Prevalence of various etiologies of hearing loss among cochlear implant recipients: Systematic review and meta-analysis

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Abstract

Objective: To investigate the etiology of deafness in cochlear implanted children and to address the question whether there is a need for more thorough diagnostics, especially concerning genetics. Design: Systematic review. Four databases were searched for studies (year 2000–2014) on cochlear implanted children (n > 100). Studies were excluded if etiology had influenced their inclusion criteria. Eligibility and methodological quality were assessed independently by three authors. The studies’ description of diagnostic evaluation was categorized in three groups. Study sample: Sixteen studies were included (5069 children). Results: The most common etiological categories were ‘Unknown’ 40.3% (95% CI 32.8 to 48.0), ‘Non-syndromic’ 22.4% (95% CI 17.1 to 28.2), and ‘Postnatal’ 11.3% (95% CI 7.2 to 16.2). Studies published after 2006 had a lower proportion of ‘Unknown’ etiology 35.3% (95% CI 28.0 to 42.8) than older 45.5% (95% CI 31.0 to 60.4). Important information was missing from several studies: 11 (69%) studies did not provide detailed description on diagnostic evaluation of the etiology of deafness and had a higher proportion of ‘Unknown’ etiology. Conclusions: In order to ensure a higher level of comparability in future studies, we recommend agreement upon an international standard of diagnostics and the introduction of an international standard for reporting etiology.

Key Words: Cochlear implant; pediatric; etiology; demographics/epidemiology; syndromes/genetics

Severe (≥70–95 dB) to profound hearing loss (≥95 dB) has an incidence of 1–2 per 1000 newborns (Nikolopoulos, 2010). The causes of deafness are many, but the treatment is the same. With the introduction of cochlear implantation (CI), a safe, efficient, and cost-effective treatment for severe to profound sensorineural hearing loss (SNHL) was found. CI is the most successful neural prostheses to date, with more than 22 000 implanted individuals worldwide in 2011 (Cosetti & Waltzman, 2011). As evidence of benefits has grown, so has the candidacy for implantation; children are now fitted with implants at an earlier age in infancy with less severe impairment compared with before.

Examination of the causes of deafness (etiologies) within the group of CI patients shows that the largest group is of unknown etiology. Studies have further investigated this subgroup and found that many children are actually deaf due to non-syndromic genetic diseases. The most frequently reported such genetic disease is caused by the GJB2 mutation, which is found in as much as 36.5% of CI recipients (Chen et al, 2009).

The incidence of deafness varies much among regions, and the prevalence of genetic congenital deafness is influenced by consanguineous marriages in some cultural groups (Parving et al, 2003). A population study including more than 40 000 newborns in a region of Turkey reported 216 CI candidates which corresponds to a frequency of 5/1000 newborns (Atas et al, 2011). Unfortunately, no etiologies were reported in that study. In the deaf communities in developed countries, a positive selection of homozygous GJB2 occurs (Petit et al, 2001).

An American study (Stern et al, 2005) used a cross-sectional design to examine the demographic characteristics of CI patients and reported significantly different implantation rates in the severely to profoundly deaf children according to race and socioeconomic status. Only 1/10 (RR = 0.10, 95% CI 0.033 to 0.328) of the deaf black children had a CI performed when the white group was used as an index. Private insurance set aside, a British population study (Fortnum et al, 2002) concluded that significantly more profoundly impaired children receive CI in affluent families than in less affluent families.

Several events have influenced diagnostics in the time span 2002–2011. Neonatal screening has been introduced which results in faster and more sensitive discovery of congenital hearing*
loss with a reported coverage of >90% of all affected children (Parving et al, 2003). The screening has affected immigrants whose language and educational barriers previously rendered them unaware of the treatment possibilities, and is expected to make them appear more frequently in the CI statistics (Parving et al, 2003). Additions to public insurance coverage (e.g. Medicaid) will also have an impact because less affluent patients are now able to receive CI (Chang et al, 2010). The widespread use of conjugate vaccines against measles, mumps, haemophilus influenza type b, and streptococcus pneumoniae are expected to reduce the ‘Postnatal’ proportion (Joint Committee on Infant Hearing, 2007), while improved treatment and survival of premature children have resulted in an increase of the ‘Perinatal’ proportion.

