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J Child Neurol published online 10 October 2013
DOI: 10.1177/0883073813499970

Journal of Child Neurology
00(0) 1-4

DOI: 10.1177/0883073813499970
jcn.sagepub.com
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Long-Term Follow-Up in Infantile-Onset Lambert-Eaton Myasthenic Syndrome

S. Portaro, MD[1,2,3], D. Parisi, MD[1], A. Polizzi, MD[4], M. Ruggieri, MD[5], F. Andreetta, PhD[6], P. Bernasconi, PhD[6], A. Toscano, MD[1], and C. Rodolico, MD[1]

Abstract

Lambert-Eaton myasthenic syndrome is a neuromuscular junction disorder characterized by proximal limb muscle weakness, fatigability, decreased deep-tendon reflexes, and autonomic symptoms. There are 2 forms of Lambert-Eaton myasthenic syndrome: one most frequently associated with small-cell lung cancer (P–Lambert-Eaton myasthenic syndrome) and the other that is a pure autoimmune form (NP–Lambert-Eaton myasthenic syndrome). Lambert-Eaton myasthenic syndrome is a very rare disorder in children younger than age 12 years. Herein, we report a 25-year-old man with NP–Lambert-Eaton myasthenic syndrome, which onset was at the age of 10 years. To date, this is the most long-term follow-up of NP–Lambert-Eaton myasthenic syndrome in childhood. In our patient, the only symptomatic treatment with 3,4-diaminopyridine phosphate has been sufficient to guarantee him a good quality of life. Our data remind physicians to keep in mind the diagnosis of Lambert-Eaton myasthenic syndrome in children with a proximal myopathic pattern and they confirm the specificity of compound muscle action potential incremental pattern after brief maximal effort in Lambert-Eaton myasthenic syndrome.

Keywords

proximal muscle weakness, anti-voltage-gated calcium channel antibodies, 3,4-diaminopyridine phosphate, Lambert-Eaton syndrome

Received May 30, 2013. Received revised June 29, 2013. Accepted for publication July 05, 2013.

Lambert-Eaton myasthenic syndrome is a neuromuscular junction disorder characterized by proximal limb muscle weakness, fatigability, decreased deep-tendon reflexes and various autonomic symptoms, most frequently associated with small-cell lung cancer.[1] The etiology of Lambert-Eaton myasthenic syndrome is the reduced exocytosis of acetylcholine from nerve endings by antibodies against voltage-gated calcium channels, which can be detected in more than 90% of patients.[1] The diagnosis of Lambert-Eaton myasthenic syndrome can be confirmed by detecting antibodies against voltage-gated calcium channels in serum and by neurophysiological studies confirming a presynaptic neuromuscular junction impairment with reduced amplitude of compound muscle action potential that increases by more than 100% after maximum voluntary activation or after 50 Hz nerve stimulation.[1]

There are 2 main groups of Lambert-Eaton myasthenic syndrome patients: those with underlying neoplasms, in whom the autoimmune dysregulation is part of a paraneoplastic syndrome (P–Lambert-Eaton myasthenic syndrome), and those without an underlying neoplasm, in whom the trigger for the autoimmune dysregulation is still not known (NP–Lambert-Eaton myasthenic syndrome).[2]

NP–Lambert-Eaton myasthenic syndrome usually occurs in 30% to 50% of Lambert-Eaton myasthenic syndrome patients.[3,4] The mean age at onset of NP–Lambert-Eaton myasthenic syndrome patients is lower than P–Lambert-Eaton myasthenic syndrome and it can range from childhood to old age.[4-8] To date, only 5% of Lambert-Eaton myasthenic syndrome reported cases are children.[4] When diagnosis of Lambert-Eaton myasthenic syndrome is made, a careful screening searching for an underlying neoplasm must be done and, if the result of the primary screening is negative, it should be repeated after 3 to 6 months and thereafter every 6 months

