



Year: 2017

Bilateral congenital deafness: What investigations should be performed?

Gürtler, Nicolas; Gysin, Claudine; Schmid, Nevenka; Pieren, Claudia; Vischer, Mattheus; Schumacher, Stefan; Oppermann, Peter; Leuba, Daniel; Veraguth, Dorothée

Abstract: **BACKGROUND:** The introduction of newborn hearing screening has led to earlier identification of children with congenital sensorineural hearing loss (SNHL). Aetiological clarification offers several benefits. There is currently a lack of agreement on which examinations should be recommended. **OBJECTIVE:** Descriptive review of the literature reporting investigations performed to establish the aetiology of congenital SNHL and comparison of the management policy in Swiss referral centres. **METHODS:** PubMed Search from 1985 to March 2016 with specific search terms; study selection according to inclusion/exclusion criteria; narrative analysis by use of defined criteria and question-naire. **RESULTS:** Ninety-two studies were finally included in this review. Forty studies investigated more than a single aetiology. Overall frequencies of aetiological parameters investigated were: genetic (47 studies), radiological (35), ophthalmic (35), serological (32), cardiac (25), renal (14), endocrine (12), neurological (8). Most of the studies were retrospective and various limitations such as poor population description, incomplete data or deficiencies in methodological quality were frequently detected. The variability detected in the investigative approach chosen by Swiss referral centres reflects the heterogeneous data seen in the literature. **CONCLUSIONS:** The evidence in the literature regarding an appropriate evaluation is mostly of low quality and difficult to assess owing to high heterogeneity. Nevertheless, imaging, genetic testing, neuropaediatric and ophthalmological evaluations, electrocardiograms and cytomegalovirus analysis have been identified as examinations to be included in the assessment of children with congenital SNHL. There is a need for international consensus on the various issues of such an evaluation, such as choice of investigations and diagnostic criteria.

DOI: <https://doi.org/10.4414/smw.2017.14416>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-149013>

Journal Article

Published Version



The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

Originally published at:

Gürtler, Nicolas; Gysin, Claudine; Schmid, Nevenka; Pieren, Claudia; Vischer, Mattheus; Schumacher, Stefan; Oppermann, Peter; Leuba, Daniel; Veraguth, Dorothée (2017). Bilateral congenital deafness: What investigations should be performed? *Swiss Medical Weekly*, 147:w14416.

DOI: <https://doi.org/10.4414/smw.2017.14416>

Bilateral congenital deafness: what investigations should be performed? A qualitative descriptive review

Nicolas Gürtler^{a,b,d}, Claudine Gysin^{c,d}, Nevenka Schmid^d, Claudia Pieren^d, Mattheus Vischer^d, Stefan Schumacher^d, Peter Oppermann^d, Daniel Leuba^d, Dorothée Veraguth^d

^a Hals-Nasen-Ohren-Universitätsklinik, University Hospital Basel, Switzerland

^b Hals-Nasen-Ohren-Klinik, Universitätskinderhospital beider Basel, Switzerland

^c Hals-Nasen-Ohren-Klinik, Children's Hospital Zurich, Switzerland

^d Working Group Paediatric Otolaryngology, Swiss Society of Otolaryngology

Summary

BACKGROUND: The introduction of newborn hearing screening has led to earlier identification of children with congenital sensorineural hearing loss (SNHL). Aetiological clarification offers several benefits. There is currently a lack of agreement on which examinations should be recommended.

OBJECTIVE: Descriptive review of the literature reporting investigations performed to establish the aetiology of congenital SNHL and comparison of the management policy in Swiss referral centres.

METHODS: PubMed Search from 1985 to March 2016 with specific search terms; study selection according to inclusion/exclusion criteria; narrative analysis by use of defined criteria and questionnaire.

RESULTS: Ninety-two studies were finally included in this review. Forty studies investigated more than a single aetiology. Overall frequencies of aetiological parameters investigated were: genetic (47 studies), radiological (35), ophthalmic (35), serological (32), cardiac (25), renal (14), endocrine (12), neurological (8). Most of the studies were retrospective and various limitations such as poor population description, incomplete data or deficiencies in methodological quality were frequently detected. The variability detected in the investigative approach chosen by Swiss referral centres reflects the heterogeneous data seen in the literature.

CONCLUSIONS: The evidence in the literature regarding an appropriate evaluation is mostly of low quality and difficult to assess owing to high heterogeneity. Nevertheless, imaging, genetic testing, neuropaediatric and ophthalmological evaluations, electrocardiograms and cytomegalovirus analysis have been identified as examinations to be included in the assessment of children with congenital SNHL. There is a need for international consensus on the various issues of such an evaluation, such as choice of investigations and diagnostic criteria.

Key words: sensorineural hearing loss; congenital; evaluation; aetiology; management

Introduction

The prevalence of bilateral congenital sensorineural hearing loss (SNHL) ranges between 1 and 3% in industrialised countries. According to epidemiological data, the origin of congenital SNHL can be traced to a genetic cause in more than 50% of cases, and the remainder are considered as acquired [1]. Genetic SNHL is further subdivided into syndromic (30%) and nonsyndromic (70%) forms.

The timely detection of congenital SNHL is of utmost importance as hearing therapy initiated before the age of 2 years (prior to the critical period for auditory development and speech acquisition) shows better results than therapy begun at a later age [2]. For this reason, universal newborn hearing screening was successfully introduced in many countries, including Switzerland since 1999, with the aim of detecting SNHL in the first few months of life [3, 4]. Early intervention once SNHL is confirmed is well established, whereas clarifying the aetiology is much less practised, although many benefits would ensue. These include prognostic counselling, avoidance of unnecessary screening investigations and, probably, a reduction in healthcare costs associated with over-investigation. On the parental side, feelings of culpability and partnership difficulties can be alleviated, and answers as to why their children have SNHL can be provided. Also, questions such as prediction of hearing outcome can be answered more precisely, as was shown for children with mutations in *GJB2* who had a homogeneously excellent outcome after cochlear implantation [5]. Although guidelines have been established, the proposed diagnostic approach for children with congenital SNHL varies [6, 7]. Therefore, recommendations for appropriate and cost-effective investigations in order to establish an aetiological diagnosis still remain unclear. New technology and heterogeneous practices further complicate the proper appraisal of investigative methods [8].

This study aimed to review the literature on assessing the aetiology of congenital bilateral SNH and to analyse the various investigations. In order to be able to focus on one group of children with hearing impairment, unilateral and late-onset hearing loss were excluded. Secondly,

findings were compared with the management policy in Swiss referral centres, in order to define areas of improvement.

Methods

The Working Group “Paediatric Otorhinolaryngology” of the Swiss Society of Otolaryngology conducted a literature search in Medline (www.pubmed.gov) for the period from 1986 to March 2016. Earlier years were not included because a major shift in the frequency of the various aetiologies of congenital SNHL occurred, mainly as a result of two factors: the implementation of vaccination programmes for rubella and *Haemophilus influenzae*, and the increasingly widespread use of computed tomography (CT) scans, which allowed the detection of new aetiological entities. The following keywords were used to extract the relevant articles in PubMed: “bilateral” AND “congenital” AND “sensorineural hearing loss” AND (each word separately) “neurology, heart, nephrology/kidney, radiology, infection, ophthalmology, genetics, endocrinology, serology”. Additional articles were identified from review of the reference lists. The inclusion criteria for the study selection were: patient age up to 18 years, any language, bilateral hearing loss, severity of hearing loss at least mild, at least one investigation defined, congenital hearing loss. Exclusion criteria were: progressive and/or unilateral hearing loss, age above 18 years.

The validity of studies regarding “aetiology” is difficult to assess, as they are always limited by their retrospective nature; hence, criteria such as those established by the Centre for Evidence Based Medicine cannot be applied. Instead, internal validity was assessed by analysis of the comprehensiveness of documentation (precise methodology, well-described population, type and frequency of investigations, positivity criteria listed). The dataset was reviewed by at least two of the authors. Disagreements were reconciled through group discussions.

Additionally, the result of the literature analysis was compared to the procedures employed in all otolaryngological tertiary referral centres in Switzerland, which cover >95% of paediatric cases with bilateral congenital SNHL. A questionnaire asking for the following information was sent to each institution: patient history, and results of neurological and ophthalmological examinations, electrocardiogram (ECG), serological and genetic analysis, endocrinology, urinalysis and radiology. Switzerland is a small country with defined tertiary referral centres for otolaryngology. The questionnaire was developed by the group. The response rate was 100%. Finally, the costs of each examination were evaluated.

Results

Literature analysis: general

After the initial literature search, the abstracts of >1600 published articles were searched for the predefined inclusion and exclusion criteria for the study selection. Twelve studies were excluded because of unspecified investigations and/or lack of precise population description [9–20]. Ninety-two were finally included in this study. For three of these only abstracts were available [21–23] (see appendix 1). Forty studies investigated more than a single aetiology [8, 24–62]. The studies were characterised by high heterogeneity of various factors: study population, patient age, type of examination, completeness of data, reporting of results (tables 1 and 2). For instance, although all studies included patients with congenital onset of hearing loss, the exact characterisation was not available in 46 (50.5%) [8, 21, 25, 27–30, 34, 35, 39–42, 44, 48–50, 53, 55–57, 59–61, 63–84]. Another complicating factor for analysis was the fact that the frequency of the various investigations was highly variable within each study population.

The following type of studies were identified in this review: retrospective case studies (47 studies), cross-sectional (13), cohort studies (11), case-control studies (11), prospective case studies (9) (see also tables 1 and 2). The following types of aetiological parameters were investigated, in order of the number of studies for which they were reported (table 3): genetic (47 studies), radiological (35), ophthalmological (35), serological (32), cardiac (25), renal (14), endocrine (12) and neurological (8).

Literature analysis: investigations

The range of the results obtained from the various investigations was very wide (tables 1 and 2). Equally, the type and number of investigations showed great variety and range of frequency across the selected studies (table 3).

History was typically investigated. In the majority of studies there was no clear indication of precisely how history was taken. Thirty percent of the studies gave a detailed description; risk factors, such as established by the Joint Committee on Infant Hearing, were referred to in the minority (tables 1 and 3) [85].

Chemistry and urinalysis were commonly ordered to detect renal involvement (tables 1 and 3) [26, 29, 31, 35–37, 39, 49, 50, 52, 53, 55–57].

Four studies additionally employed renal ultrasound [26, 29, 37, 57].

Cardiac evaluation (ECG) was performed in 25 studies, in 8 as a single examination (tables 1, 2 and 3) [9, 22, 24, 26, 29, 31, 32, 35–38, 49, 50, 52, 53, 55, 57, 58, 60, 86–92]. Echocardiography constituted an additional investigation in three studies [26, 87, 90].

Serological test results for toxoplasmosis, rubella, cytomegalovirus, herpes (commonly known as TORCH infections) and syphilis were found in 32 studies (tables 1, 2 and 3) [24, 25, 29, 31, 32, 34–37, 42–44, 46–48, 50, 51, 53–55, 57, 60–62, 64, 66, 75, 78, 80, 93–95]. Eight of these analysed infectious agents as single aetiological factors (table 2) [64, 66, 75, 78, 80, 93–95].

The benefit of and procedures used for a neurological examination were only rarely evaluated (tables 1, 2 and 3). Eight studies included developmental assessment and/or an electroencephalogram in their protocol [12, 26, 35–37, 55, 59, 61, 96].

