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Lower number of plasma exchange sessions and glomerular filtration rate decline are associated with second relapses in patients with myasthenia gravis

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Abstract

The aims were to determine the impact of dysphagia and glomerular filtration rate (GFR) in the prediction of myasthenia relapse and analyse whether different number of plasma exchange sessions could prolong the time before future relapse.

This was a retrospective, longitudinal follow-up study with 60 enrolled patients. The patients were followed-up for a total of 50 months.

Patients without relapses had significantly higher GFR and higher number of plasma exchange sessions when compared to patients with relapses. Mean time before next myasthenia relapse was significantly longer in patients with GFR ≥ 60 mL/min. Time before next and number of following myasthenia relapses were significantly higher in patients with symptoms of dysphagia.

Decline in GFR levels is strongly associated with the presence of dysphagia and independently impacts the onset of myasthenia relapses. Timely initiation of plasmapheresis therapy and adequate hydration of patients with prolonged dysphagia should be one of the treatment goals for clinicians treating this disease.

Abbreviations: AchR = anti-acetylcholine receptor, BUN = blood urea nitrogen, GFR = glomerular filtration rate, MG = myasthenia gravis, MuSK = anti-muscle specific kinase.

Keywords: dysphagia, glomerular filtration rate, myasthenia gravis, plasmapheresis, relapse

1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by anti-acetylcholine receptor antibodies (AchR), anti-muscle specific kinase (MuSK) antibodies or in rare case antibodies to other antigenes in neuromuscular junction. In rare cases, when specific autoantibodies cannot be detected, we talk about seronegative MG. Treatment modalities include administration of anticholinesterase drugs in anti-AchR positive patients, corticosteroids, immunosuppression drugs, thymectomy in anti-AchR positive patients, therapeutic plasma exchange, and intravenous immunoglobulin. The myasthenic crisis is a life-threatening complication of MG characterized by worsening of muscle weakness and possible respiratory failure. Fifteen percent to 20% of myasthenic patients experienced myasthenic crisis at least once in their lives with the median of 8 to 12 months.[1,2]

It was reported that late age of onset, high titers of AChR antibody, thymoma, the time of diagnosis from onset, and other autoimmune diseases were risk factors which could contribute to myasthenia relapse.[3–7] The risk of secondary generalization could be reduced by an early treatment with corticosteroids, azatioprine, and thymectomy.[8,9] Plasmapheresis protocol usually consists of 4 to 5 exchanges of one or 1.5 plasma volumes until the satisfactory clinical improvement. Because of re-synthesis or even rebound production of the respective autoantibodies beneficial clinical effect of plasmapheresis typically lasts only 3 to 6 weeks. Dysphagia, which is rare as a presenting symptom occurs in 15% to 40% of patients with the generalized form of myasthenia.[10,11] The prolonged duration of swallowing dysfunction could lead to dehydration and therefore decreased renal blood flow and consecutively decline of glomerular filtration rate (GFR).

The aims of the present study were to determine the impact of clinical and laboratory parameters in the prediction of myasthenia relapse and analyse whether different number of plasma exchange sessions could prolong the time before future relapse. Furthermore, we analyzed relationship of dysphagia with GFR.

2. Methods

This was a retrospective, longitudinal follow-up study. The research protocol was approved by the local Human Research Ethical Committee in accordance with the World Medical

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The authors have no conflicts of interest to disclose.

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Association Declaration of Helsinki. The informed consent has been waivered by the IRB. Inclusion criteria were: age older than 18 years, hospitalization in midst of myasthenic crisis, first worsening of disease, normal kidney function before hospitalization and follow-up (55 (50–58) months). Renal function was defined as an estimated GFR (mL/min) which was estimated daily using the Cockcroft-Gault equation.[12] Data were collected from medical records. The cut-off of GFR < 60 mL/min for dividing patients in two subgroups, one with normal and second with mild-moderate or worse GFR reduction. During the period from January 2010 to April 2013, 60 patients were admitted to Neurology unit. The MG diagnosis was based on the presence of positive AchR or MuSK antibodies. In cases with seronegative disease diagnosis was based on clinical features, responsiveness to conservative therapy and electromyography positive pattern for MG. The antibodies were determined only qualitative using standard radioimmunoassay of serum samples (positive or negative as possible results) without quantitative analysis due to our laboratory policy. Each patient underwent a complete clinical and laboratory examination at the time of admission, during hospitalization and for each myasthenia relapse. Immediately after hospitalization and clinical evaluation the patients were treated with intravenous saline for rehydration when needed. Dehydration was assessed with clinical examination and the presence of dry skin and mucose membranes and with laboratory parameters like hematocrit, blood urea nitrogen (BUN)/creatinine ratio and uric acid levels. Plasma exchange sessions were performed on all patients. Plasma exchange sessions were continued until the significant improvement of symptoms. Polypropylene plasma filters were used (Haemoselect L 0.5 Braun) and about 2.5 to 5.5 L of each patient's plasma were removed at each session with only one plasma volume exchange. Plasma exchange sessions were using the Diapact system (Braun; Hemosol BO Solutions, Inc, Gambro). Mean age of all enrolled patients was 63 years. There were 22 (36.6%) male and 38 (63.4%) female patient. Only 7 (11.6%) patients had prior diabetes and 17 (28.7%) had prior arterial hypertension in the whole group of patients. Four patients had only MuSK positive antibodies, one patient had both MuSK and AChR positive antibodies while 44 patients had only AChR positive antibodies. The demographic, clinical and laboratory data of enrolled patients are presented in Table 1.

