Neurol Sci (2014) 35:515–520
DOI 10.1007/s10072-014-1637-4

REVIEW ARTICLE

Italian recommendations for Lambert–Eaton myasthenic syndrome (LEMS) management

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Received: 10 December 2013 / Accepted: 15 January 2014 / Published online: 31 January 2014

Abstract Lambert–Eaton myasthenic syndrome (LEMS) is a pre-synaptic disorder of the neuromuscular and autonomic transmission mediated by antibodies to voltage-gated calcium channels at the motor nerve terminal. LEMS is a quite rare and probably under-diagnosed disease: the onset may be slow and clinical signs are typically fluctuating, thus adding to the delay in diagnosis. LEMS weakness typically involves lower and upper limbs and the proximal muscles are predominantly affected. A significant proportion of patients also have dysfunction of the autonomic nervous system that may include dry mouth, constipation, blurred vision, impaired sweating, and orthostatic hypotension. LEMS recognition is based on clinical, electrophysiological and immunological criteria. Nearly 50–60 % of patients with LEMS have an underlying tumour that, in almost all cases, is a small-cell lung cancer; the onset of neurological symptoms generally precedes tumour detection. A careful screening for the early detection of the possible associated cancer is a crucial step for optimal disease management. The Italian Working Group on Myasthenic Syndromes developed diagnostic and therapeutic algorithms that could serve in routine clinical practice as tools for a patient-tailored approach.

Keywords Lambert–Eaton myasthenic syndrome · Voltage-gated calcium channel antibodies · Small-cell lung cancer · 3,4-Diaminopyridine

Introduction

Lambert–Eaton myasthenic syndrome (LEMS) is a pre-synaptic disorder of the neuromuscular transmission

For the GISMIA (Gruppo Italiano sulle Sindromi MIAsteniche) Working Group.

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mediated by antibodies to P/Q-type voltage-gated calcium channels (VGCC) at the motor nerve terminal [1]. Nearly 50–60 % of patients with LEMS have an underlying tumour (T-LEMS) that in 90 % of cases is a small-cell lung cancer (SCLC). Non-tumour LEMS (NT-LEMS) is often associated with HLA-B8, DR3 haplotype and to other autoimmune diseases, such as rheumatoid arthritis, pernicious anaemia, thyroid disorders and Sjogren's syndrome [2]. The antigenic stimulus for anti-VGCC antibody production in patients with SCLC-LEMS appears to be the tumour's functional VGCC [3]. The trigger for the production of anti-VGCC antibodies in LEMS with no detectable lung cancer (non-SCLC-LEMS) is unknown.

LEMS treatment is based on a symptomatic approach and on therapies lowering circulating auto-antibody levels or interfering with their function [immunosuppressant drugs, plasmapheresis, intravenous immunoglobulin (IVIG)]. T-LEMS is a typical paraneoplastic disease as treatment of the underlying cancer significantly improves neurological symptoms, whose onset generally occurs before tumour detection. LEMS diagnosis is crucial not only to provide a proper treatment of the neurological disease but also to detect early in the course of the disease the possible underlying tumour [4]. However, early diagnosis is hampered by LEMS being a rare disease and by the fluctuating course of symptoms. Even when patient's complaints have been properly related to a neuromuscular transmission disorder, LEMS is relatively often misdiagnosed as myasthenia gravis (MG) [5]. Moreover, LEMS symptoms in tumour patients may be ascribed to general conditions decline and to the consequences of the oncologic treatment, or may be masked by other paraneoplastic disorders associated with SCLC.

To address the issues related to LEMS management, the Italian Working Group on Myasthenic syndromes (GISMIA) developed the diagnostic and therapeutic recommendations presented in this paper. The aim of this review was to propose the GISMIA consensus on LEMS management, and to provide clinicians with a practical approach that could work within the specific framework of the Italian clinical practice setting.

