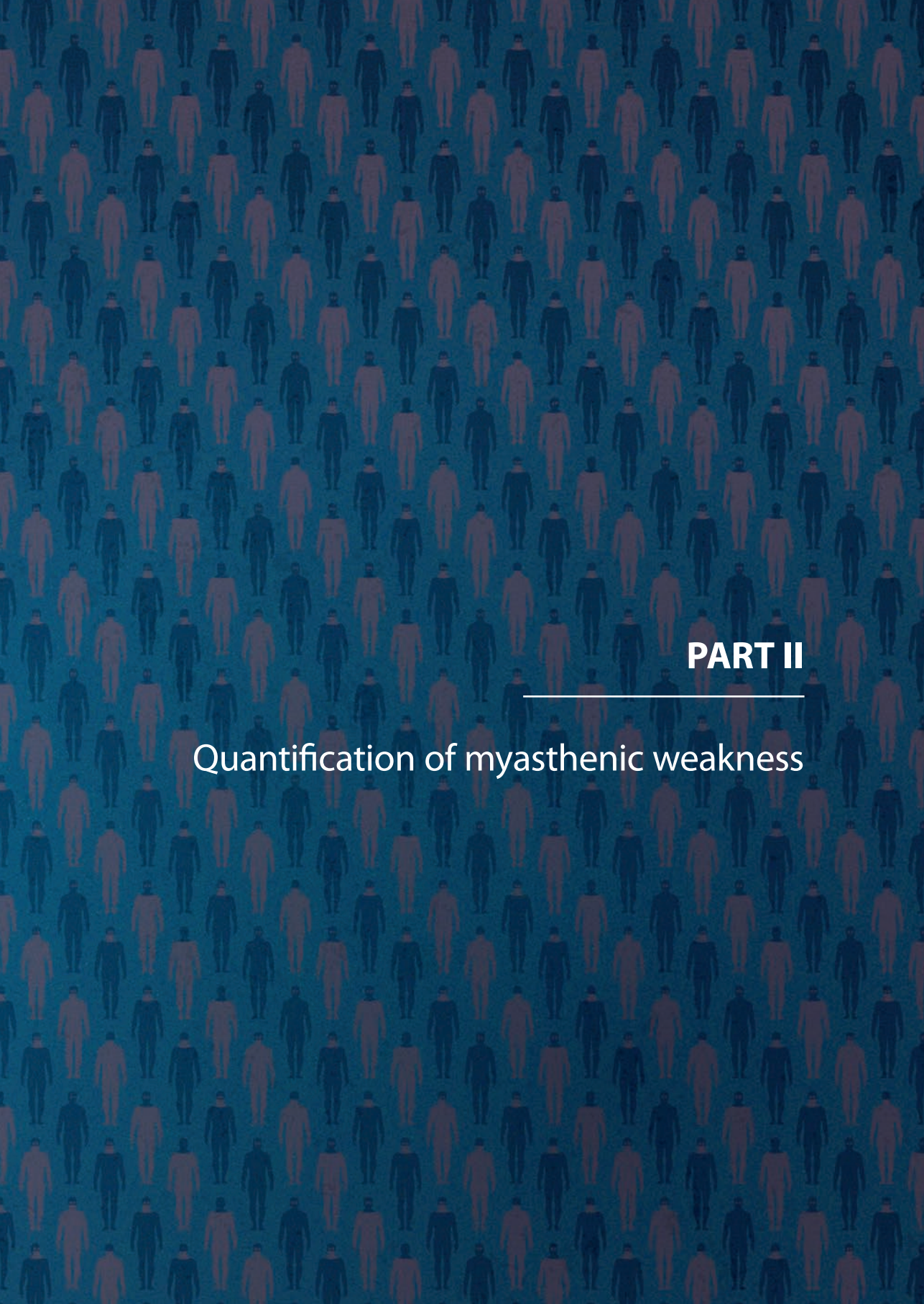
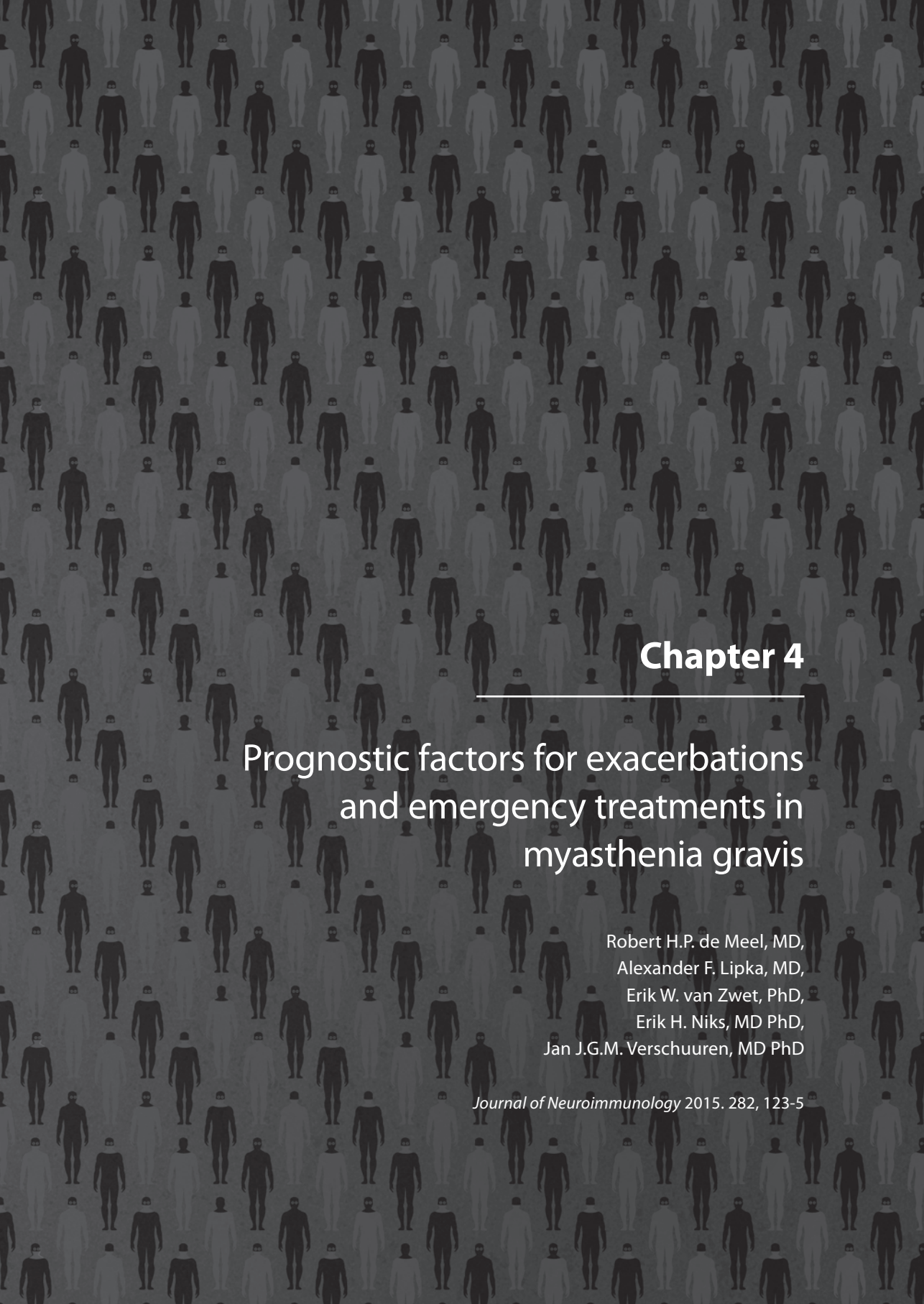
Autoimmune myasthenia gravis : the impact of heterogeneous patterns of muscle weakness on outcome measures and diagnosis

