Purpose of review
This review summarizes the most relevant developments in the fields of nerve ultrasound and MRI in the diagnosis of treatable inflammatory neuropathies over the last 18 months.

Recent findings
MRI and nerve ultrasound can accurately identify potentially treatable neuropathies and thereby help to improve diagnosis. Advanced MRI techniques also show potential to dissect pathophysiology. The apparent mismatch between nerve function and morphology is not surprising and reflects different dimensions of the disease process in neuropathies.

Summary
MRI and nerve ultrasound have become useful tools in the diagnosis of inflammatory neuropathies.

Video Abstract
http://links.lww.com/CONR/A45

Keywords
diagnostic value, MRI, neuropathy, ultrasound

INTRODUCTION
The incidence of (lower) motor neuron syndromes and axonal neuropathies exceeds by far that of chronic inflammatory neuropathies [1,2]. Consensus diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) primarily rely on clinical features and results from electrodiagnostic studies (Fig. 1) [3–5]. However, accurate identification may be complicated by the clinician’s inexperience or the considerable heterogeneity of the clinical phenotype of these rare disorders. Moreover, the execution of electrodiagnostic studies (EDX) is labor intensive and requires appropriate facilities to warm limbs prior to investigation [6,7]. Elaborate testing of multiple limbs is crucial, as is the inclusion of proximal nerve segments, because conduction block and conduction slowing are often focal and patchily distributed. Even in ideal circumstances, securing a diagnosis may remain challenging in a substantial number of patients [8]. Neuroimaging of the peripheral nerves might help and is becoming an important complement to EDX. It allows an additional means of detecting nerve involvement and thereby the identification of patients with treatable neuropathies. This review examines the most prominent developments in the fields of diagnostic nerve ultrasound and MRI of inflammatory neuropathies in the last 18 months.

EARLY MAGNETIC RESONANCE IMAGING AND NERVE ULTRASOUND STUDIES
The first published case-reports and -series suggested that inflammation and myelin dysfunction led to thickening of nerves in patients with chronic immune-mediated neuropathies that could be detected by both MRI and nerve ultrasound [9–11]. In subsequent studies, MRI was mainly used to explore the frequency of abnormalities in spinal nerve roots, whereas ultrasound studies focused more on large arm and leg nerves [12–16].
An important drawback was the lack of systematic studies addressing the diagnostic properties of imaging techniques in chronic immune-mediated neuropathies. The interpretation and comparison of available studies was complicated by the use of different protocols and patient cohorts with important differences in disease duration and treatment status. Nevertheless, these imaging studies corroborated the initial pilot studies and indicated nerve enlargement along the length of nerves in chronic immune-mediated neuropathies, this in striking contrast to the often focal abnormalities (i.e. conduction block) found during nerve conduction studies (NCS). A subsequent step was to propose several ultrasound scoring-systems in an attempt to further distinguish patterns of nerve enlargement [17–24]. These systems were based on structure (normal,

**KEY POINTS**

- MRI is particularly useful for visualizing the spinal nerve roots, whereas nerve ultrasound specifically shows high diagnostic performance in proximal segments of median nerves.
- MRI and nerve ultrasound of the brachial plexus show comparable diagnostic performance in identifying potentially treatable neuropathies.
- Neuropathies are characterized by changes in both nerve morphology and function, but these may reflect different aspects of the disease process.
- Future revision of diagnostic consensus criteria should include both MRI and nerve ultrasound as important options to complement NCS.

![Spectrum of chronic immune-mediated neuropathies](image_url)

**FIGURE 1.** Summary of distinctive features of chronic immune-mediated neuropathies. Identification of chronic inflammatory neuropathies is based on distribution of clinical, laboratory, and electrodiagnostic features: MMN [asymmetric, pure motor, with conduction block and antibodies to GM1 (anti-GM1)], CIDP, and Lewis–Sumner syndrome [often sensorimotor, rarely with cranial nerve involvement], and IgM neuropathy associated with antibodies to myelin-associated glycoprotein (anti-MAG). Each has its characteristic electrodiagnostic features and response to particular treatment modalities.
mild, regional, and diffuse enlargement), anatomic sites, and fascicular involvement.

