Taylor & Francis
Taylor & Francis Group

International Journal of Audiology 2015; 54: 924–932

International
Journal of
Audiology

Original Article

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

Niels Krintel Petersen, Anders W. Jørgensen & Therese Ovesen

Department of Otorhinolaryngology, Aarhus University Hospital, Aarhus C, Denmark

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 prosthesis to date, with more than 220 000 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

*Correspondance: Niels Krintel Petersen, Bissensgade 13, 3.tv, DK-8000 Aarhus C, Denmark. E-mail: niels.krintel.petersen@gmail.com

(Received 30 March 2015; revised 18 July 2015; accepted 31 August 2015)

ISSN 1499-2027 print/ISSN 1708-8186 online
DOI: 10.3109/14992027.2015.1091094

Abbreviations

CI	Cochlear implant
GJB2	Gap junction Beta-2 protein
JLNS	Jervell and Lange-Nielsen syndrome
NSHL	Non-syndromic hearing loss
SNHL	Sensorineural hearing loss

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 tachyarrythmia 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 pathophysiologies 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-*k*B; 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

Table 1. Search string. Last applied to PubMed on 1 September, 2014.

Search string	Comment
'Hearing loss/etiology' [MAJR] AND 'Cochlear implants' [MAJR])	Any papers with these subjects listed as major topics.
OR 'Hearing loss, Sensorineural/epidemiology' [MeSH Terms]	MeSH terms found in included articles from the primary search as well as from relevant references. Combined with 'Cochlear implantation'
OR 'Hearing loss, Bilateral/surgery' [MeSH Terms]	
OR 'Hearing loss, Sensorineural/surgery' [MeSH Terms]	
OR 'Deafness/epidemiology' [MeSH Terms]	
OR 'Cochlear implants/statistics and numerical data' [MAJR]	
OR 'Hearing loss/etiology' [MAJR]	
OR 'Deafness/etiology' [MAJR]	
OR 'Cochlear implant' [All Fields] AND 'Etiology' [All Fields]	
AND 'Cochlear implantation' [MeSH Terms]	
NOT 'Case reports'[pt]	Filters applied, excluding articles from before 2000, case reports, animal experiments and adults.
AND 'loattrfull text [sb] AND ('2000/01/01' [PDAT]: '2014/12/31' [PDAT])	
AND 'humans' [MeSH Terms]	
AND 'infant' [MeSH Terms] OR 'child' [MeSH Terms] OR 'adolescent' [MeSH Terms]	

Table 2. The ten criteria of methodological importance and number of studies fulfilling these fully, partially, or not at all.

Quality appraisal criteria	'Yes'	'Partially'	'No'
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	16	0	0
2. Are the characteristics of the participants included in the study described.	13	3	0
3. Were the cases collected in more than one center?	2	0	14
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	7	8	1
5. Were participants recruited consecutively?	8	6	2
9. Are the outcome measures clearly defined in the introduction or methods section?	12	2	2
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	13	3	0
13. Was the length of follow-up reported?	5	2	9
14. Was the loss to follow-up reported?	5	3	8
17. Are the conclusions of the study supported by the results?	13	2	1

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 (Propst 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 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 sensorineaural 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.

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

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	
Malformation/Other		

The studies were reviewed for description of diagnostic evaluation and categorized into high detail, medium detail, and low detail/no-description. The '*low/no*' category mentioned only examination of medical history or did not describe the process at all. The '*medium*' detail studies described imaging diagnostics as well as audiograms and ABR, but gave no detailed description of clinical examination, blood-samples, or genetic evaluation. The '*high*' detail studies described how conclusion on etiological diagnosis was determined through family and medical history, clinical examinations, blood samples, and which specific genetic tests were performed.

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 (I^2-value) was calculated for each prevalence proportion. I^2-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.

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*'

