8 \cdot 10^5$	0	1	1
21	0	4	24	5	-	4	50	51	4	$1.2 \cdot 10^6$	0	1	1
22	0	3	18§	0.5	-	1	75	123	5	$3.1 \cdot 10^5$	0	-	2
23	0	3	22	1	-	0	90	116	5	$7.3 \cdot 10^6$	0	1	1
24	0	3	Nw	-	2	0	-	-	2	$1.3 \cdot 10^6$	0	0	1
25	0	4	Nw	-	-	3	-	-	2	$14.8 \cdot 10^6$	0	0	1
26	0	4	18§	9	2	0	-	123	5	$2.6 \cdot 10^6$	0	-	1
Mean			**19*** **	**10****			**50**	**106**	**3.5**				

Cx26 Case	Neo Sympt	Path head move	Age of walking (mo)	Movement ABC-2 *n* = 9	Vestibular function *n* = 0	Feeding issues	Raven *n* = 7	PPVT-3 *n* = 8	SIR-2	DBS copy number	Cx26 mutations	MRI *n* =	Visual function
1	0	0	12	-	-	0	-	12	3	-	3	-	1
2	0	0	14	-	-	0	-	15	2	-	3	-	1
3	0	0	13	5	-	0	-	-	2	-	3	-	1
4	0	0	17	-	-	0	-	-	2	-	3	-	1
5	0	0	12	50	-	0	75	130	5	-	3	-	1
6	0	0	12	-	-	0	-	-	4	-	3	-	1
7	0	0	12	25	-	0	50	73	5	-	3	-	1
8	0	0	11	98	-	0	90	146	5	-	2	-	1
9	0	0	12	63	-	0	-	-	5	-	3	-	1
10	0	1	10	50	-	0	95	137	5	-	3	-	1
11	0	0	12	37	-	0	50	-	4	-	3	-	1
12	0	0	11	16	-	0	90	45	5	-	2	-	1
13	0	1	14	63	-	0	95	100	5	-	3	-	1
Mean			**12*** **	**45****			**78**	**82**	**4**				

Neo sympt = Neonatal Symptoms: 0=No symptoms; 1=Symptoms
Path head move =Pathological head movement: 0=Normal; 1=Look up at the ceiling; 2=Torticollis; 3=Severe head tossing; 4=Both severe head tossing and torticollis; 5=Low muscle tonus, poor head control; 6=Do not remember
Age of walking (in months); Nw=Not walking; §=Unsteady
Movement ABC-2: Percentile values
Vestibular function: 0=Normal bilateral; 1=Normal unilateral; 2=Hypofunction; 3=No vestibular function; ‡=Not fully tested
Feeding issues: 0=No problem; 1=No interest in food at preschool age; 2=Feeding difficulties during preschool age; 3=Frequent vomiting; 4=Feeding difficulties persisted into school age
Raven=Non-verbal cognitive test; PPVT-3= Peabody Picture Vocabulary test; SIR-2=Speech Intelligibility Rating Scale
DBS copy number: Viral copies/ml whole blood (from DBS). NA= Viral copy number not available
Cx26 mutations = Connexin26 mutations: 0=No mutation; 1=Heterozygous mutation; 2=Compound heterozygous mutations; 3=Homozygous mutations
MRI= Magnetic resonance image: number of pathologies due to CMV-infection: 0=No pathology; 1=One pathology; 2=Two-three pathologies; 3=>Three pathologies
Visual function: 1=Normal; 2=Unilateral visual impairment ***p< 0.001; **p< 0.01; * p< 0.05

Study IV

Results of all 137 children tested with the RDLS-III are shown in figure x. The results from children with cognitive delay and LI are highlighted in bold . This group of children had low scores, but not all of the children with the lowest scores belonged to this group.



The results for two subgroups were analyzed in detail and are reported separately:
-Group A (n=115), which excluded all children with cognitive delay (n=15) or LI (n=7)

-Group B (n=84), which excluded 16 children owing to deafness caused by meningitis (n=8) or severe cochlear malformation (n=8), and another 15 children with a home language other than spoken Swedish (Figure 1).

