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High Prevalence of Hearing Impairment in Primary Congenital Hypothyroidism

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Keywords
Primary congenital hypothyroidism · Deafness · Hearing impairment · Conductive hearing impairment · Sensorineural hearing impairment

Abstract

Background: An association between hearing impairment (HI) and congenital hypothyroidism (CH) has been reported previously. However, in general, studies were retrospective and had small sample sizes, and the results were variable and inconclusive. The aim of our study was to assess the prevalence of HI among patients with CH and to examine factors potentially predictive of HI including severity of CH, etiology of CH, and timing of treatment initiation. ***Methods:*** Audiometry was undertaken prospectively in 66 patients aged 3–21 years diagnosed with primary CH and 49 healthy matched controls. All patients with HI underwent examination by an otolaryngologist, and in patients with sensorineural loss, brainstem evoked response audiometry was performed. A next-generation sequencing (NGS) panel for genes involved in deafness was performed in patients with sensorineural HI to exclude additional genetic etiologies. ***Results:*** HI was found in 19 patients (28.7%). Among them, 5 (7.6%) had moderate to severe bilateral sensorineural impairment and 14 (21.2%) had mild conductive HI. Conductive HI was bilateral in 5 of these patients (36%). None of the controls had HI. No specific etiology was found in patients with HI, and no differences were identified in age at diagnosis, age at initiation of levothyroxine (LT_4) therapy, gender, or ethnicity between patients with and without HI. A nonsignificant trend toward lower mean screening TT_4 levels was found in patients with HI (compared to those without HI) (3.42 vs. 5.34 µg/dL, $p = 0.095$). No pathogenic variants in genes attributed to HI were identified by NGS in the 5 patients with sensorineural deafness, indicating that HI in these patients was likely attributable to CH rather than other genetic etiologies. ***Conclusions:*** Our findings indicate a high prevalence of HI among patients with CH, predominantly of the conductive type. HI was not associated with the etiology of CH or with delayed initiation of LT_4 therapy. Audiometry is recommended for children diagnosed with CH and repeat monitoring may be warranted to identify acquired HI and to prevent long-term sequelae of undiagnosed deafness.

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Introduction

The development of hearing in humans, as well as in rodents, is highly dependent on a sufficient supply of thyroid hormones (TH). TH deprivation during the late fetal period, or delay in TH replacement therapy in infancy may result in hearing impairment (HI) [1–3]. Deaf-mutism and HI are common in areas of iodine deficiency [4] and were reported in patients with congenital hypothyroidism (CH) prior to the implementation of thyroid neonatal screening in the 1980s [5].

TH play an important role in the development of the inner ear and auditory pathway [6–13]. In animal models, inadequate TH supply before inner ear development results in permanent cochlear defects [3, 7]. Malformations of the organ of Corti have been shown in offspring of female mice with chemically induced hypothyroidism [8]. Moreover, TH influence the development and maturation of the middle ear and the size of the ossicular bones. This association has been demonstrated in mice lacking TH receptors Thrα and Thrβ [12].

In humans, few studies have investigated HI in patients with CH; however, the samples were small, and the studies were generally retrospective with wide variable results [14–18]. A nationwide study in France of 1,202 young adult patients diagnosed with CH and treated early reported a 3-fold risk of hearing loss compared to the normal population [14]. Other studies with smaller sample sizes indicated HI prevalence of 20–47% in patients with CH, primarily sensorineural in nature [14–16]. HI was associated with the severity of CH and with prenatal onset of hypothyroidism [18] and the age of therapy initiation [17]. In contrast, other studies have demonstrated low rates of HI in patients with CH [19–22]. The objective of this study was to assess the prevalence of HI among patients with CH and to evaluate whether the severity of CH, the etiology, early initiation of treatment, or other factors predispose to HI.

Materials and Methods

Subjects

Sixty-six patients aged 3.1–21.9 years (mean age 8.65) were prospectively recruited from a cohort of 150 patients diagnosed with primary CH. All 66 patients included in the study agreed to participate and underwent audiometry testing. All were followed at the Pediatric Endocrinology Institute, Ha'Emek Medical Center. The diagnosis of CH was based on abnormal thyroid function at birth; most patients were identified by the National Thyroid Newborn Screening Program. The etiology of the CH was evaluated by ^{99}Tc scan, performed at the age of 2–3 years after 3 weeks off levothyroxine (LT_4) therapy. Patients were followed every 3 months in the first year and 6 monthly thereafter. LT_4 was adjusted to maintain TSH within the normal range. Patients with a history of recurrent otitis media, Pendred syndrome, or other known syndromes such as Down syndrome were excluded from the study.

