



## Ocular Myasthenia in South India-A prospective cohort study

Authors

**Dr Chithra.P<sup>1</sup>, Dr Thomas Iype<sup>2\*</sup>, Dr Geetha S<sup>3</sup>, Dr Murukan C. Nair<sup>4</sup>**

<sup>1</sup>Additional Professor, Dept. of Neurology, Govt. Medical College, Thiruvananthapuram

<sup>2</sup>Professor, Professor, Dept. of Neurology, Govt. Medical College, Thiruvananthapuram

<sup>3</sup>Additional Professor, Dept. of Pediatrics, SAT Hospital, Govt. Medical College, Thiruvananthapuram

<sup>4</sup>Consultant Physician, Dept. of Neurology, General Hospital, Thiruvananthapuram

\*Corresponding Author

**Dr Thomas Iype**

Professor, Professor, Dept. of Neurology, Govt. Medical College, Thiruvananthapuram, India

### Abstract

**Introduction:** *Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction (NMJ) at the postsynaptic level. Ocular MG (OMG) is a subtype of MG where the weakness is clinically isolated to the EOMs, levator palpebrae and orbicularis oculi. There is not enough data on the clinico epidemiologic profile of OMG in the Indian population.*

**Methods:** *During a period of one year (September 2007 to August 2008), out of 40 consecutive patients of MG 16 patients with a diagnosis of ocular MG presenting to the Neuromuscular clinic, Department of Neurology, at tertiary care referral were recruited for the study. All patients were followed up regularly for a minimum period of 3 years.*

**Objectives:** *To describe the clinicoepidemiologic profile and outcome of OMG.*

**Conclusion:** *Asymmetric ptosis and diplopia are the commonest manifestations in ocular myasthenia. Steroid is mostly needed in OMG.*

**Keywords:** *OMG, Antibodies, diagnosis, Thymoma, immunomodulation.*

### Introduction

Myasthenia gravis (MG) is a potentially lethal, but treatable autoimmune disorder affecting the neuromuscular junction (NMJ) with a bimodal age distribution<sup>(1)</sup>. MG is a postsynaptic disorder due to Acetylcholine receptor antibodies (AChR-Abs) or MuSK antibodies resulting in defective neuromuscular junction transmission and subsequent muscle weakness. Extra ocular muscles (EOMs) commonly get fatigued as they are fast fibres with a high frequency of synaptic

firing. Ptosis and diplopia are the presenting symptoms of the disease in over 50% of MG patients<sup>(2)</sup>. Among them, 50-80% of these patients go on to develop the generalized disease<sup>(3)</sup>.

Generalization will occur in 90% within the first 2 years after ocular symptoms begin<sup>(4)</sup>. Ocular myasthenia gravis (OMG) remains restricted to ocular muscles beyond one year with 50% being seropositive for AChR-Abs<sup>(5,6)</sup>. One-quarter of patients with MG in India have OMG<sup>(1)</sup>. OMG can mimic cranial nerve palsies, gaze palsies,

internuclear ophthalmoplegia, and blepharospasm<sup>(7)</sup>. We do not have enough literature on the OMG from India. Hence, our objective is to look at the clinical and epidemiological profile of OMG and its short-term prognosis.

## Methods

We prospectively enrolled consecutive patients with OMG from September 2007 to August 2008 attending the Neuromuscular Clinic, Department of Neurology, Government Medical College, Trivandrum, Kerala, India. We diagnosed OMG based on history, clinical examination including bedside fatigability tests, supported by one or more of the following tests: ice pack test<sup>(8)</sup>, neostigmine test, and repetitive nerve stimulation (RNS) test suggestive of the postsynaptic defect. We used a train of 10 supramaximal stimuli, at a rate of 3 per second for RNS from orbicularis oculi using Neuro Quest Nichole machine. A decrement of more than 10% from the first to the fourth compound muscle action potential responses were considered positive. Post-exercise facilitation and post-exercise exhaustion were studied after one minute isometric exercise. We also did AChR antibody testing (Radioimmunoassay) and HRCT of the thorax with contrast. Patients with onset at birth (Congenital myasthenia), family history (Familial Myasthenia) and RNS suggestive of presynaptic disease were excluded. We documented the duration of the illness, the clinical manifestation of the condition<sup>(9)</sup> and treatment received. Symptomatic treatment with 60 mg of pyridostigmine thrice a day titrated based on its effects and adverse effects to a maximum dose of 60mg four hourly<sup>(10)</sup>. We added prednisolone in an initial dose of 40 -60 mg if there is no symptomatic improvement in two weeks. Once there is an effective response for 2 to 4 weeks we started tapering prednisolone by 5–10 mg each month. We followed up these patients till August 2011 looking progression to generalized MG, crisis, remission and death. For patients who