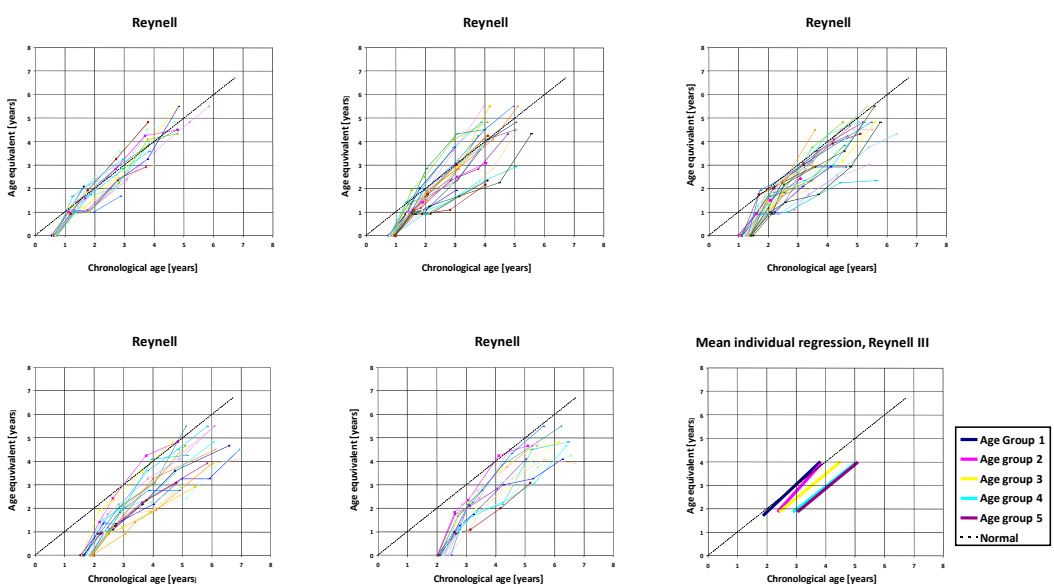
Complications, all children

No major complications of anesthesia or surgery were found, and no wounds had become infected. All children except those with DFN3 x-linked deafness (n=6) were discharged from the hospital the day after the CI-surgery.

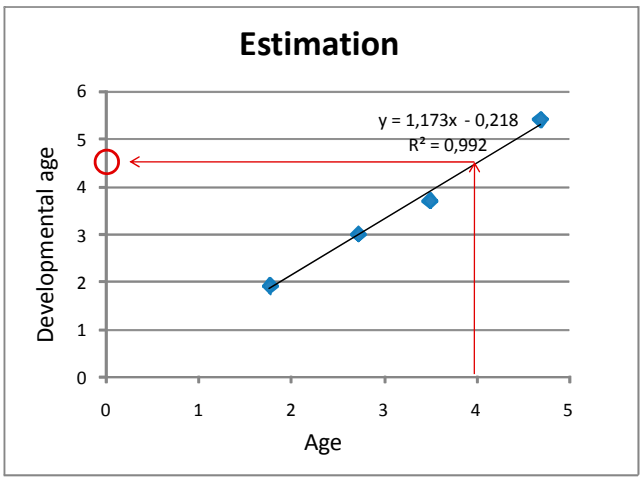
Eleven months after the primary surgery, one child had a magnet dislocation, possibly due to minor head trauma. The same magnet was repositioned under general anesthesia and has since functioned without problems.
Reoperations were performed in five of the 137 children, because of internal technical failure of the implant between one and seven years after the initial surgery. All five reoperations were successful and the children could hear equally well post-operatively as they had done before the technical failure.