Table 1

Demographic, clinical, and laboratory data of enrolled patients.

	N (60)
Age (years)	63 (20–83)
BMI (kg/m^2)	25.4 ± 3.8
Males yes (N/%)	22 (36.6)
Diabetes yes (N/%)	7 (11.6)
Hypertension yes (N/%)	17 (28.3)
Generalized type of myasthenia yes (N/%)	40 (66.6)
Thymus hyperplasia yes (N/%)	7 (11.6)
Positive antibodies yes (N/%)	49 (81.6)
Dysphagia symptoms yes (N/%)	21 (35.0)
Duration of symptoms (days)	14.3 ± 1.9
Number of following relapses	0.8 ± 0.1
Time before next myasthenia relapse (months)	37.6 ± 5.8
Time from first onset (months)	34.5 ± 4.1
WBC ($\times 10^9$/L)	10.4 ± 0.8
Hemoglobin (g/L)	104 (64–168)
Hematocrit (L/L)	42 (30–55)
Uric acid (umol/L)	392 (212–551)
Serum creatinine (umol/L)	79 (54–133)
GFR (mL/min/1.73 m^2)	81.17 ± 2.7
BUN (nmol/L)	5.9 ± 0.9
BUN/creatinine ratio	73.6 ± 6.1
Urine specific gravity (kg/L)	1.015 ± 0.2
Serum sodium (mmol/L)	140 (131–149)
C-reactive protein (mg/L)	2.9 ± 0.2
Fibrinogen (g/L)	2.69 ± 0.7
Total serum proteins (g/L)	52 (28–80)
Serum albumin (g/L)	35 (11–47)
Number of plasmapheresis	4.15 ± 0.7
Total plasma volume replacement (mL)	3250 (2250–5500)

Results are shown as mean ± SD or median (interquartile range).
BMI = body mass index, BUN = blood urea nitrogen, GFR = glomerular filtration rate, WBC = white blood count.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., New York, NY). The study size was arrived by enrolling all patients with MG in the period of inclusion and it was confirmed by power-test analysis.

Normality of data distribution was tested using Kolmogorov–Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Categorical data were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means + standard deviations and Student's *t* test for independent samples was used for comparisons between two groups. Non-normally distributed data was presented as median and interquartile range and Mann–Whitney *U* test was used in comparison between two groups. Categorical variables were compared using χ^2 test. The analysis for mean time before next relapse was done with Kaplan–Meier curves which were tested with log-rank test while hazard ratios were estimated with Cox proportional hazards regression. Multiple linear regression was used to explore the influence of different variables on number of mysthenia relapses, while logistic regression was used for categorical dependent variables. A P value < .05 (two-sided tests) was considered significant.

3. Results

When patients were divided into two subgroups regarding relapses of myasthenia we have found that patients without relapses had higher number of plasmapheresis sessions with significantly lower percentage of patients with positive antibodies and symptoms of dysphagia (Table 2). There were no differences in age and gender between two groups of patients. Patients without relapses had significantly higher GFR and lower serum creatinine values when compared to patients with relapses. No significant differences were observed in hemoglobin, white blood count, fibrinogen, serum proteins, albumin, and number of patients with generalized type of myasthenia and thymus hyperplasia. Although there was no difference in duration of symptoms in days between two subgroups, patients without relapses had significantly shorter time from first onset of myasthenia. Patients with relapses had no differences in hematocrit and BUN/creatinine ratio as indicators of dehydration when compared to patients without relapses although uric acid levels were significantly higher in group with relapses as well as higher urine specific gravity and higher sodium levels. There were no differences in number of patients treated with intravenous

Table 2

Differences in demographic, clinical and laboratory data between patients with and without relapses.

