BILATERAL NERVE CONDUCTION STUDIES IN THE EVALUATION OF DISTAL SYMMETRIC POLYNEUROPATHY

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Accepted 18 June 2019

ABSTRACT: *Introduction:* Nerve conduction studies are used to aid in the diagnosis of distal symmetric polyneuropathy (DSP). It is unclear whether bilateral lower extremity nerve conduction studies (NCS) are needed when evaluating for suspected DSP. *Methods:* We retrospectively analyzed NCS from patients who presented to the University of Michigan electromyography laboratory between July 1, 2016 and December 31, 2017 with symptoms of DSP to assess agreement and correlation between left and right lower extremity NCS parameters. *Results:* We found significant agreement between abnormalities in individual nerve parameters of the left and right lower extremities of 105 patients, most notably in the sural nerve. In the 53 patients with bilateral sural, peroneal, and tibial studies, there was also significant agreement between whether the left and right met electrodiagnostic criteria for DSP ($\kappa = 0.77$). *Discussion:* Bilateral lower extremity NCS may have limited utility in the evaluation of suspected DSP.

Muscle Nerve **60**: 305–307, 2019

Nerve conduction studies are commonly utilized to aid in the diagnosis of distal symmetric polyneuropathy (DSP). In combination with clinical history and physical examination, electrodiagnostic testing may help confirm or refute the diagnosis of polyneuropathy. It also can guide management by providing information about the category, severity, and prognosis of polyneuropathy.[1,2]

There has been an effort to standardize nerve conduction study (NCS) protocols for suspected DSP. Current research guidelines recommend evaluating the sural sensory and peroneal motor nerve in 1 lower extremity and using the results to determine whether additional studies should be performed.[3] If any of the nerves studied have an absent response, NCS of the contralateral nerve should be performed. The recommendations state that contralateral lower extremity NCS may also be performed at the discretion of the examiner, regardless of the findings on the first side.

Despite this last recommendation, little evidence exists to support the use of bilateral NCS in the diagnosis of DSP. One study found symmetry in NCS throughout the various stages of disease with repeated electrodiagnostic testing.[4] Despite this finding, the authors concluded that bilateral NCS should be used when screening patients for DSP.

Electrodiagnostic consultants would be able to make more appropriate decisions about testing if they knew whether NCS of a second limb were likely to change their overall interpretation. The purpose of this study was to assess the symmetry between right and left lower extremity NCS in a cohort of patients with symptoms of DSP.

METHODS

This study and its methods were approved by the institutional review board of the University of Michigan.

The study population was obtained retrospectively from the University of Michigan EMGPRO database for studies performed from July 1, 2016 through December 31, 2017. Cases were first filtered based on the final diagnosis code applied by the electrodiagnostic consultant. With the goal of identifying all patients who may have presented with symptoms of DSP, including those who ended up with an alternative diagnosis, we included codes for neuropathy, lower extremity plexopathy, lower extremity radiculopathy, lower extremity mononeuropathy, normal study, or indeterminate study.

We reviewed the free text referral reasons and the written histories in the electrodiagnostic reports of cases with these diagnosis codes. Only patients referred for neuropathy, polyneuropathy, or lower extremity sensory changes were included. Among these, patients were included only if their histories included lower extremity numbness, tingling, or pain, and there was no mention of unilateral or asymmetric symptoms. Finally, we only included cases in which bilateral sural sensory studies were performed.

NCS parameters on sural sensory, peroneal motor, and tibial motor nerves were gathered from patients who satisfied all inclusion criteria. Individual parameters were then classified as normal or abnormal based on published normative values.[5,6]

Correlation coefficients and Cohen's were used to determine correlation and degree of agreement between individual nerve conduction parameters of right and left sural, peroneal, and tibial nerves. Similarly, we used Cohen's kappa to assess degree of agreement for each nerve using abnormality in 1 or more parameters in each nerve to categorize abnormal.

Current consensus criteria for the diagnosis of distal symmetric polyneuropathy are an abnormality (≥99th or ≤1st percentile) of any attribute of nerve conduction in 2 separate nerves, 1 of which must be the sural nerve.[3] The subset of cases that included bilateral sural, peroneal, and tibial responses were analyzed to determine whether each side met these criteria for DSP. For each encounter, each side was categorized as normal or abnormal, and the 2 sides were then compared for degree of agreement.