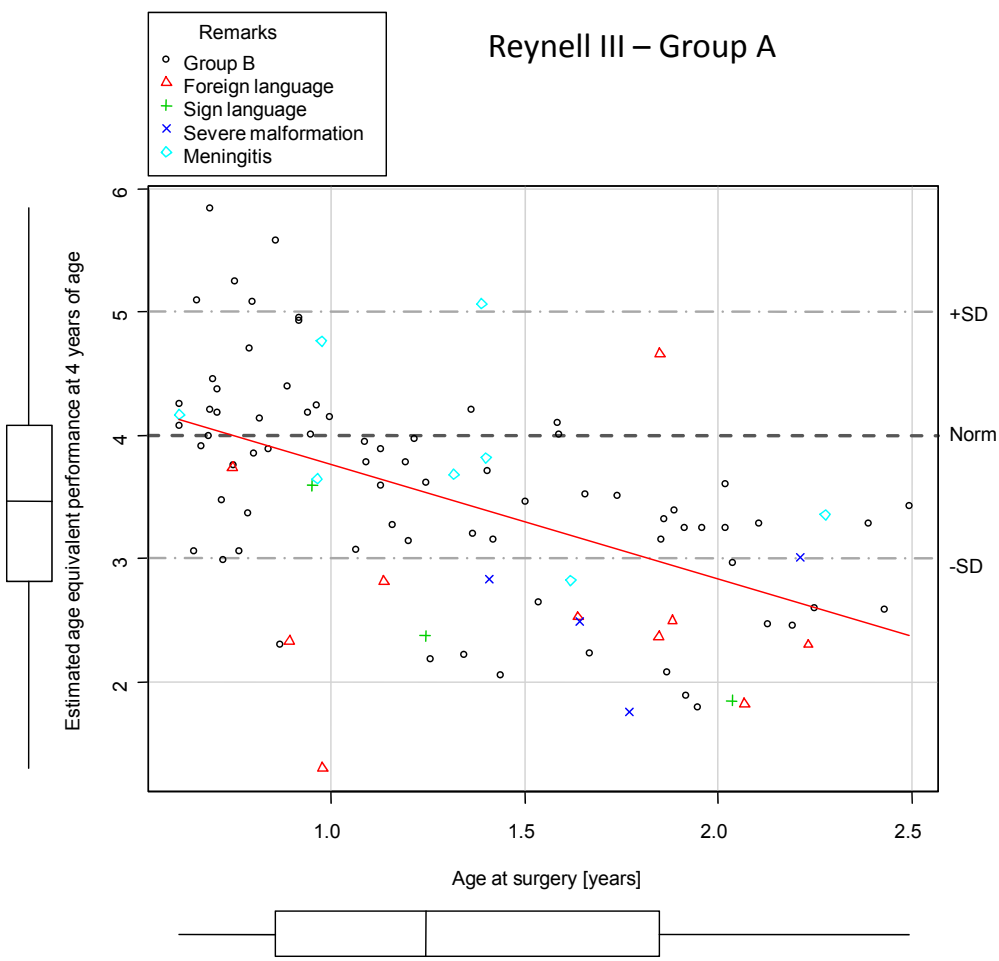
Speech perception
For Group A, the mean speech recognition was determined to be 75% and 82% for the mPB test (n=39) and fPB test (n=31), respectively. For Group B, the mean speech recognition assessments gave values of 78% and 84% for the mPB test (n=29) and fPB test (n=23), respectively. No effect of age at implantation was found in either Group A or Group B.

Spoken language abilities
Language understanding: RDLS III
The youngest children (Age Group 1) did not show any language delay and had a language growth rate similar to that of normal hearing children. All the children in Age Group 2-5 showed language delay. However, the mean language growth rate in Age group 2 was high, 1.3, indicating that these children were able to catch up in 2 - 3 years. Children operated on after 12 months of age had a language delay that lasted the whole time span of the RDLS III test. The 4-year estimation showed a significant correlation with the age of implantation for both Group A and B.



Reynell, estimation of language equivalent at 4 years of age





Receptive vocabulary: PPVT III

The PPVT III results reveal no difference between the language growth rate and delay for children in age groups 1 and 2. The initial delay apparent for group 3 had been obliterated by the time the children were 6-7 years of age. The children operated on later than 18 months, had not caught up with the normative population at any assessment time point.
The 6-year estimation revealed a significant correlation with the child's age at implantation in Group A as well as in Group B.

Expressive vocabulary: BNT

A linear regression for Group A showed no correlation between BNT-difference and age of implantation. In contrast, for Group B there was a weak correlation of 1.83 years per year (r^2=0.08; p=0.02) (Figure 8). In Age group 2, many children had bilingual background. When these children were excluded, the group mean level reached higher levels and coincided with results from the other age groups. However, the variability in the results for expressive vocabulary was higher than those for receptive vocabulary and language understanding.

Output phonology: TWPT

The age at which 80% was reached on the PCC correlated with the age at the time of surgery. The increase was about 1.2 years per year, which means that waiting one year to perform the CI intervention would increase the age for children to achieve 80 % on PCC , by a little more than a year.

Speech intelligibility: SIR

In both groups there was a strong correlation of about two years per year, between the age at which the highest score (5) was attained and the age at the time of surgery. The mean score over time for each age-group is shown in Figure x.

DISCUSSION

Studies I & III

Knowledge on permanent disability arising from cCMV infection is surprisingly scarce, in spite of the fact that the infection affects approximately 0.6 % of newborns in the developed world[44] and 1-5 % of newborns in developing countries[39]. A Swedish CMV study, using culture on urine, performed between 1980 and 1989, showed that 0.5 % of all newborns had cCMV infection[38]. This equates to 600 children with a cCMV infection annually with the present Swedish birthrate. In a more recent Swedish CMV-screening, which tested DBS samples by PCR[45], the number of cCMV infected children was lower, 0.2 %, however the reason for the lower prevalence might have been that not all children with a cCMV infection are viremic at birth.

