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Accuracy of patient-reported data for an online patient registry of autoimmune myasthenia gravis and Lambert-Eaton myasthenic syndrome

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Abstract

Disorders of the neuromuscular junction (NMJ) comprise a spectrum of rare diseases causing muscle fatigability and weakness, leading to life-long effects on quality of life. We established the Dutch-Belgian registry for NMJ disorders, based on a unique combination of patient- and physician-reported information. Information on natural course, disease burden, prevalence of complications and comorbidity is collected through patient-reported standardized questionnaires and verified using medical documentation. Currently, the registry contains information of 565 Myasthenia Gravis (MG) patients and 38 Lambert-Eaton myasthenic syndrome (LEMS) patients, constituting approximately 25% (MG) and 80% (LEMS) of patients in the Netherlands. This is a very large registry, with the highest participation rate per capita. In addition to confirming many disease characteristics previously described in the literature, this registry provides several novel insights. The reported rate of potentially corticosteroid-related comorbidity, including hypertension, heart disease, osteoporosis and type 2 diabetes was high, emphasizing the need to commence corticosteroid-sparing immune suppressive treatment as soon as possible. The reported rate of other auto-immune diseases is far higher than previously expected: 27% of MG and 38% of LEMS patients, and a surprisingly high number of MG patients (47%) is unaware of their antibody status. In conclusion, this registry provides a valuable collection of information regarding MG and LEMS disease course. Continuous collection of annual follow-up data will provide further longitudinal insights in disease burden, course and treatment effect.

Keywords: Myasthenia gravis; Lambert-eaton myasthenic syndrome; Patient-registry; Natural course; Disease burden.

1. Introduction

National and international patient databases and registries provide large-scale information on various diseases. They are essential for collecting data on the natural course of rare diseases [1–3]. The collection of detailed data on disease course, medication, comorbidity and family history, improves understanding of the disease by both physicians and patients and helps to identify potential novel therapeutic targets. We report the establishment and first results of the Dutch registry for disorders of the neuromuscular junction (NMJ), entailing a spectrum of rare disease entities, which can be due to an acquired autoimmune disease or a congenital genetic defect. The purpose of this registry is to study the epidemiology of patients with Myasthenia Gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndromes (CMS) in the Netherlands and Belgium. Second, the registry will collect longitudinal data on the natural disease course and genetic, environmental and immunological factors that may affect disease course.

MG is an autoimmune disorder (AID) with antibodies against the NMJ resulting in various degrees of muscle fatigability and weakness. All striated muscles can be involved, although the extra-ocular muscles are most commonly affected, giving rise to a fluctuating ptosis

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and diplopia. Antibodies against the acetylcholine receptor (AChR) are present in over 80% of generalized MG patients. In the pure ocular form, AChR antibodies are detectable in nearly 50% of all patients. In approximately 4%, antibodies against the postsynaptic muscle-specific receptor tyrosine kinase (MuSK) are found and in 15% of patients with generalized disease, no serum antibodies are detected [4–6]. Approximately 15% of AChR MG patients has a thymoma, in which case the disease can be classified as a paraneoplastic syndrome [5]. With a prevalence of 1 to 2 per 10.000, MG is considered a rare disease [5].

LEMS is another autoimmune disease affecting the neuromuscular junction, with a prevalence of 2.5 per million [7]. Antibodies against the presynaptic voltage-gated calcium channels (VGCC) are present in 90% of patients [8]. In over 50% of patients, LEMS is a paraneoplastic phenomenon of small-cell lung carcinoma (SCLC) [9]. Clinically, LEMS leads to fluctuating symptoms with proximal muscle weakness, especially in the legs, and autonomic dysfunction [10]. Because of its fluctuating nature, patients are at risk of being misdiagnosed as having MG, although the typical ocular onset of symptoms is rarely seen in LEMS.

The CMS comprehend a spectrum of genetic disorders, usually with an autosomal recessive inheritance pattern. Clinical symptoms commonly develop shortly after birth, but patients with late-onset expression of symptoms have been documented [5]. Symptoms and disease course depend on the target in the NMJ. There are no exact numbers on prevalence, but most reports only describe a few patients or families per mutation, classifying CMS as an ultrarare disease [11,12].

Several MG patient registries have been described [1,13–17]. For some, the data are entered by physicians [1,14,15,17], while other registries are patient-driven [13]. The major advantages of a registry using forms that can be completed online by the patient are that it can quickly reach out to a large number of patients, requires no hospital visit, and is directly available for detailed analysis. However, to obtain high quality data these registries have to be curated and checked for inconsistencies and missing data, preferentially by using the original patient letters from the treating physicians.

We describe the results of the Dutch registry for NMJ disorders with special emphasis on the quality of the patient-reported data and process of data curation.

2. Methods

2.1. Design

The Dutch registry for NMJ disorders is a collaborative initiative of 'Spierziektencentrum Nederland' (the Dutch patient support organization for neuromuscular diseases) and Leiden University Medical Center (LUMC). It was approved by the medical ethical committee of the LUMC and initiated in December 2015. It is an active longitudinal database which collects medical information obtained both from patients and treating physicians. The data is stored in a web-based data management system (Project Manager Internet Server; ProMISe) and managed by the LUMC. Privacy-sensitive data is encrypted through a third party (ZorgTTP). In 2017, the registry was renamed to the Dutch-Belgian registry to include patients from Belgium. For the purpose of this paper, we excluded the Belgian patients because of the currently small number of Belgian participants ($n = 10$, 2%).

2.2. Data collection

Patients can register voluntarily by filling out a written informed consent form and a short information sheet, which includes a request to include contact details of their current treating physician. Both can be download from the registry website [18]. Information about registration is provided on the website, by treating physicians or the patient support organization.

