# Autoimmunity at the neuromuscular synapse: pathophysiology and disease course

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CHAPTER 4

# Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome

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## Abstract

**Objective** To study survival and characterize long-term functional impairments as well as health-related quality of life (HRQOL) of Lambert-Eaton myasthenic syndrome (LEMS) patients.

**Methods** In this observational study, survival of LEMS patients, separately for non-tumor (NT) and small-cell lung cancer (SCLC), was compared to the Dutch general population and to patients with SCLC. Disease course in LEMS patients was recorded retrospectively. Several scales for functional impairments and health-related quality of life were assessed.

**Results** We included 150 LEMS patients. Survival was similar to the general population in 65 NT-LEMS patients. Tumor survival was significantly longer in 81 SCLC-LEMS patients compared to non-LEMS SCLC patients (overall median survival 17 vs. 7.0 months, $p<0.0001$). At diagnosis, 39 patients (62%) of 63 patients with complete follow-up data were independent for ADL activities, improving to 85% at 1-year follow-up. Physical HRQOL composite score (55.9) was significantly lower than in the general population (76.3, $p<0.0001$) and comparable to myasthenia gravis (60.5) Mental HRQOL composite score was 71.8 in LEMS patients, comparable to the general population (77.9, $p=0.19$) and myasthenia gravis (70.3).

**Conclusions** This study shows NT-LEMS patients have normal survival. SCLC-LEMS patients have an improved tumor survival, even after correcting for tumor stage. A majority of LEMS patients report a stable disease course and remain or become independent for self-care after treatment.

## Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by fluctuating muscle weakness, loss of tendon reflexes and autonomic dysfunction [1, 2]. Muscle weakness usually starts in the proximal leg muscles [1, 3], which can severely limit mobility. Symptoms usually progress over the first months and can often be controlled by symptomatic and immunosuppressive treatment [4-6].

After diagnosis, symptoms can vary between long-lasting remission upon treatment, frequent fluctuations, and permanent disability. Distributions of symptoms and signs have been reported in several studies [1, 3, 7-9]. Long-term follow-up of muscle strength scores, EMG and voltage-gated calcium channel (VGCC) antibody results have been reported in 47 patients [10]. Functional impairments of LEMS patients over the disease course have been described in 12 patients only [11].

Associated tumors are found in 50-60% of LEMS patients, almost invariably small cell lung cancer (SCLC) [1, 3, 7, 12]. Limited data suggest some improvement of symptoms in LEMS patients with small cell lung cancer (SCLC-LEMS) after treatment of the tumor [13]. Previous studies have shown a profound improved tumor survival in SCLC-LEMS [14-18], but no data exist on the quality of life of this period of improved survival. Hardly any data are available determining survival and quality of life of LEMS patients without associated tumors [1].

In this observational study, we aimed to characterize functional impairments over the disease course, as well as quality of life of LEMS patients. We studied survival of all LEMS patients, with and without associated tumors.

## Materials and methods

### Patient population

From 1 July 1998 to 1 October 2015, data from all consecutive Dutch LEMS patients were collected prospectively, as described before [3, 19]. Leiden University Medical Center has a tertiary neuromuscular outpatient clinic and is the nationwide referral center for LEMS in the Netherlands. Patients were also identified through diagnosis registration databases and neuromuscular databases in university centers up to 2003. Afterwards, we approached treating neurologists from all Dutch patients with positive results for VGCC antibodies (assay performed in Leiden and Rotterdam, for all Dutch hospitals). This resulted in a small number of patients added retrospectively after a positive VGCC assay and verification of diagnosis (n=7). One LEMS patient was excluded for this study, lacking most required data.

The diagnosis of LEMS was based on characteristic clinical features, supported by either presence of antibodies to VGCC or abnormal decrement and 60% increment upon repetitive nerve stimulation [2, 20]. Increment testing was performed immediately after 10-30 seconds of voluntary contraction.

### Survival

In the survival analysis, we separated the LEMS patients with and without associated SCLC, excluding non-small cell lung cancer from the analysis (n=3) as well as one SCLC patient without known date of tumor diagnosis. Patients with LEMS without associated tumor were compared to the general Dutch population as published by the Central Statistics office of the Netherlands, matching LEMS patients for age and year at LEMS diagnosis, as well as gender [21, Statline.cbs.nl, 22]. Survival, from diagnosis of tumors, in LEMS patients with associated SCLC was compared to survival in all SCLC patients in the Netherlands from 1998 to 2012, as registered in the Netherlands Cancer Registry Netherlands Cancer Registry operated by Netherlands Comprehensive Cancer Organisation, [23]. As a secondary outcome measure, both SCLC-LEMS and control SCLC patients were compared post-hoc according to tumor stage (limited or extensive disease). Within SCLC-LEMS patients, patients with and without bulbar involvement or loss of weight within 3 months from onset were compared to show whether these variables predicted survival. Survival of these patients was also calculated according to patients' Dutch-English LEMS Tumour Association Prediction (DELTA-P) scores [24]. In patients with follow-up data, medical events leading up to death were studied to determine their potential relation with LEMS.

### Functional impairments

Disease course in LEMS patients was recorded retrospectively, using a semi-structured interview in all available patients alive in 2014-2015, in combination with medical records. We used modified Rankin Scale (mRS) and Karnofsky performance scales (KPS) to grade functional impairment. For the mRS, a structured interview was performed [25, 26]. For a limited number of patients (10/63), mRS and KPS scores were solely collected from medical records. In all these, extensive follow-up data was available to derive functional limitations.

Treatment modalities and subjective response, as well as devices to assist mobility were recorded for all patients. Exacerbations were recorded, as defined both by a subjective decrease in strength reported by patients, supported by medical records, as well as exacerbations requiring emergency treatment with either intravenous immunoglobulin (IVIg) or plasmapheresis as a more robust but less frequent criterion. Maximum disease severity was also recorded, as reported by patients and supported by medical records.