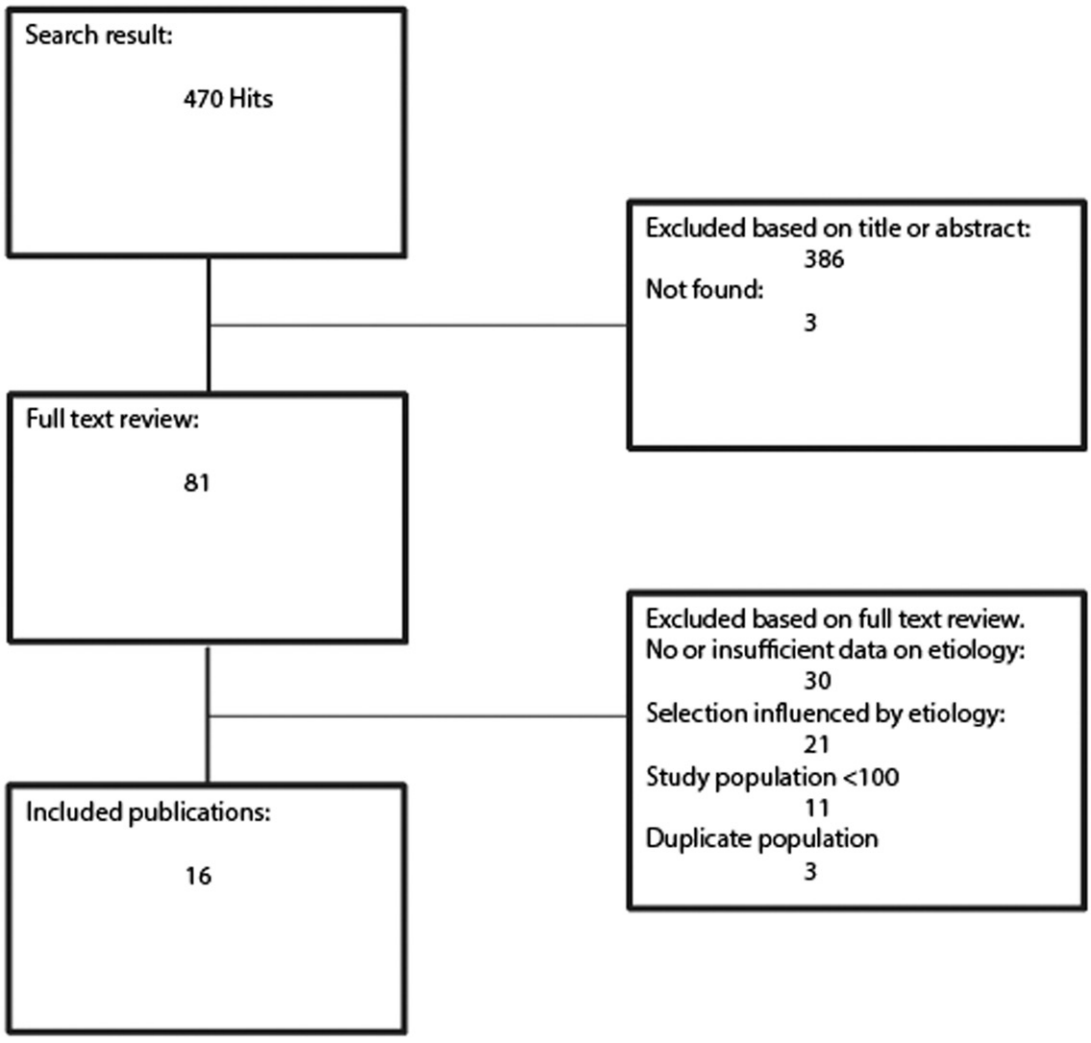

Figure 1. Flowchart of study selection. Last search carried out on 1 September 2014.

proportions (22.0% (95% CI 15.2 to 29.7) vs. 22.9% (95% CI 13.756 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, I^2-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 (I^2-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