Twenty-five studies included radiology as part of a comprehensive work-up (table 1) [8, 24–26, 29–33, 35–37, 43, 45, 47, 49, 50, 52–54, 57–61]. In an additional 10 studies radiology constituted the single investigative modality (table 2) [71, 76, 79, 97–103].

The majority of the studies (31) employed computed tomography (CT) with, where indicated, 1 to 2 mm slice thickness. Magnetic resonance imaging (MRI) was additionally performed in 16 studies [24, 26, 32, 33, 37, 45, 50, 53, 54, 58–60, 101–103] (table 3). Kimani et al. reported MRI results only [47].

Thirty-five studies reported the results of ophthalmic evaluation, 14 as a single analysis (tables 1 and 2) [12, 31, 32, 35–39, 41, 45, 49, 52, 53, 55–63, 65, 67, 69, 70, 74, 77, 82, 83, 104–108]. Six tests were performed at variable frequencies: visual acuity, refraction error measurement, funduscopy, retinoscopy, electroretinography and electro-oculography (table 3). However, the last two of these tests were listed in only six and two studies, respectively [57, 61, 62, 65, 77, 83, 105, 106].

Twelve studies included thyroid function tests; the perchlorate test was reported only once (tables 1 and 2) [29, 31, 32, 35–37, 39, 49, 50, 53, 55, 57].

A genetic investigation was reported in 47 studies, in the majority as part of a comprehensive work-up, and as a single aetiological test in 11 (tables 1 and 2) [9, 21, 23, 29, 31–38, 40–42, 44–49, 51–62, 68, 72, 73, 109–112] [8, 24, 26–28, 113, 114]. A wide range of tests performed reflected technological development and local availability: chromosome analysis, clinical genetic examination, mutation analysis (table 3). Molecular analysis has become increasingly widespread and applied.

Thirty studies included molecular screening of gap-junction protein $\beta 2$ (*GJB2*) and reported a positive finding in 1 to 59% (tables 1 and 2) [21, 23, 24, 29, 32–34, 37, 38, 40, 45–48, 51, 53–55, 59, 60, 68, 72, 73, 109–114]. Additional genes were analysed less frequently: *GJB6* (7 studies), *SLC26A4* (6), mitochondrial genes (4) and *GJB3* (1).

Literature analysis: aetiologies

Taking a thorough history yielded a positive result in 10 to 50% of cases (table 1) [14, 29, 31, 35, 36, 39, 49, 50, 52, 53, 55–57].

Abnormal results of renal investigations were found in up to 10% of patients tested (table 1). However, Alport’s syndrome or branchio-otolar syndrome were identified in two studies only, with an incidence of 2.5% at most [36, 49, 50].

Similarly, a high rate of abnormal results (prolonged QT interval) was reported in up to 16% of cardiac examinations, but the true incidence of the long QT syndrome was much lower at 0 to 4% (tables 1 and 2).

Serological testing constitutes an integral part of the work-up. Rubella shows a substantial decline as a prominent aetiological factor in countries with high immunisation rates (table 1). The virus remains in countries with poorly designed immunisation programmes or immigrants originating from these areas [8, 27, 28, 43]. In contrast, cytomegalovirus (CMV) has become more prevalent, with more recent studies consistently reporting rates of between 5 and 20% (tables 1 and 2) [32, 37, 44, 46, 47, 64, 66, 80, 94, 95]. In all these studies, analysis was performed on either dried-blood spots or umbilical cord, both of which are valid methods for detecting congenital infection. Two studies with much higher percentages stand out. One study from Iran found a 35% rate of acute immunity by determining IgM levels in blood samples [78]. The test method was not clearly identifiable in another study, from Poland, with a reported rate of 55% [51].

Exact figures for neurological findings, such as developmental delay and intellectual deficit or encephalographic abnormalities, have been found in only four studies, with a wide range and usually not clarifying the aetiology (tables 1 and 2) [26, 35, 59, 96]. The clinical approach to detecting developmental delay and intellectual deficit led to higher frequencies (33 to 70%) than electroencephalography (between 13 and 40%).

Abnormalities of the inner ear and the vestibulocochlear nerve were described in 10 to 88%. Enlarged vestibular aqueduct constituted the most frequently detected malformation [30, 50, 53, 71, 97, 98]. The remaining studies reported malformations of the cochlea, semicircular canal or vestibule as the most frequent or did not list the frequency of malformations. Two studies listed additional intracerebral findings detected on MRI [50, 59].

Ocular abnormalities were detected in up to 60%. The studies specifically examining the eyes showed a higher mean of 40% (tables 1 and 2). Visual impairment and refractive errors were the most frequent findings, with an incidence of 23 to 50%. Guy et al. reported the highest rate of

retinitis pigmentosa (5%) by recording the electroretinogram [105]. In contrast, a much lower rate (0 to 2%) was found in two other studies without electroretinogram recordings [74, 108].

Abnormal results of thyroid function tests were found in five reports, but only two of them confirmed cases of Pendred syndrome [35, 49].

A genetic cause was found in 1 to 70%. A syndromic form of congenital SNHL was detected with a mean of frequency of 12.5% (tables 1 and 2). Twenty-five studies included molecular screening of *GJB2* and reported a positive finding in 1 to 59% of those tested (mean 15%; tables 1 and 2) [21, 23, 29, 32–34, 37, 38, 40, 44–48, 51, 53–55, 59, 60, 68, 72, 73, 109–112, 115].

Additional tests (blood count, lipids, autoimmune antibodies) were used only sporadically and did not contribute to the aetiological clarification.

In spite of thorough analysis the aetiology remained unknown in about 30% of cases (table 1).

Reported practice of Swiss otolaryngological tertiary referral centres

There is high variation between the centres in the preferred examinations (table 4). Most are not performed on a routine basis. No centre undertakes a complete search. Radiological examination and genetic analysis were the preferred investigations and were ordered for 60 and 50% of patients, respectively. The frequency of the examinations ordered and the results were not available. Typical reasons for an incomplete analysis were organisational difficulties and parental restraints.

Cost analysis

The costs of all examinations are listed in table 5. The total was 1720 Swiss francs based on the Tarmed (current country-wide official tariff). The most expensive tests are genetics and radiology (analysis of *GJB2* and CT/MRI), which make up 60% of the total costs.

Table 1: List of studies (in chronological order) with >1 aetiology investigated.

First author (type of study ¹)	Year	Class of aetiological investigation (percentage with positive findings)											Number of patients ² (age ³)
		Endo- crine	Genetic	History	Cardiac	Renal	Neuro- logical	Ophthal- mic	Radio- logical	Serological	Other	UK	
Das (1)	1988	1	27.5 syn- dromic 3.7	20.7	n.a.	n.a.	33	n.a.	n.a.	9.8 (CMV 5.5 rubella 4.3)	3 (metabolic disorder)	35	164 (age: mean 21.5 m)
Lenzi (1)	1988	0.2	30	30	0.1	0.1	–	n.a.	n.a.	10 (rubella)	3	26.5	85 (age: n.a.)
Derey- maeker (2)	1991	–	39 syndromic 4	46	–	–	–	n.a.	–	16 (CMV 1, rubella 15)	–	15	155 (age: 83% <3 y)
Elango (3)	1992	–	14 syndromic 0.15	51	–	–	–	–	–	6.5 (rubella 6.4 syphilis 0.1)	–	28.5	155 (age: 1–12 y)
Elango (3)	1993	–	18 syndromic 0.1	26	–	–	–	35	–	36 (rubella)	–	20	167 (age: 7–15 y mean 9.9 y)
Vannia- segaram (3)	1993	n.a.	40	21	n.a.	n.a.	–	–	n.a.	8 (rubella 6, CMV 2)	–	30	98 (age: 2 w–12 y)
Das (1)	1996	n.a.	39 syndromic 5	20	n.a.	n.a.	n.a.	n.a.	n.a.	8 (rubella 5, CMV 3)	–	34	339 (age: mean 2 m)
Parving (1)	1997	–	48.5 syn- dromic 19.5	17	n.a.	n.a.	–	n.a.	n.a.	7.5	–	27	93 (age: n.a.)
Vartiainen (3)	1997	–	59.5 syn- dromic 20	20	n.a.	–	–	n.a.	n.a.	–	–	21.5	65 (age: mean 4.5 y)
Billings (3)	1999	–	n.a. syndrom- ic 12.5	32	–	–	–	–	8.5	–	–	27	241 (age: n.a.)
Dereköy (2)	2000	0	24	22	–	0	–	n.a.	–	–	27 (febrile convulsions)	26	130 (age: 5–16 y)
Zakzouk (3)	2001	–	47 syndromic 2.3	16	–	–	n.a.	n.a.	16.6	6 (toxoplasmosis 1.5 rubella 0.75, CMV 0.75 herpes 3)	9	21	302 (age: 3 m–12)