**Health-related quality of life**

Health-related quality of life (HRQOL) was assessed using the Short Form-36 (SF-36), a self-administered validated questionnaire which was mailed to all known living LEMS patients in March 2012. Non-responders were reminded twice. Control cohorts were a population-based cohort of 464 patients with myasthenia gravis in the Netherlands collected at the same time [27], as well as published normative data in the Dutch general population [28].

The SF-36 is organized into 8 domains, with a score ranging from 0 (worst HRQOL) to 100 (best HRQOL). The eight domains are physical functioning, Role physical (role limitations due to physical problems), Bodily pain, general health evaluation, Vitality, Social functioning, Role emotional (role limitations due to emotional problems) and mental health. These domains produce composite scores for physical (PCS) and mental health (MCS) [29].

The impact of baseline demographic and disease-related factors on both physical (PCS) and mental composite scores (MCS) quality of life was first assessed by univariate analysis. The predictors studies were chosen based on expected baseline contributors to quality of life and likely clinical predicting factors; and were age at onset (above or below 50), sex, partner, state of employment, presence of an associated tumor, presence of other autoimmune disease [30], pattern of muscle weakness, medication status and mRS score. A second, multivariate analysis was performed to determine which of these factors independently predicted HRQOL.

**Statistics**

Descriptive measures were presented as mean ± standard deviation if appropriate, or as median with interquartile range. Baseline variables between LEMS patients with and without associated lung cancer were compared using t-tests for linear and Fisher exact tests for categorical variables. Survival analysis was calculated using Kaplan-Meier plots and log rank tests for nominal variables and log rank test for trend for ordinal DELTA-P scores. HRQOL scores for all domains and composite scores were compared between LEMS, MG and normative data in the Dutch general population were compared using a one-way between-groups analysis of variance, followed by post-hoc comparison using Tukey's multiple comparison test to test all pairwise comparisons. All individual predicting variables for physical and mental composite scores were first analyzed using a t-test or one-way ANOVA for categorical variables and linear regression for mRS scores. Variables were included in a multivariate model only in case of a p-value $< 0.20$ in the univariate analysis [31]. For missing values (2.4 % of data) in this model, a 10-fold multiple imputation was performed. After missing data imputation, a generalized linear model was performed to determine which of these variables independently predicted HRQOL. Bonferroni

correction for multiple comparisons was used, correcting for the number of categories for each variable. Data analysis was performed using SPSS version 23.0 (Chicago, IL) and Graphpad Prism 6 (La Jolla, CA).

**Standard Protocol Approvals, Registrations, and Patient Consents**
The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. All patients included for follow-up of functional impairments and quality of life provided written informed consent.

**Data availability**
The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

We included 150 LEMS patients, of whom 85 (59%) had an associated lung cancer (Flowchart for inclusion available on Dryad, Figure e-1). Median time from onset to diagnosis was 18 months in patients without and 4 months in patients with an associated SCLC. Median time from LEMS diagnosis to detection of associated lung cancer was 0 months. A delay beyond two years was found in two patients (35 and 41 months). The first patient repeatedly avoided screening, while the latter was screened in 1988, according to standards of care which are currently considered insufficient. Baseline characteristics are shown in Table 1, for the total LEMS population as well as subgroups in which functional impairments and HRQOL were assessed.

| | NT-LEMS | PNS-LEMS | P-value |
|---|---|---|---|
| All patients (n=150) | 65 (43%) | 85 (57%) | n/a |
| Median age at onset (IQR; range) | 51 (41-62; 13-80) | 63 (56-68; 38-77) | <0.0001 |
| Female sex (%) | 35 (54%) | 34 (40%) | 0.064 |
| Associated lung cancer | n/a | 82 SCLC (96%)<br>3 NSCLC (4%) | n/a |
| Presence of autonomic symptoms | 57/63 (90%) | 57/65 (88%) | 0.78 |
| Presence of VGCC antibodies | 55/64 (86%) | 77/82 | 0.16 |
| Repetitive nerve stimulation | | | |
| Abnormal decrement | 63/64 (98%) | 73/74 (99%) | >0.99 |
| Abnormal increment (>60%) | 61/64 (95%) | 68/74 (92%) | 0.50 |
| Median delay onset – diagnosis in months (IQR; range) | 18 (8-39; 1-265) | 4 (2-9; 1-40) | <0.0001 |
| Median delay LEMS to tumor diagnosis in months (IQR; range) | n/a | 0 (0-1; -40 to 41) | n/a |
| Median survival (months; IQR; range) * | (not yet reached) | 17 (8-37; 1-209) | <0.0001 |
| Immunosuppression | 31/64 (48 %) | 28/85 (33%) | 0.064 |
| Chemotherapy | n/a | 74/84 (88.1%) | n/a |

| Long-term follow-up (n=63) | NT-LEMS (n=41) | SCLC-LEMS (n=22) | P-value |
|---|---|---|---|
| Median age at onset (IQR; range) | 51 (41-60; 19-80) | 65 (59-67; 50-76) | <0.0001 |
| Female sex (%) | 23 (56%) | 12 (55%) | 1.00 |
| Maximum mRS | | | |
| 5 | 2 (5%) | 4 (18%) | |
| 4 | 6 (15%) | 9 (41%) | |
| 3 | 16 (39%) | 6 (27%) | |
| 2 | 16 (39%) | 3 (14%) | |
| 1 | 1 (2%) | 0 (0%) | |
| Median time from onset to max severity (months; IQR; range) | 12 (6-60; 0-444) | 4 (2-10; 1-28) | |
| Median time from diagnosis to max severity (months; IQR; range) | -1 (-4 to 5; -253 to 354) | 0 (-1 to 2; -4 to 24) | |
| Symptomatic therapy | 40 (98%) | 22 (100%) | >0.99 |
| Immunosuppression | 21 (51%) | 10 (45%) | 0.79 |
| Chemotherapy | n/a | 17 (77%) | n/a |
| Exacerbation frequency (occurring in % of patients) | 1/6.9 patient years (61%) | 1/3.2 patient years (41%) | n/a |
| Emergency treatment frequency (IVIg/PLEX; % of patients) | 1/20.0 patient years (29%) | 1/6.7 patient years (23%) | n/a |

| HRQOL (n=42) | NT-LEMS (n=36) | SCLC-LEMS (n=6) | |
|---|---|---|---|
| Median age at onset (IQR; range) | 53 (39-62; 19-71) | 56 (51-69; 49-73) | 0.11 |
| Female sex (%) | 20/36 (56%) | 4/6 (67%) | 0.69 |
| Mean HRQOL Composite scores | | | |
| PCS | 56.8 | 51.0 | 0.58 |
| MCS | 71.4 | 74.3 | 0.77 |

