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Hearing rehabilitation in *SERAC1* related MEGD(H)EL syndrome – implications from a multi-center retrospective cohort study☆,☆☆

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ABSTRACT

Objective: 3-methylglutaconic aciduria (MEG), dystonia-deafness (D), (hepatopathy (H)), encephalopathy (E), and Leigh-like-syndrome (L) (MEGD(*H*)EL) syndrome is a rare, severely disabling progressive mitochondrial disease associated with biallelic pathogenic variants in *SERAC1*. Knowledge about hearing loss (HL) and hearing rehabilitation is scarce but highly sought after for best possible care in the absence of causative treatment.
Methods: Retrospective cross-sectional study.
Results: This study analyzed the audiometric data of 36 MEGD(*H*)EL patients (14 unpublished). Bilateral HL was diagnosed in 31 individuals (86 %). Detailed audiometric data, available for 23 of 31 patients, did not allow for general statements on site and degree of HL. HL was mostly congenital ($n = 14/31$), pre-lingual in six and post-lingual in nine cases (median age 2 years, $n = 15/31$; age unknown in $n = 2$).
In four of the five patients without HL, the severity of the other clinical-neurological symptoms was milder and less progressive, and their onset was significantly later than in the patients with HL. Five of 36 patients acquired spoken language, these were 4 of the 5 individuals without and one with HL. Twenty-two individuals received hearing rehabilitation with conventional hearing aids, followed by cochlear implant (CI) surgery in six. One of these six individuals acquired spoken language, which lessened in clarity as disease progressed.
Conclusions: Congenital HL represents a ubiquitous symptom in severe types of MEGD(*H*)EL syndrome, being absent in late onset milder forms. Regularly, severely affected MEGD(*H*)EL patients do not achieve spoken language, even with CI. Hence, hearing rehabilitation with CIs needs to be discussed very critically.

1. Introduction

MEGD(*H*)EL syndrome (3-methylglutaconic aciduria (MEG), dystonia, deafness (D), (hepatopathy, (H)) and encephalopathy (E), Leigh-like syndrome (L), MIM #614739) is associated with biallelic pathogenic variants in *SERAC1*. It is a rare, progressive mitochondrial phospholipid remodeling disease. The pathomechanism leading to the clinical phenotype is unknown, and it is thought that impaired lipid trafficking between cell structures in the organ of Corti, the auditory pathway and the auditory cortex underlies the hearing loss (HL) [1].

The spectrum of disease ranges from the (up to now) most frequently diagnosed severe neonatal onset type (nearly 100 patients published) that often leads to death in childhood [2–5] to single cases with milder phenotypes with adolescent or even adult onset of symptoms (10 patients published) [6–9] and no HL [7–10]. The course of disease is devastating in the vast majority of patients. They show severe global developmental delay/intellectual deficiency and regularly do not reach independent sitting or walking or lose it shortly after learning. Regularly, they suffer painful and progressive dystonia. Additionally, their swallowing is impaired due to dysphagia, dystonia and drooling, necessitating tube feeding. Nearly all patients do rely on all-encompassing support for all activities of daily living by caregivers.

Little is known about the specific type of HL in MEGD(*H*)EL patients, often it is reported to be congenital and even children with hearing aids (HAs) or cochlear implants (CIs) do not achieve verbal communication [4]. In view of the severe neurological impairments associated with the condition, it seems understandable that the causes for a lack of (verbal) communication go beyond those of a mere hearing loss.

In the absence of a curative treatment, decisions regarding supportive management need to be carefully weighed, particularly when considering invasive interventions. Common interventions address symptoms like dysphagia, dystonia, excessive drooling or hearing impairment [4,5].

Here we analyze data on hearing abilities and hearing rehabilitation in an international cohort of 36 patients with MEG(*H*)DEL syndrome in order to aid future decision-making, especially regarding CI surgery.

2. Material and methods

For this multicenter retrospective chart review we identified eligible individuals via international collaboration and by contacting authors who had published cases. Inclusion criteria were (likely) pathogenic variants in *SERAC1* in accordance with American College of Medical Genetics and Genomics (ACMG) criteria [11,12]. Collaborators provided pseudonymized data using a case record form, including data on sex, age, genotype, clinical phenotype, results of hearing diagnostics, type of hearing rehabilitation and information on outcome of hearing rehabilitation. Reported success of hearing rehabilitation was categorized in reference to [13], who reported on qualitative benefits of CIs, adapted to [14], for use in children with multiple handicaps. Additionally, audiometric data were requested.

The data was analyzed using descriptive statistics. This study was approved by the Institutional review board of Paracelsus Medical University Salzburg (SS22–0010-0010).

