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Safety, efficacy and steroid-sparing effect of amifampridine in Lambert-Eaton myasthenic syndrome patients — real world data

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ABSTRACT

Introduction. Lambert-Eaton myasthenic syndrome (LEMS) is an ultrarare neuromuscular disease with a triad of symptoms: muscle paresis, dysautonomy, and areflexia. Amifampridine is the symptomatic treatment of LEMS.

Aim of study. To assess the effectiveness and safety of treatment in the real world.

Material and methods. 14 patients with non-neoplastic LEMS treated with amifampridine were enrolled in the study (female 42.9%, mean age 48.8 ± 11.4 years). The patients were assessed using the Quantitative Myasthenia Gravis (QMG) scale, QMG limb domain (LD) score, spirometry, Hand Grip Strength (GRIP) test, and repetitive nerve stimulation study (RNS) at baseline and at the end of follow-up. Diagnostic delay since first symptoms was from seven months up to 22 years. Treatment delay ranged from one to 26 years. The patients were treated and reevaluated after 21.1 ± 12.0 weeks (range 13–48).

Results. All of the patients improved in QMG score. Mean improvement was 5.1 ± 2.0 (range 1–8) points ($p < 0.001$) and this showed no correlation with the duration of the disease before treatment ($p = 0.477$). 85.7% of patients (n = 12) improved ≥ 3 points (clinically meaningful) in QMG. 78.6% of the patients improved in QMG LD [mean 2.2 ± 1.6 points ($p < 0.001$)]. Also, forced vital capacity (FVC) improved after treatment ($p = 0.031$). Mean improvement in GRIP test was 7.0 ± 7.1 kg in the right hand and 5.2 ± 7.5 kg in the left hand ($p < 0.001$).

In RNS before treatment, facilitation (> 100%) was observed in 78.6% (n = 11) of patients, and was higher before treatment ($p < 0.001$). Compound muscle action potential (CMAP) amplitude was higher after treatment ($p < 0.001$). Mean increase of CMAP amplitude was 2.1 ± 1.6 times. In 64.3% (n = 9) of patients lowering of corticosteroid dose was achieved.

Conclusions. Amifampridine is an effective treatment in non-neoplastic LEMS patients, regardless of disease duration. The treatment is well-tolerated and allows to reduce dose of corticosteroids in the majority of patients.

Keywords: LEMS, treatment, amifampridine, safety, efficacy, Lambert-Eaton myasthenic syndrome

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is an ultrarare neurological disease with an estimated annual incidence of c.0.4 per million and prevalence of c.2.5 per million inhabitants [1]. Patients with LEMS can be divided into two distinct groups: the first group as paraneoplastic syndrome associated with a neoplasm, mostly small cell lung carcinoma, and the second group as an autoimmune syndrome not associated with cancer (non-neoplastic LEMS) [2]. The main clinical

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features of LEMS are proximal or proximo-distal muscle weakness and fatigability, absence of tendon reflexes, and autonomic disturbances [3, 4]. Diagnosis is based on characteristic clinical signs, electrophysiological tests (repetitive nerve stimulation, RNS), and the presence of antibodies against presynaptic voltage gated calcium channels (anti-VGCC) [5–7]. LEMS can be treated with symptomatic drugs and a wide variety of immunosuppressive agents. Several symptomatic drugs have been used to date, including guanidine, pyridazine, 4-aminopyridine, and 3,4-diaminopyridine (3,4-DAP, amifampridine). 3,4-DAP has been proven to be effective in clinical trials [8, 9], but its usefulness in treatment is limited by its biochemical instability. Therefore 3,4 diaminopyridine phosphatase (3,4--DAPP, amifampridine phosphatase) was introduced. This potassium channel blocker improves neurotransmission by prolonging presynaptic depolarisation, enhancing calcium transport into the nerve ending. The effectiveness of oral treatment with amifampridine phosphatase for LEMS was confirmed in randomised studies in 2016 and 2019 [10, 11]. 3,4-DAPP is recommended as a first-line treatment for patients with LEMS [12]. In Poland, patients were first granted access in 2022, with reimbursement via national insurance. We conducted this study to evaluate the efficacy and safety of this treatment in real-world patients, including those who experience long treatment delays.

Material and methods

14 patients with non-neoplastic Lambert-Eaton syndrome treated with amifampridine were enrolled in the study (females 42.9%) between July 2022 and January 2023. Mean age of patients at baseline was 48.8 ± 11.4 years (range 33–74). The diagnosis of LEMS was based on clinical features, facilitation in RNS, and/or positive anti-VGCC antibodies results. The patients were assessed using the QMG (Quantitative Myasthenia Gravis) scale, QMG limb domain (LD) score, spirometry, Hand Grip Strength (GRIP) test, and RNS (repetitive nerve stimulation) study before and during treatment. The mean follow-up assessment was performed 21.1 ± 12.0 weeks (range 13–48) after the baseline visit. Patients with QMG improvement while on treatment ≥ 3 points were defined as treatment responders. The study design is set out in the supplementary material (Suppl. Fig. 1).