**Table 1 Baseline characteristics for all LEMS patients**

* Median survival for SCLC was 17 months (IQR 8-37; range 1-209); one of 3 patients with NSCLC was alive at 24 months, while the other two died at 13 and 25 months.

HRQOL- Health-related quality of life, IQR- interquartile range, IVIg- intravenous immunoglobulin, mRS- modified Rankin Scale, NSCLC- non-small cell lung cancer, NT-LEMS- Lambert-Eaton myasthenic syndrome patients without associated tumor. PLEX- plasma exchange, PNS-LEMS- Lambert-Eaton myasthenic syndrome patients with associated lung cancer, SCLC- small cell lung cancer, VGCC- voltage-gated calcium channels.

## Survival

In the 65 LEMS patients without an associated tumor, life expectancy was similar to the average life expectancy in the Netherlands adjusted for gender, age and year of diagnosis (log rank test p = 0.63; hazard ratio (log rank test) 1,16 (95% confidence interval 0,59 to 2,27); Figure 1, survival percentages are available on Dryad in supplemental table e-1). In 81 LEMS patients with an associated SCLC, tumor survival was significantly longer as compared to SCLC patients without LEMS (median survival 17 vs. 7.0 months respectively, p<0.0001). According to tumor stage, SCLC-LEMS patients had a longer tumor survival both in limited (median survival 19 months vs. 12.1 months, p= 0.0015) and extensive disease (median survival 13 vs. 4.9 months, p<0.0001; Figure 2, supplemental table e-2 available on Dryad). Data were similar after additional correction for gender, age and year of tumor diagnosis (data not shown). Early bulbar muscle involvement, loss of weight and

DELTA-P scores did not significantly affect survival in SCLC-LEMS patients (p=0.41, 0.58 and 0.063 respectively).

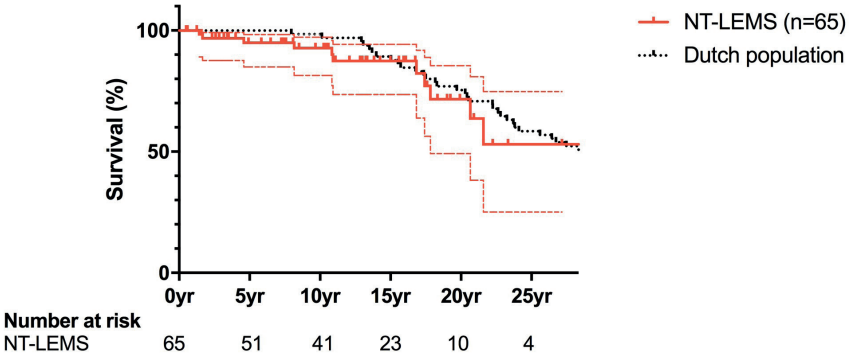


**Figure 1. Survival of NT-LEMS compared to matched Dutch life expectancy.**
Kaplan-Meier curve showing survival of LEMS patients without an associated tumor, as compared to the average life expectancy in the Netherlands, after adjustment for gender, age and year of diagnosis. Dotted thin lines represent 95% confidence interval and small vertical lines represent censored data for the LEMS patients.

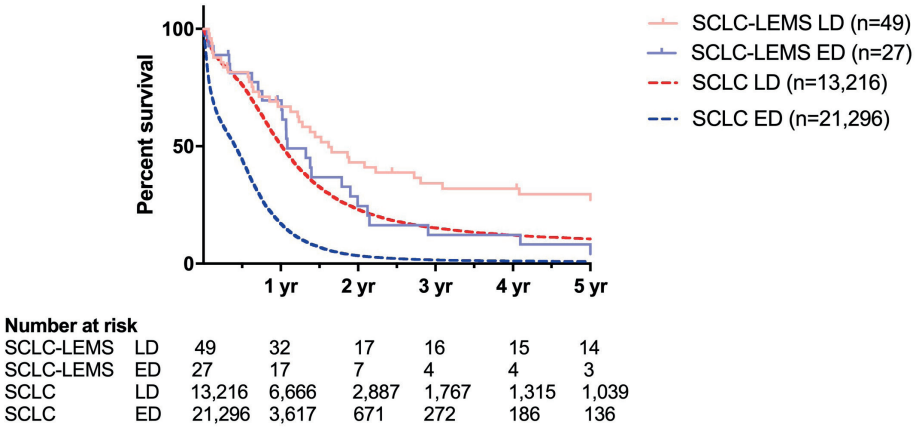


**Figure 2. Survival of SCLC-LEMS compared to all Dutch SCLC patients – limited or extensive disease.**
Kaplan-Meier curve showing tumor survival of LEMS patients with an associated SCLC (1998-2015), as compared to the average life expectancy of SCLC patients in the Netherlands (1998-2012), divided according to tumor stage. Small vertical lines represent censored data for the LEMS patients.

In contrast to the group-wise survival analysis, individually LEMS likely contributed to death in three VGCC-positive patients. Two SCLC-LEMS patients had respiratory insufficiency due to LEMS. The first had very limited response to aggressive treatment and died due

to abdominal sepsis while in ICU. The second died as a result of sudden respiratory deterioration, just following a recent ICU stay for respiratory muscle weakness. A third patient, with probably unrelated rectal carcinoma, experienced respiratory insufficiency shortly before his death. He had previously been admitted to the ICU for respiratory muscle weakness, but was not analyzed again for his dyspnea in a palliative setting. In all three patients, respiratory muscle weakness was likely a relevant contributing factor, although probably not the sole cause of death.