After completion of the registration, participants receive a digital invitation for an online baseline questionnaire (Table 1). A printed version is available upon request. After registration, a request is made to the treating physician for extensive available medical information including information on medical history, antibody status, electromyography (EMG) results and information on thymectomy and thymus pathology. After completion of the baseline questionnaire, participants receive an invitation for a follow-up questionnaire to assess information concerning disease course and newly diagnosed conditions every year When a patient does not complete all items on the questionnaire, these items are classified as missing data.

2.3. Statistics

All analyses were performed using SPSS Statistics 25. Group data are described by mean and standard deviation (±SD). We used unpaired T-tests or Mann-Whitney U tests for comparisons between two groups. Chi-square tests were applied for nominal data. Significance was accepted at $p < 0.05$. Bonferroni correction for multiple testing was applied for subgroup analysis when necessary (3 subgroups α_{altered} 0.017; 5 subgroups α_{altered} 0.01).

3. Results

3.1. Patients characteristics and demographics

On September 20th 2019, the registry contained information on a total of 608 Dutch patients: 335 (55.1%) females and 266 males. Patient characteristics are detailed in Table 2. Given the prevalence of 1,2 per 10.000, about 16–33% of all Dutch MG patients have been enrolled in the registry (17.366.356 inhabitants in the Netherlands on September 20th 2019[18]). Approximately 87% of all Dutch LEMS patients are registered in the database, when assuming a prevalence of 2.5 per million [7]. However, there are indications that the actual prevalence in the Netherlands is higher [19].

Table 1
Items of baseline (left) and follow-up (right) questionnaires.

A. Baseline questionnaire	B. Annual follow-up questionnaire
1a. Form of myasthenic syndrome; MG/ LEMS/ CMS	1. Clinical symptoms during the past year (multiple choice)
b. Age at first symptoms	2. Most limiting symptoms during the past year (multiple choice)
c. Age at diagnosis	3a. New medical conditions diagnosed in the past year (multiple choice)
2. Symptoms previously misdiagnosed	b. Diagnosis of lung cancer‡
3. Auto-antibodies detected? AChR/ MuSK/ VGCC/ other/ none/ unknown	4. Thymectomy in the past year*
4. Clinical symptoms at disease onset (first six months) (multiple choice)	5. Degree of independency in daily activities during the past year
5. Clinical symptoms past three months (multiple choice)	6. Hospital admission due to disease in the past year
6. Most limiting symptoms in the past three months (multiple choice)	7. Admission to intensive care due to disease in the past year
7. Symptoms when disease was at its worst (multiple choice)	8. Intubated due to disease in the past year
8a. Other medical conditions (multiple choice)	9. Received immune globulins for disease in the past year
b. Diagnosis of lung cancer‡	10. Received plasma exchange therapy for disease in the past year
9a. Thymectomy*	12. Use of medication during the past year
b. Age of thymectomy	13. Side-effects of medication
10. Degree of independency in daily activities	14. New medical conditions diagnosed in family in the past year (multiple choice)
11. Hospital admission due to disease	15. Weight
12. Admission to intensive care due to disease	16. Smoking
13. Ever been intubated due to disease	
14. Ever received immune globulins for disease	
15. Ever received plasma exchange therapy for disease	
16. Use of medication	
17. Side-effects of medication	
18. Family history (multiple choice)	
19. Ethnicity	
20. Weight & height	
21. Smoking	

*MG questionnaires only; ‡LEMS questionnaires only.

Table 2
patients characteristics and demographics

Characteristic	Statistic	
Registered patients, n	608	
MG, n (%)	565 (92.9%)	
LEMS, n (%)	38 (6.3%)	
CMS, n (%)	5 (0.8%)	
Mean age in years		
MG, mean ± SD	63.2 ± 15.0	
LEMS, mean ± SD	62.7 ± 10.2	
CMS, median [IQR]	64.4 [44.5-67.1]	
Female gender, %	55.1%	
MG antibody status (medical documentation), n (%)	443 (78.4%)	
AChR	80.4%	
MuSK	3.6%	
LRP4	0.7%	
Seronegative	15.3%	
Missing data, n (%)	122 (21.6%)	
LEMS antibody status (medical documentation), n (%)	33 (86.8%)	
VGCC	81.8%	
Seronegative	18.2%	
Missing data, n (%)	5 (13.2%)	
Completed baseline questionnaire, n (% of registered patients)		
MG	509 (90.1%)	
LEMS	36 (94.7%)	
CMS	4 (80.0%)	
Completed follow-up questionnaire 1 year after registration, n (% of registered patients)		
MG	334 (59.1%)	
LEMS	26 (68.4%)	
CMS	1 (20.0%)	
Prevalence of registered patients per 10.000 Dutch inhabitants‡		
MG	0.33	
LEMS	0.02	
CMS	0.003	
Age at disease onset in years	Female	Male
MG, mean ± SD	41.7 ± 19.6	56.5 ± 13.2**
<50 years	62.1%	24.8%
>50 years	37.9%	75.2%
LEMS, mean ± SD	46.6 ± 13.6	53.2 ± 13.4
<50 years	60.0%	40.0%
>50 years	40.0%	60.0%
Age at diagnosis in years	Female	Male
MG, mean ± SD	44.3 ± 18.9	57.2 ± 13.2**
LEMS, mean ± SD	48.0 ± 13.6	56.6 ± 10.2*
Time between disease onset and diagnosis in years	Female	Male
MG, mean ± SD	2.3 ± 5.5	0.7 ± 1.5**
LEMS, mean ± SD	1.4 ± 1.5	2.6 ± 5.1

‡ 17.366.356 inhabitants on September 20th 2019; *p<0.05; **p<0.001

Two participants declined retrieval of medical information. We retrieved information on antibody status in 78%, medical history in 33% and whether thymectomy was performed from 45% of participants.

