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Charcot-Marie-Tooth disease type 1A: Influence of Body Mass Index on Nerve Conduction Studies and on the Charcot Marie Tooth Exam Score

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Abstract

Introduction—Charcot-Marie-Tooth Disease type 1A (CMT1A) is caused by a duplication of the peripheral myelin protein gene 22 at chromosome 17p11.2-12. There is limited data regarding whether Body Mass Index (BMI) affects electrophysiological or clinical data in those with CMT1A.

Methods—Electrophysiological data, the Charcot Marie Tooth exam score (CMTES) and BMI from 101 patients with known CMT1A were obtained and analyzed.

Results—When controlling for age, a higher BMI does not affect ulnar motor nerve conduction studies in those with CMT1A, but rather components of the CMTES (loss of pinprick and motor strength in the lower extremities).

Conclusion—BMI and clinical components of the CMTES are correlated, but it is uncertain which came first—whether the loss of lower extremity pinprick sensation and motor strength results in a higher BMI or if the higher BMI results in these signs.

Keywords

CMT1A; BMI; Obesity; Electrodiagnostic Studies; Age; Ulnar Motor nerve conduction study; Radial sensory nerve conduction study; CMTES; Rasch analysis of the CMTNSv2

Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common subtype of Charcot-Marie-Tooth (CMT) disease and represents 80% of all demyelinating CMT.¹ CMT 1A is caused by a duplication of the peripheral myelin protein gene 22 (*PMP 22*) at chromosome 17p11.2-12, which leads to increased *PMP 22* expression, and resulting in defective myelin stability and abnormal Schwann-cell growth and differentiation.²

Despite the known pathophysiology of CMT1A, previous reports have shown that diabetes mellitus type II can lower ulnar CMAP amplitude at a significant level in those with CMT1A, worsen the CMT exam score (CMTES) as well as result in more severe motor and

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sensory impairments in those with CMT 1A while controlling for age.¹³ Various hypothesis of how diabetes mellitus type II worsens electrophysiological and clinical outcomes for those with CMT1A include a possible impairment of axonal transport and function of mitochondria in patient with diabetes.³

Typically, patients with diabetes mellitus type II have an elevated body mass index (BMI).⁴ A high BMI can result in a prolonged distal motor latency in the median nerve, and a prolonged F-wave minimal latency in the tibial nerve in adults without any medical co-morbidities.⁵ One study has shown that a higher BMI is correlated with lower sensory and mixed nerve amplitude potentials.⁶ Another study suggested that BMI has no effect on nerve conduction velocities.⁷ Data on how BMI affects nerve conduction studies (NCS) in CMT1A, however, is limited. A previous study analyzed only 11 patients with elevated BMI and CMT1A and found no significant difference in ulnar NCS, ulnar CMAP, and CMTNS compared to controls.¹ The following paper aims to discover whether one's BMI can affect nerve conduction studies or the CMTES in those with CMT1A.

Materials and Methods

Patients and Chart Review

The study was approved by the Institutional Review Board at the University of Iowa, and subjects signed an informed consent. A database of all patients with CMT is maintained at the University of Iowa. There are more than 1100 patients with CMT and more than 300 patients with CMT1A. CMT1A is diagnosed with clinical genetic testing for the presence of a 1.4 Mb duplication on chromosome 17p11.2. If a patient has a first or second degree relative with a known duplication, then a diagnosis is established with uniform motor conduction slowing of the median or ulnar nerve between 10 to 35 meters per second.

We analyzed the database for patients that had CMT1A and had a known BMI as well as a documented ulnar nerve conduction testing performed at the University of Iowa Hospitals and Clinics. We performed a retrospective analysis of data from electrodiagnostic testing (nerve conduction studies), BMI (body mass index), gender, and age at the time of the electrodiagnostic testing. Data from 101 patients with CMT1A and a known BMI as well as electrodiagnostic testing at the University of Iowa was obtained. Those with a known history of diabetes (8 patients) or chemotherapy (1 patient) were excluded.

Calculation of Neuropathy Score

A CMTES was calculated using a modified scale that had been validated previously as a measure of disability caused by CMT.⁸ Using this scale, the level of impairment is classified as follows: score of 0–10, mild impairment; score of 11–20, moderate impairment; and score of 21, significant impairment.⁸ The CMTES has 7 scored components: 3 are symptoms and 4 are signs observed by a clinician. Each measurement is scored from 0–4, for a possible total of 28 points (See Appendix 1). Additionally, a CMTNSv2 and its components were calculated using a Rasch model.⁹ The CMTNSv2 is the CMTES plus 2 additional components from electrodiagnostic testing resulting in a total of 36 points (Appendix 1).

