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Auditory phenotype in Stickler syndrome: results of audiometric analysis in 20 patients

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Abstract Hearing loss in Stickler syndrome has received little attention due to the often more disabling ocular, orofacial and skeletal manifestations. Estimates suggest a global prevalence of sensorineural hearing loss (SNHL) ranging from 50 % to about 100 % though, depending on the underlying Stickler genotype. By performing extensive audiometric analysis in Stickler patients, we aimed to further elucidate the auditory phenotype. Twenty molecularly confirmed Stickler patients (age 10–62 year), of whom sixteen with type 1 Stickler syndrome (*COL2A1* mutation) and four with type 2 Stickler syndrome (*COL11A1* mutation) underwent an otological questionnaire, clinical examination, pure tone and speech audiometry, tympanometry and otoacoustic emission testing. Cross-sectional and longitudinal regression analysis of the audiograms was performed to assess progression. In type 1 Stickler syndrome, 75 % demonstrated hearing loss, predominantly in the high frequencies. No significant progression beyond presbyacusis was observed. All type 2 Stickler patients exhibited mild-to-moderate low- and mid-frequency SNHL and moderate-to-severe high-frequency SNHL. In both types, hearing loss was observed in childhood. Otoacoustic emissions were only detectable in 7/40 ears and had very low amplitudes, even in frequency bands with normal hearing on pure tone audiometry. Type 1 Stickler syndrome is characterized by a mild high-frequency SNHL, emerging in childhood and non-progressive. Absent otoacoustic emissions are a frequent finding. Patients with type 2 Stickler syndrome exhibit early-onset moderate SNHL affecting all frequencies with a sloping audiogram. Taking into account the visual impairment in many patients, we recommend regular auditory follow-up in patients with Stickler syndrome, especially in childhood.

Keywords Stickler syndrome · Collagen · Hereditary hearing loss · *COL2A1* · *COL11A1* · Otoacoustic emissions

Introduction

Stickler syndrome or hereditary arthro-ophthalmopathy is an autosomal dominant collagenopathy with a variety of symptoms including ocular, skeletal, auditory and orofacial anomalies. The most prevalent and typical symptoms are high myopia, retinal detachment, joint hypermobility, precocious osteoarthritis, mild hearing loss, cleft palate and midfacial hypoplasia.

Based on the underlying mutated gene, Stickler syndrome is classified into different types. Type 1 Stickler syndrome is most common (estimated incidence of 1/10,000 among neonates) and is caused by a *COL2A1* mutation [1]. Type 2 Stickler syndrome with an underlying *COL11A1* mutation accounts for a minority of patients (about 0.2/10,000) and type 3 or non-ocular Stickler syndrome, caused by a *COL11A2* mutation, is even more rare (about 0.1/10,000). These three types of Stickler syndrome result in a different phenotype and are mainly distinguished by different ocular manifestations [2]. Type 1 Stickler syndrome is characterized by a membranous vitreous anomaly, whereas a beaded vitreous is typical for type 2.

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Type 3 Stickler syndrome patients do not exhibit ocular anomalies. Skeletal and orofacial features, such as early osteoarthritis and cleft palate, seem to be more consistent among the different Stickler types.

Hearing loss (HL) in Stickler patients is less well studied. Nevertheless, some degree of sensorineural hearing loss (SNHL) seems to be present in up to 70 % of the patients [3]. Temporary conductive HL is common among young Stickler patients and is mostly attributed to chronic otitis media [4]. About half of Stickler patients exhibit cleft palate, which in turn gives rise to more middle ear problems.

The prevalence and severity of HL seems to be related to the affected gene and thus type of Stickler syndrome [5]. In type 1 Stickler syndrome, HL is present in about 50–60 % of patients in whom a mild high-frequency SNHL is encountered [3]. HL in type 2 and type 3 Stickler syndrome is more prevalent than in type 1. Patients present with moderate SNHL affecting all frequencies [5, 6]. Typical age of onset and progression beyond presbyacusis have only been studied in type 3 Stickler patients and remain to be clarified in type 1 and type 2. We aim to further elucidate the auditory phenotype by audiometric analysis in patients with the most prevalent types of Stickler syndrome, namely type 1 and type 2.