3. Results

We included 36 individuals (21 female) of which 14 (#2, 8, 10, 11, 12, 14, 18, 20, 21, 27, 29, 30, 33, 34) are unpublished and 22 have previously been reported [2,4,6,15–19]. The clinical and hearing-related data are summarized in Tables 1 and 2, Table 3 shows the genotypes.

Thirty-three patients had the classical, neonatal or infantile presentation of MEGD(*H*)EL syndrome and a progressive course of disease, leading to death in 17 of them. The age of last follow-up ($n = 18$, median = 8.5 years [1–36 years]) or the age at death ($n = 11$, median = 8.0 [4–13 years]), respectively, was known for 29 patients.

For three patients, onset of symptoms was reported in adolescence (14 years in #11, 32) and one during adulthood (24 years, #31) (Table 1).

Detailed audiometric information beyond the sole existence of an investigation was available in ten individuals, of which only seven had multiple time point assessments. A statement regarding the site of hearing malfunction along the auditory pathway could not be made, due to diversity of results. However, it becomes clear that MEGD(*H*)EL patients suffer from simultaneous or consecutive damage to the receptor (the cochlea) and/or retro-cochlear / central structures.

The following three cases (#3, 12, 13) concisely represent the

[1] Authors contributed equally.

Table 1
Details on clinical phenotype, hearing loss and hearing rehabilitation.

ID#	HL	NB Hearing Screening	Age at dx HL	Degree of Hearing Loss	Audiometric Testing	Speech acquisition	Type Rehabilitation	Current Use	Category of Benefit**	Current Age (y)	Clinical Phenotype (Age at presentation (y))	Previous Publications
1	Yes	Pass	2 y (postL)	propfound, bilateral	ECHOG, ABR	No	HA	User	1	7 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.5)	[3]: Pat ID #59
2	Yes	N/A	1 y (preL)	moderate, bilateral	ABR	No	N/A	N/A	N/A	4 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.9)	Unpublished
3	Yes	Pass	2 y (postL)	profound, bilateral	OAE, ABR, SR	No	HA	User	1	9 y	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #57
4	Yes	Pass	1 y (preL)	profound, bilateral	OAE, ABR, SR	No	CI	N/A	N/A	N/A*	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	[30]: no ID
5	Yes	N/A	1 y (preL)	N/A	OAE, ABR, SR	No	None	n.a.	n.a.	N/A*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (infantile)	[3] Pat ID #56
6	Yes	Failed	9 m (c)	profound, bilateral	OAE, ABR, SR	No	HA	User/Non-user	1	N/A*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #10; [1]: Pat ID #10; [12]: Pat ID #8
7	Yes	Failed	3 m (c)	N/A	OAE, ABR, SR	No	None	n.a.	n.a.	N/A*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #24; [12]: Pat ID #12
8	Yes	Failed	1 y (c)	profound, bilateral	OAE, ABR, SR	No	HA	Non-user	1	15 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
9	Yes	Failed	1 y (c)	profound, bilateral	OAE, ABR, SR	No	HA	User/Non-user	1	N/A	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #11; [12]: Pat ID #21; [1]: Pat ID #11
10	Yes	Failed	6 w (c)	profound, bilateral	OAE, ABR, SR	No	CI	User/Non-user	1	5 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
11	No	N/A	n.a.	n.a.	OAE, ABR, PTA, SA	Yes, verbal communication	n.a.	n.a.	n.a.	22 y	MEG, axonal neuropathy l.l. (14)	Unpublished
12	Yes	Failed	6 w (c)	profound, bilateral	OAE, ABR, SR	No	HA	User/Non-user	1	8 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
13	Yes	Pass	12 y (postL)	profound, bilateral	OAE, ABR, SR	No	HA	User/Non-user	n.a.	N/A*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #37; [12]: Pat ID #24
14	Yes	Failed	4 w (c)	severe, bilateral	ABR	No	CI	User	1	7 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.3)	Unpublished
15	Yes	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	10 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.4)	[1]: Pat ID #1; [3]: Pat ID #1
16	Yes	N/A	4 y (postL)	N/A	ABR	No	HA	N/A	N/A	25 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.4)	[1]: Pat ID #3; [3]: Pat ID #1
17	Yes	Failed	6 w (c)	N/A	N/A	No	HA	Non-user	n.a.	4 y*	MEG-D-H-E-L, hypo, spast, dys, DD, ID (1)	[3]: Pat ID #29; [12]: Pat ID #10
18	Yes	Pass	1.5 y (postL)	severe, profound	OAE + ABR	No	N/A	N/A	N/A	5 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished (sibling of #20)
19	Yes	Pass	N/A	N/A	N/A	No	N/A	N/A	N/A	13 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (0.75)	[13]; [3]: Pat ID #35
20	No	Pass	n.a.	n.a.	OAE, SR	No	n.a.	n.a.	n.a.	11 y	MEG-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished (sibling of #18)