In cases with familial CH, the candidate gene approach was applied to identify the molecular genetic etiology of CH. A control group of 49 healthy children aged 4.8–17.7 years (mean age 8.98), matched for age, sex, and ethnicity was recruited. Exclusion criteria for the control group included patients with known tympanic perforations, recurrent otitis media, developmental delay, congenital syndromes, intrauterine infections, and prematurity. Clinical and biochemical data were retrieved from the participants' medical files. The biochemical parameters included TSH and total (T) T_4 levels on neonatal screening, and laboratory TSH and free (F) T_4 levels measured prior to initiation of LT_4 therapy.

National Neonatal Screening

Blood samples were collected by heel puncture 48–72 h after birth. Between 1987 and 2006, the Israeli National Newborn Screening Laboratory performed the tests using a Diagnostic Products Corp. (Los Angeles, CA, USA) radioimmunoassay TT_4 and TSH kits. Since 2006, Perkin Elmer B065-112 AutoDELFIA neonatal TT_4 and B032-312 AutoDELFIA neonatal TSH kits have been employed, both of which utilize time-resolved fluoroimmunoassays (PerkinElmer Life and Analytical Sciences, Wallac Oy, Mustionkatu 6, Turku, Finland). The Israeli CH screening program is based on TT_4 level, followed by confirmatory TSH test, such that when the level of TT_4 is below the 10th percentile for age, TSH is measured. TSH values >20 mIU/L are considered indicative of primary CH. Neonates with abnormal screening results are referred to medical centers. The results of screening TSH were not reported in accurate values but rather as >20 mIU/L; therefore, we could not calculate precisely the screening TSH results.

Hormone Analyses

TSH, FT_4, and FT_3 were measured by direct automated chemiluminescent immunoradiometric assay using the ADVIA Centaur immunoassay system (Bayer Corporation, Tarrytown, NY, USA). Laboratory TSH reference values were 0.4–4.2 mIU/L, and FT_4 normal reference was 10–20 nmol/L. Some of the TSH values were above the higher standard of the method. In these cases, no dilutions were performed, precluding calculation of the precise TSH values. TSH results were therefore not presented.

Audiometry Test

Patients or their parents if they were below 18 years of age signed an appropriate informed consent form for audiometry and underwent conventional pure tone audiometry at a single institute using GSI AudioStar Pro™ Grason Stadler audiometer. HI was classified as sensorineural or conductive. Mild HI was defined as threshold hearing between 21 and 40 dB, moderate HI between 41 and 70 dB, and severe HI above 70 dB. HI was referred as bilateral or unilateral and of low frequency when the HI was below 1,000 Hz and of high frequency when it was above 2,000 Hz. The same otolaryngologist evaluated the results of all audiometry tests. Patients with HI underwent otolaryngology evaluation including otoscopy, and in patients with sensorineural loss, brainstem evoked response audiometry. The study was approved by the institute's Ethics Committee and by the Israeli Ministry of Health.

Table 1. Clinical and biochemical characteristics of the study group and of patients with HI

	All patients	Patients with HI
Patients, *n*	66	19
Age, years	8.65±5.1 (3.1–21.9)	10.88±6.4 (3.1–21.9)
Gender (M:F)	34:32	10:9
Age at diagnosis of CH, days	11.08±9.0 (2–49)	11.19±7.0 (2–24)
Age at initiation of LT_4 therapy, days	13.21±10.8 (2–62)	13.27±6.3 (2–24)
Screening TT_4, μg/dL	4.7±2.9 (0.5–13)	3.4±2.0 (0.8–8.2)
Laboratory FT_4, pmol/L	5.6±4.6 (0.3–19.2)	4.03±2.4 (0.3–8)
Etiology		
Dysgenesis	41 (62%)	9
Agenesis	13	2
Ectopic thyroid	28	7
Dyshormonogenesis	19 (29%)	7
TPO mutations	12	7
TSHR mutations	6	0
Thyroglobulin mutation	1	0
Transient CH	5 (7.6%)	2
Unknown	1 (1.4%)	0

Values denote mean ± SD (range) or *n* (%). HI, hearing impairment; CH, congenital hypothyroidism; LT_4, levothyroxine; TT_4, total T_4; FT_4, free T_4; *TPO*, thyroid peroxidase; *TSHR*, TSH receptor.