Materials and methods

Subjects and procedures

Patients were recruited from the departments of Medical Genetics and Otorhinolaryngology from Ghent University Hospital, Belgium. All 20 participants had molecularly confirmed Stickler syndrome and completed a questionnaire including medical and family history, subjective hearing, balance and risk factors for hearing loss (perinatal information, noise exposure, long-term antibiotic use, family history and meningitis/head trauma). Subsequently, a clinical ENT examination with emphasis on micro-otoscopy and presence of a palatal defect was performed. Auditory tests included tuning fork tests (0.5 kHz), tympanometry (0.226 kHz, GSI TympStar, Grason-Stadler, Eden Prairie, USA), distortion-product otoacoustic emissions (DPOAEs, seven frequency bands between 1 and 8 kHz with stimulus 65/55 dB, OtoPort, OtoDynamics, Hertfordshire, United Kingdom), pure-tone audiometry with determination of air conduction thresholds at octave frequencies from 0.25 to 8 kHz and mid-octave frequencies 3 and 6 kHz (TDH39, Equinox 2.0, Interacoustics, Assens, Denmark) and bone conduction thresholds at octave frequencies from 0.25 to 4 kHz (B71 bone conductor), as well as speech audiometry in quiet (NVA monosyllabic Dutch word lists, TDH39). Contralateral masking was provided when appropriate. Audiometry was performed in a double-walled soundproof room. Participants gave consent to review results of previous hearing tests, vestibular tests and relevant imaging. The local Ethics Committee approved the study and all patients signed informed consent prior to participation.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6.02 (GraphPad Software Inc, La Jolla, USA). Hearing loss was described according to the GENDEAF recommendations (www.hereditaryhearingloss.org). As most patients had symmetric hearing, the average threshold of the right and left ear was used. Only in presence of asymmetric hearing (i.e. $\geq$15 dB HL difference between thresholds at two or more consecutive frequencies), thresholds of the better-hearing ear were selected. The obtained audiograms were compared with the age- and gender-specific reference thresholds (P95 values, International Organization for Standardization 2000). Thresholds better than the corresponding P95 ISO values were considered normal. In order to evaluate progression, cross-sectional linear regression analysis of the obtained audiograms was performed for patients with type 1 Stickler syndrome. Linear regression results were compared with P50 age-specific reference thresholds in which women and men are equally weighted (linear approximation in order to compare both). In patients with 3 or more consecutive audiograms (based on medical records search), individual longitudinal regression analysis was carried out. DPOAEs for a specific frequency were considered detectable if the signal-to-noise ratio was at least 3 dB [7]. Subsequently, the amplitude of the dectected DPOAEs was compared with reference values [7, 8]. The noise amplitude of the DPOAE measurements was below -4 dB SPL at all individual frequencies for all participants.

Results

Questionnaire

Sixteen of the 20 participants had a *COL2A1* mutation compatible with type 1 Stickler syndrome (median age 38 year, range 10–62 years), whereas four patients had a *COL11A1* mutation resulting in type 2 Stickler syndrome (median age 40 year, range 12–46 years; Table 1). Subjective hearing loss was reported by 14/20 participants, with variable age of onset (from birth/childhood to the fifth decade). Four of them were using bilateral hearing amplification. Nine patients reported a history of frequent ear

Table 1 Demographics and relevant questionnaire results

Patients	Gender	Age (year)	Type of Stickler syndrome	Palate	History of frequent middle ear problems	History of multiple TTDs	Other relevant factors
F1-P1	Female	47.5	Type 1	CP	–	–	–
F1-P2	Male	37.5	Type 1	HA	–	–	–
F2-P1	Male	62.0	Type 1	Normal	–	–	History of vertigo
F2-P2	Female	38.6	Type 1	Normal	+	–	–
F2-P3	Female	16.0	Type 1	Normal	+	–	–
F2-P4	Male	13.4	Type 1	HA	+	–	–
F3-P1	Female	44.0	Type 1	CP	+	+	Unilateral otosclerosis, bilateral hearing aid
F3-P2	Female	17.9	Type 1	CP	+	+	–
F4-P1	Male	14.9	Type 1	CP	+	+	–
F5-P1	Male	17.5	Type 1	CP	+	+	–
F6-P1	Male	39.0	Type 1	BU	–	–	–
F7-P1	Female	44.0	Type 1	Normal	–	–	History of vertigo
F7-P2	Male	40.4	Type 1	CP	–	–	Delayed speech/language development
F8-P1	Male	15.7	Type 1	CP	–	+	Delayed speech/language development
F9-P1	Male	48.1	Type 1	Normal	–	–	–
F9-P2	Male	10.2	Type 1	Normal	–	–	
F10-P1	Male	35.5	Type 2	SC	+	+	Bilateral hearing aid
F11-P1	Female	44.6	Type 2	Normal	–	–	–
F11-P2	Female	12.3	Type 2	CP	+	+	Bilateral hearing aid, delayed speech/language development
F12-P1	Female	45.9	Type 2	Normal	–	–	Bilateral hearing aid, recurrent recovering sudden hearing loss

CP cleft palate, *HA* high-arched palate, *BU* bifid uvula, *SC* submucous cleft, *TTD* transtympanic drain

infections, and seven patients had received multiple transtympanic drains as a child. Eleven persons have already experienced a high-pitched tinnitus and two had a history of vertigo. None of the participants reported the use of ototoxic medications, whereas four persons had been exposed to loud noises. Perinatal difficulties included oligohydramnios (1 person), hypoxia (2), preterm (1) and postterm (1) delivery, and feeding difficulties (8 persons had overt cleft palate, 1 had clefting of the soft palate). Maternal smoking or alcohol consumption during pregnancy was not reported. One participant had experienced a concussion due to a fall. Family history for hearing loss was positive for 12 participants with family members affected by Stickler syndrome and for one participant with familial otosclerosis.