(*continued on next page*)

Table 1 (*continued*)

ID#	HL	NB Hearing Screening	Age at dx HL	Degree of Hearing Loss	Audiometric Testing	Speech acquisition	Type Rehabilitation	Current Use	Category of Benefit**	Current Age (y)	Clinical Phenotype (Age at presentation (y))	Previous Publications
21	Yes	N/A	7 y (postL)	moderate left; deafness right	PTA, ABR	No	HA	User	1	10 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
22	Yes	Failed	1.5 y (c)	N/A	N/A	No	HA	N/A	N/A	N/A*	MEG-D-H-E-L, hypo, spast, dys, DD, ID (0.75)	[3]: Pat ID #16; [12]: Pat ID #11
23	Yes	Pass	3 y (postL)	severe, bilateral	ABR, BA, SR	No	CI	Non-user	1	11 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #28; [12]: Pat ID #19
24	Yes	Failed	3 m (c)	profound, bilateral	OAE, ABR	No	HA	User / Non-user	N/A	5 y*	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #19; [12]: Pat ID #6
25	Yes	Failed	9 m (c)	profound, bilateral	OAE, ABR	No	HA	User	N/A	13 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (infantile)	[3]: Pat ID #9; [12]: Pat ID #16; [1]: Pat ID #9
26	Yes	N/A	6 m (preL)	moderate right; N/A left	OAE, BA, ABR	No	HA	User	1	8 y*	MEG-D-H-*E*-L, hypo, spast, DD, ID (infantile)	[3]: Pat ID#36; [12]: Pat ID #23 (sibling of #27)
27	Yes	Pass	6 m (preL)	moderate, bilateral	OAE, BA, ABR	No	HA	User / Non-user	1	8 y	MEG-D-H-*E*-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished (sibling of #26)
28	Yes	N/A	10 m (preL)	N/A	PTA, OAE	No	None	n.a.	n.a.	10 y*	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	[3]: Pat ID #18
29	Yes	Failed	3 w (c)	severe, bilateral	OAE, ABR, BA	No	CI	User	1	5 y*	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
30	Yes	Failed	1 y (c)	severe, bilateral	ABR	No	HA	User	1	8 y	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
31	No	N/A	n.a.	n.a.	PTA	Yes, verbal communication	n.a.	n.a.	n.a.	36 y	E-L, spast, dys, DD, ID (24)	[5]
32	No	N/A	n.a.	n.a.	N/A	Yes, verbal communication	n.a.	n.a.	n.a.	24 y	MEG-E-L, spast, dys, DD, ID (14)	[14]
33	No	Pass	n.a.	n.a.	N/A	Yes, verbal communication - beginning at 13 m, complex sentences at 2 y	n.a.	n.a.	n.a.	9 y*	MEG-E-L, hypo, spast, dys, DD, ID (infantile)	Unpublished
34	Yes	Pass	4 y (postL)	moderate, bilateral	ABR	No	N/A	N/A	N/A	4 y	MEG-D-H-E-L, hypo, spast, dys, DD, ID (neonatal)	Unpublished
35	Yes	Failed	1 w (c)	N/A	N/A	No	HA	User	1	1 y	MEG-D-H-E-L, hypo, spast, DD, ID (neonatal)	[15]: Pat ID #1
36	Yes	Pass	2 y (postL)	severe, bilateral	OAE, BA	Yes, verbal communication - beginning at 20 m, short sentences at 7 y	HA left; CI right	User	2	8 y	MEG-D-H	[16]: no ID

HL = hearing loss; NB = newborn; dx = diagnosis; w = weeks; m = months; y = years; c = congenital; preL = pre-lingual; postL = post-lingual; ECHOG = electrocochleography; ABR = auditory brainstem response; SR = stapedial reflexes; PTA = pure-tone audiometry; SA = speech audiometry; BA = behavioral audiometry; HA = hearing aid; CI = cochlear implant; N/A = not available; n.a. = not applicable; **current use and category of benefit reported by caretakers, according to (25) 1 = Improved awareness to environmental sounds, 2 = Development of speaking skills; MEG = 3-Methylglutaconic aciduria; D = deafness; H = hepatopathy; E = encephalopathy; L = Leigh-like syndrome; hypo = muscular hypotonia; spast = progressive spasticity; dys = dystonia; DD = developmental delay; ID = intellectual disability; l.l. = lower limbs.

complexity of HL and its diagnosis observed in this cohort, based on the analysis of detailed clinical and audiometric data (Table 2).

Patient #3 passed newborn hearing screening (NBHS). He initially presented with audiometric findings suggestive for moderate cochlear sensorineural HL during objective measurements with audiometric brainstem responses (ABR) at the age of two years. He was fitted with HAs, accordingly. During repeated follow-up, ABR waves progressively desynchronized and gave hint for simultaneous impairment of central processing. He did not acquire verbal communication.

