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Charcot-Marie-Tooth disease type 1C: Clinical and electrophysiological findings for the c.334G>A (p.Gly112Ser) LITAF/SIMPLE mutation

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Abstract

Introduction—Charcot–Marie–Tooth disease type 1C (CMT1C) is a rare, dominantly inherited neuropathy caused by mutations in the lipopolysaccharide-induced tumor necrosis factor (*LITAF*) or small integral membrane protein of the lysosome/late endosome (*SIMPLE*) gene.

Methods—We present a case series comprised of 10 patients in whom CMT1C is caused by a Gly112Ser substitution in the encoded protein. We focus on clinical presentation, electrodiagnostic analyses, and our findings in the context of previously described cases.

Results—The Gly112Ser mutation causing CMT1C is a mild form of CMT, as patients walked on time, had less weakness than those with Charcot–Marie–Tooth disease type 1A (CMT1A), had a CMT neuropathy score (CMTNS) indicative of mild disease, and had faster ulnar and median motor nerve conduction velocities compared to those with CMT1A.

Conclusion—The G112S mutation in *LITAF* seems to be clinically indistinguishable from a mild presentation of CMT1A. *Muscle Nerve*, 2017

Charcot–Marie–Tooth disease type 1C (CMT1C) is a rare, dominantly inherited neuropathy caused by mutations in the lipopolysaccharide-induced tumor necrosis factor (*LITAF*) gene, also known as small integral membrane protein of the lysosome/late endosome (*SIMPLE*). [1–3] Given the rarity of CMT1C, we looked at our patients with the Gly112Ser (G112S) mutation and the specific clinical and electrodiagnostic phenotype associated with this mutation.

Previous reports have not focused on the G112S mutation in clinical and electrodiagnostic detail. Clinically, CMT1C has been reported to have minor symptoms with no risk of being wheelchair-bound.[4, 5] A previous report of the G112S mutation resulted in 1 patient with minimal weakness and another with severe weakness and pseudoradicular symptoms.[6] Electrodiagnostically, patients with CMT1C have been reported previously to have slowed nerve conduction velocities (<33 m/s),[4, 6] but some studies have reported conduction blocks,[7] temporal dispersion,[8] or even an axonal CMT pattern.[6]

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Herein we evaluate 10 patients with the G112S mutation and compare their electrodiagnostic and clinical features to those with the most common inherited demyelinating neuropathy, CMT1A (Charcot–Marie–Tooth disease type 1A).

METHODS

Patients and Chart Review

This study was approved by the institutional review board at the University of Iowa and informed consent was obtained from each subject. We performed a retrospective analysis of data from both electrodiagnostic testing (EDx) and clinical assessment for 10 patients previously diagnosed with CMT1C caused by the c.334G>A (p.Gly112Ser) mutation in the *LITAF* gene, which has been reported to be a pathogenic missense mutation.[6] Patients were evaluated by highly experienced neurologists in a CMT clinic, at either Wayne State University or the University of Iowa. Patients were diagnosed with CMT1C if they had either of the following: (1) a positive genetic test; or (2) a first- or second-degree relative with a positive genetic test and a CMT phenotype. Clinical and electrophysiological features of a patient with this mutation reported in this study were described previously.[6] In all patients except patient 2 an autosomal-dominant pattern of inheritance was determined. Patient 2 had a spontaneous *de-novo* mutation. In addition, for all but patient 2, the mother had a normal pregnancy and delivery. In the case of patient 2, the mother used amphetamines, methamphetamines, marijuana, and alcohol during her pregnancy.

Four women and 6 men were included in the study. The mean age at examination was 35 (range 5–72) years. EDx data were available for 7 of the 10 patients studied, and data from a complete neurological exam were available for 9 of the 10 patients. Motor nerve (MNCS) and sensory nerve conduction study (SNCS) testing of the median, ulnar, fibular, and sural nerves had been performed using conventional methods (Nicolet Viking, Synergy EMG, or Nihon-Kohden system).[9] A block in motor conduction was defined as a ≥50% reduction in the amplitude of the proximal negative (vs. distal negative) peak compound muscle action potential (CMAP), if the distal negative peak CMAP is ≥20% of the normal lower limit.[10]

Calculation of Neuropathy Score

A CMT neuropathy score (CMTNS) was calculated using a modified scale that had been validated previously as a measure of disability caused by CMT.[6] Using this scale, level-of-impairment scores were classified as follows: 0–10 = mild impairment; 11–20 = moderate impairment; and ≥21 = significant impairment.[6] The CMTNS has 9 scored components: 3 are symptoms; 4 are signs observed by a clinician; and 2 are EDx data. Each measurement is scored from 0–4, for a possible total of 36 points. For those patients who did not have EDx data, the CMTNS was out of 28 points, and thus a weighted average was used to generate an average CMTNS score.