The MRI of the plexus primarily relies on T2-weighted sequences [DIXON or 2D short tau inversion recovery (STIR)] that can reveal enlargement and/or hyperintense signal of nerve roots or postgadolinium enhancement [13]. The few studies that described the distribution of plexus abnormalities (normal, symmetric, or focal, root dominant or fusiform) were all retrospective cohort studies with modest sample sizes [15,25,26,27,28]. Reported MRI abnormalities in CIDP and MMN showed considerable variation (40–100%). Hyperintense signal is probably the most common abnormality (CIDP: 44–72%; MMN: 44–100%), while enlargement (CIDP: 13–88%; MMN: 22–30%) and postgadolinium enhancement (CIDP: 10–89%; none in MMN) are less frequently documented [9–11]. Symmetric abnormalities on plexus MRI may be associated with generalized, and focal abnormalities with asymmetric clinical weakness, but this relationship remains to be corroborated in prospective studies [28].

In contrast to ultrasound, systematic scoring-systems for MRI brachial plexus abnormalities still need to be developed. This may improve sensitivity and further strengthen the important place that brachial plexus MRI already has in the current diagnostic consensus criteria for MMN, Lewis–Sumner syndrome (LSS), and CIDP [3–5,29]. Specificity of brachial plexus MRI is context dependent. Although there are several other neuropathies that are also associated with nerve (root) abnormalities, including Charcot–Marie–Tooth (CMT) type 1, neuropathy associated with monoclonal immunoglobulin M (IgM) gammopathy, diabetic plexoradiculoneuropathy, neurolymphomatosis, neuralgic amyotrophy, vasculitis syndromes, and neurofibromatosis, most of these disorders, with the possible exception of the occasional atypical presentation of CMT type 1, can be distinguished from CIDP, LSS, and MMN on clinical grounds [3–5,29]. The specificity of MRI and nerve ultrasound to identify inflammatory neuropathies is high in the context of (lower) motor neurone syndromes and axonal neuropathy.

**WHAT’S NEW**

Last year results that support predefined scoring systems of peripheral nerve imaging were published. In this study, we used a standardized ultrasound protocol in 75 consecutive treatment-naïve patients with CIDP and MMN, and 70 clinically relevant mimics [30]. Enlargement of the median nerve at forearm and upper arm in combination with enlargement of any trunk of the brachial plexus was 99% specific for an inflammatory neuropathy. Two abnormal segments in a relatively short and user-friendly ultrasound protocol of bilateral median nerve assessment in combination with the brachial plexus showed similar high sensitivity and specificity. This study provides Class II evidence that, in the absence of clinical features suggesting a possible demyelinating hereditary neuropathy, sonographic enlargement of proximal median nerve segments and brachial plexus reliably identifies patients with CIDP, LSS, and MMN [30]. Nerve ultrasound protocols can be shortened for daily practice without losing much of the test characteristics (Fig. 2A). The study also confirmed that nerve size is the most robust sonographic parameter in neuropathies and that other sonographic parameters, such as fascicle size, echogenicity, and vascularization, have no added value for the identification of inflammatory neuropathies.

It was not known whether the diagnostic performance of MRI and sonography were comparable because only a few case-series compared the use of these techniques in CIDP [31,32]. Results from a recent study suggest that the diagnostic yield of brachial plexus sonography and MRI in a treatment-naïve cohort [33] is comparable, with abnormalities in the 63–73% range. The combination of both imaging modalities further increased diagnostic sensitivity to 83% of patients with CIDP and MMN. Both imaging techniques have their intrinsic advantages and limitations: MRI can produce optimized images for evaluation of abnormal diameter and separately for signal intensity of nerve roots, but lacks objective cut-off values for abnormality [34,35,36] and requires neuroradiological expertise; nerve ultrasound is a broadly available bedside tool which is sensitive and has a more flexible field of view (e.g., to include large arm nerves), but it requires training [37]. This study also showed that contrast enhancement on MRI, similar to hypervascularization in sonography [14], is probably an indicator of the degree of chronic inflammation rather than a disease-specific parameter.

