Evaluation of the median nerve by shear wave elastography in patients with Charcot–Marie–Tooth disease type 1A

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Abstract

Aims: Charcot–Marie–Tooth disease type 1A (CMT1A) is characterized by enlargement and stiffness of peripheral nerves due to edema with large numbers of “onion bulbs” in the endoneurium. Ultrasound elastography seems to be an ideal method to detect this condition. The aim of this study was to analyze the shear wave elastography (SWE) features of peripheral nerves in patients with CMT1A. Material and methods: We included 24 CMT1A patients with a mean age of 28 years, along with 24 age- and gender-matched controls. All patients presented with mutations of the PMP22 gene and showed length-dependent polyneuropathy. The motor nerve conduction velocity (MNCV) of the median nerve ranged from 5.2 to 37.4 m/s. SWE and cross-sectional area (CSA) were used to evaluate the bilateral median nerves at predefined sites in both patients and controls. Results: The average elastography value (EV) of the median nerve was 73.5±11.7 kPa in patients with CMT1A and 37.5±6.1 kPa in control subjects. The difference between the two groups was statistically significant (P<0.05). In CMT1A patients, the average EV at the proximal and distal parts of the median nerve were 81.4±9.4 kPa and 65.2±8.1 kPa, respectively. The average CSAs at the proximal and distal parts of the median nerve were 0.29±0.06 cm² and 0.20±0.05 cm², respectively. The EV on SWE was positively correlated with CSA (p<0.01) and negatively correlated with MNCV in the median nerve (p<0.01). Conclusions: Peripheral nerve stiffness dramatically increases in CMT1A and is correlated with the severity of nerve involvement.

Keywords: Elastography; Charcot–Marie–Tooth disease; nerve cross-sectional area; ultrasound

Introduction

Charcot–Marie–Tooth disease (CMT) is the most common group of inherited peripheral nervous system disorders and encompasses genetically and pathologically heterogeneous polyneuropathies of the peripheral sensory and motor nerves [1,2]. CMT type 1A (CMT1A), a demyelinating condition, is the most common form of CMT and is caused by a DNA duplication on chromosome 17p11.2-p12 in over 70% of patients. Some of the methods were applied to the diagnosis of CMT1A patients. Among imaging biomarkers, the free fat fraction of calf muscles as assessed by magnetic resonance imaging (MRI) has been proposed as a potential biomarker of disease progression in CMT1A [3]. Additionally, magnetic resonance neurography (MRN)–diffusion tensor imaging (DTI) evaluation of the sciatic and tibial nerves improves the detection of nerve abnormalities in patients with CMT1A [4]. However, MRI signals are unable to respond rapidly to changes. Nerve conduction studies (NCS) are the gold standard for the evaluation of peripheral neuropathies. CMT1A is the most common form of CMT and is characterized by low motor nerve conduction velocity (MNCV), an electrophysiological marker of myelin integrity. In CMT1A, MNCV is uniformly reduced in all nerves, and values <38 m/s are highly diagnostic [5]. This electrophysiological hallmark, fully penetrant beginning in the first years of life, remains fairly stable throughout life and does not correlate with disability, whereas the compound motor action potential (CMAP)
amplitude, a surrogate marker of axonal degeneration, does [6]. However, in some respects, NCS are invasive to a certain degree. These factors accentuate the need for sensitive and noninvasive methods to detect the existence and severity of neuropathy in CMT.

Recently, the usefulness of peripheral nerve ultrasound (US) in the diagnosis, differentiation and measurement of CMT patients has been demonstrated [7-9]. Nerve US is useful to identify nerve swelling and structural changes noninvasively and easily in the diagnosis of CMT. In a previous study, the great majority of peripheral neuropathy US diagnosis focused on the cross-sectional area (CSA) measurement. Nerve enlargement was commonly diffuse (89%), and nerves were generally more than twice as thick in CMT type 1 patients as in controls [10]. Nerve size is significantly associated with clinical scores in CMT1A, which suggests that it might represent a potential biomarker of CMT damage and progression [11]. US of nerves reveals specific phenotypes that differentiate CMT1A from hereditary neuropathy with liability to pressure palsies (HNPP). In CMT1A, the enlargement of nerves and fascicles is a multifocal phenomenon spanning multiple nerves, whereas in HNPP, nerve enlargement is restricted to sites of entrapment [12]. In addition, nerve US measurements in patients with CMT have been concentrated mostly on the upper limbs [13].

