The Journal of International Advanced Otology

J Int Adv Otol 2017; 13(1): 93–9 • DOI: 10.5152/iao.2017.3379

Original Article

Audiological Findings in Charcot–Marie–Tooth Disease Type 4C

Rafael Sivera[#], Laura Cavalle[#], Juan J. Vílchez, Carmen Espinós, Herminio Pérez-Garrigues, Teresa Sevilla

Department of Neurology, Hospital Francisco de Borja, Av Medicina 6, Gandia, Spain (RS, HPG)
Department of Otology, Hospital Universitario y Politècnico La Fe. Bulevar Sur s/n, Valencia, Spain (LC)
Department of Neurology, Hospital Universitario y Politècnico La Fe. Bulevar Sur s/n, Valencia, Spain (JJV, TS)
Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, Spain (JJV, CE, TS)
Department of Medicine, University of Valencia. Av/ Blasco Ibañez 15, Valencia, Spain (JJV, TS)
Program in Rare and Genetic Diseases and IBV/CSIC Associated Unit, Centro de Investigación Príncipe Felipe (CIPF). c/ Eduardo Primo Yúfera 3, Valencia, Spain (CE)
Department of Genetics, University of Valencia. Av/ Blasco Ibañez 15, Valencia, Spain (CE)

OBJECTIVE: Charcot–Marie–Tooth disease type 4C (CMT4C) is a hereditary demyelinating early onset neuropathy with prominent unsteadiness and occasional cranial nerve involvement. Vestibulopathy caused by the dysfunction of cranial nerve VIII has been demonstrated in a high percentage of these patients, but the presence and degree of auditory neuropathy are unknown. The aim of the study was to characterize the hearing abnormalities of a series of patients with CMT4C and to determine the presence and severity of auditory neuropathy (AN) in these patients.

MATERIALS and METHODS: Ten patients with genetically confirmed CMT4C underwent comprehensive clinical and audiological testing. The results were compared among patients in different age groups and also to the results of vestibular testing that had already been performed.

RESULTS: Only 3 patients had hearing problems, but 9 had hearing abnormalities on ancillary testing that were compatible with different degrees of auditory nerve dysfunction. In the mildest cases, only the abnormality of the stapedial reflex and distortion of wave I in auditory brainstem responses could be detected. In the more severe cases, tonal audiometry revealed asymmetric hearing loss. These findings were more severe in older patients, even after correcting for age-related hypoacusia. In these patients, vestibular dysfunction could also be detected and seemed to be more profound and symmetric than hearing loss.

CONCLUSION: This report confirms and defines the presence of different degrees of auditory neuropathy in all patients with CMT4C, being detectable, usually unilaterally, during infancy, and worsening with disease progression.

KEYWORDS: SH3TC2, auditory neuropathy, CMT

INTRODUCTION

Charcot–Marie–Tooth disease (CMT) refers to the heterogeneous group of inherited sensory and motor neuropathies. With the development of molecular genetics, nearly 100 distinct genetic causes have been identified, with linkage established to many others (http://molgen-www.uia.ac.be./CMTMutations). Clinically, the most frequent CMT phenotype is characterized by progressive distal weakness and sensory loss, foot deformities, and absent reflexes [1]. However, a great variability exists regarding the severity and accompanying features among the different genotypes. The presence of cranial nerve involvement is unusual but has been consistently described in certain subtypes. Hearing loss due to auditory nerve dysfunction was first described in 1979 and was subsequently described in patients with diverse subtypes of CMT [2, 3]. It can occur as a constant phenotypic feature like in CMT4D or CMTX5 or as an occasional associated feature as in *MPZ*, *PMP22*, *GJB1*, *NEFL*, and *SH3TC2* mutations [4-10].

Homozygous mutations of the *SH3TC2* gene cause early onset demyelinating neuropathy (CMT4C) characterized by unsteadiness, scoliosis, distal proximal weakness, profound sensory loss, and occasional cranial nerve involvement. The latter includes hearing loss, vestibulopathy, pupillary abnormalities, and/or tongue atrophy [11]. Cranial nerve VIII seems to be the most frequently affected cranial nerve as hearing loss has been reported in 15–40% of patients with CMT4C and vestibular unexcitability has been reported in 7 of 10 cases [12, 13].

