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Coexistence of Charcot Marie Tooth disease type 1A and diabetes in Taiwan: A clinicopathological study

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ABSTRACT

Background: Charcot Marie Tooth disease type 1A (CMT1A) is the most commonly inherited demyelinating polyneuropathy with variable phenotypes, affected by several comorbidities, especially diabetes mellitus (DM). Previous studies showed that DM exacerbates the clinical manifestations of CMT1A.
Patients and methods: We retrospectively evaluated patients with CMT1A in our hospital, and identified three groups among 12 cases, which comprised four patients with CMT1A, four with CMT1A + DM, and four with DM. We reviewed the CMT neuropathy score (CMTNS), electrophysiological data, and histomorphological parameters of the sural nerve, including fiber density, myelin thickness, axon diameter, g-ratio, regenerative clusters, and regeneration ratio.
Results: The CMTNS was significantly higher in patients with CMT1A + DM (21.5 ± 2.52) than in those with CMT1A only (10.8 ± 4.4; $p = 0.03$). Pathological findings in patients with CMT1A + DM included a significant decrease of myelinated fiber density ($p = 0.02$) and reduction in the regenerative ratio ($p = 0.01$), indicating severe degeneration with impaired regeneration. In non-parametric analyses, DM was found to play a more important role than CMT1A in influencing nerve degeneration and regeneration.
Conclusions: In patients with CMT1A, DM exacerbated clinical and pathological manifestations including increased loss of myelinated fibers, abnormal axon–myelin interaction, and impaired nerve regeneration.

1. Introduction

Charcot Marie Tooth disease type 1A (CMT1A), caused by a duplication of *PMP22* within chromosome 17, is the most commonly inherited demyelinating polyneuropathy. The classical symptoms of Charcot Marie Tooth disease type 1A (CMT1A) include symmetrical, slowly progressive, distal muscle weakness and wasting, distal sensory loss, foot deformities, and absent or diminished deep tendon reflexes. Subjects with CMT1A exhibit uniformly demyelinating sensorimotor polyneuropathy. Histopathological findings of sural nerve biopsy revealed demyelination–remyelination with onion bulb formations (OBFs) [1]. In addition, length-dependent axonal dysfunction or degeneration in patients with CMT1A was also reported as an important pathological feature, which results from primary demyelination and is the main cause of neurological disability [2]. Previous publications described intra- and inter-familial variations in clinical manifestations of CMT1A. In addition, several conditions could exacerbate the phenotypic variability of CMT1A [3,4]. However, factors influencing the CMT1A phenotype are not well understood. Theoretically, the causes of neuropathy are thought modify CMT1A phenotypes. Toxin- or medication-related worsening of neuropathy in CMT was described, especially with administration of vincristine [5]. Several cases and families of CMT in association with diabetes mellitus (DM) were reported previously [6–9]. A case–control study demonstrated that patients with CMT1A and DM show deterioration in the CMT neuropathy score (CMTNS), with more pronounced motor involvement in patients with DM than in those without DM. The electrophysiological studies showed a tendency of worsening motor impairment in patients with CMT1A and DM. The study suggested that diabetes contributed to increasing the phenotype severity in patients with CMT1A [10]. Recently, a retrospective study evaluated a large population of patients having CMT1A with different comorbidities including, DM, obesity, hypothyroidism, and exposure to toxic substances. This study reported a tendency toward worsening of the clinical and neurophysiological manifestations of CMT1A in patients with CMT1A and DM [11]. In addition, peripheral neuropathy is a well-known complication of DM. The most common cause of neuropathy is diabetes, and up to 50% of the patients eventually develop neuropathy during the course of their disease. The most frequent presentation is a distal symmetrical polyneuropathy with the typical presentation of insidious symmetrical loss of sensory modalities, including predominant small-fiber and large-fiber neuropathies [12]. Neurophysiological parameters were not affected significantly. Thus far,

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there have been no systematic pathological studies with respect to CMT1A and comorbidities such as DM. We aimed to review patients with CMT1A who were comorbid with DM, specifically focusing on the pathological aspects.

2. Materials and methods

2.1. Subjects

We retrospectively reviewed families of CMT1A whose diagnosis was confirmed by DNA analysis at our hospital. In addition, we retrieved our archives of nerve biopsy pathology. Four patients each with CMT1A, CMT1A and diabetes mellitus (CMT1A + DM), and DM and six normal subjects were identified. The clinical diagnosis of CMT1A was satisfied with the widely accepted criteria as previously reported [1]. Genetic diagnosis of CMT1A was confirmed by the method of polymorphic short tandem repeats [13]. The diagnosis of diabetes was based on the criteria of a random blood glucose level of 200 mg per dL (11.1 mmol per L) or greater if classic symptoms of diabetes (e.g., polyuria, polydipsia, weight loss) were present. Furthermore, diabetes was confirmed if the level of HbA1C was greater than 7% on two separate occasions. The CMT neuropathy score (CMTNS)—an objective score, based on the history, neurological examination, and clinical neurophysiology—was applied to patients with CMT1A and those with CMT1A + DM to quantitatively assess the progression of neuropathic impairment [14,15].