Pure-tone audiometry

Audiograms of the included patients are shown in Fig. 1. The majority of patients show symmetric hearing, but two patients had pronounced asymmetric hearing loss: F2-P1 exhibited idiopathic asymmetric SNHL in low- and mid-frequencies (30 dB HL) and F3-P1 showed symmetric bone conduction thresholds, but an additional air-bone gap on one side. This patient was the only one with a conductive component and was diagnosed with fenestral otosclerosis based on CT imaging. As Stickler syndrome is not known to give rise to asymmetric hearing loss, thresholds of the better-hearing ear of these both patients were included for statistical analysis.

When comparing the results of type 1 Stickler syndrome patients with the P95 hearing thresholds of a normal population, we found 12/16 persons with two or more consecutive thresholds worse than the P95 line. This occurred predominantly in the high frequencies (8/16), but also in the low- and mid-frequencies (5/16 and 3/16, respectively).

Considering the type 2 Stickler syndrome patients, all four demonstrated pure tone thresholds worse than the P95 hearing thresholds of a normal population for all frequencies.

Regression analysis of audiograms

Linear regression analysis per frequency is shown in Fig. 2 for type 1 Stickler syndrome patients. Based on the slope of the best-fitting straight line, hearing loss progression is

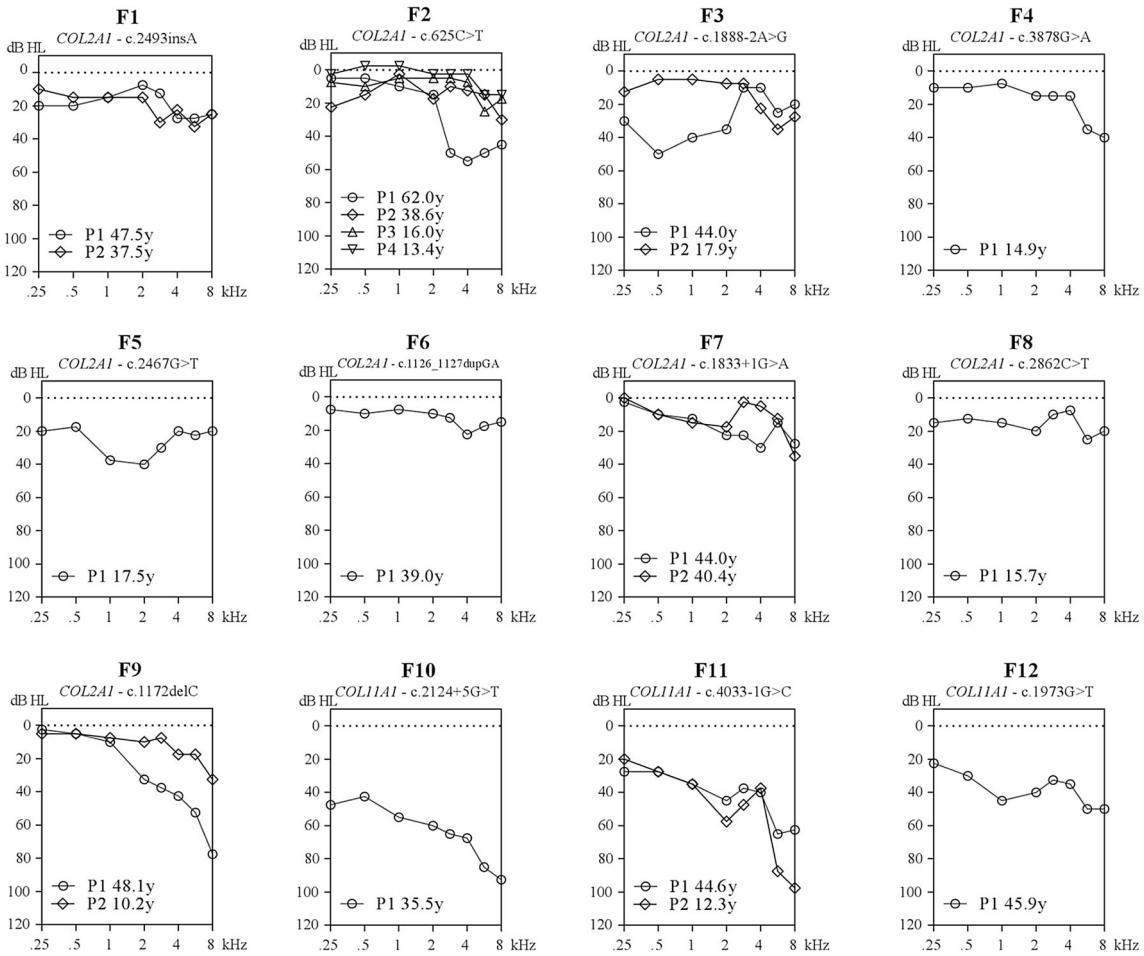

Fig. 1 Most recent pure tone audiograms of the included patients, shown by family (F1 = family 1, P1 = patient 1 from this family) and disease-causing mutation