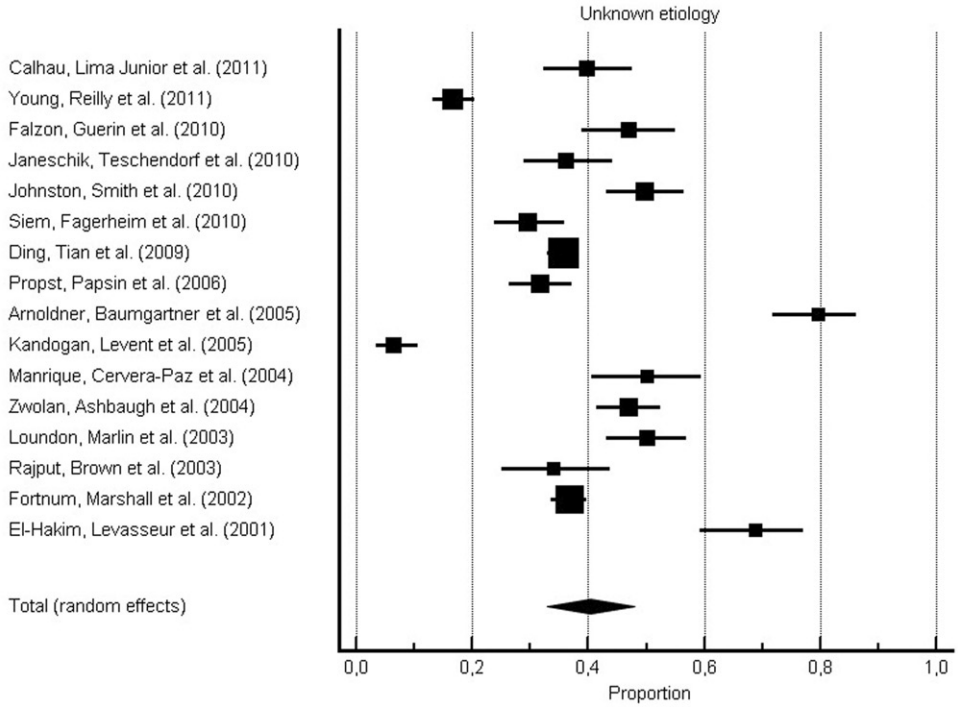

Figure 2. Meta analysis of reported prevalence: '*Unknown*'.

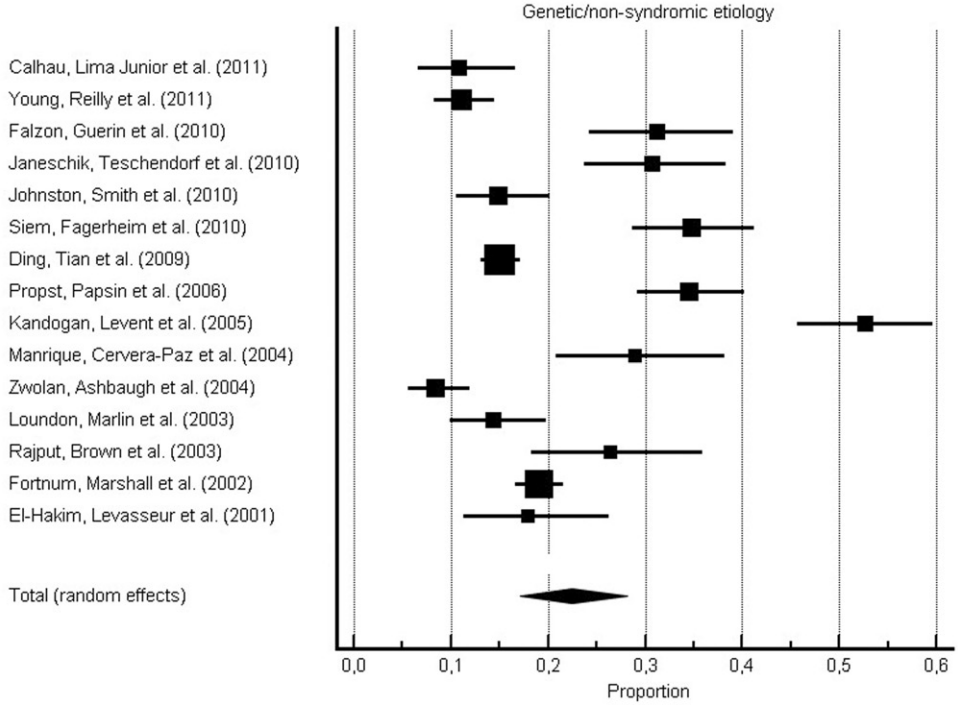

Figure 3. Meta analysis of reported prevalence: '*Genetic/Non-syndromic*'.

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.