Patient #12 failed during NBHS (OAE). Objective testing with ABR at the age of 7 weeks confirmed sensorineural HL, which continuously worsened until the age of 10 months, where the typical morphology of ABR waves disappeared completely, going along with the absence of any reaction to sound with fitted HAs. He did not acquire verbal communication.

Patient #13 passed NBHS and had early normal hearing screening results but showed inconsistent reactions to sounds at the age of three years. Objective measurements (ABR) revealed inconclusive results due to severe neurological symptoms, including epilepsy and sleep disturbances. Reliable audiometric assessment was not possible until the age of 12 years, where OAE, stapedial reflexes, as well as brainstem and upper hearing pathway responses were absent. He did not acquire verbal communication.

3.1. Prevalence of hearing loss

Hearing loss, bilateral in all cases, was reported in 31/36 individuals (86 %) (Table 1). Of the 5 patients without HL, three were milder cases with adolescent/adult onset of disease (#11, 31, 32). One patient (#20, sibling of #18 with HL) had a neonatal onset of disease and did not acquire speech despite normal hearing abilities (OAE, pure-tone audiometry) until his current age of 11 years. The fifth case without HL (#33) passed NBHS and showed age-adequate speech development (first words with 13 months). He was able to speak in sentences by the age of 2 years, though difficult to understand for strangers due to dysarthria. However, his speech worsened subsequently as did his dystonia and dysarthria, leading to death at the age of 9 years.

3.2. Age at hearing loss

The age at diagnosis of HL was known for 29 of 31 patients (Table 1). For 23 of these, data on NBHS were available. In 14 of these cases a failed NBHS was documented, hence the onset of HL can be considered congenital even when the formal diagnosis was made later. In six children, HL was diagnosed until the age of one year (with reported passed NHBS in $n = 2$), hence considered pre-lingual and mirroring progression of disease. For another nine patients (with reported passed NBHS $n = 7$), HL was diagnosed between 1.5 and 12 years (median age 2 years), again in line with a progressive course of disease.

3.3. Hearing rehabilitation

Of the 31 individuals with HL, 23 children received some form of hearing rehabilitation, three individuals did not receive any type of therapy, no data were available for the remaining five. All 23 patients received conventional HAs initially, later six of them underwent CI surgery (5 unilateral, 1 bilateral) (Table 1) as HAs were considered unsuccessfully fitted. The age at CI, available for four of six patients, ranged from 2.5 to 4.5 years.

Three of the six patients with CIs had deceased at the time of data collection. The other three children were still alive, aged five, six and seven years (#10, 14, 36). The period of reported follow-up has been eight weeks in one child (#23) and one year in another (#29), with a maximum of five years in one child with CI (#36).

Thirteen individuals (13/17, 76 %) supplied with HAs were reported active users during daily routine or at least initial users, four individuals with CI were reported users (4/6, 66 %), one of those became a subsequent non-user (#10). Only for patient #36, data logging reports of the CI device were available, with a daily usage of about 3 to 4 h.

The reported usage in four CI recipients allows at least the assumption of an effective rehabilitation by means of behavioral observations. In one patient (#23), supported with CI bilaterally at the age of three years, behavioral pure-tone audiometry in free-field showed traceable benefit, eight weeks after activation of the implant. None of the patients with CI acquired verbal communication, with exception of one individual (#36), who has been supplied with HAs and subsequently with a CI on the right side. She developed spoken language up to the age of eight years from where these skills deteriorated again. During this phase of losing verbal competences, she continued using her CI, which was perceived as clearly supporting quality of life according to relatives and caretakers.

Among all individuals with any hearing rehabilitation, the number of reported users or non-users, including consecutive non-users, is equal with $n = 10$ (for three individuals, data on usage were not available) (Table 1). Besides patient #36, none of these patients developed any form of communication, including spoken language, independent from type of hearing rehabilitation applied. Secondary development of alternative modes of communication like gestures, use of sign-language or use of devices, as well as improved communication with caregivers were not reported. The main benefit identified by investigators and caretakers was an improved awareness to environmental sounds, irrespective of the type of intervention used (Table 1).

4. Discussion

We designed this study to provide evidence-based answers to the many colleagues inquiring about CI in patients with biallelic *SERAC1* variants. We intended to collect and analyze detailed data on hearing abilities in these individuals. However, the audiometric data available turned out to be rather shallow and diverse. Moreover, audiometric assessment in many cases was done only once or twice, not allowing for

Table 2
Detailed audiometric data at hand for three exemplary individuals (# 3, 12, 13).