**Functional impairments**

Detailed follow-up data for functional impairments were available for 63 patients (41 NT-LEMS and 22 SCLC-LEMS). Median follow-up was 130 months for LEMS patients without and 12 months for patients with an associated SCLC. At diagnosis, 39 of 63 patients (62%) were independent for self-care (KPS$^{3}$70), improving to 85% at 1-year follow-up (Figure 3 for overall KPS and mRS distribution). Patients with lung cancer reported more functional impairments at any point in the disease course (Figure 4A and B). Maximal disease severity was reached at a median of 1 month before diagnosis, while 30% deteriorated beyond diagnosis. In the 32 LEMS patients with at least 5 years of follow-up, 27 patients (84%) had reached their worst mRS score in or before the first year after diagnosis. Patient-reported maximal disease severity in this group was reached in the first two years in 75% of patients.



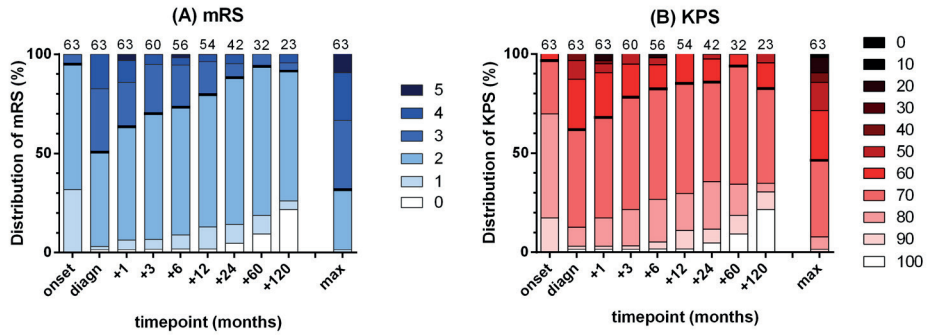


**Figure 3. Distribution of functional impairments during the disease course.**

Distribution of (A) modified Rankin Scale (mRS) and (B) Karnofsky Performance Scale (KPS) at onset of symptoms, diagnosis, 1, 3, 6, 12, 24, 60 and 120 months after diagnosis and at maximal disease severity. At diagnosis, 62% of patients were independent for self-care (KPS$^{3}$70), increasing to 68% one month later and 85% 1 year later. At maximum disease severity, 46% of patients were independent for self-care. Number of patients available at top of bar for each timepoint.

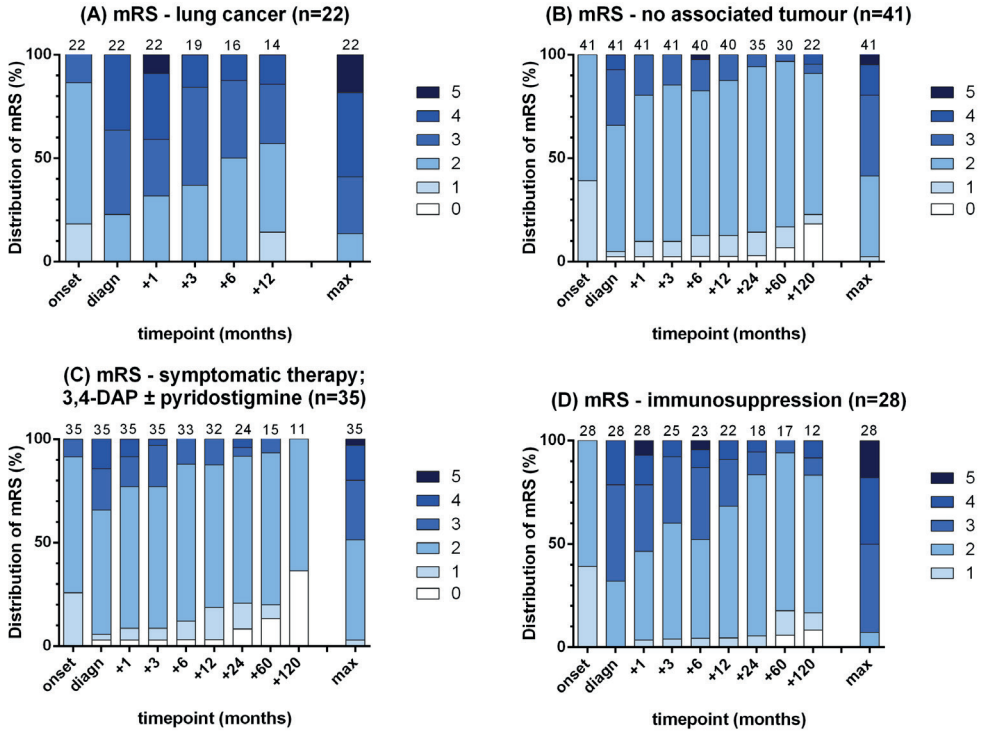


**Figure 4. Distribution of functional impairments during the disease course for subgroups.**
Distribution of modified Rankin Scale for patients (A) with and (B) without associated lung cancer; and those treated (C) symptomatically and with (D) immunosuppressants as well. Data presented at onset of symptoms, diagnosis, 1-120 months after diagnosis and at maximal disease severity. Number of patients available at top of bar for each timepoint.

During disease course, 73% of patients used any device to assist mobility. Fifty-two percent used a wheelchair, while only 6% were fully wheelchair-dependent at any point in disease course. Most patients required a wheelchair only for a limited period of time.

