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【 CASE REPORT 】

Two Lambert-Eaton Myasthenic Syndrome Patients with Ameliorated Activities of Daily Living Due to Cholinesterase Inhibitors

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Abstract:
We herein report two P/Q-type voltage-gated calcium channel (VGCC) antibody-positive Lambert-Eaton myasthenic syndrome (LEMS) patients who responded dramatically to cholinesterase inhibitors. Patient 1, a 76-year-old man, had small-cell lung cancer and developed LEMS during chemotherapy. When symptomatic treatment was started with pyridostigmine, gait disturbance was ameliorated, and his modified Rankin scale decreased from 4 points to 3 points. Patient 2, a 68-year-old man, had cancer-free LEMS. Distigmine bromide was very effective and ameliorated not only his gait disturbance but also autonomic symptoms, and his modified Rankin scale decreased from 2 points to 1 point. Cholinesterase inhibitors alone may be effective in a small portion of LEMS patients.

Key words: Lambert-Eaton myasthenic syndrome (LEMS), treatment algorithm, electrophysiological examination, 3,4-diaminopyridine, cholinesterase inhibitors

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Introduction

A research group of the Japanese Ministry of Health, Labor and Welfare recently established diagnostic criteria for Lambert-Eaton myasthenic syndrome (LEMS) and conducted a national survey. As a result, it was estimated that there were 348 LEMS patients in Japan in 2017 (1). Thanks to this study, the current clinical picture and treatment algorithm status have become clear.

The myasthenia gravis (MG) clinical practice guideline 2014 is currently under revision, and this revision also covers the guideline for LEMS. The biggest problem with the LEMS treatment algorithm is that the oral treatment of 3,4-diaminopyridine (3,4-DAP), which is the first choice in Europe and the United States (2), cannot be used in Japan. At present, there are only a few facilities in Japan where 3,4-DAP has been clinically approved by the Ethics Committee, and in most of these facilities, such approval was obtained over 10 years ago. In recent years, Ethics Committees have become very strict, so further approval of 3,4-DAP, which is treated as a strong poison, and new clinical applications may be not possible.

Given the above, we felt that a case report of two LEMS patients in which cholinesterase inhibitors were effective and ameliorated the activities of daily living (ADLs) would facilitate the treatment of LEMS in countries without the clinical application of 3,4-DAP.

Case Reports

Case 1

In February X, a 76-year-old man was diagnosed with small-cell lung cancer (SCLC; T4N3M1b) and had a good course with chemotherapy. However, from June X, double

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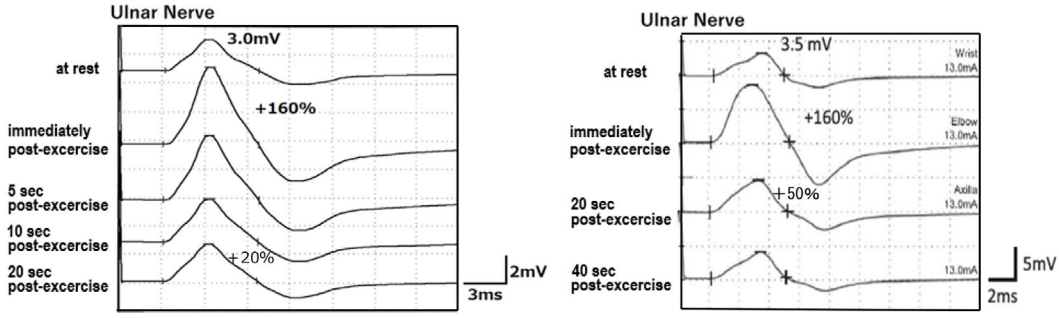

Figure. **Electrophysiological test results of patient 1 (left) and patient 2 (right). The resting CMAP of abductor digiti minimi by ulnar nerve stimulation was 3.0 mV in patient 1 and 3.5 mV in patient 2. In both patients, the CMAP amplitude immediately after 10 seconds of maximal voluntary exercise increased 2.6-fold which shows+160% in this figure. Twenty seconds after exercise, patient 1 had a CMAP amplitude of 3.7 mV (+20%) and patient 2 had a CMAP amplitude of 5.3 mV (+50%), with the post-exercise enhancement remaining.**

vision, light-headedness, and lower limb muscle weakness appeared, and he visited our department in August X.

Proximal lower limb muscle weakness and a decreased tendon reflex were observed. The edrophonium test was markedly effective and positive. Indeed, 10-20 seconds after the injection, standing was easily achieved, and the diplopia disappeared; these results lasted for 30 minutes. Based on these findings, MG was suspected, and acetylcholine receptor (AChR) antibodies, muscle-specific receptor tyrosine kinase (MuSK) antibodies, and LDL-receptor related protein 4 (Lrp4) antibodies were measured, but all were negative.