Statistical analysis

All continuous data was expressed as means and standard deviations. To test distribution of continuous variables, a Shapiro-Wilk test was used. To test differences between variables, a t test for dependent variables was used. To test differences between proportion on dependent variables, a McNemar test was used. Pearson correlation was used to test for linear relationship between quantitative variables. Statistical analysis was performed using SPSS Statistics 29.0.

Results

Mean age at onset of LEMS symptoms was 37.1 ± 14.8 years. Mean age at diagnosis was 41.4 ± 13.5 years (range 21–72). Diagnostic delay ranged from seven months to 22 years (mean 4.0 ± 6.6 years). Mean time from symptom onset until treatment with amifampridine was 11.2 ± 8.6 years (range 1–26) and mean time from diagnosis to treatment was 7.6 ± 7.1 years (range 1–21). Five patients (35.7%) were treated with amifampridine before 2022 under a different funding scheme; three of them had a 10-months gap between treatment within a clinical trial and access to reimbursed medication. All of them reported deterioration of symptoms after withdrawal of the drug, although this was not evaluated with objective scales.

In 42.9% of patients, proximal lower limb weakness was the first symptom of the disease, while in another 42.9% of patients, the symptoms started as upper and lower limb paresis. Two patients (14.3%) reported the first symptoms to be ocular (diplopia, ptosis). In four (28.6%) patients, LEMS was the first (and final) diagnosis, but the majority of patients were previously diagnosed with other diseases including myopathy (35.7%), myasthenia gravis (21.4%), and paraneoplastic syndrome (14.3%). In two cases (14.3%), seropositive myasthenia gravis coexisted. Half of the patients had positive results for anti-VGCC antibodies. In 78.6% of patients (n = 11), autonomic symptoms were observed, most commonly dry mouth (Tab. 1). Knee reflexes before treatment were absent (57.1%, n = 8) or reduced (n = 4, 28.6%); only two patients had preserved knee tendon reflexes (14.3%). All patients were treated with prednisone before amifampridine was started, four (28.6%) were receiving azathioprine, one (7.1%) was treated with methotrexate, and nine (64.3%) were receiving

Table 1. Autonomic symptoms before and after treatment with amifampridine

	Before treatment n = 11 (78.6%)	After treatment n = 8 (57.1%)
Dry mouth	11 (78.6%)	8 (57.1%)
Dry conjunctiva	2 (14.3%)	1 (7.1%)
Orthostatic syncopes	3 (23.1%)	1 (7.1%)
Impotence (males)	4 (50.0%)	4 (50.0%)

Table 2. Side effects reported by patients on stable dose of amifampridine

Transient paresthesia around mouth	13 (92.9%)
Paresthesia in upper and/or lower limbs	5 (35.7%)
Hyperhydrosis	6 (42.9%)
Paresthesia in tongue	1 (7.1%)
Feeling cold	2 (14.3%)
Muscle tremor	1 (7.1%)

anticholinesterase inhibitors. The large majority of patients had comorbidities (78.6%, n = 11) (Suppl. Tab. 1). Side effects of the treatment with amifampridine were reported by only 40% of patients spontaneously, but when asked a direct question as to an exact symptom, 13 patients reported one or more AEs (92.9%), most commonly transient paresthesias around the mouth (92.9%, n = 13); hyperhydrosis (n = 6, 42.9%), and paresthesias in upper and/or lower limbs (n = 5, 35.7%); these symptoms were mild and did not lead to withdrawal of the drug (Tab. 2). The percentage of patients reporting dysautonomic symptoms was lower after (57.1%) than before treatment (78.6%, p = 0.157, ns).

All of the patients improved in their QMG score (Fig. 1). Mean improvement in QMG was 5.1 ± 2.0 (range 1–8) points and was significant compared to baseline values ($p < 0.001$). 85.7% of patients (n = 12) had at least a 3 points improvement, and they were defined as treatment responders. Decrease in QMG scale did not correlate with the duration of the disease before treatment (p = 0.477). Mean decrease in QMG LD score was 2.2 ± 1.6 points and was observed in 78.6% (N = 11) of patients (Fig. 2). Mean QMG LD score was statistically lower after treatment than before ($p < 0.001$). FVC (forced vital capacity) within normal range (> 80%) was observed in 53.8% of patients before treatment and in 76.9% after treatment (ns, p = 0.083). Mean FVC was statistically higher after treatment than before (p = 0.031). Mean improvement in GRIP test was 7.0 ± 7.1 kg in the right hand and 5.2 ± 7.5 kg in the left hand. GRIP test for both sides was significantly improved after treatment ($p < 0.001$).

