Evaluation of optical coherence tomography findings and visual evoked potentials in Charcot-Marie-Tooth disease

Aysin Tuba Kaplan (aysintuba@yahoo.com)
Istanbul Dr Lufti Kirdar Kartal Egitim ve Arastirma Hastanesi https://orcid.org/0000-0003-0793-5530
Sibel Oskan Yalcin
Istanbul Dr Lufti Kirdar Kartal Egitim ve Arastirma Hastanesi
Safiye Gunes Sager
Istanbul Dr Lufti Kirdar Kartal Egitim ve Arastirma Hastanesi
Ayberk Türkyılmaz
Karadeniz Teknik Universitesi Tip Fakultesi
Rahşan İnan
Istanbul Dr Lufti Kirdar Kartal Egitim ve Arastirma Hastanesi

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Abstract

Purpose: To evaluate the spectral-domain optical coherence tomography (SD-OCT) findings and pattern visual evoked potential (VEP) in Charcot-Marie-Tooth (CMT) disease.

Methods: Seventeen patients with CMT disease and 17 control subjects were included in the study. The patients were divided into two groups according to conduction velocity and inheritance pattern as demyelinating type (CMT 1) and axonal type (CMT 2). The average retinal nerve fiber layer (RNFL) thickness, RNFL thicknesses of all quadrants, and thicknesses of the ganglion cell layer complex (GCC) were measured using SD-OCT. Pattern VEP recordings were evaluated in both groups.

Results: The average and four quadrants of RNFL thicknesses, and superior and inferior GCC thicknesses were significantly thinner in the CMT patients compared with healthy individuals, but there were no statistically significant differences between the CMT groups. There was a significant positive correlation between age and all RNFL and GCC thicknesses in the CMT 2 group and between age and RNFL thickness of the temporal quadrant in the CMT 1 group. P100 latencies were significantly delayed in the CMT groups compared with controls and there were no significant differences in P100 latencies between the CMT groups ($p<0.001$). VEP amplitudes were in normal ranges in the CMT groups.

Conclusion: This study showed that RNFL and GCC thicknesses were significantly reduced and VEP latencies were prolonged in patients with CMT with normal clinical examinations. Our results suggest that optic nerves may be affected more frequently in patients with CMT than is detected in clinical examinations.

Introduction

Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor sensory neuropathy (HMSN) is one of the most common inherited diseases of the peripheral nervous system. In general, it is reported that it affects 1 in 2500 individuals in society [1]. The most widely known classification integrate clinical findings with a pattern of inheritance [(autosomal dominant (OD), autosomal recessive (OR), or X-linked] and electrophysiologic or anatomic signs of disease. In the demyelinating form, the myenlin sheaths surrounding the axons of the peripheral nerves are affected and progress with a low nerve conduction velocity in electromyography (EMG). In the axonal form, it is observed that the conduction velocities are normal or slightly reduced, and axonal loss is observed in nerve biopsies [2].

In addition to the conduction velocity, the inheritance pattern also divides CMT into subcategories: CMT 1 as the demyelinating type (autosomal dominant), CMT 2 as the axonal type (OD or OR), CMTX (classically X-linked but there may be OD and OR variants) with intermediate conduction rate, and CMT 4 again as the demyelinating type.

Ocular involvement in CMT was first described as optic atrophy in the axonal subtype by Vizioli in 1889.[2] Over the years, this association has been well documented by other authors and has resulted in a

subclassification called HMSN type VI. More recent case series and studies have documented optic nerve involvement in 10-36% of patients with CMT2A, which are characterized by severe vision loss and optic atrophy [3–7]. However, visual symptoms, abnormal visual evoked potentials, and transient white matter abnormalities on magnetic resonance imaging (MRI) have been defined in patients with CMT 1 [8–11].

In our study, it was aimed to gain a better understanding of the structural and functional integrity of the optic nerve in two types of CMT and compare these groups with normal healthy individuals. Color vision, visual field, pattern VEP, and SD-OCT measurements of the RNFL and GCC thicknesses were evaluated.

