



The long exercise test as a functional marker of periodic paralysis

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Funding information

Medical Research Council, Grant/Award Numbers: Clinical Research Training Fellowship MR/M01827X/1, MRC Centre for Neuromuscular Diseases grant MR/K00; UCLH Biomedical Research Centre, Grant/Award Number: BRC401/NS/MH/101410; Wellcome Trust, Grant/Award Number: Fellowship 209583

Abstract

Aims: The aim of this study was to evaluate the sensitivity of the long exercise test (LET) in the diagnosis of periodic paralysis (PP) and assess correlations with clinical phenotypes and genotypes.

Methods: From an unselected cohort of 335 patients who had an LET we analyzed 67 patients with genetic confirmation of PP and/or a positive LET.

Results: 32/45 patients with genetically confirmed PP had a significant decrement after exercise (sensitivity of 71%). Performing the short exercise test before the LET in the same hand confounded results in four patients. Sensitivity was highest in patients with frequent (daily or weekly) attacks (8/8, 100%), intermediate with up to monthly attacks (15/21, 71%) and lowest in those with rare attacks (9/16, 56%) ($p = .035$, Mann-Whitney U -test). Patients with a positive LET without confirmed PP mutation comprised those with typical PP phenotype and a group with atypical features.

Discussion: In our cohort, the LET is strongly correlated with the frequency of paralytic attacks suggesting a role as a functional marker. A negative test in the context of frequent attacks makes a diagnosis of PP unlikely but it does not rule out the condition in less severely affected patients.

KEYWORDS

decrement, electrodiagnostic study, long exercise test (McManis), periodic paralysis, sensitivity

ABBREVIATIONS: ATS, Andersen-Tawil syndrome; CMAP, compound muscle action potential; HyperPP, hyperkalaemic periodic paralysis; HypoPP, hypokalaemic periodic paralysis; LET, long exercise test; N/A, not applicable; PP, periodic paralysis; SET, short exercise test.

Part of this study was presented by AR at the 2018 Muscle Study Group Annual Scientific Meeting, Oxford, UK (poster), and at the 2018 British Society for Clinical Neurophysiology (BSCN) Autumn Scientific Meeting, Royal Free Hospital, London, UK

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1 | INTRODUCTION

The primary periodic paralyses (PP) are characterized by episodic muscle weakness and include hypokalaemic PP (hypoPP), hyperkalaemic PP (hyperPP) and Andersen-Tawil syndrome (ATS) due to mutations in voltage gated ion channels.^{1,2} The diagnosis is based on clinical

presentation supported by genetic and electrophysiological findings but can be challenging when clinical and laboratory information do not agree.³ Genetic testing has been the gold standard for diagnosis, but a pathogenic mutation is found in only 60% to 70% of patients meeting clinical criteria for PP.¹ The literature suggests that the long exercise test (LET) is highly sensitive and specific.⁴⁻¹⁰ The aim of this study was to assess sensitivity in our cohort and correlate electrophysiology with phenotype and genotype.

2 | METHODS

A retrospective analysis of patients attending the National Muscle Channelopathy Service from 2009 to 2017 was performed to identify all patients who had undergone an LET. The study was registered and approved as part of a clinical audit with the National Hospital for Neurology and Neurosurgery Audit Committee. Because the data was obtained during routine clinical care and collected from hospital electronic records as part of a clinical audit, such evaluations do not require patient consent. Patients were selected if they fulfilled at least one criteria: a positive LET or a pathological variant in a PP associated gene. Some patients in this study were included in a previous publication that also contained data of normal controls for the LET.⁷ Patients were subdivided into three main groups: (a) genetics and LET positive, (b) genetics positive and LET negative, and (c) genetics negative and LET positive. Frequency of attacks was categorized as (1) none or rare (0-1/year, this included patients with progressive weakness and no attacks), (2) moderate (>1/year to monthly), and (3) frequent (weekly to daily).