In RNS before treatment, facilitation (> 100%) was observed in 78.6% (n = 11), and above 60% in 85.7% (n = 12) of patients; after treatment in only one patient was it > 100% (change from 383% to 220%). Facilitation was higher before treatment ($p < 0.001$, Fig. 3). CMAP (compound muscle action potential) amplitude was 3.2 (± 1.9 mV) for ulnar (n = 10), 1.1 ± 0.2 mV for radial (n = 2), and 4.8 ± 2.3 mV for median nerve (n = 2) at baseline and 5.4 ± 2.4 mV, 2.0 ± 1.6 mV, and 6.5 ± 4.7 mV after treatment respectively. CMAP amplitude was statistically higher after treatment ($p < 0.001$, Fig. 4). Mean increase of CMAP amplitude was 2.1 ± 1.6 times; in only one case the amplitude did not change after treatment. In 64.3% (n = 9) of the patients, treatment led to lowering of the corticosteroid (CS) dose. We also compared the patients treated with 3,4-DAPP before enrollment to our study to the 3,4-DAPP naive group: we found no statistically significant differences in improvement between these two subgroups, though due to the small size of the subgroups these results should be interpreted with caution.

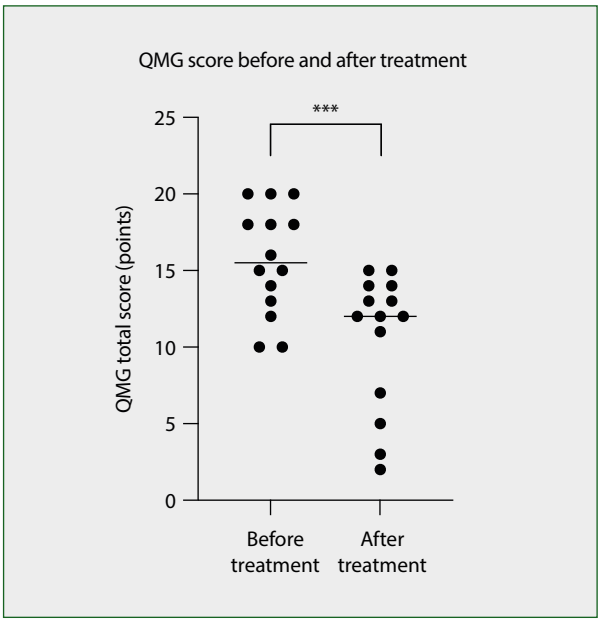

Figure 1. QMG score before and after treatment; *** statistically significant $p < 0.001$

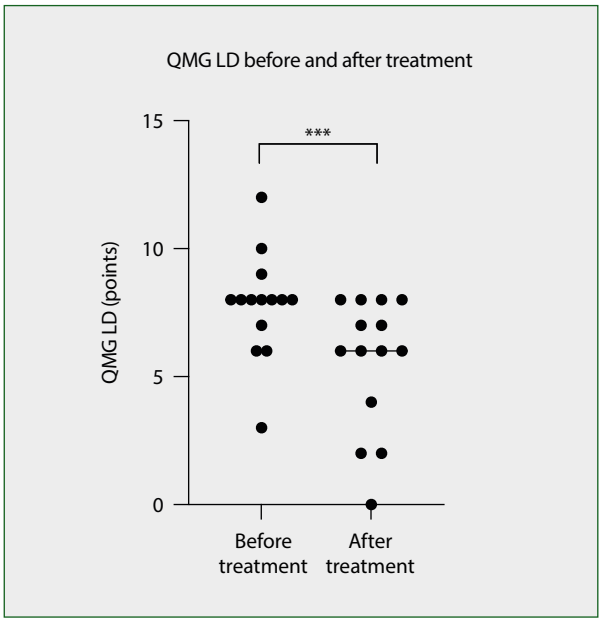

Figure 2. QMG LD (limb domain) score before and after treatment; *** statistically significant $p < 0.001$

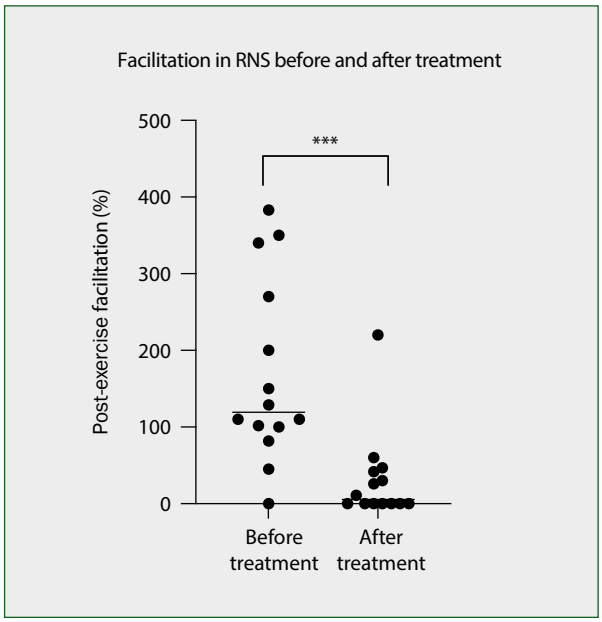

Figure 3. Post-exercise facilitation in repetitive nerve stimulation before and after treatment; *** statistically significant p < 0.001