Meel, R.H.P. de



PART II

Quantification of myasthenic weakness



Chapter 4

Prognostic factors for exacerbations and emergency treatments in myasthenia gravis

Robert H.P. de Meel, MD,
Alexander F. Lipka, MD,
Erik W. van Zwet, PhD,
Erik H. Niks, MD PhD,
Jan J.G.M. Verschuuren, MD PhD

Journal of Neuroimmunology 2015. 282, 123-5

ABSTRACT

Background

Disease course in myasthenia gravis (MG) patients is highly variable. Prognostic factors that identify patients at risk for a more severe disease course would be helpful in clinical practice.

Methods

We investigated MG patients under treatment at our university medical center between 1993 and 2013. The impact of baseline characteristics on the occurrence of exacerbations and the necessity of emergency treatments were investigated using multiple logistic regression analysis and log-rank tests for our Kaplan-Meier survival curves.

Results

We included 96 MG patients. Late age at onset (LOMG, ≥50 years) was associated with a higher risk of an exacerbation (odds ratio [OR] = 9.33, 95% confidence interval [CI] = 2.43-35.87; $p = 0.001$) and the necessity of an emergency treatment within 3 years (OR = 5.25, 95% CI = 1.21-22.80; $p = 0.027$). The presence of additional autoimmune diseases (AID) in the patient was associated with a higher risk of an exacerbation (OR = 4.03, 95% CI = 1.09-14.85; $p = 0.036$). Patients with both LOMG and an additional AID had a markedly higher risk of an exacerbation (OR = 47.00, 95% CI = 6.49-340.65; $p < 0.001$) and the necessity of an emergency treatment (OR = 26.11, 95% CI = 4.12-165.55; $p = 0.001$) compared to early-onset patients without additional autoimmune diseases.

Conclusions

Late-onset MG and the presence of additional autoimmune diseases were associated with a higher risk of exacerbations of MG and the necessity of emergency treatments.

INTRODUCTION

Myasthenia gravis (MG) is characterized by fatigability and fluctuating muscle weakness of extraocular and skeletal muscles. The clinical course of MG is highly variable, ranging from stable disease or remission to the occurrence of several exacerbations over time. Previous studies have mainly focused on prognostic factors for remission. However, prognostic factors for exacerbations, myasthenic crises and emergency treatments could also be useful to the clinician for predicting the course of the disease. These outcome measures can be used in order to better predict which patients are at risk for a more severe and debilitating disease course. We investigated the association between baseline clinical features and the risk of exacerbations and emergency treatments in 96 MG patients.

METHODS

Patients

We investigated MG patients under treatment at our university medical center between 1993 and 2013 for whom follow-up of at least 3 years was available. Myasthenia gravis was defined as the combination of clinically confirmed fluctuating muscle weakness with autoantibodies to the acetylcholine receptor (AChR MG) or muscle-specific kinase (MuSK MG). Seronegative myasthenia gravis (SNMG) was defined as a similar clinical presentation in combination with abnormal decrement (at least 10%) during low-frequency repetitive nerve stimulation, increased jitter in single-fiber EMG testing or a positive neostigmine test.[1] All patients included in this study gave informed consent.

Baseline Characteristics

Baseline variables included in this study were sex, age at onset of first symptoms below 50 years or older, MGFA clinical classification at the first visit in our center, presence of one or more additional autoimmune disease(s) (AID), presence of acetylcholine receptor (AChR) antibodies, thymectomy and presence of thymoma in the patient history. These variables were chosen based on previous prognostic studies, potential clinical relevance and reliability with which these data could be analyzed retrospectively.[1-6]

Endpoints

Primary endpoint was the occurrence of one or more exacerbation(s) within 3 years of follow-up. An exacerbation was defined as a clinical deterioration of MG that required starting with or an increase of at least 20 mg of prednisone or led to an emergency treatment. An emergency treatment was defined as the administration of intravenous immunoglobulins, plasmapheresis or mechanical ventilation. In order to define the most severe subgroup of

MG patients that had an exacerbation, the necessity of one or more emergency treatment(s) within 3 years of follow-up was also investigated as a separate secondary endpoint.

Statistical Analysis

A multiple logistic regression analysis was performed to assess the impact of baseline variables on all endpoints. We used Firth logistic regression to assess the significance of the variable 'AChR antibodies' for the secondary endpoint, since none of the AChR antibody-negative patients had required an emergency treatment, prohibiting the inclusion of this variable in a standard multiple logistic regression model.[7] We omitted this variable from further consideration, as it was not significant in the Firth logistic regression and had no impact on the primary endpoint.

The variables that were shown to be significant in the first analyses were included in a second multiple regression model in which their two-way interactions were included. Kaplan-Meier survival curves were plotted to illustrate the differences in course of the disease over time. To evaluate the differences between the curves a log-rank test was performed. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI). *P*-values lower than 0.05 were considered significant. Statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY) and GraphPad Prism version 6.02 (GraphPad Software Inc., San Diego, CA).

RESULTS

We included 96 patients with MG. Baseline characteristics of the patients, as well as the number of patients with an exacerbation or an emergency treatment within 3 years are shown in table 1.

