7T MR neurography-ultrasound fusion for peripheral nerve imaging

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Abstract

Background: We present one patient with an initial diagnosis of Guillain-Barré syndrome (GBS) and one with Charcot–Marie–Tooth disease (CMT) type 1A.

Methods: Both patients underwent ankle tibial nerve fusion-imaging of high-resolution ultrasound (HRUS) with 7T MR neurography (MRN).

Results: In GBS, the nerve was enlarged, T2-hyperintense, and showed increased vascularization 21 months after symptom onset. In CMT1A, the enlarged nerve was T2-isointense with normal endoneurial blood flow.

Conclusions: We demonstrate the utility of 7T-MRN-HRUS-fusion-imaging. In GBS, there was evidence of ongoing inflammation resulting in a changed diagnosis to acute-onset chronic demyelinating polyradiculoneuropathy and maintenance of immunotherapy. By MRN-HRUS-fusion, patients with presumed peripheral axonal degeneration could be shown to display imaging markers associated with peripheral nervous system inflammation. Thus, more accurate identification of a treatable inflammatory component may become possible.

KEYWORDS

CMT1A, fusion imaging, magnetic resonance neurography, microvascular blood flow, ultrasound

1 | INTRODUCTION

Despite rapid technical progress and continued expansion of indications for the clinical use of in vivo high-resolution ultrasound (HRUS) of the peripheral nervous system (PNS)[1] various shortcomings (e.g., user-dependence, inability to image tissue down to the bone) remain. Another challenge is to capture the extent of (ongoing) inflammation or demyelination compared to axonal processes during the course of peripheral nerve disease. Fusion imaging of real-time HRUS with 7T MR neurography (MRN) could help to overcome this challenge, and would not only help inform the evolution of PNS pathophysiology, but also aid in therapeutic decision making in patients with challenging peripheral nerve disorders. We describe two patients who underwent lower limb nerve fusion imaging.

1.1 | Patient 1

A 52-year-old woman presented with progressive neuropathic/radicular pain, symmetrical severe sensory and motor flaccid quadriparesis, reduced tendon reflexes, and bilateral facial paresis, that began 1 week after an upper respiratory tract infection and developed over 5 days. Electrodiagnostic studies 5 days after symptom onset revealed

detectable A-waves and prolonged distal motor and F-wave latencies; 3 weeks after onset compound muscle action potential (CMAP) amplitudes were low (Table 1) and needle electromyography (EMG) revealed positive sharp waves and fibrillation potentials in the tibialis anterior and deltoid muscles. Symptoms peaked within 4 weeks with loss of all voluntary limb movement, dysphagia, autonomic/respiratory failure with the need for ventilation. Four weeks after symptom onset, peripheral nerves were electrophysiologically inexcitable. Cerebrospinal fluid (CSF) revealed a mild increase in cell count (17 cells/μL) and elevated protein concentration (130 mg/dL). The patient fulfilled the Brighton criteria for Guillain-Barré syndrome (GBS) with the highest level of diagnostic certainty.[2] We excluded alternative diagnoses, such as infectious, neoplastic, vascular, and toxic etiologies, or other neuromuscular diseases, through blood and CSF immunological and microbiological testing, bone marrow aspiration, sural nerve biopsy, whole-body computed tomography, abdominal sonography, and spinal cord MR imaging.[3] Beginning 5 days after symptom onset, three plasma exchanges and three immunoadsorption sessions were performed. The patient showed a protracted and at times stagnating recovery period (see Supporting Information Table S1 and Supporting Information Figure S1, which are available online), with pain, anxiety, depression, and fatigue[4] that is still ongoing. Twenty-one months after symptom onset, examination revealed persistent moderate, distally-predominant, motor quadriparesis and mild neuropathic pain with distal sensory loss. Dysphagia and respiratory failure had fully recovered. At this time, peripheral nerves were electrophysiologically excitable, showing partial recovery (Table 1).

1.2 | Patient 2

A 22-year-old woman had longstanding, distal, symmetrical mild sensory deficits and motor weakness, atrophy of the small hand and foot muscles, and high arched feet. Genetic testing revealed Charcot–Marie–Tooth disease (CMT) type 1A with a duplication of the peripheral myelin protein 22 gene (locus 17p11.2).[5] Symptom onset was in her first decade. Motor conduction velocities were severely and uniformly slowed (< 20 m/s); CMAP amplitudes were low (Table 1).

2 | MATERIALS AND METHODS

2.1 | 7T MRN

MRN was performed with a Siemens MAGNETOM 7T scanner using a 28-channel knee-coil. The protocol included a high-resolution 2D T2-weighted turbo spin echo sequence with weak fat-saturation (echo time 64 ms; repetition time 6000 ms; flip angle 150°; field of view 120 mm; matrix size 480 × 480; slice thickness 2 mm with 0.4-mm gap; number of slices 50; voxel size after interpolation 0.125 mm × 0.125 mm × 2.4 mm).