The objectives of this systematic review are to investigate the etiology of deafness within the population of CI-implanted children and to address the question whether there is a need for more thorough diagnostics, especially concerning genetics.

Onset of deafness may be either prelingual or postlingual, meaning that the hearing loss appeared before or after the acquisition of language around the age of two years. The postlingual group is predominant in the adult CI population, while the prelingual group is more frequent in the pediatric CI population. The present study separates the two major groups into pediatric and adult. In the pediatric group, a temporal division can be practical for dividing the etiologies into pre-, peri- and postnatal; and given the field of interest of the present study, the prenatal causes were subdivided into two genetic groups: non-syndromic and syndromic.

Around 400 genetic syndromes that include hearing loss have been described, with some of the more frequent being Usher, Pendred, and Jervell and Lange-Nielsen (JLNS). Usher is the most common syndrome of autosomal recessive inheritance and can be divided into three types, USH1-3. These types have different clinical presentations depending on the degree of hearing impairment, the development of retinitis pigmentosa and vestibular dysfunction (Loundon et al, 2003). Children with USH1 suffer from profound deafness and are gradually blinded by progressive retinitis pigmentosa. Sixteen loci have been reported to be involved in the occurrence of USH and atypical USH. Among them, 12 have been identified as causative genes (Mathur & Yang, 2015). Early diagnosis and implantation are crucial to take advantage of rehabilitation before eyesight is lost (Rajput et al, 2003).

Pendred syndrome, which is caused by mutations in the PDS/SLC26A4 gene, is the second most common autosomal recessive syndrome. It is associated with SNHL and euthyroid goiter, but the latter is often subclinical until puberty or adulthood (Pagon et al, 2012). Vestibular function is affected in the majority of individuals, and the syndrome is associated with abnormality of the bony labyrinth (Mondini dysplasia or dilated vestibular aqueduct) as well.

JLNS is an autosomal recessive disease caused by mutations in the genes KCNQ1 and KCNE1. SNHL and cardiac arrhythmias are present due to potassium channel defects. The syndrome is often diagnosed on ECG with a characteristic, prolonged QTc interval usually longer than 500 ms that may result in malignant tachyarrhythmia and sudden death (Senthil Vadivu et al, 2013). The diagnosis is important because 50% of children with JLNS experience a cardiac event before the age of three years (Schwartz et al, 2006). Stickler syndrome is a connective tissue disorder characterized by ocular, skeletal, orofacial, and auditory defects. Three genes responsible for the Stickler syndrome show an autosomal dominant inheritance pattern (Acke et al, 2012). Treacher Collins is another syndrome with this pattern of inheritance, but the hearing loss is predominantly conductive due to malformation of the outer and the middle ear, and the treatment of choice is therefore bone-anchored hearing aids (Rosa et al, 2015).

More than 100 loci associated with non-syndromic hearing loss have been localized (Chen et al, 2009). Autosomal dominant and recessive, mitochondrial, X-linked, and Y-linked types of transmission have been described. Autosomal recessive inherited diseases often cause prelingual severe-to-profound hearing loss, with exceptions like DFNB8, in which the hearing impairment is postlingual and rapidly progressive. Most autosomal dominant inherited diseases cause postlingual hearing impairment, but exceptions like DFNA3 (Pagon et al, 2012) do exist.