So far, it is believed that only 20 % of children with a cCMV infection will suffer from permanent disabilities. However, in a study from Poland[67], in which 38 children identified by general cCMV screening were included, a much higher prevalence of symptoms and disabilities was found. For example, 33 % of the children in the study had speech-related problems and 37 % showed emotional sensitivity, disabilities no before associated with cCMV-infection. However, as the pattern of disabilities has not yet been clearly defined, it is probable that what we see is a "tip of the iceberg" phenomenon. Thus, the burden of cCMV infection might be even greater than previously believed.

HI is the most well-described permanent disability caused by cCMV infection. Large prospective studies in the US, have monitored hearing in cCMV-infected children[68, 69]. During the preparation of the first study in this thesis, before the large prospective studies were published, knowledge of the pattern of hearing disability secondary to a cCMV infection was sparse. However, a good correspondence was found between Study I and the studies from the US, concerning which types of HI cCMV infection were most frequently induced, namely either a severe/profound HI or a mild/unilateral HI.

Nowadays, it has been established that cCMV infection can induce HI, and that it is the main cause of permanent pediatric HI[8, 29]. Unfortunately, neither in Sweden nor in other countries has this knowledge generally led to the practice of ruling out cCMV infection as the source of the HI in children who are found to have a HI in the neonatal hearing-screening. It is self-evident that this ought to be a routine test.

The frequent tendency for a fast progression of HI caused by cCMV infection is often overlooked, and thus the child is thought to hear better than he or she actually does[70]. This leads to an unnecessary delay in performing CI interventions for the children that need a CI. Moreover, children with late onset HI will pass the neonatal hearing screening and be at risk of a substantial delay occurring before receiving a HA or a CI[71]. Knowledge concerning late onset and progressive HI arising from cCMV infection needs to be spread. More frequent hearing tests need to be conducted in children with cCMV-induced HI; regular hearing test routines during pre-school age are a necessary complement to neonatal hearing screening.

It is clinically evident that children with cCMV induced HI also suffer from a number of other permanent disabilities that have not been described before. Therefore the aim of the third study of this thesis was to examine a group of cCMV-infected children in a broader

perspective to further investigate and possibly identify new disabilities that were not described earlier. A number of problems were identified, like balance-disorders in 88% of the children, feeding issues in 50 %, a high number of neurodevelopmental disorders and affected executive functions in almost all cases.

The balance problems were especially interesting as they were so common and yet, despite this, they had not described previously. The children learnt to sit late without support and started to walk late. They also had an odd pattern of head tossing as infants, which was thought to be connected to a vestibular damage. The head-tossing pattern needs to be studied further, but already today, without knowledge about the pathophysiology behind the head tossing, it is a valuable clinical sign and a tool for diagnostics. An infant exhibiting this head-tossing pattern, should be tested for cCMV infection, especially if the child has late motor development,.

The findings of frequent and often asymmetric vestibular dysfunction among the children with cCMV show the necessity of vestibular testing prior to the CI surgery. However, if the child has a total bilateral vestibular loss, a simultaneous, bilateral CI operation might as well be performed.

Moreover, evidence based intervention through rehabilitation for vestibular impairment should be offered to all children with vestibular dysfunction as improved results are reported from such interventions[72].

As mentioned earlier, there are obstacles to CMV vaccination and antiviral treatment of cCMV infected children[39, 73]. Improved knowledge about the cCMV infections and the accompanying permanent disabilities will make decisions about vaccination and treatment easier. If an efficient vaccine can be produced, the decision about the introduction of a general vaccination-program will be based on knowledge of the burden of cCMV infection.

Many children with a cCMV infection are not diagnosed, since only 10-15% have symptoms in the neonatal period and, in addition, the early symptoms of cCMV infection are often unspecific and misinterpreted. Thus, general CMV screening is the only means of identifying all children with a cCMV infection. However, since not all children with a cCMV infection develop permanent disabilities, there is a need for factors to be identified that will make it possible to predict whether permanent disabilities will occur or not. The only predicting factor known today is the blood viral load: a low CMV blood viral load predicts normal development with a reasonable certainty[74, 75]. In both Studies I and III, viral loads were measured from DBS samples, showing high numbers in all cases, which was in accordance with the literature. Thus, a low viral load could be an important indicator for helping the clinician to decide whether to give anti-viral treatment or not when a newborn is diagnosed with cCMV infection.