Symptomatic treatment consisted of 3,4-diaminopyridine in 95% of patients and pyridostigmine in 68%. Of patients treated with 3,4-diaminopyridine and pyridostigmine, 88% noticed a subjective improvement in symptoms due to 3,4-diaminopyridine and 67% due to pyridostigmine. Immunosuppressive treatment was started in 49%, of which the most common therapies were either prednisone combined with azathioprine (29%), or prednisone alone (14%). The frequency of both immunosuppressive and emergency treatments showed no significant differences between LEMS patients with and without SCLC [data not shown]. Positive treatment effect, as shown by an improvement in mRS scores after diagnosis, was heterogeneous but generally reached in 6-12 months (figure 4C and D). Patients treated with immunosuppressive drugs reported more functional impairments at diagnosis as compared to those treated symptomatically, but had a comparable mRS distribution 2 and 5 years after diagnosis.

Exacerbations reported by patients occurred in 54% of patients. These self-reported exacerbations overall occurred once in every 5.7 patient-years. Exacerbations requiring emergency treatment with either IVIG or plasmapheresis were less frequent, occurring in 27% of patients, overall once in every 16 patient-years of follow-up. Nine SCLC-LEMS patients had follow-up data available after tumor recurrence, of which only two had a simultaneous worsening of LEMS. One of these however had a concurrent pancreatitis as well and the other had experienced two previous LEMS exacerbations without tumor recurrence. Five patients went into full remission and were able to stop all treatment at a median of 4 years after diagnosis, and remained in remission without any symptoms or treatment on long-term follow-up (median 12 years). One of these was treated for SCLC and one with immunosuppressants. Two other patients were only treated symptomatically and the last patient with a short disease course received no treatment at all, suggesting that even spontaneous remission without immunomodulating therapy is possible.

Two patients in the SCLC-LEMS group had paraneoplastic cerebellar degeneration as a second paraneoplastic disease. These had relevant effects on physical limitations, but they ultimately had a mRS time course comparable to other patients.

**Health-related quality of life**

Forty-four of 67 (66%, 6 with SCLC) LEMS patients alive and included at the time responded to our SF-36 questionnaire Two questionnaires were excluded due to incomplete data. LEMS patients scored lower on the physical HRQOL than the general Dutch population (physical composite scores of 55.9 (95% confidence interval (CI) 48.9-62.9) versus 76.3 (95% CI 75.0-77.5) respectively; $p<0.0001$), reflected in lowered scores in 3 of 4 related domains (physical functioning, role-physical, general health; figure 5, scores for all domains are available on Dryad in supplemental table e-3). HRQOL scores were comparable for the mental composite score (71.8 (95% CI 65.4-78.3) vs. 77.9 (95% CI 76.8-79.0); $p=0.19$), although lower for the domains vitality and social functioning (supplemental table e-3 available on Dryad). Between LEMS and MG, the composite scores and most of the domain subscores were comparable, except for lower scores for LEMS patients in the physical functioning subdomain (45.8 vs. 62.2 in MG, $p=0.0001$), which is dominated by questions involving leg strength.

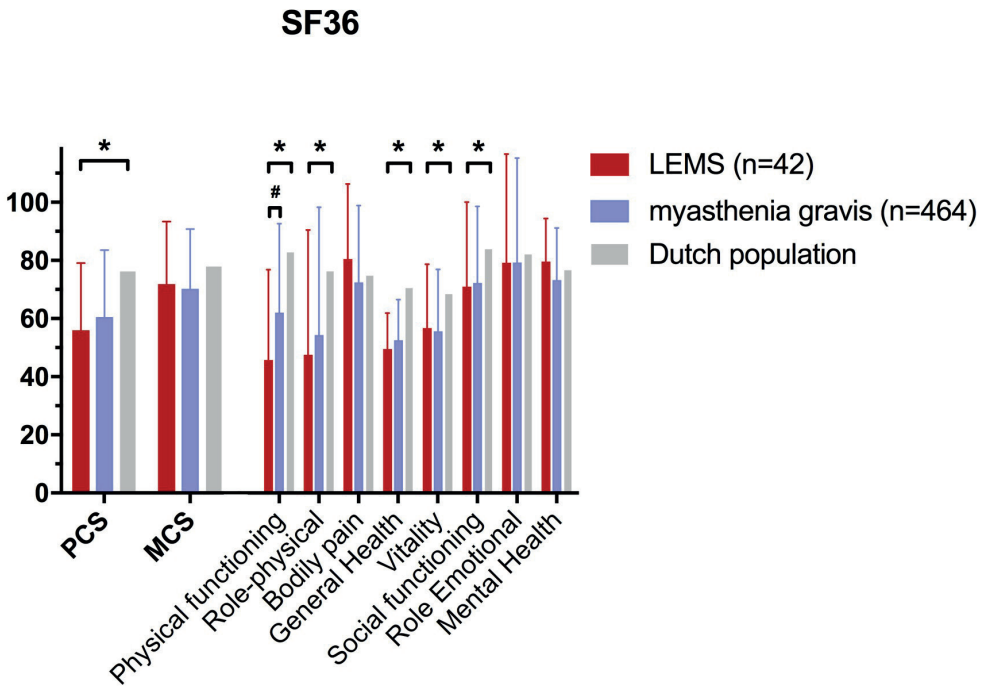


**Figure 5. Health-related quality of life in LEMS, compared to myasthenia gravis and the Dutch general population.**

All scores range from 0-100. * represents a significant difference between LEMS patients and the Dutch general population. # represents a significant difference between LEMS and MG.