	With relapse (N = 28)	Without relapse (N = 32)	*P*
Age (years)	48 (31–63)	51 (33–72)	.48
BMI (kg/m^2)	24.9 ± 3.8	25.7 ± 3.8	.43
Males yes (N/%)	8 (28.6)	14 (43.7)	.22
Diabetes yes (N/%)	5 (17.8)	2 (6.0)	.16
Hypertension yes (N/%)	5 (17.8)	12 (37.5)	.09
Generalized type of myasthenia yes (N/%)	16 (57.1)	24 (75.0)	.14
Thymus hyperplasia yes (N/%)	3 (10.7)	4 (12.5)	.91
Positive antibodies yes (N/%)	27 (96.4)	22 (68.7)	<.01
Dysphagia symptoms yes (N/%)	16 (57.1)	5 (15.6)	<.001
Duration of symptoms (days)	14.3 ± 1.4	14.2 ± 2.1	.96
Time from first onset (months)	38.7 ± 5.3	24.2 ± 3.9	<.01
WBC ($\times 10^9$/L)	10.8 ± 0.8	10.0 ± 0.6	.47
Hemoglobin (g/L)	134 (88–179)	141 (95–186)	.09
Hematocrit (L/L)	43 (32–55)	41 (30–53)	.11
Uric acid (umol/L)	477 (374–565)	321 (181–438)	<.01
Serum creatinine (umol/L)	87 (61–118)	78 (52–110)	.04
GFR (mL/min/1.73 m^2)	75.3 ± 3.4	86.2 ± 3.8	.04
BUN (nmol/L)	6.3 ± 0.4	5.6 ± 0.3	.19
BUN/creatinine ratio	74.6 ± 5.1	72.5 ± 4.4	.75
Urine specific gravity (kg/L)	1.021 ± 0.3	1.008 ± 0.1	.02
Serum sodium (mmol/L)	146 (136–150)	137 (132–143)	.04
C-reactive protein (mg/L)	3.7 ± 0.9	2.2 ± 0.5	.33
Fibrinogen (g/L)	2.55 ± 0.5	2.81 ± 0.8	.15
Total serum proteins (g/L)	67 (42–91)	68 (43–93)	.50
Serum albumin (g/L)	43 (20–67)	42 (20–66)	.25
Number of plasmapheresis	3.9 ± 0.6	4.3 ± 0.6	.01
Total plasma volume replacement (mL)	3544 (2500–5250)	3521 (2750–5400)	.90

Results are shown as mean ± SD or median (interquartile range).

BMI = body mass index, BUN = blood urea nitrogen, GFR = glomerular filtration rate, WBC = white blood count.

immunoglobulins, prednisone or pyridostigmine bromide between these two groups of patients as well as with oral prednisone and immunosuppressants like calcineurin inhibitors. There were no differences in number of thymectomized patients between these two subgroups. When patients were divided by gender, the bulbar and generalized type of myasthenia and by positive and negative antibodies we have not found significant differences between these subgroups.

The values of GFR correlated significantly negative with age ($r = -0.449$, $P < .001$), number of following relapses ($r = -0.281$, $P = .03$) and with symptoms of dysphagia ($r = -0.324$, $P = .03$). In the bivariate regression model, lower number of plasmapheresis sessions, longer time from onset of myasthenia, symptoms of dysphagia and reduced GFR had OR for myasthenia relapse of 0.35 [CI 0.13, 0.95], 1.02 [CI 1.00,1.04]; OR 0.98 CI [CI 0.97,0.99], and 0.96 [CI 0.93,0.99). The number of myasthenia relapses were significantly negatively associated only with basal GFR and number of plasmapheresis sessions ($\beta = -0.347$, Std. error 0.009; $\beta = -0.267$, Std. error 0.246) in the linear regression analysis (Table 3). Interestingly, prednisone or pyridostigmine therapy, thymectomy, high-dose intravenous immunoglobulin or oral prednisone therapy were not associated with onset and

Table 3

Linear regression model on association of number of myasthenia relapses with different variables.

Coefficients*

	Unstandardized coefficients		Standardized coefficients		
Beta model	***B***	**Std. error**	β	***t***	**Sig.**
(Constant)	5.548	1.597		3.474	.001
Age	−0.018	0.012	−0.245	−1.542	.129
PP number	−0.526	0.246	−0.267	−2.138	.037
Thymus hyperplasia (yes)	0.019	0.067	0.073	0.735	.244
Dysphagia symptoms (yes)	0.024	0.054	−0.239	0.894	.186
GFR	−0.024	0.009	−0.347	−2.536	.014
Positive antibodies (yes)	0.041	0.114	0.045	0.134	.687
Time from first onset	0.005	0.232	0.093	0.068	.099
Intravenous immunoglobulin therapy (yes)	−0.010	0.410	−0.182	−0.024	.133
Steroids (yes)	−0.056	0.378	−0.114	−0.673	.108

GFR = glomerular filtration rate, PP = plasmapheresis.