The alternative to general CMV screening is to perform a retrospective assay on all children with HI and/or symptoms that are consistent with cCMV infection, including the disabilities found in Study III. Children who test positive for a cCMV infection, could then be offered assessment by a multidisciplinary.

Sweden has had good experience of identifying children with a cCMV infection by analyzing the DBS sample with the PCR technique[45, 76] and this was also shown in Studies I and III. However, the accuracy of using DBS cards for the diagnosis of CMV has been discussed. In a large study from Birmingham, US, promoting sampling of CMV in saliva[77], analysis of DBS cards was considered to be a low sensitivity option. Later, it was shown, that in the study from Birmingham, a low-sensitivity DNA-extraction method was employed, indicating the importance of a high quality laboratory[78]. In the Birmingham

study, other explanations can be found for the finding of low sensitivity from the analysis of DBS samples, compared to saliva samples. One might be that children with a mild cCMV infection, without CMV DNA in their blood at birth, i.e. without viremia at birth, would not be identified through PCR on DBS samples. However, as the risk of symptomatic cCMV infection or permanent disabilities for these children is negligible, there is no need to identify these children. Thus, it is possible to retrospectively diagnose the children at risk of suffering consequences in terms of symptoms or disabilities from a cCMV infection by the use of stored DBS-samples.

Study II

After cCMV induced HI, the second most common cause of permanent HI in children is attributable to mutations in the *GJB2* gene. If the HI is non-syndromic and autosomal recessive, *GJB2* mutations are often frequently occurring, and 35delG the most common mutation. In Study II, the aim was to investigate if Cx26 mutations among children with non-syndromic HI were as common in Sweden as in other European countries and to describe the mutations found, including 35delG.
We found either one or two *GJB2* mutations in 35% of the 79 children included in the study. Moreover, 28% of the children had the bi-allelic 35delG mutation or mono-allelic 35delG mutation in combination with another mutation. This was in line with other, similar studies from the Nordic countries. However, in a Danish study, in which a pool of moderately HI children were investigated, the proportion of *GJB2* mutations were much lower, at just 9.7%. One possible explanation for the difference could be the more moderate HI among the selected Danish children, with few children carrying the mutation 35delG, which is found foremost among persons with severe HI.

Three of the 46 children, who were included in both Studies I and II, had co-occurrence of *GJB2* mutations and cCMV infection. In two cases the children had homozygous mutations and in one case the mutation was heterozygous. Previously Ross et al[79] showed that among children with cCMV infection and HI, the frequency of heterozygote *GJB2* mutations were much higher than expected, an possible indication of a link between CMV and genes. In order to explore this possibility, all children in Study III were tested for both cCMV infection and *GJB2* mutations. However, among the 26 children with cCMV-infection studied, only one child had a *GJB2* mutation in addition to their infection. 1/26 (4%) is close to the carrier frequency for Cx26 mutations in Sweden, thus the results of the present study do not concur with the results of the study by Ross et al. Of the 13 children with *GJB2* mutations in the control group, not one had co-occurrence of a cCMV infection. However, the number of participants are, in this context, low and these results have therefore to be judged with caution.

To achieve a high quality CI intervention, knowledge about the etiology of the child's HI is vital to be able to make an early and correct HI diagnosis as well as to give the child tailored support for their HI. Another important factor for a successful CI intervention is the age at which the child receives the implant. Because of this, we conducted a longitudinally, retrospective study: Study IV. The aim of this study was to investigate the results for a cohort of children receiving a CI, and look at the effects the age of the child has on successful interventions.

Study IV

Data from several studies considering early CI operations are now available, showing the benefits of CI intervention among infants. CI surgery is performed at a younger and younger age, which raises certain issues that needs to be resolved. Neonatal hearing screening is performed in almost all developed countries and children who do not pass the test have to be subjected to further investigation. To be able to perform CI surgery before the infant is 5 - 6 months of age, the diagnosis has to be made, a HA fitted and assessed, vestibular testing conducted and neuroradiology performed. A strict post screening protocol is needed to manage this in a short time-span. ABR, ASSR, and MRI can be performed during natural sleep, saving the child from the need to be anesthestised, and vestibular testing is manageable even at this early age. The experience from the CIC in Stockholm is that parents are less stressed by a tight schedule of appointments, than by long delays and months of waiting for the assessments. Up to now, however, it has been the resourceful families who can advocate their case, that have had their children operated on at 5-6 months of age. The post-screening protocol would help to resolve this problem, making it possible for all children, irrespective of family background to receive an early CI intervention.