Previous nerve US studies have focused mostly on grayscale values. Therefore, studies on nerve stiffness are still insufficient. Shear wave elastography (SWE), a promising technology in the field of US, can be applied at a large spatial scale to explore organs such as the thyroid [14], the liver [15] and even the muscles and nerves. Bilateral analysis showed that there was no significant difference in nerve stiffness between the left and right median nerves or tibial nerves in patients with diabetic peripheral neuropathy, and the stiffness was increased in these patients compared to controls [16]. Elastography in patients with acromegaly detected severe stiffening of the nerves [17]. SWE imaging was also applied in patients with carpal tunnel syndrome to evaluate the severity of the disease combined with diffusion tensor imaging [18]. As the inflammatory processes involved in CMT1A neuropathy may result in nerve edema, elasticity imaging is a potential assessment tool. It is a significant adjunct diagnostic method in soft tissue US images, and SWE can quantitatively evaluate tissue and provide a guide for disease monitoring and diagnosis by US.

To date, there has been little information about the use of SWE in CMT1A patients. In this study, we focused on the important role of nerve stiffness as measured by SWE in relation to CSA and NCS evaluation in CMT1A patients.

Materials and methods

Subjects

Between November 2017 and October 2021, 24 patients (n=24, male=15) with CMT1A and 24 asymptomatic healthy controls (HCs), matched to the patient group for age and gender, were recruited prospectively at Peking University First Hospital. All CMT1A patients were confirmed by genetic testing and had demyelinating features consistent with an inherited polyneuropathy. All patients and HCs underwent clinical neurological examination and nerve ultrasound diagnostics including elastography and CSA measurement. The mean ages of the CMT1A patients and HCs were 28.1±9.9 and 26.4±9.3 years, respectively. There were no significant differences in the age, weight, or height of the groups. The Ethics Committee of the Peking University First Hospital approved our study protocol, and all patients and HCs signed an informed consent in accordance with the Declaration of Helsinki.

US studies

All US examinations were performed by using a 4-15 MHz linear-array transducer (Aixplorer; SuperSonic Imagine, Les Jardins de la Duranne, Aix en Provence, France). The subjects lay in a supine position, and the upper and lower limbs were kept relaxed. The position of all participants was standardized to prevent any ankle or forearm movement that might affect the stiffness of the soft tissue. The nerve was scanned in the cross-section, and the CSA was measured. Six predetermined sites were measured on each median nerve; these sites were located at the midpoint of the wrist crease, 4 cm proximal to the wrist crease, halfway between the wrist crease and elbow, on the elbow, 4 cm proximal to the elbow, and 8 cm proximal to the elbow. These 6 sites were marked as P1–P6 from distal to proximal for the right and left median nerves respectively.

The transducer was adjusted to be perpendicular to the nerve to obtain the appropriate cross-sectional image. The CSA of the median nerve was measured at predetermined sites using a continuous boundary traced along the inner hypoechoic border, excluding the surrounding echogenic rim. CSA calculations were automatically performed by the software.

SWE was performed with gentle application of the probe; a sufficient ultrasonic coupling agent was used to avoid the need for firm contact between the probe and the surface of the skin so that the underlying tissue would not be compressed. First, the median nerve was identified in the transverse imaging plane; then, the probe was rotated 90° to obtain longitudinal imaging, which was the plane parallel to the nerve fiber direction. The size of the region...
of interest (ROI) ranged from 3 mm to 5 mm with variations in the nerve. The circular ROI was placed inside the nerve epineurium border. The stiffness (in kPa) of the ROI was then generated automatically based on the integrated SWE software.

The entire study group was independently assessed by two ultrasound physicians, each of whom had 2 years of experience. The CSA and SWE of the nerves were measured twice at each site to increase reproducibility, with the average value being used for the following analysis. The observers were blinded to both the images obtained at previous examinations and the results of the previous examinations, including the patients’ clinical history and NCS results. Observer 1 repeated the elastographic measurement 1 week after the initial interpretation.

**NCS**

The CMAP amplitude (mV) and MNCV (m/s) were measured in the median nerve. During the NCS, the skin temperature was maintained at 34 °C [19]. Sensory NCS data were not included in the analysis because they could not be recorded for most patients with CMT1A. All the patients had an abnormally slow (<38 m/s) MNCV [20]. If no CMAP could be elicited, a value of 0.001 mV was recorded [21-23].

**Statistical analysis**

SPSS (version 22.0) software was used to analyze the data. The Mann–Whitney U test was used for pairwise comparisons, and statistical significance was defined by a two-tailed P value of ≤0.05. Pearson and Spearman correlation coefficients were calculated to evaluate the associations between the NCS, CSA and EV data of CMT1A patients. Continuous variables are expressed as the means ± standard deviations. p values<0.05 were considered statistically significant.