Another recent development is further refinement of MRI protocols with more advanced T2-based sequences that may improve resolution [27,35,38–41]. It is our experience that this approach is feasible and that this may boost image quality and thereby diagnostic value (Fig. 2B). Nevertheless, more systematic studies in unselected patient populations and controls to define disease-specific cut-off values for abnormality are needed to accurately determine their effect on diagnostic performance. Expanding the field of view with whole body MRI-neurography is another potentially interesting development. This allows screening for nerve enlargement among multiple nerves on MRI [42], but currently has inferior
image resolution compared to the dedicated plexus protocols. Similar to the higher diagnostic yield of ultrasound protocols that assess multiple nerves, we expect that whole body MRI-neurography may ultimately prove an important step forward.

Finally, relatively novel magnetic resonance techniques that are used routinely for imaging of the central nervous tissue [e.g., diffusion tensor imaging (DTI)] may be tools to study pathophysiological processes, disease progression, or treatment effects in chronic inflammatory neuropathies [43–45]. In a proof of principle study, diffusivity was reduced in the forearm of patients with MMN compared with healthy individuals and patients’ motor neurone disease [43]. These protocols can and need to be further improved, but DTI apparently can yield qualitative in addition to quantitative data. We need to further explore its usefulness to study pathophysiology of MMN and CIDP or as a biomarker of response to treatment [43–45].

**COMPARISON OF NERVE CONDUCTION AND IMAGING**

An important question is whether imaging and nerve conduction abnormalities reflect the same underlying pathophysiological processes. Multiple studies have compared parameters of nerve imaging with those of nerve conduction, but suffer from multiple methodological weaknesses. The lack of standardization of anatomical sites, limb temperature during NCS, and distances complicates the interpretation of the available comparative studies. At present, we think the available data do not suggest a relation between nerve morphology (MRI/ultrasound) and nerve function (EDX) [46–50].
The reports that did suggest such an association did not address important methodological questions how comparisons at nerve level [10,44,51,52] using selected sets of EDX and imaging parameters can be properly performed. Comparison between techniques is for example only possible at the segmental level of arm and leg nerves. It is not possible to reliably compare morphological changes to nerve conduction abnormalities at the level of the plexus. For example, prolonged F-wave latency or conduction block at the level of the shoulder in only one nerve cannot be associated with plexus thickening as other parts of the plexus may well be abnormal without similar associated nerve conduction abnormalities in other (arm) nerves. Future comparative studies also need to address neighboring nerve segments (e.g., include proximal/distal/contralateral segments of same nerve or ipsilateral equivalent in other nerve) as an intra-individual control of their findings on possible associations.

Moreover, the apparent mismatch between function and morphology in neuropathies is not only far from unique but also seen in other neurological conditions (e.g., silent ischemic or pure radiological increase of new multiple sclerosis lesions on brain MRI). In fact, it implies that the underlying pathological processes that lead to functional and morphological disturbances are not necessarily the same (Fig. 3). Inflammation and edema, ischemia, fibrosis, and myelin dysfunction probably all lead to nerve hypertrophy. Routine electrodiagnostic studies only evaluate groups of axons within nerves, i.e., the sum of most fast conducting fibers. Therefore, standard EDX does not appreciate pathological changes that occur in individual axons, such as different degrees of myelin, nodal, and axonal dysfunction between axons within the same nerve. There may be alternatives such as nerve excitability that better reflect function of myelinated axons, such as sodium-pump function, but this remains to be established in more detail [53–55].

Summarizing, nerve imaging and nerve conduction yield complementary sets of information about nerve condition and should be combined rather than compared in neuropathies. Their combined use can help to maximize the diagnostic yield of inflammatory neuropathies.

