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Clinical Profile of Ocular Myasthenia Gravis: A Prospective Study from Tertiary Care Centre

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Abstract

Background: Ocular myasthenia gravis (OMG) is the most common focal form of myasthenia gravis (MG) characterized by variable weakness and fatigability of extraocular muscles (EOMs), levator, and orbicularis oculi. Most of the OMG patients will subsequently progress to develop more disabling and life threatening generalized myasthenia gravis (GMG). No definitive laboratory tests are available for the diagnosis of OMG. Hence, we aimed at characterizing the clinical profile of ocular myasthenia gravis in Indian population.

Methods: We evaluated 30 suspected cases of ocular myasthenia referred from various parts of country (India) under the Department of Neurology, NIMHANS, Bangalore from October 2010 to October 2013. Detailed demographic and clinical data was extracted in a systematic manner using a predetermined proforma. All patients were investigated with neostigmine test, icepack test, Repetitive Nerve Stimulation (RNS), serum acetylcholine receptor (AChR) antibody assay and Single Fiber Electromyography (SFEMG).

Results: Twenty of 30 patients were recruited. Among these twenty patients, 18 patients fulfilled SFEMG criteria (SFEMG ADHOC committee criteria, 1994) and remaining 2 patients (who were not willing for SFEMG) had clinical features of OMG and showed positive results in other tests.Among those, 17 (85%) were male and 3 (15%) were female. Ptosis was the most common symptom and was seen in 19 (95%) patients. Diplopia, the second commonest symptom was seen in 12 (60%). Eighty five percent (85%) ptosis and 75% of diplopia had shown diurnal variation. Shifting ptosis was observed in 20%.

Conclusion: Systematic elicitation of clinical signs and symptoms has very important role in the diagnosis of OMG. Variable and fatigable ptosis and diplopia with diurnal variations are the diagnostic symptoms of OMG. Shifting ptosis and Coganýÿs lid twitch sign are the very important signs of OMG.

Keywords: Eextraocular Muscles; Ptosis; Fatigable Weakness; Acetylcholine Receptor; Neostigmine.

Introduction

Myasthenia gravis (MG) is potentially serious condition, but treatable autoimmune neuromuscular junction disorder affecting skeletal muscles. MG is a generalized disorder that often manifests initially as focal weakness. The most common focal presentation is ocular musculature and it is termed as ocular myasthenia gravis (OMG). OMG is characterised by fatigable weakness involving the extraocular muscles (EOMs), levators, or orbicularis oculi in up to 65% of patients [1].

"Although there may be electrophysiological evidence of myasthenia in lower facial or limb muscles, if the weakness is limited to the ocular muscles, it is designated as "ocular myasthenia gravis (OMG)". Eye muscle weakness at the onset of MG is evident in 85–90% of patients [2]. Pure ocular myasthenia (i.e. without clinical evidence of coexisting bulbar or limb weakness at the onset) varies from 18% to 59% in different series.

MG is uncommon with an estimated prevalence of approximately 5 to 15per 100,000 [3,4]. Fifty to sixty percent of OMG patients will subsequently develop

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generalized myasthenia gravis (GMG), with 80% progressing within the first year and 90% within 3 years, while after 3 years the chance of generalization is not greater than 10- 13%. About 30% will have episodes of spontaneous remission and be symptom-free [5,2].

OMG can mimic isolated cranial nerve palsies, gaze palsies, internuclear ophthalmoplegia, blepharospasm, and even a stroke. No definitive diagnostic tests available for the diagnosis of OMG. Even though Single Fiber Electromyography (SFEMG) is very useful in the diagnosis of OMG, it is very technically demanding electrophysiological test and only experienced person can do it accurately. So, clinical signs and symptoms are very important in the diagnosis of OMG in developing countries like India. The purpose of this study is to highlight the clinical features of ocular myasthenia gravis (OMG).

Materials and Methods

It is a prospective study done in a tertiary care institute. We evaluated 30 suspected cases of ocular myasthenia referred from various parts of country (India) under the Department of Neurology, NIMHANS, Bangalore from October 2010 to October 2013. Institutional ethical clearance was obtained. Cases were recruited based on inclusion and exclusion criteria after taking the written consent. Detailed demographic and clinical data was extracted in a systematic manner using a predetermined proforma. Inclusion criteria consisted of symptoms suggestive of clinically evident ocular myasthenia and no subjective symptoms or clinical findings suggestive of generalized myasthenia gravis (any muscle weakness below the neck or facial muscles except orbicularis oculi). We used following criteria for clinical diagnosis of ocular myasthenia [6];

1. Ptosis of one or both eyelids not due to local eyelid disease, preferably that could fatigue or improves with rest
2. Extra ocular muscles weakness and/or diplopia with clear cut fatigability or recovery
3. Weakness of one or both orbicularis oculi
4. Fatigue of affected muscle with clear cut worsening of ptosis after upward gaze for 30-60 seconds or worsening of monocular duction after 120 sec of gaze in the direction of action, recovery of ptosis after 30 to 5 min eye closure or recovery monocular duction after 120 sec of gaze in the direction antagonist muscle.
5. No pupillary abnormality.