ID#	NB Hearing Screening, Interpretation	Age at diagnosis of HL	Audiometric Test Modality, Interpretation, Age at testing	Audiometric Test Modality, Interpretation, Age at testing	Audiometric Test Modality Interpretation Age at testing	HA Fitting Age	HA Referral Age
3	OAE, Pass	2 y	Click ABR, Moderate HL, 2 y	Click ABR, Progressive HL with neuropathic features, 3 y	VRA Profound HL 3 y	2 y	.
12	OAE, Failed	3 w	Click ABR, AI, OAE, Moderate HL, 3 w	Click ABR, Desynchrony of ABR waves, 7 w	Click ABR, VRA, ABR waves disappeared, Profound HL, 10 m	10 m	<1.5 y
13	OAE, Pass	12 y	Click ABR; OAE, ASSR, MMN, No responses at all, 12 y	.	.	12.5 y	13 y

HL = Hearing loss, OAE = Otoacoustic Emission, w = weeks; m = months; y = years; ABR = Auditory brainstem response, VRA = Visual reinforcement audiometry, AI = Acoustic impedance, ASSR = Auditory steady state response, MMN = Mismatch Negativity, HA = Hearing aid.

Table 3
Genotypes and variant interpretation.

ID#	Gender	*SERAC1*, NM_032861.4 (NP_116250.3) VARIANT 1	ACMG rating	ACMG categories	VARIANT 2	ACMG rating	ACMG categories	New Variant (s)	Previous Publications
1	F	c.916C > T (p.Arg306Ter)	P	PVS1, PM2, PP4	c.1493G > C (p.Ser498Thr)	LP	PM2, PM3, PP3, PP4	No/No	[4]: Pat ID #59
2	F	c.1403 + 200 A > G (p.?)	LP	PM2, PP4	homozygous	.	.	Yes	Unpublished
3	M	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #57
4	M	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[30]: no ID
5	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #56
6	F	c.1309_1313dup (p.Trp438Ter)	P	PVS1, PM2, PP4	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	No/No	[4]: Pat ID #10; [2]: Pat ID #10; [15]: Pat ID #8
7	M	c.1642dup (p.Tyr548LeufsTer20)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #24; [15]: Pat ID #12
8	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	Unpublished
9	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	c.1924C > T (p.Gln642Ter)	P	PVS1, PM2, PP4	No/No	[4]: Pat ID #11; [15]: Pat ID #21; [2]: Pat ID #11
10	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	Unpublished
11	M	c.538G > T (p.Gly180Cys)	LP	PM2, PM3, PP3, PP4	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	Yes/No	Unpublished
12	F	c.916C > T (p.Arg306Ter)	P	PVS1, PM2, PP4	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	No/No	Unpublished
13	M	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #37; [15]: Pat ID #24
14	F	c.1765G > A (p.Glu589Lys)	LP	PM2, PP3, PP4	homozygous	.	.	Yes	Unpublished
15	F	c.1167_1170 del (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[2]: Pat ID #1; [4]: Pat ID #1
16	F	c.442C > T (p.Arg148Ter)	P	PVS1, PM2, PP4	homozygous	.	.	No	[2]: Pat ID #3, [4]: Pat ID #1
17	F	c.916C > T (p.Arg306Ter)	P	PVS1, PM2, PP4	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	No/No	[4]: Pat ID #29; [15]: Pat ID #10
18	M	c.903del (p.Gln302ArgfsTer17)	P	PVS1, PM2, PP4	c.1122_1124dup (p.Tyr375Ter)	P	PVS1, PM2, PP4	Yes/Yes	Unpublished
19	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	No	[16]; [4]: Pat ID #35
20	M	c.903del (p.Gln302ArgfsTer17)	P	PVS1, PM2, PP4	c.1122_1124dup (p.Tyr375Ter)	P	PVS1, PM2, PP4	Yes/Yes	Unpublished (sibling of #18)
21	F	c.438del (p.Thr147ArgfsTer22)	P	PVS1, PM2, PP4	homozygous	.	.	Yes	Unpublished
22	M	c.202C > T (p.Arg68Ter)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #16; [15]: Pat ID #11
23	F	c.763_770dup (p.Pro258MetfsTer22)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #28; [15]: Pat ID #19
24	M	c.1339C > T (p.Arg447Ter)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #19; [15]: Pat ID #6
25	M	c.1598_1599ins17 (p.Gly536IlefsTer56)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID #9; [15]: Pat ID #16, [2]: Pat ID #9
26	F	c.1112_1113delTG (p.Val371AlafsTer22)	P	PVS1, PM2, PP4	homozygous	.	.	No	[4]: Pat ID#36; [15]: Pat ID #23
27	M	c.1112_1113delTG (p.Val371AlafsTer22)	P	PVS1, PM2, PP4	homozygous	.	.	No	Unpublished (sibling of #26)
28	F	c.1822_1828 + 10delinsACCAACAGG (p.?)	P	PVS1, PM2, PP4	del exon 4–8	P	PVS1, PM2, PP4	No/No	[4]: Pat ID #18
29	M	c.1643_1646dupATCT (p.Leu550SerfsTer19)	P	PVS1, PM2, PP4	homozygous	.	.	Yes	Unpublished
30	F	c.1403 + 1G > C (p.?)	P	PVS1, PM2, PP4	homozygous	.	.	Yes	Unpublished
31	M	c.1347_1350dupATCT (p.Val451IlefsTer5)	P	PVS1, PM2, PP4	c.1598C > T (p.Pro533Leu)	LP	PM2, PM3, PP3, PP4	No/No	[6]
32	F	c.1916 G > C (p.Arg639Pro)	LP	PM2, PM3, PP3, PP4	del exon 9–10	P	PVS1, PM2, PP4	No/No	[17]
33	M	c.227_228dup (p.Val77MetfsTer7)	P	PVS1, PM2, PP4	c.548G > A (p.Arg183Gln)	LP	PM2, PP3, PP4	Yes/Yes	Unpublished
34	M	c.277C > T (p.Gln93Ter)	P	PVS1, PM2, PP4	homozygous	.	.	Yes	Unpublished
35	F	c.1920_1924dupTTTAC (p.Gln642LeufsTer9)	P	PVS1, PM2, PP4	homozygous	.	.	No	[18]: Pat ID #1
36	F	c.1601A > T (p.His534Leu)	LP	PM2, PM3, PP3, PP4	del exon 2–4	P	PVS1, PM2, PP4	Yes/Yes	[19]

