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Plasmapheresis in Patients with Positive Antiacetylcholine Receptor Antibodies

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ABSTRACT

Introduction: Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction (NMJ) at the postsynaptic level. The distribution is age and sex related, with women affected nearly three times more frequently than men prior to age 40, while the incidence is roughly equal after the age of 40. In more than 80% of patients, antibodies directed against the acetylcholine receptor (AChR) at the NMJ cause failure of neuromuscular transmission, pathologic fatigue and weakness.

Materials and Methods: This was a descriptive case study conducted at the Department of Neurology Shaheed Zulfiqar Ali Bhutto Medical University/Pakistan Institute of Medical Sciences Islamabad for 2 year from January 2016 to December 2017. A total of 60 patients of Myasthenia Gravis were enrolled using non probability consecutive sampling. Patients were categorized according to the presence of AChR. antibodies status into two groups: 1-Patients having positive AChR. Antibodies were labelled as seropositive 2-Patients having negative AChR antibodies and negative anti muscle specific tyrosine kinase (Anti MuSK) antibodies were labelled as seronegative. The need of plasmapheresis was assessed in males and females in both the groups.

Results: A total of 60 Myasthenia Gravis patients were included in the study. Out of 60 patients 32 (53.3%) were females and 28 (46.6%) were males. The age range for males was 18 to 65 years and the females from 13 to 80. 29 patients underwent plasmapheresis. Out of these 29 patients, 11 patients underwent plasmapheresis either due to myasthenic crisis or disease worsening despite treatment and 18 patients had plasmapheresis prior to thymectomy surgery, however, these patients were not included in study.

Conclusion: We observed almost equal frequency of AChR antibodies both in males and females. But the frequency of myasthenic crisis and disease worsening, and ultimately the need for plasmapheresis is more among females. This difference highlights the need to categorize the patients who are at risk of developing myasthenic crisis or disease worsening and hence needs aggressive management so as to prevent such complications, improve the symptomatic profile and quality of life.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction (NMJ) at the postsynaptic level. Although the cause of the disorder is unknown, the role of immune responses (circulating antibodies directed against the nicotinic acetylcholine receptor) in its pathogenesis is well established [1].

Prevalence rates of MG have increased over time with recent estimates approaching 20/100,000 in the US population [2]. The distribution is age and sex related, with women affected nearly three times more frequently than men prior to age 40, while the incidence is roughly equal after the age of 40 [3]. In more than 80% of patients, antibodies directed against the acetylcholine receptor (AChR) at the NMJ cause failure of neuromuscular transmission, pathologic fatigue and weakness [4]. Generalized MG with AChR auto antibodies may be divided into early-onset and late-onset disease, with early-onset MG usually defined as beginning before age 40 [5]. Patients with onset after age 40 are more often male and usually have normal or atrophic thymus glands, although the full range of thymic pathology in these patients is not clear since thymectomy is rarely performed in patients over the age of 50 unless they have a thymoma. In addition to anti-AChR antibodies, these patients frequently have antibodies

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to non-AChR, striated muscle proteins such as titin and the ryanodine receptor [6], which have been associated with more severe, generalized or predominantly oropharyngeal weakness [7]. Usually the diagnosis is primarily made on the clinical history and examination findings indicating a specific pattern of easy fatigability and weakness along with many other features. Myasthenia gravis is confirmed by various diagnostic tests, especially by finding out serum anti-AChR antibodies. At once it was a fatal disease but now treated effectively in most of the patients with minimal morbidity.

MATERIALS & METHODS

This was a descriptive case study conducted in the Department of Neurology Pakistan Institute of Medical Sciences Islamabad for 2 year from 2016 to 2017. A total of 60 patients of Myasthenia Gravis were enrolled using non probability consecutive sampling. Sample size was calculated using WHO sample size. An informed written consent was taken from all the patients. All patients of both genders with Myasthenia Gravis were enrolled in this study. The clinical diagnosis was confirmed by the acetylcholine receptor antibodies and the typical response to repetitive nerve stimulation. Patients presents with ptosis, diplopia and easy fatigability especially towards end of the day. Patients were categorized according to the presence of AChR antibodies status into two groups: 1-Patients having positive AChR Antibodies were labelled as seropositive 2-Pateints having negative AChR Antibodies were labelled as seronegative. According to latest definition if patient is acetylcholine receptor antibodies and anti-MuSK antibodies (anti muscle specific tyrosine kinase) negative they are called seronegative (SNMG). In our study we used previous definition of seronegative M.G in which patient is acetylcholine receptor antibodies negative only as Anti MuSK antibodies were not available for most of our patients. The distribution of the weakness was categorized as: l=Patients having MGFA classification-I were defined as Occular Myashenic and, 2= Patients having MGFA classification-II were defined as Generalized Myasthenic. MG has been divided clinically and epidemiologically into two groups, ocular and generalized [8].