[1] Department of Neurosciences, University of Messina, Italy
[2] Department of Clinical and Experimental Medicine, University of Messina, Italy
[3] IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy
[4] Institute of Neurological Sciences, National Research Council, Catania, Italy
[5] Department of Educational Sciences, University of Catania, Italy
[6] Department of Neurosciences, "C. Besta" Institute, Milan, Italy

Corresponding Author:
Carmelo Rodolico, MD, Department of Neurosciences, University of Messina, Via C. Valeria, Messina 98125, Italy.
Email: crodolico@unime.it

for up to 2 years.[4,6] In general, once a patient with Lambert-Eaton myasthenic syndrome has been symptomatic for more than 5 years, without discovery of an underlying malignancy, Lambert-Eaton myasthenic syndrome is unlikely to be paraneoplastic and it is probably caused by a primary autoimmune process.[9] In NP–Lambert-Eaton myasthenic syndrome, a mean interval between the onset of symptoms and the diagnosis is longer than in P–Lambert-Eaton myasthenic syndrome cases.[4-7] Most patients benefit from 3,4-diaminopyridine. Tumor removal is the primary treatment for P–Lambert-Eaton myasthenic syndrome. In those cases with severe weakness, intravenous gamma globulin or plasmapheresis confer short-term benefits. Prednisolone, when administered alone or in combination with immunosuppressive drugs, can achieve long-term control of the disorder.[10]

Lambert-Eaton myasthenic syndrome is a very rare disorder in children before 12 years of age and, to date, few cases have been reported describing this entity in this stage of life. Only 3 of the 16 previously published pediatric patients with Lambert-Eaton myasthenic syndrome had the antibodies against voltage-gated calcium channels tested, 2 of them with increased antibodies titres.[11] P–Lambert-Eaton myasthenic syndrome in childhood has been, in some cases, associated with hematologic malignancies,[12] whereas NP–Lambert-Eaton myasthenic syndrome has been linked to other autoimmune diseases.[11]

Herein, we report a 25-year-old man affected by Lambert-Eaton myasthenic syndrome since the age of 10 years; difficulty in diagnosis, laboratory, neurophysiological findings, and the response to therapy in a very long-term follow-up period are discussed.

Case Summary

We describe a 25-year-old man, who started to complain, since the age of 10 years, of fatigability, lower limb muscle weakness with tendency to fall, dysphonia, and dysphagia. Because of these symptoms, he was admitted to a neuropediatric department: serum creatine kinase level was normal, antibodies against acetylcholine receptors were within the normal limits, a single-fiber electromyography suggested a neuromuscular junction impairment, and a provisional diagnosis of myasthenia gravis was made. He was treated with pyridostigmine (up to 240 mg/d) for about 2 years, without benefits. A thorax computed tomographic (CT) scan revealed a slight increase in thymic gland volume, so he underwent a thymectomy; gland biopsy revealed a condition of follicular hyperplasia.

Finally, at the age of 12 years, he came to our attention. Cardiac, respiratory, and abdominal examinations were unremarkable. There was no effusion, increased temperature, or erythema of any joint or adjacent skin in all extremities. The range of motion of the neck, shoulders, and all major joints of the upper and lower extremities was normal bilaterally. Muscular atrophy was absent. Coordination, pinprick, light touch, position, and vibratory sensation in the upper and lower extremities were normal. He had a slight bilateral ptosis. Dysphonia was evident. He had a slight waddling gait with difficulty in climbing stairs and rising from the floor. A mild weakness of quadriceps and iliopsoas muscles was present. Deep tendon reflexes were absent at 4 limbs. He also referred, since 4 months, dry mouth. The diagnosis of Lambert-Eaton myasthenic syndrome was then suspected and an electroneurography was performed, detecting the right median nerve compound muscle action potential at rest and after a short maximal effort, recording from abductor brevis pollicis. It revealed a small compound muscle action potential amplitude at baseline (2.4 mV), which increased to 10.7 mV after few seconds of maximal effort, with a percentage of increment of compound muscle action potential more than 300% (Figure 1). Serum anti–voltage-gated calcium channel antibodies were dosed and they were found to be slightly increased (87.84 pmol/L, with normal values below 80 pmol/L). These findings were consistent with a diagnosis of Lambert-Eaton myasthenic syndrome. 3,4-Diaminopyridine (as galenic formulation) was administered (5 mg 4 times a day), with a significant improvement of fatigability, dysphonia, dry mouth and proximal lower limbs muscle weakness.