RESULTS

Clinical Symptoms

A complete list of clinical symptoms for all patients is listed in Table 1. All patients walked on time (at or before 18 months) and the first symptoms included being the slowest runner, walking on toes, or having a foot deformity. Motor and sensory symptoms in the lower extremities were observed in 60% of patients. All patients had foot deformities. The average CMTNS was 7.5, range 2–11 (0 = normal, 36 = maximum abnormal score).[6] All patients complained of cramps and pain in feet or legs. Fifty percent of patients complained of exertional calf pain, which was worse after exercise or at the end of the day.

Clinical Signs

In patients with the CMT1C G112S mutation, sensory findings and foot deformities were similar to those reported for CMT1A, but muscle weakness and areflexia occurred less frequently (Fig. 1).

MNCS in CMT1C

No conduction block or temporal dispersion was seen in patients with the CMT1C G112S mutation. Velocity of motor conduction ranged from 19.7 to 38.5 m/s (Table 2). When compared with the EDx in those with CMT1A, the CMT1C motor nerve conduction studies had a higher CMAP, faster conduction velocities, and shorter distal motor latencies.

SNCS in CMT1C

The sural sensory nerve action potential (SNAP) was absent in all patients tested, and the median and ulnar SNAPs were absent in 43% of patients tested. Sensory nerve conduction velocities ranged from 20 to 41 m/s (Table 3).

DISCUSSION

CMT1C is a rare hereditary demyelinating neuropathy with few data regarding clinical outcomes for various disease-causing mutations. Herein we have analyzed 10 patients with the G112S mutation in the *LITAF* gene.

Previous reports of CMT1C have suggested that this condition results from conduction block, temporal dispersion, or axonal neuropathy.[6, 7] However, our study did not reveal either conduction blocks or temporal dispersion in any of the patients expressing the CMT1C-associated G112S form of *LITAF*, suggesting that this protein causes a uniformly demyelinating form of CMT.

The patients in our study more frequently displayed lower more than upper extremity symptoms, and the lower extremity problems were predominantly structural, involving mainly eversion of the foot. Although all of the patients had abnormal foot structure and 90% complained of problems with their feet, only 44% had weakness in the lower extremities (Table 1). In addition, only 30% had undergone foot surgery. Consistent with this finding, over half of the patients had preserved reflexes (Tables 1 and 2) and did not exhibit

as much weakness as their CMT1A counterparts on physical examination (Table 1). We also observed a lower CMTNS in patients with CMT1C G112S (7.5 of 36, on average); this is milder than the average CMTNS for patients with CMT1A (~13–14).[11, 12]

Fifty percent of our patients exhibited exertional calf pain; this is not typical of the usual foot pain seen in the majority of CMT1A patients.[13]

Consistent with previous reports, we observed some variability in the age at which symptoms became apparent.[2, 4, 7] Although in the majority of patients the symptoms began in childhood, in 2 patients the symptoms did not emerge until later in life; 1 presented in his fourth decade and the other in his sixth decade. Therefore, the G112S mutation causing CMT1C does not appear to have a consistent age at which symptoms become apparent.

Previous reports have suggested that nerve conduction studies of the lower limbs are more frequently abnormal in those with CMT1C.[7] Previous reports have also identified patients with CMT1C with a few reported intermediate nerve conduction velocities and conduction block.[7, 14] In our study of those with the G112S mutation, the sural SNAP was absent in all patients, whereas the ulnar CMAPs and SNAPs were affected in only a subset, consistent with the lower extremities being more frequently involved electrodiagnostically. Conduction block was not noted in our patients. Also, in our study, only 2 nerve conduction velocities in the intermediate range were observed: 38 m/s and 39 m/s. However, it should be noted that conduction velocity values for a single nerve are not sufficient to classify CMT as intermediate. The term “intermediate” reflects the type of CMT and takes into account axonal and demyelinating pathology; it does not reflect an nerve conduction velocity (NCV) value.[14] EDx abnormality in CMT1C due to the G112S mutation is found in the lower extremities more than the upper extremities. Findings are in the demyelinating, not intermediate, range with no evidence of conduction block. Although the NCVs are in the demyelinating range for CMT1C, they are slightly faster in the upper extremities compared with the lower extremities and have a higher CMAP amplitude (Table 2), suggesting that the motor nerve conduction studies are milder in those with CMT1C compared to those with CMT1A.