All patients requiring plasmapheresis because of myasthenic crisis either impending or manifesting, or patient having clinical disease worsening were included. Patients who required plasmapheresis prior to thymectomy surgery were not included as these patients were not having features of myasthenic crisis or disease worsening.

The patients were followed and monitored for any respiratory distress or ventilator support. Patients were regularly taking pyridostigmine. No patient in this study was given rituximab or steroids. The data was entered on standard performa. Data was entered and analyzed using SPSS version 17. Mean and standard deviations were calculated for numeral variables. Frequencies and percentages were calculated for categorical variables. P value <0.05 was considered significant for all the results.

RESULTS

A total of 60 Myasthenia Gravis patients were included in the study. Out of 60 patients, 32 (53.3 %) were females and 28 (46.6%) were males. The age range for males was 18 to 65 years and the females from 13 to 80 33 patients had abnormal repetitive nerve stimulation (RNS) test. 10 patients had normal RNS, of 1 patient RNS was inconclusive and for 17 patients RNS was not available. Repetitive nerve stimulation (RNS) is a variant of the nerve conduction study where electrical stimulation is delivered to a motor nerve repeatedly several times per second. Repetitive nerve stimulation is used to diagnose neuromuscular junction (NMJ) disorders, the most common of which is myasthenia gravis. A decremental response (a smaller and smaller muscle response with each repetitive stimulus) is abnormal and indicates neuromuscular junction (NMJ) dysfunction.

27 patients out of these 60 patients had positive Acetylcholine receptor antibodies (AchR-Ab), 12 patients were negative for AchR-Ab and for 21 patients AChR antibodies were not available. The patients in which antibodies were positive its value ranges between 0.12 nmol/l to 120 nmol/l.

24 patients had enlarged thymus on CT-Scan chest. 26 patients showed normal CT-Scan chest. In 5 patients, CT scan chest was not available. Thymectomy was done in 18 patients. On histological analysis result of 17 patients came out to be Thymoma and 5 patients showed hyperplasia. All these results are given in **Table 1 and Figure 1**.

29 patients underwent plasmapheresis as showed in **Table 2 and Figure 2**. Out of these 29 patients, 11 patients underwent plasmapheresis either due to myasthenic crisis or disease worsening despite treatment and 18 patients had plasmapheresis prior to thymectomy surgery as shown in **Table 3 and Figure 3**, however, these patients were not included in study. A total 80 sessions of plasmapheresis were done in all these 3 conditions i.e. myasthenic crisis, disease worsening or before thymectomy surgery.

11 out of these 29 patients needed ICU admission and mechanical ventilation either because of myasthenic crisis or disease worsening.

DISCUSSION

In this study we found an increased frequency of MG among females with age less than 50 years. In our population 69.2% prevalence of AChR antibodies was found in patients with generalized MG that is comparable to an international study in which the sero prevalence of AchR antibody in different series was varied, being in the 67-93% range and these antibodies are virtually absent in normal controls or in patients with other neurological or immunological diseases [9,10] while prevalence is less than another study in which

Table 1. Details and results of patients who were involved in the study.

Sex			**Male**	**Female**	**Total**
RNS	Normal	Count	3	7	10
		%	11.10%	21.90%	16.70%
	Abnormal	Count	18	15	33
		%	66.70%	46.90%	55.00%
	Inconclusive	Count	0	1	1
		%	0.00%	3.10%	1.70%
	NA	Count	4	6	11
		%	14.80%	18.80%	18.30%
	NA	Count	2	3	5
		%	7.40%	9.40%	8.30%
CT Scan Chest	NA	Count	4	1	5
		%	14.80%	3.10%	8.30%
	Normal	Count	11	14	26
		%	40.70%	43.80%	43.30%
	Enlarged Thymus	Count	9	15	24
		%	33.30%	46.90%	40.00%
	NA	Count	3	2	5
		%	11.10%	6.30%	8.30%
AchrAb.	Positive	Count	14	13	27
		%	51.90%	40.60%	45.00%
	Negative	Count	5	6	12
		%	18.50%	18.80%	20.00%
	NA	Count	3	2	5
		%	11.10%	6.30%	8.30%
	NA	Count	5	11	16
		%	18.50%	34.40%	26.70%

Acetylcholine receptor (AChR) antibodies are detected in the serum of more than 80-90% patients with generalized myasthenia gravis, about 50% with pure ocular myasthenia and rarely in healthy people [9]. In our study 30.7% patients with generalized MG were negative. In an international study approximately, 12-17% of patients with generalized MG lack demonstrable serum AChR antibodies, and they are referred to as the seronegative group. [11-13]. Soliven *et al.* [13] reported that there was no difference in the age of onset, gender, duration of symptoms or frequency of crises between the seropositive and seronegative patients that is consistent with our study. Myasthenia gravis was the second most common indication for TPE in 1997 and was first described as a form of treatment for MG in 1976 by Pinching and Peter. They performed plasma exchange in 3 patients and found partial improvement in muscle weakness and fatigue, suggesting that a humoral factor in the plasma was causing the disorder of neuromuscular transmission [14]. In our study 29 out of 60 patients underwent plasmapheresis either due to myasthenic crisis or disease worsening affecting females