The patients entered the scanner feet first; one leg was inside the coil at any time, for a scanning time of 6 min each. Before the scan, three markers (vitamin E capsules) were applied to the skin in a triangular pattern (Figure 1A) as reference markers for later fusion.

2.2 | High-Resolution 7T MRN-Ultrasound Fusion Imaging

Ultrasound fusion imaging was carried out immediately after the 7T scan on a high-resolution ultrasound device (Philips Medical Systems, Affiniti 70G with PercuNav navigation and fusion system, with an eL18-4 18 MHz broadband ultrasound probe); imaging settings remained identical for both patients. The duration of the fusion process was 10–15 min for registration and 15–20 min for measurements with each patient.

Patient 1 underwent 7T and fusion imaging 21 months after symptom onset, and patient 2 after approximately 15 years after symptom onset. Neither patient was receiving disease-specific treatment at the time of imaging.

Co-registration between MRN and HRUS is demonstrated in Figure 1.

3 | RESULTS

3.1 | Patient 1

In GBS, the ankle tibial nerve showed a distinct hyperintense T2 signal of the prominent and well visualized nerve fascicles across the entire cross-sectional nerve area (CSA) (Figure 2A$_1$). HRUS confirmed tibial nerve CSA (left 19 mm^2, right 18 mm^2) and fascicle size enlargement (Figure 2A$_2$). Power Doppler (pD) ultrasound indicated several color-encoded lines and spots of microvascular blood flow signals in the endoneurial vessels, i.e., increased nerve vascularization (Figure 2A$_3$). 7T-MRN-HRUS-fusion took advantage of the different nerve information provided by each of the two imaging modalities at exactly the same nerve position (Supporting Information Video S1).

3.2 | Patient 2

In CMT1A, the signal of the (again well visualized) enlarged fascicles was conversely T2 isointense (Figure 2B$_1$). HRUS confirmed tibial nerve CSA (left 25 mm^2; right 25 mm^2) and fascicle size enlargement as well (Figure 2B$_2$), but pD ultrasound revealed only a few color-encoded spots, compatible with normal endoneurial blood flow (Figure 2B$_3$). Subsequent 7T-MRN-HRUS-fusion is demonstrated in the Supporting Information Video S1.

4 | DISCUSSION

The technical capability of 7T-MRN-HRUS fusion imaging is demonstrated in this "proof-of-concept" report of the ankle tibial nerve of one GBS and one CMT1A patient.

In both, we expected axonal processes to predominate. Based on electrophysiological studies, many clinicians would expect that, in patient 1, the inflammatory component had "burnt out" and axonal

TABLE 1 Standard nerve conductions studies in relation to disease onset and fusion imaging date

Patient		GBS (f, 52 y)												CMT1A (f, 22 y)			
Time Point		W 1				W 3				W 91, FID				FID			
Nerve	**Stimulation**	DML (ms)	CMAP (mV)	MCV (m/s)	F-wave	DML (ms)	CMAP (mV)	MCV (m/s)	F-wave	DML (ms)	CMAP (mV)	MCV (m/s)	F-wave	DML (ms)	CMAP (mV)	MCV (m/s)	F-wave
Motor																	
Peroneal	Ankle	**6.1 (5.0)**	**1.4 (2.1)**		NR		NR		NR		NR		NR	**11.8 (5.0)**	**0.2 (2.1)**		NR
	Fibula (head)		**0.5 (2.1)**	**38.4 (41)**			NR				NR				**0.1 (2.1)**	**11.1 (41)**	
Tibial	Ankle	**5.3 (5.1)**	8.5 (2.9)		NR		NR		NR		NR		NR	**12.6 (5.1)**	**0.2 (2.9)**		NR
	Popliteal fossa		5.1 (2.9)	**40.6 (40)**			NR				NR				**0.1 (2.9)**	**13.2 (40)**	
Median	Wrist	**5.0 (4.5)**	5.0 (2.9)		**27.9 (35)**	**8.1 (4.5)**	**0.7 (2.9)**		NR	**11.4 (4.5)**	2.9 (2.9)		NR	**6.2 (4.5)**	3.7 (2.9)		NR
	Elbow		4.3 (2.9)	**49.5 (49)**			**0.8 (2.9)**	**50.5 (49)**			2.3 (2.9)	**26.4 (49)**			3.0 (2.9)	**14.0 (49)**	
Ulnar	Wrist	3.4 (3.5)	6.7 (2.5)		**33.4 (35)**	**7.0 (3.5)**	**0.4 (2.5)**		NR	**9.3 (3.5)**	3.7 (2.5)		NR	**11.1 (3.5)**	5.0 (2.5)		NR
	Elbow		6.7 (2.5)	55.9 (48)			**0.1 (2.5)**	**20.2 (48)**			2.0 (2.5)	**21.3 (48)**			2.6 (2.5)	**14.3 (48)**	
Sensory			SNAP (µV)	SCV (ms)			SNAP (µV)	SCV (ms)			SNAP (µV)	SCV (ms)			SNAP (µV)	SCV (ms)	
Sural	Ankle		2.4 (3.5)	**57.7 (38)**			NR				NR				NR		
Median	Digit II		5.3 (2)	49.5 (44)			NR				NR				NR		
Ulnar	Digit V		**1.6 (2)**	**41.7 (43)**			NR				NR				NR		