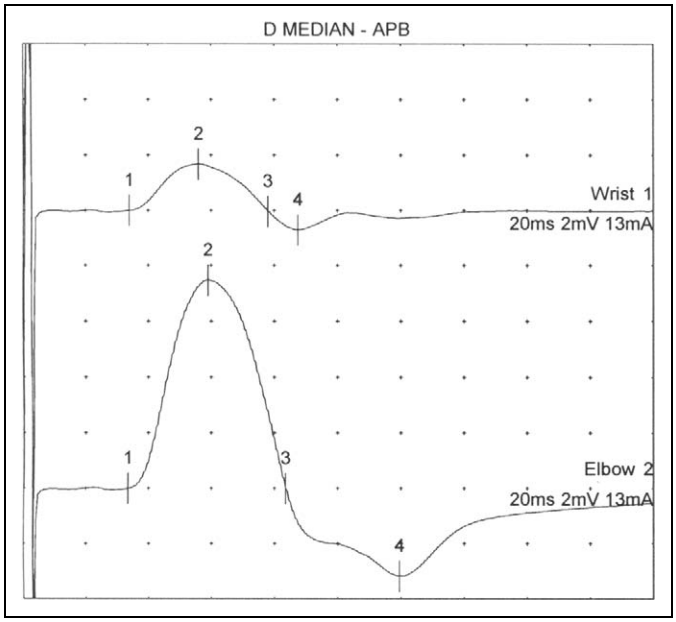

Figure 1. Compound muscle action potential (cMAP) of the tight median nerve recording from abductor brevis pollicis, at rest (upper trace) and after a short maximal effort (lower trace): small compound muscle action potential amplitude at baseline, which increases more than 300% after few seconds of maximal effort.

Despite vigorous examination, including a complete blood count, serum chemistries, serum electrophoresis, rheumatoid factor, antinuclear antibodies, extractable nuclear antigens, anti-Sm antibodies, antineutrophil cytoplasmic antibody, anti-dsDNA antibodies, CT of chest and abdomen, ultrasound of pelvis and testis, no malignancies or autoimmune disorders have been found. The malignancy and autoimmune workup was regularly repeated every 6 months up to 5 years, except for CT scan of chest and abdomen, which was repeated after 2 and 5 years from disease onset. The anti–voltage-gated calcium channel antibody titer has been tested every 2 years since the diagnosis, and found to be always at an increased level, but

no higher than 120 pmol/L, for about 7 years. Since then, the anti–voltage-gated calcium channel antibodies titer, repeated every 2 years, disclosed an incremental pattern, with the highest values of 150.17 pmol/L.

The efficacy of 3,4-diaminopyridine is still evident and over the years, the dosage has been increased up to 30 mg/d; since 2 years, when commercially available in Italy, the patient is assuming 3,4-diaminopyridine phosphate, maintaining a good quality of life. To date, he complains of slight easy fatigability and generalized and episodic muscle weakness; dysphonia and difficulty in climbing stairs appear only if he does not take the medication.

Discussion

Lambert-Eaton myasthenic syndrome is the second most common neuromuscular junction disorder after myasthenia gravis,[13] but in children it is very rare, accounting for approximately 5% of the reported cases.[4,14,15] Our case illustrates the opportunity to keep in mind the diagnosis of Lambert-Eaton myasthenic syndrome in children with a proximal myopathic pattern, especially if it is associated with bulbar symptoms. Increased jitter on single-fiber electromyography can reveal an impaired neuromuscular transmission, but the more specific detection of small compound muscle action potentials with an incremental pattern after brief maximal effort or after repetitive nerve stimulation is crucial for a diagnosis.