* Dependent variable: number of myasthenia relapses.

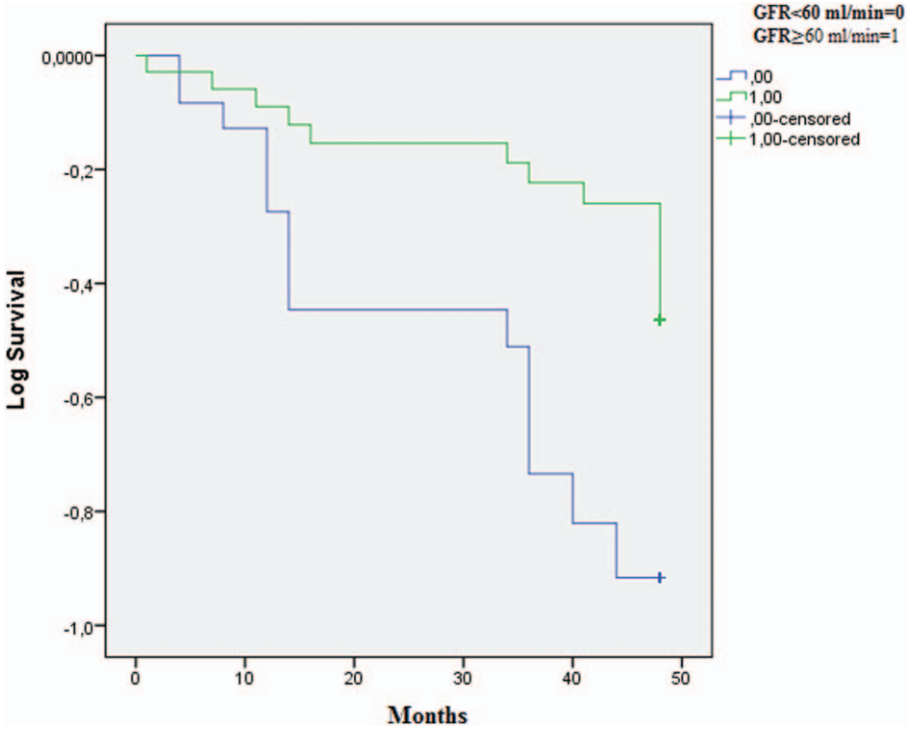

Figure 1. Myasthenia relapse in patients with GFR < 60 mL/min and GFR ≥ 60 mL/min at the end of follow-up. GFR = glomerular filtration rate.

number of mysthenia relapses. Lower GFR (HR 0.97 [0.96, 0.98]) and higher number of plasmapheresis sessions (HR 0.52 [0.50, 0.54]) were associated with myasthenia relapses.

The patients were followed-up for a total of 50 months. Mean time before next myasthenia relapse was significantly longer in patients with GFR ≥ 60 mL/min than in patients with GFR < 60 mL/min (41.6 [95% CI 36.9, 46.3] vs 32.0 [95% CI 25.4, 38.6] months, log-rank $P = .035$) (Fig. 1). The most patients (96.4%) with relapses had a decline in GFR levels during the follow-up period at each onset with similar values from the first episode. These patients had significantly higher GFR values in the remission period when compared to each onset of relapse. Most of them (92.8%) had the presence of dysphagia during the follow-up period.