Note: Pathological values are marked bold. Reference values are given in brackets.

Abbreviations: FID, fusion imaging date; DML, distal motor latency; MCV, motor conduction velocity; NR, not recordable; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; W, week; f, female; y, years.
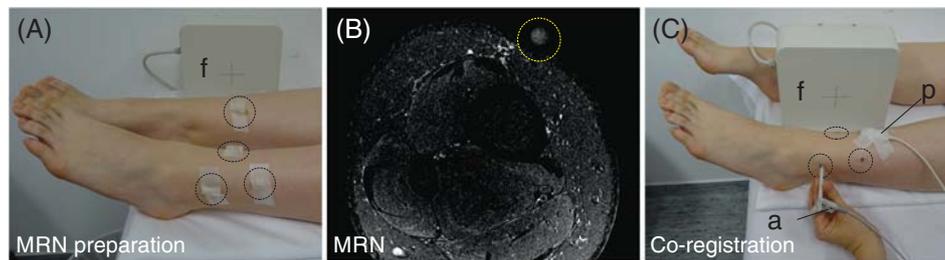
FIGURE 1   7T MRN-ultrasound fusion imaging process. A-C, The technical aspects of the 7T MRN-ultrasound fusion. A, Three markers were applied to the patient's skin (circled). B, One of the markers in the resulting MRN T2 sequence is visible (circled). C, Co-registration between MRN and HRUS is shown: image fusion was made possible by tracking the position and rotation information of tracking sensors in the form of dedicated trackers (a), measuring the electro-magnetic field generated by the field generator (f). Co-registration of MRN and ultrasound images was achieved by selecting the marker positions in the MRN slab (B) and then indicating the corresponding position of these markers on the examinee (B, circled) with the tracker (C, a). C, A patient tracking sensor (p) was placed on the lower leg to detect (in)voluntary movements and to enable continuous motion compensation preserving the previously set co-registration [Color figure can be viewed at wileyonlinelibrary.com]
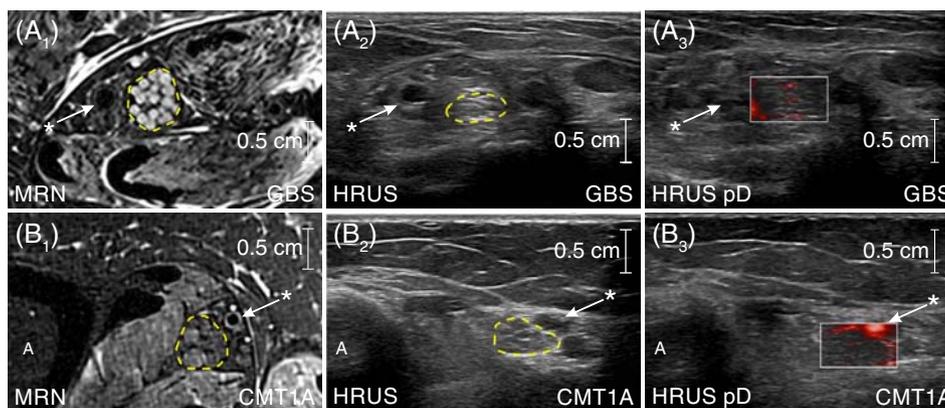
FIGURE 2   7T ultra-high resolution MRN and ultrasound. In GBS, the tibial nerve (TN) was T2-hyperintense (A_1), with sonographic nerve area/fascicle enlargement (A_2), and increased microvascular blood flow (A_3, rectangle). In CMT1A, the TN was T2-isointense (B_1), with sonographic nerve area/ fascicle enlargement (B_2), and normal microvascular blood flow (B_3, rectangle). A_1, A_2, B_1, B_2, Dashed lines outline the transverse left ankle TN. B_1-B_3, A, tibia. A_1–B_3, Asterisks, tibial artery [Color figure can be viewed at wileyonlinelibrary.com]

processes, either damage (secondary to demyelination or primary through inflammation) or regeneration/reinnervation, would be the main substrate of any ongoing PNS changes.[6,7] Permanent motor axon loss and very slow axonal regeneration are further likely responsible for the patient's long-term disability and delayed clinical recovery,[6,8,9] observable in the Supporting Information Table S1.