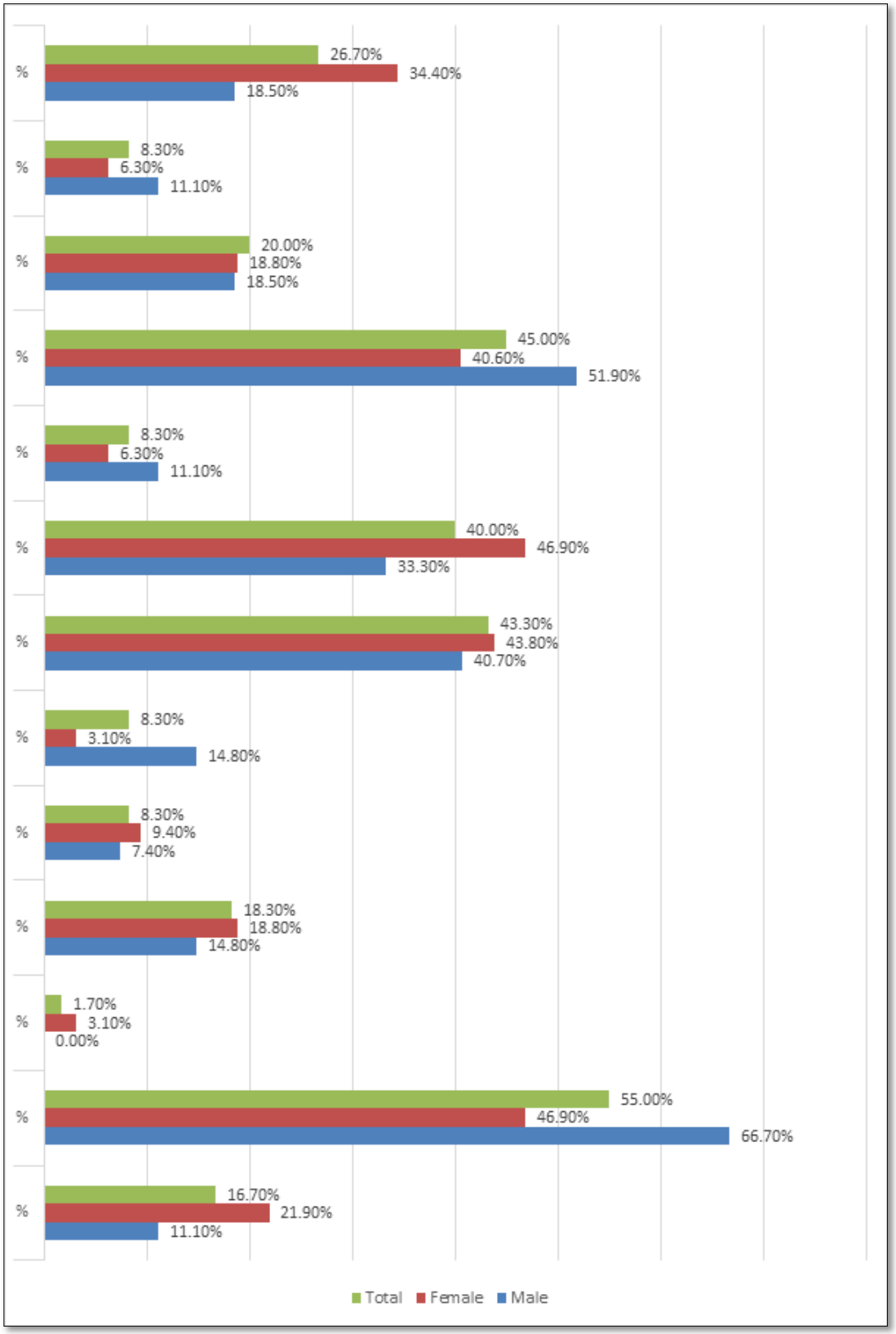

Figure 1. Details and results of patients who were involved in the study.

Table 2. Details of patients who underwent plasmapheresis.