In our study, it was shown that children who received implants before the age of nine months did not have any spoken language delay at all and that their acquisition of speech intelligibility was faster than that of children implanted at a later age. The clinically observed benefits of performing a CI intervention in a child below nine months of age were even greater. However, the lack of tools to thoroughly test and describe the child's early preverbal language acquisition left us without data to substantiate these observed benefits.

Moreover, it was shown in Study IV that many children who were operated on between 9 and 11 months of age caught up with the children who were operated on below nine months of age within two to three years, when spoken language development was measured. Even many children who received implants between 12 and 17 months, caught up with the children operated on before the age of one year, when tested for receptive vocabulary at early school age.

Looking behind the figures, it was obvious that children from homes where both parents spoke another mother tongue than Swedish did not catch up in the same way as children from homes where Swedish was spoken. In several other studies of CI-operated children, such a negative effect from bilingualism was not found[80]. However, a German study by Teschendorf et al[81], based on language estimating, had very similar results to ours. The typical child, with a low performance after CI intervention in the German study, had parents who spoke poor German and who had a low educational level. Moreover the children did not speak the parent's native language. This situation is also common in Sweden and in Study IV, over 20 % of the children were from families with this kind of background; where the parents do not speak Swedish fluently. This group of children need both a CI very early on in life and a more tailored family intervention during pre-school age if they are to avoid a persistent language delay.

CONCLUSION

- The prevalence of cCMV infection among children with HI of unknown etiology is 20 %.

- All types of HI can result from a cCMV infection, but the present study showed that either mild/unilateral or severe to profound bilateral HI were the most common. The prevalence of bilateral Cx26 mutations among a cohort of children with nonsyndromic HI, in which 87 % had a severe to profound HI, were 24/79 (30 %). The most common Cx26 mutation, 35delG, was found in 22 of the cases with bilateral mutations.

- Co-morbid disabilities due to cCMV infection found in the study were:

  Balance impairment:
  - The children started to walk significantly later than the control group.
  - The children had pathological head tossing, torticollis or muscle hypotonia in 21 of 25 evaluated cases (84 %), compared to none in the control group.
  -The motor screening instrument M-ABC showed that the children had significantly lower results than in the control group.
  - Vestibular testing of 11 children showed that only one had normal function. None in the control group were tested, thus no comparison between the groups can be made.

  Neurodevelopmental disabilities:
  - Four children had previously been diagnosed with ASD, another two children with ADHD and additionally two children were under investigation for a ADHD diagnosis. All together 8 out of the 26 children (31%) were an unexpected large proportion. No children in the control group had ASD or ADHD diagnosed.

  Feeding problems:
  - 46 % of the parents reported that their children had feeding difficulties, as problems to swallow, frequent vomiting or no interest of food. These problems were mainly present during the first years of life, but could last throughout the preschool period. No similar feeding problems were reported in the control group.

  Spoken language abilities:
  - No significant differences between the study group and the control group were found.

  Visual impairment:
  - 20 % had severe ocular pathology, mainly chorioretinal scars affecting one eye, whereas no children in the control had similar impairments.

In conclusion, these findings show that cCMV infection do not only affect the cochlea, but might affect other sense organs, as well as the general development of the brain, and gives rise to a complex pattern of disabilities.

- When early CI intervention was performed, the findings were:

  Spoken language abilities
  - The children in the youngest age group, CI surgery before 9 months of age, had no spoken language delay and had a faster acquisition of speech intelligibility compared to the children operated on at later ages.
  - The children operated on between 9-11 months caught up with the younger group in 2-3 years, if they were from homes in which Swedish were spoken as the main language.
  - The children operated on between 12-17 months of age caught up when tested for receptive vocabulary at early school age.
  - The children operated on later than 18 months of age did reach age-equivalent levels in any of the language assessments.

  Speech perception
  - No effect of age at implantation was found when speech-perception was measured.

To conclude, early implantations is especially important to conduct during the developmental phase of the HI child, when normal hearing infants usually establish initial listening skills and preverbal abilities in order to promote optimal spoken language over time.

- Complications with early CI surgery

  The complication rate for early CI surgery was low and comparable to the incidence of complications in children operated on at a later ages.