All participants received an invitation to complete the baseline questionnaire (Table 1a). A total of 509 MG, 36 LEMS and 4 CMS patients completed the questionnaire (90%, 95% and 80% of all participants, respectively). The mean (±SD) disease duration at the time of completing the baseline questionnaire was 12.6 (±13.3) years. Participants who completed the baseline questionnaire received an invitation to complete a follow-up questionnaire (Table 1b). A total of 334 MG, 26 LEMS and 1 CMS patient responded (59%, 68%, 20%, respectively). The mean (±SD) time between completing the baseline and follow-up questionnaire was 2.0 (±0.6) years. CMS patients were excluded from further analysis because of their small number ($n = 5$).

3.2. Antibodies

Medical documentation on antibody status was available from 78% of all participants with MG (Table 2). Of these, 80.4% were AChR positive, 3.6% MuSK and 15% seronegative. Antibody status was also queried in the baseline questionnaire (Tables 3 and 4). Forty-one percent

Table 3
MG baseline and follow-up questionnaires.

MG characteristics	Statistic
Disease duration in years, mean ± SD	
Baseline questionnaire	12.5 ± 13.2
Follow-up questionnaire 1 year after registration	14.5 ± 12.3
Patient reported antibody status,%	
AChR	41.0%
MuSK	2.8%
AChR and MuSK	0.1%
Seronegative	8.9%
Unsure of antibody status	47.3%
Missing data, n (%)	14 (2.8%)
Initial symptoms in first 6 months of disease,%	
Pure ocular	14.3%
Oculobulbar	6.8%
Generalized	78.8%
Missing data, n (%)	24 (4.7%)
Symptoms when disease at worst,%	
Pure ocular	8.7%
Oculobulbar	5.9%
Generalized	84.9%
Missing data, n (%)	34 (6.7%)
Symptoms in 3 months prior to completing baseline questionnaire,%	
Pure ocular	9.9%
Oculobulbar	7.2%
Generalized	67.6%
No symptoms	14.5%
Missing data, n (%)	9 (1.8%)
Symptoms at follow-up 1 year after registration,%	
Pure ocular	8.4%
Oculobulbar	5.1%
Generalized	73.2%
No symptoms	13.3%
Missing data, n (%)	2 (0.6%)
Pure ocular disease course > 2 years,% of total	5.0%
Pure ocular disease course > 2 years,% of initial ocular	37.3%
Progression after pure ocular disease course > 2 years,% of total	0.9%
Thymectomy,%	52.7%
Time in years between disease onset and thymectomy, mean ± SD	2.6 ± 5.3
Missing data, n (%)	67 (13.2%)
Hospitalization neurology ward due to MG ≥1 time,%	45.4%
Hospitalization ICU due to MG ≥1 time,%	39.5%
Ventilation necessary during ≥1 ICU admission,%	50.7%
Missing data, n (%)	43 (8.4%)
Concomitant AID in medical history,%	26.7%
Missing data, n (%)	38 (7.5%)

Table 4
LEMS baseline and follow-up questionnaires.

LEMS characteristics	Statistic
Disease duration in years, mean ± SD	
Baseline questionnaire	10.7 ± 11.4
Follow-up questionnaire 1 year after registration	12.7 ± 12.6
Patient reported antibody status,%	
VGCC	52.8%
Seronegative	11.1%
Unsure of antibody status	36.1%
Missing data, n (%)	0
Initial symptoms in first 6 months of disease,%	
Pure ocular	2.8%
Oculobulbar	0%
Generalized	97.2%
Autonomic symptoms	84.8%
Missing data, n (%)	3 (8.3%)
Symptoms when disease at worst,%	
Pure ocular	0%
Oculobulbar	0%
Generalized	100%
Autonomic symptoms	87.5%
Missing data, n (%)	4 (11.1%)
Symptoms in 3 months prior to completing baseline questionnaire,%	
Pure ocular	2.8%
Oculobulbar	0%
Generalized	94.3%
Autonomic symptoms	88.2%
No symptoms (excl. autonomic symptoms)	2.8%
No symptoms (incl. autonomic symptoms)	0%
Missing data, n (%)	2 (5.6%)
Symptoms at follow-up 1 year after registration,%	
Pure ocular	0%
Oculobulbar	0%
Generalized	80.8%
Autonomic symptoms	72.0%
No symptoms (excl. autonomic symptoms)	19.2%
No symptoms (incl. autonomic symptoms)	8.0%
Missing data, n (%)	1 (2.8%)
Diagnosis of lung cancer,%	8.6%
Missing data, n (%)	1 (2.8%)
Hospitalization neurology ward due to LEMS ≥1 time,%	22.2%
Hospitalization ICU due to LEMS ≥1 time,%	18.2%
Ventilation necessary during ≥1 ICU admission,%	33.3%
Missing data, n (%)	3 (8.3%)
Concomitant AID in medical history,%	38.2%
Missing data, n (%)	2 (5.6%)

of MG participants reported having AChR antibodies, 2.8% reported having MuSK antibodies and 8.9% reported being seronegative. Remarkably, almost half of the MG participants did not know their antibody status.

A documented antibody status was available from 87% of participants with LEMS (Table 2). VGCC antibodies were present in 82%, 18% was seronegative. In the baseline questionnaire, 53% reported VGCC antibodies, 11% to be seronegative and 36% didn't know (Table 4).

3.3. Age at disease onset and diagnosis

Female MG patients were significantly younger at disease onset compared to male MG patients ($p < 0.001$). This holds true for both AChR MG patients ($p < 0.001$) and patients with missing data on antibody status ($p < 0.001$) (Fig. 1). The same distribution was found in LEMS, but this did not reach significance ($p = 0.16$, Table 2).