detailed objective measurement or continuous follow-up. A key factor contributing to this lack of data at hand may be the general severity of disease, attributing the symptom of hearing loss less relevant in comparison to other symptoms perceived as more "important". Of note, almost half of the patients reported had died already during infancy and affected individuals regularly completely relied on their caretakers for any daily routine. Any additional investigation represents a vast effort.

There are several reports on successful hearing rehabilitation through cochlear implantation, mainly in adults individuals with other types (mostly m.3243 A > G related) of mitochondrial disease with a less severe course than seen in MEGD(*H*)EL syndrome and a post-lingual HL [20–24]. This may have risen hope that hearing rehabilitation may improve quality of life in MEGD(*H*)EL patients, too. Based on our results, CI surgery in this fragile patient group needs to be handled with care. Hearing rehabilitation led to speech acquisition in only one individual with post-lingual HL in our group (Fig. 1).

Audiometric features of MEGD(*H*)EL individuals include unique and variable aspects of HL. At first, hearing screening tests, performed in a newborn period, may show normal results. Subsequent objective measurements show features of auditory neuropathy spectrum disorder (ANSD) or retro-cochlear impairment [1]. Auditory neuropathy in MEGD(*H*)EL syndrome develops secondarily to degenerative changes in the central nervous system and leads to progressive hearing deterioration. In affected patients, ABR responses are usually absent from early stages of the disease, which may impair assessment of extent of hearing loss. MEGD(*H*)EL patients may exhibit absence of otoacoustic emissions either before or after the diagnosis of auditory neuropathy. This may lead to the assumption that an individual suffers from sensorineural hearing loss of cochlear origin. However, since *SERAC1* has impact on intracellular cholesterol homeostasis in any tissue, including the cochlea and the auditory nerve [1,4], simultaneous constraint may be expected. Therefore, hearing levels used for the definition of degree may vary significantly and may be transient in case of ANSD [25]. Degrees of hearing loss displayed in Table 1 are based on site-specific interpretation and reports of individual audiometric results, at hand.

Assessment of reaction to sounds in MEGD(*H*)EL patients is challenging due to impaired sound perception and to neurological limitations related to the simultaneous development of extrapyramidal symptoms including spasticity, dystonia, hypersalivation, low facial expression etc. Most patients also do not use natural gestures and have poor non-verbal communication based on low facial expression. Ultimately, the multifactorial nature of hearing impairment in MEGD(*H*)EL syndrome, involving neuronal pathways, the central nervous system, receptor damage in the inner ear, and the broader context of a progressive neurological disorder, does not allow for a clear definition of the extent of HL in many cases. The phenomenon of the retro-cochlear damage is closely related with a sequence of very specific changes in the brain of MEGD(*H*)EL patients, which were observed and described based on subsequently performed brain MRI examinations. The results of the brain MRI revealed atrophic changes, involving basal ganglia, with a development of typical picture called "putaminal eye" [15]. Basal ganglia function is necessary for speech perception and learning [26,27].