FUTURE PERSPECTIVE

This thesis raises many new research questions.
The knowledge about the broad variety of disabilities due to cCMV infection is still unclear and not totally explored. Thus the burden of cCMV infection cannot be measured. There is a need for a prospective cCMV study, in which all newborn are tested for cCMV. Children found to have cCMV infection need to be followed longitudinally hereafter, with a multidisciplinary approach.

The awareness of cCMV infection among health care workers and the public is low, even though the infection is common, more common than most disorders that are included in newborn screening programs, both in Europe and in US. Thus cCMV infection needs an increased attention.

The high proportion of genetic reasons to HI in early childhood is well known. While waiting for the possibility for a broad screening of several genes known to be involved in HI, one need to screen all children with HI for the most common mutations - the mutations in the GJB2 gene.

With regards to CI surgery in infants the question is, how early it is possible to have a confident HI diagnosis and to do safe surgery. As described in the present thesis and other studies the knowledge of the benefits with early CI intervention is growing. More studies will add to this knowledge the coming month and years.
Better diagnostic tools to characterize the HIs among infants are needed. Better assessment tools to follow the preverbal language development are also necessary.
Children from homes in which Swedish is not the main language, have poorer results. This phenomenon has to be studied more in detail and a more tailored intervention is needed promptly.

SVENSK SAMMANFATTNING

Hörselskada är en folksjukdom som drabbar en stor del av befolkningen. Tidigt i livet är risken för hörselskada relativt sett låg och enbart 3 promille av alla nyfödda har en hörselskada av varierande svårighetsgrad. I nästan alla fall av permanent, medfödd hörselskada rör det sig om en skada i innerörats hörselorgan. Efter födelsen tillkommer permanenta hörselskador successivt under livet och följden blir att ju äldre man blir, desto större är risken att drabbas av hörselnedsättning. Man uppskattar att minst 50 % av 80-åringar har nedsatt hörsel som påverkar deras livskvalitet.

Även om få barn föds med, eller tidigt förvärvar, permanent hörselskada är följderna av en tidig hörselskada allvarlig. Det är hjärnan som tolkar ljuden och det finns en ”förprogrammerade tid” då hjärnan har möjlighet att lära sig att höra och tolka ljud, nämligen mellan 0-3 års ålder. Det är därför viktigt att barnen får höra så bra som möjligt under denna, för hörseln viktiga tid. Forskning har visat att efter denna tidslucka minskar möjligheten för en person som född döv att lära sig höra, prata och förstå talat språk.

Det motsatta gäller för personer som har hört och lärt sig att prata via sin hörsel och som senare under livet tappar hörseln. För dessa personer finns minnet av hörsel och hur man tolkar ljud bevarat i hjärnan. Hörande, som har tappat hörseln senare i livet, kan således genomgå hörselförbättrande operation decennier efter sin hörselförlust.

Det finns en lång rad orsaker till att barn föds med hörselskada, men två är de enskilt vanligaste: medfödd cytomegalovirus (CMV)-infektion och Connexin 26 (Cx26) mutationer. CMV-infektionen kan, förutom hörselskadan, medföra att barnet får andra skador t.ex. utvecklingsförsening, CP-skada eller synskada. Har barnet dubbla Cx26 mutationer får barnet en medfödd hörselskada, som är genetiskt betingad, men i de allra flesta fall inte några ytterligare handikapp.

Huvudsyftet med denna avhandling var att beskriva hur resultaten, mätt i hörsel och talspråksförmåga, var för en grupp av 137 barn som fått CI mellan år 2002 och 2011. Speciellt studerades hur åldern vid CI operationen påverkade resultaten. Dessutom var ett mål att klargöra hur vanligt det var med medfödd CMV- infektion eller Cx 26 mutationer som orsak till hörselnedsättning. Dessutom hade barnen med hörselskada orsakad av medfödd CMV-infektion så många symtom, som inte hade beskrivits tidigare, och detta behövde undersökas och beskrivas vetenskapligt.

I avhandlingens första studie var syftet att kartlägga i hur stor omfattning medfödd CMV-infektion orsakade hörselskada hos barn. Studiegruppen var 90 barn med okänd orsak till sin hörselnedsättning. Barnen hade allt från ensidig/lindrig till grav hörselskada.