significant for the 3 and 4 kHz frequencies ($p = 0.024$ and $p = 0.006$, respectively, linear regression t test), whereas progression is not significant for the remaining frequencies. However, when comparing with physiological age-specific hearing deterioration, no significant progression could be observed. The slope of the 0.5, 3 and 4 kHz frequencies is only slightly worse than the P50 slope, whereas the other frequencies show less deterioration in Stickler patients compared with the P50 deterioration, especially at 6 and 8 kHz. An age-related typical audiogram (ARTA) is constructed for type 1 Stickler syndrome and is presented in Fig. 3 [9].

Individual longitudinal regression analysis was performed in patients F2-P1 (4 measurements between 55.5 and 62.4 years), F2-P3 (3 measurements between 10.5 and 16.0 years) and F11-P2 (7 measurements between 5.1 and 12.3 years). The two type 1 Stickler syndrome patients (F2-P1 and F2-P3) did not exhibit significant progression in any frequency. In contrast, the type 2 Stickler patient (F11-P2) showed significant progression for the 2 and 8 kHz frequencies ($p = 0.005$ and $p < 0.001$, respectively, linear regression t test), but not for the others (3 and 6 kHz not analysed, Fig. 4).

Other audiometric tests

Speech recognition thresholds (SRT) per ear correlated well with the pure tone average (PTA; Table 2). The median SRT was 17 dB HL for the type 1 Stickler patients and 42 dB HL for the type 2 Stickler patients.

Tympanometry showed normal middle ear pressure in 39/40 ears (median −8 daPa, range −65 to 40 daPa) and lowered pressure in 1 ear (−200 daPa, F4-P1, history of cleft palate). The median static acoustic admittance was 1.1 mmho (range 0.3–5.8 mmho). Of the tympanic membranes with a static acoustic admittance of >1.5 mmho (15/40, 37.5 %, Table 2), 11/15 were assessed as normal by otomicroscopy, whereas 4/15 were rather sclerotic ($p = 1.00$ compared with ears with normal admittance, Fisher exact test). A history of multiple transtympanic