The most frequent of the hereditary etiologies is DFNB1, which is caused by a mutation in the gene coding for connexin26 (GJB2). GJB2 is a structural component of gap junctions. Gap junctions are intercellular channels necessary for transportation of ions as well as macromolecules and second messengers between the connected cytoplasm of neighboring cells. Gap junction assembly consists of the docking of a connexon (hemichannel) from each adjacent cell, and each connexon is composed of six transmembrane connexin molecules (Dror & Avraham, 2009).

Different pathophysiologicals of deafness in relation to defective gap junctions have been suggested. Recent studies using patch clamp techniques have shown that homozygote humans with GJB2 mutations had no affection of potassium conductance. However, these gap junctions were not able to propagate larger molecules, like glucose, which led to higher intracellular levels of reactive oxygen species leading to cell damage and death. The connexins also seem to affect intracellular signaling pathways due to decreased propagation of calcium. The cytosolic changes affect the expression of the NF-κB; a calcium-sensitive transcription factor that controls connexin expression (Dror & Avraham, 2009).

Twenty-one genes have been identified as belonging to the connexin family, whereas mutations in five of these (GJB2, GJB6, GJB5, GJB3, and GJA1) have been associated with human SNHL. GJB2-related deafness is often caused by a specific deletion (35delG). It is characterized by an autosomal recessive inheritance pattern (DFNB1), but autosomal dominant inheritance (DFNA3) has also been observed. (Petit et al, 2001). The incidence of 35delG heterozygotes among the healthy European population has been estimated to be 2.5% in Spain and 4.0% in Italy (Denoyelle, 1999) with a south-north European gradient. This high carrier rate can result in a pseudo-dominant inheritance pattern in some families.

Patients with DFNB1 deafness have been found to be excellent candidates for CI because they perform equal to or better than other CI patients in reading comprehension, nonverbal cognition, speech performance, language perception, speech perception, and speech intelligibility. This was recently documented in a large systematic review (Black et al, 2011). One reasonable explanation for the positive outcome of CI in this group is that the pathogenic
known gene responsible for X-linked NSHL was POU3F4, but since the pediatric population (Petersen et al, 2008). Until recently, the only onset of hearing loss and are therefore not encountered in the common ones like Alport syndrome and Fabry disease have a late diseases on the X chromosome. However, some of the more syndromic etiological categories. Many syndromes are caused by hearing loss, and it is present in both the non-syndromic and late consequences of these genetic mutations are confined to the cochlea and spare the integrity of the auditory nerve and central auditory pathway, which are essential for the function of the CI.

DFNB1 results in non-progressive moderate-to-profound SNHL, but leaves few clinical characteristics, although some studies have shown a positive correlation with malformations of the inner ear (Probst et al, 2006). This makes it difficult to diagnose the syndrome without genetic testing (Denoyelle, 1999). Genetic testing is problematic because of the extreme genetic heterogeneity and the frequent lack of phenotypic variability among the genetic forms of NSHL. Multi-gene screening panels for NSHL have therefore been developed by several groups (Shearer et al, 2010).

Around 1% of prelingual NSHL is caused by mutations in mitochondrial DNA (mtDNA), which is inherited only from the mother. People carrying mtDNA mutations always have an SNHL, often with a symmetrical, progressive presentation and debuting in childhood. An environmental interaction that is especially pertinent to medical personnel is that certain subtypes of mutations in mitochondrial DNA (mtDNA), which is inherited only from the mother, people carrying mtDNA mutations always have an SNHL, often with a symmetrical, progressive presentation and debuting in childhood. An environmental interaction that is especially pertinent to medical personnel is that certain subtypes of mutations in mtDNA are more sensitive to the ototoxicity of aminoglycosides. The A1555G mutation in the MTRNR1 gene, which encodes the small subunit rRNA, is the most common variant.