Auditory neuropathy (AN) can be defined as the presence of normal evoked otoacoustic emissions (OAEs) and/or cochlear microphonics (CM) with an absent or abnormal auditory brainstem response (ABR) [14]. The presence of OAEs or CM indicates the preser-

Corresponding Address: [#]Rafael Sivera and Laura Cavalle have contributed equally to this paper. E-mail: rafasivera@gmail.com

Submitted: 13.12.2016 **Revision received:** 16.02.2017 **Accepted:** 07.03.2017

Table 1. Clinical characteristics and nerve conduction studies

No. (sex)/ Age	Genotype	Onset (years)	Sensory loss	Motor UL/LL	Cranial nerves	Vestibulopathy	FDS	CMTNS	Nerve conduction studies			
									Age	MMNCV	CMAPUL/LL	SNAPUL/LL
1 (M) 45y	p.R1109X/ p.R1109X	Delayed walking	All	+/++	HL	C	5	23	24 y	31 m/s	7/0	0.6/0
2 (F) 12y	p.R1109X/ p.R1109X	Delayed walking	All	+/+++	-	C	3	18	3y	17 m/s	NP/NP	NP
3 (F) 20y	p.R1109X/ p.C737_P738 delinsX	Delayed walking	P, V	+/++	-	C	3	19	12y	23 m/s	10.6/0.5	1.9/0
4 (M) 58y	p.R529Q/ p.R529Q	Unstable 10y	P, V	+/+++	HL	C	4	24	39y	27 m/s	2.2/0	1/0
5 (F) 33y	p.R1109X/ p.R1109X	Delayed walking	All	+/+++	-	I	6	23	20y	19 m/s	4/0	0/0
6 (M) 56y	p.R1109X/ p.R1109X	Delayed walking	All	+/++	HL Trigeminal neuralgia	C	5	20	53y	25.8 m/s	4,3/0	0/0
7 (F) 20y	p.R1109X/ p.R1109X	Delayed walking	All	+/+	-	C	2	16	10y	33 m/s	10/0.1	0.8/0
8 (M) 37y	p.H1102LfsX14/ p.H1102LfsX14/	Unstable 12y	P, V	+/++	-	C	3	16	30y	33 m/s	5.9/0	1.5/0
9 (F) 27y	p.R1109X/ p.C737_P738 delinsX	Pes cavus 9y	P, V	+/++	-	I	3	17	26y	31 m/s	NP/0	0/0
10 (F) 24y	p.R1109X/ p.C737_P738 delinsX	Falls, 2y	All	++/+++	-	I	5	23	20y	27 m/s	4.3/0	0/0

No: number; UL: upper limb; LL: lower limb; P: pinprick; V: vibratory; HL: hearing loss; C: complete vestibulopathy (unexcitable vestibular system); I: incomplete vestibulopathy; MMNCV: median motor nerve conduction velocity (normal values>51.6 m/s); CMAP: compound muscle action potential; data of the UL: median nerve (normal values>13.8 mV); LL: peroneal nerve (normal values>7.4 mV); SNAP: sensory nerve action potential; data of the UL: median nerve (normal values >16.5 mV); LL: sural nerve (normal values>18mV); NP: not performed

vation of the function of outer hair cells in the cochlea; therefore, the absence of ABR demonstrates a dysfunction in the inner hair cells of the cochlea, the synapse with the auditory nerve, and/or the auditory nerve itself. A pathological examination of the cochlea in a patient with an *MPZ* mutation and AN revealed marked loss of auditory ganglion cells and central and peripheral auditory nerve fibers within the cochlea, with relative preservation of the cochlear hair cells [7].

Thus, the aim of the study was to characterize the hearing abnormalities in a series of patients with CMT4C and to determine the presence and severity of AN in these patients.

MATERIALS and METHODS

Subjects

Ten patients with genetically confirmed CMT4C were prospectively included in this study. Of these, 6 were males and 4 were females; cases 1 and 5 were siblings, as were cases 9 and 10. All were of Gypsy ethnicity, except cases 4 and 8 who belonged to two Caucasian families with no apparent consanguinity. Written informed consent was obtained from all patients, and the protocols were approved by the Ethics Committee of the hospital.