As shown in Table 4, there were no differences in age, BMI, gender, diabetes, hypertension, number of plasmapheresis sessions, hemoglobin, white blood count, fibrinogen, serum proteins, albumins and percentage of patients with semi-quantitative urine positive proteins and generalized type of myasthenia between patients with and without symptoms of dysphagia. Patients with dysphagia had significantly lower values of GFR and percentage of patients with positive antibodies. Time before next myasthenia relapses was significantly shorter and number of following myasthenia relapses were significantly higher in patients with symptoms of dysphagia. Patients with dysphagia had no differences in hematocrit and BUN/creatinine ratio when compared to patients without dysphagia but uric acid levels were significantly higher in group with dysphagia as well as higher urine specific gravity and higher sodium levels. There were no differences in number of patients treated with intravenous immunoglobulins, prednisone or pyridostigmine bromide between these two groups of patients as well as with oral prednisone and immunosuppressants like calcineurin inhibitors. There were no differences in number of thymectomized patients between these two subgroups. The presence of dysphagia significantly correlated with the number of following relapses of myasthenia ($r = 0.331$, $P = .01$). Mean time before next myasthenia relapse was significantly longer in patients without dysphagia than in patients with dysphagia (41.9 [95% CI 37.4, 46.5] vs 29.5 [95% CI 22.7, 36.3] months, log-rank $P < .001$) (Fig. 2). The number of following myasthenia relapses was significantly negatively correlated with the number of plasmapheresis sessions and GFR ($r = -0.331$, $P = .02$; $r = -0.402$, $P = .04$) while positively with time from first onset, positive antibodies and the presence of dysphagia ($r = 0.387$, $P = .01$; $r = 0.332$, $P = .03$; $r = 0.422$, $P < .001$). As shown in Table 5, there were no differences in BMI, gender, diabetes, hypertension, number of plasmapheresis sessions, hemoglobin, white blood count, fibrinogen, serum proteins, albumins, and percentage of patients with semi-quantitative urine positive proteins and generalized type of myasthenia between patients with GFR < and >60 mL/min while patients with GFR < 60 mL/min were significantly older than patients with GFR > 60 mL/min. Patients with GFR < 60 mL/min had significantly higher percentage of patients with positive antibodies. Time before next myasthenia relapses was significantly shorter and number of following myasthenia relapses were significantly higher in patients with GFR < 60 mL/min. Patients with GFR < 60 mL/min had no differences in hematocrit and BUN/creatinine ratio when compared to patients with GFR > 60 mL/min but uric acid levels were significantly higher in group with GFR < 60 mL/min as well as higher urine specific gravity and higher sodium levels. There were no differences in number of patients treated with intravenous immunoglobulins, prednisone or pyridostigmine bromide between these two groups of patients as well as with oral prednisone and immunosuppressants like calcineurin inhibitors. There were no differences in number of

Table 4

Differences in demographic, clinical, and laboratory data between patients with and without dysphagia.

	With dysphagia (N = 21)	Without dysphagia (N = 39)	*P*
Age (years)	51 (30–69)	49 (21–67)	.54
BMI (kg/m^2)	25.9 ± 3.8	25.1 ± 3.8	.44
Males yes (N/%)	10 (47.6)	12 (30.7)	.19
Diabetes yes (N/%)	3 (14.3)	4 (10.2)	.64
Hypertension yes (N/%)	6 (28.6)	11 (28.2)	.94
Generalized type of myasthenia yes (N/%)	15 (71.4)	25 (64.1)	.56
Thymus hyperplasia yes (N/%)	3 (14.3)	4 (10.3)	.44
Positive antibodies yes (N/%)	21 (100.0)	28 (71.8)	<.001
Duration of symptoms (days)	14.1 ± 1.3	14.4 ± 2.2	.91
Number of following relapses	1.4 ± 0.3	0.5 ± 0.2	.01
Time before next myasthenia relapse (months)	29.5 ± 3.5	41.9 ± 2.2	<.01
Time from first onset (months)	40.1 ± 7.2	31.6 ± 5.5	.36
WBC ($\times 10^9$/L)	11.2 ± 1.0	10.0 ± 0.6	.24
Hemoglobin (g/L)	137 (91–182)	137 (93–181)	.97
Hematocrit (L/L)	42 (31–54)	42 (32–53)	.93
Uric acid (umol/L)	453 (366–558)	332 (193–451)	<.01
Serum creatinine (umol/L)	90 (64–124)	78 (52–111)	.02
GFR (mL/min/1.73 m^2)	72.7 ± 4.9	85.7 ± 4.5	.02
BUN (nmol/L)	6.4 ± 0.3	5.7 ± 0.3	.17
BUN/creatinine ratio	74.5 ± 4.5	72.0 ± 4.9	.73
Urine specific gravity (kg/L)	1.028 ± 0.3	1.006 ± 0.1	<.01
Serum sodium (mmol/L)	147 (138–150)	136 (134–142)	.02
C-reactive protein (mg/L)	1.4 ± 0.4	3.7 ± 1.2	.19
Fibrinogen (g/L)	2.68 ± 0.5	2.70 ± 0.8	.90
Total serum proteins (g/L)	68 (43–92)	68 (43–93)	.92
Serum albumin (g/L)	42 (21–65)	42 (20–65)	.82
Number of plasmapheresis	4.1 ± 0.6	4.2 ± 0.6	.38
Total plasma volume replacement (mL)	3700 (2650–5400)	3440 (2600–5250)	.18

BMI = body mass index, BUN = blood urea nitrogen, GFR = glomerular filtration rate, WBC = white blood count; results are shown as mean ± SD or median (interquartile range).