2.1 | Genetics

Patients were considered to have genetically confirmed PP if pathogenic PP mutations were found in relevant genes (*CACNA1S*, *KCNJ2*, *SCN4A*, *RYR1*). Testing was done by direct Sanger sequencing (hotspot testing in earlier cohorts or family mutations) or next generation sequencing using a “muscle channel panel.”

2.2 | Neurophysiology

The LET was performed as described by McManis et al.⁴ Compound muscle action potentials (CMAP) from abductor digiti minimi were monitored at baseline, during 5 min of exercise and for 50 min post-exercise. The same electrodes were used during short exercise test (SET), which preceded the LET, when applicable with a maximum interval between SET and LET of 30 min. A post-exercise decrement of more than 40% from peak CMAP amplitude indicated a positive test. As we previously observed a significant decrement occurring after SET (3 × 10 s bouts of exercise separated by 1 min), we considered the LET positive if there was >40% decrement between peak SET amplitude and the post-LET exercise CMAP. We used the largest SET CMAP amplitude to calculate the overall decrement.

2.3 | Analysis

Sensitivity was calculated using genetic testing as the gold standard. Statistical analysis was conducted using *SPSS Statistics* for Macintosh, Version 25.0. (IBM, Armonk, NY). For individual tests see Table 1 and Appendix S1, which is available online. The level of statistical significance was set at $p < .05$.

3 | RESULTS

3.1 | Patient characteristics

We identified 335 patients who had undergone the LET, of which 248 had neither positive LET nor PP genetics. The presenting symptom was intermittent paralysis and/or progressive muscle weakness. Analysis focused on 67 patients who had a positive LET and/or genetically confirmed PP (Figure 1, Table 1). A total of 35 patients had an SET prior to the LET. In six of these patients the calculated overall decrement was >5%–10% larger and in nine patients >10% larger than the decrement based on LET data alone, leading to re-classification of four individuals from LET negative to LET positive. LET sensitivity was 71% and did not significantly differ between genotypes, although subgroups were small. Estimated LET specificity for genetically confirmed PP was 92.4% (268/290) in the entire cohort undergoing an LET.

3.2 | Attack frequency and LET result

LET results correlated with frequency of attacks ($p = .035$, Mann-Whitney *U*-test, Figure 2). More genetically confirmed PP patients with a positive LET result were on PP treatment (20/32, 62.5%) compared to those with a negative LET (3/13, 23.1%), $p = .016$.

3.3 | Positive LET but negative PP genetics

Typical PP features were seen in 10/22 patients with a positive LET but negative PP genetics. 9/10 patients with typical PP phenotype had negative genetic results after next generation sequencing of *CACNA1S*, *KCNJ2*, and *SCN4A* genes. The nine patients with a mixed or atypical phenotype presented with exercise-induced fatigue with stiffness and cramps or exercise intolerance and fatigue.

3.4 | LET parameters and variability

A total of 16/67 patients had a repeat LET with a mean test-to-test intra-individual CMAP amplitude decrement variability of 12% (range 2%–27%). There was no clear relationship between medication changes and result of the repeat LET. Attack frequency data at the time of repeat testing was not available in sufficient numbers for analysis.