Intraclass correlation coefficients (ICCs) were used to assess the inter- and intraobserver reproducibility of the median nerve EV measurements. The intraobserver ICC was calculated only for the more experienced of the two observers.

**Results**

A comparison of the baseline demographic data between the control and CMT1A groups is displayed in Table I. The groups were well matched for age and gender. No significant differences were found between CMT1A patients and HCs regarding age or gender (P>0.05). There were also no significant differences between the right and left median nerves (P>0.05). No significant differences in height, weight or body mass index (BMI) were found between the two groups.

| Table I. Comparison of the mean values of clinical variables between the CMT1A and HC groups. |
|-----------------------------------------------|-----------------|-----------------|<br>| age, years                                      | CMT1A (n=24) | HC (n=24) | p       |
| gender:                                       |                 |                 |
| male                                         | 26.4±9.3        | 28.1±9.9        | >0.05 |
| female                                       | 15              | 15              | -     |
| Height, cm                                   | 166±15          | 167±16          | >0.05 |
| Weight, kg                                   | 65±17           | 66±17           | >0.05 |
| BMI, kg/m²                                    | 23±3            | 22±3            | >0.05 |
| CSA, cm²                                     | 0.24±0.07       | 0.06±0.01       | <0.01 |
| EV, kPa                                       | 73.5±11.7       | 37.5±6.1        | <0.01 |
| MNCV, m/s                                    | 21.0±5.0(5.2-37.4) | -          | -     |
| CMAP, mV                                      | 3.2±2.2         | -               | -     |

CSA: cross section area; CMT1A: Charcot–Marie–Tooth disease type 1A; HC: healthy controls; CSA: cross section area; EV: elastography values; MNCV: motor nerve conduction velocity; CMAP: compound motor action potential

| Table II. Comparison of the mean CSA at the 6 predefined sites between the CMT1A and HC groups. |
|-----------------------------------------------|-----------------|-----------------|<br>| P1                                           | CMT1A          | p-value |
| P2                                           | 0.04±0.01       | 0.20±0.05       | <0.05 |
| P3                                           | 0.05±0.01       | 0.19±0.05       | <0.05 |
| P4                                           | 0.05±0.01       | 0.24±0.07       | <0.05 |
| P5                                           | 0.06±0.01       | 0.26±0.07       | <0.05 |
| P6                                           | 0.07±0.01       | 0.27±0.06       | <0.05 |
| CSA: cross section area; CMT1A: Charcot–Marie–Tooth disease type 1A; HC: healthy control; P1: midpoint of the wrist crease; P2: 4 cm proximal to the wrist crease; P3: halfway between the wrist crease and elbow; P4: on the elbow; P5: 4 cm proximal to the elbow; P6: 8 cm proximal to the elbow

**CSA results**

In the CMT1A group, CSAs were markedly increased at one or more sites along each of the examined nerves compared with the corresponding sites in the HCs (Table II). Moreover, the average CSA was increased in the proximal part of the median nerve (0.29±0.06 cm²) compared with the distal part (0.20±0.05 cm²).

**Elastography value (EV) results**

The median nerves of the CMT1A group were significantly stiffer than those of the control groups (p<0.001) (fig 1, Table III). Moreover, the average EV was increased in the proximal part of the median nerve (81.4±9.4 kPa) compared with the distal part (65.2±8.1 kPa).

**NCS results**

The MNCV and CMAP amplitude of the median nerve were the most frequently detectable electrophysiological parameters, and the MNCV of this nerve was below 38 m/s (range 5.2–37.4 m/s) in all 24 CMT1A pa-
Patients. The MNCVs and CMAP amplitudes of our study participants are shown in Table I.

**Correlation**

There were some positive associations between CSA and SWE, along with a negative correlation between EV and MNCV in the median nerve. In addition, the CSA and MNCV demonstrated a negative correlation, while there were few associations between CMAP results and CSA and EV in the CMT group (Table IV).

**ICC values**

The average ICC value for intraobserver and interobserver reproducibility was 0.9 (95% CI, 0.918–0.947).

**Discussion**

Our study evaluated the use of elastography and CSA measurements to assess variations in the median nerve in patients with CMT1A. The variations validated by EV were associated with the NCS results and combined CSA. NCS is regarded as the fundamental diagnostic method for peripheral polyneuropathy, but in some neuropathies, such as CMT, the nerves may become inert, and subtle abnormalities associated with neuropathy progression may be undetectable. In this case, swelling of the median nerve can be visualized as an increase in the CSA and EV on high-resolution US.