Late-onset MG (LOMG) was independently associated with a higher risk of an exacerbation within 3 years (odds ratio [OR] = 9.33, 95% confidence interval [CI] = 2.43-35.87; $p = 0.001$). Presence of another AID, in addition to MG, was also independently associated with a higher risk of an exacerbation (OR = 4.03, 95% CI = 1.09-14.85; $p = 0.036$). The most frequently observed additional autoimmune diseases were thyroid disease ($n = 8$), psoriasis ($n = 4$) and SLE ($n = 3$). Some patients had more than one additional autoimmune disease. Outcomes for the first endpoint are reported in table 2.

Table 1. Baseline characteristics of 96 patients with MG and the number of patients with an exacerbation and the necessity of an emergency treatment within 3 years after presentation in our university medical center are shown. Data are presented as number of patients (%) for categorical variables and as mean ± SD for continuous variables.

		Exacerbations <3 years	**Emergency treatments <3 years**
Age, y	56.4 ± 19.7		
Age at onset, y	41.6 ± 20.1		
<50	62 (65)	5 (8)	4 (7)
≥50	34 (35)	16 (47)	10 (29)
Sex			
Female	61 (64)	9 (15)	5 (8)
Male	35 (36)	12 (34)	9 (26)
Disease duration, y	14.6 ± 11.7		
Antibodies			
AChR antibodies	85 (89)	20 (24)	14 (17)
MuSK antibodies	1 (1)	0 (0)	0 (0)
Seronegative MG	10 (10)	1 (10)	0 (0)
Additional AID			
Yes	20 (21)	8 (40)	6 (30)
No	76 (79)	13 (17)	8 (11)
MGFA at baseline			
0	11 (11)	2 (18)	2 (18)
1	34 (35)	7 (21)	2 (6)
2	32 (33)	4 (13)	3 (9)
3	14 (15)	5 (36)	5 (36)
4	3 (3)	1 (33)	0 (0)
5	2 (2)	2 (100)	2 (100)
Thymectomy			
Yes	23 (24)	4 (17)	4 (17)
No	73 (76)	17 (23)	10 (14)
Histology			
No abnormalities	15 (65)	2 (13)	2 (13)
Thymus hyperplasia	2 (9)	0 (0)	0 (0)
Thymoma	6 (26)	2 (33)	2 (33)

Abbreviations: AChR = acetylcholine receptor; MuSK = muscle-specific kinase; AID = autoimmune disease(s) MGFA = Myasthenia Gravis Foundation of America.

Table 2. Results of the first and second, subgroup-based, logistic regression for the occurrence of an exacerbation within 3 years are shown. The subgroups were defined by the variables age at onset and additional AID. Data are presented as number of patients (%) and OR (95% CI). The category or subgroup with OR = 1 was used as reference group.

Exacerbations	No. of patients	No. of patients with ≥1 exacerbation(s)	OR (95% CI)	*p* Value
Sex				
Female	61	9 (15)	1	
Male	35	12 (34)	1.78 (0.54-5.89)	0.345
Age at onset, y				
<50	62	5 (8)	1	
≥50	34	16 (47)	9.33 (2.43-35.87)	0.001
MGFA at first visit				
≤1	43	10 (23)	1	
>1	53	11 (21)	1.56 (0.48-5.12)	0.463
Additional AID				
No	76	13 (17)	1	
Yes	20	8 (40)	4.03 (1.09-14.85)	0.036
AChR antibodies				
No	11	1 (9)	1	
Yes	85	20 (24)	2.02 (0.21-19.58)	0.543
Thymectomy				
No	73	17 (23)	1	
Yes	23	4 (17)	0.77 (0.10-5.99)	0.802
Thymoma				
No	90	19 (21)	1	
Yes	6	2 (33)	1.64 (0.10-26.12)	0.728
Subgroups				
EOMG & AID –	50	3 (6)	1	
EOMG & AID +	12	2 (16)	3.13 (0.46-21.27)	0.242
LOMG & AID –	26	10 (39)	9.79 (2.39-40.08)	0.002
LOMG & AID +	8	6 (75)	47.00 (6.49-340.65)	< 0.001

Abbreviations: EOMG = early-onset MG; LOMG = late-onset MG; MGFA = Myasthenia Gravis Foundation of America; AID = autoimmune disease(s); AID – = no additional autoimmune disease(s); AID + = additional autoimmune disease(s); AChR = acetylcholine receptor; OR = odds ratio; CI = confidence interval.