Clinical Study

The detailed history and complete neurological examination results were recorded. Assessment included the following: strength, muscle atrophy, sensory loss, reflexes, foot deformities, and scoliosis. Muscle strength was scored using the standard Medical Research Council scale. The CMT neuropathy score (CMTNS) was used to determine neurological impairment [15]. Functional status was evaluated using the Functional Disability Scale (FDS) [16]. Electrophysiological studies were conducted in all patients following the same protocol that was previously described [17].

Patients were specifically questioned regarding the onset of symptoms and characteristics of hearing loss. A complete history of audiological disturbances in other family members was obtained, as was the history of exposure to ototoxic drugs or to an excessively noisy environment.

Genetic Study

The search for mutations in the *SH3TC2* gene was performed by Sanger sequencing of the PCR products of exons and their intronic flanking sequences in an ABI Prism 3130xl autoanalyser (Applied Biosystems, Foster City, CA, USA) using primers as described elsewhere [13]. The genotype is detailed in Table 1.

Audiological Study

After otoscopic examination, hearing was evaluated using tympanogram and stapedial reflex, tone and speech audiometry, OAEs, and ABR.

Tympanograms and stapedial reflex thresholds were measured using a GSI 38 Tympanometer. Tympanometry was performed using a 226 Hz probe tone, with a sweep pressure start point of +200 daPa and an end point of −400 daPa. Ipsilateral acoustic reflexes were bilaterally assessed with pure tone activator stimuli of 0.5, 1, 2, and 4 kHz .

Pure tone audiometry was performed by trained personnel using an Interacoustics A/S AC40 audiometer including TDH39 headphones (ISO 389/ANSI S3.6-1996) and a Radioear B71 bone vibrator transducer (ISO 7566/ANSI S3.43-1992). Pure tone threshold audiometry was performed at 250, 500, 1000, 2000, 4000, and 8000 Hz. Mean pure tone averages (PTAs) (250–8000 Hz) were calculated for both ears. The severity of hearing impairment was established according to the BIAP (Oficina Internacional de Audiologia) criteria: normal: < 20 dB, mild: 20–40 dB, moderate: 40–70 dB, severe: 70–90 dB, and profound, >90 dB.

Speech audiometry in quiet was performed using a set of 50 open spondaic bisyllabic word lists. Patients were asked to repeat words to the audiologist, and scores were tallied as the percent correct value, speech recognition threshold (lowest level at which speech can be identified at least half the time), and maximum discrimination level (intensity in dBs at which patients get a higher percentage of correct words).

To study the discrimination in noise, we used the self-assessment Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire [18]. In this paper we evaluated scores about difficulty in communication in background noise as follows: always (99%), almost always (87%), generally (75%), half the time (50%), occasionally (25%), seldom (12%), and never (1%).

OAEs were obtained using MAICO ERO•SCAN™, an automatic OAE test system that provides a measurement of distortion products at several frequencies. Four frequencies were tested (frequency range=2 –5 kHz). The intensity of F1 was 65 dB SPL and of F2 was 55 dB SPL. The averaging time was 4 s per frequency, and the pass signal-to-noise ratio was 6 dB. A positive distortion product was considered when the number of passing frequencies for the overall test pass was 3.

The ABR were obtained using AEP Bio-logic. The stimulus parameters were as follows: type click, duration 100 ms, rate 13/s, alternating polarity, and a Beyer DT48 transducer. The acquisition parameters were as follows: electrodes, Cz to ipsilateral mastoid with forehead ground; filter settings, 100–3000 Hz, notch filter, none; filter slopes, 6 dB/octave; analysis period, 10.24–15.36 ms; number of sweeps, 1024 with two replications. High level stimuli (80–95 dB nHL) were used to obtain ABR recordings.

To study the relationship between age and audiological findings, the patients were divided into three groups: group I (cases 2, 3, and 7), group II (cases 5, 9, and 10) and group III (cases 1, 4, 6, and 8). For each group, the mean PTA in each ear was determined and compared with the mean PTA values (Q=50%) of different age groups in the normal population, thus obtaining the PTA loss corrected by age [18]. The presence of AOE and the ABR wave morphology were also recorded in the different age groups.

RESULTS

Relevant clinical features are summarized in Table 1. The series comprised 10 patients with a moderate or severe phenotype as judged using CMTNS and important functional disability.