Our findings reveal that CMT1A patients show the expected increases in EV and CSA compared with HCs. The EV and CSAs were partially similar to the findings in patients with severe diabetic polyneuropathy [24] and patients with chronic inflammatory demyelinating neuropathy [25]. Increased EV indicated stiffness along the nerves, which was probably related to the structural variation reflected by the enlarged CSA of the peripheral nerves. In line with previous studies, we detected prominent and uniform enlargement of the median nerves and fascicles in subjects with CMT1A [26,27]. In this predominantly demyelinating neuropathy, the proliferation of Schwann cells and the formation of “onion bulbs” due to demyelination and remyelination [28,29] might be the

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**Table III.** Comparison of the mean EV at the 6 predefined sites between the CMT1A and HC groups.

<table>
<thead>
<tr>
<th>Sites</th>
<th>HC</th>
<th>CMT1A</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>38.6±6</td>
<td>65.2±8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P2</td>
<td>40.2±5.7</td>
<td>68.7±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P3</td>
<td>37.9±5.9</td>
<td>72.0±7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P4</td>
<td>33.3±6.3</td>
<td>78.0±9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P5</td>
<td>34.2±5.8</td>
<td>75.7±8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P6</td>
<td>35.8±5.8</td>
<td>81.4±9.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EV: elastography value; CMT1A: Charcot–Marie–Tooth disease 1A; HC: healthy control; P1: midpoint of the wrist crease; P2: 4 cm proximal to the wrist crease; P3: halfway between the wrist crease and elbow; P4: on the elbow; P5: 4 cm proximal to the elbow; P6: 8 cm proximal to the elbow.

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**Table IV.** The relationship among NCS results, EV and CSA in CMT1A patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV*CSA</td>
<td>-0.685**</td>
<td>0.561**</td>
<td>0.476**</td>
<td>0.687**</td>
<td>0.439*</td>
<td>0.534**</td>
</tr>
<tr>
<td>MNCV*CSA</td>
<td>-0.685**</td>
<td>-0.739**</td>
<td>-0.795**</td>
<td>-0.832**</td>
<td>-0.752**</td>
<td>-0.730**</td>
</tr>
<tr>
<td>CMAP*CSA</td>
<td>0.105</td>
<td>0.109</td>
<td>0.219</td>
<td>0.143</td>
<td>-0.003</td>
<td>-0.035</td>
</tr>
<tr>
<td>MNCV*EV</td>
<td>-0.449*</td>
<td>-0.479*</td>
<td>-0.488*</td>
<td>-0.803**</td>
<td>-0.648**</td>
<td>-0.682**</td>
</tr>
<tr>
<td>CMAP*EV</td>
<td>0.090</td>
<td>0.033</td>
<td>0.310</td>
<td>0.061</td>
<td>0.253</td>
<td>-0.113</td>
</tr>
</tbody>
</table>

CSA: cross section area; EV: elastography value; MNCV: motor nerve conduction velocity; CMAP: compound motor action potential; P1: midpoint of the wrist crease; P2: 4 cm proximal to the wrist crease; P3: halfway between the wrist crease and elbow; P4: on the elbow; P5: 4 cm proximal to the elbow; P6: 8 cm proximal to the elbow.
underlying reasons for the uniform, sonographically detectable median nerve and fascicle hypertrophy [19]. In addition, the proliferation of the nerve stroma, including the epineurium, in the nerves of CMT1A patients may provide a possible explanation for the elevated EV. Robaglia-Schlupp et al [30] reported that PMP22 overexpression enhanced collagen synthesis by fibroblasts and noted the possibility that structures other than Schwann cells were affected in CMT1A [23]. Furthermore, long-term edema of the median nerve is known to trigger fibroblast invasion, resultant accumulation of scar tissue inside the nerve, and an increase in its stiffness [31]. These changes could be associated with the fiber response as well as demyelination, the latter being the primary pathology of CMT1A [32]. Accordingly, we found a significant positive correlation between the CSA and EV of the median nerve in patients with this disease.

There was a significant difference between the proximal EV and CSA values. There was a positive correlation between the CSA and EV. These EV results may indicate that the disease process or the stiffening process is more pronounced proximally, whereas nerve CSA findings may represent increased water due to a pathological process occurring proximally more than distally. Our findings of median nerve enlargement in CMT1A patients compared with controls were comparable to findings previously reported by Sinclair et al [33]. CMT1A patients had more than twice the nerve CSA of controls. Sinclair et al reported a much larger CSA than that observed in our study (136 mm² vs. 54 mm²), which may be explained by the more proximal scanning sites in their study.