**FUTURE IMPLEMENTATION**

Although important advances have been made, there are still several gaps in knowledge on nerve imaging studies, which need to be addressed. Objective and disease-specific cut-off values for MRI parameters and systematic evaluation of their diagnostic yield are warranted to standardize interpretation. This will undoubtedly help to optimize its application in routine clinical practice. Other important remaining questions are comparison of the diagnostic yield of lumbosacral versus brachial plexus MRI, and a thorough evaluation of the added value of more advanced MRI techniques (e.g., further development of STIR, neurography with maximal intensity projection (MIP)).

Nerve ultrasound is an important addition to the repertoire of ancillary investigations that complements EDX and MRI. The available evidence supports combined EDX and nerve imaging in the diagnostic work-up of patients who may have an inflammatory neuropathy. Although nerve imaging clearly improves detection of treatment-responsive conditions.
neuropathies, the balance of extra yield and false positives is unknown. Prospective studies are needed in large unbiased patient cohorts that apply nerve imaging alongside standardized EDX to all cases in a routine clinical setting. For the time being, both nerve ultrasound and MRI should be considered as ‘imaging’ modalities and eventually be included in future revisions of diagnostic consensus criteria for chronic inflammatory neuropathies. In Fig. 4, we present an outline of what revised diagnostic criteria could look like after addition of ultrasound based on a synthesis of the current EFNS/PNS guideline and Utrecht criteria for CIDP and MMN respectively (3–5): clinical (core, supportive, and exclusion), EDX (definite, probable, and possible) and supportive criteria, and diagnostic categories that adopt neuroimaging more prominently than other supportive criteria. Note that specific conditions need to be ruled out in order to progress to the final diagnostic categories (e.g., severe diabetic neuropathy, chronic renal failure, paraproteinemid neuropathies, and some late onset CMT may present with considerable conduction slowing that fulfills formal EDX criteria for CIDP and/or give rise to substantial nerve enlargement). The authors previously published ultrasound criteria, with disease-specific cut-off values for nerve enlargement in CIDP and MMN. Reproduced from [30**]. EFNS/PNS, European Federation of Neurological Societies (currently the European Academy of Neurology [EAN])/Peripheral Nerve Society.

**FIGURE 4.** Summary of proposed revised diagnostic criteria for chronic inflammatory neuropathies. Outline on revised diagnostics criteria that include nerve ultrasound, based on a synthesis of the current EFNS/PNS guideline and Utrecht criteria for CIDP and MMN respectively (3–5): clinical (core, supportive, and exclusion), EDX (definite, probable, and possible) and supportive criteria, and diagnostic categories that adopt neuroimaging more prominently than other supportive criteria. Note that specific conditions need to be ruled out in order to progress to the final diagnostic categories (e.g., severe diabetic neuropathy, chronic renal failure, paraproteinemid neuropathies, and some late onset CMT may present with considerable conduction slowing that fulfills formal EDX criteria for CIDP and/or give rise to substantial nerve enlargement). The authors previously published ultrasound criteria, with disease-specific cut-off values for nerve enlargement in CIDP and MMN. Reproduced from [30**]. EFNS/PNS, European Federation of Neurological Societies (currently the European Academy of Neurology [EAN])/Peripheral Nerve Society.

ultrasound clearly lies in its promising test characteristics that allows the clinician to identify patients with CIDP and MMN, even when EDX is inconclusive or negative [31,32,56,57]. On the contrary, it is unlikely that imaging modalities can replace EDX.

**CONCLUSION**

MRI and nerve ultrasound have become adjunctive diagnostic tools for potentially treatable neuropathies. Future MRI studies are needed to provide objective and disease-specific cut-off values for abnormality, particularly for spinal nerve roots, whereas ongoing prospective sonography studies will determine the diagnostic yield and frequencies of false positive findings.
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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


First comparative study of MRI and nerve ultrasound in treatment-naïve chronic inflammatory neuropathies.


