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Mitochondrial Disease and Hearing Loss in Children: A Systematic Review

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Abstract

Objectives: Hearing loss is a clinical symptom, frequently mentioned in the context of mitochondrial disease. With no cure available for mitochondrial disease, supportive treatment of clinical symptoms like hearing loss is of the utmost importance. The aim of this study was to summarize current knowledge on hearing loss in genetically proven mitochondrial disease in children and deduce possible and necessary consequences in patient care.

Methods: Systematic literature review, including Medline, Embase, and Cochrane library. Review protocol was established and registered prior to conduction (International prospective register of systematic reviews—PROSPERO: CRD42020165356). Conduction of this review was done in accordance with MOOSE criteria.

Results: A total of 23 articles, meeting predefined criteria and providing sufficient information on 75 individuals with childhood onset hearing loss was included for analysis. Both cochlear and retro-cochlear origin of hearing loss can be identified among different types of mitochondrial disease. Analysis was hindered by inhomogeneous reporting and methodical limitations.

Conclusion: Overall, the findings do not allow for a general statement on hearing loss in children with mitochondrial disease. Retro-cochlear hearing loss seems to be found more often than expected. A common feature appears to be progression of hearing loss over time. However, hearing loss in these patients shows manifold characteristics. Therefore, awareness of mitochondrial disease as a possible causative background is important for otolaryngologists. Future attempts rely on standardized reporting and long-term follow-up.

Key Words: mitochondrial disease, mitochondriopathy, mitochondria, hearing, hearing loss, audiometry, audiometric testing, auditory neuropathy, brainstem evoked auditory potentials, treatment.

Level of Evidence: NA

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INTRODUCTION

The spectrum disorder of mitochondrial diseases (MDs) encapsulates a large group of mostly hereditary rare diseases[1] that all have an impairment of mitochondrial ATP production in common. As there are more than 1500 mitochondrial proteins involved in the synthesis of ATP via the tricarboxylic acid cycle and oxidative phosphorylation, mutations in any of the numerous encoding genes can lead to a relatively serious condition for the affected individual. The genetic information is thereby under dual control of both the nuclear as well as the mitochondrial (mt) genome. Currently, pathogenic variants in more than 300 genes have been related to human diseases (mitochondrial disease genes).[2] One of the challenges of MDs is the marked clinical and genetic variation ("any age, any symptom, any mode of inheritance"), which regularly delays diagnosis, especially in adults. Although all organs can be affected, typically symptoms of the most energy consuming organs (central and peripheral nervous system, skeletal and heart muscle) are seen, often in combination.

The increasing use of next generation sequencing techniques like exome sequencing has not only led to an elevated number of total diagnoses but also to diagnoses at an earlier stage of disease. Networks of specialized clinical centers and laboratories, like the German

mitoNET[3] or within METAB-ERN,[4] have been established to share experience in diagnosis and treatment for this challenging group of diseases.

The clinical symptom of hearing loss (HL), as part of the phenotypic spectrum of MDs, has been cited frequently,[5–7] and is also claimed by some authors as the one symptom that is shared most in the heterogenic symptom complex of MDs.[7,8] However, due to further, more life-threatening signs and symptoms, there has been little emphasis on the definition of the type and degree of HL in MDs.[9,10] With no curative and very limited supportive treatment options for individuals with MD, there is an unmet need for reliable audiometric data to provide solid recommendations for hearing rehabilitation.

Hearing rehabilitation and associated success essentially relies on suitable audiometric measurement and diagnostics. To define adequate screening protocols for audiometric care in the case of MD, including time periods, sufficient testing modalities, and knowledge of the type of hearing loss, its onset and clinical course are mandatory.

Gold and Rapin presented a first review on the relationship between mitochondrial inheritance and hearing loss in 1994, reporting on a total of 162 patients, of whom 32 had hearing loss.[11] The authors insisted on the need of longitudinal audiometric studies in this group of patients. One has to take into consideration, that knowledge of the actual number of manifold MDs was limited at that time. In 2003, Sinnathuray et al.[12] published a review on cochlear implant results in patients affected by mitochondrial sensorineural hearing loss, providing audiometric outcome data as a function of type of MD.

Although hearing loss in the context of MD is predominantly considered to be progressive and of cochlear origin,[13,14] there are also reports on retro-cochlear dysfunction and auditory neuropathy (AN).[15,16] Despite an increasing number of publications in the field of MD-associated HL, there is still little knowledge of its pathophysiology, the distribution of HL pattern in regards to the genotype, and the possible benefits of hearing rehabilitation. Moreover, HL may be underestimated in the literature on MDs, because appearance may be subclinical or audiometric testing applied may not have been sufficient for detection.[15,16] Leruez et al. reported diverse audiometric findings, including auditory brainstem responses (ABR), within a group of patients with HL and confirmed mutations in the *OPA1* gene, emphasizing the importance of ABR for all-encompassing audiometric diagnosis.[16] Clarification of the whole auditory pathway may allow future recommendations for possible HL rehabilitation for specific types of MD.

To create an overview of the current knowledge, we present a systematic literature review on primary hearing phenotypes found in pediatric patients with MDs.

TABLE I.
PICOS Criteria Defined for This Systematic Literature Review.

P (patient population or disease being addressed)	Female and male patients under the age of 18 with diagnosis of mitochondrial disease, confirmed by genetic testing. Patients affected by mitochondrial disease, known to result in susceptibility for aminoglycoside-induced hearing loss will not be included.
I (interventions or exposure)	The intervention of interest to be analyzed to answer the review question is audiometric testing, including objective measurement. Audiometric investigations should be performed under defined, locally standardized circumstances by trained audiometric staff. Further co-investigations do not affect eligibility for inclusion.
C (comparator/control group)	A comparative group or control group is not included for analysis.
O (outcome or endpoint)	The outcomes of interest to answer the review objectives are following parameters: 1. Type of hearing loss a. Conductive hearing loss b. Cochlear sensorineural hearing loss c. Auditory neuropathy 2. Characteristics of hearing loss a. Onset b. Severity c. Development over time 3. Effective date of diagnosis to determine whether hearing loss appeared a. Pre-lingually b. Post-lingually c. Congenitally
S (study design chosen)	Study design of studies to be chosen for inclusion is going to be of any type or hierarchy, concerning quality. The majority of studies expected to be included, based on the review objectives, will be observational studies.