Table 1 (continued)													
Bojano (1)	2002	n.a.	62.5 syndromic 13	13.5	n.a.	n.a.	–	n.a.	n.a.	n.s.	4	20	178 (age: n.a.)
Mafong (3)	2002	0	n.a.	n.a.	1	0	–	–	n.a.	0 (only syphilis)	0	n.a.	95 (age: n.a.) (unknown aetiology only)
Fageeh (2)	2003	–	70	n.a.	–	–	–	–	5	8 (toxoplasmosis 3, rubella 5)	–	n.a.	100 (age: mean 2 y)
Deben* (3)	2003	–	39 syndromic 4.5	8.5	0.1	0	13	13	15	9 (rubella 1.5, CMV 7)	–	52	179 (age: 2–14 y, median 8.5 y)
Al Khabori (3)	2004	–	n.a.	13	–	–	–	–	–	1.5 (rubella)	–	53	1400 (age: n.a.)
Preciado* (3)	2004	0	18 (GJB2/SLC26A4)	–	0.1	0	–	14	25 (CT n.a., MRI n.a.)	0	0	n.a.	496 (age: n.a.) (unknown aetiology only)
Dent (2)	2004	–	32 syndromic 16 (GJB2, A1555G, A7445G)	n.a.	0	–	–	n.a.	–	–	4	64	24 (age: n.a.)
Silan (2)	2004	–	63 syndromic 18	19	–	n.a.	–	n.a.	–	–	–	18	443 (age: 1 m–4 y, median 2.4 y)
DeNo-brega (1)	2005	–	17	25	–	–	–	–	–	18 (rubella)	–	40	244 (0–2 y)
Riga (3)	2005	n.a.	47 syndromic 11 (GJB2(35delG only) 4.5)	35.5	n.a.	n.a.	n.a.	n.a.	–	2.5 (CMV 2, rubella 0.5)	n.a.	15	153 (1 m–13 y, average 3 y)
Yoong (3)	2005	–	70 (GJB2 0)	7	0	–	–	n.a.	0	n.a.	–	23	42 (age: n.a.)
Lasisi (3)	2006	–	54	42	–	–	–	–	n.a.	0	0	4	48 (mean 6 y)
Declau* (4)	2008	0	60 syndromic 2 (GJB2, GJB6 9.5)	21	0.9	0	NS	4.5	30 (CT 27, MRI 21)	8 (CMV)	–	45	68 (age: 1–3 m)
Dietz (3)	2009	–	46 syndromic 11 (GJB2 14)	14	–	–	–	–	–	–	–	40	92 (age: median 5 y)
Bajaj (2)	2009	n.a.	60 syndromic 15 (GJB2 17)	18	n.a.	n.a.	–	–	n.a.	0.8 (CMV)	n.a.	22	134 (age: 9 m–18 y, average 11.6 y)
Boude-Wyns (4)	2009	n.a.	41.5 syndromic 5 (GJB2 5)	15	n.a.	–	–	n.a.	n.a.	7 (CMV)	–	56	59 (age: n.a.)
Korver (1)	2010	–	39 syndromic 16 (GJB2/SLC26A4)	35	–	–	–	–	–	10 (CMV9, rubella)	–	26	171 (age: 3–5y)
Kimani (3)	2010	–	10 (GJB2 9, A1555G 1)	–	–	–	–	–	37 (MRI)	10 (CMV 9)	–	–	95 (age: 1–5y)
Johnston (3)	2010	–	42 syndromic 25 (GJB2 5)	n.a.	–	–	–	32	n.a.	–	–	n.a.	77 (age: mean 7 y)
Chan (3)	2010	–	20 (GJB2)	–	–	–	–	–	14 (CT)	–	–	–	271 (age: mean 5.8 y)
Siem (3)	2010	–	42 syndromic 15 (GJB2/GJB6 22, SLC26A4 4)	22	2.5	–	–	–	n.a. (CT/MRI)	2 (CMV 1.5, rubella 0.5)	–	29	197 (age: median 6 y)
Wiley* (3)	2011	–	30 syndromic 9 (GJB2 10)	21	–	–	70	55	34 (CT 3/ MRI 32)	–	19 (structural anomalies)	32	90 (age: 1 m–17 y)
Furutate (3)	2011	–	22 (GJB2 5, SLC26A4 7)	–	–	–	–	–	–	9 (CMV)	–	–	46 (age: 11–39 m)
Milewska (3)	2011	–	27 (GJB2)	–	–	–	–	–	–	55 (CMV)	–	–	157 (age: n.a.)
Karltorp (1)	2012	–	4 (GJB2)	–	–	–	–	–	–	17 (CMV)	–	–	87 (age: n.a.)
Elziere (3)	2012	–	45	40	–	–	–	n.a.	30 (CT)	5 (rubella)	–	15	20 (age: mean 7 y)
Dahl (1)	2013	–	24 (GJB2 13, SLC26A4 2)	17	–	–	–	–	–	8 (CMV)	–	64	364 (age: n.a.)
Ramos (1)	2013	–	42 (GJB2/ GJB6, A1555G)	29	–	–	–	–	10	n.a.	–	26	38 (age: 5–21 m)
Mean		0.2	37	25	0.3	0	39	29.8	20	6.8	Not calculated	31.4	Total number: 7362
Range		0–1	4–70	8.5–51	0–2.5	0–0.1	13–70	13–55	5–37	0.75–17		4–64	

CMV = cytomegalovirus; CT = computed tomography; GJB2 = gap-junction protein β2 (connexin 26); GJB3 = gap-junction protein β3 (connexin 31); GJB6 = gap-junction protein β6 (connexin 30); MRI = magnetic resonance imaging; n.a. = not available (cannot be indicated owing to lack of information, mixed population etc.); SLC26A4 = solute carrier family 26 member 4 (Pendrin); 12S rRNA/tRNAs^{er} = mitochondrial genes; UK = unknown

* More substantive studies with regard to established quality criteria

† Type of study: (1) = cohort study, (2) = cross-sectional study, (3) = retrospective case study, (4) = prospective case study

‡ Patients with bilateral hearing loss

§ Age at time of diagnosis or examination

Table 2. List of studies (in chronological order) with a single aetiology investigated.

Class of aetiological investigation	First author (type of study*)	Year	Investigation	Percentage of positive results	Number of patients (age)
Genetic 11 studies	Kenna (1)	2001	<i>GJB2</i>	18	n.a. (age: n.a.)
	Dahl (2)	2001	<i>GJB2</i>	21	243 (age: 1 m–16 y, median 4 y)
	Wang (3)	2002	<i>GJB2</i>	7	169 (age: 4–18 y)
	Lim (4)	2003	<i>GJB2</i>	17	160 (age: <19 y)
	Gurtler (3)	2003	<i>GJB2</i>	15	20 (age: < 2 y)
	Erbe (1)	2004	<i>GJB2, GJB6</i>	26	68 (age: 2 m–18 y)
	Evirgen (4)	2008	<i>GJB2, GJB6</i> (only 35delG, 167delT, del(GJB6-D13S1830))	8.5	47 (age: 8–18 y)
	Yuan (3)	2009	<i>GJB2, GJB3, GJB6, SLC26A4, 12S rRNA, and tRNAser</i>	n.a.	94 (age: n.a.)
	Hayashi (3)	2011	<i>GJB2</i>	30	126 (age: 0–3 y)
	Lalaïants (1)	2011	<i>GJB2</i>	59	66 (age: several months)
	Javidnia (4)	2014	<i>GJB2, GJB6</i>	<1%	122 (<18 y)
			Median (range): 20 (1–59)		
Cardiac 8 studies	Ocal (4)	1997	ECG (additionally in 2.5%: Holter-ECG, echocardiography)	0.5	350 (age: 6–18 y)
	Rokicki	2002	ECG	1.2	162 (age: 3–15 y, mean 10.5 y)
	El Habbal (3)	2002	ECG, echocardiography	0	52 (age: 0.2–17 y, median 8.4 y)
	Sopon-tammarak (5)	2003	ECG	0.7	276 (age: n.a.)
	Sathya-murthy (5)	2009	ECG	0	127 (age: 1.2–10 y)
	Chinagudi (5)	2010	ECG	4	50 (age: 6–18 y)
	Niaz (5)	2011	ECG	3	104 (age: n.a.)
	Kang (4)	2011	ECG	0.7	193 (age: n.a.)
			Median (range): 0.6 (0–4)		
Ophthalmic 14 studies	Woodruff (4)	1986	Visual acuity, refraction error, funduscopy, retinoscopy	55	460 (age: n.a.)
	Rogers (5)	1988	Visual acuity, refraction error, funduscopy, retinoscopy, electroretinogram	43	n.a. (age: n.a.)
	Leguire (5)	1992	Visual acuity, refraction error, electroretinogram, electro-oculogram, visual-evoked responses	24	505 (age: 6–22 y, mean 12 y)
	Elango (5)	1994	Visual acuity, refraction error, funduscopy, retinoscopy	58	165 (age: n.a.)
	Siatkowski (4)	1994	Visual acuity, refraction error, funduscopy, retinoscopy	61	54 (age: 2–14 y, mean 6 y)
	Armitage (3)	1995	Visual acuity, refraction error, funduscopy, retinoscopy	46	83 (age: 16 m–16 y, mean 9.5 y)
	Young (4)	1996	Visual acuity, refraction error, funduscopy, retinoscopy, electroretinogram	10	47 (age: 6 m–9 y, average 3 y)
	Brinks (1)	2001	Visual acuity, refraction error, funduscopy, retinoscopy, electroretinogram	48	4 (age: 10–21 y)
	Mafong (4)	2002	n.a.	31	95 (age: n.a.)
	Guy (4)	2003	Visual acuity, refraction error, funduscopy, retinoscopy, electroretinogram	44	110 (age: 8 m–16.9 y)
	Hanioglu (4)	2003	Visual acuity, refraction error, funduscopy, retinoscopy	40	104 (age: 7–20 y)
	Bakhshae (5)	2009	Visual acuity, refraction error, funduscopy, retinoscopy	32	50 (age: 3–7 y, mean 4.3 y)
	Sharma (4)	2009	n.a.	22	174 (age: n.a.)
	Falzon (4)	2010	Visual acuity, funduscopy, retinoscopy	42	141 (age: 16 m–9y, mean 28 m)
			Median (range): 40 (10–61)		
Infection/ serological 8 studies	Samileh (3)	2008	CMV	35	75 (age: n.a.)
	Noor-bakhsh (3)	2008	Toxoplasmosis	12	75 (age: n.a.)
	Choi (3)	2009	CMV	3	n.a. (age: infant)
	Tagawa (4)	2009	CMV	12	36 (age: n.a.)
	Avettand (1)	2012	CMV	8	100 (age: 2–37 m, mean 15 m)
	DeVries (1)	2012	CMV	14	76 (age: <6 y)
	Toumpas (4)	2014	CMV	5	118 (age: <18 y)
	Courtmans (4)	2015	CMV	11	75 (age: 1 m–15 y)
			Median (range): 12.5 (3–35)		

Table 2 (continued)

Radiological 10 studies	Shusterman (4)	1992	CT	13	32 (age: 1–21 y, average 6.7 y)
	Cross (4)	1999	CT	11	71 (age: 13–20 y)
	Antonelli (4)	1999	CT	31	n.a. (age: n.a.)
	Westerhof (4)	2001	CT, MRI	88	21 (age: 5 m–8 y, mean 3 y)
	Sennaroglu (4)	2002	CT, MRI	48	27 (age: 3–26 y, mean 11 y)
	McClay (4)	2002	CT	17	72 (age: n.a.)
	Purcell (4)	2003	CT	n.a.	15 (age: 2–11 y, mean 8 y)
	Huo (4)	2012	CT	69	65 (age: 1–14 y, average 3.8 y)
	Nakano (4)	2013	CT	19	114 (age: 0–20y, median 6 y)
	Agarwal (1)	2014	CT, MRI	14	280 (age: 1–14 y)
			Median (range): 34.5 (11–88)		
Neurological, 1 study	El-Badry	2014	Electroencephalogram	42	90 (age:1–13 y, mean 3.8 y)

CT = computed tomography; CMV = cytomegalovirus; ECG=electrocardiogram; *GJB2* = gap-junction protein $\beta 2$ (connexin 26); *GJB3* = gap-junction protein $\beta 3$ (connexin 31); *GJB6*: gap-junction protein $\beta 6$ (connexin 30); MRI = magnetic resonance imaging; n.a. = not available (cannot be indicated owing to lack of information); *SLC26A4* = solute carrier family 26 member 4 (Pendrin); *12S rRNA/tRNAser* = mitochondrial genes. – * Type of study: (1) = prospective case-study; (2) = cohort-study; (3) = retrospective case-study; (4) = case-control study; (5) cross-sectional study. – Total number of patients = 5763

Table 3: Number (percent) of studies including various aetiological investigations and type of examination.