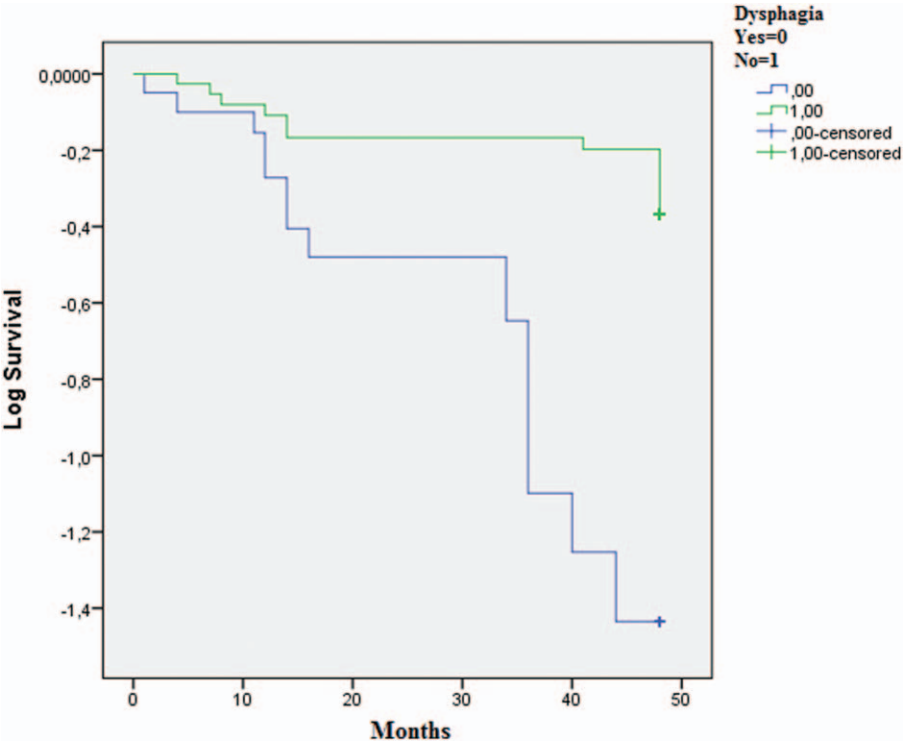

Figure 2. Myasthenia relapse in patients with and without dysphagia at the end of follow-up.

Table 5

Differences in demographic, clinical and laboratory data between patients with GFR < 60 and GFR > 60 mL/min.

	GFR < 60 mL/min (N = 25)	GFR > 60 mL/min (N = 35)	*P*
Age (years)	55 (32–71)	45 (18–64)	.02
BMI (kg/m^2)	25.9 ± 3.8	25.0 ± 3.7	.35
Males yes (N/%)	11 (44.0)	11 (31.4)	.27
Diabetes yes (N/%)	3 (12.0)	4 (11.4)	.47
Hypertension yes (N/%)	7 (28.0)	10 (28.5)	.96
Generalized type of myasthenia yes (N/%)	16 (64.0)	24 (68.5)	.73
Thymus hyperplasia yes (N/%)	3 (12.0)	4 (11.4)	.68
Positive antibodies yes (N/%)	24 (96.0)	25 (71.4)	.01
Duration of symptoms (days)	14.5 ± 1.4	14.2 ± 2.0	.90
Number of following relapses	1.2 ± 0.3	0.5 ± 0.2	.03
Time before next myasthenia relapse (months)	32.0 ± 4.1	41.6 ± 2.2	.03
Time from first onset (months)	35.2 ± 6.3	34.1 ± 5.9	.91
WBC ($\times 10^9$/L)	11.0 ± 1.0	9.9 ± 0.8	.33
Hemoglobin (g/L)	137 (91–182)	138 (94–182)	.75
Hematocrit (L/L)	42 (31–54)	42 (32–54)	.94
Uric acid (umol/L)	458 (366–561)	325 (191–458)	<.01
Urine specific gravity (kg/L)	1.024 ± 0.3	1.011 ± 0.3	.01
Serum sodium (mmol/L)	147 (138–150)	137 (133–143)	.02
C-reactive protein (mg/L)	2.3 ± 1.2	3.3 ± 1.0	.49
Fibrinogen (g/L)	2.70 ± 0.8	2.68 ± 0.5	.91
Total serum proteins (g/L)	68 (43–93)	67 (44–92)	.25
Serum albumin (g/L)	42 (21–65)	42 (21–64)	.95
Number of plasmapheresis	4.1 ± 0.6	4.1 ± 0.6	.92
Total plasma volume replacement (mL)	3510 (2610–5280)	3550 (2650–5330)	.84