METHODS

PICOS

The review question was divided into two objectives:

Objective 1: Is there a specific type of hearing loss in the case of mitochondrial disease?
Objective 2: Is there a specific clinical course of audiologic symptoms in relation to mitochondrial disease, concerning onset, severity, and progress?

Based on these objectives, PICOS elements were defined, summarized in Table I.

Search Strategy and Data Sources

This systematic review was developed by the authors S.R., A.O., both medical doctors and author C.L., a librarian, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] According to PRISMA guidelines, with respect to study designs other than randomized clinical trials being analyzed, established protocols such as the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[18] proposal and checklist are recommended for guidance. Therefore, a flow diagram (Fig. 1) displaying the whole working process was created according to the PRISMA 2009[19] template and a completed MOOSE checklist is provided as Supplemental Material.

The final protocol was registered in PROSPERO[20] (ID: CRD42020165356).

A systematic search of the literature was conducted in MEDLINE/PubMed, Embase, and in the Cochrane Central Register of Controlled Trials for studies published from the first

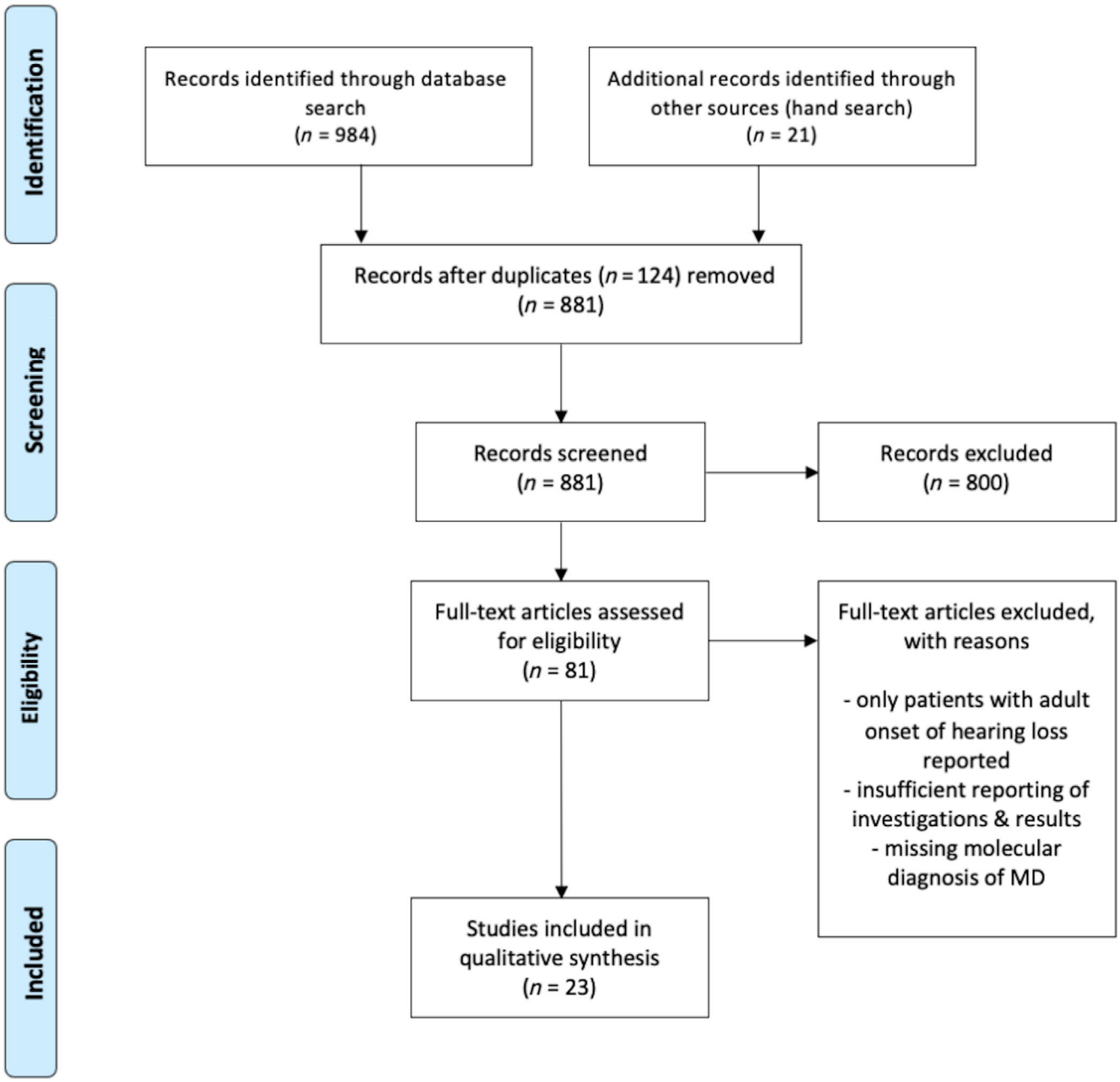

Fig. 1. Flowchart according to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA), displaying review and selection process. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. *PLoS Med*. 2009;6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

available year of online indexing up to September 2021, in English and German. Restriction to these languages was based on lack of language resources. Our search strategy included subject headings and free-text terms for the concepts "mitochondrial disease," "hearing loss," and "audiometric testing." The detailed search strategy for the databases is available as Supplemental Material and in PROSPERO.[20]

Study Selection

A primary search was performed by authors A.O. and S.R., independently, by scanning titles and abstracts. Study types incorporated were of any hierarchy, including conference abstracts. The decision to include conference abstracts was based on expected low evidence in the field of MD and hearing loss, making it worthwhile to include as much information as possible.[21] Gray literature, labeled as conference abstracts by the search engine, was comprehensively searched on homepages of publishing societies and authors were contacted for further information.

Results of primary search were discussed and compared between A.O. and S.R. In case of disagreement or uncertainty, author S.W., also a medical doctor, was involved to find consensus on inclusion or exclusion for further analysis.