Age at time of diagnosis was significantly lower for female MG ($p < 0.001$) and LEMS patients ($p = 0.042$) compared to males. The mean (±SD) time from disease onset to diagnosis was significantly longer for females compared to male MG patients: 2.3 (±5.5) vs. 0.7 (±1.5) years ($p < 0.001$), again the trend was similar in LEMS, but again this was not

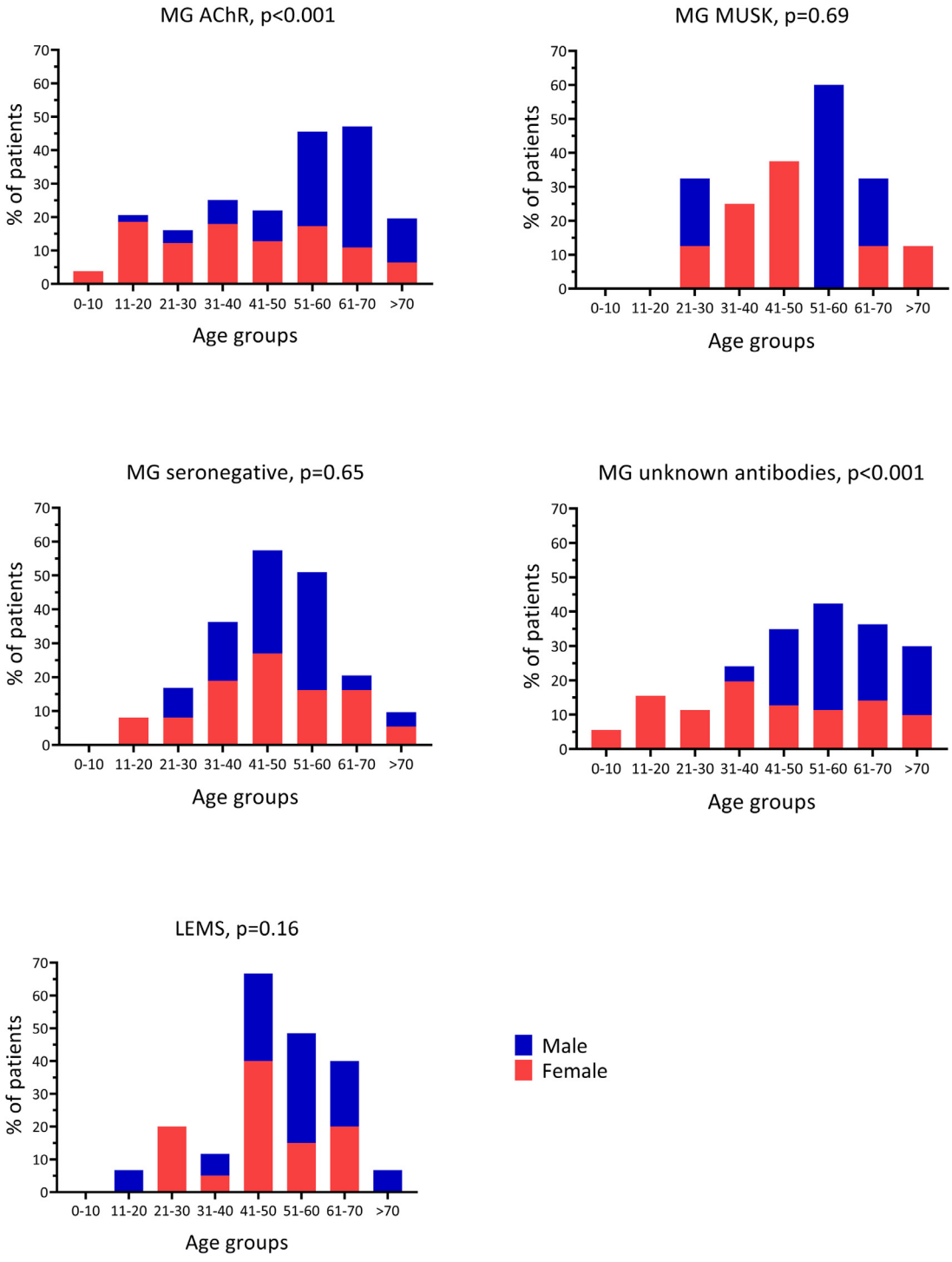

Fig. 1. Age at disease onset, MG subgroups and LEMS. *P*-values represent female-male differences.

significant, possibly due to the low number of patients ($n = 16$ and 22, respectively).

3.4. Signs and symptoms

The mean (±SD) disease duration for MG patients at the time of completing the baseline questionnaire was 12.5 (±13.2) years; 85% had a disease duration longer than two years. In the baseline questionnaire, most MG patients (79%) reported generalized symptoms within the first six months of the disease course (Table 3). Pure ocular symptoms were present in 14% and isolated oculobulbar symptoms in 6.8% within the first six months. When the disease was at its worst, 85% of all patients had generalized symptoms and 8.7% experienced only ocular symptoms. In the three months prior to completing the baseline questionnaire, 15% of the MG patients reported having no symptoms. Of all MG patients with a disease duration of two years or longer, 5.0%

reported a pure ocular disease course without any bulbar or generalized weakness. This corresponds with 25 (37%) out of 67 initial ocular patients. At the first follow-up questionnaire, three (0.9%) MG patients reported progression of symptoms to bulbar or generalized weakness after an initial pure ocular disease course and a disease duration of more than years at the baseline questionnaire.

Only one LEMS patient had pure ocular symptoms during the first 6 months of the disease, all others (97%) had generalized symptoms. Autonomic symptoms, including constipation, sicca symptoms and erectile dysfunction are frequent among LEMS patients: 85% reported at least one autonomic symptom in the initial six months and 88% when the disease was at its worst. All patients reported having clinical symptoms in the three months prior to the baseline questionnaire. Only one patient reported autonomic symptoms without muscle weakness. At the first follow-up questionnaire, more than 80% of LEMS patients reported generalized symptoms during the previous year. Surprisingly, 19% ($n=5$) reported no clinical symptoms or only autonomic symptoms. Of these five LEMS patients without clinical symptoms, only one patient did not use any medication. All other patients used symptomatic medication (3,4-DAP and/or pyridostigmine); one patient used corticosteroids and one patient received plasma-exchange therapy in the previous year.