X-linked inheritance is also a rare cause of sensorineural hearing loss, and it is present in both the non-syndromic and syndromic etiological categories. Many syndromes are caused by diseases on the X chromosome. However, some of the more common ones like Alport syndrome and Fabry disease have a late onset of hearing loss and are therefore not encountered in the pediatric population (Petersen et al, 2008). Until recently, the only known gene responsible for X-linked NSHL was POU3F4, but since the beginning of this decade three new genes have been found (PRPS1, SMPX, COL4A6) (Schraders et al, 2011; Liu et al, 2010; Rost et al, 2014).

**Methods**

**Search strategy**

PubMed was searched for studies reporting on the etiology of deafness in CI-implanted children (<18 years) (Table 1). The search was limited to the period from 2000 to 2014 because standard tests for diagnostic evaluation were previously uncommon. Cinahl, Cochrane, EMBase were also searched using adapted search strategies.

Two of the authors independently screened the citations and included studies if they contained more than 100 subjects. Studies were excluded if the study population was selected based on etiology of deafness, unilateral CI only, or bilateral CI only. In case of disagreement, consensus was reached through discussion.

**Appraisal of methodological quality**

All three authors independently appraised the methodological quality of the included studies using a validated 18-criteria checklist for case series (Moga et al, 2012). In case of disagreement, consensus was reached through discussion. As recommended in the instructions, 10 criteria of significant methodological importance were selected a priori (Table 2). This quality assessment tool was found to be the most appropriate because, to our knowledge, the majority of studies on CI children are case series.
Results

Search results

Our search identified 470 unique citations. After screening the titles and abstracts, 81 articles were available in full text versions and 16 were included (Figure 1).

Study characteristics

The study characteristics are presented in Table 4. The included studies were published from the year 2001 to the year 2011. All were case series with 11 retrospective, three prospective, and two combined study designs. Data was available on 5069 patients from 13 different countries. The average mean age at implantation was 4.3 (95% CI 4.0 to 4.3) years (Table 4). More than 20 etiologies were identified prior to categorization.

Quality appraisal

None of the studies fulfilled all of the quality appraisal criteria on the checklist (Table 2 and Table 4). The majority of the studies (n = 12 (75%)) fulfilled 50% or more of the quality appraisal criteria. All studies (n = 16) had a clear objective/hypothesis. Only two studies (12.5%) were multicenter studies. Inclusion/exclusion criteria were fully or partially present in 15 studies (93.5%), while 13 (81.3%) studies described the characteristics of the participants fully. In eight of the studies (50%), patients had been recruited consecutively. Outcome measures were defined fully in 12 studies (75%), partially in two (12.5%), and not at all in two (12.5%); the outcome measures were appropriately measured in 13 (81.3%) (Table 2).

Length of follow-up and loss to follow-up were reported in five studies (31.3%), but was not considered to influence the etiological proportions. In 13 studies (81.3%), the conclusions were fully supported by the results; in two only partially; and in one, no support was found (Table 2).

Etiological categories

Data on each etiological category are shown in Table 5. The most common etiologies were those in the categories ‘Unknown’ with a prevalence of 40.3% (95% CI 32.8 to 48.0), ‘Non-syndromic’ with a prevalence of 22.4% (95% CI 17.1 to 28.2), and ‘Postnatal’ with a prevalence of 11.3% (95% CI 7.2 to 16.2). The meta-analysis of the most common etiological categories is presented in Figures 2, 3, and 4.

Studies published after 2006 (n = 8) had a lower ‘Unknown’ proportion (35.3% (95% CI 28.0 to 42.8)) than older publications (n = 8) (45.5% (95% CI 31.0 to 60.4)). When a fixed effect analysis was applied, the difference was statistically significant. There was no difference when comparing the ‘Non-syndromic’

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Table 3. Examples of reported etiologies. Bold type indicates categorization used in this study.