Methods

This study was approved by the ethics committee of Kartal Dr. Lütfı Kırdar City Hospital with 2021/514/215/3 decision number and was performed in accordance with the Declaration of Helsinki. All patients were informed about the purpose of the study and informed consent was obtained.

Patient Selection

Patients with genetic neuropathy meeting the clinical and/or electromyography (EMG) diagnostic criteria defined by Piscotta et al. were included in the study [12]. Patients with the following clinical presentation were included in the study: Patients with normal early developmental process followed by gradual weakness and sensory loss during the first two decades of life, positive family history and/or presentations in childhood, slow progression, the presence of foot deformities, and no positive sensory symptoms (e.g. dysesthesias, paresthesias) in the presence of sensory signs. Inflammatory, toxic, or infectious polyneuropathies and those accompanying other genetic diseases (such as metachromatic leukodystrophy, Refsum disease) were not included in the study.

All patients underwent a comprehensive neuro-ophthalmologic examination including color vision, visual field (30–2 SITA program, Humphrey VFA; Carl Zeiss, USA), visual acuity, intraocular pressure measurement, and fundus examinations. Snellen chart was used for visual acuity [evaluated as logarithm of the minimum angle of resolution (LogMAR)] and color vision was assessed using Ishihara color plate testing.

Secondary optic nerve or retinal diseases such as glaucoma, papillitis, optic neuropathies of different etiologies, or age-related macular degeneration were considered as exclusion criteria.

Optical coherence tomography

The GCC and RNFL thicknesses were obtained using SD-OCT (Nidek RS-3000 Advance, Japan). The peripapillary RNFL thickness in each 90-degree quadrant (superior, inferior, temporal, and nasal) was calculated within a 3.45-mm diameter scan circle around the optic disc. The GCC thickness was accepted as between the internal limiting membrane and the inner plexiform layer in the macular region. In the GCC chart (Nidek RS3000), the macular region was divided into two sectors around the fovea as superior and

inferior (in 9 mm size). Only high-quality scans with high reliability were assessed in the analysis. All SD-OCT parameters were analyzed by the same experienced technician.

Visual evoked potential

Visual evoked potential recordings (EMG/EP MEB-2300K, Nihon Kohden, Tokyo, Japan) were performed according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards [13]. The study was done in a dark and quiet room at a 1 m distance by the same technician. According to the International 10-20 system, the active electrode was at Oz and the reference electrode was at Fz location. Visual stimulation was performed using a white and black checkerboard, using a pattern-reversal method at 1/sec frequency with a check size 50'. The recordings were evaluated separately for each eye. At least 100 stimuli from two recordings were averaged. The P100 wave was defined as the first major positive peak response with a latency of approximately 100 milliseconds (ms). The latency of P100 wave and amplitude were evaluated. For our laboratory, the normal ranges were 98-115 ms for the P100 latency and 5.8-16 microvolts (μV) for the P100 amplitude. Abnormal P100 latency was considered as values above the mean ± 2SD of the normal group.

Statistical analysis

All data were evaluated using the IBM SPSS Statistics Standard Concurrent User V 26 statistical package program (IBM Corp., Armonk, New York, USA). Descriptive statistics are given as the number of units (*n*), percent (*%*), mean ± standard deviation, median (*M*), minimum (*min*), maximum (*max*), and interquartile range (*IQR*). The normality of data distribution of the numerical variables was evaluated using the Shapiro-Wilk test of normality. Age comparisons were made using the Mann-Whitney *U* test. A comparison of eye parameters was performed using the Kruskal-Wallis H test. Dunn-Bonferroni test was used as a multiple comparison test. Chi-square and Fisher's exact tests were used to compare groups with categorical variables. Correlations between age variables and eye parameters were evaluated using Spearman correlation analysis. The results were rated according to the variation of the rho range as weak (0.0-0.19), low (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80–1.00) correlations. A p-value of <0.05 was accepted statistically significant.

