Quantitative MRI outcome measures in CMT1A using automated lower limb muscle segmentation

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ABSTRACT

Background

Lower limb muscle magnetic resonance imaging (MRI) obtained fat fraction (FF) can detect disease progression in Charcot-Marie-Tooth disease 1A (CMT1A) patients. However, analysis is time-consuming and requires manual segmentation of lower limb muscles. We aimed to assess the responsiveness, efficiency and accuracy of acquiring FF MRI using an artificial intelligence (AI)-enabled automated segmentation technique.

Methods

We recruited 20 CMT1A patients and 7 controls for assessment at baseline and 12 months. The 3-point-Dixon fat water separation technique was used to determine thigh- and calf-level muscle FF at a single slice using regions of interest (ROI) defined using Musclesense, a trained artificial neural network for lower limb muscle image segmentation. A quality control (QC) check and correction of the automated segmentations was undertaken by a trained observer.

Results

The QC check took on average 30 seconds per slice to complete. Using QC checked segmentations, the mean calf-level FF increased significantly in CMT1A patients from baseline over an average follow-up of 12.5 months (1.15±1.77%, paired t-test p=0.016). Standardised response mean (SRM) in the patients was 0.65. Without any QC checks, the mean FF change between baseline and follow-up, at 1.15±1.68% (paired t-test p=0.01), was almost identical to that seen in the corrected data, and the overall SRM similar at 0.69.

Conclusions
Using automated image segmentation for the first time in a longitudinal study in CMT, we have demonstrated that calf FF thus obtained has similar responsiveness to previously published data, is efficient with minimal time needed for QC checks and is accurate with minimal corrections needed.

INTRODUCTION

CMT is the most common form of inherited neuropathy, with a prevalence of 1 in 2,500.[1,2] CMT1A, resulting from a duplication of the gene encoding for peripheral myelin protein 22 (PMP22), accounts for more than half of all cases.[2,3]

Genetic therapies for inherited neuropathies are already being used in diseases such as hereditary transthyretin amyloidosis (ATTRv).[4,5] Treatments for CMT1A are on the horizon, with successful pre-clinical studies already published.[6,7] However, a barrier in the development of efficacious therapies is the lack of sensitive outcome measures that are able to detect a clinically meaningful response to treatment during the 1 to 2-year duration of a clinical trial.[8,9] Of importance is the responsiveness of an outcome measure which we define as the ability of a measure to change over a prespecified timeframe.[10] This is illustrated with the CMT neuropathy score (CMTNS) in the ascorbic acid trials for CMT1A, which demonstrated low responsiveness in the placebo group.[11]

Highly responsive biomarkers are needed to overcome these difficulties in measuring slow disease progression in diseases like CMT. Using a Neuromuscular MRI Protocol, we have previously demonstrated quantitative calf-level MRI intramuscular FF to have large responsiveness in CMT1A with subsequent validation of this method at a second international site.[12,13] Using this same protocol, we have also demonstrated its validity in hereditary sensory neuropathy type 1 (HSN1).[14]

A limitation of the current MRI methodology is that it requires time-consuming manual segmentation, is mainly limited to analysis of single slices and has a risk of inter-rater bias. A promising technology to circumvent this, is in the form of AI-enabled automated segmentation which allows reduced processing times and more complex analyses, utilising data from numerous acquired slices and eliminates inter-observer bias.[15] Recently, we developed a trained, artificial neural network architecture in an application we named Musclesense for the anatomical segmentation of MRI images in neuromuscular diseases.[15] Musclesense analysis displayed excellent overlap between manual and computationally derived segmentations of 571 MRI acquisitions and high reproducibility with low scan-rescan differences in calculated mean muscle FF measured at separate time-points.[15]

We aimed to determine if lower limb muscle MRI FF derived using Musclesense could achieve similar responsiveness in CMT1A, published from our group[12] and investigate both the efficiency and accuracy of this new AI-enabled technique.