Early diagnosis, based on NBHS and concise audiometric follow-up, allows for early rehabilitation, which comprises HA fitting as an initial step. Since speech perception and speech development will not be achieved due to severity of disease in nearly all patients, hearing aids may at least support non-verbal communication and awareness to environmental sounds as seen in our cohort. The additional effort of audiometric testing needs to be explained and discussed with parents, to emphasize the potential advantage of sensory input for the child through hearing rehabilitation [13,28]. However, acquisition of repeated objective data on hearing abilities for fitting purposes represents a major challenge, especially in severely and multiply diseased individuals, as stated before. Moreover, concomitant development of neurological problems, typical for MEGD(*H*)EL syndrome, may result in a deterioration of patients' auditory discrimination and a weakening of habitual response like movement or facial expression in response to environmental sounds.

Seventeen individuals with hearing loss were fitted with conventional hearing aids for rehabilitation, with twelve (70 %) of them being users or at least initial users (Table 1). This finding provides at least a subtle clinical hint for an initial temporary benefit of hearing aids in MEGD(*H*)EL patients.

Six patients underwent CI surgery. Each individual decision for CI was based on a progressive, profound hearing loss, with insufficient supply through conventional HAs and the lack of convincing literature data on unsatisfactory results of CI in MEGD(*H*)EL patients. Surgery was uneventful in five cases. In one case, intraoperative resuscitation was successfully carried out due to an unreproducible cause. Patient #36 with a moderate to severe phenotype developed spoken language as a result of bimodal rehabilitation with a HA on the left and a CI on the right side. Improved reaction to sound was successfully achieved in all patients, at least (Table 1). It remains unclear whether potential benefits of CI have been negatively impacted by cognitive impairment and progressive symptoms due to primary disease [21], going along with an impairment of central auditory processing. Parents of three patients were generally reserved when asked to provide feedback on their children's CI surgery. However, parents of individual #36 clearly have seen their decision in favor of a cochlear implant confirmed, even though verbal output has decreased over time. Attending staff of individual #36 stated that decision for CI was based on detailed pre-operative counselling including not only audiometric diagnostics and criteria but also speech-language and neuropsychological evaluations. The patient actively participated in these investigations.

When considering these various clinical courses, individual counselling and distinct pre-operative education on realistic assumptions concerning outcome is mandatory when CI supply is taken into consideration in this severely diseased group of patients.

The number of non-users and subsequent non-users is high in both the HA and the CI group – 8/17 (47 %) and 2/6 (33 %), respectively (Table 1). This represents a further clinical, indirect hint for the complexity of hearing deprivation, which takes place progressively and may not be compensated by neither HAs nor CIs in many cases.

In general, hearing rehabilitation in MEGD(*H*)EL patients appears rather challenging and unsuccessful in comparison to hearing-impaired, non-MEGD(*H*)EL peers. The general goal of hearing rehabilitation in children is development of spoken language, a goal which is not realistic for children with MEGD(*H*)EL syndrome. Therefore, outcome measures in affected children might need to be adapted [29] to include parent-, caregiver-, and healthcare provider-reported qualitative outcome measures of benefit and function.

Finally, MEGD(*H*)EL syndrome represents a broad phenotypic spectrum, ranging from a severe, neonatal-infantile type to a milder juvenile/adult-onset type [7]. This fact is consistent with our observation of normal hearing in four alive patients with juvenile onset of symptoms. Persistent follow-up on hearing abilities in this subgroup is needed to allow for further statements in this subgroup.

This study is a retrospective narrative synthesis of data collected from several international centers at one specific point in time with consecutive limitations. The sample size of 36 remains small, although this needs appropriate contextualization given the ultra-rare nature of this disease and our findings summarize the available data to aid in decision making. There is considerable missing data on affected individuals' hearing abilities. This may be a result of general severity of disease and a subsidiary role of hearing diagnostics. Data logging information from five CI patients was missing. Finally, central processing

F = female; M = male; LP = likely pathogenic; P = pathogenic; PVS, PM, PP = categories of pathogenity according to [11]; * = deceased; y = years; N/A = not available.