Severity of the disease was assessed by using Quantitative myasthenia gravis (QMG) scale of MGFA [7]. All patients were investigated with neostigmine test, icepack test, Repetitive Nerve Stimulation (RNS), serum acetylcholine receptor (AChR) antibody assay and single fibre electromyography (SFEMG).

Inclusion Criteria

Patients with ≥ 10 years of age, fulfilling clinical criteria (Kupersmith MJ, 2003) for ocular myasthenia gravis and one of following.

1. Repetitive nerve stimulation (RNS) studies with more than 10% decremental response
2. Single fiber electromyography (SFEMG) with abnormal jitter and normal fibre density
3. Positive neostigmine test.

Exclusion Criteria

- Patients with involvement extending beyond the ocular muscles
- Identification of another diagnosis to explain the clinical profile

Results

Based on these results, 20 of 30 patients were recruited. Among these twenty patients, 18 patients fulfilled SFEMG criteria for myasthenia gravis (SFEMG ADHOC committee criteria, 1994) [8] and remaining 2 patients (who were not willing for SFEMG) had clinical features of OMG and showed positive results in other tests.

Ten patients were excluded from study. Among these ten patients, 7 patients had had isolated ptosis (5 had unilateral ptosis and 2 had symmetrical bilateral ptosis) and remaining 3 patients had also ptosis with eye movement restriction. Only 2 patients had mild diurnal variation and none had diplopia and orbicularis ocluli weakness. Among these 10 patients, 9 patients did not show positive result in any of tests included in the study. Another patient, 66years old lady presented with progressive drooping of both eyelids right more than left with mild diurnal variation without double vision, history suggestive relapses and remissions of 12 years duration. Examination revealed asymmetrical ptosis without any signs of fatigability. Evaluation revealed no decremental response in RNS, ice pack test was

positive, anti AChR antibody was borderline positive and SFEMG of frontalis muscle had shown abnormal jitter with blockings. On phone call conversation after 2 years, patient reported no change in her symptoms and not taking any medications.

Among those twenty ocular myasthenia gravis (OMG) patients, 17(85%) were male and 3(15%) were female. Mean age of the patients was 40.09±16.77 years (11 - 84years). Age of onset of the disease varied from 14-74years (Mean - 40.05±17.36).

Ptosis was the most common symptom and was seen in 19 (95%) patients. Diplopia, the second commonest symptom was seen in 12 (60%) patients. One patient presented with diplopia as the only symptom. Symptoms suggestive of fatigability like diurnal variation were seen in 17 (85%) patients, worsening of symptoms on visual strain in 17 (85%) patients and improvement after afternoon nap seen in 16 (80%) patients. No patient had afternoon ectropion or seasonal variations. Six patients (30%) had prior symptoms suggestive of relapse and remissions. Other details of ptosis and diplopia are given in Table 1.

No patient had history suggestive of orbicularis oculi weakness. There was no history suggestive of bulbar or limb muscle involvement in any of the patients.

With respect to the associated diseases in patients with ocular myasthenia, two elderly patients had hypertension, one patient had both Type 1 DM and

Table 1: Clinical Symptomatologyin patients with ocular myasthenia

Parameters			N
Ptosis	Total number patients with ptosis		19 (95%)
	Duration of ptosis (days)		76.47 ± 83.45
	Onset of ptosis	Right side	12 (63.2%)
		Left side	7 (36.8%)
	Ptosis side at presentation	Right side	7 (36.8%)
		Left side	3 (15.7%)
		Bilateral	9 (47.4%)
	Diurnal variation		17 (85%)
Diplopia	Duration of diplopia (days)		81.25±105.3
	Total number of patients		12 (60%)
	Diplopia in	Horizontal gaze	4 (33.3%)
		Vertical gaze	1 (0.08%)
		Both	7 (58.3%)
	Diurnal variation		9 (75%)
	Squint		2 (16.6%)

Table 2: Objective findings in Ocular myasthenia

Parameters			N = 20
Examination of ptosis	Shifting ptosis		4 (20%)
	Fatigable ptosis		17 (85%)
	Fatigable ptosis severity*	Severe	1 (0.05%)
		Moderate	5 (29.4%)
		Mild	11 (64.7%)
	Recovery after 5min eye closure		16 (84%)
	Cogan's lid twitch sign		2 (10.5%)
	Enhanced ptosis sign		4 (21%)
	Lid hopping sign		0
Examination of ocular movements and diplopia	Restriction of ocular movements		11 (55%)
		Unilateral	2 (18%)
		Bilateral	9 (81.8%)
	Variation in eye movements with fatigable EOMS		3 (27.2%)
	Ocular quiver		3 (27.2%)
	Pseudo INO		2 (18%)
	Diplopia		9 (45%)
		Horizontal	2 (22.2%)
		Vertical	3 (33.3%)
		Both	4 (44.4%)

Note:
1. Pseudo INO – pseudo internuclear ophthalmoplegia; EOMS – extraocular muscles. 2) *Graded by using 1min upward gaze test as severe – spontaneous, moderate – 1 -10seconds, mild – 10 – 60seconds, none - >60seconds

hyperthyroidism, one patient had hypothyroidism and features suggestive of connective tissue disorder and another had only features suggestive of connective tissue disorder.