TABLE 1 Results of patients with positive genetics for PP and/or positive LET

Variables	Genetics positive LET positive	Genetics positive LET negative	Genetics negative LET positive	p-Value	Statistical test
Patients	n = 32	n = 13	n = 22	N/A	N/A
Age (y)	36.6 ± 14.2 (15–64)	44.4 ± 15.4 (18–77)	36.4 ± 12.8 (17–63)	.197	ANOVA
Gender M/F (M:F ratio)	26/6 (4.3: 1)	8/5 (1.6: 1)	21/1 (21: 1)	.040	Fisher
No. of patients on PP medication (%)	20 (62.5%)	3 (23.1%)	2 (9.1%)		
Largest CMAP in mV	8.1 ± 1.8 ^a (4.2–11.6)	9.1 ± 1.8 (4.4–12.8)	10.5 ± 2.1 ^a (6.0–15.2)	<.001	ANOVA
Increment in %	28.4 ± 26.4 (–11–119)	11.8 ± 15.1 (–13–48)	28.1 ± 14.9 (4–58)	.017	Kruskal-Wallis
Decrement from peak in %	55.0 ± 11.6 (33–80)	28.7 ± 6.4 (15–39)	51.3 ± 8.4 (42–68)	N/A ^b	N/A
Decrement from baseline in %	41.8 ± 19.1 (–12–81)	20.1 ± 11.2 (0–38)	37.9 ± 12.2 (12–57)	N/A ^b	N/A
Time to 40% decrement in minutes	21.4 ± 13.0 ^c (4–54)	N/A	28.7 ± 12.6 (3–46)	.051	t

Note: Continuous quantitative data were plotted as mean ± SD (range).

Abbreviations: F, female; M, male; N/A, not applicable.

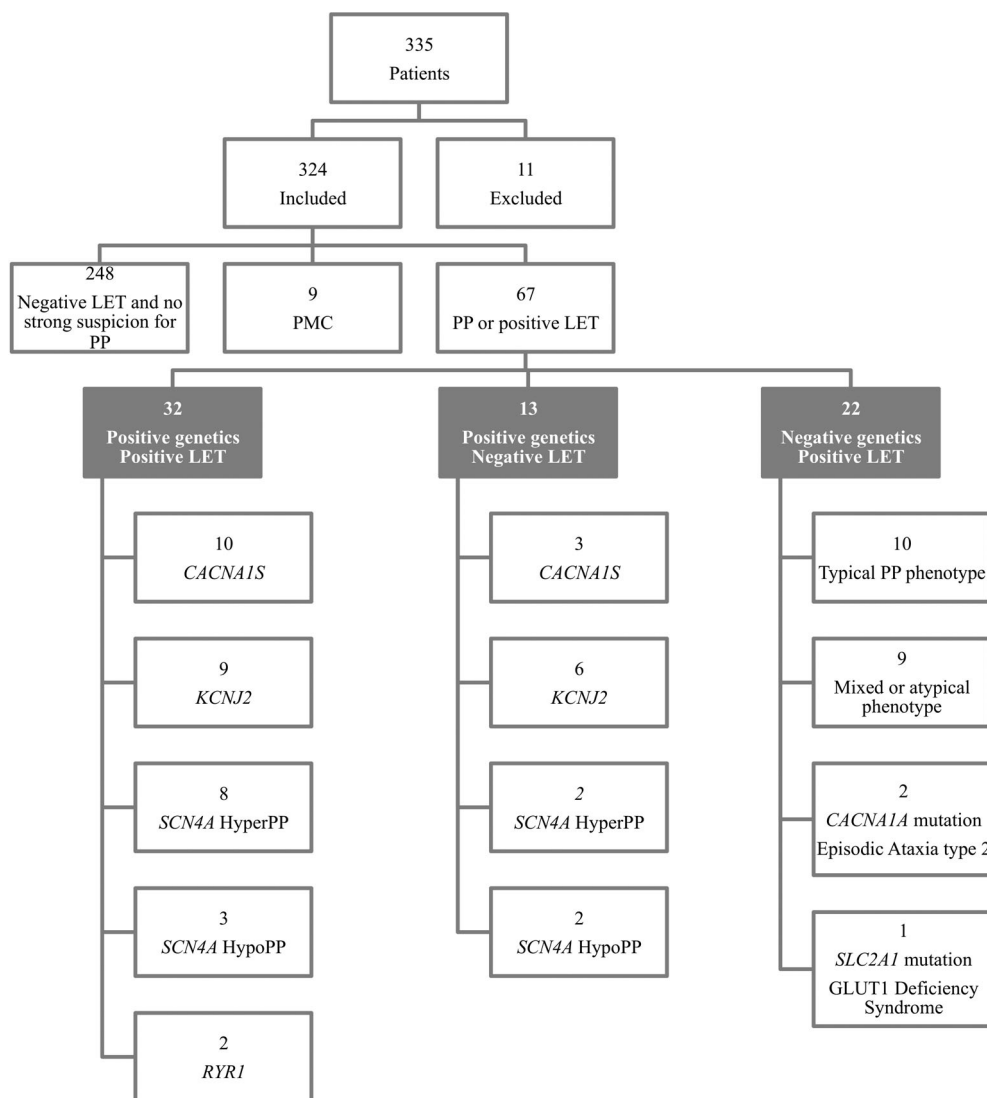
^aGroups with statistically significant differences.