Epidemiological overview on LEMS

LEMS is a rare disease, with scarce epidemiologic data mostly coming from national neuromuscular referral centres. The estimated annual incidence is nearly 10 times lower than that of MG and its frequency in SCLC patients is around 3 % [2]. In a 10-year study (1990–1999) run in a population of 1.7 million inhabitants in South Holland, the annual incidence rate of LEMS (0.48×10^{-6}) and its prevalence (2.32×10^{-6}) were 14 times and 46 times lower, respectively, than of MG in the same region [6]. Subsequent data on the same population showed that LEMS incidence in Netherlands rose to 0.75×10^{-6}, with a prevalence of 3.42 per million, probably due to an improved recognition of the disorder [5]. Such data confirm that LEMS is quite rare and probably under-diagnosed.

On the basis of the Netherlands studies, in Italy the expected incidence and prevalence should be around 25–40 cases per year and 140–200 cases, respectively. Although LEMS registry data could clarify this aspect, the frequency of the disease in Italy seems to be quite lower than expected, most likely because of under-diagnosis.

LEMS diagnosis

Clinical findings

Diagnosis of LEMS is based on clinical data, electrophysiological studies (showing a pre-synaptic defect of the neuromuscular transmission) and immunological testing (anti-VGCC antibody assay). LEMS should be suspected in (mostly) adult patients presenting with proximal muscle weakness, particularly of legs, together with reduced/absent tendon reflexes. The clinical suspicion is strengthened by concomitant signs of autonomic dysfunction, with dry mouth, erectile dysfunction and constipation as the most frequently reported symptoms [7].

The distribution of muscle weakness during disease progression has been investigated in several studies [7–10]. Proximal leg muscle weakness is always present and is the most frequent complaint at onset; weakness of the arms is a common and early sign as well, reflecting a typical clinical pattern: weakness generally spreads proximally to distally and caudally to cranially, involving feet and hands and finally reaching cranial muscles [5]. The evidence of post-exercise facilitation (transient normalisation of tendon reflexes and improvement of muscle strength after a brief maximal contraction) is a disease hallmark, although it is evident in only 40 % of cases [11]. Bulbar symptoms are generally less severe than in MG. Ptosis and diplopia are less frequent and usually of moderate degree, even though patients with exclusively ocular signs have been described [12]. The disease is usually more rapidly progressive in T-LEMS patients.

Electrophysiological studies

A clinical suspicion of LEMS should be confirmed by electromyography (EMG). Although in these patients, weakness is more evident in proximal districts, electrophysiological findings are more easily detected on distal muscles [13]. LEMS diagnosis is based on the presence of the typical triad: (1) low amplitude of the compound muscle action potential (CMAP) at rest (0.1–6 mV); (2) further decrease of CMAP amplitude during low-rate (2–5 Hz)