progressed to generalized MG, we added an immunomodulatory drug like azathioprine and subjected them to thymectomy.

## Results

We recruited 40 patients with MG during the study period out of which 16 patients had OMG. OMG patients had a mean age of 42.69(SD 13.81) (range 18-65) years, a male: female ratio of 0.8:1 and a mean follow up of 3.7 years(2.1). Males had a mean age of 41 (11.26) years compared to the female with 44.38(16.6) years (p-value = 0.5). Seropositive patients (n=7, 43.75%) had lower mean age ( $37.5 \pm 15.9$ ) compared to seronegative patients ( $47.87 \pm 9.73$ ) years (0.005). Seropositive patients had a lower mean age of onset ( $35.6 \text{ years} \pm 14.1$ ) than seronegative patients ( $46.1 \pm 9.01$ ) years (.05).

Table showing the clinical profile of OMG

Eye involvement		Positive
Symptoms at onset	Lid Fatiguability	10(62.5%)
	Ptosis	14(87.5%)
	Unilateral ptosis	11(68.8%) (8 Right, 3 Left)
	Bilateral ptosis	3(18.8%)
	Diplopia	2(12.5%)
Signs at presentation	Unilateral ptosis	3(18.8%)
	Bilateral ptosis	11(68.8%)
	Lid Fatiguability	12(75%)
	Cogan's lid twitch	5(31.25%)
	Lid retraction	2(12.5%)
	Peek sign	8(50%)
EOM involvement	Enhancement of contralateral ptosis on lifting of ptotic eyelid	11(68.8%)
	All direction	1(6.3%)
	LR	4(25%)
	MR	3(18.8%)
	SR	2(12.5%)
Test	Squint	4(25%)
	Ice pack	14(87.5%)
	Neostigmine	13(81.3%)
	RNS	5(31.3%)

87.5% of patients had ptosis and 12.5% had diplopia at the onset. Though 62.5% had symptomatic fatiguability of eyelid, 75% were found to be having lid fatiguability. Peek sign positive in 50%. Cogan's lid twitch is positive in

31.25%. 12.5% who showed positive lid retraction were hyperthyroid.

Out of 11 patients with unilateral ptosis, eight (72%) had right-sided ptosis at the onset of OMG. Eight (72%) out of the 11 patients with unilateral ptosis subsequently developed bilateral ptosis. All patients with bilateral ptosis had asymmetrical ptosis. All had enhancement of ptosis in the contralateral eye on lifting of the ptotic eyelid. Eight out of the 14(57%) patients with ptosis subsequently developed diplopia also.

None of the OMG patients had thymoma. One seropositive male patient had comorbid hyperthyroidism. One seronegative male patient with ptosis controlled on pyridostigmine alone had a recurrence of well-differentiated squamous cell carcinoma (left buccal mucosa) two months after the onset of ocular myasthenia.

### Tests

Ice pack test was positive in all the 14(100%) patients with ptosis. Thirteen patients out of 14 patients with ptosis had neostigmine test positive. Repetitive Nerve stimulation(RNS) was positive for five patients.

### AchR Antibody

Nine patients out of the 16 tested positive (cutoff of  $\geq 0.4$ IU) for AchR Antibody(Ab) titre had a mean Ab titer of 2.61(0.03) in contrast to seronegative patients with a mean Ab titer of 0.13  $\pm$  0.03 (0.5). The AchRAb range from 0.08 to 5.23 among ocular MG. Comparing the titre in two genders, male had lower mean 0.91(1.75) and in females it was 1.96(1.97). p value 0.5 .