The studies ultimately chosen had to fulfill the following eligibility criteria, each based on specific considerations. MD reported had to be described in a comprehensible way based on molecular testing. Description of hearing abilities and measurements were analyzed for potential inclusion based on the following considerations: Given the fact that malfunction of mitochondria may not only affect the inner ear itself, but also post-cochlear structures such as spiral ganglion cells, the auditory nerve, and the central nervous system, only studies reporting on objective auditory evoked potential measurements such as ABR were included for further analysis.

Studies reporting on secondary HL related to application of aminoglycoside antibiotics in relation to the m.1555A>G or other mtDNA variants[14,22] were excluded from further analysis, because HL characteristics in patients with aminoglycoside-susceptibility due to mitochondrial DNA variants cannot be attributed to the impact of MD itself.

In case of missing access to articles of interest, authors were contacted by S.R. and A.O. via email or internet-based platforms and asked for either further information or the article itself.

Finally, a manual search of reference lists of included articles was performed by S.R. and A.O., ensuring coverage of potentially relevant information, which was undetected during the primary search of databases.

Data Extraction Methods and Data Synthesis

Data extraction was done by A.O. and S.R. with the help of a self-created, software-based data sheet (Microsoft® Excel, Version 16.43), including variables and their coding as stated in the review protocol.

In contrast to the initial expectation of the authors during the review planning phase, age of onset has been beyond 18 years for a substantial number of included publications. Therefore, each article included for analysis was additionally screened for reported age of onset. Finally, only patients with reliable onset of hearing loss during childhood were chosen from each article and included for final analysis.

Statistical Analysis

Data synthesis and statistical analysis were done in close collaboration with a statistician (author G.Z.). Because individual studies were very heterogeneous with respect to study characteristics and design, as well as limited sample sizes (partially also due to missing data), a comprehensive descriptive summary of the available data was preferred over a meta-analysis.

Quality Assessment

The Newcastle–Ottawa Scale[23] (NOS) was chosen for quality assessment, representing the most appropriate tool for assessing case reports. However, several adaptions had to be implemented, because NOS is primarily designed for case–control and cohort studies. The predefined assessment scale for cohort studies was adapted for relevant factors of the review question and specific features of case reports. The adapted scale may be found in Supplemental Material. The adaption was carried out in consideration of the recommendations of Murad et al.,[24] and in agreement between authors S.R. and G.Z. Utilization of a uniform and quantitative assessment scale for all study types included allowing for a general statement on quality of articles included for analysis.

RESULTS

The search strategy yielded 984 records (Fig. 1 and Table II), of which 23, detailing a total of 75 individuals with genetically proven MD and sufficient data on hearing loss, were eligible for final inclusion and analysis.[10,16,25–45]

Case Characteristics

Genotypes and phenotypes are provided in Table III. Forty individuals had variants in the mtDNA, and a further 35 in nuclear genes. The most common mode of inheritance was maternal inheritance ($n = 40$), followed by autosomal recessive ($n = 20$) and autosomal dominant ($n = 15$). Variants in the *MT-TL1* gene were reported most commonly ($n = 26$).

The phenotypic spectrum ranged from isolated hearing loss ($n = 4$), via isolated (sensory) neuropathy ($n = 20$), to individuals presenting a broad neurological ($n = 18$) or encephalomyopathic ($n = 4$) phenotype. Multiorgan disease was the most commonly reported ($n = 27$). In two patients reported ($n = 2$), clinical details were missing. That none of the included individuals showed an isolated presentation of diabetes, plus hearing loss, may reflect the circumstance, that in this special MD, the hearing loss precedes the diabetes for years, if not decades, and therefore might not be detected as part of an MD when appearing as a singular symptom in childhood.[46–48]

Types of Hearing Loss Identified

Type of hearing loss reported was either of cochlear ($n = 42$) or retro-cochlear origin ($n = 33$) (Tables II and IV). One study[44] reported on two individuals, showing audiometric signs of both cochlear and retro-cochlear hearing loss. These two were assigned to the group of individuals with retro-cochlear origin in the context of this review. Conductive hearing loss has not been reported.

Both cochlear as well as retro-cochlear hearing loss were reported in association with genetic variants accountable for mitochondrial disease. Table IV provides an overview of both types identified for each specific variant. Relative frequencies for subgroups (gene affected), cochlear versus retro-cochlear hearing loss, are in the case of *MT-TK*: $n = 1$ (50%) and $n = 1$ (50%), for *MT-TL1*: $n = 20$ (77%) and $n = 6$ (23%), for *OPA1*: $n = 1$ (6%) and $n = 14$ (94%) and in the case of *PC*: $n = 1$ (50%) and $n = 1$ (50%). For all of the remaining variants reported hearing loss was either of cochlear or retro-cochlear origin (Table IV). In seven individuals with large-scale deletions or combinations of large-scale deletions and duplications within the mtDNA, only cochlear hearing loss was reported.

Characteristics of Hearing Loss

Repetitive audiometric assessment was available for 44 individuals (Table II). Progression of hearing impairment was reported in 34 cases, whereas no progression was reported in six children with *MT-TL1* variants over a

TABLE II.
Publications Included for Final Analysis ($n = 23$), Including Bibliographic Data, Number of Patients Included for Analysis, Gender, Reported Genes Affected, and Hearing Loss Characteristics.