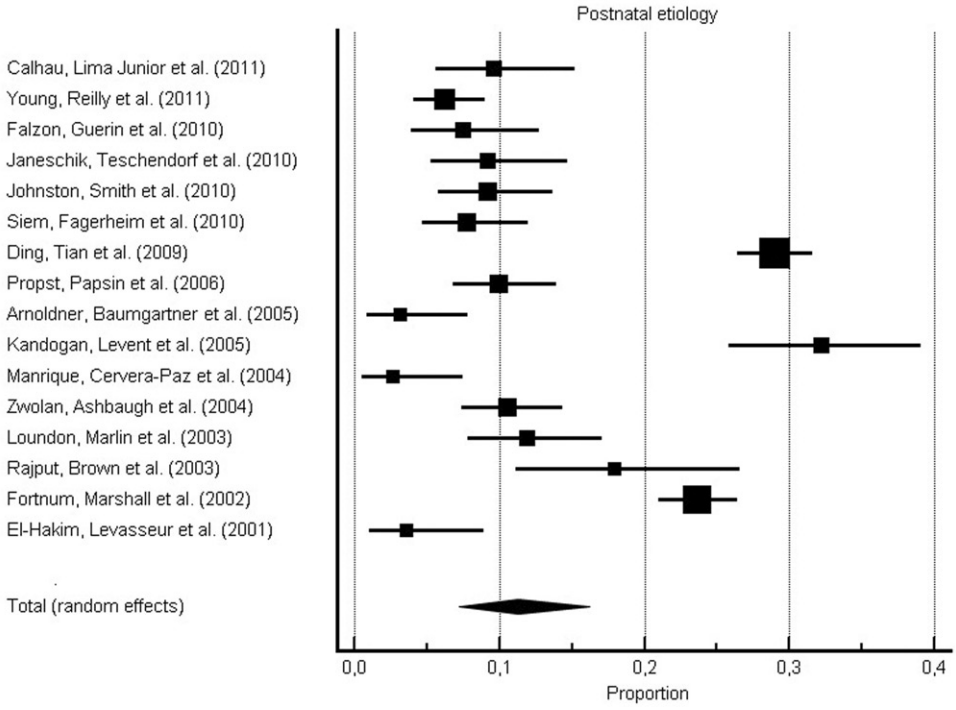

Figure 4. Meta analysis of reported prevalence: '*Postnatal*'.

Table 4. Study characteristics and quality appraisal results.

Study & publication year	Nationality	Design	Mean age (years)	Patients	Quality appraisal criteria fulfilled*	Reporting on diagnostics
Calhau et al, 2011	Brazil	Pro	3.5	166	50%	Low
Young et al, 2011	USA	Retro	4.2	417	40%	High
Falzon et al, 2010	Ireland	Retro	2.3	160	30%	Low
Janeschik et al, 2010	Germany	Retro + Pro	5.2	163	10%	Low
Johnston et al, 2010	Canadian	Retro	5.5	229	80%	Low
Siem et al, 2010	Norway	Retro + Pro	3.0	233	70%	High
Ding et al, 2009	China	Retro	4.8	1227	80%	Low
Propst et al, 2006	Canada	Pro	4.7	301	70%	High
Arnoldner et al, 2005	Austria	Retro	5.0	128	60%	None
Kandogan et al, 2005	Turkey	Retro	-	205	40%	None
Manrique et al, 2004	Spain	Pro	2.7	114	50%	Low
Zwolan et al, 2004	USA	Retro	5.4	324	90%	None
Loundon et al, 2003	France	Retro	6.1	210	80%	High
Rajput et al, 2003	UK	Retro	4.0	106	70%	High
Fortnum et al, 2002	UK	Retro	-	974	70%	None
El-Hakim, et al, 2001	Canada	Retro	5.1	112	50%	None

*Percentage of questions answered with 'Yes'.

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

Table 5. Prevalence of various etiologies and test for heterogeneity results.

Etiological categories	No. of patients (total)	No. of studies	Prevalence*	95% CI	I^2
Syndromic	336 (4745)	15	7.6%	5.0 to 10.7	92.3%
Genetic/non-syndromic	998 (4941)	15	22.4%	17.1 to 28.2	95.2%
Unknown	1884 (5069)	16	40.3%	32.8 to 48.0	96.6%
Prenatal	244 (3637)	14	6.2%	4.5 to 8.2	79.6%
Perinatal	300 (3073)	11	7.2%	3.0 to 13.2	96.6%
Postnatal	878 (5069)	16	11.3%	7.2 to 16.2	95.9%
Malformation + Other	429 (3648)	8	9.68%	3.7 to 17.9	98.0%

*Calculated using the random-effects (DerSimonian and Laird) method for meta-analysis.

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 symptomatic, 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.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Acke F.R., Dhooge I.J., Malfait F. & De Leenheer E.M. 2012. Hearing impairment in Stickler syndrome: A systematic review. *Orphanet J Rare Dis*, 7, 84.

Arnoldner C., Baumgartner W.D., Gstoettner W. & Hamzavi J. 2005. Surgical considerations in cochlear implantation in children and adults: A review of 342 cases in Vienna. *Acta Otolaryngol*, 125, 228–234.

Atas B., Altunhan H., Eryilmaz M.A. & Atas E. 2011. Frequency of congenital hearing loss in 43 503 healthy newborn infants in Konya, Turkey. *J Pak Med Assoc*, 61, 727–728.