Abbreviations: DSP, distal symmetric polyneuropathy; NCS, nerve conduction study

Key words: bilateral; electromyography; nerve conduction studies; neuropathy; symmetry

Funding: No funding was received for this research.

Conflicts of Interest: None of the authors have any conflicts of interest to disclose.

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Published online 22 June 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.26616

Table 1. Correlation and agreement between right and left lower extremity.

Nerve	*n*	κ	*P*-value	*n*	Correlation	*P*-value
Sural	105	0.76	<0.01			
Amplitude	105	0.79	<0.01	105	0.94	<0.01
Latency	105	0.85	<0.01	105	0.79	<0.01
Conduction velocity	105	0.77	<0.01	105	0.78	<0.01
Peroneal	65	0.75	<0.01			
Amplitude	70	0.68	<0.01	70	0.75	<0.01
Latency	69	0.54	<0.01	54	0.69	<0.01
Conduction velocity	65	0.77	<0.01	51	0.86	<0.01
Tibial	58	0.76	<0.01			
Amplitude	60	0.74	<0.01	60	0.85	<0.01
Latency	59	0.81	<0.01	54	0.69	<0.01
Criteria for DSP*	53	0.77	<0.01			

DSP, distal symmetric polyneuropathy.

**From England* et al.[3]

RESULTS

NCS parameters were gathered from 105 patients. Of these encounters, 53 studies included bilateral sural sensory, peroneal motor, and tibial motor studies. The demographics of patients were: sex, 49% female; age, 63.4 ± 12.0 (mean $\pm$ SD) years; height, 68.4 ± 4.3 inches; and weight, 200.7 ± 50.2 lbs. Of the encounters, 76 were coded as neuropathy, 19 as normal or indeterminate, 4 as mononeuropathy, and 6 as radiculopathy.

A high degree of agreement was observed for abnormalities of any parameter between the right and left lower extremity for the sural, peroneal, and tibial nerves (Table 1). There was also significant agreement between individual nerve parameters of the right and left lower extremities, which was most notable in the sural and tibial nerves. Additional analyses showed significant correlation in individual nerve parameters between sides across all 3 nerves. When we analyzed the subset of electrodiagnostic encounters with bilateral studies of all 3 nerves to assess criteria for DSP, we found agreement between sides in 89% (47 of 53) of cases.[3] Of the 47 patients with symmetry, 23 had bilateral polyneuropathy and 24 did not meet criteria for polyneuropathy on either side.

DISCUSSION

In patients with symmetric signs and symptoms of neuropathy, there was a high degree of agreement in NCS between lower extremities, including abnormalities between individual nerves and in meeting criteria for DSP. In the correct clinical context, NCS on a second lower extremity may not add diagnostic value. Electrodiagnostic testing is one of the most frequently used tests when evaluating for suspected DSP.[2] Conversely, DSP is among the most common reasons for referral for electrodiagnostic testing.[1,7] This has practical implications for electrodiagnostic consultants and for neuropathy research. Limiting lower extremity testing to 1 limb in this population may reduce cost, minimize patient discomfort, and improve provider efficiency.

There are several limitations to our study. Of the 105 patients included, only 53 had bilateral sural, peroneal, and tibial studies, which limited our ability to assess symmetry of polyneuropathy between sides. The normative values used in the study were not adjusted for age. We also did not assess symmetry of F-waves, which are an important parameter when testing for polyneuropathy.

It should also be noted that our study was done at a large tertiary referral center. If we expanded our study beyond our center, we may have seen a difference in agreement due to variations in clinical practice and electrodiagnostic testing. Another limitation of our study is that the clinical decisionmaking that led to these patients having bilateral lower extremity NCS was unknown. A possibile explanation is that some providers at our institution routinely evaluate suspected neuropathy with bilateral NCS, whereas others do not, but we did not gather provider data to evaluate this theory. It is also conceivable that there were undocumented clinical features that led providers to study both lower extremities in certain cases and not others. Future work could survey electrodiagnostic consultants to better determine practice patterns in the community.

Although we demonstrated significant agreement between sides, it is difficult to determine what degree of agreement is enough to justify performing only unilateral NCS. Future research could assess how the finding of asymmetry in NCS affects clinical decisions in this population.