Although demyelination is the pathological hallmark in CMT1, secondary axonal degeneration is the cause of the clinical signs and symptoms.[10] Consistent with this, electrophysiological studies in longstanding CMT1A demonstrate predominantly axonal injury.[11] Active de- and remyelination are evident in nerve biopsies in early childhood CMT1A; in contrast, there is characteristically nearly no ongoing de- and remyelination in older CMT1A subjects.[12,13]

The combination of 7T MRN and HRUS provided, somewhat unexpectedly, evidence of ongoing inflammation (T2 signal and endoneurial blood flow increase)[14,15] in the our patient with GBS, whereas it confirmed axonal degeneration in the CMT1A patient.

GBS is a clinically diverse disorder that includes several distinctive variants and atypical cases.[3] Around 5% of patients initially fulfilling

diagnostic criteria for GBS will later be classified as having acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[16] Distinction between GBS and acute-onset CIDP is of pivotal importance as the latter may respond to maintenance immunomodulatory treatment. In the absence of reliable biomarkers, acute-onset CIDP is commonly diagnosed on clinical grounds, i.e. deterioration 9 weeks after symptom onset and/or at least three relapses.[17] Our GBS patient, however, did not meet these clinical criteria for CIDP, as there was protracted recovery but no deterioration/relapses (see Supporting Information Figure S1). Fusion imaging provided the data that led to a change of the diagnosis during the course of disease because ongoing nerve inflammation (active disease) is a feature of CIDP but would not be expected many months after onset of GBS.[18] The diagnosis of CIDP led to treatment with immunotherapy in the form of intravenous immunoglobulin.

Based on these findings, it appears that some patients with presumed peripheral axonal degeneration can be shown to display imaging markers thought to be associated with PNS inflammation[19,20] by using combined MRN and HRUS. Thus, more accurate identification of a

treatable inflammatory component in patients with primary axonal disease (e.g., amyotrophic lateral sclerosis) may become possible.[21,22]

Additional advantages of the fusion technology are that it could allow for the precise correlation of MRN and HRUS findings, identification of biomarkers, and characterization of the time course of fascicular and deep nerve microstructural changes in axonal and demyelinating disorders.

The technical equipment required for the fusion process is not yet commonplace, and where available, is presently used mostly for biopsies and other percutaneous interventional procedures.[23,24] Moreover, compared to established PNS imaging methods, fusion imaging requires additional processing time, which might not always be feasible in clinical settings. A growing number of device manufacturers are offering similar 3D navigation systems, though, and it is expected that these will become more commonplace in the future, allowing for systematic studies in larger cohorts to confirm the potential utility of the fusion imaging technique.

In conclusion, this report addresses the feasibility of fusing ultrasound and MRN. The thoughtful use of this approach might enhance our understanding of challenging peripheral nerve pathophysiology.

CONFLICT OF INTEREST

None of the authors has any conflicts of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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The utility of a single simple question in the evaluation of patients with nondiabetic polyneuropathy

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Abstract

Introduction: A single and simple question, namely "What percentage of normal (PoNL) do you feel regarding your disease?" is feasible and valid in myasthenia gravis. In this study, we aimed to determine the validity of this question in patients with nondiabetic polyneuropathy.

Methods: Clinical, electrophysiological, and functional and disability assessments were performed in 151 patients with nondiabetic polyneuropathy. One hundred forty patient answers were recorded for the PoNL question, and these were included in the current study.

Results: The PoNL correlated moderately with functional and disability scales.

Discussion: "What PoNL do you feel?" is a simple, quick, and valid question, which correlates moderately with functional and disability scales in nondiabetic polyneuropathy, and it may be incorporated in polyneuropathy assessment.

KEYWORDS

disability, functional scales, percentage of normal, TNCS

1 | INTRODUCTION

The number of patient-reported scales has been increasing in the last several years, as neurological examination, electrophysiological, imaging, and laboratory test findings do not include significant information regarding patients' experiences, and they are inadequate to assess quantitatively several important disease components, such as pain and fatigue.[1] However, as some of these scales are time-consuming, they may not be feasible in situations in which time is limited.

We have previously shown that a single simple question, which is not time consuming, namely "What percentage of normal do you feel regarding your disease?" is feasible and valid in myasthenia gravis (MG).[2] In the current study, we aimed to determine the validity of this question in patients with polyneuropathy.

2 | METHODS

We performed a prospective study at the Prosserman Family Neuromuscular Clinic, Toronto General Hospital, University Health Network,