On examination ptosis was present in 95% of the patients. Shifting ptosis was observed in 20%. Ptosis was fatigable in 85% of the patients; in 55% of the patients, fatiguability was only mild. Among 9 patients with bilateral ptosis, 88.8% patients had asymmetrical onset. Recovery of ptosis after 5 minutes of eye closure was observed in 80% of the patients. Lid hopping sign was not present in any of the patient. Other details of ptosis given in Table 2. 55% of the patients had restricted ocular movements and 80% of them had bilateral restriction. Diplopia was present in 45% of the patients and it was evident in horizontal in 10%, vertical 15% and both gaze in 20%. Ocular quiver and variation in eye movements were seen in 15% and pseudo INO was in 10%. 25% of patients had mild weakness of orbicularis oculi with no patient was having Peek sign. Bulbar and limb muscle weakness was absent in all the patients.

Disease severity was assessed by using Quantitative Myasthenia Gravis (QMG) severity score of Myasthenia Gravis Foundation of America (MGFA) for all patients. The mean score was 1.55 (SD 1.09); most frequent score was 1, observed in 60.0% of patients (Table 3).

Table 3: Baseline QMG severity scores

QMG score	Frequency	Percent
0	1	5%
1	12	60%
2	4	20%
3	2	10%
5	1	5%

Discussion

We aimed at systematic characterization of clinical features of diagnosed ocular myasthenia gravis patients as it is diagnostically challenging even with available diagnostic modalities. Ocular myasthenia gravis is a rare entity and we recruited a good number of patients for our prospective study. In our study there was no interobserver bias as clinical data was extracted by a single examiner.

Present study showed OMG has male preponderance (85%) with age of the onset at 40.09 years (SD, 16.7) which is similar to the previous study [9]. In one survey of patients with OMG, 10% had ptosis only, 90% had a combination of diplopia and ptosis [10]. In a study by Kim JH et al in 2003, less than 10% of patients had ptosis only, less than 30% had diplopia only, while the majority (64%) had both diplopia and ptosis [11]. In our study of ocular myasthenia, 40% had only ptosis, 5% had diplopia only, 55% had combination diplopia and ptosis. An interesting finding was right sided (63.2%) ptosis onset was more common. Ptosis was the most common symptom seen in 95% of the patients and diplopia was seen in 60%. In addition to features suggestive of fatigability like diurnal variation (85%), worsening of symptoms on visual strain (80%) and improvement after afternoon nap (85%), 30% patients had symptoms suggestive of relapses and remission in their past. No patient had reverse diurnal variation, after noon ectropion and seasonal variations.

Fatigable ptosis is seen in 89.5% of the patients. Shifting ptosis and Enhanced ptosis sign seen in 21%. No patient had Lid hopping sign. Pupil sparing, asymmetrical ptosis is the characteristic feature of OMG. However, in the present study, among the 9 patients with bilateral ptosis, symmetrical ptosis was observed in 78.8%. Reported sensitivity of the rest test is 50% and a specificity of 97% for the diagnosis of OMG [12]. In our study, recovery after 5min eye closure was seen in 80%. Eric L. Singman et al in 2011 [13] found specificity of the Cogan's lid twitch sign for diagnosing MG in this sample of patients was 99%, while the sensitivity was 75%. In our study, 2 (10.5%) patients with ocular myasthenia had Cogan's lid twitch sign.

In a study by Kupersmith et al in 2005 [14], combined horizontal and vertical ocular misalignment seen in 43.5% of the study population and horizontal deviation alone in 34.1% and vertical deviation alone in 22.4% of the patients. We found 55% patients had restricted ocular movements and 80% of them had bilateral restriction. Ocular quiver and variation in eye movements were seen in 27.7% and pseudo INO was in 18%. None of our patient ocular myasthenia had lid hopping sign. Twenty five percent of our patients had weakness of orbicularis oculi. Similar observation was made by Evoli A et al in 19988 [10] in their case series of ocular myasthenia gravis

patients. Osher RH et al in 1979(15) observed Peek sign in 3 of their 25 patients and none of normal control patients had this sign. None of our patients had Peek sign.

Conclusions

Clinical profile of ocular myasthenia gravis mimics many other diseases and early diagnosis of this focal entity of more sever generalized myasthenia gravis is utmost important for the further management. As available modalities of investigation has limited role in the diagnosis of ocular myasthenia gravis, proper clinical examination is very important. Diagnosis of ocular myasthenia gravis should be considered in a patient with variable and fatigable ptosis and diplopia with diurnal variation. Though shifting ptosis, enhanced ptosis sign and Cogan's lid twitch sign are rarely seen, they are the diagnostic signs for the diagnosis of OMG.

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