Audiological Study

All patients reported normal speech development and no exposure to ototoxic drugs or a noisy environment. No family history of hearing loss was present, and one patient (case 5) had a history of right ear recurrent otitis media during childhood. Only 3 patients had subjective hearing loss. No patients were fitted with hearing aids.

Table 2. Pure tone and speech audiometry

		Pure Tone Audiometry RE (dB)							Pure Tone Audiometry LE (dB)							Speech audiometry maximum discrimination level		APHAB
Case	Subjective HL	250 Hz	500 Hz	1 KHz	2 KHz	4 KHz	8 KHz	PTA	250 Hz	500 Hz	1 KHz	2 KHz	4 KHz	8 KHz	PTA	RE	LE	Background noise
1	Adolescence	40	50	55	55	60	65	54.2	50	55	50	55	45	55	51.7	92%-90dB	80%-90dB	Never
2	NR	10	10	10	10	10	10	10.0	10	10	10	10	10	10	10.0	100%-35dB	100%- 35dB	Never
3	NR	20	20	10	10	10	20	15.0	20	20	30	35	40	25	28.3	NT	NT	NT
4	Early adulthood	20	40	40	45	60	80	47.5	35	45	60	60	90	90	63.3	90%-75dB	80%-90 dB	Half the time
5	OD: Infancy* OI: NR	60/25	65/40	65/50	60/55	40/40	30	53.3/42	20	25	30	30	30	30	27.5	100%-80dB	100%-50 dB	Occasionally
6	Early adulthood	90	90	75	70	80	80	80.8	80	85	80	70	50	65	71.7	75%-95dB	80%-95 dB	Never
7	NR	20	15	25	15	15	10	16.7	25	20	10	10	5	10	13.3	100%-35dB	100%-35 dB	Half the time
8	NR	30	30	35	35	45	45	36.7	40	40	40	35	55	65	45.8	100%-60dB	100%-60 dB	Never
9	NR	20	15	10	10	10	20	14.2	35	20	20	25	35	20	25.8	100%-25dB	100%-45 dB	Never
10	NR	10	15	15	25	20	15	16.7	20	25	30	40	40	40	32.5	100%-35dB	100%-50dB	Never

dB: decibels; HL: hearing loss; NR: no subjective hearing loss; NT: not tested (*) otitis; RE: right ear; LE: left ear; PTA: pure tone average 250 Hz–8KHz; APHAB: Abbreviated Profile of Hearing Aid Benefit questionnaire; NR: normal