| Etiological category | Examples |
|----------------------|----------|
| Unknown              | Genetic  |
| Syndromic            | CHARGE   |
|                      | Jervel & Lange-Nielsen |
|                      | Pendred  |
|                      | Usher    |
|                      | Waardenburg |
| Non-syndromic        | GJB2     |
|                      | GJB6     |
|                      | OTOF     |
|                      | Family history/Consanguinity |
| Prenatal             | Maternal Infection |
|                      | CMV      |
|                      | Rubella (CRS) |
|                      | Auditory neuropathy |
|                      | Cochlear malformation |
| Perinatal            | Hypoxia  |
|                      | Hyperbilirubinæmi |
|                      | NICU     |
| Postnatal            | Ototoxicity |
|                      | Meningitis |
|                      | Trauma   |

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Data extraction

Data extraction was carried out by a single author and included all data on population demographics and etiology from text, tables, and figures. To produce a comparable result, the prevalence of the various etiologies was categorized as ‘Unknown’, ‘Non-syndromic’, ‘Syndromic’, ‘Prenatal’, ‘Perinatal’, ‘Postnatal’, and ‘Malformation + Others’ (Table 3). The categorization was inspired by previous studies (Morzaria et al, 2004, Heman-Ackah et al, 2012).

Data analysis

The results of the quality assessment were calculated as the percentage of questions that could be answered with a ‘Yes’. Each etiological category was processed individually and a pooled prevalence proportion was calculated using the random effects (DerSimonian & Laird) method for meta-analysis. If a study presented no data on an etiological group, its population was excluded from the calculation for this specific group. To test for heterogeneity among the results of the included studies, the inverse variance index (I²-value) was calculated for each prevalence proportion. I²-values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively. The median year of publication was chosen as the point of division in the comparison of older studies with newer ones.
proportions (22.0% (95% CI 15.2 to 29.7) vs. 22.9% (95% CI 13.7 to 33.6)).

The studies with ‘high’ level of diagnostic detail reporting (n = 5) had a lower ‘Unknown’ proportion (31.8% (95% CI 20.8 to 43.9)) than studies with ‘low/no’ detail (n = 11, 44.3% (95% CI 35.0 to 53.8)). When a fixed effect analysis was applied, the difference was statistically significant. There was no difference when comparing the ‘Non-syndromic’ proportions (23.5% (95% CI 13.3 to 35.5) vs. 21.9% (95% CI 15.6 to 28.9)). ‘Syndromic’ showed a significantly larger prevalence proportion in the group with ‘high’ diagnostic detail with 13.6% (95% CI 10.6 to 17.0) vs. 5.1 (95% CI 2.9 to 7.8).

A high degree of heterogeneity, I²-value >75%, was found when each etiological prevalence proportion was calculated (Table 5).

Discussion
This systematic review of etiological prevalence in the population of CI children encompasses analysis of 16 studies published from 2001–2011 with 5069 patients. We found that more than a third (40.3% (95% CI 32.8 to 48.0)) of the children implanted with a CI had an ‘Unknown’ etiological diagnosis. Studies offering a thorough description of the applied diagnostic evaluation program had a lower prevalence proportion with ‘Unknown’ etiology, although this difference was only statistically significant when a fixed-effects model was used. The same applied to studies published before vs. after 2006; and this finding could be a matter of power. The ‘Syndromic’ category was significantly larger in the group with ‘high’-level detail when random effects were used.

To our knowledge, this is the first systematic review of the etiology of deafness in CI children. The strength of the study is its methodological approach, which involves analysis by three individual reviewers, a reproducible search string, and the use of a validated quality assessment tool (Moga et al, 2012). In order to estimate which results were most valid, the extracted data were analysed using a random effects model (Dersimonian and Laird).