This single-center study has demonstrated that patients with symmetric neuropathy symptoms have a high degree of agreement in nerve conduction study parameters between sides. Given the limitations of a retrospective, single-center study, prospective studies in multiple centers are needed to inform future guidelines about the utility of bilateral NCS.

Ethical Publication Statement: We (the authors) 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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ASSOCIATION BETWEEN MUSK ANTIBODY CONCENTRATIONS AND THE MYASTHENIA GRAVIS COMPOSITE SCORE IN 3 PATIENTS: A MARKER OF RELAPSE?

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Accepted 5 June 2019

ABSTRACT: *Introduction:* Muscle-specific tyrosine kinase (MuSK) autoantibody related myasthenia gravis is characterized by bulbar and respiratory manifestations, a poor response to anticholinergics, and a generally good response to plasma exchange and rituximab. It is not known if MuSK-antibody (Ab) levels could be used to predict the clinical course *Methods:* Three patients for whom frequent long-term monitoring of MuSK-Ab levels and the Myasthenia Gravis Composite (MGC) scores were performed are described. *Results:* A close relationship existed between the MuSK-Ab concentrations and the MGC score. Furthermore, a rise in Ab concentration preceded a more serious clinical relapse in all patients *Conclusions:* These findings suggest that MuSK-Ab concentrations may be a useful biomarker for the long-term monitoring of MuSK myasthenia gravis, particularly while in clinical remission. This may allow preemptive escalation of therapy to prevent clinical relapse, and conversely permitting greater weaning of unnecessary immunosuppression.

Muscle Nerve **60**: 307–311, 2019

Additional supporting information may be found in the online version of this article.

Abbreviations: Ab, antibody; AChR, acetylcholine receptor; BID, twice daily; IVIG, intravenous immunoglobulin; L, level; Lrp4, low density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase

Key words: biomarker; immunotherapy; muscle-specific tyrosine kinase; myasthenia gravis; myasthenia relapse; rituximab

Conflicts of Interest: Dr's Triplett, Riminton, Hardy and Chu report no conflicts of interest. Stephen Reddel disclosure statement: Funds over the last 5 years including but not limited to travel support, honoraria, trial payments, research and clinical support to the neurology department of which I am a member has been received from bodies and charities: NHMRC, NIH, USMDA, NSWMDA, MGANSW, MGAQLD, MAA, Beeren foundation, anonymousdonors; and from pharmaceutical/biological companies: Aspreva, Baxter, Bayer Schering, Biogen Idec, CSL,Genzyme, Grifols, Merck, Novartis, Sanofi Aventis Genzyme, Servier, TEVA. Additional interests and potential conflicts of interest include: Co-founder / shareholder of Medical Safety Systems (grant and contracts with Genzyme > $25000 AUD including a per patient payment, potential application to multiple drugs), National IVIG Governance Advisory Council & Specialist Working Group Australia (Neurology) (paid), Australian Technical Advisory Group on Immunisation Varicella Zoster working party (unpaid), Nerve Research Foundation board member (unpaid).

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Published online 8 June 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.26609

Muscle-specific tyrosine kinase (MuSK) autoantibody related myasthenia gravis (MuSK-MG) makes up approximately 5% of cases of myasthenia gravis.[1,2] MuSK-MG is characterized by prominent bulbar and respiratory weakness and an often poor response to cholinesterase inhibitors and standard immune-therapies.[3,4] Plasma exchange is often more effective than intravenous immunoglobulin (IVIG). Rituximab, an anti-CD-20 monoclonal antibody can be effective in the management of MuSK-MG, with post treatment clinical improvement associated with reduced MuSK antibody levels (MuSK-Ab-L).[5,6]

MuSK-Ab-L were shown to be broadly associated with severity using the limited Myasthenia Gravis Foundation of America (MGFA) score.[7] MuSK antibodies are predominantly IgG4,[1,2] and functionally akin to an antagonist ligand. MuSK antibodies disrupt the normal agrin-induced MuSK-low density lipoprotein receptor-related protein 4 (MuSK-Lrp4) interactions, inhibit MuSK activation and result in acetylcholine receptor (AChR) loss at the muscle endplate, whereupon neuromuscular transmission fails and weakness results.[8]

We present a report of three patients treated with rituximab in whom regular monitoring of MuSK-Ab-L demonstrated a close relationship between antibody levels and the Myasthenia Gravis Composite (MGC) score, and in whom rising levels predated relapses requiring retreatment.