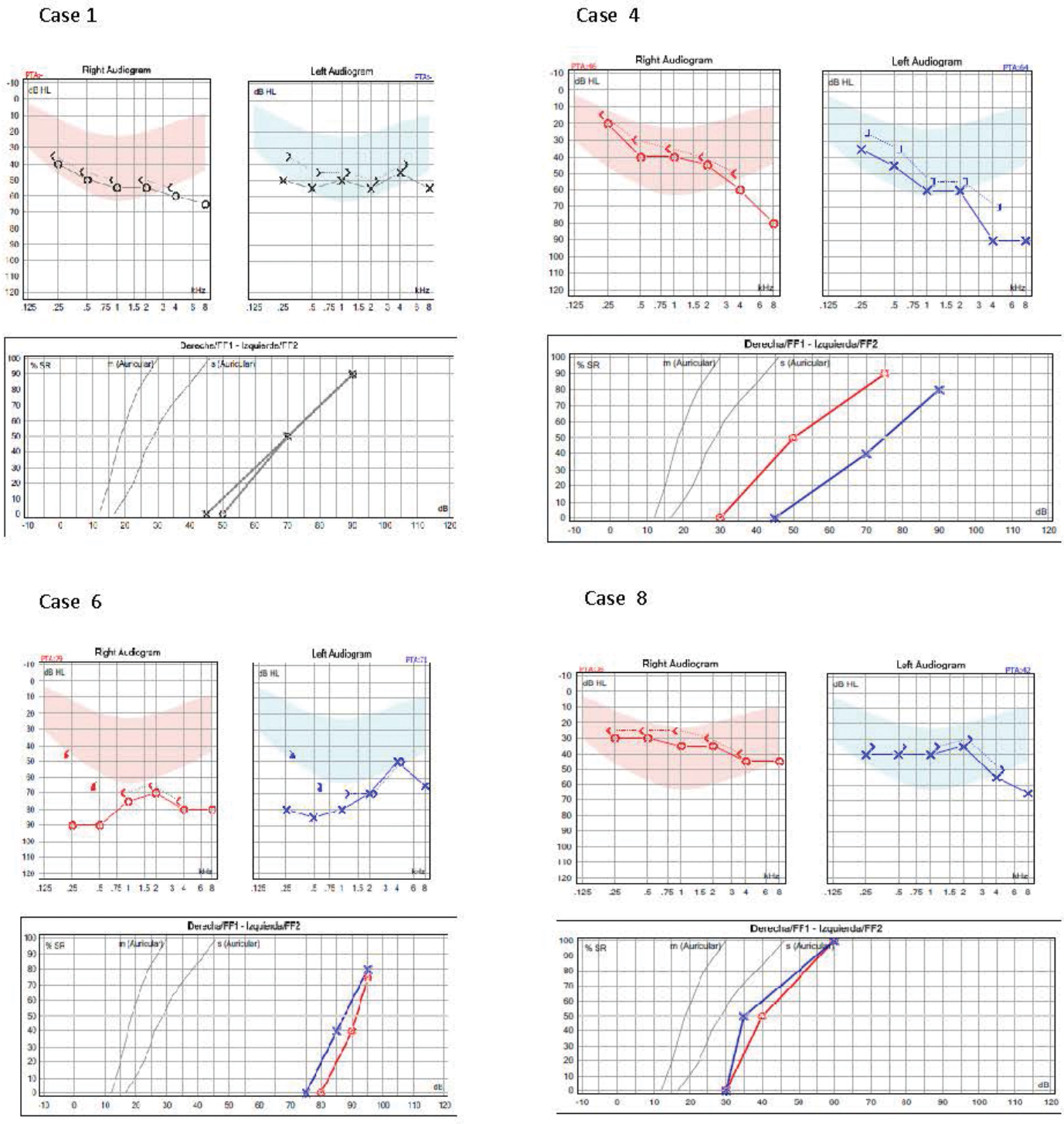

Figure 1. Pure Tone Audiometry and Speech Audiometry of 4 patients

Pure tone and speech audiometry results are represented in Figure 1 and Table 2. Normal hearing thresholds on performing pure tone audiometry were present in only two patients (cases 2 and 7). Three patients (cases 3, 9, and 10) had unilateral mild hearing loss in one ear and normal hearing in the opposite ear. The configuration of the audiogram was flat in case 3 and with more affectation of high frequencies in cases 9 and 10. Speech audiometry in the affected ear showed 100% speech recognition at 45 and 50 dB in cases 9 and 10, respectively, and was not performed in case 3. Four patients (cases 1, 4, 6, and 8) had bilateral mild-to-severe hearing loss. Audiograms were flat in cases 1, 6, and 8, and in case 4 high frequencies were more affected. The maximum speech recognition scores (Table 2) were correlated with audiometry PTA (hearing thresholds). Case 8 did not notice any hearing problem while the other 3 cases were aware of progressive hearing difficulties. Case 5 had severe mixed hearing loss in the right side, which was probably related to recurrent otitis media during childhood. Only 3 patients had comprehension difficulties in background noise without a clear relation with auditory dysfunction.

Table 3. Tympanometry and otoacoustic emissions

Cases	Tympanometry	PTA RE (dB)	PTA LE (dB)	SR RE Threshold (500-4KH)	SR LE Threshold (500-4KH)	OAE RE	OAE LE
1	NR	54.2	51.7	Negative	Negative	Absent	Absent
2	NR	10.0	10.0	Negative	Negative	Present	Present
3	NT	15.0	28.3	NT	NT	NT	NT
4	NR	47.5	63.3	Negative	Negative	Absent	Present
5	NR	40 *	27.5	Negative	Negative	Absent	Present
6	NR	80.8	71.7	Negative	Negative	Absent	Absent
7	NR	16.7	13.3	Negative	Negative	Absent	Present
8	NR	36.7	45.8	Negative	Negative	Absent	Absent
9	NR	14.2	25.8	95/95/105/95 dB	100/100/105/100 dB	Present	Absent
10	NR	16.7	32.5	90-100-100-95 dB	90-95-105-100 dB	Present	Absent