An electrophysiological examination of the ulnar nerve showed a decrease in the compound muscle action potential (CMAP) and a 160% increment immediately after 10 seconds of maximal voluntary exercise (Figure, left). P/Q-type voltage-gated calcium channel (VGCC) antibodies (107.0 pmol/L, upper limit of normal value: 20.0) (3), Hu antibodies, and SOX1 antibodies were positive. He was therefore diagnosed with LEMS that developed during the treatment of SCLC.

As symptomatic treatment, pyridostigmine 180 mg/day was started, and the quantitative MG score was improved from 12 to 7 points, the MG-ADL score improved from 11 to 6 points, and the modified Rankin scale (mRS) improved from 4 to 3 points. Unfortunately, he died due to SCLC 10 months after starting treatment.

Case 2

A 68-year-old man had been aware of constant thirst for a few years. From April X, he became aware of general fatigue and dullness when climbing stairs. He also felt that both of his eyelids were drooping. From May X, he began staggering while walking and felt tired after walking, so he visited our department in June X.

Neurological findings showed mild bilateral blepharoptosis and no diplopia. In the extremities, proximal lower limb muscle weakness and decreased tendon reflex were observed. An electrophysiological examination of the ulnar nerve showed a decreased CMAP and a 160% increment immediately after 10 seconds of exercise (Figure, right). The edrophonium test was negative, and the degree of ptosis was unchanged. The AChR antibodies were negative and the P/Q-type VGCC antibodies (193.2 pmol/L, upper limit of normal: 20.0) were positive (3). The search for malignant tumors, such as via chest computed tomography and positron emission tomography, was negative, and the diagnosis was LEMS without cancer.

Initially, pyridostigmine 180 mg/day was prescribed as a symptomatic treatment, but it had side effects of nausea and abdominal pain, and the duration of the effect was short. Therefore, we instead prescribed distigmine bromide 5 mg/day once daily, which was very effective and ameliorated the lower limb malaise, blepharoptosis, and dry mouth without the above side effects. LEMS symptoms were stable after four years, and no malignant tumor was found. The mRS was 2 points at the first visit, 1 immediately after the start of 5 mg of distigmine bromide, and 0 after 4 years.

Discussion

The first-line treatment for LEMS guidelines is 3,4-DAP. Cholinesterase inhibitors are thought to be positioned as a combination with 3,4-DAP (4). Indeed, a randomized control trial denied the effect of pyridostigmine (4). However, in the opinion of experts, such as Oh et al., the effect of pyridostigmine is overall positive, and in some cases, it is effective alone (5). Based on Oh's paper and our two case reports, we suspect that although the frequency is not high, there are some LEMS patients whose ADL is ameliorated by effective treatment with pyridostigmine alone. Unfortunately, this clinical evidence is not reflected in the LEMS treatment algorithm (6). Therefore, in response to the question; "In which patients are cholinesterase inhibitors effective?", we speculate as follows: "If LEMS is severe, the amount of acetylcholine released from the motor nerve endings is too low for cholinesterase inhibitors to be effective,

and these agents do not contribute to the improvement of clinical symptoms. However, if LEMS is mild, acetylcholine is released to some extent from the motor nerve endings, and cholinesterase inhibitors suppress the degradation of acetylcholine, thereby resulting in increased amounts of acetylcholine and ameliorated clinical symptoms."

In the literature, the CMAP amplitude and P/Q-type VGCC antibody titer have not been reported to be factors that predict the long-term prognosis of LEMS patients without SCLC; however, the muscle strength measurement (mild LEMS) at the first visit has been reported to be such a factor (7). In addition, in a case report of asymptomatic LEMS, the CMAP amplitude in the ulnar nerve/hypothenar muscle was in the 3-mV range, and the CMAP amplitude was more than tripled at 15 seconds after exercise, showing an enhancing effect (8) (Figure). In our two cases, the CMAP amplitudes in the same ulnar innervation muscle as in the above report (8) were in the 3-mV range, and the amplitudes also had an enhancing effect 20 seconds after exercise.

In our clinical experience, severe LEMS patients have lower resting CMAP amplitudes and less of a lasting enhancement effect after exercise than mild LEMS patients. Therefore, our patients were suspected to be mild LEMS patients.

In the future, more accurate electrophysiological indicators of patients with mild and severe LEMS should be identified. However, 3,4-DAP treatment is not currently available in Japan, so cholinesterase inhibitors should be used as the first symptomatic treatment.

Conclusion

Cholinesterase inhibitors alone may be effective in a small portion of LEMS patients.

The authors state that they have no Conflict of Interest (COI).

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