An observational study of asymmetry in CMT1A

Charcot-Marie-Tooth (CMT) disease is a clinically and genetically heterogeneous group of inherited neuropathies that was first described in 1886. CMT1A is the commonest form of CMT and accounts for 70% of demyelinating CMT (CMT1). It is an autosomal dominant neuropathy due to a 1.4 Mb duplication or rarely a triplication on chromosome 17p11.2 that contains the peripheral myelin protein 22 (PMP22) gene. Potential pathogenic mechanisms include alterations in protein homeostasis, cholesterol dysregulation, increased calcium influx via P2X7 upregulation resulting in dysmyelination and/or disruption of axon-glia interactions contributing to axonal loss. The characteristic phenotype delineated by Harding and Thomas is of childhood-onset distal wasting, weakness and sensory loss, which progresses slowly over decades in a length-dependent, symmetrical manner. One study of paediatric CMT reported asymmetry of foot alignment and ankle flexibility in 3–5% of patients and found that asymmetry was associated with greater overall neuropathy severity according to CMTNS scale but there was no breakdown according to specific CMT genotypes. Careful clinical descriptions from many large CMT1A cohorts have not reported significant asymmetry in muscle strength or sensory deficits.

However, rare cases of superimposed inflammatory neuropathy or radiculopathy, either secondary to degenerative spinal disease or as a complication of enlarged nerve roots, have been reported in CMT1A. There has been one reported case of marked asymmetry with unilateral footdrop without an alternative explanation despite extensive assessment in a 19-year-old male patient. Interestingly, this patient was one of a pair of monozygotic twins with CMT1A who had similar electrophysiological markers of the disease but significant differences in semiotics. In practice, it is important to know how much asymmetry is allowed in this condition so as not to assume that asymmetry always suggests a differential or coincidental diagnosis. No study to date has systematically examined this issue.

We performed a retrospective case series review in a cohort of patients with clinically and genetically confirmed CMT1A followed up at least annually at the inherited neuropathy clinic in the National Hospital for Neurology and Neurosurgery. Routine practice involves annual clinical assessment using the CMT Examination Score (CMTES), which includes Medical Research Council (MRC) scoring of muscle strength and validated scales for quantification of pin-prick (PP) and vibration sensation (VS) deficit. We recorded presence of asymmetry in strength in the commonly affected first dorsal interosseous (FDIO) and abductor pollicis brevis (APB) muscles in the upper limbs (UL) and ankle dorsiflexion and plantarflexion in the lower limbs (LL). Asymmetry was defined as a difference of greater than 1 MRC grade in contralateral muscles (without differentiation between grade 4−, 4 and 4+) and asymmetry of sensation as a difference of 1 point on the CMTES PP and vibration scales. We excluded patients with electrophysiological evidence of superimposed compressive neuropathy and those with examination findings suggesting significant foot, ankle and hip problems or spinal deformities, which are commonly associated orthopaedic complications in inherited neuropathy that can contribute to non-neuropathic motor deficits.

One hundred and eighty patients were included in this review; 40.1% male, mean (SD) age at examination was 41.7 (14.8) years. Asymmetry of strength was seen in 38 patients (21.1%), of whom 24 (13.3%) had asymmetrical UL and 17 (9.4%) asymmetrical LL strength. The distribution of asymmetry in UL was as follows: FDIO (range: 1–2 points on MRC scale) in 13 patients (7.2%) and APB (range: 1–3 points) in 14 patients (7.8%). In the LL: ankle dorsiflexion (range: 1–2 points) in 17 (9.4%) and ankle plantarflexion (range: 2–3 points) in two patients (1.1%; table 1). In three patients asymmetry was noted in both upper and LL; weaker left FDIO and right ankle dorsiflexion in one patient, weaker right APB and right dorsiflexion in a second, and right FDIO and right ankle dorsiflexion in the third. Patients
with motor asymmetry were older (mean (SD)=49.2 (12.9) years with asymmetry; 39.35 (14.48) years without asymmetry; (p<0.005) and had a more severe neuropathy (mean (S.D.) CMTES=13.4 (4.7) with asymmetry, 9.7 (4.5) without asymmetry; (p=0.000). There was no correlation between weaker side and handedness (r=0.11, p=0.52). The proportion of affected relative to probands was similar in both groups; 32.3% probands in symmetrical and 36.8% in asymmetrical patients (p=0.49).

In terms of sensation, asymmetry was noted in 23 patients (12.8%); PP asymmetry (range: 1–3 points on CMTES scale) in nine patients (5%) and VS (range 2–4) in 10 (5.6%; table 1). Asymmetry in sensory deficit was more common in the LL 20/23 than in the UL (3/23). In patients with asymmetry, alternative pathologies were ruled out through careful clinical review by an experienced consultant neurologist (MMR), and directed electrophysiological and neuroimaging (MRI of the brain, spinal cord, nerve roots ±plexii). All differences reported were attributed to CMT1A. The evolution of these signs and paraclinical evidence suggests this finding as compatible with the natural history of the condition, a phenomenon which has not been previously reported. It may be that dynometry and/or routine electrophysiological examination of all four limbs may increase sensitivity for subtle asymmetry in CMT1A but was beyond the scope of this observational clinical study.

In conclusion, we observed motor and sensory asymmetry in a significant minority of patients in this well phenotyped CMT1A cohort. The presence of asymmetry alone in CMT1A does not necessarily suggest that an alternative explanation needs to be sought.

Ana L Pelayo-Negro,1,2 Aisling S Carr,1 Matilde Laura,1 Mariola Skorupinska,1 Mary M Reilly3

1MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK
2Service of Neurology, University Hospital "Marqués de Valdecilla (IDIVAL)", University of Cantabria (UC) and “Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNE)” Santander, Spain
3MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, Box 108, Queen Square, London WC1N 3BG, UK; m.reilly@ucl.ac.uk

Acknowledgements MMR is grateful to the Medical Research Council (MRC), MRC Centre grant (G0601943), and MMR and ML are grateful to the National Institutes of Neurological Diseases and Stroke and Office of Rare Diseases (U54NS065712) for their support. This work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme.

Contributors MS is responsible for consent, data input and upkeep of the CMT Natural History Study database. ALP-N collected and analysed the data and wrote the first draft of the paper. ASC helped with drafting and revision of the paper. MMR conceived the study and contributed to revision of the final paper.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The collection of clinical data under the Charcot-Marie-Tooth and related disorders: A Natural History Study is ongoing. Further details may be available on discussion from the principal investigator and corresponding author of this paper: MMR.

REFERENCES
An observational study of asymmetry in CMT1A

Ana L Pelayo-Negro, Aisling S Carr, Matilde Laura, Mariola Skorupinska and Mary M Reilly

J Neurol Neurosurg Psychiatry 2015 86: 589-590 originally published online October 13, 2014
doi: 10.1136/jnnp-2014-309096

Updated information and services can be found at:
http://jnnp.bmj.com/content/86/5/589

References
This article cites 7 articles, 3 of which you can access for free at:
http://jnnp.bmj.com/content/86/5/589#BIBL

Open Access
This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See:
http://creativecommons.org/licenses/by/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Open access (241)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/