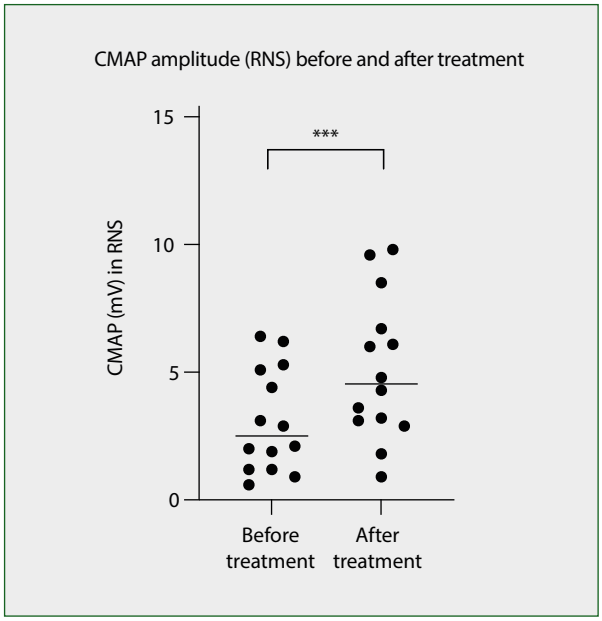

Figure 4. CMAP amplitude in repetitive nerve stimulation before and after treatment; *** statistically significant p < 0.001

Discussion

Our results confirm a satisfactory response to treatment with 3,4-DAPP. We have shown improvements both clinically and electrophysiologically. In our study, improvement was seen regardless of the delay to 3,4-DAPP treatment.

All of our patients were treated with immunosuppressants before initiating 3,4-DAPP. Corticosteroids are the first-line immunosuppressive treatment in LEMS [12], although long term usage leads to many side effects [13]. Reducing the CS dose while improving the function of the patients is one of the most important aims of the treatment and was achieved in over 60% of our patients treated with 3,4-DAPP. To the best of our knowledge, a steroid-sparing effect of 3,4-DAPP, including the patients with long treatment delay, has not been reported previously.

Our data confirmed the safety of 3,4-DAPP. In the current study, 40% of patients reported adverse effects (AEs) spontaneously, but when asked a direct question as to an exact AE, more than 90% did. The most frequently reported AE was transient perioral paresthesias; AEs were mild and well tolerated, and none of our patients discontinued the drug. During the observation period, there were no serious adverse events (SAEs). Our results are consistent with those reported to date. In a 2016 clinical trial, 14/54 patients enrolled to part 1 of the trial did not complete the study, but only five due to an adverse event (AE) [10]. Another study showed 23% AEs in 13 patients in the amifampridine phosphatase group, with most of them reporting mild to moderate intensity [11]. One of the largest groups studied recently was the European LEMS Registry, with 96 participitants, including 50 treated with 3,4-DAPP. 50% of them reported an AE, and 8.3% a SAE, although the SAE, due to the registry design, in the opinion of the authors could have been attributable to comorbidities. Different rates of reported AEs could be related to variable time of observation, ranging from 13–48 weeks in our study, up to 105 months in the European LEMS Registry [14]. Another important indicator reflecting treatment tolerability is the discontinuation rate. None of our patients discontinued treatment. In the 2016 trial, 10/54 patients withdrew from the drug, but only five due to an AE (most of the AEs were perioral and digital parasthesias) [10]. In the European LEMS Registry, 18 /50 using 3,4-DAPP discontinued the treatment: 10 died, five were lost to follow-up, two to other reasons, and one due to an unknown reason [14].

Mean duration from disease onset to diagnosis in our cohort was 4.0 ± 6.6 years (range 7 months to 22 years), and this was similar to that found in other studies: 4.4 ± 6.2 years (range 0.0–20.0) in the Harms et al. study [15] and 4.2 years (range 0.16–25) in the Pellkofer et al. study [16]. LEMS is an ultrarare disease that still poses a diagnostic challenge, especially in patients with slow progression of symptoms, as seen in the non-cancer group.

Our study confirms the efficacy, safety and good tolerability of 3,4-DAPP in real world settings. We conclude that treatment is effective in patients regardless of disease duration or treatment delay, and contributes to a reduction of CS dose in most patients within the first year after introducing therapy.

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