BMI = body mass index, BUN = blood urea nitrogen, GFR = glomerular filtration rate, WBC = white blood count; results are shown as mean ± SD or median (interquartile range).

thymectomized patients between these two subgroups. Mean time before next myasthenia relapse was significantly longer in patients treated with four to five plasmapheresis sessions than in patients treated with three sessions (41.1 [95% CI 32.9, 49.2] and 37.3 [95% CI 31.9, 42.6] vs 31.9 [95% CI 20.7, 43.1 months, log-rank $P = .04$) (Fig. 3). We have not found differences in mean time before next myasthenia relapse regarding different plasmapheresis sessions in patients divided by a cut-off

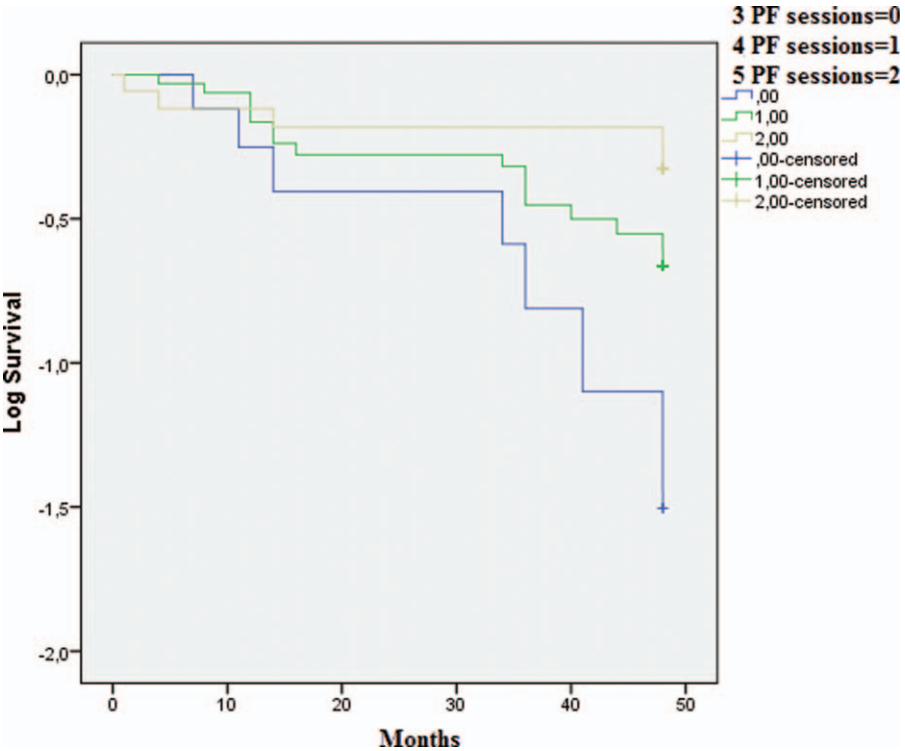

Figure 3. Myasthenia relapse in patients with three, four, and five plasmapheresis sessions at the end of follow-up.

of GFR < 60 mL/min. We have not found differences in mean time before next myasthenia relapse in patients with and without dysphagia.

4. Discussion

Myasthenia gravis, especially the midst of mysthenic crisis, is among the most common indications for plasmapheresis. Complete treatment which consists from five plasma exchanges is considered optimal. Plasma exchange directly removes AChR antibodies or other kind of autoantibodies against neuromuscular junction from the circulation and therefore significantly clinically and functionally improves these patients.[13,14] When the AchR titers rebound clinical relapses occur so plasmapheresis is not regarded as a useful long-term treatment. There are many possible risk factors responsible for myasthenia relapses like age of disease onset, thymus hyperplasia, ptosis or diplopia and the time of diagnosis from onset (<1 year).[9,15–17]

This is the first study, to the best of our knowledge, which reported GFR as a risk factor for second myasthenia relapse where patients without relapses had significantly higher GFR levels. Higher number of plasma exchange sessions and the shorter time of diagnosis from onset were as expected in favor for patients which had no following relapses. Never-the-less the number of myasthenia relapses were, except higher number of plasma exchange sessions, only significantly associated with GFR in the linear regression analysis. Furthermore, mean time before next myasthenia relapse was significantly longer in patients with GFR ≥ 60 mL/min. These results could be observed through the more pronounced symptoms of dysphagia in patients with relapses than in previous reports. GFR values significantly correlated with the presence of dysphagia symptoms and these patients had significantly shorter time before the next myasthenia relapse. There are many factors which are affecting GFR. Unregulated hypertension is one of the leading causes of declining GFR but mostly pre-renal causes which lead to decreased renal blood flow are responsible for this alteration. In more severe volume depletion caused by dehydration GFR values decline but most commonly are reversible with adequate hydration.

