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CLINICAL RESEARCH SHORT REPORT

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Lowering the cutoff value for increment increases the sensitivity for the diagnosis of Lambert-Eaton myasthenic syndrome

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Abstract

Background: Increment of compound muscle action potential amplitude is a diagnostic hallmark of Lambert-Eaton myasthenic syndrome (LEMS). Making a diagnosis can be challenging, therefore, a proper cutoff for abnormal increment is highly relevant for improved recognition of this rare disease.

Methods: We determined the sensitivity and specificity of 60% and 100% cutoff values in all consecutive patients who underwent increment testing in our hospital from 1999 to 2016.

Results: We included 156 patients, 63 with LEMS and 93 without LEMS. Sensitivity of a 60% cutoff for increment testing was 77.8% (95% confidence interval 65.5%–87.3%) and 58.7% (45.6%–71.0%) for 100%. Specificity was 98.9% (94.2%–100%) and 100% (96.1%–100%) using a threshold of 60% and 100%, respectively.

Conclusions: Lowering the cutoff value for abnormal increment to 60% greatly increases sensitivity to diagnose LEMS without an overt loss in specificity.

KEYWORDS

compound muscle action potential amplitude, increment, Lambert-Eaton myasthenic syndrome, repetitive nerve stimulation, sensitivity, specificity

1 | INTRODUCTION

Repetitive nerve stimulation (RNS) and increment testing are the most important electrophysiological tests to diagnose Lambert-Eaton myasthenic syndrome (LEMS).[1,2] Typical findings include a triad of low compound muscle action potential (CMAP) amplitude at rest, decrement upon low-frequency repetitive nerve stimulation and an increase or "increment" of the CMAP amplitude after 10–30 s of exercise or upon high-rate stimulation.[2,3] Historically, 100% increment of this CMAP amplitude has been used as a cutoff for diagnosis of LEMS.[2,3] Although highly specific, sensitivity using this threshold is limited, dependent on the number of muscles tested.[4–6] Because making a diagnosis can be challenging, an optimal cutoff value for abnormal increment is highly relevant for improved recognition of this rare disease.

One study reported a 60% cutoff threshold for abnormal increment to increase sensitivity of this test, while maintaining specificity when compared with myasthenia gravis (MG).[4] However, since its publication, several studies have still variably used either a 60%[3,7] or 100%[8–10] cutoff in diagnostic criteria. We, therefore, compared diagnostic characteristics of 60% and 100% increment thresholds in the diagnosis of LEMS in a second, independent cohort of patients.

2 | METHODS

2.1 | Patients

We retrospectively studied all consecutive patients who underwent RNS as well as increment testing from 1999 to 2016 at the Leiden University Medical Center, during a diagnostic evaluation of patients in whom LEMS was part of the differential diagnosis.

2.2 | Diagnostic criteria

Diagnosis of LEMS is usually based on fluctuating muscle weakness, decreased tendon reflexes and autonomic symptoms, supported by either presence of antibodies to voltage-gated calcium channels (VGCC) or abnormal decrement and increment upon RNS.[2] Because abnormal increment is the subject of the current study, this criterion cannot be used. Therefore, for this study, diagnosis was based on fluctuating muscle weakness, decreased tendon reflexes, and abnormal decrement, supported by either presence of antibodies to VGCC or prominent autonomic symptoms.

2.3 | Electrodiagnostic testing

Patients were asked to refrain from using 3,4-diaminopyridine or pyridostigmine at least 12 h before investigation, although this was not enforced. RNS was administered as trains of 10 stimuli at 1, 3, and 5 Hz using a Nicolet Viking IV machine (Nicolet Medical, Madison, WI) until 2004 and a Medelec Synergy 11.0 (Oxford Instruments, Abingdon, Oxfordshire, UK) thereafter. The optimal stimulation site on the skin was identified using inframaximal stimuli and the limit of supramaximal intensity was established. The working intensity was ~130% of that threshold. RNS was performed on the hypothenar, nasalis, and trapezius muscles.[11–13] Abnormal decrement was defined as at least 10% decrease in amplitude of the lowest CMAP of the train compared with the first CMAP.[1,11,12] The increment test involved acquiring a baseline CMAP at rest, followed by the first CMAP amplitude measured immediately after 10 or 30 s of voluntary contraction. Abnormal increment was defined as either 60 or 100% increase in CMAP amplitude after contraction. High-rate RNS was not routinely performed.