PCS- physical composite score, MCS- mental composite scores

Univariate analysis of potential predicting variables for physical and mental HRQOL composite scores showed employment status, pattern of muscle weakness and mRS scores to be significantly associated with physical composite scores (Table 2a). State of employment and whether or not patients had a partner were associated with mental composite scores. A multivariate analysis, aiming to detect independent predictors for quality of life (Table 2b), showed having a partner and employment status to be independently associated to higher physical and mental composite scores. In addition, a higher HRQOL was linked to a more limited pattern of muscle weakness for the PCS and male gender for the MCS. The modified Rankin Scale did not affect either PCS or MCS in this multivariate model.

| | Number of patients | PCS (95% CI) | p | MCS | p |
|---|---|---|---|---|---|
| Age | | | 0.78 | | 0.96 |
| < 50 | 19 | 57.1 (46-68) | | 72.0 (61-82) | |
| ≥50 | 23 | 55.0 (45-64) | | 71.6 (63-81) | |
| Sex | | | 0.22 | | 0.18 |
| Female | 23 | 51.9 (42-62) | | 67.7 (58-78) | |
| Male | 19 | 60.8 (50-72) | | 76.7 (68-86) | |
| Partner | | | 0.079 | | 0.018 |
| Yes | 34 | 60.0 (51-67) | | 75.6 (69-82) | |
| No | 8 | 43.0 (22-64) | | 55.8 (35-76) | |
| Employment | | | 0.035 | | 0.042 |
| Employed | 10 | 71.8 (56-88) | | 85.8 (81-91) | |
| Housekeeping | 4 | 53.4 (22-85) | | 58.1 (28-115) | |
| Disability | 9 | 41.6 (32-52) | | 71.0 (45-71) | |
| Retired | 19 | 54.9 (43-67) | | 71.7 (59-83) | |
| Associated tumor | | | 0.58 | | 0.77 |
| no tumor | 36 | 56.8 (49-64) | | 71.4 (65-78) | |
| SCLC | 6 | 51.0 (19-83) | | 74.3 (42-107) | |
| Other autoimmune disease | | | 0.57 | | 0.54 |
| Yes | 11 | 59.4 (44-75) | | 68.4 (52-85) | |
| No | 31 | 54.7 (46-63) | | 73.0 (65-81) | |
| Muscle weakness | | | <0.0001 | | 0.14 |
| No weakness | 9 | 83.3 (71-95) | | 84.5 (69-100) | |
| Limited to legs only | 6 | 57.2 (28-87) | | 69.1 (42-96) | |
| Generalised | 27 | 46.6 (40-53) | | 68.2 (60-76) | |
| Medication | | | 0.39 | | 0.21 |
| None | 6 | 66.3 (35-98) | | 79.6 (52-107) | |
| Symptomatic | 23 | 54.9 (47-63) | | 74.1 (67-81) | |
| Immunosuppression | 10 | 51.0 (35-67) | | 63.0 (46-80) | |
| Modified Rankin Scale | | | 0.008 | | 0.085 |
| Correlation coefficient (r) | | | -0.44 | | -0.29 |
| 0 | 2 | 68.6 (-234 - 372) | | 62.9 (-306 - 432) | |
| 1 | 2 | 77.8 (-30-185) | | 85.4 (17-153) | |
| 2 | 25 | 52.2 (45-60) | | 72.3 (65-79) | |
| 3 | 6 | 44.3 (18-71) | | 59.6 (30-89) | |
| 4 | 1 | 8.8 (n/a) | | 18.3 (n/a) | |

**Table 2a. Predictors of quality of life in patients with LEMS – univariate analysis.**
CI- confidence interval; MCS- mental composite score; PCS- physical composite score; SCLC- small cell lung cancer

| | Number of patients | PCS | p | MCS | p |
|---|---|---|---|---|---|
| Sex | | | n/a | | 0.031 |
| Female | 23 | | | 67.7 | |
| Male | 19 | | | 76.7 | |
| Partner | | | 0.018 | | 0.015 |
| Yes | 34 | 60.0 | | 75.6 | |
| No | 8 | 43.0 | | 55.8 | |
| Employment | | | 0.036 | | 0.012 |
| Employed | 10 | 71.8 | | 85.8 | |
| Housekeeping | 4 | 53.4 | | 58.1 | |
| Disability | 9 | 41.6 | | 71.0 | |
| Retired | 19 | 54.9 | | 71.7 | |
| Muscle weakness | | | <0.001 | | n.s. * |
| No weakness | 9 | 88.3 | | 84.5 | |
| Limited to legs only | 6 | 57.2 | | 69.1 | |
| Generalised | 27 | 46.6 | | 68.2 | |
| Modified Rankin Scale | | | 0.25 | | 0.31 |
| 0 | 2 | 68.6 | | 62.9 | |
| 1 | 2 | 77.8 | | 85.4 | |
| 2 | 25 | 52.2 | | 72.4 | |
| 3 | 6 | 44.3 | | 59.6 | |
| 4 | 1 | 8.8 | | 18.3 | |

**Table 2b. Predictors of quality of life in patients with LEMS – multivariate analysis.**
* Bonferroni correction (of post-hoc pooled parameter estimates of the generalized linear model) results in a p-value > 1. MCS- mental composite score; PCS- physical composite score.

## Discussion

This study shows that LEMS patients without an associated tumor have a normal survival, confirms that SCLC-LEMS patients have an improved tumor survival compared to SCLC without LEMS, and LEMS patients can have a relatively well-controlled life with mainly physical limitations and normal mental quality of life.

In contrast to myasthenia gravis patients, we show survival in LEMS patients without an associated tumor was similar to the average life expectancy in the Netherlands [32-34]. The increased mortality in MG was at least partially related to an increase in respiratory disease as a cause of death [35], likely related to respiratory muscle weakness, which can occur in both MG and LEMS but might be less frequent in LEMS patients given the lack of an increase in mortality.

Our study shows that tumor survival is increased in all SCLC-LEMS patients both with limited and extensive disease. Median survival is doubled in SCLC-LEMS patients with extensive disease compared to SCLC patients without LEMS and also overall 5-year survival is increased from 4.4% to 21%. Interestingly, survival in SCLC patients without LEMS (limited disease) is comparable to SCLC-LEMS patients with extensive disease. Several

previous, smaller studies have reported this improved survival [14, 15, 36], including a recent prospective cohort study of SCLC patients with and without LEMS [17]. Our study shows that this improved survival cannot merely be attributed to tumor stage (SCLC-LEMS patients are more frequently found while still having limited disease). There will be an inevitable lead-time bias, due to earlier diagnosis of SCLC because of neuromuscular symptoms, but this cannot fully explain the survival difference. This additional improvement in survival supports a biochemical or immunological cause, like an anti-tumor immune response.