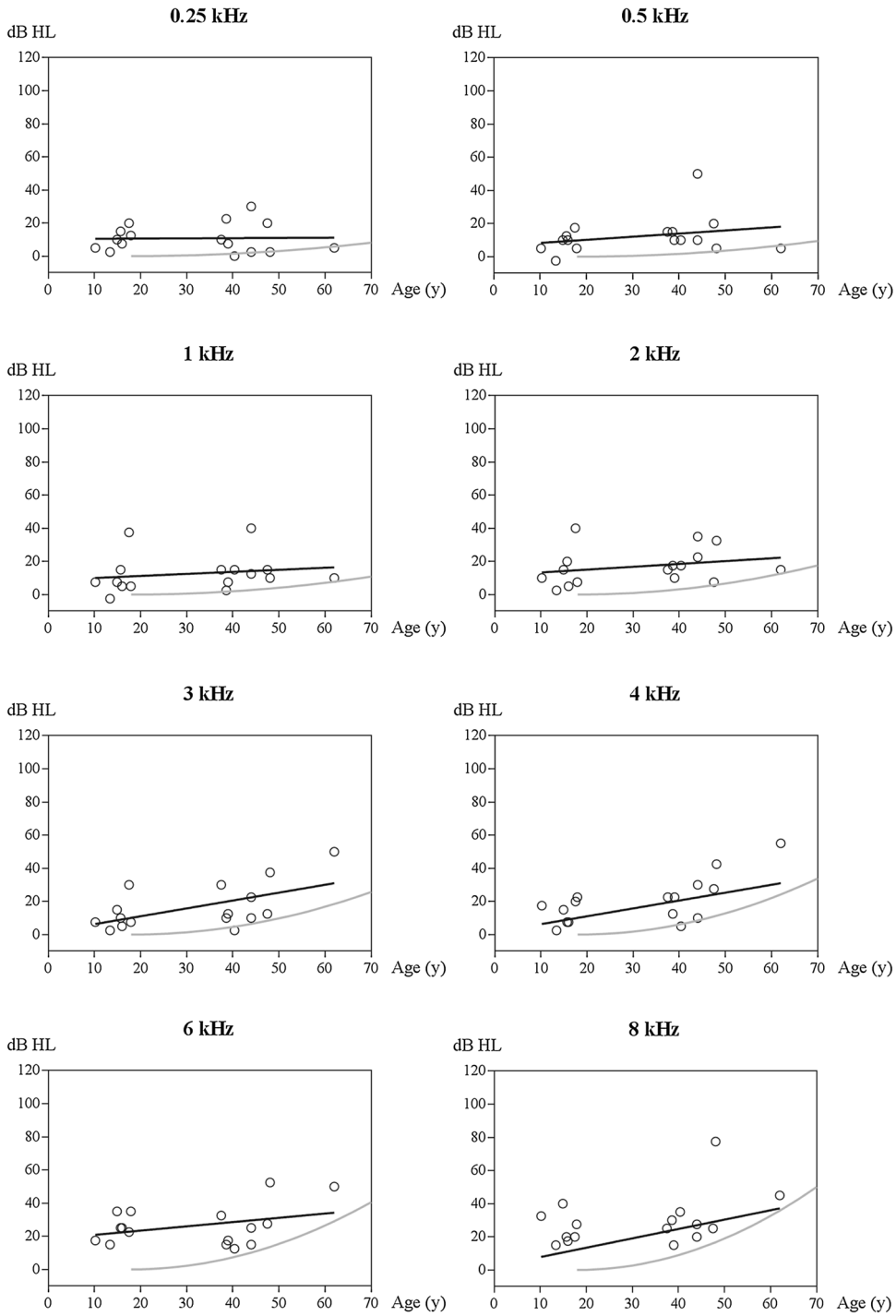

Fig. 2 Cross-sectional linear regression analysis for the different frequencies. The *black line* represents the best-fitting straight line of the type 1 Stickler syndrome patients (individual measurements shown with *circle*), whereas *the grey line* represents the P50 hearing thresholds of the general population

drains assessed by questionnaire was reported in 10/15 ears with increased admittance ($p = 0.002$ compared with normal admittance, Fisher exact test).

DPOAEs were detected (signal-to-noise ratio $\geq$3 dB) in at least three consecutive frequencies in 7/40 ears (Table 2). Because DPOAEs were only detected in type 1 Stickler syndrome patients, we have focused on this population (16 patients). Median PTA of the ears with detectable DPOAEs was 6 dB HL (range −2 dB HL to 15 dB HL), whereas the median PTA of ears without otoacoustic emissions was 20 dB HL (range 3–76 dB HL). Absence of DPOAEs was significantly correlated with higher PTA and SRT (both $p < 0.001$, Mann–Whitney U test). In contrast, the detection of OAEs was not correlated with the tympanic membrane admittance ($p = 0.82$, Mann–Whitney U test), or with a history of otitis media or transtympanic drains

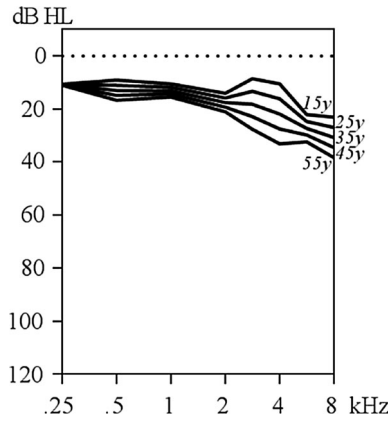

Fig. 3 Age-related typical audiogram (ARTA) of type 1 Stickler syndrome

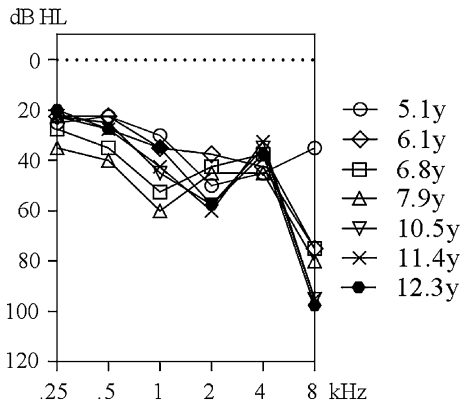

Fig. 4 Consecutive audiograms of patient F11-P2 with type 2 Stickler syndrome. Air conduction thresholds are shown. No air-bone gap was detected at the most recent measurement, although a mild air-bone gap at younger age may have been present

($p = 1.00$ and $p = 0.39$ respectively, Fisher exact test). The amplitudes of the detected DPOAEs are shown in Table 3. Of the pure tone thresholds below 20 dB for a specific frequency, only 36.3 % had detectable DPOAEs for the corresponding frequency. Moreover, the majority of amplitudes of these detected DPOAEs were significantly lower than reference values for normal and even for presbyacusis samples [8]. Only two patients had DPOAEs within the normal range for more than one frequency band (F6-P1 left ear and F9-P2 right ear).