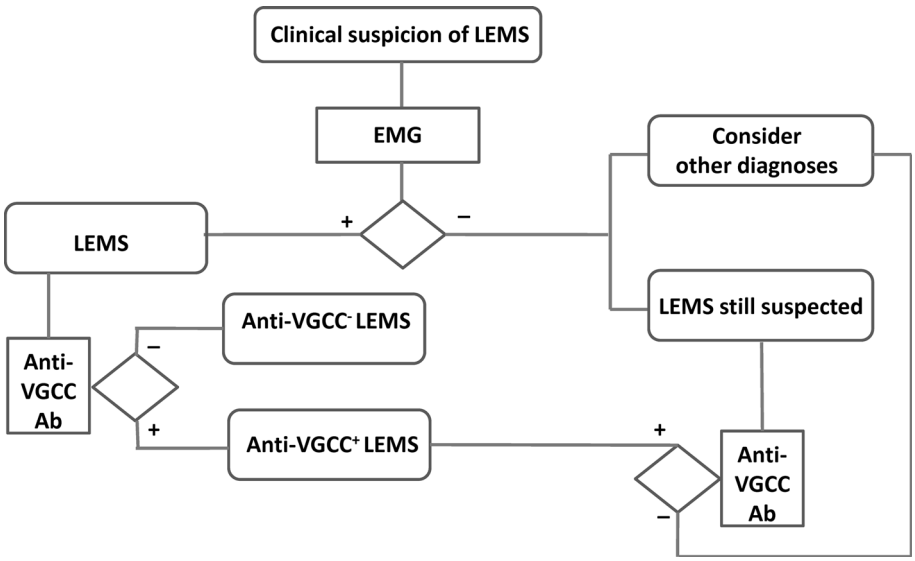

Fig. 1 LEMS diagnosis algorithm. *EMG* electromyography, *anti-VGCC Ab* antibodies to voltage-gated calcium channels. When LEMS is suspected on clinical grounds, EMG is usually the first diagnostic step. If EMG criteria are met, LEMS is highly likely. Anti-VGCC antibody (Ab) detection confirms the diagnosis, while a negative Ab assay does not exclude the diagnosis (anti-VGCC negative LEMS), rather it makes the chance of small-cell lung cancer association less likely. If EMG is negative, the diagnosis of LEMS relies on anti-VGCC antibody detection: a negative Ab assay in this context makes LEMS diagnosis very unlikely

repetitive nerve stimulation (RNS); (3) CMAP amplitude increase during high-rate RNS (20–50 Hz) or immediately after a brief maximal voluntary contraction (15–20 s). The latter is the technique of choice as it is better tolerated [2]. Screening should be performed at least in two distal muscles. For technical convenience and relative comfort for the patient, the abductor digiti minimi is often studied.

A decrease of >10 % of the CMAP amplitude (decrement) during low-rate RNS does not discriminate between LEMS and MG; therefore, it is important to apply the whole protocol in every case where a neuromuscular transmission disorder is suspected. An increment in CMAP amplitude/area (post-tetanic/post-exercise facilitation) of 100 % or greater, in at least two tested muscles, is fairly typical of LEMS, with a sensitivity ranging from 84 to 96 %. A reduction in the normal limit for post-exercise facilitation from 100 to 60 % was reported to increase diagnostic sensitivity to 97 %, while retaining a specificity of 99 % [14]. Sensitivity is also increased by withdrawal of symptomatic medication 12 h before electrodiagnostic testing. However, low amplitude of CMAP as well as post-tetanic/post-exercise facilitation can be found in other disorders including overlap myasthenic syndrome, botulism, drug-induced paralysis and periodic paralysis, although, in these conditions, facilitation is less pronounced than in LEMS. Therefore, low amplitude of CMAP at rest or an incremental response per se does not establish a diagnosis of LEMS, but these findings must be evaluated within the clinical context. Furthermore, facilitation may not be evident in those rare cases presenting with severe weakness [8]. Low-frequency RNS during maximal contraction could increase EMG test sensitivity [15]. Single-fibre EMG might be more sensitive than RNS but it does not distinguish between MG and LEMS.

Antibody assay

Antibodies to P/Q VGCC are present in 75–90 % of LEMS patients; positivity rate can approach 100 % in T-LEMS cases, and is generally associated with high-antibody titres [16]. P/Q-type antibodies are highly specific to LEMS, having been only described in association with paraneoplastic SCLC-related cerebellar ataxia and in 2–3 % of SCLC patients without neurological dysfunction [16]. Seronegative LEMS (without detectable anti-VGCC antibodies) does not show distinctive clinical features, except for the lower association with SCLC [17].

Anti-VGCC antibody detection represents a highly specific diagnostic confirmation. The absence of these antibodies does not exclude a diagnosis of LEMS, though it reduces the probability of association with SCLC.

The diagnostic algorithm for LEMS we are proposing (Fig. 1) has been developed based on the Italian healthcare environment. While EMG studies can be performed in most neurological clinics, the availability of the anti-VGCC antibody assay is less widespread, even if commercial kits are available. As a matter of fact, both tests have a comparable diagnostic specificity, and antibody detection in a patient with consistent symptoms confirms the diagnosis of LEMS even without EMG confirmation.