A previous report of an analysis of patients with the c.430G>A p.Val144Met mutation in *LITAF* demonstrated that this mutation results in clinical features similar to those reported in our study.[2] Although conduction blocks were not reported, the age of onset was variable, and patients displayed a demyelinating neuropathy. As in our study of the G112S mutation, patients with the Val144Met variant had normal tendon stretch reflexes, were more affected in the lower extremities, and reported foot pain in both mother and son.[2] Thus, our study brings to light another mutation in *LITAF* that results in a milder form of CMT. In addition, a study involving 38 patients with 4 missense mutations (p.Ala111Gly, p.Gly112Ser, p.Pro135Ser, p.Pro135Thr) included several adults who presented with minor symptoms, and none of the 38 patients were wheelchair-bound.[4] The report of a family with the p.Pro135Ser mutation suggested variable age of onset, variable clinical presentation (from mild symptoms of sensory loss, bilateral plantar ulcers, and no muscle weakness to more

significant gait difficulties and distal weakness), and the presence of a demyelinating neuropathy with conduction blocks without excessive temporal dispersion.[7]

It is suspected that CMT1C resembles CMT1A because of the possible function of *LITAF*, a mutation that could potentially result in an excess of peripheral myelin protein-22 (PMP-22). *LITAF* is highly expressed in peripheral nerves and Schwann cells.[15] The G112S mutation in *LITAF* near the transmembrane domain has been suggested to result in mislocalization of the LITAF protein to the mitochondria rather than to the endosome or lysosome.[16] It has been hypothesized that PMP-22 could be one of the substrates of the *LITAF* pathway in protein degradation.[6] Further studies characterizing mutations that target other regions of *LITAF* and analyses of potential differences in their clinical phenotypes are expected to be informative with regard to understanding the cellular and molecular mechanisms that underlie CMT.

In conclusion, we have studied a group of patients with the G112S mutant form of *LITAF*. Our findings demonstrate that patients with this mutation have a degree of sensory loss and foot deformity similar to those observed in patients with CMT1A, but muscle weakness and areflexia are milder. The motor nerve conduction studies are also milder. Thus, the G112S-causing mutation in *LITAF* results in a mild form of a demyelinating CMT that is almost clinically indistinguishable from mild CMT1A. One distinguishing trend seen in half of our patients with the G112S mutation is exertional calf pain that is not typically seen in those with CTM1A; this trend would be of interest to assess in future cases of CMT1C with the G112S mutation.

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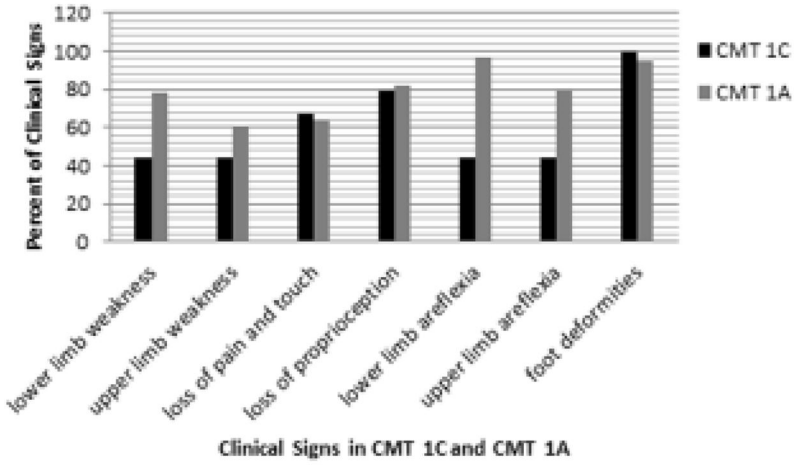

Figure 1.