Previous imaging and vestibular tests

Four patients had undergone imaging of the auditory system. Three had undergone MRI imaging of the inner ear and auditory pathways, which proved to be normal in these patients. The patient with conductive hearing loss showed no anomalies other than unilateral fenestral otosclerosis on CT imaging of the middle ear (F3-P1).

Only one patient (F7-P1) had a complete vestibular work-up and showed compensated vestibular hypofunction on electronystagmography. In another patient vestibular examination was inconclusive because of the comorbid eye disease.

Discussion

Hearing loss in Stickler syndrome proves to be frequent, with overall 80 % of patients affected. The hearing loss arises at young age and is not progressive in adulthood. Based on the audiogram, distinction can be made between type 1 and type 2.

Sensorineural hearing loss in type 1 Stickler syndrome is presumed to exclusively affect the high frequencies [4, 10], which has even been proposed to be part of diagnostic criteria [3]. Based on the current study, we can confirm that the higher frequencies (3–8 kHz) are predominantly affected (50 % of included patients), however, we also observed slightly worse low- and mid-frequency thresholds (31 % of included patients). Hearing loss in type 1 Stickler patients is mild and in some patients even asymptomatic. It occurs at young age (6 out of 7 minors) and can be considered as non-progressive apart from presbyacusis. Interestingly, progression at 6 and 8 kHz tends to occur slower than can be expected for presbyacusis. Otoacoustic emissions were detected in only 22 % of the ears of type 1 Stickler syndrome patients. Moreover, the amplitude of the majority of detected DPOAEs was significantly decreased. It is known that middle ear pathology might largely influence DPOAE measurements [7], but it remains unclear to what extent hypermobile tympanic membranes might affect otoacoustic emissions. We could not show a link between the detection/absence of DPOAEs and the presence of a hypermobile tympanic membrane. Taking into account the normal pure tone thresholds for several frequencies in most patients, DPOAEs seem to have a decreased amplitude or absence in a majority of type 1 Stickler syndrome patients. This might imply (outer) hair cell dysfunction, and thus, a sensory type of cochlear hearing impairment [11]. The expression of *COL2A1* mRNA in inner and outer hair cells supports this hypothesis. However, type II collagen has also been detected in the tectorial membrane of the developing cochlea [12].

Hearing loss in type 1 Stickler syndrome resembles early-onset presbyacusis, and is strikingly similar to hearing loss in myotonic dystrophy type 1 caused by a mutation in the *DMPK* gene, which is supposed to interact with the motility of outer hair cells [13]. In Usher type II patients, characterized by a predominantly high-frequency SNHL that is more severe than in Stickler syndrome type 1, a sensory type of cochlear hearing impairment has been

Table 2 Speech reception thresholds (SRT), pure tone average (PTA, average of air conduction thresholds 0.5, 1, 2 and 3 kHz), tympanic membrane admittance and detection of distortion-product otoacoustic emissions (DPOAEs) at three consecutive frequencies per ear in Stickler patients

Patients	SRT right (dB)	PTA right (dB)	Admittance right (mmho)	DPOAEs right	SRT left (dB)	PTA left (dB)	Admittance left (mmho)	DPOAEs left
F1-P1	18	13	0.4	Absent	18	15	0.7	Absent
F1-P2	7	13	0.3	Absent	20	25	0.3	Absent
F2-P1	13	20	1.5	Absent	52	45	1.5	Absent
F2-P2	11	11	1.1	Absent	17	11	2.2	Absent
F2-P3	13	3	2.8	Absent	15	10	4.5	Absent
F2-P4	7	−2	1.0	Detectable	13	3	0.7	Detectable
F3-P1	70	76	1.7	Absent	29	34	0.9	Absent
F3-P2	7	5	2.9	Detectable	11	8	2.8	Absent
F4-P1	16	14	0.5	Absent	23	10	0.9	Absent
F5-P1	30	28	5.5	Absent	32	35	5.8	Absent
F6-P1	11	15	1.7	Detectable	8	5	3.2	Detectable
F7-P1	17	14	1.3	Absent	22	20	1.2	Absent
F7-P2	17	10	1.1	Absent	16	13	1.1	Absent
F8-P1	17	11	1.3	Absent	17	18	1.8	Absent
F9-P1	26	16	0.7	Absent	33	26	0.6	Absent
F9-P2	12	9	0.8	Detectable	11	6	1.0	Detectable
F10-P1	48	52	3.4	Absent	60	59	4.0	Absent
F11-P1	42	39	0.6	Absent	29	34	0.8	Absent
F11-P2	41	43	2.7	Absent	43	41	4.4	Absent
F12-P1	42	36	0.8	Absent	38	38	0.9	Absent