The considerable difference between the distal and proximal parts of the nerve highlights the need for consistency in the scanning points among patients. Compared to the distal part of the nerve, there was a prominent difference in the EV and CSA at the proximal part. This finding indicates that there is a relationship between the structural changes reflected by EV and the severity of neuropathy in CMT due to variations at both levels. However, in this study, the CMT neuropathy score (CMTNS) was not applied during patient recruitment; and further studies should take symptom severity into account. Our EV and CSA results may illustrate that the stiffening process and pathologically driven increase in water content occur more readily at proximal sites than at distal sites. Moreover, in the upper arm, the median nerve may lie relatively close to the bone surface, which might produce hardening artifacts [34]. Such artifacts occur when the studied structure is near a hard planar surface (e.g., the surface of a bone) that prevents homogeneous propagation of shear waves at depth and contributes to local stress inhomogeneity [35]. These findings demonstrated that the combination of CSA and elastography measurement could be of practical significance in future studies for the classification of neuropathies. Furthermore, consecutive scanning along the nerve and measurements at multiple sites by ultrasound could supply more detailed morphological information.

CMT1A is characterized by uniformly reduced nerve conduction velocity that is fully penetrant from the first years of life [6], remains fairly stable throughout life [36] and does not correlate with disability. In a previous study, a negative correlation was demonstrated between CSA and MNCV in patients suffering from peripheral neuropathy. MNCV and CSA were negatively correlated in ulnar neuropathy at the elbow; in addition, at the location of nerve entrapment at the humerorulnar aponeurosis, slowing was not as evident as it was between that location and the medial epicondyle [37]. Moreover, in patients with myelin protein zero–related Charcot–Marie–Tooth disease, the CSA was negatively correlated with upper-limb MNCV and not increased at entrapment sites [22]. This finding demonstrated the negative correlation between MNCV and EV in a previous study. Li et al [38] revealed that sciatic nerve stiffness as measured by SWE was negatively correlated with MNCV in diabetic rats, and the increased values of SWE, along with the increased duration of nerve compression, could reflect the severity of nerve entrapment in diabetic rats. In CMT1A patients, MNCVs may reflect the severity of the congenital myelin defects. This finding demonstrated the negative correlation between EV and MNCV in our study, which may suggest that nerve stiffness is related to the remodeling of myelin thickness. Excessively thick myelin may also conceivably be a cause of demyelination that might further influence NCV slowing. Experimental models have shown that reduced expression of neuregulin 1 (Nrg1), a master regulator of myelin thickness, causes a reduction in myelin thickness, resulting in reduced NCV [39]. On the other hand, Fledrich et al have demonstrated that the overexpression of Nrg1 in CMT1A rats does not restore myelin sheath thickness and accordingly does not rescue the impaired NCV [40]. The CMAP amplitude did not correlate with any of the clinical or electrophysiological measures, indicating a lower sensitivity than the MNCV parameters.

In a previous study, children with CMT1A had significantly increased nerve CSA compared to controls, and the increase in nerve CSA with age was disproportionately large in CMT1A patients, suggesting ongoing nerve hypertrophy throughout childhood [8]. Age had a limited effect on the CSA. The CSAs of some CMT1A patients largely overlapped with the distribution found in other demyelinating types of CMT [21]. Additionally, the shear
wave velocity of peripheral nerves was not associated with age in recent research [41]. Our study demonstrated that there was no distinct connection between SWE and age in CMT1A patients.

Limitations of this study include its relatively small sample size, single-center design, and the limitations of elastography imaging as described above. Even though multiple sites of the median nerve were detected in the study, future studies should examine additional peripheral nerves, such as the nerves of the lower limbs, and assess multiple parts of these nerves. Furthermore, the relationship between nerve stiffness and the degree of CMT neuropathy was not measured in detail in this study. Thus, longitudinal studies are essential to elucidate the temporal changes in nerve stiffness. However, the ICC statistical analysis demonstrated relatively stable reliability.

Conclusion

In conclusion, SWE revealed that the nerves of patients with CMT1A neuropathy were stiffer than those in the control group. In addition, a positive association was found between EV and CSA measurement. Meanwhile, a negative association was found between EV and MNCV as measured by NCS evaluation. In summary, these findings indicate that SWE-based stiffness measurement of the nerve is a potential auxiliary detection method that can be combined with CSA measurement and NCS for the detection of CMT1A.

Conflicts of interest: none

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References