Endocrine	Thyroid function test:12 (100) Perchlorate test:1 (8.5)	12
Genetic	Clinical: 10 (21) <i>GJB2</i> : 30 (64) <i>GJB6</i> : 7 (15) <i>SLC26A4</i> : 6 (13) Mito. Genes: 4 (8.5) n.a.: 4 (8.5)	47
History	Specified: 11 (30) n.a.: 26 (70)	37
Cardiac	Electrocardiography: 24 (96) Echocardiography: 5 (20) n.a.: 1(4)	25
Renal	Urin alysis: 13 (93) Creatinine: 3 (21) Ultrasound: 4 (28.5) n.a.: 1 (7)	14
Neurological	Electroencephalography: 2 (25) n.a.: 6 (75)	8
Ophthalmic	Fundoscopy: 17 (48.5) Retinoscopy: 16 (46) Visual acuity: 15 (43) Refraction error: 14 (40) ERG: 6 (17) EOG: 2 (6) n.a.: 15(43)	35
Radiological	CT: 31 (88.5) MRI: 16 (46) X-ray: 2 (7) n.a.: 1 (3)	35
Serological	CMV: 19 (59) TORCH: 8 (25) Syphilis: 7 (22) Rubella: 1 (3) n.a.: 3 (9)	32
Other	Complete blood count: 5 (71) Electrolytes: 2 (28) ESR: 3 (43) Lipids: 2 (28) Glucose: 3 (43) Antinuclear antibody: 1 (14) Rheumatoid factor: 1 (14)	7

CMV = cytomegalovirus; CT = computed tomography; EOG = electro-oculography; ERG= electroretinogram; ESR = erythrocyte sedimentation rate *GJB2* = gap-junction protein $\beta 2$ (connexin 26); *GJB6* = gap-junction protein $\beta 6$ (connexin 30); MR I= magnetic resonance imaging; n.a. = not available; TORCH = toxoplasmosis, rubella, cytomegalovirus, herpesvirus; *SLC26A4*: solute carrier family 26 member 4 (Pendrin)

Table 4: Number (%) of major Swiss tertiary referral centres ordering various investigations.

Type of investigation	Yes	No	Not routinely
History	8 (100%)	0	0
Radiological (CT/MRI)	5 (62.5%)	2 (25%)	1 (12.5%)
Urinalysis	2 (25%)	0	6 (75%)
ECG	1 (12.5%)	0	7 (87.5%)
Neurological	1 (12.5%)	0	7 (87.5%)
Serological	1 (12.5%)	0	7 (87.5%)
Ophthalmological	1 (12.5%)	0	5 (62.5%)
Genetic	4 (50%)	3 (37.5%)	1 (12.5%)
Endocrine	0	3 (37.5%)	5 (62.5%)

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

Table 5: Costs of investigations.

Price	Type of investigation								
	CT/ MRI	ECG	Urinalysis	Serological	Neurological	<i>GJB2</i> (connexin 26)	Endocrine	Ophthalmic	Total
CHF (EUR, US\$)	650 (585, 650)	30 (27, 30)	15 (13.5, 15.)	150 (135, 150)	240 (216, 240)	500 (450, 500)	25 (22.5, 25)	110 (100, 110)	1720 (1549, 1720)

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging
 All prices are for 2016 and in Swiss francs according to the official Swiss medical tariff (www.fmh.ch/TARMED Version 1.08.00)
 Exchange rates: 1.1 EUR/CHF; 1 US\$/

Discussion

With the successful launch of the newborn hearing screening in most of the so-called industrialised countries, children with congenital hearing loss are identified early and auditory rehabilitation including cochlea implants is well established. However, aetiological focus is often lacking [3]. There is no consensus on an evidence-based approach to an effective aetiological work-up. There is a lack of agreement not only on what to screen, but also on how to screen. This qualitative review aimed to clarify the current status of aetiologies and investigations for children with bilateral congenital SNHL in order to support evidence-based management and identify areas for future action.

General descriptive analysis

Various factors leading to very high heterogeneity in the published studies prompted the authors to follow a narrative approach in the discussion section. Deficiencies in methodological quality are a commonly observed fact. For instance, a standardised questionnaire for history taking was only used in 10 out of 18 studies (55%). Populations with different types of hearing loss were often mixed and were not analysed separately, leading to confounding percentages [31, 57, 61]. Incomplete testing of the populations contributing to variable percentages represented another frequent problem.

Descriptive analysis of investigations/aetiologies

The proper identification of the aetiology remains a challenge, as the exact contribution of a positive finding might be difficult to evaluate. Roizen et al. had already pointed out uncertainties in diagnosis in 2003 after analysing nongenetic factors [116]. Hyperbilirubinaemia and therapy with aminoglycosides represent such examples. For both factors, neither the level nor duration of exposure causing hearing impairment has been defined. Therefore, even if the history is positive and is based on available recommendations such as those provided by the Joint Committee on Infant Hearing, additional aetiological factors have to be considered [85]. In this context, the question of positivity criteria should be further discussed, although a thorough discussion is beyond the scope of this review. Ten case-control studies identified in this review [63, 75, 76, 78, 87, 93, 96, 111, 112, 114], mostly concerning genetics and infections, reported a higher prevalence of an aetiological factor in the hearing-impaired population compared with the controls. Additionally, possible “dual” aetiologies, especially for *GJB2* mutations and CMV, have been reported [46, 93]. Unless clear diagnostic criteria are established, uncertainties remain regarding interpretation of results and will lead to a diagnostic challenge.

Various investigations were ordered with the aim of detecting syndromic hearing loss, which was reported in the studies with a range of 0.1 to 25%. Exact identification is important, as it may allow associated complications to be anticipated and appropriately managed. Only 15% of the studies (2 out of 13, table 1) reported positive findings for urinalysis [36, 49]. In both cases either additional features or follow-up led to the final

diagnosis of Alport syndrome or branchio-oto-renal-syndrome. The same is valid for thyroid function tests, with an extremely low yield approaching 0% (Table 1). A third investigation, imaging, was regularly ordered for the same purpose. In fact, enlarged vestibular aqueduct was the most frequent finding and may direct subsequent genetic analysis to confirm Pendred or enlarged vestibular aqueduct (EVA) syndromes. Imaging has additional advantages. Counselling can be improved, as malformations such as enlarged vestibular aqueducts are known to predispose individuals to sudden hearing loss after head trauma and are associated with a higher risk of meningitis [117]. A third benefit can be derived. Audio-rehabilitation, such as cochlear implantation, is better managed if inner ear anomalies such as absence or presence of the cochleovestibular nerve or cochlear malformations are known. The choice of CT or MRI currently depends mainly on the surgeon's or institution's practice. In a comparative study, both modalities showed the same detection rate of anomalies of the inner ear, and MRI was superior in evaluating the vestibulocochlear nerve [102]. Additional factors influencing the decision process were radiation exposure in the case of CT and the need for anaesthesia in the case of MRI. However, current protocols and technology allow the radiation dose of a temporal bone CT to be reduced to less than 1 mSv and acquisition time for an MRI has become shorter, eventually eliminating the need for sedation.

Another two types of investigation, ophthalmological and neurological, had a dual role in the evaluation process. The high prevalence of accompanying ophthalmic and neurological disorders stands in contrast to their power for identification of syndromes. The application of electrography clearly raises sensitivity and specificity to detect retinitis pigmentosa and, as a result, Usher syndrome (the most frequent oculoauditory syndrome) [105]. However, because the onset of retinitis pigmentosa is mostly during the first decade of life or even later (depending on the subtype), early investigation will underestimate the true incidence of Usher syndrome in children with congenital SNHL [118]. On the other hand, knowledge of the ocular status is important, as visual impairment can hinder sign language and pose a severe handicap to developing communication skills. The same is true for neurological deficits such as developmental delay, which might require additional educational care. The prevalence seems to be high, although exact percentages were reported in only four studies [12, 35, 36, 59].

A routine complete serological analysis can be regarded as not indicated, with the exception of CMV serology. In studies and reviews, such as those by Avettand et al. and Morton et al., CMV has been confirmed as the most prevalent environmental cause for congenital SNHL in recent years, with an incidence of up to 10% [3, 64]. However, this is only valid for countries with established immunisation programmes against rubella. There are some difficulties associated with the diagnosis of CMV infection, which explains at least partially the hitherto unknown exact incidence and its variation. Diagnosis can only be ascertained in the first three weeks of life by detection of the virus in biological fluids such as urine or saliva. As confirmation of possible failure of newborn hearing screening occurs later, one has to analyse dried blood spots (DBSs). Whereas specificity for DBS testing is high, a wide range of sensitivity

has been reported. However, a recent study showed high sensitivity can be achieved by use of an appropriate extraction method [119]. The role of genetics in congenital SNHL has seen the most dramatic evolution during the last 15 years and contributes to the aetiological identification in various ways. Genetic abnormalities are the leading causative factors for SNHL, as seen in table 1 and 3 and confirmed through numerous studies [1, 3]. Although the frequency of genetic abnormalities was similar to other investigations, the range around the median was high. Possible explanations are quite obvious. A restricted number of genes were analysed, mainly *GJB2*, *SLC26A4* and mitochondrial genes. The first two genes show a highly ethnicity-specific mutation spectrum [120]. In Western Europe, the United States and some Asian countries, analysis of *Cx26* and *SLC26A4* is the most predictive diagnostic test [114, 121–124]. Consanguinity is an important issue in some countries, for instance 54% in Saudi Arabia, and renders genetic analysis and counselling much less precise and more difficult [61]. Just about two thirds of the genes involved in the inner ear (out of an estimated number of about 150) have been identified. For many of the 400 syndromic forms of hearing loss, genes have yet to be discovered (<http://hereditaryhearingloss.org>). This incomplete knowledge and the existing heterogeneity have prevented rapid and cheap analysis up to now. New genetic methods, like the microarray technique, show promising results in reducing costs and increasing the number of genes that can be simultaneously screened [125]. Genetic testing can help clarify or confirm a syndromic aetiology. Diagnosis of Jervell-Lange-Nielsen syndrome is facilitated by a diagnostic score, the so-called Schwartz criteria, but definite confirmation is only obtained by genetic analysis. Thus, unnecessary medication can be avoided and sudden death in other family members prevented [126]. As a prolonged QT interval seems to be more prevalent in people with congenital SNHL, an ECG and subsequent molecular analysis should be recommended [81, 88–90, 92]. Additionally, syndromic identification may allow associated complications to be anticipated and direct appropriate management. Counselling can also be improved in nonsyndromic hearing loss. The confirmation of a mutation in *GJB2* improves prediction of the outcome of hearing rehabilitation [5].

Although guidelines have been formulated by various professional bodies, they differ in their recommendations [6–8]. The most recent, by the British Association of Audiovestibular Physicians, presented a detailed search methodology and grading system and largely overlaps with the findings of this review. The limitation of this guideline is the period covered (just 6 years).

Limitations of the review

This study has some limitations. First, a systematic literature review is limited by the effectiveness of its predefined search strategy (search terms, databases used, inclusion/exclusion criteria, etc.) to identify all the relevant articles on the topic of interest. However, the review of reference lists substantially counteracted this limitation. Nonetheless, relevant studies not listed in PubMed or reference lists of included papers might have been overlooked. Second, the data are difficult to compare across studies as a result of the diversity in study methodology, including classification of patients and type of examinations. The total number of studies and the high heterogeneity prevented the creation of subgroups for possible pooled analysis. Although criteria were established to assess the studies, they are subjective and not validated. Third, any conclusion of this study is limited by the retrospective analysis.

Analysis of the current Swiss approach and costs

The results of the questionnaire sent to the tertiary centres of Switzerland reflected the results of the literature review. Examinations were requested and performed with incomplete penetrance. This is especially true for genetic analysis, which is expensive. An audit in the UK found that guidelines for an aetiological investigation were only partially followed [60]. As in Switzerland, lack of funding and parental choice were key reasons why the guidelines were not followed. After the successful

implementation of newborn hearing screening and early identification of congenital SNHL, the establishment of a screening programme with aetiological focus constitutes an urgent next step in improving the management of congenital SNHL.