Antibodies against synaptotagmin [18] and M1 muscarinic acetylcholine receptors [19] have also been described occasionally in LEMS patients. Such antibodies are not routinely tested and currently have no diagnostic use.

T-LEMS: diagnosis of the associated cancer

Oncologic screening

Once LEMS is diagnosed, screening for a possible associated cancer is mandatory. More than 90 % of T-LEMS patients are affected by SCLC. Other types of tumours underlying LEMS (lung, prostate and breast carcinoma, thymoma and lymphoma) have been rarely reported [2, 5].

In LEMS patients, factors associated with a higher risk of SCLC are older age (≥50 years) at disease onset, rapid disease progression, high anti-VGCC antibody levels and being a smoker. All patients should undergo an oncologic screening as early as possible after LEMS diagnosis.

Oncologic risk assessment

SOX (sry-like high-mobility group box) proteins belong to different families of transcriptional factors that are expressed in the developing nervous system and in the adult cerebellum (Bergmann's cells), as well as in some neuroendocrine cancers [20].

Anti-SOX antibodies, especially those against the main antigen SOX1, are important serological markers of SCLC. They are detected in SCLC-related paraneoplastic neurological syndromes (PNS) and are strongly associated with T-LEMS [20]. In particular, anti-SOX1 antibodies are found in 64–67 % of patients with SCLC-LEMS, in 22–32 % of SCLC patients without PNS, but in only 5 % of NT-LEMS cases [21, 22].

According to the guidelines of the European Federation of Neurological Societies (EFNS) [23], screening for SCLC should be performed with computerised tomography of the thorax (thorax-CT) followed, when negative, by positron emission tomography (PET) or integrated PET-CT. If the first screening is negative, oncologic surveillance should be continued by periodic screenings for at least 2 years after LEMS onset [23].

Assessing the oncologic risk in each patient is crucial to establish how long the search for SCLC should continue. As reported above, anti-SOX antibodies have a 67 % sensitivity as T-LEMS markers, but they are not extensively available. Neuron-specific enolase (NSE) has a sensitivity of 65 % as tumour marker in SCLC patients. NSE positivity is, however, dependent on the tumour-stage, and it is less frequent in patients with limited disease [23]. Recently, a clinical scoring system (Dutch-English LEMS Tumour Association Prediction [DELTA-P]) to predict SCLC in LEMS patients has been proposed [24]. DELTA-P consists of recording, within 3 months from the onset, the following parameters whose presence/absence are graded 1/0: (D) dysarthria, dysphagia, neck weakness (bulbar symptoms), (E) erectile dysfunction (in women this parameter is scored 0), (L) loss of weight ≥5 %, (T) tobacco use, (A) age of onset ≥50 years, and, (P) Karnofski performance status <70 [25]. DELTA-P score ranges from 0 to 6, and higher scores correlate with an increasing risk of SCLC association [5]. Thus, in LEMS patients, DELTA-P can be useful in deciding for how long oncologic screenings should be repeated when the first CT/PET-CT study is negative [5].

LEMS treatment

A treatment algorithm is shown in Fig. 2. Based on randomised clinical trials, symptomatic treatment of LEMS with 3,4-diaminopyridine (3,4-DAP) is effective and well tolerated [26], representing the first therapeutic approach in all patients. A novel calcium channel agonist (GV-58), which works slowing deactivation of the channels, is currently being evaluated for the treatment of neuromuscular weakness [27].

In T-LEMS, treatment of the associated tumour generally induces a significant improvement of neurologic symptoms. When symptoms are disabling, prednisone therapy is indicated and can be started during the oncologic screening, if necessary. In patients with severe disease, in whom a rapid therapeutic response is required, high-dose prednisone can be associated with plasmapheresis or intravenous immunoglobulin (IVIG). In T-LEMS patients, use of immunosuppressants other than steroids is controversial: the general trend is to avoid them as far as possible, even though there is no definite contraindication to azathioprine treatment [5].