Because of easy fatigability and dysphagia, a differential diagnosis with myasthenia gravis is mandatory: Lambert-Eaton myasthenic syndrome never begins with ocular weakness and, usually, weakness is more pronounced in legs than arms. Respiratory involvement is very rare, whereas bulbar involvement might include dysphagia (22% to 56%) and dysarthria (up to 80%). Extraocular muscle involvement is very rare in Lambert-Eaton myasthenic syndrome: ptosis is occasional, as well as diplopia or eye movement limitation. Moreover, deep tendon reflexes are absent in Lambert-Eaton myasthenic syndrome and they can transiently reappear after a brief maximal voluntary contraction or after a repeated tendon percussion.[15] The presence of impotence in males, the dryness of mouth and eyes, as signs of an autonomic involvement, and the more pronounced proximal leg weakness, could be an helpful clinical tool for Lambert-Eaton myasthenic syndrome suspicion. Differential diagnosis must be performed also with other myopathies: family history, creatine kinase levels, electromyography and muscle biopsy, when necessary, could help to reach a proper diagnosis in these cases.

In the rare cases of NP–Lambert-Eaton myasthenic syndrome with childhood onset to date reported, the treatment was more aggressive than in our case: cyclosporine, prednisolone, and azathioprine have been successfully used, without symptomatic associated treatment.[11,16] The rationale for immunosuppressant administration is because Lambert-Eaton myasthenic syndrome is an antibody-mediated disease and immunotherapy is recommended for more severe cases. Recommendations for conventional immunosuppression are similar to those for MG. Prednisolone plus a steroid-sparing agent, such as azathioprine, mycophenolate mofetil, cyclosporin, or methotrexate, are used. Plasmapheresis can stabilize the patient in a Lambert-Eaton myasthenic syndrome crisis. Alternatively, intravenous immunoglobulins have been shown in a small randomized, placebo-controlled, crossover trial to improve limb strength in Lambert-Eaton myasthenic syndrome patients.[17] However, immunosuppression is only recommended for patients in whom symptomatic treatment is not satisfying.[17] In our case, the use of immunosuppressive agents was not required, considering all their possible side effects. The patient has been treated, since Lambert-Eaton myasthenic syndrome diagnosis, only with 3,4-diaminopyridine phosphate, which is the first-line treatment for Lambert-Eaton myasthenic syndrome, as recently suggested by the Task Force of the European Federation of Neurological Diseases.[18]

To date, the beneficial effect of 3,4-diaminopyridine phosphate persists and the patient has a good quality of life: he is able to sustain physical efforts and to play sports, as well as his peers. On the other hand, antibodies against voltage-gated calcium channels showed an increasing pattern over the years, with no correlation with symptoms, treatment response, development of another associated autoimmune or neoplastic disorder. Another autoimmune disorder can usually occur after 6 months in 28% to 33% of NP–Lambert-Eaton myasthenic syndrome patients.[4,7] We can suppose that the case reported represents an isolated autoimmune disease of the neuromuscular junction at the presynaptic level. Nevertheless, we consider it mandatory to perform an autoimmune screening every year.

To date, there have been no long-term follow-up studies of patients with NP–Lambert-Eaton myasthenic syndrome, although mortality statistics are available on patients with P–Lambert-Eaton myasthenic syndrome.[6,19,20] Herein, we have reported a very long-term follow-up of an infantile-onset NP–Lambert-Eaton myasthenic syndrome. Even though in our case the only symptomatic treatment has been sufficient to ensure guarantee the patient a good quality of life, the incremental titer for anti–voltage-gated calcium channel antibodies and the intimate essence of the disease represent a stimulus to develop a specific immunotherapy, targeting the aberrant production of the pathogenic antibodies, which should become the possible therapeutic strategy for Lambert-Eaton myasthenic syndrome.

Author Contributions

SP wrote the first draft of the manuscript; DP compiled the bibliography and performed neurophysiological studies; AP and MR cared for the patient during childhood/adolescence; FA and PB have done biohumoral assays; AT analyzed the data; CR cared for the patient in adulthood, wrote the final version of the manuscript, and supervised the study.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

This Case Report did not require specific ethics approval.

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