Clinical signs. Comparison of CMT1C Gly112Ser mutation with CMT1A. Histogram shows percent of clinical signs in patients with CMT1C (n = 9) and CMT1A (n = 119).[17]

Table 1

Clinical symptoms of CMT1C G112S

Clinical symptoms	**Number of patients with CMT1C (%) (*n* = 10)**
1. [a]	
Only 1 patient wore a foot orthotic.	
Childhood onset of presentation	8 (80%) (in the other 2 patients, age of onset was 30 and 60 years, respectively)
Walked on time (≤18 months)	10 (100%)
Ethnicity	French, German, Welsh, Russian, Polish, Slavic
First symptom	
Slowest runner	3 (30%)
Toe walker	4 (40%)
Foot deformity	3 (30%)
Motor symptoms	
Lower limbs (trip, catch toes, shoe inserts, slap feet, ankle–foot orthotica)	9 (90%)
Upper limbs (difficulty with buttons)	1 (10%)
Foot surgery	3 (30%)
Cramps and pain	10 (100%)
Sensory symptoms:	
Lower limbs (reduction or loss of sensation)	6 (60%)
CMTNS	7.5 of 36 (range 2–11)

Table 2

Motor nerve conduction findings in patients with CMT1C Gly112Ser *LITAF/SIMPLE* mutation and in those with CMT1A

	Normal	CMT1C (*n* = 7)	CMT1A[17] (*n* = 119)
1. Data expressed as mean ± standard deviation (range). CMAP, compound muscle action potential (motor, millivolts); DML, distal motor latency; MNCV, motor nerve conduction velocity; amplitudes represent baseline to peak values; TA, tibialis anterior.			
2. [a]			
		Fibular motor recording from the tibialis anterior (TA) was not performed.	
Median nerve		No response = 0	No response = 4
DML (ms)	<4.5	6.1 ± 1.3 (4.6–7.9)	9.8 ± 2.6 (4.6–22.3)
CMAP (mV)			
Distal		4.9 ± 1.4 (3.6–7.5)	2.4 ± 1.9 (0.1–9.5)
Proximal	>4	4.2 (2.7–5.8)	
MNCV (m/s)	>48	27.9 ± 6.4 (20–38)	20.2 ± 4.9 (7–33)
Ulnar nerve		No response = 0	No response = 0
DML (ms)	<3.5	4.3 ± 0.81 (2.9–5.4)	8 ± 3.1 (4.5–16.4)
CMAP (mV)			
Distal	>6	5.5 ± 1.93 (2.9–5.4)	2.4 ± 1.6 (0.1–9.5)
Proximal	>6	4.0 (0.99–7.5)	
MNCV (m/s)	>49	28 ± 7.2 (20.3–38.5)	17.3 ± 5.1 (6–30)
Fibular nerve/EDB		No response = 1	No response = 24
DML (ms)	<5.5	9.5 ± 3.1 (5.8–13.3)	11.9 ± 3.4 (6–19.4)
CMAP (mV)			
Distal	>3	1.9 ± 5.7 (0.27–4)	0.9 ± 1.2 (0.07–4)
Proximal	>3	1.4 (0.2–2.97)	
MNCV (m/s)	>41	20 ± 0.058 (19.7–20)	17 ± 4.6 (5–24)
Fibular nerve, TA		No response = 0	Not available[a]
DML (ms)	<6.7	4.6 ± 0.86 (3.8–6)	Not available[a]
CMAP (mV)			Not available[a]
Distal	>5	3.7 ± 0.11 (3.2–4.5)	
Proximal	>5	3.4 (2.7–4.4)	
MNCV (m/s)	>44	26 ± 2.83 (19.7–33)	

Table 3

Sensory nerve conduction findings in 7 patients with the Gly112Ser *LITAF/SIMPLE* mutation

	Normal	Mean	Range	No response
1. Amplitudes represent baseline to peak values. SNAP, sensory nerve action potential (sensory, microvolts); DSL, distal sensory latency; SNCV, sensory nerve conduction velocity.				
Median nerve				
DSL (ms)	<3.5	5.1	3.5–6.6	3
SNAP (μV)	>5	9.9	6.9–13	
SNCV (m/s)	>45	36.5	32–41	
Ulnar nerve				
DSL (ms)	<3.5	5	2.6–7.1	3
SNAP (μV)	>18	7.9	7.3–8.8	
SNCV (m/s)	>45	31	20–40	
Sural nerve				7