In LEMS not associated with tumour (NT-LEMS), treatment is similar to that of MG. Patients with disabling symptoms, not adequately controlled with 3,4-DAP, are given prednisone starting at high dose with subsequent dosage tapering according to the clinical response. In patients with an inadequate response to prednisone, requiring high dosages or suffering from steroid-related adverse events, treatment with immunosuppressants is indicated (azathioprine as first choice, cyclosporine or mycophenolate mofetil as second-choice drugs). Patients with severe relapsing symptoms can be treated with plasmapheresis or IVIG in any phase of the disease [2, 28]. Some recent evidence has shown rituximab to be effective in treating LEMS, as in other immune-mediated diseases [29] (Fig. 2).

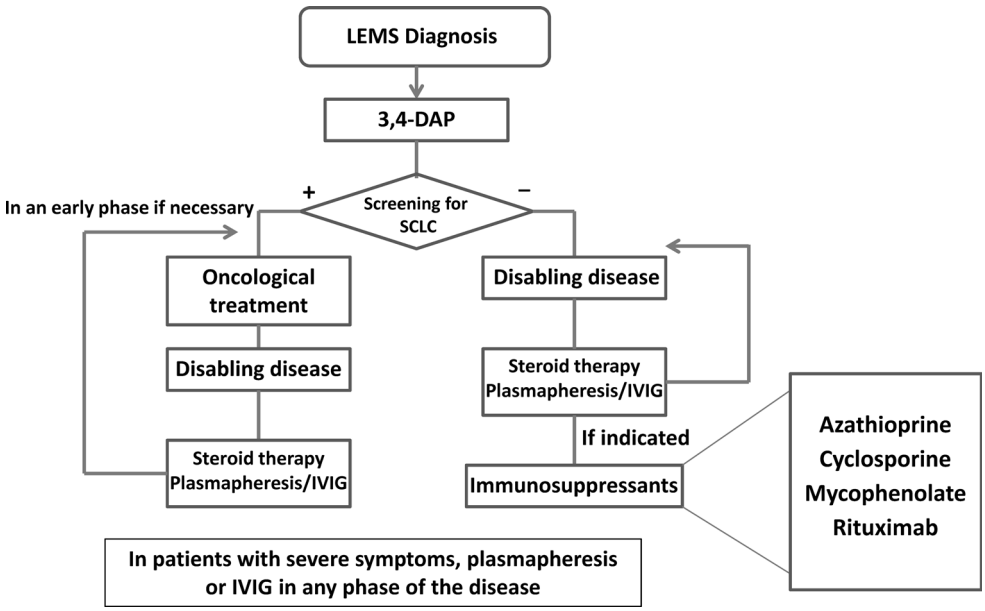

Fig. 2 Treatment algorithm for LEMS patients. *3,4-DAP* 3,4-diaminopyridine, *SCLC* small-cell lung carcinoma, *IVIG* intravenous immunoglobulin, *T-LEMS* tumour-LEMS, *NT-LEMS* non-tumour LEMS. Symptomatic treatment with 3,4-DAP represents the first therapeutic approach in all LEMS patients. In T-LEMS, oncologic treatment usually improves the neurological disease; for patients with disabling symptoms not satisfactorily controlled by 3,4-DAP, prednisone (associated with plasmapheresis or IVIG when needed) is indicated also at an early stage of the disease. In NT-LEMS, severely affected patients are treated with prednisone in the initial phase; in the subsequent course, some of these cases require immunosuppressants, such as azathioprine, cyclosporine A, or mycophenolate mofetil; rituximab has been used for refractory disease. Plasmapheresis and IVIG can be used to treat disease relapses in association with prednisone and/or immunosuppressants

Conclusions

Many advances have been made in optimising tumour screening in LEMS as well as its treatment. The awareness of this rare disease is also improving, so it is crucial to have specific tools to guide diagnosis and treatment, based on good clinical practice. The algorithms presented in this review are the results of the Italian GISMIA Working Group consensus and are intended to provide a practical clinical approach to LEMS management.