PTA: pure tone average; dB: decibels; SR: stapedial reflex; OAE: otoacoustic emissions; NT: not tested; RE: right ear; LE: left ear
*Air conduction was used to determine the PTA

Table 4. Auditory brainstem response

		ABR RE 90 dB				ABR LE 90 dB		
Case	PTA RE (dB)	Wave morphology	Wave I	Wave V	PTA LE (dB)	Wave morphology	Wave I	Wave V
1	54.2	Severely distorted	Absent	Present	51.7	Severely distorted	Absent	Present
2	10.0	Normal	Present	Present	10.0	Normal	Present	Present
3	15.0	NT	NT	NT	28.3	NT	NT	NT
4	47.5	Distorted	Present	Present	63.3	Severely distorted	Absent	Absent
5	53.3	Normal	Present	Present	27.5	Normal	Present	Present
6	80.8	Severely distorted	Present	Present	71.7	Severely distorted	Present	Present
7	16.7	Distorted	Present	Present	13.3	Distorted	Present	Present
8	36.7	Distorted	Absent	Present	45.8	Distorted	Absent	Present
9	14.2	Distorted	Absent	Present	25.8	Distorted	Absent	Present
10	16.7	Distorted	Present	Present	32.5	Distorted	Absent	Present

PTA: pure tone average; RE: right ear; LE: left ear; NT: not tested; OAE: otoacoustic emissions; ABR: auditory brainstem response; dB: decibels; NS: neurosensorial hearing loss; AN: auditory neuropathy; NH: normal hearing

Table 5. Audiological findings in different age groups

Group	Mean age (years)	PTA RE (dB)	PTA LE (dB)	OAE	ABR Wave I amplitude		
					Normal	Low	Very low
I	16.67	13.9	17.2	2/2	1 bil	1 bil.	
II	27.67	22.47	27.44	3/3	1 bil.	2 bil.	
III	48	46.44	47.82	1/4		1 uni.	2 bil/1 uni.

PTA: pure tone average corrected according to the values of the normal population in different age groups (Q=50%); RE: right ear; LE: left ear; OAE: otoacoustic emissions; ABR: auditory brainstem response

Tympanometry results and OAEs are summarized in Table 3. Tympanometry results were normal in all patients tested. Ipsilateral stapedial reflex was affected in all tested patients; in case 7, it was bilaterally absent. Cases 9 and 10 had abnormally elevated thresholds. OAEs were present in 6 patients: bilateral in 1 (case 2) and unilateral in 5 (cases 4, 5, 7, 9, and 10). Three patients had an absence of OAEs (cases 1, 6, and 8), and they were not performed in case 3.

ABRs are summarized in table 4. All patients, except cases 2 and 5, had atypical ABRs with distortion in the wave form and amplitude reduction. Some had severely distorted ABRs with very low amplitude (5 ears), and others had distorted ABRs with low amplitude waves. Wave I was absent in 8 ears and present in 10 ears. Wave V was present in all ears except in one (case 4 LE).

The relationship between age and audiological findings are summarized in Table 5. An increase in the PTA loss, less ears with normal OAEs, and more distortion of ABR waves with age were observed.

DISCUSSION

The presence of hearing loss in patients with CMT4C has been previously reported, but the underlying audiological characteristics and frequency are unknown. In our series, only 3 of 10 patients had hearing problems, but after performing a comprehensive study, 8 had hearing abnormalities and 5 met all criteria for AN.

Hearing loss was confirmed with pure tone audiometry in 8 of 10 patients, with thresholds that ranged from normality to severe hearing loss. On performing speech audiometry, understanding in silence was concordant with hearing thresholds on performing pure tone audiometry. Speech understanding is generally poor with noise in AN, but only 3 patients reported subjective difficulties with noise in the APHAB questionnaire. OAEs were present in 6 of 9 patients and were bilaterally present only in the youngest patient. The presence of OAEs indicates the normality of OHCs but can be absent because of multiple causes, including aging [19]. In fact, the 3 patients without OAEs were the oldest and had prominent hearing loss on performing tonal audiometry.

These results were complemented with the abnormality of the stapedial reflex in the 9 patients in whom it was tested, which has been associated with damage to the distal auditory pathways [20]. Auditory brainstem potentials were altered in 7 of 9 patients, and in all patients, wave I was more affected than V, which was consistent with damage to the cochlear nerve.