We show a majority of LEMS patients have a relatively stable disease course after diagnosis and treatment. Most patients either remain or become independent for self-care over time, after appropriate treatment. Since disease severity directly impacts treatment decisions, especially whether to add immunosuppressive treatment, we could not compare the effect of individual treatments. We did note that patients treated symptomatically improve sooner after diagnosis than those treated with immunosuppressive drugs (probably a confounder by indication), but both groups ultimately reach a relatively stable level of limitations about 2 years after diagnosis. Maximum disease severity has already been reached before diagnosis in a majority of patients and within the first two years in about 80%, the latter of which is very similar to myasthenia gravis [34, 37]. LEMS patients with associated lung cancer report more functional impairments over the entire disease course. Both LEMS symptoms, which can be more progressive in SCLC-LEMS [3, 16, 24], as well as lung cancer and related treatment are likely to contribute to disability in this group. SCLC-LEMS patients also seem to have a higher exacerbation rate, although this should be interpreted with caution, since follow-up in this group is shorter and exacerbations seem more likely to occur in the first years after diagnosis. It should however be noted that most of these patients still become independent for activities of daily life after treatment and seem to have overall HRQOL comparable to LEMS patients without an associated tumor (Table 2a). This supports the notion that low performance scores due to muscle weakness in SCLC-LEMS should not be a reason to refrain from tumor treatment, especially since tumor treatment can improve symptoms in paraneoplastic disease [13].

In LEMS patients with associated lung cancer, LEMS symptoms usually precede tumor diagnosis. However, after initial treatment and improvement of both diseases, frequently no exacerbation of LEMS occurs upon tumor progression as a (repeated) warning. This could either mean that tumor progression does not elicit such a strong immune response as the initial tumor presentation, or that an exacerbation of LEMS would require more time to develop, as is the case before start of the disease.

The reduced HRQOL in LEMS patients was comparable to myasthenia gravis and mostly related to physical limitations. General demographic factors seemed to predict variation in HRQOL at least as strong as disease-specific variables in our population, especially for mental health. Several previous studies in myasthenia gravis have reported reduced HRQOL in myasthenia gravis patients for most domains of the SF-36 [27, 38-40]. Our study showed female gender, generalized disease and lack of employment to be associated with reduced HRQOL, comparable to results in two large myasthenia gravis studies [27, 41]. In contrast to the pattern of muscle weakness, the modified Rankin scale as a marker for disease severity did not independently predict HRQOL. This could be related to the

limited number of patients, limited overall variation in mRS scores or confounding by also including the pattern of weakness in the model.

The largest previous study concerning disease course in LEMS (n=47) focused on muscle strength scores as well as EMG and antibody results. In contrast, we report patient-oriented outcomes including functional impairments and quality of life [10]. Maddison et al. also reported a variable prognosis, with sustained clinical remission in 43% of patients and about a quarter of patients remaining (at least partially) wheelchair-dependent at follow-up. In this cohort, both treatment with immunosuppressants and sustained clinical remission occurred more frequently as compared to our study. Although this might suggest an association between the two, we consider it more likely a difference in definition of clinical remission, since many patients in our study still report a decrease in their level of work and social activities even after substantial or apparent full clinical improvement without major objective weakness at the outpatient clinic. A smaller study of 12 LEMS patients reported lifestyle limitations comparable to our cohort, with restrictions in activities of daily living in 75% of patients, poor reported health status and low health-related quality of life scores as measured by EQ-5D utility scores [11]. Previous follow-up of 16 SCLC-LEMS patients reported sustained improvement of LEMS after tumor treatment [13]. Our study confirms that SCLC-LEMS patients can improve and regain independence for self-care, but these patients still experience limitations in daily life.

Limitations of our study include a relatively small sample size inherent to the rarity of this disease, the partly retrospective nature of the study and the use of different subpopulations for disease course and HRQOL. The limited number of deaths in our study precludes a certain conclusion that survival is normal in LEMS patients without associated tumor. Lacking sufficient EMG or lab parameters for comparison, we specifically focused on patient-oriented outcomes, as these represent patients' limitations best. Functional impairments could have been influenced by comorbidity, but this effect is groupwise minimal as only two of 22 SCLC-LEMS patients had another paraneoplastic neurological disease (cerebellar degeneration). Additionally, in the few patients with relevant comorbidity, the level of physical functioning appeared to be mainly determined by LEMS.

This study provides detailed information on long-term prognosis and limitations in LEMS. This can guide expectations of doctors and patients, and be of potential relevance for treatment choices. Although LEMS is usually a chronic disease, with long-term physical limitations and reduced quality of life, appropriate treatment results in a relevant decrease in functional impairments for most patients.