Acknowledgments There were no funding sources for this work. The authors have no conflict of interest to disclose.

References

1. Graus F, Lang B, Pozo-Rosich P, Saiz A, Casamitjana R, Vincent A (2002) P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. Neurology 59(5):764–766
2. Juel VC, Sanders DB (2012) The Lambert–Eaton myasthenic syndrome. In: Engel AG (ed) Myasthenia gravis and myasthenic disorders, 2nd edn. Oxford University Press, Oxford, pp 156–169
3. Roberts A, Perera S, Lang B, Vincent A, Newsom-Davis J (1985) Paraneoplastic myasthenic syndrome IgG inhibits $45Ca^{2+}$ flux in a human small cell carcinoma line. Nature 317(6039):737–739
4. Lipka AF, Verschuuren JJ, Titulaer MJ (2012) SOX1 antibodies in Lambert–Eaton myasthenic syndrome and screening for small cell lung carcinoma. Ann N Y Acad Sci 1275:70–77. doi:10.1111/j.1749-6632.2012.06772.x
5. Titulaer MJ, Lang B, Verschuuren JJ (2011) Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 10(12):1098–1107. doi:10.1016/S1474-4422(11)70245-9
6. Wirtz PW, Nijnuis MG, Sotodeh M, Willems LN, Brahim JJ, Putter H, Wintzen AR, Verschuuren JJ (2003) The epidemiology of myasthenia gravis, Lambert–Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. J Neurol 250(6):698–701. doi:10.1007/s00415-003-1063-7
7. Titulaer MJ, Wirtz PW, Kuks JB, Schelhaas HJ, van der Kooi AJ, Faber CG, van der Pol WL, de Visser M, Sillevis Smitt PA, Verschuuren JJ (2008) The Lambert–Eaton myasthenic syndrome 1988–2008: a clinical picture in 97 patients. J Neuroimmunol 201–202:153–158. doi:10.1016/j.jneuroim.2008.05.025
8. O'Neill JH, Murray NM, Newsom-Davis J (1988) The Lambert–Eaton myasthenic syndrome. A review of 50 cases. Brain 111(Pt 3):577–596
9. Sanders DB (1995) Lambert–Eaton myasthenic syndrome: clinical diagnosis, immune-mediated mechanisms, and update on therapies. Ann Neurol 37(Suppl 1):S63–S73
10. Wirtz PW, Smallegange TM, Wintzen AR, Verschuuren JJ (2002) Differences in clinical features between the Lambert–Eaton myasthenic syndrome with and without cancer: an analysis of 227 published cases. Clin Neurol Neurosurg 104(4):359–363
11. Odabasi Z, Demirci M, Kim DS, Lee DK, Ryan HF, Claussen GC, Tseng A, Oh SJ (2002) Postexercise facilitation of reflexes is not common in Lambert–Eaton myasthenic syndrome. Neurology 59(7):1085–1087
12. Rudnicki SA (2007) Lambert–Eaton myasthenic syndrome with pure ocular weakness. Neurology 68(21):1863–1864. doi:10.1212/01.wnl.0000264798.56174.df