All tests were performed with a skin temperature of at least 32°C. Quality criteria for RNS and increment testing were[12]: (1) the stimulus artefact should return to baseline before onset of the CMAP; (2) the CMAP should begin with a negative phase or an initial positive phase smaller than approximately one-fourth of the amplitude of the negative phase; (3) the CMAP waveform should be essentially biphasic; and (4) the amplitude of the negative phase of the CMAP should preferably be over 1 mV. In case of lower amplitudes, we enforced all other quality criteria scrupulously. Technically inadequate investigations were excluded.

2.4 | Statistics

Sensitivity and specificity are reported as percentages with 95% confidence intervals (CI), and calculated using SPSS version 24.0 (Chicago, IL) and Graphpad Prism 7 (La Jolla, CA).

3 | RESULTS

Increment testing was performed in 164 patients during the study period, of whom 156 were ultimately analyzed, including 63 LEMS patients (Table 1; Supporting Information Figure S1 flowchart for inclusion and disease groups, which is available online). The hypothenar muscle was tested in all but four patients (97.5%). The nasalis muscles were tested in 19 patients (11.7%), while tibialis anterior, trapezius, and abductor pollicis brevis muscles were tested in one patient each.

Sensitivity and specificity are reported in Table 2, showing increased sensitivity for the 60% as compared to the 100% cutoff. Exclusion of three seronegative LEMS patients with typical clinical symptoms (including prominent autonomic symptoms) resulted in a sensitivity of 80.0% (67.7%–89.2%) for a 60% increment threshold and 61.7% (48.2%–73.4%) using a 100% threshold. Limiting the control group only to 23 patients with myasthenia gravis and congenital myasthenic syndromes, specificity was 95.7% for the 60% threshold and 100% for the 100% threshold. The single false positive patient had a normal initial CMAP amplitude, 56% decrement and 68% increment in the hypothenar muscle. She had generalized MG with acetylcholine receptor (AchR) antibodies and a severe axonal polyneuropathy.

TABLE 1 Baseline characteristics

Baseline	Patients	Gender (M/F)	Median age (range; y)	Thymoma (%)	SCLC (%)	Abnormal decrement (%)
LEMS	63	30/33	56.0 (14–85)	0 (0%)	17 (27.0%)	60/61[aa] (98.3%)
AChR MG	16	4/12	55.9 (16–77)	2 (12.5%)	0 (0%)	11 (68.8%)
Other myasthenia	7	5/2	52.4 (23–84)	0 (0%)	0 (0%)	3 (42.9%)
Other NMD	35	15/20	59.3 (30–83)	n.a.	n.a.	2 (5.7%)
no NMD	35	15/20	58.9 (38–75)	n.a.	n.a.	0 (0%)

Abbreviations: AChR MG, acetylcholine receptor antibody-positive myasthenia gravis; LEMS, Lambert-Eaton myasthenic syndrome; MuSK MG, muscle-specific kinase antibody-positive myasthenia gravis; n.a., data not available; NMD, neuromuscular disease; SCLC, small cell lung cancer.
[a]Presence of abnormal decrement not tested for two LEMS patients at the time of investigation.

TABLE 2 Sensitivity and specificity for 60% and 100% cut-off value for diagnosis of Lambert-Eaton myasthenic syndrome

	Number of patients	LEMS patients	Patients without LEMS	Sensitivity 60% (%; 95% CI)	Specificity 60% (%; 95% CI)	Sensitivity 100% (%; 95% CI)	Specificity 100% (%; 95% CI)
Any muscle	156	63	93	77.8 (65.5–87.3)	98.9 (94.2–100)	58.7 (45.6–71.0)	100 (96.1–100)
Hypothenar	152	62	90	74.2 (61.5–84.5)	98.9 (94.0–100)	54.8 (41.7–67.5)	100 (96.0–100)
Nasalis	17	10	7	80.0	100	50.0	100
Other muscles[a]	3	1	2	100	100	100	100

Abbreviations: CI, confidence interval; LEMS, Lambert-Eaton myasthenic syndrome.
[a]See the Results section. Confidence intervals for nasalis and other muscles were omitted because of the limited number of patients.

Sensitivity was higher in the 18 untreated LEMS patients, and in LEMS patients without associated lung cancer for the 60% cutoff (Supporting Information Table S1). Of three seronegative LEMS patients with typical clinical symptoms who were already treated symptomatically, one had a clinically meaningful increment (95%) in the hypothenar muscle.

Increment in nasalis muscles was mainly tested in patients with ocular or facial weakness (in 11 of 17 patients) or low CMAP amplitude of the nasalis muscle (10/17). This resulted in detection of >100% increment in two patients without increment in the hypothenar muscle.