LOMG also independently increased the risk of the necessity of an emergency treatment within 3 years (OR = 5.25, 95% CI = 1.21-22.80; $p = 0.027$). The relationship between an additional AID and the occurrence of an emergency treatment showed a similar OR as for an exacerbation, although this failed to reach statistical significance (OR = 3.64, 95% CI = 0.94-14.11; $p = 0.062$). For the other baseline variables no significant differences were found. All outcomes for the second endpoint are reported in supplement 1.

LOMG in combination with an additional AID was strongly associated with a higher risk of an exacerbation within 3 years as compared to early-onset MG without an additional AID (OR = 47.00, 95% CI = 6.49-340.65; $p < 0.001$). The combination also strongly increased the risk of an emergency treatment (OR = 26.11, 95% CI = 4.12-165.55; $p = 0.001$). Four subgroups can be defined using combinations of these two variables. Survival curves for the time courses without exacerbations and emergency treatments of these four subgroups are illustrated in figure 1.

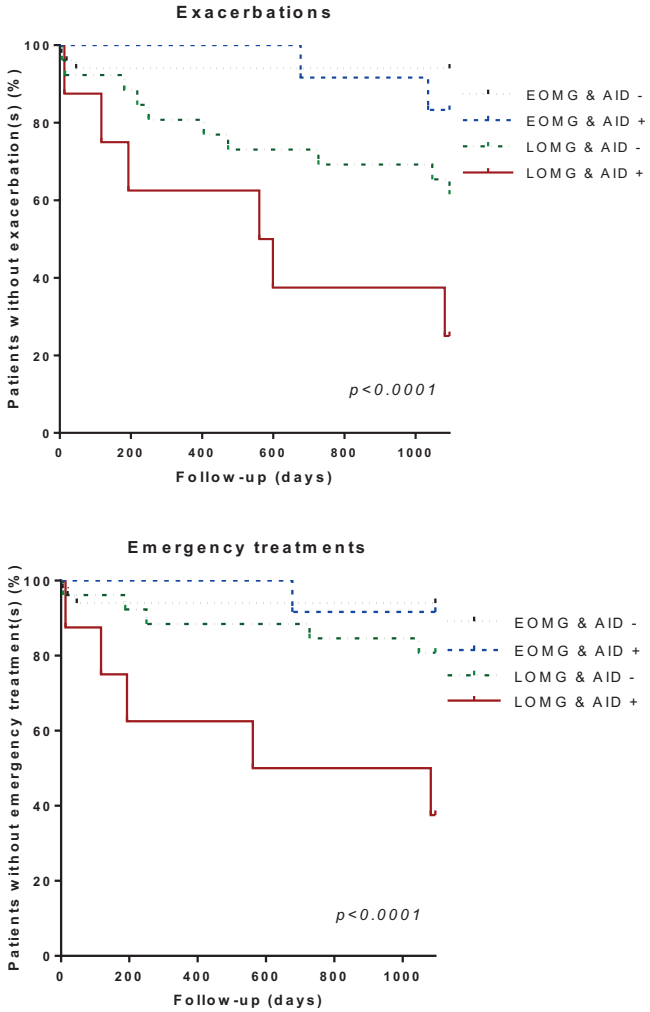


Figure 1. Kaplan-Meier survival curves for the time courses without exacerbations and emergency treatments of MG patients, subdivided by age at onset and presence of additional AID, are shown. To evaluate the differences between the curves a log-rank test was performed. The *p*-values are shown in the figure.
Abbreviations: EOMG = early-onset MG; LOMG = late-onset MG; AID – = no additional autoimmune disease(s); AID + = additional autoimmune disease(s).

DISCUSSION

LOMG patients had a higher risk of an exacerbation and an emergency treatment within 3 years. This is in line with the reported association of LOMG with a lower remission rate and a higher frequency of progression to more severe disease, although the effect size on exacerbations in our study was considerably higher than those found for remission and progression of disease severity in previous studies.[3-6, 8, 9] The presence of an additional AID was also associated with a higher risk of an exacerbation. Moreover, patients with both LOMG and an additional AID had a markedly higher risk of an exacerbation and an emergency treatment.

