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

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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 homogenously 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 influenza*, 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, fundoscopy, 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 β2 (*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-oto-renal 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†)	Year	Class of aetiological investigation (percentage with positive findings)											Number of patients‡ (age§)
		Endocrine	Genetic	History	Cardiac	Renal	Neurological	Ophthalmic	Radiological	Serological	Other	UK	
Das (1)	1988	1	27.5 syndromic 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.)
Dereymaeker (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)
Vanniasegaram (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 syndromic 19.5	17	n.a.	n.a.	–	n.a.	n.a.	7.5	–	27	93 (age: n.a.)
Vartiainen (3)	1997	–	59.5 syndromic 20	20	n.a.	–	–	n.a.	n.a.	–	–	21.5	65 (age: mean 4.5 y)
Billings (3)	1999	–	n.a. syndromic 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*/*tRNAser* = 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	*GJB2*	18	n.a. (age: n.a.)
	Dahl (2)	2001	*GJB2*	21	243 (age: 1 m–16 y, median 4 y)
	Wang (3)	2002	*GJB2*	7	169 (age: 4–18 y)
	Lim (4)	2003	*GJB2*	17	160 (age: <19 y)
	Gurtler (3)	2003	*GJB2*	15	20 (age: < 2 y)
	Erbe (1)	2004	*GJB2, GJB6*	26	68 (age: 2 m–18 y)
	Evirgen (4)	2008	*GJB2, GJB6* (only 35delG, 167delT, del(GJB6-D13S1830))	8.5	47 (age: 8–18 y)
	Yuan (3)	2009	*GJB2, GJB3, GJB6, SLC26A4, 12S rRNA*, and *tRNAser*	n.a.	94 (age: n.a.)
	Hayashi (3)	2011	*GJB2*	30	126 (age: 0–3 y)
	Lalaiants (1)	2011	*GJB2*	59	66 (age: several months)
	Javidnia (4)	2014	*GJB2, GJB6*	<1%	122 (<18 y)
				Median (range): 20 (1–59)	
Cardiac 8 studies	Ocal (4)	1997	ECG (additionally in 2.5%: Holter-ECG, cchocardiography)	0.5	350 (age: 6–18 y)
	Rokicki	2002	ECG	1.2	162 (age: 3–15 y, mean10.5 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, fundoscopy, retinoscopy	55	460 (age: n.a.)
	Rogers (5)	1988	Visual acuity, refraction error, fundoscopy, 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, fundoscopy, retinoscopy	58	165 (age: n.a.)
	Siatkowski (4)	1994	Visual acuity, refraction error, fundoscopy, retinoscopy	61	54 (age: 2–14 y, mean 6 y)
	Armitage (3)	1995	Visual acuity, refraction error, fundoscopy, retinoscopy	46	83 (age: 16 m–16 y, mean 9.5 y)
	Young (4)	1996	Visual acuity, refraction error, fundoscopy, retinoscopy, electroretinogram	10	47 (age: 6 m–9 y, average 3 y)
	Brinks (1)	2001	Visual acuity, refraction error, fundoscopy, 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, fundoscopy, retinoscopy, electroretinogram	44	110 (age: 8 m–16.9 y)
	Hanioglu (4)	2003	Visual acuity, refraction error, fundoscopy, retinoscopy	40	104 (age: 7–20 y)
	Bakhshaee (5)	2009	Visual acuity, refraction error, fundoscopy, 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, fundoscopy, 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 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); *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) *GJB2:* 30 (64) *GJB6:* 7 (15) *SLC26A4:* 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 β2 (connexin 26); *GJB6* = gap-junction protein β6 (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	*GJB2* (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/CHR; 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. Audiorehabilitation, 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 stepwise 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.

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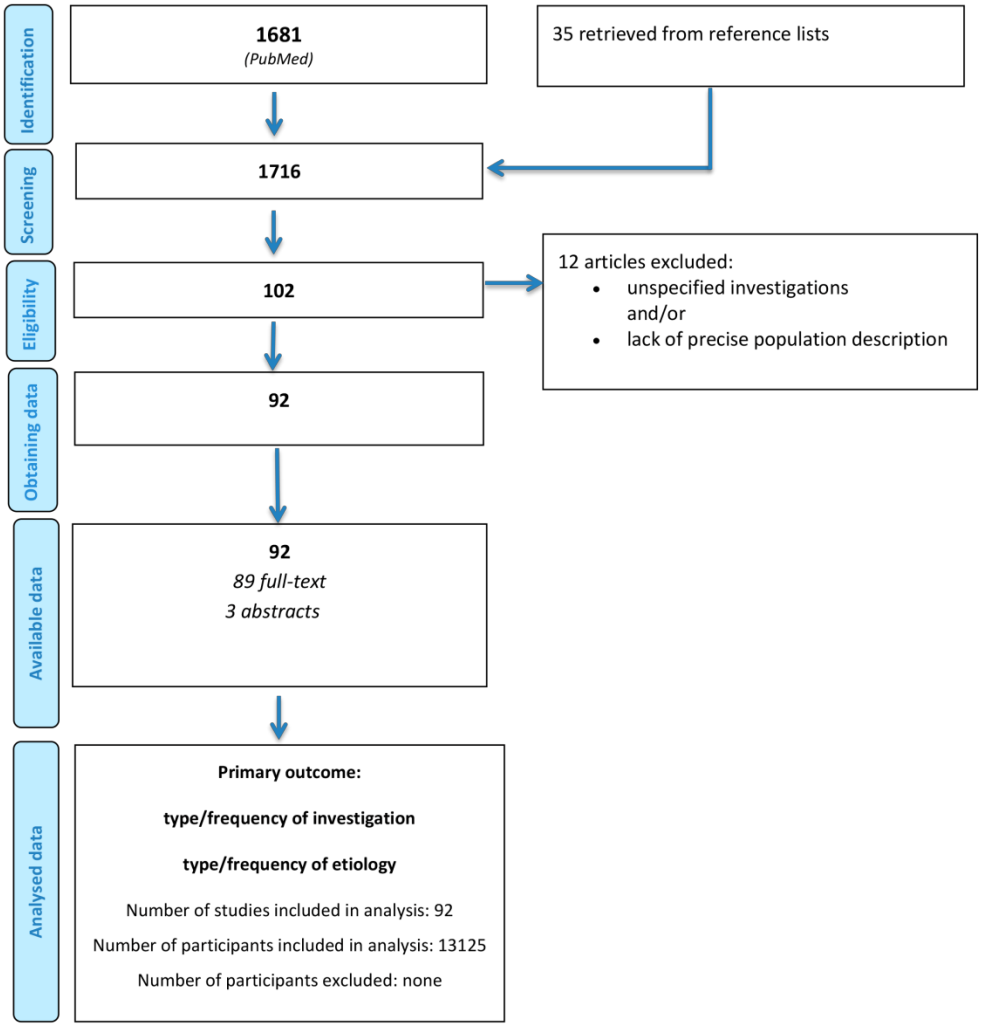
Appendix: The Prisma individual patient data flow diagram



The PRISMA IPD flow diagram