The most limiting symptoms during the past three months are displayed in Fig. 2a–c. The top three most limiting symptoms in the AChR MG group were fatigue (35%), leg weakness (15%) and diplopia (13%). For MuSK MG patients the most limiting symptom was fatigue (46%) followed by weakness of the hands (15%). Leg weakness (63%), fatigue (20%) and incontinence (5.7%) were the most limiting symptoms for LEMS patients.

Medical files with documentation of initial symptoms were available for 162 (29%) MG patients and 9 (24%) LEMS patients. According to documentation at the time, 41% of MG patients presented with pure ocular symptoms, 24% oculobulbar and 36% started with generalized symptoms. When comparing the initial symptoms in the medical file with the patient-reported questionnaire, the medical documentation reported fewer or different symptoms in 52% of MG patients. In LEMS, 100% started with generalized symptoms. This was similar to what the patients reported in the questionnaires.

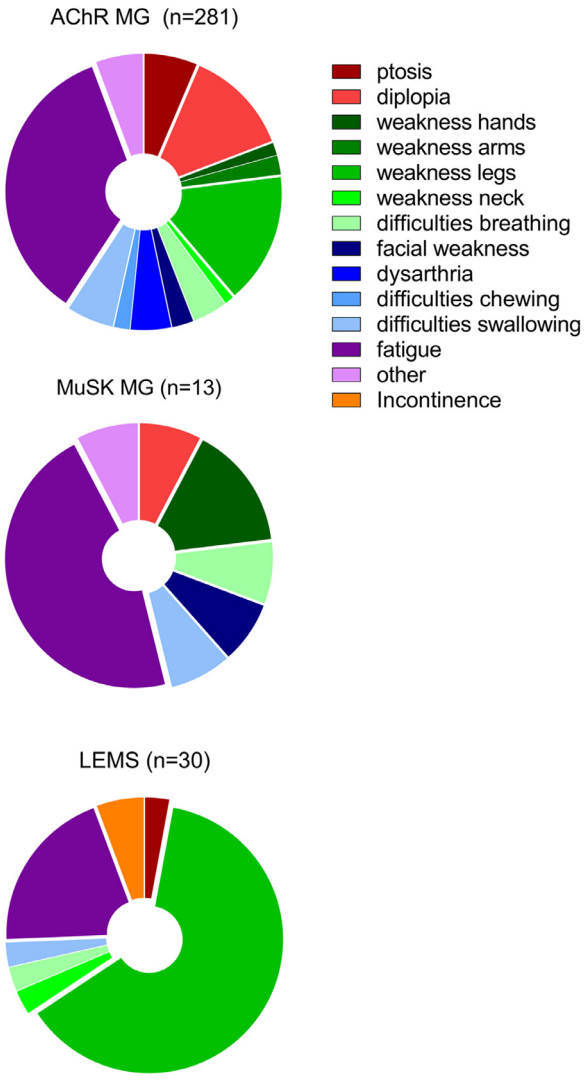

Fig. 2. Most limiting symptom in past 3 months.

3.5. Medication

The most frequently used medication is pyridostigmine (74%) in MG and 3,4-diaminopyridine (100%) in LEMS. Of MG patients, 8.4% did not use any disease specific medication in the three months prior to completing the baseline questionnaire and 22% used only pyridostigmine (Fig. 3). A form of immunomodulating therapy was used by 69% of the MG patients; most frequently steroids (46%) and azathioprine (37%). Corticosteroids as a mono-immunosuppressive therapy, with or without pyridostigmine, were used by 13%; azathioprine was used by 11%. A combination of steroids and a second immunomodulating therapy was used by 31%, most commonly corticosteroids and azathioprine. Intravenous immunoglobulins were used by 15% of MG patients, compared to 6.5% of LEMS patients. Of LEMS patients, 71% used a combination of 3,4-diaminopyridine and pyridostigmine. Immunomodulating therapy was used by 49% of LEMS patients. The most frequently used therapies were corticosteroids (36%) and azathioprine (16%).

3.6. Comorbidity

Fig. 4 shows the patient-reported comorbidities. A documented medical history provided by the treating physician was available for 198 (33%) patients in our cohort. Cardiovascular, potentially corticosteroid-related comorbidities were reported frequently: 47% of both MG and LEMS patients. The highest prevalences were for hypertension (MG 35%; LEMS 31%) and heart diseases (including heart failure and arrhythmias) (MG 18%; LEMS 25%). Type 2 diabetes was reported by 11% of MG patients and 2.8% of LEMS patients. Fig. 5 shows