F1 family 1, *P1* patient 1 from this family

detected as well. *USH2A* is essential in the morphogenesis of the stereocilia bundle in hair cells [14].

Sensorineural hearing loss in type 2 Stickler syndrome has been described as more frequently occurring, more severe and initiating at a younger age compared with type 1 [5]. We found mild-to-moderate low-frequency and moderate-to-severe high-frequency hearing loss in all four type 2 patients. Progression has been found in one young patient with serial audiograms (at frequencies 2 and 8 kHz), but her hearing loss seems to stabilize in recent years. We presume that hearing loss in type 2 Stickler syndrome originates and/or progresses in early childhood, which is also the most likely age of diagnosis [15, 16]. Patients with mild congenital hearing loss may pass neonatal hearing screening, so a congenital onset cannot be excluded. Hearing loss seems to stabilize in adulthood which is supported by the subjective findings of our participants and comparison of their audiograms. The number of type 2 Stickler patients included in this study is rather low though.

Hearing loss in type 2 Stickler syndrome (heterozygous *COL11A1* mutation) is strikingly similar to that of the rare type 3 Stickler syndrome (heterozygous *COL11A2* mutation). The mean threshold in a large family of type 3 Stickler patients was 40 dB and increased in the higher frequencies, giving rise to a U-shaped to sloping audiogram [6]. HL in these patients is non- or only slowly progressive and does not develop into profound hearing loss [6, 17]. Extensive audiometric testing in these patients suggested an intracochlear conductive type of hearing impairment [18] attributed to alterations in the physical characteristics of the cochlear duct. Similar findings were shown in DFNA13, a non-syndromic form of hearing loss caused by a heterozygous *COL11A2* mutation [19]. They can be explained by expression of *COL11A1* and *COL11A2* in the tectorial membrane [20]. In contrast, compound heterozygosity for 2 *COL11A1* mutations can also give rise to a recessive Stickler phenotype with profound hearing loss [21].

Neither in type 1 Stickler syndrome nor in type 2 Stickler syndrome, conductive hearing loss is a typical feature. However, one might expect more conductive pathology as a result of recurrent otitis media in young Stickler patients affected by cleft palate. In our series, one patient had a unilateral conductive hearing loss due to otosclerosis segregating in the family, which seems to be coincidental. To our knowledge, only one other family of Stickler patients has been reported to exhibit conductive HL attributed to stapes ankylosis [22].

Table 3 Comparison of DPOAE signal-to-noise ratio (SNR) and amplitude (ampl, dB SPL) with thresholds obtained by pure tone audiometry (PT, dB HL) of the corresponding frequencies