Plasmapheresis			Sex			Total
			F	Percentage	M	Percentage	
Yes		Count	16	55.2%	13	44.8%	29
No		Count	17	54.8%	14	45.2%	31
Total		Count	33	55.0%	27	45.0%	60

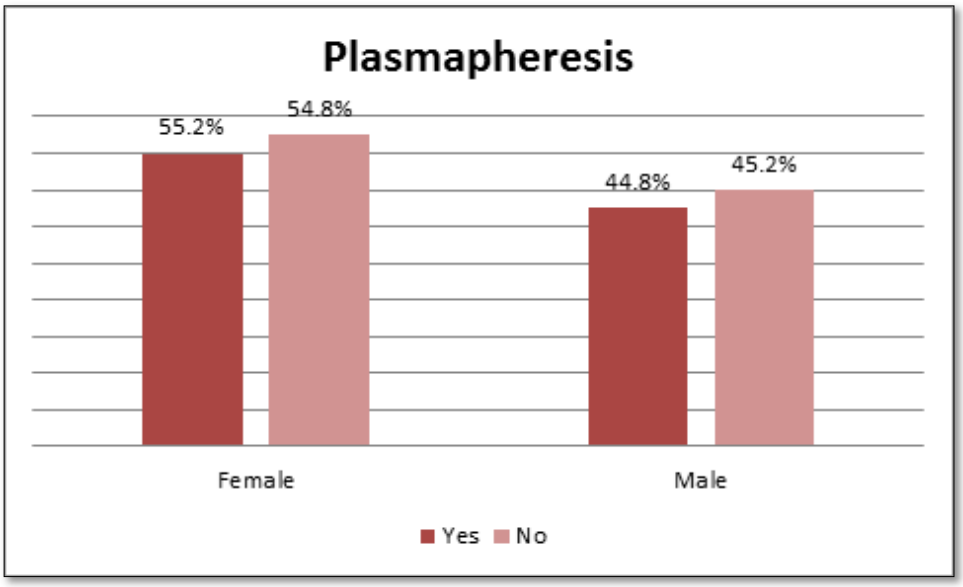

Figure 2. Details of patients who underwent plasmapheresis.

Table 3. Details of patients who underwent plasmapheresis prior to thymectomy surgery.

	Sex				
	Female		Male		Total
	n	Percentage	n	Percentage	N
Plasmapheresis	8	72.7%	3	27.3%	11
Plasmapheresis with Thymectomy	8	44.4%	10	55.6%	18
Total	33	55.0%	27	45.0%	60

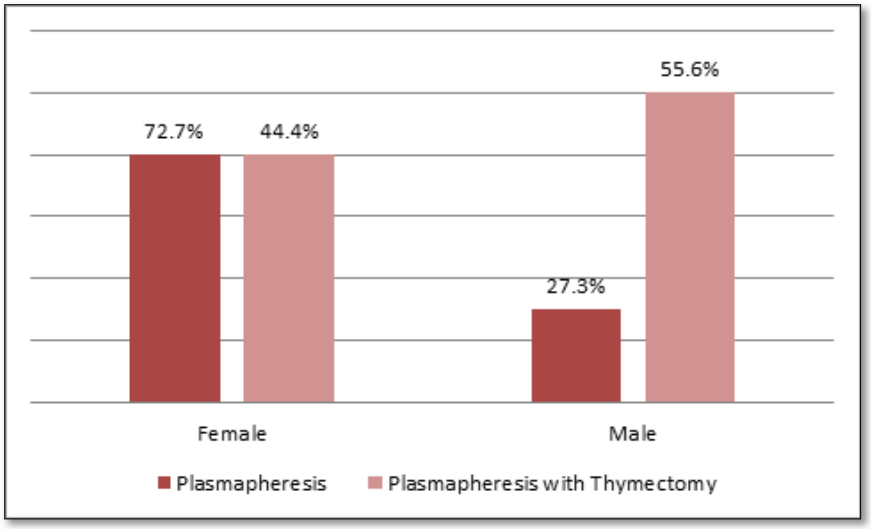

Figure 3. Details of patients who underwent plasmapheresis prior to thymectomy surgery.

more i.e 55.2% than males i.e 44.8%. In one study, the proportion female: male ratio was 2:1. TPE was indicated due to myasthenic crisis in 23 (65.7%) patients and progressive worsening despite treatment in 12 (34.3%) [15]. Myasthenic crisis is a complication of myasthenia gravis characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation. Advances in critical care have improved the mortality rate associated with myasthenic crisis. Fifteen to 20% of myasthenic patients are affected by myasthenic crisis at least once in their lives [16]. Respiratory support is imperative in the management of myasthenic crisis. Two-thirds to 90% of patients with myasthenic crisis require intubation and mechanical ventilation [17]. In conclusion, in a descriptive case study of myasthenia gravis, we observed almost equal frequency of AChR antibodies both in males and females. But the frequency of myasthenic crisis and disease worsening, and ultimately the need for plasmapheresis is more among females. This difference highlights the need to categorize the patients who are at risk of developing myasthenic crisis or disease worsening and hence needs aggressive management so as to prevent such complications, improve the symptomatic profile and quality of life.

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