2.2. Electrophysiological studies

Electrophysiological studies were performed using a Medlec electromyograph. All patients underwent motor nerve conduction studies in the upper and lower extremities, including median, ulnar, tibial, and peroneal nerves. Ring electrode recordings were carried out to assess sensory conduction of the median, ulnar, tibial, peroneal, and sural nerves. The parameters of distal latency, nerve conduction velocity, amplitude of compound muscle action potential, amplitude of sensory action potential, and minimal F response were recorded. Needle electromyography was performed for evidence of denervation in selected muscles. The normal electrophysiological data obtained from 33 normal subjects were applied as a control.

2.3. Nerve biopsy

A fascicular sural nerve biopsy was performed behind the lateral malleolus under local anesthesia. Specimens were fixed in 2.5% glutaraldehyde in 0.05 M Na cacodylate buffer, post-fixed in 1% osmium tetroxide, and processed with Araldite®. The proximal 1 cm of the nerve was stored in unpolymerized Araldite® for teasing. Transverse sections of 10-μm thickness were stained with toluidine blue, hematoxylin, and eosin. A light microscope (Leica AG, CH-9435, Heerbrugg, Switzerland) with image software (Image-Pro Plus Version 4.5, Media Cybernetics, Silver Spring, MD, US) was used to measure the fascicular area, total myelinated fibers, size of myelinated fibers and axons, myelin thickness, and perimeters. For determination of the g-ratio (axon diameter/fiber diameter), measurements were made of the axon and total fiber area and were converted to the diameter of a circle having an equivalent area. Regenerative cluster formation was defined as three or more compact myelinated fibers within a basal membrane. The regenerative clusters of each sural nerve were counted individually. The cluster ratio was calculated as the number of regenerating clusters per 1000 myelinated fibers [16,17].

2.4. Statistical analysis

In this study, we used the mean, standard deviation, median, minimum, and maximum values. We analyzed several clinical and

Table 1
General data, Charcot Marie Tooth (CMT) neuropathy scores, and results of the nerve conduction study of patients.

Patients		Age (yr)/gender	DM history (yr)	HbA1c (%)	Fasting sugar (mg/dL)	CMT neuropathy score	Median nerve		Ulnar nerve		Tibial nerve		Sural nerve	
							NCV (m/s)	Amp. (mV)	NCV (m/s)	Amp. (mV)	NCV (m/s)	Amp. (mV)	D.L. (ms)	SAP (μV)
CMT1A	1	24/F	–	–	–	8	23	6.7	17	4.1	23	0.8	NP	NP
	2	25/M	–	–	–	6	29.5	7.3	25	5.9	24.4	3.6	6.9	4.1
	3	62/F	–	–	86	15	32.4	2.3	35.1	1.6	NP	NP	NP	NP
	4	79/M	–	–	84	14	NP	NP	23	2.4	NP	NP	NP	NP
	Average	47.5 ± 27.5				10.8 ± 4.4	28.3 ± 4.8	5.4 ± 2.7	25.0 ± 7.5	3.5 ± 1.9	23.7 ± 0.1	2.2 ± 2.0		
CMT1A + DM	5	40/M	3	12.6	233	21	16.6	0.1	16.4	0.2	NP	NP	NP	NP
	6	43/F	12	13	250	21	19.8	0.6	14.7	0.4	NP	NP	NP	NP
	7	52/M	10	7.4	91	19	18.9	0.8	15.4	2.0	NP	NP	NP	NP
	8	58/F	11	7.3	138	25	21	2.0	NP	NP	NP	NP	NP	NP
	Average	48.3 ± 8.3	9 ± 4.1	10.1 ± 3.2	179 ± 76	21.5 ± 2.5	19.1 ± 1.9	0.9 ± 0.8	15.5 ± 0.9	0.9 ± 1.0				
DM	9	46/M	5	5.4	146		48.9	11.9	57.7	9	44.9	11.3	3.3	6
	10	69/M	10	7.5	343		NP	NP	43.5	0.04	NP	NP	NP	NP
	11	75/M	0.8	5.3	87		50.5	6	51.9	6.6	39.7	3	NP	NP
	12	76/M	8	8.8	192		50	7	50	11.2	33.5	5.2	3.5	8
	Average	66.5 ± 14.0	6.0 ± 4.0	6.8 ± 1.7	192 ± 109		49.8 ± 3.2	8.3 ± 3.2	50.8 ± 5.9	6.71 ± 4.8	39.4 ± 5.7	6.5 ± 4.3		
Normal	(n = 33)			4.2–6.2	65–115		58.9 ± 4.3	13.2 ± 3.6	62.1 ± 3.7	11.9 ± 3.0	51.6 ± 5.2	14.2 ± 5.0	3.0 ± 0.3	12.5 ± 5.2

NCV: nerve conduction velocity; SAP: sensory action potential; NP: no pick-up.