Author (Year)	Type of Study (Total No. of Individuals Reported)	Total No. of Individuals Included for Analysis	Sex		Number of Adults with Documented Onset of HL during Childhood	Genes Affected + Type of HL		Severity of HL Reported According to Pure-Tone Audiometry (No. of Individuals)	Onset of HL	Median Age at Diagnosis of HL	Mean Age at Diagnosis of HL	Median Age at Onset of HL	Mean Age at Onset of HL	Course of HL	Individuals Treated with HA or CI	Success of Hearing Rehabilitation Reported
			F	M		Cochlear HL (No. of Individuals)	Retro-Cochlear HL (No. of Individuals)									
Amati-Bonneau et al. (2005)[25]	R: case series ($n = 5$)	3	2	1	2		*OPA1* ($n = 3$)	Mild ($n = 1$); moderate ($n = 1$); severe ($n = 1$)	Postlingual	15.0 years	15.66 years	7.0 years	10.0 years	All progressive	NA	NA
Amati-Bonneau et al. (2008)[26]	R: case series ($n = 8$)	2	1	1	2	*OPA1* ($n = 1$)	*OPA1* ($n = 1$)	Moderate ($n = 1$); severe ($n = 1$)	Postlingual	38.5 years	38.5 years	12.0 years	12.0 years	$n = 1$ progressive	1 of 2—HA	NA
Berio et al. (2017)[27]	R: case report ($n = 1$)	1	0	1	0	Large scale single deletion ($n = 1$)		NA	Postlingual	13 years	13 years	9 years	9 years	NA	NA	NA
Breen et al. (2013)[28]	R: case report ($n = 2$)	2	2	0	0	PC ($n = 1$)	PC ($n = 1$)	Profound ($n = 2$)	Congenital	<6 mo	<6 mo	NA	NA	NA	NA	NA
Chennupati et al. (2011)[29]	R: case series ($n = 26$)	1	NA	NA	0		*MT-TK* ($n = 1$)	Mild to moderate ($n = 1$)*	Postlingual	17 years 4 mo	17 years 4 mo	NA	NA	NA	NA	NA
Iwanicka-Pronicka et al. (2012)[30]	R: cohort ($n = 34$)	6	3	3	6	*MT-TL1* ($n = 6$)		Mild ($n = 4$); moderate ($n = 2$)	Postlingual	NA	NA	9.5 years	10.5 years	No progression	0 of 6	NA
Iwanicka-Pronicka et al. (2019)[31]	P: case series ($n = 80$)	10	5	5	0	*RRM2B* ($n = 2$); *SERAC1* ($n = 8$)		Severe ($n = 8$); NA ($n = 2$)	*SERAC1*: congenital ($n = 6$); prelingual ($n = 2$); *RRM2B*: congenital ($n = 2$)	8.0 mo	16.8 mo	0.25 mo	0.825 mo	NA	1 of 10—HA	NA
Kon et al. (2000)[32]	R: case series ($n = 30$)	1	1	0	0	*MT-TL1* ($n = 1$)		NA	Postlingual	16 years	16 years	NA	NA	All progressive	NA	NA
Leng et al. (2013)[33]	R: case report ($n = 1$)	1	0	1	0		*MT-ND3* ($n = 1$)	Normal ($n = 1$)	Postlingual	14 years	14 years	14 years	14 years	All progressive	NA	NA
Leruez et al. (2013)[16]	R: case series ($n = 8$)	4	2	2	2		*OPA1* ($n = 4$)	Mild ($n = 1$); moderate ($n = 2$); severe ($n = 1$)	Postlingual	18.0 years	21.25 years	13.5 years	12.25 years	All progressive	NA	NA
Liu et al. (2014)[10]	P: case series ($n = 73$)	3	1	2	0	*MT-TL1* ($n = 1$)	*MT-TL1* ($n = 2$)	Normal ($n = 3$)	NA	15.0 years	15.0 years	NA	NA	NA	NA	NA
Maeda-Katahira et al. (2019)[45]	R: case series ($n = 4$)	4	1	3	4		*OPA1* ($n = 4$)	Mild ($n = 1$); moderate ($n = 2$); severe ($n = 1$)	Postlingual	28.0 years	27.0 years	16.0 years	16.0 years	NA	2 of 4—CI	yes
Paul et al. (2017)[34]		7	6	1	7		*FDXR* ($n = 7$)	NA	Postlingual	NA	NA	13.0 years	12.33 years	NA	NA	NA

(Continues)

TABLE II.
Continued

Author (Year)	Type of Study (Total No. of Individuals Reported)	Total No. of Individuals Included for Analysis	Sex		Number of Adults with Documented Onset of HL during Childhood	Genes Affected + Type of HL		Severity of HL Reported According to Pure-Tone Audiometry (No. of Individuals)	Onset of HL	Median Age at Diagnosis of HL	Mean Age at Diagnosis of HL	Median Age at Onset of HL	Mean Age at Onset of HL	Course of HL	Individuals Treated with HA or CI	Success of Hearing Rehabilitation Reported
			F	M		Cochlear HL (No. of Individuals)	Retro-Cochlear HL (No. of Individuals)									
	R: case series ($n = 8$)															
Roubertie et al. (2015)[35]	P: case series ($n = 22$)	2	NA	NA	2		*OPA1* ($n = 2$)	Moderate to severe ($n = 1$)*; severe ($n = 1$)	Postlingual	33.0 years	33.0 years	11.5 years	11.5 years	$n = 1$ progressive	1 of 2—CI	yes
Sakai et al. (2004)[36]	R: case report ($n = 2$)	1	1	0	0		*MT-ATP6* ($n = 1$)	Severe to profound ($n = 1$)*	Prelingual	1 year	1 year	1 year	1 year	Fluctuating	0	NA
Scaglia et al. (2006)[37]	R: case series ($n = 115$)	7	5	2	7	*MT-TL1* ($n = 5$); *MT-TC* (*tRNA* cysteine) ($n = 1$)	*MT-ND6* ($n = 1$)	NA	Postlingual	NA	NA	8.0 years	8.0 years	All progressive	NA	NA
Sue et al. (1998)[38]	P: case series ($n = 18$)	4	3	1	4	*MT-TL1* ($n = 4$)		Mild ($n = 1$); severe ($n = 1$); profound ($n = 2$)	Postlingual	27.5 years	27.25 years	14.5 years	14.25 years	All progressive	1 of 4—HA; 1 of 4—CI	yes
Tamagawa et al. (1997)[39]	R: case series ($n = 9$)	3	2	1	1	*MT-TL1* ($n = 2$)	*MT-TL1* ($n = 1$)	Mild ($n = 3$)	Postlingual	17.0 years	17.0 years	14 years	14.33 years	All progressive	NA	NA
Tsutsumi et al. (2001)[40]	R: case report ($n = 3$)	1	1	0	0	*MT-TK* ($n = 1$)		Mild ($n = 1$)	Postlingual	15 years	15 years	13 years	13 years	NA	NA	NA
Van Hove et al. (2010)[41]	R: case report ($n = 1$)	1	1	0	0	*SUCLG1* ($n = 1$)		NA	Congenital	13.5 mo	13.5 m	NA	NA	NA	NA	NA
Vandana et al. (2016)[42]	R: case series ($n = 8$)	2	0	2	0	*MT-TL1* ($n = 1$)	*MT-TL1* ($n = 1$)	Severe ($n = 1$); NA ($n = 1$)	Postlingual	14.0 years	14.0 years	12.9 years	12.9 years	$n = 1$ progressive in retro-coch	NA	NA
Wang et al. (2016)[43]	R: case report ($n = 1$)	1	0	1	0		*MT-ND6* ($n = 1$)	Normal ($n = 1$)	Postlingual	17 years	17 years	NA	NA	NA	NA	NA
Zwirner and Wilichowski (2001)[44]	R: case series ($n = 12$)	8	NA	NA	2	Large scale single deletion ($n = 2$); no further specified deletion and duplication ($n = 4$)	*MT-TL1* ($n = 2$)	Mild ($n = 3$); moderate ($n = 2$); severe ($n = 3$)	Postlingual	11.0 years	12.88 years	9.0 years	9.75 years	All progressive	5 of 8—HA	NA