Genetic Analysis

In patients diagnosed with thyroid dyshormonogenesis, a candidate gene approach was performed to identify the etiology of the CH. In cases with a known familial mutation, a targeted gene-sequencing approach was employed in the proband.

In view of the high rate of consanguinity in our population, next-generation sequencing (NGS) was performed in patients with sensorineural HI using a hearing loss panel to exclude other genetic etiologies for hearing loss. The panel included 198 genes associated with deafness. NGS was performed by Illumina NextSeq and 97% of the variants were identified by BWA algorithm and analyzed using variant studio (Illumina), ANNOVAR, and Genoox software (see online suppl. material 1; for all online suppl. material, see www.karger.com/doi/10.1159/000509775).

Statistical Methods

Statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Cary, NC, USA). A series of χ^2 tests or Fisher's exact tests (when the assumptions of the parametric χ^2 test were not met) and a nonparametric Mann-Whitney U test were conducted to analyze the difference between patients' characteristics in both groups. We computed the 2-tailed *p* values, where $p < 0.05$ was considered statistically significant.

Results

Characteristics of the patients diagnosed with CH are given in Table 1. CH was caused by thyroid dysgenesis in 62% (agenesis or ectopic thyroid), dyshormonogenesis in 29% (thyroid peroxidase [*TPO*], *TSH* receptor [*TSHR*], or thyroglobulin gene mutations), and transient CH in 7.6% of patients (Table 1). Maternal thyroid disorders were not reported for any patients included in the study. The control group included 49 patients with a mean age of 8.98 years. No significant differences were found between the controls and the study group in gender, ethnicity, or age at the time of the study.

HI was identified in 29% of the CH patients (Table 2), whereas all controls had normal hearing. Among patients with HI, 14 (74%) had conductive hearing loss and 5 (26%) had sensorineural hearing loss. Conductive HI was mild in all patients and found to be bilateral in 5 (36%) at variable frequencies (44% with high frequency and 56% with low frequency). All 5 patients with sensorineural hearing loss had moderate to severe bilateral impairment. Otoscope examination in all HI patients was normal, except for 1 patient who had mild serous otitis media. A comparison between patients with and without HI revealed no differences in age at diagnosis, age at LT_4 initiation, gender, ethnicity, or CH etiology (Table 2). A nonsignificant trend toward lower screening TT_4 was noted in patients with hearing loss (3.42 vs. 5.34 μg/dL, $p = 0.095$) (Table 2). The etiology of CH was variable among patients with HI: those with conductive hearing loss had ectopic thyroid gland (6 patients), *TPO* mutation

Table 2. Characteristics of patients with and without HI

	Normal hearing	HI	*p* value
Patients, *n*	47	19	
Age at the study, years	7.7±4.25 (3.1–17.4)	10.98±6.4 (3.1–21.9)	0.153
Age at diagnosis, days	11.0±9.94 (3.0–49.0)	11.2±7.0 (2–24)	0.566
Age at LT_4 initiation, days	13.2±12.55 (3.0–62.0)	13.26±6.3 (2–24)	0.245
Gender (M:F)	24/23	10/9	0.909
Screening TT_4, μg/dL	5.3±3.06 (0.5–13.0)	3.4±2.0 (0.8–8.2)	0.095
Laboratory FT_4, pmol/L	6.1±5.0 (0.4–19.2)	4.0±2.4 (0.3–8.0)	0.450

Values denote mean ± SD (range) or *n* (%). HI, hearing impairment; LT_4, levothyroxine; TT_4, total T_4; FT_4, free T_4.

Table 3. Clinical and laboratory characteristics of 5 patients with sensorineural HI

No.	Age, years[a]	Gender	Consanguinity	Initiation of LT_4, days	FT_4,[b] pmol/L	TSH,[b] mIU/L	Age at diagnosis of HI, years	Etiology	Comments
1	16.5	M	No	10	NA	NA	8.5	Agenesis	Psychomotor retardation
2	20.2	M	No	17	2.4	750	9.5	TPO	Total thyroidectomy due to MNG
3	15.3	M	No	2	2.3	92	6	TPO	Total thyroidectomy due to MNG
4	5.8	M	Yes	12	6.0	>150	1	Ectopic	
5	20.6	M	Yes	14	8.9	46.4	8	TPO	MNG

Patients 2 and 3 are brothers. HI, hearing impairment; LT_4, levothyroxine; FT_4, free T_4; TPO, thyroid peroxidase; MNG, multinodular goiter. [a] Age at time of study. [b] At diagnosis.