Thus, auditory testing in our patients revealed hearing abnormalities in all patients ranging from an abnormality of the stapedial reflex and/or ABR to severe hearing loss on performing tonal audiometry. In 5 of the 6 patients (7 ears) in which OAEs were present, the criteria for AN were fulfilled, and in the other 11 ears, sensorineural hearing loss was demonstrated, but the normality of OHC function could not be formally established. These findings could be complemented with CM, but they are not available in our center. In any case, the SR was absent in all our patients, which was probably the first marker of auditory dysfunction in these patients [20], and the ABR were also altered in 7 of 9 patients. These findings are compatible with damage to the auditory nerve, which is expected in the disease process of CMT4C [3].

The audiological findings in these patients differed according to age, suggesting the development of audiological abnormalities with disease progression (Table 5). The three youngest patients had normal mean tonal thresholds, but the stapedial reflex and ABR were mildly abnormal. On the other hand, the four oldest patients had very high bilateral mean tonal thresholds and severe disruption of waveform I in the ABR. Although there is a decline in PTA that can be attributed to aging [21], after correcting the values with the mean PTA values in the different age groups, the PTA loss clearly increased as the disease progressed.

Another salient feature is that hearing loss was usually asymmetric. In fact, the mild abnormalities detected on performing tonal audiometry in young patients were always unilateral (cases 3, 9, and 10). Even in severely affected patients with bilateral hearing loss, it was usually asymmetric. This asymmetry in cranial nerve involvement has been described in other cranial nerve dysfunctions like regarding pupillary abnormalities, trigeminal neuralgia, or accessory nerve palsies [10].

In this same series of patients, we had previously performed extensive vestibular testing, which confirmed the presence of significant vestibular impairment compared to age- and sex-matched controls. Even though the results are not directly comparable, as the tests employed in vestibular and audiological testing were completely different, the degree of vestibulopathy was strikingly profound in most patients (70% had completely unexcitable vestibular systems) and more symmetric than the auditory impairment. The 3 patients with less severe vestibular involvement (cases 5, 9, and 10) suffered from mild unilateral hearing loss. The ABR was normal in case 5. On the other hand, cases 2 and 7, who had a normal tonal audiometry results, suffered from complete vestibulopathy. Taking this into account, it seems that although the physiopathological process affecting cranial nerve VIII in CMT4C can be similar in the auditory and vestibular fascicles of the nerve, the clinical consequences are not analogous. This may partly be due to the different relative sensibilities of the tests employed and to the intrinsic difference in the physiological pathways. We speculate that the vestibular reflexes important to postural balance are more affected by the disruption and slowing of nerve conduction than the auditory pathways.

This report confirms and defines the presence of different degrees of auditory abnormalities in all patients with CMT4C, being detectable, usually unilaterally, during infancy, and only with SR or ABR, which worsens with disease progression.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hospital Universitario y Politecnico La Fe.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.S., H.P.G.; Design - T.S., H.P.G.; Supervision - T.S., H.P.G.; Data Collection and/or Processing - R.S., L.C., C.E.; Analysis and/or Interpretation - R.S., L.C.; Literature Search - R.S., L.C.; Writing Manuscript - R.S., L.C.; Critical Review - J.J.V., C.E., H.P.G., T.S.

Acknowledgements: We would like to acknowledge the patients and their families for their collaboration.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Pareyson D, Marchesi C. Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. Lancet Neurol 2009; 8: 654-7. [CrossRef]
2. Satya-Murti S, Cacace AT, Hanson PA. Abnormal auditory evoked potentials in hereditary motor-sensory neuropathy. Ann Neurol 1979; 5: 445-8. [CrossRef]
3. Rance C, Ryan MM, Bayliss K, Gill K, O'Sullivan C, Whitechurch M. Auditory function in children with Charcot-Marie-Tooth disease. Brain 2012; 135: 1412-22. [CrossRef]
4. Kalaydjieva L, Gresham D, Gooding R, Heather L, Baas F, de Jonge R, et al. N-myc downstream-regulated gene 1 is mutated in hereditary motor and sensory neuropathy-Lom. Am J Hum Genet 2000; 67: 47-58. [CrossRef]
5. Kim HJ, Sohn KM, Shy ME, Krajewski KM, Hwang M, Park JH, et al. Mutations in PRPS1, which encodes the phosphoribosyl pyrophosphate synthetase enzyme critical for nucleotide biosynthesis, cause hereditary peripheral neuropathy with hearing loss and optic neuropathy (CMTX5). Am J Hum Genet 2007; 81: 552-8. [CrossRef]