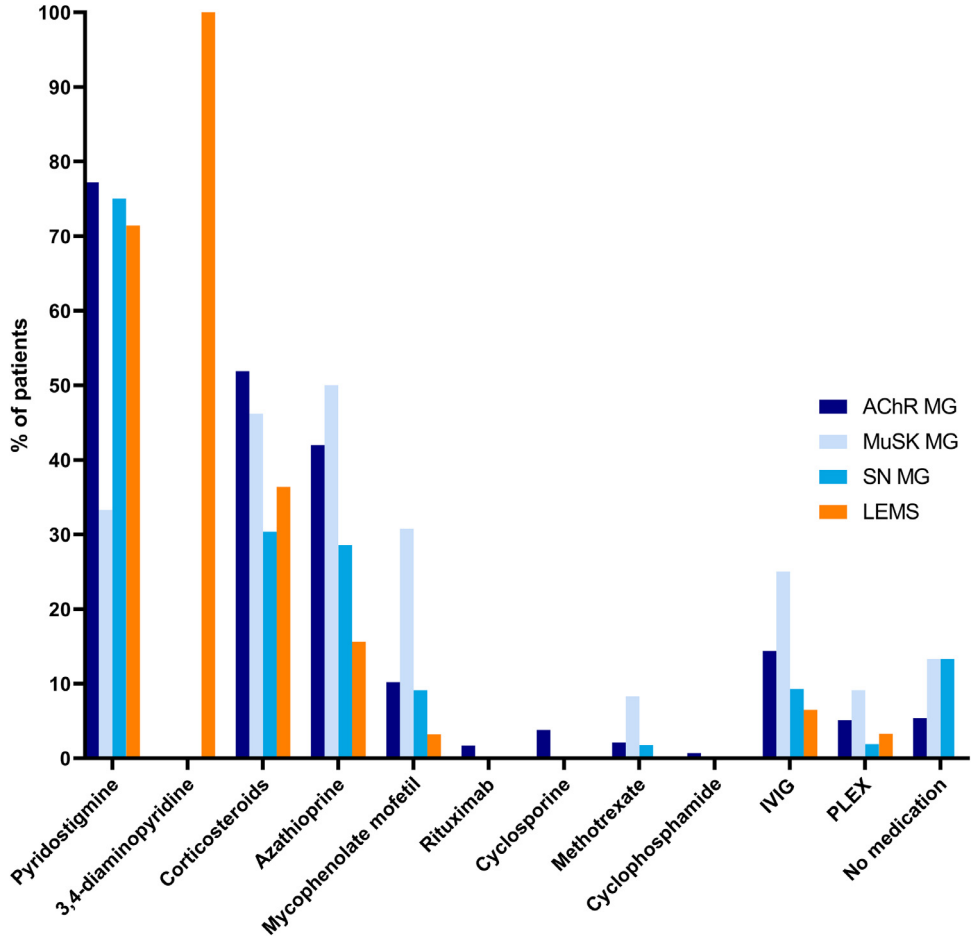

Fig. 3. Patient-reported medication use. Abbreviations: PLEX: plasma-exchange therapy; IVIG: intravenous immunoglobulins.

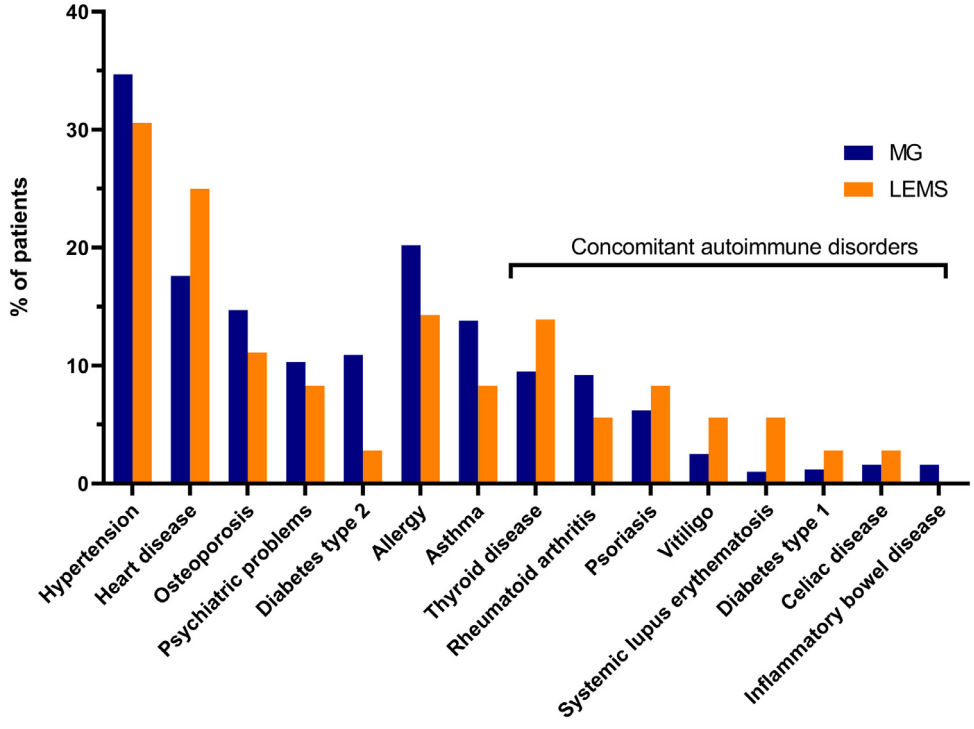

Fig. 4. Patient-reported comorbidity. Small-cell lung cancer and thymoma not displayed in figure.

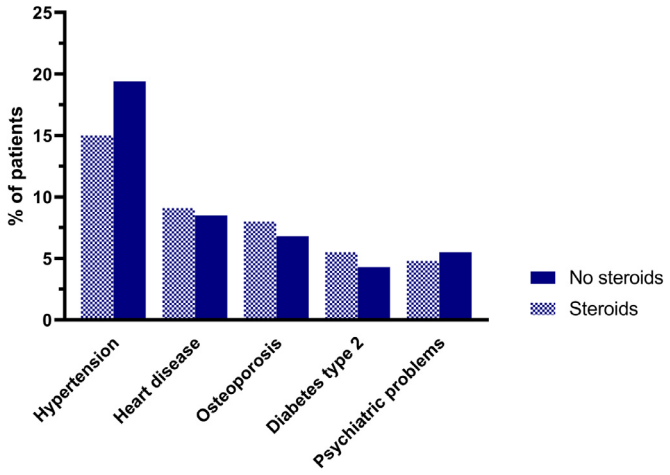

Fig. 5. Prevalence of potential side-effects of corticosteroid use, all patients.

the differences in these comorbidities between patients currently on corticosteroids (or during the past three months) compared to patients without corticosteroids for at least three months. Heart diseases were significantly more prevalent in patients currently using corticosteroids: $p=0.039$. There was a non-significant trend towards a higher prevalence of type 2 diabetes and osteoporosis in those using corticosteroids compared to patients without steroids ($p=0.065$; $p=0.242$). No differences were found in the prevalence of hypertension and psychiatric problems ($p=0.553$; $p=0.684$). A concomitant AID was reported by 27% of MG patients and 38% of LEMS patients (Tables 2 and 3, Fig. 4). The most prevalent second AID was thyroid disease (MG 8.5%; LEMS 14%) The prevalence for a second AID in the physician-provided medical history was 32% in MG and 47% in LEMS. Thyroid disease was the most prevalent AID in both. Lung cancer was reported by 3 (8.6%) of 35 LEMS patients, in accordance with information from their medical files. Other tumours that were reported in the medical documentation were as following: sigmoid adenoma, adenocarcinoma colon and pulmonary neuro-endocrine tumor.