The costs for full testing amounted to CHF 1720 (Table 5). Preciado et al. calculated a cost of 1932 US dollars for a full laboratory workup, temporal bone scan and *GJB2* screen [53]. The authors proposed a step-wise approach in order to reduce costs. In view of diagnostic uncertainties and evidence for frequent comorbidities such as ophthalmic and neurological findings, we advocate a complete work-up.

Future directions and recommendations

An international consensus to establish guidelines for aetiological interventions and a defined reporting system would increase our knowledge of congenital SNHL and improve future management of these patients. Recommendations should include directives for organisational management to reduce familial stress associated with exhaustive testing and increase participation. Financial and local constraints might hinder effective implementation of such programmes in countries with limited resources.

Based on this analytic review, we propose a uniform approach to the child with congenital SNHL in Switzerland, preferably based on international consensus, and recommend following examinations: imaging, genetic testing, neuropaediatric and ophthalmological evaluations, ECG and CMV analysis. Recommendation of these investigations aims to improve counselling and management of these patients and future healthcare delivery.

Conclusion

With the introduction of newborn hearing screening, aetiological investigation and evaluation of a child with bilateral congenital SNHL has been shifted to the first year of life. The evidence in the literature regarding an appropriate evaluation is mostly of low quality and difficult to assess owing to high heterogeneity. Nevertheless imaging, genetic testing, neuropaediatric and ophthalmological evaluations, ECG and CMV analysis have been identified as examinations to be included in the assessment. There is a need for prospective studies addressing the various issues of such an evaluation.

Correspondence:

Nicolas. Gürtler, MD
HNO-Universitätsklinik
Universitätsspital Basel
Petersgraben 4
CH-4031 Basel
[nicolas.guertler\[at\]usb.ch](mailto:nicolas.guertler[at]usb.ch)

Acknowledgements

We would like to thank M. Briel, privatdozent at the department of clinical research of the University of Basel, for methodological advice, and R. Probst, professor and former head of the department of ORL of the University Hospital Zurich, for valuable comments.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

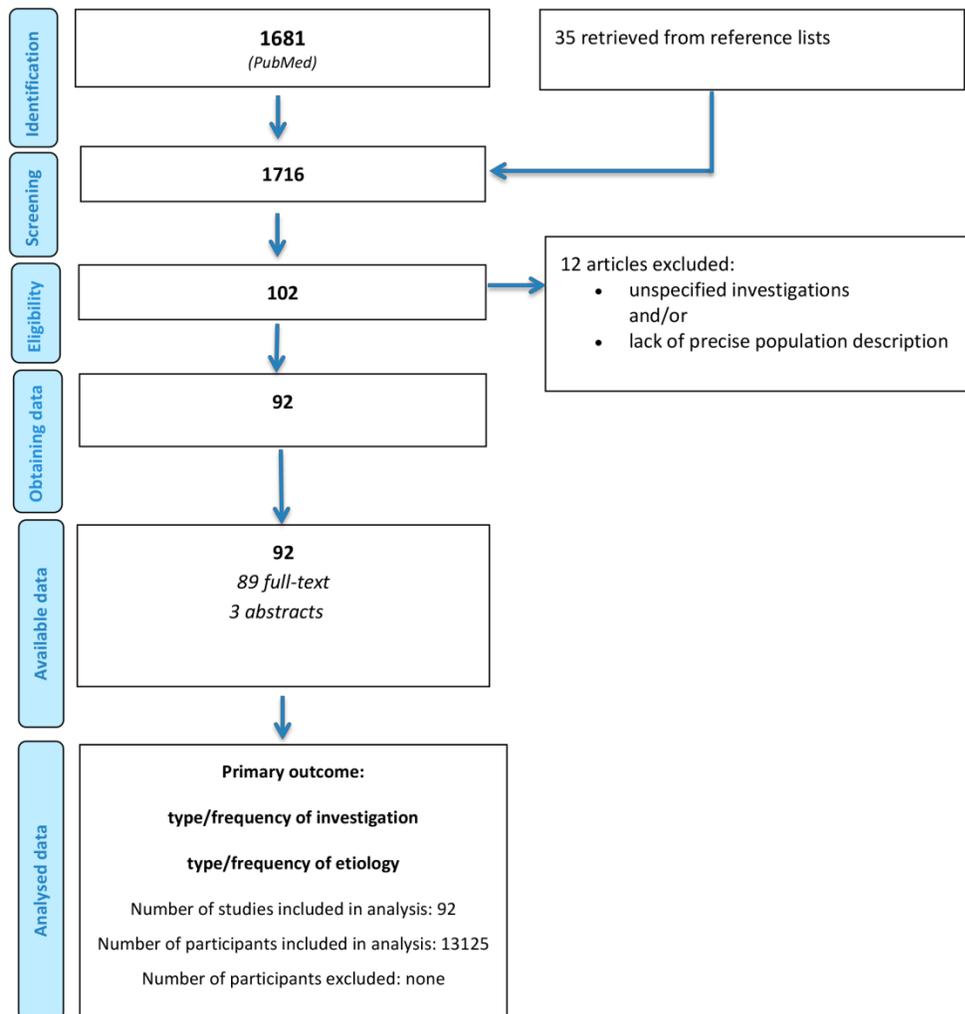
- Marazita ML, Ploughman LM, Rawlings B, Remington E, Arnos KS, Nance WE. Genetic epidemiological studies of early-onset deafness in the U.S. school-age population. *Am J Med Genet.* 1993;46(5):486–91. doi:<http://dx.doi.org/10.1002/ajmg.1320460504>. PubMed
- Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. *Pediatrics.* 1998;102(5):1161–71. doi:<http://dx.doi.org/10.1542/peds.102.5.1161>. PubMed
- Morton CC, Nance WE. Newborn hearing screening—a silent revolution. *N Engl J Med.* 2006;354(20):2151–64. doi:<http://dx.doi.org/10.1056/NEJMra050700>. PubMed