Black J., Hickson L., Black B. & Perry C. 2011. Prognostic indicators in paediatric cochlear implant surgery: a systematic literature review. *Cochlear Implants Int*, 12, 67–93.

Calhau C.M., Lima Junior L.R., Reis A.M., Capistrano A.K., Lima Ddo V. et al. 2011. Etiology profile of the patients implanted in the cochlear implant program. *Braz J Otorhinolaryngol*, 77, 13–18.

Chang D.T., Ko A.B., Murray G.S., Arnold J.E. & Megerian C.A. 2010. Lack of financial barriers to pediatric cochlear implantation: Impact of socioeconomic status on access and outcomes. *Arch Otolaryngol Head Neck Surg*, 136, 648–657.

Chen D., Chen X., Cao K., Zuo J., Jin X. et al. 2009. High prevalence of the connexin 26 (GJB2) mutation in Chinese cochlear implant recipients. *ORL J Otorhinolaryngol Relat Spec*, 71, 212–215.

Cosetti M.K. & Waltzman S.B. 2011. Cochlear implants: Current status and future potential. *Expert Rev Med Devices*, 8, 389–401.

Denoyelle F. 1999. Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: Implications for genetic counselling. *The Lancet (British edition)*, 353, 1298–1303.

Ding X., Tian H., Wang W. & Zhang D. 2009. Cochlear implantation in China: Review of 1237 cases with an emphasis on complications. *ORL J Otorhinolaryngol Relat Spec*, 71, 192–195.

Dror A.A. & Avraham K.B. 2009. Hearing loss: Mechanisms revealed by genetics and cell biology. *Annu Rev Genet*, 43, 411–437.

El-Hakim H., Levasseur J., Papsin B.C., Panesar J., Mount R.J. et al. 2001. Assessment of vocabulary development in children after cochlear implantation. *Arch Otolaryngol Head Neck Surg*, 127, 1053–1059.

Falzon K., Guerin M., Fulcher T. & Viani L. 2010. Ophthalmological screening of a paediatric cochlear implant population: A retrospective analysis and 12-year follow-up. *Eye (Lond)*, 24, 1031–1036.

Fortnum H.M., Marshall D.H. & Summerfield A.Q. 2002. Epidemiology of the UK population of hearing-impaired children, including characteristics of those with and without cochlear implants: Audiology, aetiology, comorbidity, and affluence. *Int J Audiol*, 41, 170–179.

Heman-Ackah S.E., Roland J.T. Jr, Haynes D.S. & Waltzman S.B. 2012. Pediatric cochlear implantation: Candidacy evaluation, medical and surgical considerations, and expanding criteria. *Otolaryngol Clin North Am*, 45, 41–67.

Janeschik S., Teschendorf M., Arweiler-Harbeck D. & Bagus H. 2010. Development of hearing and speech abilities in cochlear implant users in relation to cause of deafness. *Cochlear Implants Int*, 11(Suppl 1), 312–314.

Johnston J.C., Smith A.D., Fitzpatrick E., O'Connor A., Angus D. et al. 2010. Estimation of risks associated with paediatric cochlear implantation. *Cochlear Implants Int*, 11, 146–169.

Kandogan T., Levent O. & Gurol G. 2005. Complications of paediatric cochlear implantation: Experience in Izmir. *J Laryngol Otol*, 119, 606–610.

Kenneson A. and Cannon M.J. 2007. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*, 17, 253–276.

Liu X., Han D., Li J., Han B., Ouyang X. et al. 2010. Loss-of-function mutations in the PRPS1 gene cause a type of nonsyndromic X-linked sensorineural deafness, DFN2. *Am J Hum Genet*, 86, 65–71.

Loundon N., Marlin S., Busquet D., Denoyelle F., Roger G. et al. 2003. Usher syndrome and cochlear implantation. *Otol Neurotol*, 24, 216–221.

Manrique M., Cervera-Paz F.J., Huarte A. & Molina M. 2004. Advantages of cochlear implantation in prelingual deaf children before 2 years of age when compared with later implantation. *Laryngoscope*, 114, 1462–1469.

Mathur P. & Yang J. 2015. Usher syndrome: Hearing loss, retinal degeneration and associated abnormalities. *Biochim Biophys Acta*, 1852, 406–420.

Moga C., Guo B., Schopflocher D. & Harstall C. 2012. *Development of a quality appraisal tool for case series studies using a modified Delphi technique*. Edmonton, Canada: Institute of Health Economics.