*Asymmetric hearing loss.
CI = cochlear implant; F = female; HA = hearing aid; HL = hearing loss; M = male; mo = months; P = prospective; R = retrospective.

TABLE III.
Mitochondrial Diseases Reported among all Publications of Final Analysis, Arranged According to Causative Gene.

						Summarized Magnitude of Disease								
Gene	OMIM ID	Reference Sequence Number	Reported Variant	Inheritance	Reported Phenotype	Isolated Hearing Loss	Isolated Neuropathy	Broad Neurological Phenotype Not Restricted to Neuropathy	Encephalomyopathy	Hearing Loss + Diabetes	Multi Organ Diseases	Clinical Details not Available	Author	Year
FDXR	* 103270	NM_024417.4	c.[916C>T]; c.[916C>T]	AR	Auditory neuropathy and optic atrophy		5						Paul et al.	2017
FDXR	* 103270	NM_024417.4	c.[643C>G]; c.[1429G>A]	AR	Auditory neuropathy and optic atrophy		2						Paul et al.	2017
MT	NA	NC_012920.1	mt.large scale single deletion	Maternal	PEO, pigmentary retinopathy, short stature						2		Zwirner and Wilichowski	2001
MT	NA	NC_012920.1	mt.not further specified deletion and duplication	Maternal	4 × PEO, 4 × pigmentary retinopathy, 4 × short stature, 3 × additional hypoparathyreoidism, 2 × additional renal problems, 1 × additional Pearson syndrome				3		1		Zwirner and Wilichowski	2001
MT	NA	NC_012920.1	mt.large scale single deletion	Maternal	Facial dysmorphism, corneal clouding, ptosis, nystagmus, short stature, hypoparathyroidism						1		Berio et al.	2017
MT-ATP6	* 516060	NC_012920.1	m.[8993T>G]	Maternal	Epilepsy, specific CT findings			1					Sakai et al.	2004
MT-ND3	* 516002	NC_012920.1	m.[10197G>A]	Maternal	Seizures, headaches, stroke like episodes, bilateral basal ganglia lesions (Leigh sy)			1					Leng et al.	2013
MT-ND6	* 516006	NC_012920.1	m.[14484T>C]	Maternal	LHON		1						Wang et al.	2016
MT-ND6	* 516006	NC_012920.1	m.[14459G>A]	Maternal	Short stature, Leigh MRI						1		Scaglia et al.	2006
MT-TC (tRNA cysteine)	* 590020	NC_012920.1	m.[5783G>A]	Maternal	Short stature, retinitis pigmentosas, renal failure, peripheral neuropathy, cardimyopathy, cyclic vomiting						1		Scaglia et al.	2006
MT-TK	* 590060	NC_012920.1	m.[8344A>G]	Maternal	"MERRF" no more details			1					Chennupati et al.	2011
MT-TK	* 590060	NC_012920.1	m.[8344A>G]	Maternal	"MERRF" no more details			1					Tsutsumi et al.	2001
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	Stroke-like episodes			2					Vandana et al.	2016
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	2 × DD, 3 × short stature, 1 × cardiomayopathy, 2 × stroke like episodes, 2 × diabetes, 3 × muscular hypotonia						5		Scaglia et al.	2006
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	1 × PEO, 1 × pigmentary retinopathy, 1 × short stature, 2 × cerebellar symptoms, 2 × ID, 2 × muscle weakness, 2 × seizures, 2 × stroke like episodes			1			1		Zwirner and Wilichowski	2001
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	1 × diabetes, 1 × stroke like episodes, 1 × epilepsy, 2 × ataxia, 1 × muscle weakness, 1 × encephalopathy, 2 × migraine, 1 × short stature, 1 × intestinal pseudoobstruction	1	1	1			1		Sue et al.	1998

(Continues)