- 4 Zehnder A, Probst R, Vischer M, Linder T. Erste Resultate des allgemeinen Neugeborenen-Hörscreenings in der Schweiz. [First results of a national hearing screening program in Switzerland]. *Schweiz Med Wochenschr.* 2000;Suppl 125:71S–4S. Article in German. [PubMed](#)
- 5 Reinert J, Honegger F, Gürtler N. High homogeneity in auditory outcome of pediatric CI-patients with mutations in Gap-Junction-Protein Beta2. *Int J Pediatr Otorhinolaryngol.* 2010;74(7):791–5. doi:<http://dx.doi.org/10.1016/j.ijporl.2010.04.002>. [PubMed](#)
- 6 British Association of Audiovestibular Physicians. Guidelines for aetiological investigation into severe to profound bilateral permanent childhood hearing impairment. April 2015. Available from: http://www.baap.org.uk/Portals/0/Guidelines_for_aetiological_investigation_into_unilateral_permanent_childhood_hearing_impairment.
- 7 Paludetti G, Conti G, Di Nardo W, DE Corso E, Rolesi R, Picciotti PM, et al. Infant hearing loss: from diagnosis to therapy Official Report of XXI Conference of Italian Society of Pediatric Otorhinolaryngology. *Acta Otorhinolaryngol Ital.* 2012;32(6):347–70. [PubMed](#)
- 8 Elziere M, Roman S, Nicollas R, Triglia JM. Value of systematic aetiological investigation in children with sensorineural hearing loss. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2012;129(4):185–9. doi:<http://dx.doi.org/10.1016/j.anorl.2011.05.009>. [PubMed](#)
- 9 Dias O, Andrea M. Childhood deafness in Portugal—aetiological factors and diagnosis of hearing loss. *Int J Pediatr Otorhinolaryngol.* 1990;18(3):247–55. doi:[http://dx.doi.org/10.1016/0165-5876\(90\)90148-K](http://dx.doi.org/10.1016/0165-5876(90)90148-K). [PubMed](#)
- 10 Eckel HE, Richling F, Streppel M, Roth B, Walger M, Zorowka P. Ätiologie mittel- und hochgradiger Schwerhörigkeiten im Kindesalter. [Etiology of moderate and profound deafness in childhood]. *HNO.* 1998;46(3):252–63. Article in German. doi:<http://dx.doi.org/10.1007/s001060050234>. [PubMed](#)
- 11 Egeli E, Çiçekçi G, Silan F, Öztürk O, Harputluoğlu U, Onur A, et al. Etiology of deafness at the Yeditepe School for the deaf in Istanbul. *Int J Pediatr Otorhinolaryngol.* 2003;67(5):467–71. doi:[http://dx.doi.org/10.1016/S0165-5876\(03\)00002-8](http://dx.doi.org/10.1016/S0165-5876(03)00002-8). [PubMed](#)
- 12 Hirsch A. Hearing loss and associated handicaps in preschool children. *Scand Audiol Suppl.* 1988;30:61–4. [PubMed](#)
- 13 Minja BM. Aetiology of deafness among children at the Buguruni School for the Deaf in Dar es Salaam, Tanzania. *Int J Pediatr Otorhinolaryngol.* 1998;42(3):225–31. doi:[http://dx.doi.org/10.1016/S0165-5876\(97\)00137-7](http://dx.doi.org/10.1016/S0165-5876(97)00137-7). [PubMed](#)
- 14 Ohlms LA, Chen AY, Stewart MG, Franklin DJ. Establishing the etiology of childhood hearing loss. *Otolaryngol Head Neck Surg.* 1999;120(2):159–63. doi:[http://dx.doi.org/10.1016/S0194-5998\(99\)70400-6](http://dx.doi.org/10.1016/S0194-5998(99)70400-6). [PubMed](#)
- 15 Öztürk O, Silan F, Oghan F, Egeli E, Belli S, Tokmak A, et al. Evaluation of deaf children in a large series in Turkey. *Int J Pediatr Otorhinolaryngol.* 2005;69(3):367–73. doi:<http://dx.doi.org/10.1016/j.ijporl.2004.11.001>. [PubMed](#)
- 16 Park AH, Duval M, McVicar S, Bale JF, Hohler N, Carey JC. A diagnostic paradigm including cytomegalovirus testing for idiopathic pediatric sensorineural hearing loss. *Laryngoscope.* 2014;124(11):2624–9. doi:<http://dx.doi.org/10.1002/lary.24752>. [PubMed](#)
- 17 Walch C, Anderhuber W, Köle W, Berghold A. Bilateral sensorineural hearing disorders in children: etiology of deafness and evaluation of hearing tests. *Int J Pediatr Otorhinolaryngol.* 2000;53(1):31–8. doi:[http://dx.doi.org/10.1016/S0165-5876\(00\)00307-4](http://dx.doi.org/10.1016/S0165-5876(00)00307-4). [PubMed](#)
- 18 Fu S, Chen G, Dong J, Zhang L. Prevalence and etiology of hearing loss in primary and middle school students in the Hubei Province of China. *Audiol Neurootol.* 2010;15(6):394–8. doi:<http://dx.doi.org/10.1159/000307346>. [PubMed](#)
- 19 Gray RF. Causes of deafness in schools for the deaf in Madras. *Int J Pediatr Otorhinolaryngol.* 1989;18(2):97–106. doi:[http://dx.doi.org/10.1016/0165-5876\(89\)90062-1](http://dx.doi.org/10.1016/0165-5876(89)90062-1). [PubMed](#)
- 20 Wonkam A, Noubiap JJ, Djomou F, Fieggen K, Njock R, Toure GB. Aetiology of childhood hearing loss in Cameroon (sub-Saharan Africa). *Eur J Med Genet.* 2013;56(1):20–5. doi:<http://dx.doi.org/10.1016/j.ejmg.2012.09.010>. [PubMed](#)
- 21 Dahl HH, Saunders K, Kelly TM, Osborn AH, Wilcox S, Cone-Wesson B, et al. Prevalence and nature of connexin 26 mutations in children with non-syndromic deafness. *Med J Aust.* 2001;175(4):191–4. [PubMed](#)
- 22 Rokicki W, Markiewicz-Loskot G, Michalewska A, Włodarczyk W, Mizia M. Preliminary cardiological examinations in deaf children. *Przegl Lek.* 2002;59(9):737–9. [PubMed](#)
- 23 Lalaiants MR, Bliznits EA, Markova TG, Poliakov AV, Tavartkiladze GA. [The results of audiological examination of children presenting with sensorineural loss of hearing due to GJB2 gene mutations during the first year of life]. *Vestn Otorinolaringol.* 2011;(3):31–5. Article in Russian. [PubMed](#)
- 24 Siem G, Fagerheim T, Jonsrud C, Laurent C, Teig E, Harris S, et al. Causes of hearing impairment in the Norwegian paediatric cochlear implant program. *Int J Audiol.* 2010;49(8):596–605. doi:<http://dx.doi.org/10.3109/14992021003743269>. [PubMed](#)
- 25 Lasisi OA, Ayodele JK, Ijoduola GT. Challenges in management of childhood sensorineural hearing loss in sub-Saharan Africa, Nigeria. *Int J Pediatr Otorhinolaryngol.* 2006;70(4):625–9. doi:<http://dx.doi.org/10.1016/j.ijporl.2005.08.009>. [PubMed](#)
- 26 Deben K, Janssens de Varebeke S, Cox T, Van de Heyning P. Epidemiology of hearing impairment at three Flemish Institutes for Deaf and Speech Defective Children. *Int J Pediatr Otorhinolaryngol.* 2003;67(9):969–75. doi:[http://dx.doi.org/10.1016/S0165-5876\(03\)00186-1](http://dx.doi.org/10.1016/S0165-5876(03)00186-1). [PubMed](#)
- 27 Al Khabori M. Causes of severe to profound deafness in Omani paediatric population. *Int J Pediatr Otorhinolaryngol.* 2004;68(10):1307–13. doi:<http://dx.doi.org/10.1016/j.ijporl.2004.05.002>. [PubMed](#)
- 28 de Nobrega M, Weckx LL, Juliano Y. Study of the hearing loss in children and adolescents, comparing the periods of 1990-1994 and 1994-2000. *Int J Pediatr Otorhinolaryngol.* 2005;69(6):829–38. doi:<http://dx.doi.org/10.1016/j.ijporl.2005.01.019>. [PubMed](#)
- 29 Bajaj Y, Sirimanna T, Albert DM, Qadir P, Jenkins L, Cortina-Borja M, et al. Causes of deafness in British Bangladeshi children: a prevalence twice that of the UK population cannot be accounted for by consanguinity alone. *Clin Otolaryngol.* 2009;34(2):113–9. doi:<http://dx.doi.org/10.1111/j.1749-4486.2009.01888.x>. [PubMed](#)
- 30 Billings KR, Kenna MA. Causes of pediatric sensorineural hearing loss: yesterday and today. *Arch Otolaryngol Head Neck Surg.* 1999;125(5):517–21. doi:<http://dx.doi.org/10.1001/archotol.125.5.517>. [PubMed](#)
- 31 Bojano AM. Epidemiology of Childhood Hearing Impairment in a Province of Southern Italy. *Int Pediatr.* 2002;17(2):115–9.
- 32 Boudewyns A, Declau F, Smets K, Ursi D, Eyskens F, Van den Ende J, et al. Cytomegalovirus DNA detection in Guthrie cards: role in the diagnostic work-up of childhood hearing loss. *Otol Neurotol.* 2009;30(7):943–9. doi:<http://dx.doi.org/10.1097/MAO.0b013e3181b76b22>. [PubMed](#)
- 33 Chan DK, Schrijver I, Chang KW. Diagnostic yield in the workup of congenital sensorineural hearing loss is dependent on patient ethnicity. *Otol Neurotol.* 2011;32(1):81–7. doi:<http://dx.doi.org/10.1097/MAO.0b013e3181fc786f>. [PubMed](#)
- 34 Dahl HH, Ching TY, Hutchison W, Hou S, Seeto M, Sjahalam-King J. Etiology and audiological outcomes at 3 years for 364 children in Australia. *PLoS One.* 2013;8(3):e59624. doi:<http://dx.doi.org/10.1371/journal.pone.0059624>. [PubMed](#)
- 35 Das VK. Aetiology of bilateral sensorineural deafness in children. *J Laryngol Otol.* 1988;102(11):975–80. doi:<http://dx.doi.org/10.1017/S0022215100107054>. [PubMed](#)
- 36 Das VK. Aetiology of bilateral sensorineural hearing impairment in children: a 10 year study. *Arch Dis Child.* 1996;74(1):8–12. doi:<http://dx.doi.org/10.1136/adc.74.1.8>. [PubMed](#)
- 37 Declau F, Boudewyns A, Van den Ende J, Peeters A, van den Heyning P. Etiologic and audiologic evaluations after universal neonatal hearing screening: analysis of 170 referred neonates. *Pediatrics.* 2008;121(6):1119–26. doi:<http://dx.doi.org/10.1542/peds.2007.1479>. [PubMed](#)
- 38 Dent KM, Kenneson A, Palumbos JC, Maxwell S, Eichwald J, White K, et al. Methodology of a multistate study of congenital hearing loss: preliminary data from Utah newborn screening. *Am J Med Genet C Semin Med Genet.* 2004;125C(1):28–34. doi:<http://dx.doi.org/10.1002/ajmg.c.30002>. [PubMed](#)
- 39 Dereköy FS. Etiology of deafness in Afyon school for the deaf in Turkey. *Int J Pediatr Otorhinolaryngol.* 2000;55(2):125–31. doi:[http://dx.doi.org/10.1016/S0165-5876\(00\)00390-6](http://dx.doi.org/10.1016/S0165-5876(00)00390-6). [PubMed](#)
- 40 Dietz A, Löppönen T, Valtonen H, Hyvärinen A, Löppönen H. Prevalence and etiology of congenital or early acquired hearing impairment in Eastern Finland. *Int J Pediatr Otorhinolaryngol.* 2009;73(10):1353–7. doi:<http://dx.doi.org/10.1016/j.ijporl.2009.06.009>. [PubMed](#)
- 41 Elango S. Aetiology of deafness in children from a school for the deaf in Malaysia. *Int J Pediatr Otorhinolaryngol.* 1993;27(1):21–7. doi:[http://dx.doi.org/10.1016/0165-5876\(93\)90033-Y](http://dx.doi.org/10.1016/0165-5876(93)90033-Y). [PubMed](#)
- 42 Elango S, Chand RP, Purohit GN. Childhood deafness in Malaysia. *Int J Pediatr Otorhinolaryngol.* 1992;24(1):11–7. doi:[http://dx.doi.org/10.1016/0165-5876\(92\)90061-S](http://dx.doi.org/10.1016/0165-5876(92)90061-S). [PubMed](#)
- 43 Fageeh NA. Prospective study of hearing loss in schools for deaf children in Assir region, Saudi Arabia. *West Afr J Med.* 2003;22(4):321–3. [PubMed](#)
- 44 Furutate S, Iwasaki S, Nishio SY, Moteki H, Usami S. Clinical profile of hearing loss in children with congenital cytomegalovirus (CMV) infection: CMV DNA diagnosis using preserved umbilical cord. *Acta Otolaryngol.* 2011;131(9):976–82. doi:<http://dx.doi.org/10.3109/00016489.2011.583268>. [PubMed](#)
- 45 Johnston DR, Curry JM, Newborough B, Morlet T, Bartoszesky L, Lehman S, et al. Ophthalmologic disorders in children with syndromic and nonsyndromic hearing loss. *Arch Otolaryngol Head Neck Surg.* 2010;136(3):277–80. doi:<http://dx.doi.org/10.1001/archoto.2010.13>. [PubMed](#)
- 46 Karltopf E, Hellström S, Lewensohn-Fuchs I, Carlsson-Hansén E, Carlsson PI, Engman ML. Congenital cytomegalovirus infection - a common cause of hearing loss of unknown aetiology. *Acta Paediatr.* 2012;101(8):e357–62. doi:<http://dx.doi.org/10.1111/j.1651-2227.2012.02711.x>. [PubMed](#)