^bStatistical analysis was not performed as group allocation was according to peak decrement.

^cA total of 4/32 patients incorporated after SET calculations could not be included as a 40% decrement was not achieved during LET.

FIGURE 1 Study sample.

There was no statistically significant correlation between the LET results and genotype (X^2 $p = .625$). Patients with paramyotonia congenita (PMC) were not included in the main sample as the LET pattern is often different from periodic paralysis and a positive LET is not a diagnostic criterion for this condition, which has a typical response pattern on SET particularly after cooling



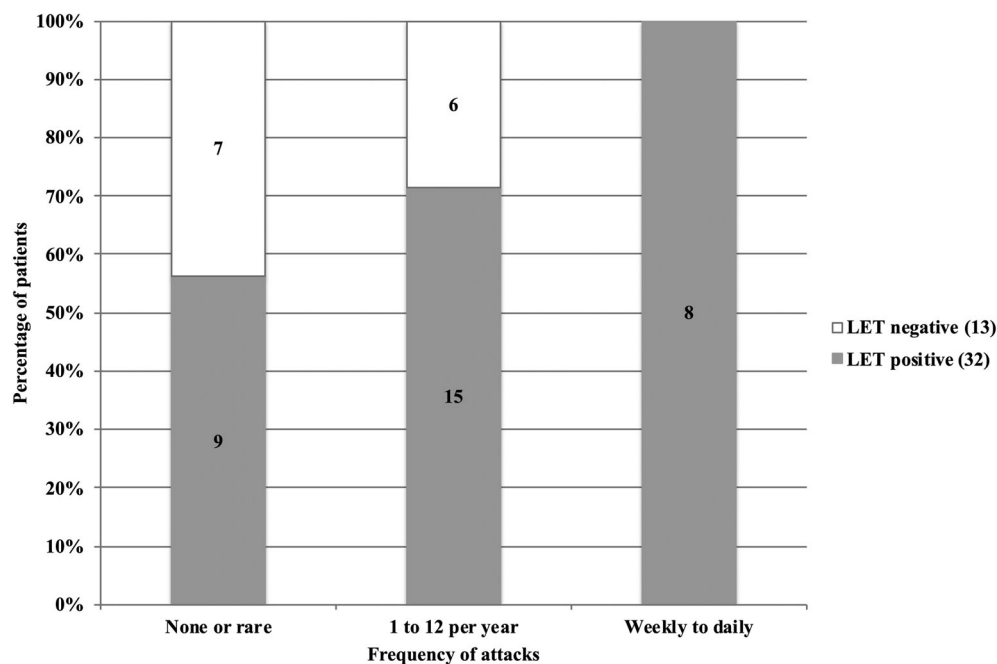


FIGURE 2 Frequency of attacks in patients with genetically confirmed PP and correlation with long exercise test (LET) results, $p = .035$ (Mann-Whitney *U*-test)