TABLE III.
Continued

						Summarized Magnitude of Disease								
Gene	OMIM ID	Reference Sequence Number	Reported Variant	Inheritance	Reported Phenotype	Isolated Hearing Loss	Isolated Neuropathy	Broad Neurological Phenotype Not Restricted to Neuropathy	Encephalomyopathy	Hearing Loss + Diabetes	Multi Organ Diseases	Clinical Details not Available	Author	Year
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	Broad spectrum	3					3		Iwanicka-Pronicka et al.	2012
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	"MELAS"			3					Liu et al.	2014
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	"MELAS"			1					Kon et al.	2000
MT-TL1	* 590050	NC_012920.1	m.[3243A>G]	Maternal	"MELAS"			3					Tamagawa et al.	1997
OPA1	* 605290	NM_015560.2	c.[1334G>A]	AD	Auditory neuropathy and optic atrophy		2						Roubertie et al.	2015
OPA1	* 605290	NM_015560.2	c.[1334G>A]	AD	Auditory neuropathy and optic atrophy		3						Amati-Bonneau et al.	2005
OPA1	* 605290	NM_015560.2	c.[1334G>A]	AD	Auditory neuropathy and optic atrophy		4						Leruez et al.	2013
OPA1	* 605290	NM_015560.2	c.[1316G>T]	AD	Optic atrophy, ataxia, sensory-motor axonal neuropathy, cerebral and cerebellar atrophy, bilateral basal ganglia alterations, lactic acidosis			1					Amati-Bonneau et al.	2008
OPA1	* 605290	NM_015560.2	c.[1069G>A]	AD	optic atrophy, ptosis, CPEO, muscle weakness, sensory-motor axonal neuropathy				1				Amati-Bonneau et al.	2008
OPA1	* 605290	NM_015560.2	c.[1334G>A]; c.[1618A>C]; c.[892A>C]	AD	optic atrophy, auditory neuropathy, vestibular dysfunction, ataxia, myopathy, progressive external ophthalmoplegia		2	2					Maeda-Katahira	2019
PC	* 608786	NM_000920.3	c.[506G>A]; c.[506G>A]	AR	lactic acidosis, no clinical details							1	Breen et al.	2013
PC	* 608786	NM_000920.3	c.[1154_1155delGC]; c.[1154_1155delGC]	AR	lactic acidosis, no clinical details							1	Breen et al.	2013
RRM2B	* 604712	NM_015713.4	c.[414_415delCA]; c.[(321 + 1_322–1)_(684 + 1_685–1)del]	AR	"mitochondrial encephalopathy," respiratory insufficiency, early death						1		Iwanicka-Pronicka et al.	2019
RRM2B	* 604712	NM_015713.4	c.[686G>T]; c.[686G>T]	AR	microcephaly, encephalopathy, respiratory insufficinecy, cataracts						1		Iwanicka-Pronicka et al.	2019
SERAC1	* 614725	NM_032861.3	c.[1924C>T]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"						1		Iwanicka-Pronicka et al.	2019
SERAC1	* 614725	NM_032861.3	c.[1309_1313dup]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"						1		Iwanicka-Pronicka et al.	2019
SERAC1	* 614725	NM_032861.3	c.[1642dup]; c.[1642dup]	AR	"MEGDEL"						1		Iwanicka-Pronicka et al.	2019
SERAC1	* 614725	NM_032861.3	c.[1822_1828 + 10delinsACCAACAGG]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"						1		Iwanicka-Pronicka et al.	2019

SERAC1	*614725	NM_032861.3	c.[1822_1828 + 10delinsACCAACAGG]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"	1	Iwanicka-Pronicka et al.	2019
SERAC1	*614725	NM_032861.3	c.[1822_1828 + 10delinsACCAACAGG]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"	1	Iwanicka-Pronicka et al.	2019
SERAC1	*614725	NM_032861.3	c.[1822_1828 + 10delinsACCAACAGG]; c.[1822_1828 + 10delinsACCAACAGG]	AR	"MEGDEL"	1	Iwanicka-Pronicka et al.	2019
SERAC1	*614725	NM_032861.3	c.[1822_1828 + 10delinsACCAACAGG]; c.[916C>T]	AR	"MEGDEL"	1	Iwanicka-Pronicka et al.	2019
SUCLG1	*611224	NM_003849.4	c.[40A>T]; c.[40A>T]	AR	DD, liver failure, hepatomegaly, dystonic posturing, early death due to respiratory insufficiency	1	Van Hove et al.	2010

4	20	18	4	0	27	2
Total of patients with isolated hearing loss	Total of patients with isolated neuropathy	Total of patients with broad neurological phenotype	Total of patients with encephalo-myopathy	Total of patients with hearing loss plus diabetes	Total of patients with multi organ diseases	Total of patients with missing clinical details

Note: Clinical characteristics reported as well as authors are included.
Abbreviations: AD = autosomal dominant; AR = autosomal recessive; CPEO = chronic progressive external ophthalmoplegia; CT = computed tomography; DD = developmental delay; ID = impaired development; LHON = Leber's hereditary optic neuropathy; MEGDEL = 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy with ragged red fibers; MRI = magnetic resonance imaging; MT = mitochondrial; PEO = progressive external ophthalmoplegia.

10-year period.[30] Only one individual affected with a *MT-ATP6* variant reported fluctuating hearing loss.[36] From 10 articles, no further information on the course of hearing loss could be extracted. This is displayed in Table II with "NA."

Age at Onset

The ages of onset of hearing loss reported in the included studies ranged from 0 to 16.0 years.

Only three studies reported on congenital or prelingual onset: Iwanicka-Pronicka et al.[31]; Breen et al.[28] and Van Hove et al.[41] Variants reported by these authors affected *RRM2B*; *SERAC1*; *PC*, and *SUCLG1*. In all of the remaining reports and variants, onset of hearing loss was post-lingual (Table II).

Severity of Hearing Loss

Severity of hearing loss, based on pure-tone audiometric measurements, was reported in 18 articles, including a total of 55 individuals (Table II). Severity ranged from mild to profound. In five patients normal hearing thresholds are reported, four of them subsequently diagnosed with retro-cochlear hearing loss. Hearing loss reported has been symmetric in 72 individuals, and asymmetric in three individuals.

Quality Assessment

Mean and median score of quality assessment according to the NOS, indicated with stars (with a maximum of 9.0 stars possible), were both equal to 5.0 (min = 2.0, max = 8.0; first quartile = 3.0, third quartile = 6.0). Results are displayed in Table V. The detailed

TABLE IV.
Type of Hearing Loss Reported, Displayed as a Function of Gene Affected.

	Type of Hearing Loss	
Gene Affected	Cochlear	Retro-Cochlear
FDXR	0	7
MT large-scale deletion	3	0
MT large-scale deletion and duplication	4	0
MT-ATP6	0	1
MT-ND3	0	1
MT-ND6	0	2
MT-TC	1	0
MT-TK	1	1
MT-TL1	20	6
OPA1	1	14
PC	1	1
RRM2B	2	0
SERAC1	8	0
SUCLG1	1	0
Total	42	33

TABLE V.
Scores Given in Stars [*] of Newcastle Ottawa Scale for Quality Assessment.