(4 patients), thyroid agenesis (1 patient), *TSHR* mutation (1 patient), or transient CH (2 patients), and those with sensorineural HI had *TPO* mutation, ectopic sublingual thyroid, or thyroid agenesis (Table 3). Detailed characteristics of NGS sequencing performed on the 5 patients with sensorineural HI are presented in Table 4. Although 4 variants in the heterozygous state were identified in 3 patients, they were not associated with clinical phenotypes (online suppl. material 2).

Discussion

In this prospective study, we identified HI in almost 30% of patients with CH, among them 74% with mild conductive impairment and 26% with moderate to severe sensorineural impairment. HI was not associated with the etiology of CH, gender, ethnicity, and the age at therapy initiation. A nonsignificant trend toward lower screening TT_4 was observed. No previous study has conclusively excluded other genetic etiologies for HI in patients with CH. We utilized NGS panel testing to exclude other genetic causes, confirming that sensorineural HI is likely attributable to CH.

The prevalence of HI in the USA is 1.6:1,000 newborns [23] and 4% in people younger than 45 years [24]. In Israel, since 2010, all newborns undergo hearing screening using transient evoked otoacoustic emission (TEOAE) at 2 days of age. Those that do not pass are referred for brainstem evoked response audiometry. The precise prevalence of HI in the Israeli population is unknown, but 0.5% of newborns in Israel do not pass the transient evoked otoacoustic emission screening [25]. Only 4 patients in our cohort were born after 2010 and none had HI detected on screening. The lack of newborn audiometry screening in most of our cohort might explain the delay in the diagnosis of HI among our patients. However, it is likely that some hearing loss in CH develops over time and is not necessarily congenital, such that repeated screening is necessary. In this study, we found a high prevalence of HI in CH patients, whereas control patients were unaffected. HI early in life results in delayed language acquisition and has an impact on learning and cognitive abilities [26, 27]. A previous study based on self-

Table 4. Audiometry results and genetic findings using next-generation sequencing in 5 patients with sensorineural hearing impairment

No.	Audiometry result			NGS panel	Variant	
1	Bilateral	Mild-moderate	High frequency	Hetero-*PCDH15*	c.4603_4607delCAAGT, p.Gln535ILefs*25	VUS
				Hetero-*SFS1*	c.2129C>G; p.Thr710Ser	rs.200136995
2	Bilateral	Moderate-severe	All frequencies	No pathological variant		
3	Bilateral	Moderate	All frequencies	Hetero-*CACNA1D*	c.298T>C; p.Ser97Pro	VUS
4	Bilateral	Left mild Right moderate	High frequency	No pathological variant		
5	Bilateral	Moderate-severe	All frequencies	Hetero-*COL4A3*	c.3321_3329delAAGTCCTGG; p.Ser1108_Gly1110del	VUS

Patients 2 and 3 are brothers diagnosed with homozygous *TPO* mutation (c.1618C>T; p.R540X), patient 5 has homozygous *TPO* mutation (c.875C>T; S292F), both previously described [35]. NGS, next-generation sequencing; Hetero, heterozygous; VUS, variant of uncertain significance; *TPO*, thyroid peroxidase.

reported data indicated a 3-fold higher rate of HI (predominantly sensorineural) among CH patients compared to the normal population, with a particularly high incidence in patients with thyroid agenesis and severe disease at diagnosis (as assessed by delayed epiphyseal ossification) [14]. In other studies, HI was associated with the severity of CH [16, 18], age of therapy initiation [17], and prenatal onset hypothyroidism [18] but not with the etiology of CH [16]. In our study, a trend toward lower neonatal screening TT_4 was identified in patients with HI, supporting an association with more severe CH at diagnosis. No correlation was found between HI and various etiologies of CH, nor was the prevalence higher in infants with thyroid agenesis.

Delayed initiation of LT_4 supplemental therapy or inadequate therapy results in delayed psychomotor development and is associated with higher rates of HI [2]. Interestingly, in our study, there was no difference in the age at initiation of supplemental therapy between patients with HI and those with normal hearing. Mean age at LT_4 initiation was 13.21 days but age ranged from 2 to 62 days. All patients were diagnosed after the implementation of neonatal screening in Israel; nonetheless, diagnosis was delayed in some. Patients born in the last decade were diagnosed earlier and LT_4 was initiated sooner than in older patients. Moreover, the LT_4 dose at initiation of therapy has increased from 7 to 10–15 μg/day in the last decade. These changes in the management of infants with CH may have impacted the study outcome.