Patient	Age	Side	1 kHz		1.4 kHz	2 kHz		2.8 kHz	3 kHz	4 kHz		6 kHz		8 kHz	
			DPOAE SNR (ampl)	PT	DPOAE SNR (ampl)	DPOAE SNR (ampl)	PT	DPOAE SNR (ampl)	PT	DPOAE SNR (ampl)	PT	DPOAE SNR (ampl)	PT	DPOAE SNR (ampl)	PT
F1-P1	47.5	Right	–	15	–	–	5	–	10	–	–	–	–	–	–
		Left	–	15	–	–	10	–	15	–	–	–	–	–	–
F1-P2	37.5	Right	–	10	–	–	10	8.2 (0.3)	–	–	10	–	–	–	–
		Left	–	–	–	–	–	–	–	–	–	–	–	–	15
F2-P1	62.0	Right	–	10	7.7 (−2.4)	–	15	–	–	–	–	–	–	–	–
		Left	–	–	–	–	–	–	–	–	–	–	–	–	–
F2-P2	38.6	Right	7.0 (−2.9)	0	7.4 (−0.8)	–	15	–	10	4.3 (−6.1)	10	7.2 (0.2)	10	–	–
		Left	–	5	4.6 (−2.5)	–	–	–	10	–	15	–	–	–	–
F2-P3	16.0	Right	6.6 (−3.5)	0	6.5 (−3.8)	–	0	–	0	–	0	–	–	–	15
		Left	6.2 (−3.7)	10	5.9 (−4.6)	–	10	–	10	–	15	–	–	–	–
F2-P4	13.4	Right	5.9 (−0.6)	−5	7.3 (−1.4)	–	0	–	0	5.5 (−8.5)	0	10.0 (1.1)	0	6.1 (−8.2)	5
		Left	5.5 (−4.3)	0	4.8 (−8.6)	5.2 (−7.7)	5	–	5	8.1 (−6.1)	5	–	–	–	–
F3-P1	44.0	Right	–	–	–	–	–	–	–	–	–	–	–	–	–
		Left	–	–	–	–	–	–	10	–	10	–	–	–	–
F3-P2	17.9	Right	7.7 (−1.4)	5	7.9 (−1.9)	4.5 (−7.0)	5	–	5	–	–	–	–	–	–
		Left	–	5	7.7 (−6.0)	–	10	–	10	–	–	–	–	–	–
F4-P1	14.9	Right	–	10	–	–	15	–	–	–	–	–	–	–	–
		Left	–	5	–	–	15	–	10	3.1 (−7.2)	10	–	–	–	–
F5-P1	17.5	Right	–	–	–	–	–	–	–	–	15	–	–	–	–
		Left	–	–	–	–	–	–	–	–	–	–	–	–	–
F6-P1	39.0	Right	–	15	3.1 (−7.3)	3.0 (−7.0)	15	3.5 (−6.6)	15	–	–	–	–	–	–
		Left	15.1 (7.7)	0	16.7 (9.1)	16.4 (5.5)	5	9.8 (−1.1)	10	9.4 (−4.3)	10	–	15	–	10
F7-P1	44.0	Right	7.4 (−1.6)	10	–	–	–	–	–	–	–	–	15	–	–
		Left	–	15	–	–	–	–	–	–	–	–	15	–	–
F7-P2	40.4	Right	3.3 (−3.2)	15	–	–	15	–	0	–	10	–	15	–	–
		Left	–	15	7.2 (−4.1)	–	–	–	5	–	0	–	10	–	–
F8-P1	15.7	Right	–	10	–	–	–	–	5	4.6 (−9.2)	10	–	–	–	–
		Left	–	–	–	–	–	–	15	–	5	–	–	–	–
F9-P1	48.1	Right	8.3 (−0.9)	5	6.8 (−3.3)	–	–	–	–	–	–	–	–	–	–
		Left	–	15	–	–	–	–	–	–	–	–	–	–	–
F9-P2	10.2	Right	11.9 (7.5)	5	18.0 (9.8)	–	10	9.1 (−5.9)	10	8.3 (−6.8)	15	8.7 (−2.6)	15	–	–
		Left	10.2 (6.1)	10	9.8 (−0.9)	10.1 (4.8)	10	9.8 (−3.5)	5	–	–	–	–	–	–

Only pure tone thresholds better than 20 dB HL are shown. Of interest, none of the type 2 Stickler syndrome patients had thresholds better than 20 dB HL, so only the 16 type 1 Stickler syndrome patients are shown

Hypermobility of the tympanic membranes in Stickler patients was first detected in 2001 [4]. This was attributed to previous otitis media episodes and/or to the presence of type II collagen in the tympanic membrane and ossicular joints. We also found an elevated admittance of the tympanic membrane (>1.5 mmho) in 37.5 % of the ears, both in type 1 (34 %) and type 2 (50 %) Stickler patients. Increased admittance can result from a variety of causes including previous otitis media episodes and transtympanic drain placement [23], which we were able to confirm in our Stickler population. We therefore support the theory of previous otitis media as the main cause of hypermobile tympanic membranes in Stickler patients.

Mutations in Stickler syndrome are usually different in each family. Type 1 Stickler syndrome is caused by a *COL2A1* mutation, predominantly leading to haploinsufficiency [24]. The mutations of the included patients in this study all give rise to a premature termination codon, whether or not via frameshift or cryptic splice site. Interfamilial and even some intrafamilial variability in hearing is present, and cannot uniformly be explained by the location or type of mutation, nor by the presence or absence of risk factors for hearing loss.

In summary, we confirm a mild and predominantly high-frequency SNHL in type 1 Stickler patients, which is characterized by an early onset and is non-progressive compared with normal age-specific hearing thresholds. The absence of otoacoustic emissions is a frequent finding and is probably inherent to the impact of a *COL2A1* mutation in the inner ear. In type 2 patients, the audiogram demonstrates mild-to-moderate low- and mid-frequency SNHL and moderate-to-severe high-frequency SNHL. This hearing loss has an early onset as well, and seems to be non-progressive in adult age. We recommend strict and regular auditory follow-up in patients with Stickler syndrome, especially during childhood and particularly because of the visual impairment present in many patients.

Compliance with ethical standards

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