- 47 Kimani JW, Buchman CA, Booker JK, Huang BY, Castillo M, Powell CM, et al. Sensorineural hearing loss in a pediatric population: association of congenital cytomegalovirus infection with intracranial abnormalities. *Arch Otolaryngol Head Neck Surg.* 2010;136(10):999–1004. doi:<http://dx.doi.org/10.1001/archoto.2010.156>. PubMed
- 48 Korver AM, Admiraal RJ, Kant SG, Dekker FW, Wever CC, Kunst HP, et al.; DECIBEL-collaborative study group. Causes of permanent childhood hearing impairment. *Laryngoscope.* 2011;121(2):409–16. doi:<http://dx.doi.org/10.1002/lary.21377>. PubMed
- 49 Lenzi A, Zaghis A. Incidence of genetic factors in the causation of deafness in childhood. *Scand Audiol Suppl.* 1988;30:37–41. PubMed
- 50 Mafong DD, Shin EJ, Lalwani AK. Use of laboratory evaluation and radiologic imaging in the diagnostic evaluation of children with sensorineural hearing loss. *Laryngoscope.* 2002;112(1):1–7. doi:<http://dx.doi.org/10.1097/00005537-200201000-00001>. PubMed
- 51 Milewska-Bobula B, Lipka B, Radziszewska-Konopka M, Sielska-Badurek E, Niepokój K, Wertheim-Teysarowska K, et al. Analiza przyczyn niedosluchu oraz zastosowanego leczenia u dzieci w materiale Kliniki Niemowlecej Instytutu "Pomnik - Centrum Zdrowia Dziecka" w Warszawie. [Analysis of causes and treatment of hearing loss in children from Department of Infant Diseases the Children's Memorial Health Institute, Warsaw]. *Przegl Lek.* 2011;68(1):54–8. Article in Polish. PubMed
- 52 Parving A, Stephens D. Profound permanent hearing impairment in childhood: causative factors in two European countries. *Acta Otolaryngol.* 1997;117(2):158–60. doi:<http://dx.doi.org/10.3109/00016489709117759>. PubMed
- 53 Preciado DA, Lim LH, Cohen AP, Madden C, Myer D, Ngo C, et al. A diagnostic paradigm for childhood idiopathic sensorineural hearing loss. *Otolaryngol Head Neck Surg.* 2004;131(6):804–9. doi:<http://dx.doi.org/10.1016/j.otohns.2004.06.707>. PubMed
- 54 Ramos PZ, de Moraes VC, Svidnicki MC, Soki MN, Castilho AM, Sartorato EL. Etiologic and diagnostic evaluation: algorithm for severe to profound sensorineural hearing loss in Brazil. *Int J Audiol.* 2013;52(11):746–52. doi:<http://dx.doi.org/10.3109/14992027.2013.817689>. PubMed
- 55 Riga M, Psarommatas I, Lyra Ch, Douniadakis D, Tsakanikos M, Neou P, et al. Etiological diagnosis of bilateral, sensorineural hearing impairment in a pediatric Greek population. *Int J Pediatr Otorhinolaryngol.* 2005;69(4):449–55. doi:<http://dx.doi.org/10.1016/j.ijporl.2004.11.007>. PubMed
- 56 Silan F, Demirci L, Egeli A, Egeli E, Onder HI, Ozturk O, et al. Syndromic etiology in children at schools for the deaf in Turkey. *Int J Pediatr Otorhinolaryngol.* 2004;68(11):1399–406. doi:<http://dx.doi.org/10.1016/j.ijporl.2004.05.007>. PubMed
- 57 Vanniasegaram IT, Bellman S. A 5-year review of children with deafness in a multiethnic community. *Journal of Audiological Medicine.* 1993;2:9–19.
- 58 Vartiainen E, Kempainen P, Karjalainen S. Prevalence and etiology of bilateral sensorineural hearing impairment in a Finnish childhood population. *Int J Pediatr Otorhinolaryngol.* 1997;41(2):175–85. doi:[http://dx.doi.org/10.1016/S0165-5876\(97\)00080-3](http://dx.doi.org/10.1016/S0165-5876(97)00080-3). PubMed
- 59 Wiley S, Arjmand E, Jareenmeizen-Derr, Dixon M. Findings from multidisciplinary evaluation of children with permanent hearing loss. *Int J Pediatr Otorhinolaryngol.* 2011;75(8):1040–4. doi:<http://dx.doi.org/10.1016/j.ijporl.2011.05.019>. PubMed
- 60 Yoong S, Spencer N. Audit of local performance compared with standards recommended by the national guidelines for aetiological investigation of permanent childhood hearing impairment. *Child Care Health Dev.* 2005;31(6):649–57. doi:<http://dx.doi.org/10.1111/j.1365-2214.2005.00558.x>. PubMed
- 61 Zakzouk SM, Al-Anazy F. Sensorineural hearing impaired children with unknown causes: a comprehensive etiological study. *Int J Pediatr Otorhinolaryngol.* 2002;64(1):17–21. doi:[http://dx.doi.org/10.1016/S0165-5876\(02\)00029-0](http://dx.doi.org/10.1016/S0165-5876(02)00029-0). PubMed
- 62 Dereymaeker AM, Fryns JP, Ars B, Andresescou J, Van den Berghe H. On the etiology of hearing loss in a population of 155 institutionalized children. *Acta Otorhinolaryngol Belg.* 1991;45(3):283–91. PubMed
- 63 Armitage IM, Burke JP, Buffin JT. Visual impairment in severe and profound sensorineural deafness. *Arch Dis Child.* 1995;73(1):53–6. doi:<http://dx.doi.org/10.1136/adc.73.1.53>. PubMed
- 64 Avetand-Fenoël V, Marlin S, Vauloup-Fellous C, Loundon N, François M, Couloigner V, et al. Congenital cytomegalovirus is the second most frequent cause of bilateral hearing loss in young French children. *J Pediatr.* 2013;162(3):593–9. doi:<http://dx.doi.org/10.1016/j.jpeds.2012.08.009>. PubMed
- 65 Brinks MV, Murphy WH, Cardwell W, Otos M, Weleber RG. Ophthalmologic screening of deaf students in Oregon. *J Pediatr Ophthalmol Strabismus.* 2001;38(1):11–5. PubMed
- 66 Courtmans I, Mancilla V, Ligny C, Le Bon SD, Naessens A, Foulon I. Incidence of congenital CMV in children at a hearing rehabilitation center. *B-ENT.* 2015;11(4):303–8. PubMed
- 67 Elango S, Reddy TN, Shriwas SR. Ocular abnormalities in children from a Malaysian school for the deaf. *Ann Trop Paediatr.* 1994;14(2):149–52. doi:<http://dx.doi.org/10.1080/02724936.1994.11747708>. PubMed
- 68 Erbe CB, Harris KC, Runge-Samuels CL, Flanary VA, Wackym PA. Connexin 26 and connexin 30 mutations in children with nonsyndromic hearing loss. *Laryngoscope.* 2004;114(4):607–11. doi:<http://dx.doi.org/10.1097/00005537-200404000-00003>. PubMed
- 69 Falzon K, Guerin M, Fulcher T, Viani L. Ophthalmological screening of a paediatric cochlear implant population: a retrospective analysis and 12-year follow-up. *Eye (Lond).* 2010;24(6):1031–6. doi:<http://dx.doi.org/10.1038/eye.2009.248>. PubMed
- 70 Hanioglu-Kargi S, Köksal M, Tomaç S, Uğurba SH, Alpaya A. Ophthalmologic abnormalities in children from a Turkish school for the deaf. *Turk J Pediatr.* 2003;45(1):39–42. PubMed
- 71 Huo L, Wang H. Characteristics and application of inner ear CT in 20 cases of sensorineural hearing loss in children. *Acta Otolaryngol.* 2012;132(12):1261–5. doi:<http://dx.doi.org/10.3109/00016489.2012.702354>. PubMed
- 72 Kenna MA, Wu BL, Cotanche DA, Korf BR, Rehm HL. Connexin 26 studies in patients with sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg.* 2001;127(9):1037–42. doi:<http://dx.doi.org/10.1001/archotol.127.9.1037>. PubMed
- 73 Lim LH, Bradshaw JK, Guo Y, Pilipenko V, Madden C, Ingala D, et al. Genotypic and phenotypic correlations of DFNB1-related hearing impairment in the Midwestern United States. *Arch Otolaryngol Head Neck Surg.* 2003;129(8):836–40. doi:<http://dx.doi.org/10.1001/archotol.129.8.836>. PubMed
- 74 Mafong DD, Pletcher SD, Hoyt C, Lalwani AK. Ocular findings in children with congenital sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg.* 2002;128(11):1303–6. doi:<http://dx.doi.org/10.1001/archotol.128.11.1303>. PubMed
- 75 Noorbakhsh S, Memari F, Farhadi M, Tabatabaei A. Sensorineural hearing loss due to *Toxoplasma gondii* in children: a case-control study. *Clin Otolaryngol.* 2008;33(3):269–73. doi:<http://dx.doi.org/10.1111/j.1749-4486.2008.01687.x>. PubMed
- 76 Purcell DD, Fischbein N, Lalwani AK. Identification of previously "undetectable" abnormalities of the bony labyrinth with computed tomography measurement. *Laryngoscope.* 2003;113(11):1908–11. doi:<http://dx.doi.org/10.1097/00005537-200311000-00009>. PubMed
- 77 Rogers GL, Fillman RD, Bremer DL, Leguire LE. Screening of school-aged hearing impaired children. *J Pediatr Ophthalmol Strabismus.* 1988;25(5):230–2. PubMed
- 78 Samileh N, Ahmad S, Mohammad F, Framariz M, Azardokht T, Jomeh E. Role of cytomegalovirus in sensorineural hearing loss of children: a case-control study Tehran, Iran. *Int J Pediatr Otorhinolaryngol.* 2008;72(2):203–8. doi:<http://dx.doi.org/10.1016/j.ijporl.2007.10.009>. PubMed
- 79 Shusterman D, Handler SD, Marsh RR, Bilaniuk L, Tom LW. Usefulness of computed tomographic scan in the evaluation of sensorineural hearing loss in children. *Arch Otolaryngol Head Neck Surg.* 1992;118(5):501–3. doi:<http://dx.doi.org/10.1001/archotol.1992.01880050047012>. PubMed
- 80 Toumpas CJ, Clark J, Harris A, Beswick R, Nourse CB. Congenital cytomegalovirus infection is a significant cause of moderate to profound sensorineural hearing loss in Queensland children. *J Paediatr Child Health.* 2015;51(5):476–7. PubMed
- 81 Tutar E, Tekin M, Uçar T, Comak E, Ocal B, Atalay S. Assessment of ventricular repolarization in a large group of children with early onset deafness. *Pacing Clin Electrophysiol.* 2004;27(9):1217–20. doi:<http://dx.doi.org/10.1111/j.1540-8159.2004.00612.x>. PubMed
- 82 Woodruff ME. Differential effects of various causes of deafness on the eyes, refractive errors, and vision of children. *Am J Optom Physiol Opt.* 1986;63(8):668–75. doi:<http://dx.doi.org/10.1097/00006324-198608000-00011>. PubMed
- 83 Young NM, Mets MB, Hain TC. Early diagnosis of Usher syndrome in infants and children. *Am J Otol.* 1996;17(1):30–4. PubMed
- 84 Sharma A, Ruscetta MN, Chi DH. Ophthalmologic findings in children with sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg.* 2009;135(2):119–23. doi:<http://dx.doi.org/10.1001/archoto.2008.546>. PubMed
- 85 American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. *Pediatrics.* 2007;120(4):898–921. doi:<http://dx.doi.org/10.1542/peds.2007-2333>. PubMed
- 86 Chinagudi S, Patted SM, Herur A. A study of electrocardiographic changes in congenital deaf school children. *Indian J Otolaryngol Head Neck Surg.* 2010;62(1):44–8. doi:<http://dx.doi.org/10.1007/s12070-010-0008-6>. PubMed
- 87 El Habbal MH, Mahoney CO. QT interval in children with sensory neural hearing loss. *Pacing Clin Electrophysiol.* 2002;25(4):435–9. doi:<http://dx.doi.org/10.1046/j.1460-9592.2002.00435.x>. PubMed
- 88 Kang SL, Jackson C, Kelsall W. Electrocardiogram screening of deaf children for long QT syndrome: are we following UK national guidelines? *J Laryngol Otol.* 2011;125(4):354–6. doi:<http://dx.doi.org/10.1017/S0022215110002379>. PubMed