METHODS

Study design and participants

We performed a prospective longitudinal observational study of 20 CMT1A patients recruited from inherited neuropathy clinics at the Queen Square Centre for Neuromuscular Diseases, London. Participants were screened to ensure they had no contraindications to MRI scanning and all CMT patients had genetically proven CMT1A (chromosome 17p11.2 duplication). Seven Healthy control participants were recruited and screened to exclude any neuromuscular disease.

Procedures
Patients with CMT1A were assessed with the CMT examination score version 2 (CMTESv2), a subscore of the CMTNS where neurophysiology is excluded. This 28-point score is based on signs and symptoms where 28 is very severely affected.[16]

Our Neuromuscular MRI Protocol acquired 2-dimensional multi-slice 3-point-Dixon fat-water separation images to create FF maps (0-100%) as published previously.[12-14] Calf- and thigh-level 3-point Dixon MRI was performed centred at a fixed distance from the knee joint. Whole muscle segmentation was performed using Musclesense (figure 1A, 1B).[15] A trained observer (LFO) selected the slice for analysis as previously published.[12,13] The automated segmentation at each slice was visually QC checked, and any necessary minor corrections performed (figure 1A, 1B). The observer was blinded to participant identification and timing of the MRI scan. The finalised segmentations were applied to the generated FF maps using custom written software to extract FF for all muscle voxels at this level and calculate their mean (figure 1A, 1B). This process was repeated for the same Musclesense derived segmentations prior to any QC checks to assess the accuracy of the AI technique (figure 1A, 1B). All FF maps were visually checked for artefact and any data outliers were also cross checked.

Statistical analysis
IBM-SPSS Statistics version 28.0 was used. Longitudinal changes were assessed with paired samples t-tests and group data were compared with independent samples t-tests. Correlation between measures were assessed with Spearman correlation. Outcome measure responsiveness was determined using the SRM, calculated by dividing the group mean change by the standard deviation of the change.

ETHICS
This study (IRAS project ID: 261343) has been approved by the local ethics committee (London-Fulham Research Ethics Committee, REC reference 19/LO/0868). Written informed consent was obtained from each participant.

RESULTS
AI-enabled automated segmentation process
Once the computational segmentation was complete, the average time needed to check and manually correct one individual slice per limb was approximately 30 seconds for the AI generated ROI, comparing with 10 minutes and 15 minutes required for conventional manual segmentation of individual muscles on one slice for the calf and thigh respectively.[12] The average percentage of voxels added to visually correct the selected AI generated ROI was 0.43% for the calf and 0.25% for the thigh. The average percentage of voxels trimmed was 1.09% for the calf and 0.64% for the thigh.

Accuracy of longitudinal analysis using automated segmentation
Two CMT1A patient follow-up MRI scans (one thigh-level and one calf-level MRI scan) were excluded from analysis due to significant artefact. The mean calf-level FF increased significantly from baseline over an average follow-up of 12.5 months in the CMT1A patients (1.15±1.77%, paired t-test p=0.016) but not in controls (0.07±0.19%, paired t-test p=0.54). The change in CMT1A patients at calf-level was also significant when compared with the change in controls (independent t-test p=0.02, figure 1C) but not at thigh-level (mean change 0.44±1.3% vs 0.3±0.47%, independent t-test p=0.84, figure 1C). The overall SRM of the change in the patients was 0.65. These results were nearly identical when this process was completed without the QC checks (figure 1C; blue boxplots). This resulted in an overall mean calf-level FF change between baseline and follow-up for the pure AI group of 1.15±1.68% (paired t-test p=0.01, independent t-test p=0.02, figure 1C), which was almost identical to that seen in the corrected data. The overall SRM was also very similar at 0.69. A highly significant correlation was demonstrated between mean baseline FF results obtained using Musclesense alone

versus those obtained with Musclesense after QC changes, for both calf and thigh (r_s 0.998, p=<0.001, figure 1D).