Results

We studied 17 patients with CMT, nine with CMT 1 (seven males, two females), and eight with CMT 2 (four males, four females). The mean age was 32.6±14.4 (range, 8-48) years in the CMT 1 group and 24.0±12.5 (range, 12-40) years in the CMT 2 group. Eleven (64.7%) of the patients in the CMT group and 12 (70.6%) of the individuals in the healthy group were males. The ages of all participants were between 8.0 and 50.0 years. The age and sex distributions of the groups were statistically similar (Table 1). Genetic mutation in the PMP22 gene was detected in all CMT1 (n=9) patients. DCFA8 (n=2), HINT1 (n=2), NEFL (n=1), and AARS1 (n=1) mutations were detected in patients with CMT 2 (Table 2). Despite having a family history and positive EMG findings, no mutation was detected in two patients. There were no

scotomas in visual fields and color vision was normal in both CMT groups. The visual acuity was 0.06±0.1 LogMAR in the CMT 1 group and 0.02±0.02 LogMAR in the CMT 2 group. The anterior segment and intraocular pressure were normal in both groups. There was no optic atrophy in any patients.

Table 1
Descriptive characteristics of the study groups

	Study Groups		**Test Statistics**	
	CMT *n*=17	Healty *n*=17	Test value	*p* value
Sex, *n* (%) Male Female	11 (64.7) 6 (35.3)	12 (70.6) 5 (29.4)	$\chi^2 = 0.134$	0.999
Age, (*years*) *mean*±SD *M* (*min-max*)	28.5±13.8 34.0 (8.0-48.0)	27.6±13.6 31.0 (9.0-50.0)	*z*=0.173	0.865

sd: Standard deviation, *M*: Median, *min*: minimum, *max*: Maximum, χ^2: Chi-square test, *z*: Mann-Whitney *U* test

Table 2
Descriptive characteristics of the CMT groups

	CMT Groups		**Test Statistics**	
	Demyelinating *n*=9	Axonal *n*=8	Test value	*p* value
Gender, *n* (%) Male Female	7 (77.8) 2 (22.2)	4 (50.0) 4 (50.0)	χ^2 = 1.431	0.335
Age, (*years*) *mean*± *sd* *M* (*min-max*)	32.6±14.4 39.0 (8.0-48.0)	24.0±12.5 22.5 (12.0-40.0)	*z*=1.543	0.139
Genetic, *n* (%) None OD OR	0 (0.0) 9 (100.0)	2 (25.0) 3 (37.5) 3 (37.5)	χ^2 = **7.070**	**0.009**
Mutation, *n* (%) AARS1 DCAF8 HINT1 None NEFL PMP22	0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 9 (100.0)	1 (12.5) 2 (25.0) 2 (25.0) 2 (25.0) 1 (12.5) 0 (0.0)	χ^2 = **10.733**	**0.003**

In the evaluation of SD-OCT parameters, the average RNFL thickness was 101.0 µm in CMT 1 patients, 98.0 µm in CMT 2 patients, and 109.0 µm in the control subjects. No statistically significant differences were found between the CMT groups; however, the average RNFL thickness was significantly higher in healthy controls compared with the CMT groups (p<0.001). The RNFL thicknesses of all quadrants (nasal, temporal, superior, and inferior), and superior and inferior GCC thicknesses were similar in the CMT 1 and CMT 2 groups, but all were statistically significantly thinner than the controls (p<0.001, p<0.001, p=0.006, p=0.022, p<0.001, and p<0.001, respectively) (Table 3)(Figure 1A,B). There was a significant positive correlation between age and OCT parameters in all RNFL and GCC thicknesses in the CMT 2 group and between age and temporal quadrant RNFL thickness in the CMT 1 group (Table 4). Median VEP P100 latencies were 117.4 (8.9) ms in the CMT 1 group and 121.9 (19.9) ms in the CMT 2

group. P100 latencies were significantly prolonged in both CMT groups compared with the controls (p<0.001) and there were no significant differences in P100 latencies between the CMT groups. VEP amplitudes were within normal limits in all patients (Table 3).

Table 3
Statistical analyses of the comparison of OCT parameters and VEP findings among the three groups.