4 | DISCUSSION

In this study, we confirm that a 60% threshold for increment greatly increases sensitivity while maintaining a high specificity in a large group of LEMS patients and a different control group than previously studied.[4]

Specificity of increment for LEMS using either threshold was very high. False-positive increment was present in one otherwise typical AChR MG patient and could be pseudo-facilitation or related to the low CMAP amplitude (2.8 mV). Lowering the threshold to 60%, therefore, facilitates the diagnosis of LEMS, which may eliminate the need for additional testing such as high-frequency stimulation, which can be quite painful, and may hasten diagnosis. We used a practical approach and mainly tested the hypothenar muscle, which is likely to be the most reliable and sensitive muscle for detecting increment.[5,6] Additional testing of the nasalis muscle was only performed when clinically appropriate. In contrast to the previous study of Oh et al., our study tested not only MG patients, but also several other patients in whom neuromuscular junction disorders were suspected.[4]

Several previous studies have described diagnostic characteristics of increment testing. Oh et al. also showed an increase in sensitivity from 85% to 97% when lowering the cutoff threshold to 60% in 34 LEMS patients.[4] This study had a more strict definition of LEMS diagnosis, possibly selecting for a more severe subgroup. Increment was tested in the hypothenar muscle both at high-rate stimulation (HRS) and after voluntary contraction. Specificity of a 60% threshold was still 99% using a larger population of 538 MG patients, but was not tested in other control groups. A follow-up study comparing seropositive and seronegative LEMS patients showed a 60% increment cutoff is especially important for seronegative LEMS patients, in whom increment is less prominent.[14] Another study including 10 LEMS patients also reported 50% increment might be sufficient and more sensitive than the 100% threshold for LEMS diagnosis, reporting less than 50% increment in all muscles in controls.[6]

Other studies have focused on duration of exercise before increment testing, as well as comparison with HRS (20–50 Hz). Most investigations in our study were performed after 30 s, while a previous study suggested that 10 s might be more sensitive.[15] Previous studies have shown conflicting results regarding diagnostic yield of increment testing by either HRS or after exercise.[3,4,16] As we mainly performed postexercise stimulation, we could not analyze the diagnostic yield of both thresholds using HRS.

Limitations include a lower overall sensitivity increment for LEMS diagnosis compared with previous studies; several explanations are likely to contribute to this difference. Most of our patients were referred to our tertiary clinic for a second opinion. Therefore, many patients were already treated at the time of electrophysiological testing. In line with this, sensitivity in our study was considerably higher in 18 untreated LEMS patients. In this group a threshold of 60% still resulted in a large absolute increase in sensitivity. The limited number of LEMS patients with an associated SCLC (27%) might also result from referral bias. Previous studies of the diagnostic yield of increment testing often used a more extensive testing protocol, including multiple muscle groups for most patients and/or testing both HRS as well as increment after voluntary contraction.[3–6]

In conclusion, we confirm that lowering the cutoff value for abnormal increment from 100% to 60% for diagnosis of LEMS greatly increases sensitivity.[4] Together with the results of the previous study from Oh et al., we now have two heterogeneous studies, reaching the same conclusion. We propose using a threshold for abnormal increment of 60%, as this should lead to improved diagnosis of patients with this rare neuromuscular disease.

CONFLICT OF INTEREST

M.J. Titulaer received research funds for serving on a scientific advisory board of MedImmune, for consultation at Guidepoint Global, an unrestricted research grant from Euroimmun AG, and a travel grant for lecturing in India from Sun Pharma, India. J.J.G.M. Verschuuren reports involvement in a National Institutes of Health-sponsored thymectomy trial (ClinicalTrials.gov, number NCT00294658); reports a FP7 European MG grant (602420); and is a consultant for Alexion Pharmaceuticals and arGEN-X. The remaining authors have no conflicts of interest.

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Intrathecal delivery of nusinersen in individuals with complicated spines

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Abstract

Background: The treatment of spinal muscular atrophy (SMA) with nusinersen requires intrathecal medication administration, which can be challenging in individuals with complicated spines. This retrospective case series reviews the nusinersen treatment experience at one academic medical center with children and adults with SMA and complicated spines.

Methods: Twenty medical records of individuals receiving nusinersen were reviewed and administration methods summarized and assessed.

Abbreviations: BMI, body mass index; CT, computed tomography; mGy, milligray; SMA, spinal muscular atrophy; SMN, survival motor neuron.