The variables sex, MGFA, AChR antibodies, thymectomy and thymoma showed no significant associations with exacerbations. In contrast, studies focusing on remission found associations with thymectomy, clinical stage at onset and maximal worsening.[2, 4-6]

Limitations of our study include the single center of inclusion, a relatively small sample size, definition of our primary endpoint and retrospective analysis. We tried to minimize these by choosing variables that could reliably be analyzed afterwards. The current study is tertiary clinic-based and may not fully reflect the total MG population due to a referral bias. As for our primary endpoint, there is currently no consensus regarding a definition for exacerbation. [10] For this study we defined an exacerbation as a clinical deterioration of MG that required starting with or an increase of at least 20 mg of prednisone or led to an emergency treatment. The cut-off point of 20 mg was based on clinical experience and was chosen to exclude clinically non-significant fluctuations, which result in small adaptations of the dose but do not represent genuine exacerbations of the disease.

Late-onset of symptoms and the presence of additional autoimmune diseases were shown to be prognostic factors for exacerbations and the necessity of emergency treatments in MG. More stringent control of care and treatment could help prevent exacerbations and emergency treatments in these high-risk patients. Besides remission, exacerbations and emergency treatments could also be considered as endpoints in future studies.

REFERENCE LIST

1. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475-490.
2. Baggi F, Andreetta F, Maggi L, et al. Complete stable remission and autoantibody specificity in myasthenia gravis. Neurology 2013;80:188-195.
3. Mao ZF, Mo XA, Qin C, Lai YR, Olde Hartman TC. Course and prognosis of myasthenia gravis: a systematic review. Eur J Neurol 2010;17:913-921.
4. Beghi E, Antozzi C, Batocchi AP, et al. Prognosis of myasthenia gravis: a multicenter follow-up study of 844 patients. J Neurol Sci 1991;106:213-220.
5. Mantegazza R, Baggi F, Antozzi C, et al. Myasthenia gravis (MG): epidemiological data and prognostic factors. Ann N Y Acad Sci 2003;998:413-423.
6. Cosi V, Romani A, Lombardi M, et al. Prognosis of myasthenia gravis: a retrospective study of 380 patients. J Neurol 1997;244:548-555.
7. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med 2002;21:2409-2419.
8. Zivkovic SA, Clemens PR, Lacomis D. Characteristics of late-onset myasthenia gravis. J Neurol 2012;259:2167-2171.
9. Donaldson DH, Ansher M, Horan S, Rutherford RB, Ringel SP. The relationship of age to outcome in myasthenia gravis. Neurology 1990;40:786-790.
10. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2012, Issue 12. Art. No.: CD002277. DOI: 10.1002/14651858.CD002277.pub4.

Supplemental material

SUPPLEMENT 1

Logistic regression for the occurence of emergency treatments

Emergency Treatments	No. of patients	No. of patients with ≥1 emergency treatment(s)	OR (95% CI)	*p* Value
Sex				
Female	61	5 (8)	1	
Male	35	9 (26)	2.24 (0.59-8.54)	0.237
Age at onset, y				
<50	62	4 (7)	1	
≥50	34	10 (29)	5.25 (1.21-22.80)	0.027
MGFA at first visit				
≤1	43	8 (19)	1	
>1	53	6 (11)	0.86 (0.23-3.15)	0.818
Additional AID				
No	76	8 (11)	1	
Yes	20	6 (30)	3.64 (0.94-14.11)	0.062
AChR antibodies[a]				
No	11	0 (0)	-	
Yes	85	14 (17)	-	-
Thymectomy				
No	73	10 (14)	1	
Yes	23	4 (17)	1.51 (.20-11.45)	0.690
Thymoma				
No	90	12 (13)	1	
Yes	6	2 (33)	1.85 (0.13-26.93)	0.653
Subgroups				
EOMG & AID –	50	3 (6)	1	
EOMG & AID +	12	1 (8)	1.42 (0.14-15.03)	0.769
LOMG & AID –	26	5 (19)	3.73 (0.82-17.07)	0.090
LOMG & AID +	8	5 (63)	26.11 (4.12-165.55)	0.001

Results of the first and second, subgroup-based, logistic regression for the occurrence of an emergency treatment within 3 years are shown. The subgroups were defined by the variables age at onset and additional AID. Data are presented as number of patients (%) and OR (95% CI). The category or subgroup with OR = 1 was used as reference group.

[a] For statistical reasons it was impossible to include the serum AChR antibodies variable in our multiple logistic regression analysis for the secondary endpoint (see methods).

Abbreviations: EOMG = early-onset MG; LOMG = late-onset MG; MGFA = Myasthenia Gravis Foundation of America; AID = autoimmune disease(s); AID – = no additional autoimmune disease(s); AID + = additional autoimmune disease(s); AChR = acetylcholine receptor; OR = odds ratio; CI = confidence interval.