	Newcastle-Ottawa Scale for Case Series and Case Reports						
	Selection		Comparability		Outcome		Total Quality Score
Author (Year)	Representativeness of the Sample	Ascertainment of Mitochondrial Disease	Controlled for Further Factors of Hearing Loss	Follow-Up Performed	Assessment of Outcome	Reporting	Maximum of Nine Stars Possible
Amati-Bonneau et al. (2005)[25]		**			*		3
Amati-Bonneau et al. (2008)[26]	*	**			*		4
Berio et al. (2017)[27]		*			*		2
Breen et al. (2013)[28]		**			*		3
Chennupati et al. (2011)[29]	**	*			**		5
Iwanicka-Pronicka et al. (2012)[30]	*	**	*	*	*		6
Iwanicka-Pronicka et al. (2019)[31]	**	**			*	*	6
Kon et al. (2000)[32]	*	*	*		**	*	6
Leng et al. (2013)[33]		**			*		3
Leruez et al. (2013)[16]	**	**	*	*	*	*	8
Liu et al. (2014)[10]	*	*	*		**		5
Maeda-Katahira et al. (2019)[45]	*	**			**	*	6
Paul et al. (2017)[34]		**			*		3
Roubertie et al. (2015)[35]	**	**	*	*	*	*	8
Sakai et al. (2004)[36]		**		*	**		5
Scaglia et al. (2006)[37]	**	**	*		*		6
Sue et al. (1998)[38]	*	**	*		**	*	7
Tamagawa et al. (1997)[39]		*	*	*	*	*	5
Tsutsumi et al. (2001)[40]		**			**	*	5
Van Hove et al. (2010)[41]		**			*		3
Vandana et al. (2016)[42]	*	**			**	*	6
Wang et al. (2016)[43]		*	*		**		4
Zwirner and Wilichowski (2001)[44]	*	**	*	*	*	*	7

description of the adapted scale may be found as Supplemental Material.

Article types included in this systematic literature review are all Level 4 evidence articles, according to the OCEBM Levels of Evidence Working Group—"The Oxford 2011 Levels of Evidence."[49]

DISCUSSION

The objectives of this literature review were to identify the existence of a specific type and a specific clinical course of audiologic symptoms, including onset, severity, and progress, in cases of MD (Table I). Based on the results of the descriptive pooled analysis of the literature,

there is no sufficient conclusion to our predefined objectives, as the audiological phenotype is quite heterogenous, making it difficult to establish a straightforward diagnosis. Moreover, data on hearing rehabilitation in MD patients are limited. Healthcare providers in the field of otolaryngology should therefore be attentive to the potential differential diagnosis of mitochondrial disease, independent from audiological symptoms, to enable optimal patient care.

Limitations

Due to the considerable heterogeneity of study designs and characteristics, limited sample sizes, and missing data—in accordance with a mean NOS score of 5.0 from 9.0 (Table V)—pooling all individual patient data and analyzing this pooled dataset descriptively was preferred over conducting a meta-analysis. Due to the pooling, however, some caution is required when interpreting the summary descriptive statistics. Therefore, these statistics might be interpreted as a rough indicator rather than unbiased and precise estimates. Nevertheless, the findings of the present review may point to interesting trends that warrant a comprehensive evaluation in future research.

A methodical limitation results from the exclusion of individuals from analysis with adult onset of hearing loss, based on the predefined study protocol. Therefore, a relevant amount of data on hearing loss characteristics in MD is missing.

Hearing Loss and Hearing Rehabilitation in Children with MD

Based on the analysis of $n = 23$ studies included, both types of hearing loss, for example, cochlear and retro-cochlear type, may be identified among patients with MD (Tables II and IV). Taking into account that MD-associated HL has been considered mainly of cochlear origin,[5,6,13,37,38,50] the number of genetic variants associated with retro-cochlear hearing loss identified in this analysis appears high ($n = 8$) (Tab. IV). However, authors like Gold et al.[11] have reported of a mixed type of hearing loss in patients with MD, and in recent year there has been a growing number of authors reporting on MD patients with hearing loss originating from any structure central to the cochlea.[29,37] Authors mainly referred to a publication by Starr et al. from 1996,[15] describing auditory characteristics of AN in detail.

Variation of the origin of HL was not only identified in-between different MDs, but also among patients with the same gene affected (Tables II and IV). Many authors argue that malfunction of mitochondria affects the most energy dependent tissues, like hair cells of the cochlea,[5] prompting the question, why an identical genetic variant in different individuals, causing the same energy deficit, can lead to different phenotypes? Possible explanations include the existence of heteroplasmy (percentage of mitochondria with mutated mtDNA), or specific distribution of mutated mtDNA to certain tissues, but the pathogenesis is not completely understood as of yet.[51] This observed variability of the phenotype within MD patients is also seen in other organ systems (Table III).

Contrary to pre-analytic assumptions, the majority of studies published reported an onset of HL in adulthood. However, because the focus of this systematic review is on the paediatric population (Table I), analysis of hearing loss description was done for both effective time of diagnosis and effective time of onset. Therefore, both time points are displayed in Table II, and individual adult patients with reliable onset of hearing loss during childhood were included for analysis. The majority of publications included ($n = 18$) reported on a post-lingual onset of hearing loss. Mean age at onset for 70 individuals analyzed in this review ranged from 0 to 16.0 years, supporting the general assumption of postlingual onset. Congenital hearing loss was described in patients with variants of *PC* ($n = 1$ patient), *SERAC1* ($n = 6$ patients), *RRM2B* ($n = 2$ patients), and *SUCLG1* ($n = 1$ patient) (Table II).

Severity of hearing loss, reported in $n = 18$ articles (Table II), varied from mild to profound. Considering the fact that most articles reported on a specific point in time, a general assumption on severity cannot be made. Normal pure tone hearing thresholds were mostly found in patients, diagnosed with retro-cochlear origin of hearing loss, in accordance with other publications.[10,33,43]

Although hearing loss related to MD has usually been described as progressive,[11,52] the information on hearing loss characteristics extractable from the included studies referred mainly to clinical course and onset. The assumption of general progression could not be reproduced, as the majority of publications reported on a specific point in time. A certain period of follow-up was reported in at least six studies (see Table V), showing the potential for a progressive HL. Possible deterioration of hearing should not only instigate a constant observation and care of affected patients but also the variety of the age of HL onset. With a possible symptom onset at any age and no known factors to influence HL, regular surveillance of hearing levels from birth to adulthood seems reasonable in cases of MD.