A thymectomy was performed in 233 (53%) out of a total of 442 MG patients, 67 patients (13%) did not complete this item of the questionnaire (Table 3). Of the responding AChR MG patients 54% reported a previous thymectomy, 36% of the responding MuSK MG patients and 30% of the responding seronegative MG patients. The mean (±SD) time between disease onset and thymectomy was 2.6 (±5.3) years. Time from disease onset to thymectomy after publication of the large thymectomy trial of the MGTX study group in 2016[20] was 3.4 (±7.6) years, which was not significantly different than before the trial: 2.4 (±4.7) years ($p=0.405$). Unfortunately, a histological report of the thymus was available in only 26% of all thymectomies. Of all available reports, 60% noted the presence of a thymoma and 20% described normal findings.

3.7. Hospitalization

More MG patients reported having been admitted to a Neurology ward at least once due to their disease compared to LEMS patients, 46% vs 22% ($p=0.007$, Tables 3 and 4). Within MG subtypes, seronegative patients reported significant less admissions to a Neurology ward (16%) compared to both AChR MG (52%, $p < 0.001$) and MuSK MG (47%, $p=0.012$). There was no difference in admissions between AChR MG and MuSK MG ($p=0.674$).

Intensive Care Unit (ICU) admissions were also reported more frequently by MG patients, 40% compared to 18% in LEMS ($p=0.015$). There was no difference between the percentage of MG and LEMS patients who reported to have been ventilated during an ICU admission (51% vs. 33%, $p=0.405$). When focusing on MG subtypes, there was no differences between AChR MG and MuSK MG in ICU admissions (40% vs 62%, $p=0.121$) nor ventilation (22% vs 40%, $p=0.184$). Seronegative patients were significantly less frequently admitted to an ICU (26%) compared to MuSK MG ($p=0.015$) but not to AChR MG ($p=0.052$). Ventilation during an ICU admission was also less frequently reported by seronegative patients (8%) compared to AChR MG ($p=0.038$) and MuSK MG ($p=0.009$).

4. Discussion

Our database includes up to one third of the Dutch MG patients and the majority of the Dutch LEMS patients, which makes it a large and valuable dataset. The complementary combination of patient-reported and physician-reported information helps to study the quality of the patient-reported data and the process of data curation. This is important, especially since patient-reported data is prone to subjectivity and (recall) bias is inevitable [13].

4.1. Validity of data

Despite the fact that medical information obtained from treating physicians was often incomplete, we managed to gather a documented antibody status of 476 (79%) MG and LEMS patients. Interestingly, a large number of patients was unable to report their own antibody status, suggesting a need for patient education. The age-distribution in the subgroup with missing data on antibody status resembles the pattern of the AChR MG subgroup (Fig. 1), suggesting that the majority of these patients are AChR positive. We found no large discrepancies between the patient-reported and the physician-reported antibody status. Only 7 (2.3%) AChR MG patients reported being seronegative, 5 (1.6%) AChR MG patients reported having MuSK antibodies and 3 (5%) seronegative patients reported that AChR antibodies had been detected. In the group of LEMS patients, 2 (8%) of the VGCC positive patients reported being seronegative. In comparison, a recent publication on a large MG patient registry found that patients were unsure or gave no response on AChR or MuSK antibody status in 67% vs. 86% [13]. This

percentage is higher than the patient-reported numbers in our cohort, but both studies suggest that patient education can be improved.

Medical documentation on the nature of first symptoms was available for 171 (28%) patients. In more than half of MG patients there was a discrepancy between the reported symptoms in the questionnaires and the symptoms recorded in the medical file at the time of diagnosis. This may be explained in part by the fact that the questionnaire queried symptoms within the first six months of the disease, whereas medical reports at the time of diagnosis usually describe only the very first symptoms, covering a shorter time period. Alternatively, the results from the questionnaire may have been influenced by recall bias, or the description of symptoms in the initial report may have been incomplete. Ocular symptoms are the presenting symptom in 85% of all MG patients, but 20% will progress to generalized symptoms within one month and 48% within six months [21]. If pure ocular symptoms are present after two years of onset, the disease will most likely remain restricted to the eyelids and extra-ocular muscles. Indeed, we found only three MG patients (0.9%) who reported generalized symptoms in the follow-up questionnaire after having reported a pure ocular course and a disease duration of more than two years at the baseline questionnaire. However, this number is likely an underestimation as it does not include patients who developed generalized symptoms at least two years after disease onset, but before the first questionnaire.

We found a pure ocular MG (OMG) disease course in 5.0% of our entire MG cohort, which is lower than what could be expected based on previous research [21,22]. One explanation is that our cohort may have an overrepresentation of more severe MG patients because of the voluntary nature of the registry. Secondly, the origin of some generalized symptoms is multi-interpretable, especially weakness in hands, arms or legs, and some patients might have attributed these symptoms to their MG. The distribution of weakness in our LEMS patients follows previously reported patterns [10]. Almost all patients started with limb weakness, predominantly legs, and all patients had generalized symptoms when the disease was at its worst.