In this study there was a significantly higher number of patients with the presence of dysphagia and relapses which was not related to the bulbar or generalized type of myasthenia. This is very important finding because even the swallowing disturbances may be a hallmark of MG and dysphagia (the oropharyngeal, pharyngeal, pharyngoesophageal, or esophageal) is underestimated in myasthenic patients. According to the recent study published by Umay et al[18] swallowing functions in patients with MG may be affected even without symptoms typical for dysphagia. These patients could not adequately intake the required amount of fluid through the prolonged period of time (14 days) and therefore were dehydrated which is the most plausible explanation for the decline of GFR in this group of patients especially when taking into account the lack of higher percentage of established risk factors like diabetes or long-year treatment of hypertension. This result could be supported with higher uric acid and sodium levels and higher urine specific gravity as markers for dehydration found in patients with relapses and dysphagia. The additional role of declined GFR as a risk factor for future myasthenia relapse could be observed in normal GFR values in the remission period. Both AChR and MUSK antibodies are comprised of the IgG which is not excreted through kidney except in cases with the presence of glomerular disease. These antibodies are only detectable in serum of the patients with MG due to their high molecular weight but their metabolites like AChR alpha 1 antibody have smaller molecular weight (around 54 kDa) and therefore could be excreted through kidneys. This could be one of the possible explanations why patients with lower GFR values had more frequent relapses of myasthenia and the possible role of kidneys in elimination of these antibodies or their metabolites which are still not detectable in urine. Even a small decline in GFR values, as in this study, should be considered as a risk factor for more frequent relapses of myasthenia. Valli et al[19] reported three patients with myasthenia which developed membranous and pauciimmune extracapillary glomerulonephritis, one developed renal failure and one developed end-stage renal disease. It was associated with myasthenia with or without thymoma or thymectomy. We have not found this association in our group of patients where only 11.7% patients had semi-quantitative urine positive proteins without differences between patients with and without remission and without nephrotic-range proteinuria. The role of kidney in elimination of antibodies is still not yet investigated as well as determination of antibody metabolites in urine which could be a possible marker for disease severity and future onsets of myasthenia relapses.

Our work has several limitations. First, the study was a retrospective one and it was performed in a single centre and results represent a single center experience which may not be generalizable to other populations and it could be limited by a small sample size. Second, the antibodies were only determined qualitatively and not quantitatively. This disabled us in determining the effect of plasma exchange on reduction of antibodies titer. The effect of plasma exchange was only observed through clinical improvement of patients and not antibodies titer which probably led to cases with only three plasma exchange sessions, therefore smaller removal of antibodies and consequently shorter time before next myasthenia relapse. These differences are a limitation that weakens the argument that GFR levels independently impacts the onset of future myasthenia relapse but in the other hand confirms that elimination of antibodies through more plasma exchange sessions are mandatory in patients with the midst of myasthenic crisis. Third, diuresis was not measured in our group of patients which is a very limitating factor due to the fact that possible dehydration as a direct result of prolonged dysphagia could only be speculated. Unfortunately, proposed decline in GFR as a possible result of decreased kidney blood flow could not be analyzed which would certainly additionally improve obtained results. Fourth, we have analyzed possible proteinuria only by semi-quantitative urine analysis. Although the enrolled patients did not have more than two crosses of proteins in only two cases the 24-h urine collection is a routine diagnostic tool for glomerular disease related proteinuria. Fifth, plasma exchange treatment did not start at the same time for all patients therefore some of them had prolonged duration of symptoms and possibly dehydration and declined GFR levels were more pronounced in these patients where plasma exchange could not be efficient enough for prevention of future relapses.

Higher number of plasma exchange sessions and decline in GFR levels impacts the onset of future myasthenia relapses. The possible role of kidneys in elimination of antibodies or their metabolites should be examined in the future and on more patients especially when taking into account a strong association of reduced GFR with the presence of dysphagia and consequently

shorter time before next myasthenia relapses and higher number of following myasthenia relapses. Adequate hydration of patients with the midst of myasthenia crisis especially those with prolonged dysphagia should be one of the treatment goals for clinicians treating this disease.

Author contributions

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