Morzaria S., Westerberg B.D. & Kozak F.K. 2004. Systematic review of the etiology of bilateral sensorineural hearing loss in children. *Int J Pediatr Otorhinolaryngol*, 68, 1193–1198.

Nikolopoulos T.T. 2010. Treating options for deaf children. *Early Hum Dev*, 86, 669–674.

Pagon R., Bird T. & Dolan C. (eds.) 2012. *GeneReviews: Deafness and Hereditary Hearing Loss Overview.* http://www-ncbi-nlm-nih-gov.ez.statsbiblioteket.dk:2048/books/NBK1434/:

Parving A., Hauch A.M. & Christensen B. 2003. Hearing loss in children: Epidemiology, age at identification, and causes through 30 years. *Ugeskr Laeger*, 165, 574–9.

Petersen M.B., Wang Q. & Willems P.J. 2008. Sex-linked deafness. *Clin Genet*, 73, 14–23.

Petit C., Levilliers J. & Hardelin J.P. 2001. Molecular genetics of hearing loss. *Annu Rev Genet*, 35, 589–646.

Propst E.J., Papsin B.C., Stockley T.L., Harrison R.V. & Gordon K.A. 2006. Auditory responses in cochlear implant users with and without GJB2 deafness. *Laryngoscope*, 116, 317–327.

Radulescu L., Martu C., Birkenhager R., Cozma S., Ungureanu L. et al. 2012. Prevalence of mutations located at the dfnb1 locus in a population of cochlear implanted children in eastern Romania. *Int J Pediatr Otorhinolaryngol*, 76, 90–94.

Rajput K., Brown T. & Bamiou D.E. 2003. Aetiology of hearing loss and other related factors versus language outcome after cochlear implantation in children. *Int J Pediatr Otorhinolaryngol*, 67, 497–504.

Rosa F., Coutinho M.B., Ferreira J.P. & Sousa C.A. 2015. Ear malformations, hearing loss and hearing rehabilitation in children with Treacher Collins syndrome. Acta Otorrinolaryngol Esp. Epub ahead of print.

Rost S., Bach E., Neuner C., Nanda I., Dysek S. et al. 2014. Novel form of X-linked nonsyndromic hearing loss with cochlear malformation caused by a mutation in the type IV collagen gene COL4A6. *Eur J Hum Genet*, 22, 208–215.

Schraders M., Haas S.A., Weegerink N.J., Oostrik J., Hu H. et al. 2011. Next-generation sequencing identifies mutations of SMPX, which encodes the small muscle protein, X-linked, as a cause of progressive hearing impairment. *Am J Hum Genet*, 88, 628–634.

Schwartz P.J., Spazzolini C., Crotti L., Bathen J., Amlie J.P. et al. 2006. The Jervell and Lange-Nielsen syndrome: Natural history, molecular basis, and clinical outcome. *Circulation*, 113, 783–790.

Senthil Vadivu A., Sampath R., Paramasivan V.K., Mohan M. & Kameswaran M. 2013. Cochlear implantation and cardiac associations. *Int J Pediatr Otorhinolaryngol*, 77, 1303–1307.

Shearer A.E., DeLuca A.P., Hildebrand M.S., Taylor K.R., Gurrola J. 2nd. et al. 2010. Comprehensive genetic testing for hereditary hearing loss using massively parallel sequencing. *Proc Natl Acad Sci USA*, 107, 21104–21109.

Siem G., Fagerheim T., Jonsrud C., Laurent C., Teig E. et al. 2010. Causes of hearing impairment in the Norwegian paediatric cochlear implant program. *Int J Audiol*, 49, 596–605.

Stern R.E., Yueh B., Lewis C., Norton S. & Sie K.C.Y. 2005. Recent epidemiology of pediatric cochlear implantation in the United States: Disparity among children of different ethnicity and socioeconomic status. *Laryngoscope*, 115, 125–131.

Thorsen A., Devantier L. & Ovesen T. 2009. Attitudes towards prenatal diagnosis of deafness among parents to children with cochlear implants. *Ugeskr Laeger*, 171, 1387–91.

Young N.M., Reilly B.K. & Burke L. 2011. Limitations of universal newborn hearing screening in early identification of pediatric cochlear implant candidates. *Arch Otolaryngol Head Neck Surg*, 137, 230–234.

Zwolan T.A., Ashbaugh C.M., Alarfaj A., Kileny P.R., Arts H.A. et al. 2004. Pediatric cochlear implant patient performance as a function of age at implantation. *Otol Neurotol*, 25, 112–120.