Autoimmunity at the neuromuscular synapse: pathophysiology and disease course

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CHAPTER 5

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

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Abstract

Introduction 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 cut-off for abnormal increment is highly relevant for improved recognition of this rare disease.

Methods We determined the sensitivity and specificity of 60% and 100% cut-off 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% cut-off 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.

Discussion Lowering the cut-off value for abnormal increment to 60% greatly increases sensitivity to diagnose LEMS without an overt loss in specificity.

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 seconds of exercise or upon high-rate stimulation.[2,3] Historically, 100% increment of this CMAP amplitude has been used as a cut-off for diagnosis of LEMS.[2,3] Although highly specific, sensitivity using this threshold is limited, dependent on the number of muscles tested.[4-6] Since making a diagnosis can be challenging, an optimal cut-off value for abnormal increment is highly relevant for improved recognition of this rare disease.

One study reported a 60% cut-off threshold for abnormal increment to increase sensitivity of this test, while maintaining specificity when compared to myasthenia gravis (MG).[4] However, since its publication, several studies have still variably used either a 60%[3,7] or 100%[8-10] cut-off 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.

Methods

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.

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] Since 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.

Electrodiagnostic testing

Patients were asked to refrain from using 3,4-diaminopyridine or pyridostigmine at least 12 hours prior to 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 to 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 seconds 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 about 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.

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).

Results

Increment testing was performed in 164 patients during the study period, of whom 156 were ultimately analyzed, including 63 LEMS patients (Table 1, supplemental figure 1 flowchart for inclusion and disease groups). The hypothenar muscle was tested in all but 4 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 1 patient each.

Baseline	Patients	Gender (M/F)	Median age (range; yrs)	Thymoma (%)	SCLC (%)	Abnormal decrement (%)
LEMS	63	30/33	56.0 (14-85)	0 (0%)	17 (27.0%)	60/61* (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%)

Table 1. Baseline characteristics.

*Presence of abnormal decrement not tested for 2 LEMS patients at the time of investigation. N.a.- data not available. AChR MG- acetylcholine receptor antibody-positive myasthenia gravis, LEMS- Lambert-Eaton myasthenic syndrome, MuSK MG- muscle-specific kinase antibody-positive myasthenia gravis, NMD- neuromuscular disease, SCLC- small cell lung cancer.

Sensitivity and specificity are reported in Table 2, showing increased sensitivity for the 60% as compared to the 100% cut-off. Exclusion of 3 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.

	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*	3	1	2	100	100	100	100

Table 2. Sensitivity and specificity for 60% and 100% cut-off value for diagnosis of Lambert-Eaton myasthenic syndrome.
*See Results section. Confidence intervals for nasalis and other muscles were omitted because of the limited number of patients. CI- confidence interval, LEMS-Lambert-Eaton myasthenic syndrome.

Sensitivity was higher in the 18 untreated LEMS patients, and in LEMS patients without associated lung cancer for the 60% cut-off (Supplemental Table 1). 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.

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

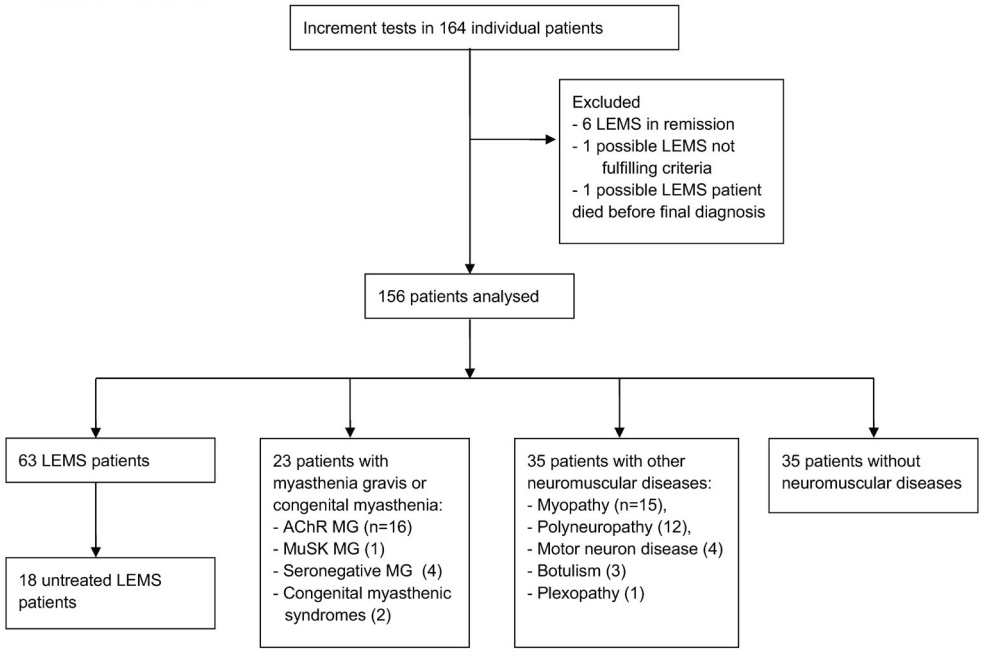
testing such as high-frequency stimulation, which can be quite painful, and may hasten diagnosis. We used a practical approach and mainly tested the hypothenar muscle, which is likely to be the most reliable and sensitive muscle for detecting increment.[5,6] Additional testing of the nasalis muscle was only performed when clinically appropriate. In contrast to the previous study of Oh, 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 cut-off 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 cut-off 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 (20-50Hz). Most investigations in our study were performed after 30 seconds, while a previous study suggested that 10 seconds 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 post-exercise stimulation, we could not analyze the diagnostic yield of both thresholds using HRS.

Limitations include a lower overall sensitivity increment for LEMS diagnosis as compared to 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.[3,4,6,5]

In conclusion, we confirm that lowering the cut-off 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.



Supplemental Figure S1. flowchart of inclusion.

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	Any muscle	Hypothenar	Nasalis	Other muscles*
Number of patients	156	152	17	3
of which LEMS patients	63	62	10	1
patients without LEMS	93	90	7	2
Sensitivity 60% (%; 95% CI)	77.8 (65.5-87.3)	74.2(61.5-84.5)	80.0	100
Untreated patients (n=18)	94.4 (72.7-99.9)	94.4 (72.7-99.9)	66.7	
SCLC-LEMS (n=17)	64.7 (38.3-85.8)	64.7 (38.3-85.8)	100	
NT-LEMS (n=46)	82.6 (68.9-92.2)	77.8 (62.9-88.8)	77.8	100
Specificity 60% (%; 95% CI)	98.9 (94.2-100)	98.9 (94.0-100)	100	100
Sensitivity 100% (%; 95% CI)	58.7 (45.6-71.0)	54.8 (41.7-67.5)	50.0	100
Untreated patients (n=18)	72.2 (46.5-90.3)	72.2 (46.5-90.3)	0	
SCLC-LEMS (n=17)	58.8 (32.9-81.6)	58.8 (32.9-81.6)	0	
NT-LEMS (n=46)	58.7 (43.2-73.0)	53.3 (37.9-68.3)	55.6	100
Specificity 100% (%; 95% CI)	100 (96.1-100)	100 (96.0-100)	100	100

Supplemental table 1. Sensitivity and specificity for 60% and 100% cut-off value for diagnosis of Lambert-Eaton myasthenic syndrome, including LEMS subgroups.

*See Results section. Confidence intervals for nasalis and other muscles were omitted because of the limited number of patients. CI- confidence interval, LEMS- Lambert-Eaton myasthenic syndrome. NT- non-tumor patients, SCLC- small cell lung cancer.

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