- 89 Niaz A, Rizvi SF, Khurram D. Prevalence of long QT syndrome and other cardiac defects in deaf-mute children. *J Ayub Med Coll Abbottabad*. 2011;23(1):5–8. [PubMed](#)
- 90 Öcal B, Imamoglu A, Atalay S, Ercan Tutar H. Prevalence of idiopathic long QT syndrome in children with congenital deafness. *Pediatr Cardiol*. 1997;18(6):401–5. doi:<http://dx.doi.org/10.1007/s002469900215>. [PubMed](#)
- 91 Sopontammarak S, Khongphathanayothin A, Sa-Nguanchua P. Prevalence of idiopathic long QT syndrome in congenital sensori-neural hearing loss students of Songkhla School for the Deaf. *J Med Assoc Thai*. 2003;86(12):1149–55. [PubMed](#)
- 92 Sathyamurthy I, Jayanthi K, Dash J, Srinivasan KN. Long QT syndrome in children with congenital deafness. *Indian Pediatr*. 2009;46(6):507–8. [PubMed](#)
- 93 Choi KY, Schimmenthal LA, Jurek AM, Sharon B, Daly K, Khan C, et al. Detection of cytomegalovirus DNA in dried blood spots of Minnesota infants who do not pass newborn hearing screening. *Pediatr Infect Dis J*. 2009;28(12):1095–8. doi:<http://dx.doi.org/10.1097/INF.0b013e3181af6230>. [PubMed](#)
- 94 de Vries JJ, Vesseur A, Rotteveel LJ, Korver AM, Rusman LG, Wessels E, et al. Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness. *J Clin Virol*. 2013;56(2):113–7. doi:<http://dx.doi.org/10.1016/j.jcv.2012.10.008>. [PubMed](#)
- 95 Tagawa M, Tanaka H, Moriuchi M, Moriuchi H. Retrospective diagnosis of congenital cytomegalovirus infection at a school for the deaf by using preserved dried umbilical cord. *J Pediatr*. 2009;155(5):749–51. doi:<http://dx.doi.org/10.1016/j.jpeds.2009.04.033>. [PubMed](#)
- 96 El-Badry MM, Hamdy NA, Sobhy S, Gamal R. Epileptiform electroencephalogram abnormality in children with congenital sensorineural hearing loss. *Int J Pediatr Otorhinolaryngol*. 2014;78(4):623–30. doi:<http://dx.doi.org/10.1016/j.ijporl.2014.01.018>. [PubMed](#)
- 97 Antonelli PJ, Varela AE, Mancuso AA. Diagnostic yield of high-resolution computed tomography for pediatric sensorineural hearing loss. *Laryngoscope*. 1999;109(10):1642–7. doi:<http://dx.doi.org/10.1097/00005537-199910000-00018>. [PubMed](#)
- 98 Cross NC, Stephens SD, Francis M, Hourihan MD, Reardon W. Computed tomography evaluation of the inner ear as a diagnostic, counselling and management strategy in patients with congenital sensorineural hearing impairment. *Clin Otolaryngol Allied Sci*. 1999;24(3):235–8. doi:<http://dx.doi.org/10.1046/j.1365-2273.1999.00262.x>. [PubMed](#)
- 99 McClay JE, Tandy R, Grundfast K, Choi S, Vezina G, Zalzal G, et al. Major and minor temporal bone abnormalities in children with and without congenital sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg*. 2002;128(6):664–71. doi:<http://dx.doi.org/10.1001/archotol.128.6.664>. [PubMed](#)
- 100 Nakano A, Arimoto Y, Matsunaga T. Cochlear nerve deficiency and associated clinical features in patients with bilateral and unilateral hearing loss. *Otol Neurotol*. 2013;34(3):554–8. doi:<http://dx.doi.org/10.1097/MAO.0b013e3182804b31>. [PubMed](#)
- 101 Sennaroglu L, Saatci I, Aralasmak A, Gursel B, Turan E. Magnetic resonance imaging versus computed tomography in pre-operative evaluation of cochlear implant candidates with congenital hearing loss. *J Laryngol Otol*. 2002;116(10):804–10. doi:<http://dx.doi.org/10.1258/00222150260293619>. [PubMed](#)
- 102 Westerhof JP, Rademaker J, Weber BP, Becker H. Congenital malformations of the inner ear and the vestibulocochlear nerve in children with sensorineural hearing loss: evaluation with CT and MRI. *J Comput Assist Tomogr*. 2001;25(5):719–26. doi:<http://dx.doi.org/10.1097/00004728-200109000-00009>. [PubMed](#)
- 103 Agarwal SK, Singh S, Ghuman SS, Sharma S, Lahiri AK. Radiological assessment of the Indian children with congenital sensorineural hearing loss. *Int J Otolaryngol*. 2014;2014:808759. doi:<http://dx.doi.org/10.1155/2014/808759>. [PubMed](#)
- 104 Bakhshaei M, Banaei T, Ghasemi MM, Nourizadeh N, Shojaei B, Shahrari S, et al. Ophthalmic disturbances in children with sensorineural hearing loss. *Eur Arch Otorhinolaryngol*. 2009;266(6):823–5. doi:<http://dx.doi.org/10.1007/s00405-008-0821-7>. [PubMed](#)
- 105 Guy R, Nicholson J, Pannu SS, Holden R. A clinical evaluation of ophthalmic assessment in children with sensori-neural deafness. *Child Care Health Dev*. 2003;29(5):377–84. doi:<http://dx.doi.org/10.1046/j.1365-2214.2003.00355.x>. [PubMed](#)
- 106 Leguire LE, Fillman RD, Fishman DR, Bremer DL, Rogers GL. A prospective study of ocular abnormalities in hearing impaired and deaf students. *Ear Nose Throat J*. 1992;71(12):643–6. [PubMed](#)
- 107 Regenbogen L, Godel V. Ocular deficiencies in deaf children. *J Pediatr Ophthalmol Strabismus*. 1985;22(6):231–3. [PubMed](#)
- 108 Siatkowski RM, Flynn JT, Hodges AV, Balkany TJ. Ophthalmologic abnormalities in the pediatric cochlear implant population. *Am J Ophthalmol*. 1994;118(1):70–6. doi:[http://dx.doi.org/10.1016/S0002-9394\(14\)72844-2](http://dx.doi.org/10.1016/S0002-9394(14)72844-2). [PubMed](#)
- 109 Evirgen N, Solak M, Dereköy S, Erdoğan M, Yildiz H, Eser B, et al. Genotyping for Cx26 and Cx30 mutations in cases with congenital hearing loss. *Genet Test*. 2008;12(2):253–6. doi:<http://dx.doi.org/10.1089/gte.2007.0106>. [PubMed](#)
- 110 Hayashi C, Funayama M, Li Y, Kamiya K, Kawano A, Suzuki M, et al. Prevalence of GJB2 causing recessive profound non-syndromic deafness in Japanese children. *Int J Pediatr Otorhinolaryngol*. 2011;75(2):211–4. doi:<http://dx.doi.org/10.1016/j.ijporl.2010.11.001>. [PubMed](#)
- 111 Wang YC, Kung CY, Su MC, Su CC, Hsu HM, Tsai CC, et al. Mutations of Cx26 gene (GJB2) for prelingual deafness in Taiwan. *Eur J Hum Genet*. 2002;10(8):495–8. doi:<http://dx.doi.org/10.1038/sj.ejhg.5200838>. [PubMed](#)
- 112 Yuan Y, You Y, Huang D, Cui J, Wang Y, Wang Q, et al. Comprehensive molecular etiology analysis of nonsyndromic hearing impairment from typical areas in China. *J Transl Med*. 2009;7(1):79. doi:<http://dx.doi.org/10.1186/1479-5876-7-79>. [PubMed](#)
- 113 Javidnia H, Carson N, Awubwa M, Byaruhanga R, Mack D, Vaccani JP. Connexin gene mutations among Ugandan patients with nonsyndromic sensorineural hearing loss. *Laryngoscope*. 2014;124(9):E373–6. doi:<http://dx.doi.org/10.1002/lary.24697>. [PubMed](#)
- 114 Gürtler N, Kim Y, Mhatre A, Müller R, Probst R, Lalwani AK. GJB2 mutations in the Swiss hearing impaired. *Ear Hear*. 2003;24(5):440–7. doi:<http://dx.doi.org/10.1097/01.AUD.0000090440.84513.B3>. [PubMed](#)
- 115 Misono S, Sie KC, Weiss NS, Huang ML, Boeckh M, Norton SJ, et al. Congenital cytomegalovirus infection in pediatric hearing loss. *Arch Otolaryngol Head Neck Surg*. 2011;137(1):47–53. doi:<http://dx.doi.org/10.1001/archoto.2010.235>. [PubMed](#)
- 116 Roizen NJ. Nongenetic causes of hearing loss. *Ment Retard Dev Disabil Res Rev*. 2003;9(2):120–7. doi:<http://dx.doi.org/10.1002/mrdd.10068>. [PubMed](#)
- 117 Noordman BJ, van Beeck Calkoen E, Witte B, Govertts T, Hensen E, Merkus P. Prognostic factors for sudden drops in hearing level after minor head injury in patients with an enlarged vestibular aqueduct: a meta-analysis. *Otol Neurotol*. 2015;36(1):4–11. [PubMed](#)
- 118 Mathur P, Yang J. Usher syndrome: Hearing loss, retinal degeneration and associated abnormalities. *Biochim Biophys Acta*. 2015;1852(3):406–20. doi:<http://dx.doi.org/10.1016/j.bbdis.2014.11.020>. [PubMed](#)
- 119 Koontz D, Baecher K, Amin M, Nikolova S, Gallagher M, Dollard S. Evaluation of DNA extraction methods for the detection of Cytomegalovirus in dried blood spots. *J Clin Virol*. 2015;66:95–9. doi:<http://dx.doi.org/10.1016/j.jcv.2015.03.015>. [PubMed](#)
- 120 Tsukada K, Nishio SY, Hattori M, Usami S. Ethnic-specific spectrum of GJB2 and SLC26A4 mutations: their origin and a literature review. *Ann Otol Rhinol Laryngol*. 2015;124(1 Suppl, Suppl 1):61S–76S. doi:<http://dx.doi.org/10.1177/0003489415575060>. [PubMed](#)
- 121 Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature*. 1997;387(6628):80–3. doi:<http://dx.doi.org/10.1038/387080a0>. [PubMed](#)
- 122 Antoniadi T, Grønskov K, Sand A, Pampanos A, Brøndum-Nielsen K, Petersen MB. Mutation analysis of the GJB2 (connexin 26) gene by DGGE in Greek patients with sensorineural deafness. *Hum Mutat*. 2000;16(1):7–12. doi:[http://dx.doi.org/10.1002/1098-1004\(200007\)16:1<7::AID-HUMU2>3.0.CO;2-A](http://dx.doi.org/10.1002/1098-1004(200007)16:1<7::AID-HUMU2>3.0.CO;2-A). [PubMed](#)
- 123 Albert S, Blons H, Jonard L, Feldmann D, Chauvin P, Loundon N, et al. SLC26A4 gene is frequently involved in nonsyndromic hearing impairment with enlarged vestibular aqueduct in Caucasian populations. *Eur J Hum Genet*. 2006;14(6):773–9. doi:<http://dx.doi.org/10.1038/sj.ejhg.5201611>. [PubMed](#)
- 124 Rabionet R, Gasparini P, Estivill X. Molecular genetics of hearing impairment due to mutations in gap junction genes encoding beta connexins. *Hum Mutat*. 2000;16(3):190–202. doi:[http://dx.doi.org/10.1002/1098-1004\(200009\)16:3<190::AID-HUMU2>3.0.CO;2-I](http://dx.doi.org/10.1002/1098-1004(200009)16:3<190::AID-HUMU2>3.0.CO;2-I). [PubMed](#)
- 125 Sivakumaran TA, Husami A, Kissell D, Zhang W, Keddache M, Black AP, et al. Performance evaluation of the next-generation sequencing approach for molecular diagnosis of hereditary hearing loss. *Otolaryngol Head Neck Surg*. 2013;148(6):1007–16. doi:<http://dx.doi.org/10.1177/0194599813482294>. [PubMed](#)
- 126 Schwartz PJ. Practical issues in the management of the long QT syndrome: focus on diagnosis and therapy. *Swiss Med Wkly*. 2013;143:w13843. [PubMed](#)

Appendix: The Prisma individual patient data flow diagram



The PRISMA IPD flow diagram

© Reproduced with permission of the PRISMA IPD Group, which encourages sharing and reuse for non commercial purposes