TH play a key role in auditory system development. Studies in rodents have identified the cochlea as a major site of TH action. Prenatal TH deficiency causes impaired maturation of the sensory epithelium and delayed myelination of the cochlear nerve, resulting in permanent deafness [11] and TH supplement administered during critical period of hearing development can prevent deafness in CH mice [28]. THRβ is expressed in the inner ears, and mice lacking Thr have cochlear deafness [29].

Prior to the widespread implementation of neonatal screening in the 1980s, children with CH, as well as those with endemic cretinism due to iodine deficiency, presented with clinical phenotypes of severe cognitive and neurological impairment, extreme short stature [4], hearing loss, and deaf-mutism [4, 5]. About 20% of patients with *THRβ* mutations exhibit hearing loss, including conductive HI [30], and about 50% have recurrent ear infections [31].

In our study, a higher rate of conductive HI was identified than in previous studies, in which sensorineural HI predominated [14–17]. As already noted, TH receptor controls maturation of the middle ear and the size of the ossicular bones in animal models [12]. Patients with *THRβ* mutations exhibit HI, including the conductive type. Furthermore, conductive HI has been shown to be associated with nonadherence to thyroid supplement therapy in patients with acquired hypothyroidism [32]. All these suggest that TH have a role in hearing beyond the neonatal period. In our study, the diagnosis of HI occurred at a mean age of 8.65 years, but the age of onset is unclear, as is the natural history. Conductive losses can fluctuate, deteriorate, or improve with age. Furthermore, adherence to therapy may also impact. The prevalence of sensorineural and conductive deficits identified in our cohort highlights the importance of neonatal screening, as well as regular

screening throughout childhood for children with CH, to facilitate early intervention and minimize the developmental impact of HI in this high-risk population.

In patients found to have sensorineural deafness, we performed an NGS panel including the known genes associated with HI, in order to exclude other genetic causes for HI. We identified a high prevalence of variants in genes reportedly associated with HI; however, all variants were heterozygous and patients did not present with phenotypes described with homozygous mutations in these genes. However, we cannot exclude that heterozygous variants may act as modulating factors, exacerbating the severity of HI in patients with CH or increasing the risk of HI in the setting of hypothyroidism. Interestingly, 3 of the 5 patients with sensorineural HI had *TPO* mutations. *TPO* mutations in association with sensorineural deafness have been reported previously in some case reports [33–35], as well as in animal models [36], indicating that the TPO enzyme itself may have a role in the development of the auditory system.

This prospective, controlled study benefited from having all audiometry performed at a single center and interpreted by 1 physician, ensuring consistent results. In addition, we were able to exclude other genetic etiologies of HI by using the recently developed NGS panel for genetic etiologies of congenital deafness. The study is limited by its relatively small number of participants, which may have obscured an association between HI and initial severity or etiology of CH. Further studies are required to determine the age at development of HI and to investigate long-term outcomes.

Conclusions

HI was identified in nearly 30% of patients with CH and was predominantly conductive in nature, affecting both high and low frequencies. Twenty-six percent had moderate to severe sensorineural loss, and in all of them, other genetic causes of sensorineural HI were excluded. HI was not associated with the etiology of CH or with delayed initiation of LT_4 therapy. Audiometry is recommended for children diagnosed with CH, and repeat monitoring may be warranted to identify acquired HI and to prevent long-term sequelae of undiagnosed deafness.

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Statement of Ethics

The study protocol was approved by the institute's committee of Ha'Emek Medical Center and the Israeli Ministry of Health (HT 5226).

Conflict of Interest Statement

All authors have nothing to disclose.

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Author Contributions

T.A. designed the study, collected and evaluated the data, drafted the initial manuscript, and reviewed and revised the manuscript; Y.T.-R. designed the study, collected and evaluated the data, and reviewed carefully and revised the manuscript; D.N. and Z.S. performed and interpreted the audiometry tests and reviewed the manuscript; S.R., G.E.-A., O.H., and G.H. collected data and reviewed and revised the manuscript; Y.Z., R.S., and D.B. interpreted the molecular genetic results and reviewed and revised the manuscript; S.A. collected thyroid screening data and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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