### Outcome

All the 16 patients were symptomatically managed with Pyridostigmine Out of these 16 patients, eight patients were controlled on pyridostigmine alone and we could taper it off on follow up. Six patients out of the eight patients who went into remission on pyridostigmine alone had ptosis and two patients had additional diplopia. Eight patients who had persistent diplopia after starting pyridostigmine were started on prednisolone 40-60mg per day. The dose of

steroid was tapered and stopped over 3 -4 months in 6 patients. Two patients on steroids and pyridostigmine did not go into remission. Out of this one male patient, who had comorbid hyperthyroidism required high dose steroid therapy for 6 months. Subsequently prednisolone was tapered and continued at 10 mg on alternate day for 3 years. The other seropositive female patient needed steroids for 7 months. She subsequently evolved into generalized MG by the end of 10 months of onset of OMG. Azathioprine was added and she underwent thymectomy 2 months after generalization.

Table showing outcome at 3 years

Outcome	Total	
	Male	Female
Remission(n=8)	3	5
Remained OMG(n=7)	4	3
Generalized MG(n=1)	0	1

### Discussion

The mean age of OMG was 42.69 years. Even though the mean age of patients with OMG was similar to the study by Kupersmith<sup>(11)</sup>, seropositive patients had earlier age of onset compared to seronegative OMG patients. We observed slight female preponderance unlike the male dominance reported by Kupersmith. We observed Acetylcholine receptor antibody seropositivity in 56.25% of OMG patients in the present study similar to the experience in other studies<sup>(12)</sup>. The only one patient who progressed to generalized myasthenia had high titres of AchR antibodies(5.07nmol/L). Seronegativity was associated with milder disease<sup>(13)</sup>. Even though Kupersmith found seropositivity to be related to generalization of MG, higher antibody titres did not predict generalized MG<sup>(11)</sup>. Due to our small sample we couldn't relate antibody titre and generalization.

We documented unilateral ptosis to be a common initial manifestation, most often on the right side (72%). Bilateral ptosis was often asymmetric, with enhancement of ptosis on contralateral eye on lifting the ptotic eye. We often resorted to

neostigmine test due to non-availability of edrophonium test. In Kupersmithetal, 96.3% had positive edrophonium test which is comparable to 92.8% neostigmine test positivity (13/14) in our study. Lid fatigability test, ice pack test and neostigmine tests are for the diagnosis of MG.

Involvement of lateral rectus is not uncommon in MG. In this study lateral rectus(25%) is slightly more frequently involved than medial rectus (18.8%)<sup>(14)</sup>. In contrast Finelli et al observed medial rectus involvement followed by the superior rectus<sup>(15)</sup>. Decremental response in RNS is seen in only 33% of patients with MG which is comparable with our study(31.3%).<sup>(16)</sup>

All the patients with ptosis alone went into remission spontaneously and they required symptomatic management with pyridostigmine. Only 1 patient required prolonged steroid therapy for 6 months and continued at lower dose for longer periods. In study by Kupersmithetal steroids were given in similar doses as ours to 61.7%, but they had continued steroids at lower dose for longer periods.

Most patients with diplopia required immunomodulation with steroid and we could taper off steroids in a shorter period than the experience of Kupersmith. This suggests the need for studies to determine the duration of steroid therapy in MG. Our study reiterates the fact that MG is not associated with thymoma<sup>(11)</sup> and thymectomy may not be needed. In the majority of cases progression of MG to its generalized form will occur within the first 2 years after ocular symptoms begin<sup>(17)</sup>. It is similar to our study where generalization occurred within 1 year of ocular symptoms

### Conclusion

Asymmetrical ptosis and diplopia are the most common manifestations of MG. Association of thymoma is very rare with MG and thymectomy may not be needed. Acetylcholine esterase inhibitors is the initial treatment in all MG. Immunomodulation has a pivotal role in MG with diplopia and only short term steroid is required

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