13. Maddison P, Newsom-Davis J, Mills KR (1998) Distribution of electrophysiological abnormality in Lambert–Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 65(2):213–217
14. Oh SJ, Kurokawa K, Claussen GC, Ryan HF Jr (2005) Electrophysiological diagnostic criteria of Lambert–Eaton myasthenic syndrome. Muscle Nerve 32(4):515–520. doi:10.1002/mus.20389
15. LoMonaco M, Milone M, Padua L, Tonali P (1997) Combined low-rate nerve stimulation and maximal voluntary contraction in the detection of compound muscle action potential facilitation in Lambert–Eaton myasthenic syndrome. Muscle Nerve 20(9):1207–1208
16. Lang B, Waterman S, Pinto A, Jones D, Moss F, Boot J, Brust P, Williams M, Stauderman K, Harpold M, Motomura M, Moll JW, Vincent A, Newsom-Davis J (1998) The role of autoantibodies in Lambert–Eaton myasthenic syndrome. Ann N Y Acad Sci 841:596–605
17. Nakao YK, Motomura M, Fukudome T, Fukuda T, Shiraishi H, Yoshimura T, Tsujihata M, Eguchi K (2002) Seronegative Lambert–Eaton myasthenic syndrome: study of 110 Japanese patients. Neurology 59(11):1773–1775
18. Takamori M, Komai K, Iwasa K (2000) Antibodies to calcium channel and synaptotagmin in Lambert–Eaton myasthenic syndrome. Am J Med Sci 319(4):204–208
19. Takamori M, Motomura M, Fukudome T, Yoshikawa H (2007) Autoantibodies against M1 muscarinic acetylcholine receptor in myasthenic disorders. Eur J Neurol 14(11):1230–1235. doi:10.1111/j.1468-1331.2007.01931.x
20. Tschernatsch M, Gross O, Kneifel N, Kaps M, Blaes F (2009) SOX-1 autoantibodies in patients with paraneoplastic neurological syndromes. Autoimmun Rev 8(7):549–551. doi:10.1016/j.autrev.2009.01.015
21. Sabater L, Titulaer M, Saiz A, Verschuuren J, Gure AO, Graus F (2008) SOX1 antibodies are markers of paraneoplastic Lambert–Eaton myasthenic syndrome. Neurology 70(12):924–928. doi:10.1212/01.wnl.0000281663.81079.24
22. Titulaer MJ, Klooster R, Potman M, Sabater L, Graus F, Hegeman IM, Thijssen PE, Wirtz PW, Twijnstra A, Smitt PA, van der Maarel SM, Verschuuren JJ (2009) SOX antibodies in small-cell lung cancer and Lambert–Eaton myasthenic syndrome: frequency and relation with survival. J Clin Oncol 27(26):4260–4267. doi:10.1200/JCO.2008.20.6169
23. Titulaer MJ, Soffietti R, Dalmau J, Gilhus NE, Giometto B, Graus F, Grisold W, Honnorat J, Sillevis Smitt PA, Tanasescu R, Vedeler CA, Voltz R, Verschuuren JJ (2011) Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 18(1):19-e13. doi:10.1111/j.1468-1331.2010.03220.x
24. Titulaer MJ, Maddison P, Sont JK, Wirtz PW, Hilton-Jones D, Klooster R, Willcox N, Potman M, Sillevis Smitt PA, Kuks JB, Roep BO, Vincent A, van der Maarel SM, van Dijk JG, Lang B, Verschuuren JJ (2011) Clinical Dutch-English Lambert–Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. J Clin Oncol 29(7):902–908. doi:10.1200/JCO.2010.32.0440
25. Timmermann C (2013) 'Just give me the best quality of life questionnaire': the Karnofsky scale and the history of quality of life measurements in cancer trials. Chronic Illn 9(3):179–190. doi:10.1177/1742395312466903
26. Keogh M, Sedehizadeh S, Maddison P (2011) Treatment for Lambert–Eaton myasthenic syndrome. Cochrane Database Syst Rev (2):CD003279. doi:10.1002/14651858.CD003279.pub3
27. Tarr TB, Valdomir G, Liang M, Wipf P, Meriney SD (2012) New calcium channel agonists as potential therapeutics in Lambert–Eaton myasthenic syndrome and other neuromuscular diseases. Ann N Y Acad Sci 1275:85–91. doi:10.1111/nyas.12001
28. Maddison P, Newsom-Davis J (2005) Treatment for Lambert–Eaton myasthenic syndrome. Cochrane Database Syst Rev (2):CD003279. doi:10.1002/14651858.CD003279.pub2
29. Maddison P, McConville J, Farrugia ME, Davies N, Rose M, Norwood F, Jungbluth H, Robb S, Hilton-Jones D (2011) The use of rituximab in myasthenia gravis and Lambert–Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 82(6):671–673. doi:10.1136/jnnp.2009.197632