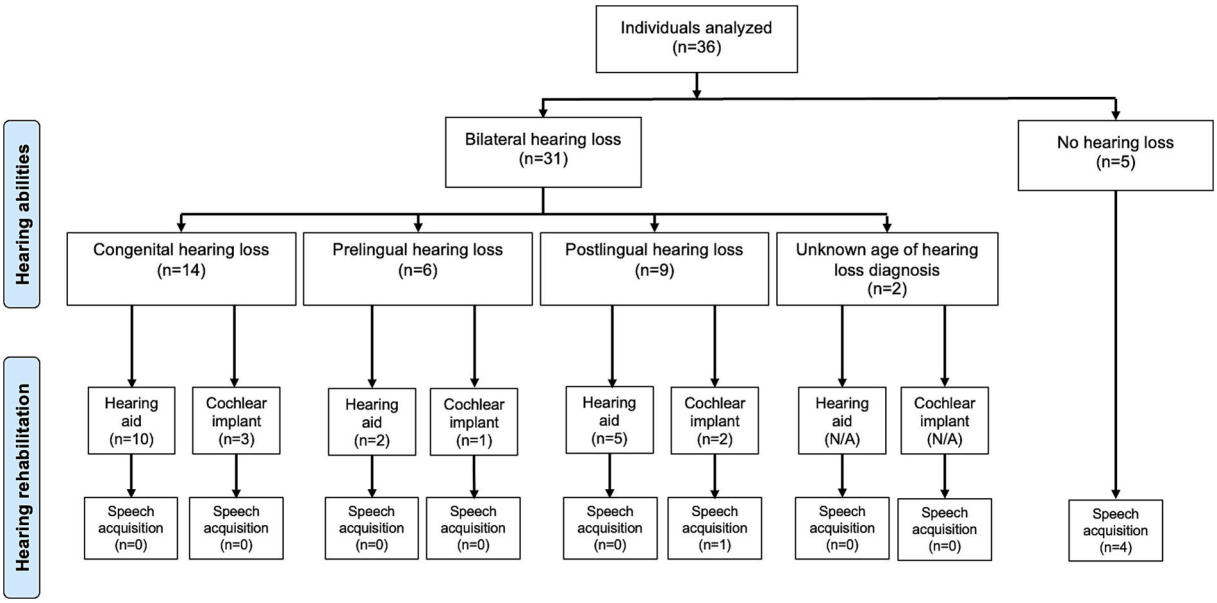

Fig. 1. Summary of findings on hearing loss and hearing rehabilitation.

of audiometric input was not measured. This may represent an unpredictable factor for hearing rehabilitation success.

In conclusion, congenital HL represents a ubiquitous symptom in severe types of MEGD(*H*)EL syndrome, being absent in late onset milder forms. Regularly, severely affected MEGD(*H*)EL patients do not achieve spoken language or alternative communication skills, even with cochlear implantation. Hence, hearing rehabilitation with cochlear implants needs to be discussed very critically with counselling centered around realistic expectations for quality-of-life improvements rather than spoken language outcomes.

Additional information

This study was approved by the Institutional review board of Paracelsus Medical University Salzburg (SS22-0010-0010). Consent for participation was not collected since data analysis was performed retrospectively and pseudo-anonymized.

N/A = not available.

CRediT authorship contribution statement

Sebastian Roesch: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anna O'Sullivan:** Writing – original draft, Methodology, Data curation. **Stefan Tschani:** Validation, Methodology, Formal analysis. **Anna Baghdasaryan:** Writing – review & editing, Data curation. **Shanti Balasubramaniam:** Writing – review & editing, Data curation. **Ivo Barić:** Writing – review & editing, Data curation. **Lonneke de Boer:** Writing – review & editing, Data curation. **Sarah C. Grünert:** Writing – original draft, Data curation. **Anna Guzek:** Writing – review & editing, Data curation. **Mirian Janssen:** Writing – review & editing, Data curation. **Zita Krumina:** Writing – review & editing, Data curation. **Mary Kay Koenig:** Writing – review & editing, Data curation. **Ashleigh M. Lewkowitz:** Writing – review & editing, Data curation. **Fanny Mochel:** Writing – review & editing, Data curation. **Arianne Monge Naldi:** Writing – review & editing, Data curation. **Barbara Plecko:** Writing – review & editing, Data curation. **Kerem Öztürk:** Writing – review & editing, Data curation. **Lauren O'Grady:** Writing – review & editing, Data curation. **Gillian Riordan:** Writing – review & editing, Data curation. **Daisy Rymen:** Writing – review & editing, Data curation. **Inderneel Sahai:** Writing – review & editing, Data curation. **René Santer:** Writing – review & editing, Data curation. **Manuel Schiff:** Writing – review & editing, Data curation. **Georg M. Stettner:** Writing – review & editing, Data curation. **Konstantinos Tsiakas:** Writing – review & editing, Data curation. **Sema Kalkan Uçar:** Writing – review & editing, Data curation. **Özlem Ünal Uzun:** Writing – review & editing, Data curation. **Corina Weigel:** Writing – review & editing, Data curation. **Peter Witters:** Writing – review & editing, Data curation. **Kajus Merkevicius:** Writing – review & editing, Validation, Data curation. **Johannes A. Mayr:** Writing – review & editing, Validation, Formal analysis, Data curation. **Saskia B. Wortmann:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Katarzyna Iwanicka-Pronicka:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Patient data that support the findings of this study are not openly available due to reasons of sensitivity, therefore an URL or link do not exist. Data are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Department of Otolaryngology Head and Neck Surgery of Paracelsus Medical University Salzburg.

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