Electrodiagnostic testing

Ulnar motor nerve conduction studies (MNCS) and radial sensory nerve conduction studies (SNCS) of the left upper extremity were performed by standard techniques using conventional methods (Nihon Kohden system). Amplitudes measured from baseline to peak were used. Skin temperature was maintained above 32°C and surface electrodes were used. Ulnar compound motor action potential (CMAP) was recorded from the abductor digiti minimi while stimulating at the wrist, below, and above elbow. Ulnar and radial responses are routinely used because peroneal and sural potentials are typically absent even in demyelinating CMT.⁸ The following variables were obtained from the electrodiagnostic testing: CMAP, sensory nerve action potential (SNAP), motor conduction velocity (MCV), sensory conduction velocity (SCV) distal motor latency (DML), and distal sensory latency (DSL). F-waves were not evaluated routinely in the CMT clinic.

Statistical analysis

Percentages and means were compared using the Student t-test, and differences were considered significant at $p < 0.03$ accounting for multiple comparisons. Nerve conduction parameters were compared amongst two groups—those with a high BMI greater than or equal to 30 (clinical definition of obesity) and those with a low or normal BMI less than 30. A regression model was made to compare results confounded by BMI and age.

Results

Results from 101 patients were sorted by BMI and age. The overall average age was 41 and average BMI was 28; there were 50 females and 51 males. There were 32 patients with obesity (mean BMI 36) and 69 patients without obesity (mean BMI 23). Those with a higher BMI were 8 years older than those with a lower BMI (age 45 compared to 37). The youngest patient was 3 years old as in CMT1A, neurophysiologic abnormalities are present in all children from the age of 2 years.¹⁰

Ulnar motor nerve conduction responses were obtained in all patients. Eighty-nine out of the 101 (88%) patients had absent radial sensory responses.

Table 1 demonstrates how ulnar nerve conduction parameters are not significantly different and how the CMTES is significantly different in those with obesity compared to those without obesity. It also demonstrates that age is significantly different, and thus age seems to be a confounding variable. Tables 2 and 3 demonstrate how there is a significant difference between older age versus younger age in two out of the three nerve conduction parameters. Table 4 illustrates ulnar motor nerve conduction velocity changes when controlling for either age or BMI. Table 4 shows that the CMTNS is the only measure significantly associated with BMI after controlling for the effects of age, and that ulnar nerve conduction study parameters are not affected by BMI. Age is positively associated with two measures (ulnar MNCV and CMTES) after adjusting for BMI as seen in Table 4 below.

Table 5 shows how age and BMI affect the CMTNSv2. Each component of the CMTNSv2 worsened over time with age when controlling for the effects of BMI. A higher BMI lead to worsening pinprick loss and motor strength in the lower extremities.

Discussion

Previous reports have suggested that in adults with no medical co-morbidities, a higher BMI results in prolonged distal motor latencies of the median nerve, and lower sensory and mixed nerve amplitude potentials.⁵⁶ Little has been investigated on the effect of BMI on NCS in those with CMT1A.

Results from our analysis of BMI, ulnar MNCS, radial SNCS, age, and CMTES in 101 patients with CMT1A show that BMI alone when controlled for age doesn't affect ulnar MNCS as reported previously.¹ A radial SNAP was obtained more often in those who were non-obese compared to those who were. It is uncertain if this result was secondary to the obesity itself or if excessive fat deposition at stimulation or recording sites might interfere could have interfered with obtaining the NCS results.

These results confirm our hypothesis that the neurophysiological patterns of CMT1A are caused by varying degrees of increased *PMP 22* expression resulting in defective myelin stability and genetic modifiers rather than by the epigenetic effects of BMI.

Upon investigating further, we noticed that BMI was associated positively with a Rasch version of the CMTNSv2—a higher BMI resulted in a worse (or higher) CMTNSv2. This was analyzed further by investigating each component of the CMTNSv2 and performing a regression of these components with BMI while controlling for age. The results showed that a higher BMI worsened lower extremity pinprick loss and lower extremity motor strength on exam.

Although it's possible that a higher BMI can result in worsening lower extremity strength and pinprick sensation, it's also possible that worsening lower extremity strength and pinprick sensation lead to a higher BMI due to lack of ability to do physical activity as a result of these symptoms.

Increasing age has been known to affect CMT1A over time and our results confirm this. Older age is associated with a higher (or worse) CMTES; Shy et al reported an average increase of 0.69 points increase of the CMTES score per year for natural progression.¹¹ Specifically, in our study, an increasing age affected or worsened all parameters of the CMTES. Age resulted in the ulnar motor nerve velocity to be faster, which is unexpected as previous reports involving subjects without CMT1A suggest age to slow nerve conduction velocity due to a suspected decrease in number of nerve fibers with increasing age.^{12, 13} This result is possibly due to a technical artifact as wrist to elbow measures can be falsely increased due to distance measurement factors including extra skin tissue, which can be seen with aging.