	Groups			**Test Statistics**	
	Demyelinating *M* (*IQR*)	Axonal *M* (*IQR*)	Healty *M* (*IQR*)	*H* value	*p* value
Average RNFL	101.0 (17.7)[a]	98.0 (7.2) [a]	109.0 (14.2)[b]	**19.673**	**<0.001**
Nasal RNFL	68.0 (10.5)[a]	70.5 (20.7)[a]	82.0 (13.2)[b]	**20.527**	**<0.001**
Temporal RNFL	64.0 (8.5)[a]	67.0 (24.2)[a]	74.0 (8.2)[b]	**24.795**	**<0.001**
Superior RNFL	121.0 (14.0)[a]	123.5 (11.2)[a]	137.0 (17.7)[b]	**10.239**	**0.006**
Inferior RNFL	122.5 (20.0)[a]	125.0 (34.5)[a]	136.0 (13.2)[b]	**7.642**	**0.022**
Superior GCC	92.0 (5.2)[a]	93.5 (15.5)[a]	100.0 (5.5)[b]	**22.565**	**<0.001**
Inferior GCC	96.0 (6.0)[a]	97.0 (14.0)[a]	103.5 (6.2)[b]	**24.172**	**<0.001**
VEP P100	117.4 (8.9)[a]	121.9 (19.9)[a]	108.0 (5.2)[b]	**23.178**	**<0.001**
Amplitude	6.4 (3.3)	7.4 (2.9)	7.9 (2.6)	2.879	0.237

RNFL: Retinal nerve fiber layer GCC: Ganglion cell complex VEP: Visual evoked potential M: Median, *IQR*: Interquartile range, *H*: Kruskal-Wallis test, *a*, *b*, and *c* superscripts indicate differences between groups. There is no statistical difference between groups with the same superscripts.

Table 4
Correlation of age and OCT parameters

	Study groups *n*=68		**Demyelinating** *n*=18		**Axonal** *n*=16		**Healty** *n*=34	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Average RNFL	0.039	0.755	-0.370	0.130	**0.899**	**<0.001**	-0.126	0.476
Nasal RNFL	0.049	0.694	-0.129	0.610	**0.624**	**0.010**	0.184	0.299
Temporal RNFL	0.166	0.175	**0.555**	**0.017**	**0.683**	**0.004**	0.083	0.640
Superior RNFL	-0.176	0.151	-0.008	0.974	**0.686**	**0.003**	**-0.540**	**0.001**
Inferior RNFL	**-0.242**	**0.046**	**-0.540**	**0.021**	**0.752**	**0.001**	**-0.569**	**<0.001**
Superior GCC	0.174	0.156	-0.023	0.928	**0.786**	**<0.001**	-0.018	0.917
Inferior GCC	-0.018	0.884	-0.119	0.638	**0.587**	**0.017**	-0.254	0.148

RNFL: Retinal nerve fiber layer GCC: Ganglion cell complex rho: Spearman correlation coefficient

Discussion

In this study, 17 patients with CMT with normal visual acuity, color vision, and visual fields were evaluated. The RNFL and GCC thicknesses were similar in the CMT 1 and CMT 2 groups; however, there were statistically significant reductions in average RNFL thickness, RNFL thicknesses of all quadrants, and GCC thicknesses in the CMT groups compared with healthy controls. In the literature, studies on CMT are mostly case series, especially case series of optic atrophy associated with CMT 2A [3, 14–18]. Mutations in the mitofusin 2 (MFN2) protein are the primary cause of autosomal dominant CMT, also named CMT 2A. MFN2 is the essential intrinsic membrane protein for mitochondrial axonal transport in the gene, of which more than a hundred mutations have been reported to date [19].