6. Stojkovic T, Latour P, Vandenberghe A, Hurtevent JF, Vermersch P. Sensorineural deafness in X-linked Charcot-Marie-Tooth disease with connexin 32 mutation (R142Q). Neurology 1999; 52: 1010-4. [CrossRef]
7. Starr A, Michalewski HJ, Zeng FG, Fujikawa-Brooks S, Linthicum F, Kim CS, et al. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145->Ser). Brain 2003; 126: 1604-19. [CrossRef]
8. Zuchner S, Vorgerd M, Sindern E, Schroder JM. The novel neurofilament light (NEFL) mutation Glu397Lys is associated with a clinically and morphologically heterogeneous type of Charcot-Marie-Tooth neuropathy. Neuromuscul Disord 2004; 14: 147-57. [CrossRef]
9. Verhagen WI, Huygen PL, Gabreëls-Festen AA, Engelhart M, van Mierlo PJ, van Engelen BG. Sensorineural hearing impairment in patients with PMP22 duplication, deletion, and frameshift mutations. Otol Neurotol 2005; 26: 405-14. [CrossRef]
10. Colomer J, Gooding R, Angelicheva D, King RH, Guillén-Navarro E, Parman Y, et al. Clinical spectrum of CMT4C disease in patients homozygous for the p.Arg1109X mutation in SH3TC2. Neuromuscul Disord 2006; 16: 449-53. [CrossRef]
11. Claramunt R, Sevilla T, Lupo V, Cuesta A, Millán JM, Vílchez JJ, et al. The p.R1109X mutation in SH3TC2 gene is predominant in Spanish Gypsies with Charcot–Marie–Tooth disease type 4. Clin Genet 2007; 71: 343-9. [CrossRef]
12. Yger M, Stojkovic T, Tardieu S, Maisonobe T, Brice A, Echaniz-Laguna A, et al. Characteristics of clinical and electrophysiological pattern of Charcot-Marie-Tooth 4C. J Peripher Nerv Syst 2012; 17: 112-22. [CrossRef]
13. Perez-Garrigues H, Sivera R, Vílchez JJ, Espinós C, Palau F, Sevilla T. Vestibular impairment in Charcot-Marie-Tooth disease type 4C. J Neurol Neurosurg Psychiatry 2014; 85: 824-7. [CrossRef]
14. Starr A, Picton TW, Sininger YS, Hood LJ, Berlin CI. Auditory neuropathy. Brain 1996; 119: 741-53. [CrossRef]
15. Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, et al. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 2005; 64: 1209-14. [CrossRef]
16. Birouk N, Gouider R, Le Guern E, Gugenheim M, Tardieu S, Maisonobe T, et al. Charcot-Marie-Tooth disease type 1A with 17p11.2 duplication: clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain 1997; 120: 813-23. [CrossRef]
17. Sevilla T, Cuesta A, Chumillas MJ, Mayordomo F, Pedrola L, Palau F, et al. Clinical, electrophysiological and morphological findings of Charcot-Marie-Tooth neuropathy with vocal cord palsy and mutations in the GDAP1 gene. Brain 2003; 126: 2023-33. [CrossRef]
18. Cox RM, Alexander GC. The abbreviated profile of hearing aid benefit. Ear Hear 1995; 16: 176-86. [CrossRef]
19. Deltenre P, Mansbach AL, Bozet C, Clercx A, Hecox KE. Temporal distortion products (kernel slices) evoked by maximum-length-sequences in auditory neuropathy: evidence for a cochlear pre-synaptic origin. Electroencephalogr Clin Neurophysiol 1997; 104: 10-16. [CrossRef]
20. Berlin CI, Hood LJ, Morlet T, Wilensky D, St John P, Montgomery E, et al. Absent or elevated middle ear muscle reflexes in the presence of normal otoacoustic emissions: a universal finding in 136 cases of auditory neuropathy/dys-synchrony. J Am Acad Audiol 2005; 16: 546-53. [CrossRef]
21. Acoustics. Statistical distribution of hearing thresholds as a function of age ISO 7029:2000.