A weakness of the results of this systematic review is the large degree of heterogeneity (I²-value >75%) across all etiological categories in the studies analysed. This heterogeneity was due to multiple factors such as differences in diagnostic, ethnical, and temporal factors. We found a large degree of discrepancy between

Figure 1. Flowchart of study selection. Last search carried out on 1 September 2014.
studies in terms of their examination, reporting, and categorization of etiology. Thirteen studies (81.3%) described the full characteristics of the participants, while three only partially fulfilled this criterion. This incoherence of presentation of etiology creates a degree of misclassification. The lack of information on applied diagnostics makes it difficult to address how populations were examined and to which extent they are comparable. Finally, the inclusion of 13 different nationalities in this study raises issues pertaining to the ethnic and genetic variance as well as cultural and socioeconomic factors.
Reducing the 'unknown' proportion

More than 50% of congenital hearing loss is due to genetic factors, and molecular genetics therefore plays an essential role in the etiological evaluation. In one population, the use of focused genetic analysis reduced the proportion of patients with 'Unknown' etiology by more than 40% (Siem et al, 2010).

In Denmark, a series of single gene testing is applied to identify CI candidates. The rationale of this approach rests on epidemiological data, and tests performed seek to trace mutations in GJB2 and GJB6 and in the six most frequent mutations of the SLC26A4 gene.

Although this methodology will detect many of the genetic etiologies, multi-gene screening panels are even more sensitive and they should be applied in future studies to minimize the prevalence proportion of 'Unknown' etiologies; however, multi-gene screening is costly and economic aspects of such screening should be taken into consideration.

Genetic counseling is an important prerequisite for thorough genetic testing of patients and family members. There is a 25% recurrence risk that parents having one child with GJB2-related deafness will have another child with the same genotype. There is a 66% risk that the second child will have mild-to-moderate HL and a
34% risk that the HL will be more severe if the first child has mild-to-moderate HL (Radulescu et al, 2012). Prenatal diagnostics is possible, but contemplation of termination of pregnancy in the face of a risk of a minor handicap raises pertinent ethical issues, not least considering the positive outcome that may be achieved with CI. A Danish group (Thorsen et al, 2009) performed a questionnaire study among parents of implanted children to measure their attitudes towards genetic testing. A total of 83% of the responding parents would like a test themselves and 61% would have wanted earlier knowledge of their child’s deafness in order to prepare themselves for their child having a CI. Only one of 17 would terminate the pregnancy knowing that the child would be deaf.

The non-genetic prenatal causes are dominated by the maternal transfer of the TORCH infections (toxoplasmosis, rubella, CMV, herpes). Especially frequent is cytomegalovirus with a birth prevalence of 0.64%. Only 10% of the CMV infections are asymptomatic, and it is estimated that 4.4% of the asymptomatic cases develop unilateral or bilateral SNHL (Kenneson & Cannon, 2007). All newborns in Denmark have a blood sample drawn which is stored in a biobank. If they are diagnosed with SNHL at the neonatal hearing screening, they are tested for CMV antigen, and any future analysis of these data may confirm whether prenatal CMV is an underestimated etiology.

**Conclusion**

By reviewing the literature and registering the heterogeneity of the etiological descriptions, it is apparent that much benefit would accrue from standardization of diagnostics as well as analysis of this information in future studies. A large percentage of implanted patients remain in the ‘Unknown’ group, many of whom could be diagnosed with an improved genetic testing battery. Besides the genetic causes, it is suspected that asymptomatic CMV is responsible for a noteworthy number of cases.

Knowledge of the genetics of deafness has proven to be a valuable tool when determining the prognostic outcome and for providing genetic counseling. Furthermore, the creation of a large volume of accessible genetic data could improve the foundation of future research, e.g. within new therapeutic strategies like gene therapy.

The heterogeneity of the reported etiological prevalence proportions may be ascribed to discrepancy in geography, inheritance, CI candidate criteria, and diagnostic investigation. Therefore, it is recommended that description of etiology become a minimum requirement in order to further analysis of more comparable results on the outcome of CI in the future.

To ensure the highest level of comparability of future research, it is commendable that agreement be established as to the following should be agreed upon:

- An international standard of diagnostics
- An international standard of reporting etiology.

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