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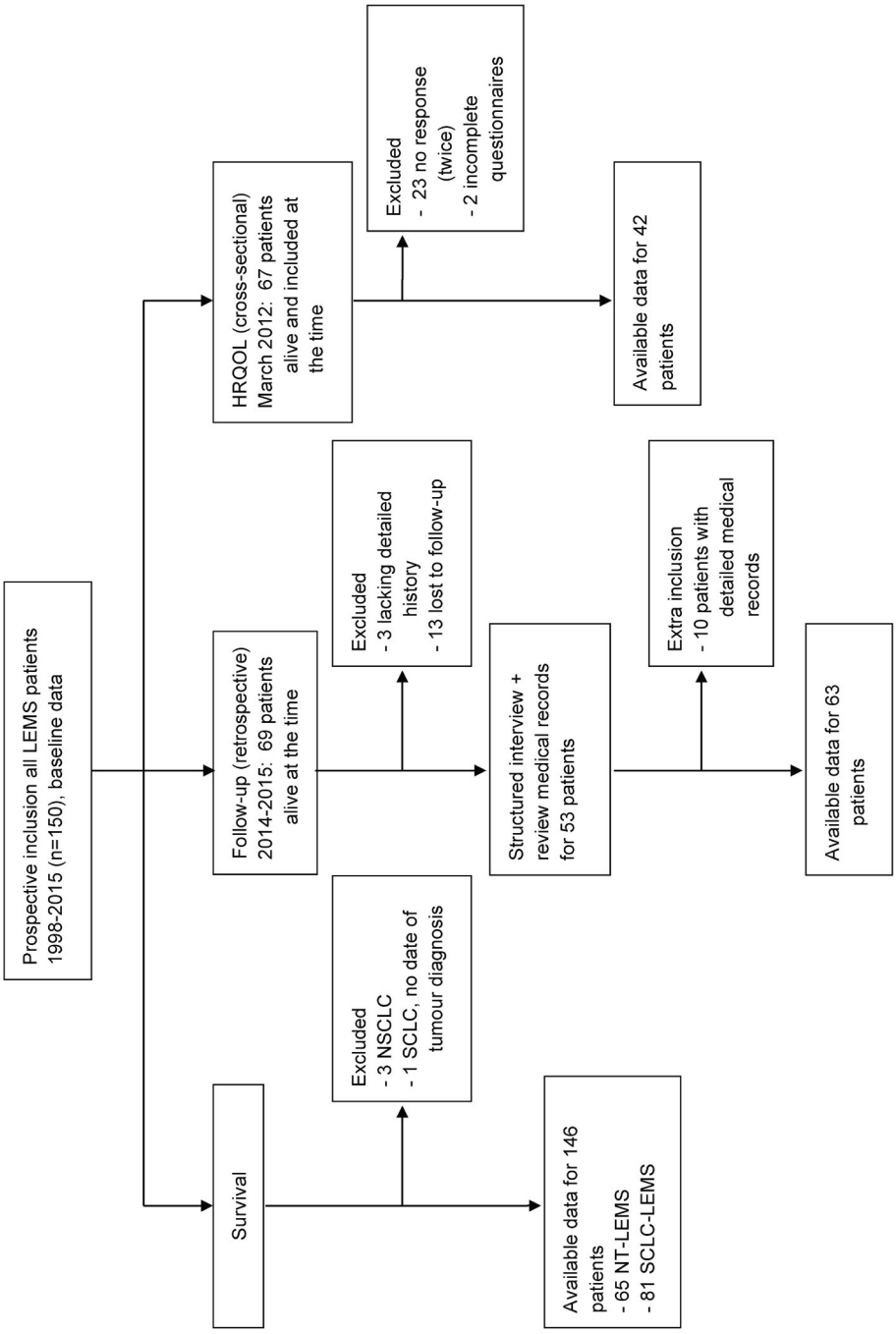


**Supplemental figure 1. Flow diagram of inclusion**

| Time after diagnosis | NT-LEMS | The Netherlands |
|---|---|---|
| 5 yrs | 95% | 100% |
| 10 yrs | 92% | 98.5% |
| 15 yrs | 87% | 89.2% |
| 20 yrs | 72% | 75.4% |
| 25 yrs | 53% | 58.5% |

**Supplemental table e-1.**
Survival percentages after LEMS diagnosis, as compared to the average life expectancy in the Netherlands, after adjustment for gender, age and year of diagnosis. NT-LEMS- non-tumor LEMS patients.

| Median survival (months) | SCLC-LEMS | SCLC |
|---|---|---|
| LD | 19 | 12,2 |
| ED | 13 | 4,9 |
| 1yr survival | | |
| LD | 69% | 50.5% |
| ED | 70% | 17.1% |
| 2yr survival | | |
| LD | 43% | 21.9% |
| ED | 25% | 3.4% |
| 3yr survival | | |
| LD | 34% | 13.4% |
| ED | 12% | 1.5% |
| 5yr survival | | |
| LD | 30% | 10.5% |
| ED | 8% | 1.0% |

**Supplemental table e-2.**
Median survival and survival percentages after SCLC diagnosis, as compared to the average life expectancy of SCLC patients in the Netherlands, adjusted for tumor stage. ED- extensive disease, LD-limited disease, SCLC-small cell lung cancer, SCLC-LEMS- LEMS patients with associated small cell lung cancer.

| | LEMS (n=42) | MG (n=464) | Dutch population (n=1742) | p-value (LEMS vs. Dutch population; vs. MG) |
|---|---|---|---|---|
| SF-36 (mean, SD) | | | | |
| Physical functioning | 45.8 (31.1) | 62.2 (30.7) | 83.0 (22.8) | <0.0001; 0.0001 |
| Role physical | 47.6 (43.1) | 54.5 (44.0) | 76.4 (36.3) | <0.0001; 0.50 |
| Bodily pain | 80.7 (25.9) | 72.6 (26.5) | 74.9 (23.4) | 0.27; 0.09 |
| General health | 49.6 (12.4) | 52.7 (14.0) | 70.7 (20.7) | <0.0001; 0.59 |
| Vitality | 56.9 (22.0) | 55.8 (21.3) | 68.6 (19.3) | 0.0005; 0.94 |
| Social functioning | 71.1 (29.2) | 72.4 (26.4) | 84.0 (22.4) | 0.001; 0.94 |
| Role emotional | 79.4 (37.5) | 79.5 (36.0) | 82.3 (32.9) | n.s. |
| Mental health | 79.8 (14.8) | 73.4 (18.0) | 76.8 (17.4) | 0.51; 0.06 |
| Physical composite score | 55.9 (23.1) | 60.5 (23.0) | 76.3 (25.8) | <0.0001; 0.50 |
| Mental composite score | 71.8 (21.6) | 70.3 (20.5) | 77.9 (23.0) | 0.19; 0.91 |

**Supplemental table e-3. HR-QOL domains**

All SF-36 scores for domains as well as composite scores for LEMS, myasthenia gravis and the general Dutch population are reported, as presented in Figure 5. P-values of Tukey's post-hoc test adjusted for multiple-comparison are shown comparing LEMS patients to the general Dutch population and Dutch myasthenia gravis patients; only in case of a significant overall result of a one-way ANOVA.

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