The patient-reported prevalence of a second AID was comparable to the physician-reported prevalence. We found that in 22 (5.9%) patients, a second AID was reported by patient, but was not listed in their medical information provided by their physician. In the general population the prevalence of AIDs is estimated between 7.6–9.4% and many autoimmune diseases are associated with AID co-occurrence [23]. Surprisingly, both the patient- and physician-reported rate of a second AID in our cohort is much higher than previously stated in literature (approximately 15% for MG and 20% for LEMS) [24–26]. We did not collect original data on laboratory results or ancillary tests concerning this AID for verification. An unknown number of cases of reported thyroid disease might in fact not be autoimmune mediated but have another etiology. Importantly, a concomitant AID is a prognostic factor for exacerbations and emergency treatments, especially in combination with late-onset MG (>50 years of age) [27].

The reported prevalence of cardiovascular comorbidities (e.g., hypertension, type 2 diabetes) was very high. Additionally, a recent publication showed that 41% of MG patients was overweight and 21% had a body mass index (BMI) corresponding with obesity (BMI > 30) [28]. Corticosteroids are likely to contribute to gain weight. Second, a decreased level of physical activity caused by their disease [28,29] could also be a contributing factor in the development of cardiovascular diseases. In combination with reduced physical activity, these comorbidities pose a serious health risk for patients. Corticosteroid use should therefore be limited and steroid-sparing treatment should be commenced as soon as possible. In addition adequate patient education on the risk of long term corticosteroid use, prevention and treatment is important [30].

The prevalence of SCLC in LEMS has previously been estimated to be around 50% [9]. Given the short life expectancy of tumor-associated LEMS it is not surprising that the prevalence of LEMS patients with lung cancer was only 8.6% in our study.

Data on pathology after thymectomy is inconclusive. A pathology report was received in only 26% of patients who underwent a thymectomy. The major overrepresentation of thymomas (60%) is probably due to the fact that normal findings or hyperplasia are less likely to be reported in the medical file.

4.2. Treatment and disease impact

Thymectomy with prednisone compared to prednisone alone has been proven beneficial in non-thymomatous AChR MG patients with a disease duration up to five years [20,31]. Thymectomy may also be considered in seronegative MG patients with generalized symptoms if immunosuppressive treatment fails. There is no indication for thymectomy in patients with MuSK, LRP4 or agrin antibodies [32,33]. In our cohort, 53% of 443 MG patients reported a previous thymectomy with a mean (±SD) disease duration of 2.5 (±5.3) years. The majority of these patients were AChR positive or their antibody status was unknown. Four out of 11 MuSK positive patients (36%) reported a previous thymectomy, which were performed in 1983 and 1993, before MuSK antibodies were identified [34].

Almost 74% of MG patients used pyridostigmine in the three months prior to completing the baseline questionnaire, which should be part of the initial treatment of MG, according to the international consensus guideline [32].

Only 22% MG patients were on monotherapy pyridostigmine. Interestingly, 72% of these experienced generalized symptoms during the past three months, although international guideline advises to start immunomodulating therapy (steroids or non-steroids) in all patients who

have not met treatment goals after an adequate trial of pyridostigmine [32]. This finding underlines the importance of an advising role for specialized neuromuscular centers. When immunomodulating therapy is started, steroids and azathioprine are the most commonly prescribed medications, consistent with national and international treatment recommendations.

Half of MG patients and more than 20% of LEMS patients have been admitted to a Neurology ward at least once during their disease course. Publications on admissions related to MG are scarce. Recently, a Finnish study reported on hospital admissions over a 10 year time-period with MG as primary diagnosis or MG as additional diagnosis with a primary infection [35] and found that approximately 54% of the Finnish MG population has been hospitalized at least once because of their MG. This is comparable with the results reported here. Although MuSK patients would seem to be more at risk of an MG crisis because cranial and bulbar muscles are often more severely affected [5], we did not find a difference between MuSK and AChR MG in admissions to a Neurology ward, intensive care unit or the need for ventilation. The rate of ventilatory support in MuSK MG is similar to previous results: one third to half of the patients [36].

A remarkable finding is that the rate of admissions due to MG have not diminished, but increased over time, whereas hospital admission for other autoimmune diseases, such as multiple sclerosis (MS) has decreased [35–38], despite an increasing prevalence of MS. The increasing available treatment options for MS compared to MG have been suggested as a possible explanation for this difference [35]. Second, intravenous treatment for MG with immune globulins or plasmapheresis often require hospitalization.

Currently, the registry does not provide longitudinal data on admission rates in the Netherlands, but annual follow-up questionnaires should provide future insights.

4.3. Limitations

Limitations of our study include different forms of potential bias: first, selection bias is likely, due to the voluntary nature of the registry. This could lead to an overrepresentation of more severe patients. Second, patient-reported questionnaires with retrospective questions are susceptible to recall bias. For example, patients are asked about their symptoms within the first six months of disease, which was on average 12.6 (±13.3) years ago at the time of the questionnaire. Another limitation is that medical records received from treating physicians were often incomplete. We managed to gather medical information from treating physicians on antibody status in 79%, but medical history in only 33% and information on a previously performed thymectomy in 45% of patients. During their disease course, patients are often treated in more than one hospital. This could be an explanation for the incomplete medical file provided by the treating physician.

5. Conclusion

This registry provides a valuable collection of information regarding the disease course of Dutch MG and LEMS patients. The large number of participants demonstrates the willingness of patients to be actively involved in scientific efforts to better understand their disease. The unique combination of patient- and physician-reported information enables validation and confirms the reliability of patient-reported data. The reported rate of other auto-immune diseases is far higher than previously expected: 27% of MG and 38% of LEMS patients. Second, the reported rate of other comorbidities, like hypertension and type 2 diabetes, is higher than in the general population. Current clinical practice could be improved by informing patients not only of their own antibody status but also to provide adequate information on the risk of long term steroid use, and prevention and treatment of cardiovascular comorbidities. The continuous efforts to obtain annual follow-up data through questionnaires will provide further longitudinal insights in disease burden, course and treatment effect.

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