To allow for adequate hearing rehabilitation, exact diagnosis and topographic classification of HL represent a prerequisite. The distinction between HL resulting from cochlear, or further centrally located structures (retro-cochlear), has a serious impact on subsequent therapeutic interventions. Hearing aid trials should be provided in any type of hearing loss, even though hearing aid fitting may be more difficult in case of a retro-cochlear origin, due to altered ABR results and dependence on behavioral testing.[53] Moreover, the efficacy of hearing rehabilitation through hearing aids may be reduced in case of a retro-cochlear origin.[54] However, prior to invasive steps, such as cochlear implantation (CI), hearing aid trials are recommended.[55] In spite of expected similar restrictions in the case of CI performance in children with retro-cochlear HL, results show at least comparable results to those with HL of cochlear origin.[56] A possible explanation is a further differentiation within retro-cochlear HL between synaptic and neural site of origin,[57] with the synaptopathy being located close enough to the cochlea and

therefore allowing for promising CI results.[58] However, the availability of data does not allow for a clear statement whether synaptopathy is frequently present in MD or not. This observation needs to be incorporated into future evaluation of CI outcome in MD patients with proven retro-cochlear origin of HL. Taken together, careful consideration of potential risks and benefits of CI prior to surgery is mandatory, especially in a vulnerable population such as pediatric patients with MD presenting with multisystem disorders (Table III) and associated potential risks during anesthesia.[59]

Six studies reported on applied hearing rehabilitation in individuals were included for analysis (Table II). Eight individuals were treated with hearing aids and four with cochlear implants. Statements on success of hearing rehabilitation were mainly found in CI patients with retro-cochlear HL due to *OPA1* variants ($n = 3$).[35,45]

Missing Information

Contrary to our expectations, only 23 of the 984 articles included in the primary search met the criteria for further evaluation and analysis. Even though HL is one of the most commonly described symptoms in MD, it has not often been the focus of scientific reports. This may be due to accompanying life-threatening symptoms in MDs attracting more attention,[10] or the fact that most of the identified studies are not published in journals for otolaryngology. The main reasons for the exclusion of specific reports were insufficient measurement and testing of hearing, or the lack of an adequate description of results. Frequently, only basic or no audiometric data were available, whereas nonspecific terms such as sensorineural hearing loss were used for both cochlear and retro-cochlear HL, and if brainstem evoked response audiometry (BERA) or ABR was apparent, their description often simply consisted of statements like "abnormal" or "missing" without further characterization.

Relevant Diagnostics

To discriminate objectively the origin of HL, the performance of a BERA (also referred to as ABR) is necessary. Especially when dealing with pediatric patients, assessment relies on independent measurement, and speech audiometric testing is not suitable for this population. A further fact underlining the need for objective measurement is a potential underestimation of retro-cochlear hearing loss, which may appear clinically inconspicuous while consequently delaying detection time.[16] In the case of conspicuous BERA results, further testing via otoacoustic emissions (OAEs) or cochlear microphonics (CM) is required to distinguish between a retro-cochlear from a cochlear malfunction. Although OAEs are easy to perform, they only provide information about the outer hair-cell function.[15] CM, however, which can be obtained during BERA[15] as presynaptic potentials during monopolar stimulation (rarefaction/condensation), seems to be a more robust indicator for outer hair cell function compared with OAEs.[60] Detectable OAE or CM in combination with prolonged BERA latencies or absent potentials are pathognomonic for disturbances of the retro-cochlear auditory pathway, referred to as AN.[15] Further measurements, providing additional information for differentiation, like stapedial reflex testing, including reflex thresholds[61] might provide additional information for differentiation.

Proposed Consequences

To gain more information and experience in MD patient care, an interdisciplinary and standardized diagnostic approach, following standardized reporting, needs to be established, preferably including centers with large case numbers. Our opinion is in accordance with a recently published article by Qian et al.,[62] emphasizing the need of standardization in diagnostic workup for children with hearing loss. Concerning reporting of mitochondrial disease, molecular diagnostics, identifying individual genetic background needs to be clearly stated. Sole description of clinical phenotype does not allow for any assumptions. Description of hearing loss must, at a minimum include, the date of onset, date of diagnosis, performance and reliable description of evoked potential measurements, including CM, and performance of OAE measurements. We further recommend reporting absolute latency numbers for waves I, III, and V given in milliseconds, interpeak latencies for waves I and V given in milliseconds, stimulus levels given in decibels, and amplitudes of waves given in microvolts, for different levels, compared with normative values, for example, provided by Chalak et al.[63]

Moreover, terminology for hearing loss description needs to be conclusive, avoiding unclear phrasing like "sensorineural" in this context. Finally, meaningful data on clinical course and hearing rehabilitation rely on long-term follow-up or further reports on cases already published. Based on our experience gained during the review process and its results, we would like to provide a proposal for a checklist for future investigations and reporting on the topic, including recommendations for diagnosis of mitochondrial disease, as well as for hearing testing in pediatric patients with potential retro-cochlear hearing loss. This checklist is included as Supplemental Material.

CONCLUSION

Hearing loss in children with mitochondrial disease shows manifold characteristics, especially with regards to type of hearing loss, onset, and severity. Retro-cochlear hearing loss seems to be more frequently found in these patients than expected, and therefore needs to be specifically addressed during diagnostic workup. A common feature appears to be overall progression over time. This phenotypic heterogeneity may hinder straightforward diagnosis of MD, and awareness of this possible causative background is important for otolaryngologists for further interdisciplinary workup.

To broaden knowledge and ultimately improve patient care, consistent diagnostics for definition and description of mitochondrial disease and hearing loss need to be

established. Finally, long-term observation of patients affected needs to be performed prospectively to evaluate hearing rehabilitation approaches.

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