4 | DISCUSSION

Our study demonstrates that the sensitivity of the LET is strongly correlated with disease activity. All patients with frequent attacks had a positive LET compared to just over half of those with rare attacks or progressive weakness. This confirms that patients who have more frequent spontaneous attacks of weakness are more likely to have an attack following a standardized provocation maneuver. It is also useful in clinical practice as it indicates patients with frequent attacks but negative LET are unlikely to have PP, whereas those with rare attacks and negative LET should be considered for genetic testing if clinical suspicion is strong. Our findings correlate with the observation by Tengan et al¹¹ who investigated 14 individuals from two families with hypoPP and four individuals with thyrotoxic periodic paralysis and found a positive LET only in patients with recent PP attacks while individuals with no recent attacks had a negative LET. We show that this can be applied to an unselected PP cohort of hypoPP, hyperPP and ATS. It is known that women with PP are often less severely affected and more likely to present with progressive weakness,⁸⁻¹¹ which correlates with the larger number of women in the negative LET group in our study.

Even patients with rare discrete attacks of paralysis may report frequent fluctuations of strength and this could explain why a number of patients in this group still have a positive LET. Indeed a positive LET may indicate a treatable element of their condition, which can be difficult to distinguish clinically from the progressive myopathy that develops later in the disease. This hypothesis could be investigated by correlating LET with muscle MRI as a means of differentiating between reversible oedema versus irreversible fatty infiltration.

In several patients the SET confounded LET results by inducing a significant decrement on its own. Our practice is to perform the SET

at room temperature and after cooling in one hand and the LET in the other hand if both are required.

The sensitivity of 71% seen in this study is within the lower range of published data (71% to 95%⁵⁻⁷). This may reflect identification of patients with milder disease in more recent years due to better recognition of the clinical phenotype and wider availability of comprehensive genetic testing.

Previous studies have focused on improving the sensitivity of the LET including lowering the upper limits of normal.⁹ Simmons et al¹² applied Bayesian principles and elegantly showed that a higher sensitivity/specificity may be achieved using different cutoff values by incorporating pre-test probabilities. In practice this approach may be difficult if patients are seen by clinicians unfamiliar with these rare disorders.

In patients with typical PP phenotype but negative genetics secondary causes of PP should be considered but none were identified in our cohort. Patients with a positive LET, negative PP genetics, and atypical phenotype are an interesting group with likely heterogeneous underlying pathology. Two of the patients had mutations in the *CACNA1A* gene, encoding a calcium channel expressed in the central and peripheral nervous system and linked to episodic ataxia.¹³ A patient presenting with paralytic attacks and a novel *CACNA1A* mutation but with a negative long exercise test has been reported recently.¹⁴ We now routinely screen patients with strong clinical evidence of periodic paralysis and negative PP genetics for *CACNA1A* mutations.

Limitations of this study included incomplete clinical data due to the retrospective nature, small subgroups, different operators and equipment over time potentially introducing variability.

We propose a re-appraisal of the role of the LET in the diagnosis of primary PP in the context of improved access to genetic evaluation.

In the past, it was used as a standard diagnostic test to rule-in or rule-out the diagnosis. In patients with frequent attacks this remains a useful strategy but in those with less severe or less frequent episodes of weakness and/or atypical clinical features caution is needed in interpreting a negative LET. Our data suggest that the LET can be regarded as a functional marker of PP, and, in patients who describe fixed but fluctuating weakness; it may indicate benefit can still be derived from pharmacological therapy.

ACKNOWLEDGMENT

This work has been supported by the MRC Centre for Neuromuscular Diseases grant MR/K000608/1 and the UCLH BRC Neuromuscular Disease Theme grant BRC401/NS/MH/101410. KJS was supported by an MRC Clinical Research Training Fellowship (MR/M01827X/1) and EM by a Wellcome Trust Clinical Research Career Development Fellowship (209583).

CONFLICT OF INTERESTS

None of the authors has any conflict 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.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ribeiro A, Suetterlin KJ, Skorupinska I, et al. The long exercise test as a functional marker of periodic paralysis. *Muscle & Nerve*. 2021;1-5. doi:10.1002/mus.27465