A limitation of our study includes the fact that only an ulnar motor response and radial sensory response was evaluated for each patient. Additionally, the unusual result of the ulnar motor nerve conduction velocity increasing with age signals that there could possibly be technical factors that could have affected our data.

Our results support the hypothesis that a higher BMI when controlling for age doesn't affect ulnar motor nerve conduction velocity. We have still yet to determine if a higher BMI worsens certain parameters of the CMTES such as lower extremity pinprick loss and lower extremity motor strength on exam or more severe lower extremity signs due to the CMT itself result in a higher BMI.

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Table 1

Comparison of mean and standard deviation of ulnar motor nerve conduction in the obese with CMT1A

	CMT 1A obese (BMI ≥ 30) N= 32	CMT 1A non-obese (BMI < 30) N = 69	p-Value
Ulnar CMAP (mV)	3.26 (2.24)	3.93 (2.21)	P < 0.13
Ulnar Distal Motor Latency (ms)	7.57 (2.54)	6.93 (1.57)	P< 0.17
Ulnar Motor Conduction Velocity (m/s)	20.48 (4.85)	18.97 (4.67)	P< 0.18
Radial SNAP present	1	12	P< 0.0001
Average Age	45 (15.53)	37 (18.95)	P< 0.009
CMTES	11.06 (5.37)	7.83 (4.98)	P<0.0001

Table 2

Comparison of mean and standard deviation of ulnar motor nerve conduction in the elderly with CMT1A

	CMT 1A elderly (age ≥ 35) N= 61	CMT 1A young (age < 35) N = 40	p-Value
Ulnar CMAP (mV)	3.44 (2.15)	4.21 (2.30)	P< 0.016
Ulnar Distal Motor Latency (ms)	7.15 (1.90)	7.13 (2.04)	Not significant
Ulnar Motor Conduction Velocity (m/s)	20.97 (3.95)	17.13 (5)	P< 0.0001
Radial SNAP present	8	5	P< 0.95
Average BMI	29.07 (7.31)	23.9 (7.42)	P< 0.009
CMTES	10.86 (5.34)	5.92 (3.67)	P< 0.0001

Regression analysis of the effect of BMI and age on nerve conduction study parameters divided into very obese, obese and non-obese groups:

Table 3

Outcome	Associated with BMI < 30, adjusted for age (p-value)	Associated with BMI < 30 (p-value)	Associated with BMI 30 (p-value)	Associated with BMI 30 (p-value)	Associated with BMI 35 (p-value)	Associated with BMI 35 (p-value)
Distal Motor Latency of the Ulnar Nerve	No (p<0.77)	No (p<0.39)	No (p<0.95)	No (p<0.61)	No (p<0.74)	No (p<0.79)
Compound Motor Action Potential	No (p<0.37)	No (p<0.75)	No (p<0.67)	Yes, negative association, (p<0.037)	No (p<0.55)	Borderline significant, negative association, (p<0.06)
Nerve Conduction Velocity	No (p<0.22)	Yes, positive association, (p<0.00014)	No (p<0.316)	No (p<0.83)	No (p<0.73)	No (p<0.49)

Table 4

Regression analysis of BMI and age affecting ulnar nerve conduction parameters when controlling for age and BMI respectively

Outcome	Associated with BMI, adjusted for age (p-value)	Associated with Age, adjusted for BMI (p-value)
Ulnar CMAP	No (p<0.174)	No (p< 0.253)
Ulnar Distal motor latency	No (p<0.147)	No (p<0.561)
Ulnar motor conduction velocity	No (p<0.178)	Yes, positive association (p<0.002)
CMTES	Yes, positive association (p<0.004)	Yes, positive association (p<0.004)

Table 5

Regression analysis of BMI's effect on CMTNSv2 (adjusted using a Rasch model) parameters when controlling for age

Outcome	Associated with BMI, adjusted for age (p-value)	Associated with age, adjusted for BMI (p-value)
CMTNSv2	No (p<0.287)	Yes, positive association (p<0.0)
Sensory symptoms in legs	No (p<0.345)	Yes, positive association (p<0.034)
Motor symptoms in legs	No (p<0.757)	Yes, positive association (p<0.001)
Motor Symptoms in arms	No (p<0.936)	Yes, positive association (p<0.002)
Pinprick loss in lower extremities	Yes, positive association (p<0.03)	Yes, positive association (p<0.001)
Vibration loss in lower extremities	No (p<0.611)	Yes, positive association, (p<0.005)
Motor strength exam legs	Yes, borderline positive association (p< 0.088)	Yes, positive association (p<0.0)
Motor strength exam arms	No, (p<0.955)	Yes positive association, (p<0.0)
Ulnar Motor Response	No, (p<0.581)	No, (p<0.328)
Radial Sensory Response	No, (p<0.938)	No, (p<0.734)