Baseline and longitudinal clinical results
Baseline demographic and clinical parameters are represented in table 1. In the CMT1A patients, the CMTES did not change significantly over an average interval of 12.5 months (p=0.15), resulting in low responsiveness (SRM 0.36).

Discussion

This is the first study to demonstrate the responsiveness of lower limb muscle MRI FF in CMT obtained using AI-enabled automated segmentation. This technique was sensitive enough to reproduce similar change in calf-level FF at 12 months versus baseline in patients seen in our other published studies of CMT1A patients.[12,13] The SRM from this study was slightly lower at 0.69 versus 0.83 in our original study.[12] This may reflect the patients' disease severity distribution, as SRM is lower in more mildly affected patients.[13] We have developed a foot muscle MRI protocol and shown it is sensitive to change over 12 months in these milder patients (unpublished data). Similarly to our previous studies, we did not see significant change in CMTES over 12 months.[12,13]

We have demonstrated practical advantages to using our AI-enabled automated segmentation technique, namely reduced analysis time, more numerous slice analysis with high accuracy. The process is on average 20 times faster per slice for the calf than the conventional manual segmentation of individual lower limb calf muscles. The speed of the process allowed for the QC check of all 10 calf MRI slices per limb in half the time taken to manually segment the individual muscles of one calf slice. This is reflected in the minimal average percentage voxel changes required following visual QC check per selected slice for the calf and thigh, reaching an average of just over 1% of voxels trimmed for the calf slices. In the outlier that did require the largest number of voxels to be trimmed (figure 1A, 1D), the resultant FF change (36.8% vs 40.7%), does highlight that currently the QC process is worthwhile to ensure complete accuracy of the technique. However, despite this, the mean FF longitudinal change in this pure AI example was 4.58%, which was very similar to the mean FF longitudinal change obtained with manual QC changes of 4.94%. This meant that even without the QC corrections, the combined overall mean fat fraction change calculated between baseline and follow-up was nearly identical, at 1.15±1.68% (paired t-test p=0.01), to that calculated with the corrected data, along with the SRM of 0.69. This provides evidence as to the overall accuracy of the technique for analysing longitudinal data.

Several limitations exist for this study. This is a new AI technique in a small sample size. Hence definitive conclusions cannot be made regarding overall validity and responsiveness. However given our previous successful experience with this AI-enabled automated segmentation technology[15] coupled with prior evidence of quantitative FF MRI in CMT1A,[12,13] it is likely that this approach will be an alternative, much faster option to manual segmentation. Although there were a reduced number of control patients in this study compared to our previous work, those studies provided evidence that control patient muscle MRI FF does not significantly change over these timescales.[12] This study has also only investigated longitudinal changes over a mean interval of 12.5 months; longer studies with larger patient numbers are thus underway.[17]

In conclusion, this study has demonstrated the effectiveness of a novel AI-enabled automated segmentation approach, with similar responsiveness to other published studies of MRI FF quantification in CMT1A patients over time.[12] Given the potential therapies for CMT1A,[6,7] this new technique has the potential to support the efficiency and timely completion of clinical trials in CMT where lower limb MRI FF is being used as an outcome measure.

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Competing interests
HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

Table

Demographics	CMT1A group	Control group	p value
Sex			0.76
Male	10	3	
Female	10	4	
Age (years)	45.0 (14.8)	47.4 (18.5)	0.72
Clinical parameters			
Age of onset (years)*	6.5 (4.1)	NA	NA
Disease duration (years)*	36.2 (14.9)	NA	NA
CMTES (0-28)*	10.6 (3.2)	NA	NA

Table 1: Baseline characteristics. Data are presented as mean values (SD). NA=not applicable. CMTES=Charcot-Marie-Tooth disease examination score. *Controls had no neuromuscular symptoms and were normal on neurological examination, hence CMTES, age of onset and disease duration were not applicable.

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