MFN2 plays an important role in mitochondrial fusion with the MFN1 and OPA1 genes in the mitochondrial membrane. Although the OPA1 gene is the most common cause of autosomal dominant optic atrophy, it is not surprising that optic atrophy develops in CMT 2A due to MFN2 mutations [20, 21]. Hamedani et al. compared patients with CMT 1A, CMT 2A, and CMT X1 and reported no significant differences in average RNFL thickness, GCC thickness, and contrast acuity between the patients. However, they did not compare their patients with healthy individuals. They detected optic atrophy in one of their five patients with CMT2A and did not include this patient's outliers in the study, ultimately suggesting that optic atrophy was specific to certain mutations in patients with CMT2A [6]. Chung et al. studied 21 patients with the MFN2 mutations and they demonstrated optic atrophy only in patients with highly severe axonal CMT with an early age at onset and not in those with a late age at onset. They suggested that axonal CMT with optic neuropathy harboring MFN2 mutations might be a variation of an early-onset CMT2A phenotype [22]. Similarly, Zuchner et al. reported a more benign process and higher

visual improvement in patients with later onset of disease and more severe visual symptoms and a progressive prognosis in patients with earlier onset of disease [23]. In our study, a positive correlation was also shown between age and OCT parameters. In patients with CMT2 with early age of onset, the RNFL thicknesses of four quadrants and superior-inferior GCC thicknesses were significantly thinner, whereas, in patients with early-onset CMT1, temporal RNFL thickness was significantly thinner than those with late age at onset.

Botsford et al. evaluated four patients with CMT (2 CMT2A, 2 CMT1A) and found reduced RNFL and GCC thicknesses in all patients with CMT2A, and normal RNFL thickness in all patients with CMT1A, and mildly decreased GCC thickness in one patient with CMT1A. They also evaluated pattern VEP recordings and reported prolonged latency in a patient with CMT2A and a patient with CMT1A [7]. Bird et al. reported prolonged pattern VEP latencies in 16% of patients with CMT (24 CMT1 and 1 CMT 2). They also found no consistent correlation between pattern VEP and disease severity [9]. Leblhuber et al. showed no pathologic changes in pattern VEP latencies between patients with CMT and healthy individuals, there was no correlation between motor nerve velocity and P100 latencies, but they demonstrated significant alterations of P 100 latencies in a family [24]. Similarly, significant prolongation of P100 latency was detected in both CMT groups compared with healthy controls and amplitudes were within normal levels in our study. Alajouanine et al. reported demyelination of the optic nerve at autopsy examination in a 65-year-old man with CMT, and blindness and optic neuropathy developed 40 to 50 years after disease onset [9].

In clinical examinations, our patients had no signs of optic neuropathy, and the detected pattern VEP and OCT abnormalities were not correlated with the clinical findings of the patients. Delayed conduction time in the optic nerve and thinning of the GCC thickness may be due to demyelination or axonal damage at the level of the retina. The frequency of pathologic changes suggests that the optic nerve in patients with CMT is involved more frequently than predicted from clinical examination.

The limitation of our study is the small sample size, but as far as we know, there is no study evaluating the pattern VEP with RNFL and GCC thicknesses in patients with CMT by comparing them with healthy individuals.

In conclusion, OCT and pattern VEP testing are potentially useful to evaluate optic nerve function and integrity in patients with axonal and demyelinating CMT with normal clinical examination. Further studies will be required to determine the prevalence of ganglion cell loss in this disease.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest in this manuscript.

The authors certify that they have obtained all appropriate patient consent forms.

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Figures

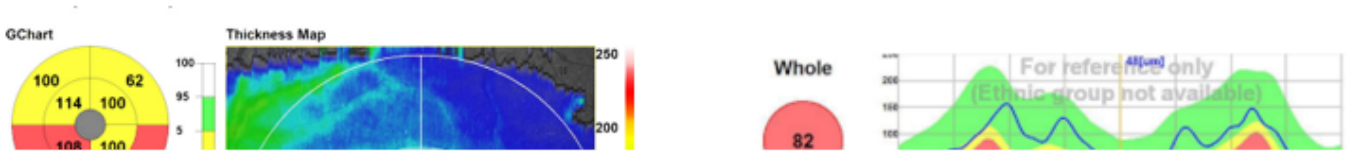

Figure 1

Retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thinning in a 12 years old patient with CMT 2. **A** GCC thinning in superior and inferior quadrants **B** Thinnig of average RNFL and the quadrants of temporal and inferior RNFL.