Medfödd CMV-infektion måste diagnostiseras med ett blod-, saliv- eller urinprov från det nyfödda barnet, för att kunna särskilja medfödda infektioner från infektioner som förvärvats efter födelsen. I denna studie analyserades barnens sparade PKU lappar (blodprov från det nyfödda barnet) med avseende på CMV DNA. I PKU lappar från 18 barn, dvs i 20 % av fallen, fann man CMV DNA. Medfödd CMV infektion visade sig därmed vara en betydligt vanligare orsak till hörselskada hos barn, både vad gäller lindrig och grav hörselskada.

I avhandlingens andra delarbete var syftet att studera i hur stor omfattning Cx26 mutationer orsakade hörselnedsättning hos svenska barn. I andra jämförbara länder hade visat att Cx26 mutationer var vanligt förekommande hos hörselskadade barn, men inte i Sverige.

I studien ingick 79 hörselskadade barn och ungdomar, alla elever på Birgitta skolan i Örebro, som fick sina PKU-lappar analyserade med avseende på Cx26 mutationer. Barnen/ungdomarna hade okänd orsak till sin hörselnedsättning och deras hörselnedsättning var inte en del av ett syndrom. 87 % av barnen i studien hade en uttalad/grav hörselnedsättning och 13 % hade en medelsvår hörselnedsättning.

Resultatet från analyserna i studien visade att 24 av barnen (30 %) hade två Cx26 mutationer, dvs Cx26 mutationer var orsak till hörselskadan i dessa fall. Denna frekvens av dubbla Cx26 mutationer var jämförbar med frekvensen av dubbla mutationer i t.ex. Norge, Finland och Island. Vid analys av PKU-prov från tre av barnen, fann man både Cx26 mutationer och CMV DNA , dvs tecken på medfödd CMV infektion. Således hade dessa barn två möjliga orsaker till sin hörselnedsättning.

I den tredje delstudien var syftet att klarlägga i vilken omfattning barn med hörselnedsättning orsakad av medfödd cytomegalovirus (CMV)-infektion har andra funktionsnedsättningar än sin hörselskada.

26 barn i åldrarna 0-16 år med medfödd CMV-infektion deltog i studien. Alla barnen hade en grav hörselnedsättning och hade genomgått cochleaimplantat (CI)-operation. Barnen utreddes med avseende på andra funktionsnedsättningar av ett multidisciplinärt team, bestående av barnläkare, barnneurolog, logoped, öron- näs- och halsläkare, ögonläkare och ortoptist. Hörselundersökningar, BVC-journaler, utdrag från födelseregistret samt magnetkamerabilder granskades. Barnens föräldrar svarade på en enkät som tagits fram med avseende på ADHD symtom (Five-To-Fifteen questionnaire). Som kontrollgrupp deltog 13 barn med hörselnedsättning orsakad av Cx26 mutationer. Även dessa barn hade genomgått CI operation.

Studien visade att flera av barnen hade ADHD och/eller autismspektrumdiagnoser, liksom ögonskador. Detta bekräftade resultaten från andra forskningsgrupper. Nya resultat som framkom var att barnen hade balansrubbningar i 88 % av fallen, att 50 % av barnen hade eller hade haft födointagsproblematik och att majoriteten av barnen hade påverkade exekutiva funktioner.

I avhandlingens sista delarbete var frågeställningen i hur hög grad åldern vid vilken ett barn opereras med CI påverkar resultatet. Resultatet mäts i den hörsel-och talspråksförmåga som barnet förvärvar. Alla barn som opereras med CI följs upp med regelbundna hörsel- och talspråkskontroller.

I studien ingick 137 barn som opererats med CI mellan år 2002 och 2011 och som var yngre än 2.5 år vid operationstillfället. Barnen delades in i fem åldersgrupper efter åldern vid CI-operationen; <9 månader, 9-11 månader; 12-17 månader; 18-23 månader och 23-29 månader.

Resultaten från studien visar att barn som opererats före nio månaders ålder inte hade någon försening i sin talspråksutveckling jämfört med normalhörande barn. För barn som opererats senare uppmättes en försenad talspråksutveckling och ju äldre barnen var vid CI-operationen, ju större blev förseningen. Många barn som opererats före 18 månaders ålder kunde dock hämta upp förseningen med tiden, och komma upp till åldersadekvat nivå vid tidig skolålder. För barn opererades efter 18 månaders ålder var det betydligt färre barn som fick ett åldersadekvat talspråk. Vad gäller hörselförmågan, kunde ingen skillnad uppmätas, vare sig barnen var opererade tidig, före nio månaders ålder, eller senare.

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