

**Original Article**

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## **Clinical Profile of Patients with Myasthenia Gravis in A Tertiary Center of Nepal**

Myasthenia gravis(MG) has a cosmopolitan distribution and can affect people of all age-group. Sometimes atypical presentation causes difficulty in the early diagnosis and management. Our aim is to study the clinical subtypes and manifestations of MG along with serological and electrophysiological diagnostic methods. Patients who were admitted in Neurology department or presented in Neurology outpatient department of Tribhuvan University Teaching Hospital from 2015 March to 2016 November were retrospectively reviewed. Out of 28 patients reviewed, 23 patients were included in the study. Their mean age of onset was  $40.4 \pm 19.2$  years; range=12 – 78 years, and 12 of them were female ( 52.2%). Eight patients (34.8%) were diagnosed with ocular myasthenia and 15 were patients (65.2%) of General Myasthenia. Seventeen patients (73.9%) were acetylcholine receptor (AChR) antibodies positive, one female patient was found to be muscle specific kinase (MuSK) positive. Decremental pattern in Repetitive Nerve stimulation (RNS) was reported in 11 patients (47.8%) and ice pack test was positive in 16 patients (69.3%). Ophthalmological findings are the most common presentation of MG patients. Icepack test is an easy clinical diagnostic tool for outpatient department which has both high sensitivity and specificity. RNS and antibody tests are the supporting tests useful for confirming the diagnosis.

**Key Words:** acetylcholine receptor, muscle specific kinase, myasthenia gravis, ocular myasthenia

**M**yasthenia gravis is an autoimmune disease in which different antibodies are directed towards neuromuscular junction at postsynaptic level. Thus resulting in fatigability and weakness of frequently used skeletal muscles of face, neck, and limbs. Acetylcholine

receptor (AChR) antibodies and muscle specific kinase (MuSK) antibodies are the commonly detected antibodies, in about 80-90%.<sup>4</sup> Recently other antibodies are also being studied: LRP4, Agrin, Titin, Kv1.4, Ryanodine Receptor (RyR), Collagen Q and Cortactin.<sup>7</sup>

In recent years, both incidence and prevalence of Myasthenia gravis has been found to be increasing.<sup>2, 23</sup> Advancement in the diagnostic techniques, patient's awareness regarding disease, and long-term survival in patients might be the reason for this. A previous Nepalese study among ocular myasthenia patients has shown that 20% of patients were found to have AChR antibody positive, 75% were ice pack test positive and 83.3% had neostigmine test positive.<sup>22</sup> In this study, we will classify the clinical subtypes and understand the clinical manifestations along with serological and electrophysiological findings.

### Materials and Methods

We retrospectively included patients who were diagnosed with Myasthenia Gravis presented to Neurology inpatient or outpatient department of Tribhuvan University Teaching Hospital from 2015 March to 2016 November. Inclusion criteria were the clinical manifestation of ocular or generalised myasthenia, positive response to acetylcholinesterase inhibitor. Complete blood count, renal function test, Liver functional test, chest x-ray, electrocardiogram, computed Tomography(CT) Chest were done in all patients. Repetitive nerve stimulation test and AchR antibodies test were done in all patients. MUSK antibody test was done if AchR antibodies were negative.

Patients were classified according to Myasthenia Gravis Foundation of America: grade I: any ocular muscle weakness; grade II: mild weakness affecting other than ocular muscles; grade III: moderate weakness affecting other than ocular muscles; grade IV Severe weakness affecting other than ocular muscles; and grade V: Defined by tracheal intubation, with or without mechanical ventilation, except when employed in routine postoperative management.<sup>9</sup>

Repetitive nerve stimulation (RNS) test was done to see any decremental changes during rest and post exercise.<sup>19</sup> More than 10% in the decrement in the peak amplitude between first and fourth responses was considered as significant. One-minute post exercise RNS test was done if the initial RNS showed normal decremental response. Muscles selected for this test were Orbicularis oris, Nasalis and Abductor digiti minimi.

### Results

Out of 28 patients reviewed, 23 patients were included in the study. Five patients were excluded due to incomplete investigations: AChR antibody or RNS not done. Their mean age of onset was 40.4±19.2 years; range=12 – 78 years; 12 of them were female ( 52.2%); 11 were male (47.8%) and

male: female ratio was 0.92:1. 10 patients (43.5%) were native of Kathmandu, and 13 patients (56.6%) were from other different parts of the country. 78.3% of patients were first evaluated by ophthalmologists, and rest by general physicians. Patients were referred to Neurologists at a mean duration of 9.3±13.0 weeks of symptoms onset. Patients with age of onset was more than fourth decade in 14 patients (61%), distribution was equal in female patients, and 72.7% male patients were ≥40 years. No any statistical significance was established in different clinical characteristics between male and female groups (**Table 1**).

Clinical Characteristics	Male (n=11)	Female (n=12)	P Value
Age (mean ±SD) years	42.2±16.6	38.7±21.9	0.671 <sup>c</sup>
Age group			
Below 40 years	3 (27.3%)	6 (50%)	0.4 <sup>a</sup>
≥40 years	8 (72.7%)	6 (50%)	0.4 <sup>a</sup>
Dysarthria	5 (45.5%)	6 (50%)	1 <sup>a</sup>
Drooping Eyelid	11 (100%)	11(91.7%)	1 <sup>a</sup>
Nasal Voice	5 (45.5%)	9(75.5%)	0.214 <sup>a</sup>
Headache	5 (45.5%)	2(16.7%)	0.193 <sup>a</sup>
Restricted eye movements	10 (90.9%)	10(83.3%)	1 <sup>a</sup>
Dysphagia	5 (45.5%)	6 (50%)	1 <sup>a</sup>
Limb Weakness	5 (45.5%)	5(41.7%)	1 <sup>a</sup>
Dyspnea	3 (27.3%)	2(16.7%)	0.640 <sup>a</sup>
Crisis	2 (18.2%)	2 (16.7%)	1 <sup>a</sup>
AChR Antibodies	9 (81.8%)	8 (66.7%)	0.640 <sup>a</sup>
MuSK Antibodies	Not done	1 (8.3%)	b
DecrementalRNS	6(54.5%)	3 (25%)	0.214 <sup>a</sup>
Subtype			
Ocular	5 (45.5%)	3 (25%)	0.4 <sup>a</sup>
Generalized	6 (54.5%)	9 (75%)	0.4 <sup>a</sup>
Icepack Test	10 (90.9%)	6 (50%)	0.069 <sup>a</sup>

Table 1: Baseline Demographic Data

Data are expressed as n(%) or mean±standard deviation; a: Fisher Exact Test; b: P value not applicable; c: Student T test; SD: Standard Deviation; AChR: Acetylcholine receptor; MuSK: Muscle specific Kinase; RNS: Repetitive nerve stimulation

Eight patients (34.8%) were diagnosed with ocular myasthenia and 15 patients (65.2%) were Generalized Myasthenia. According to Myasthenia Gravis Foundation of America, patients were classified into different grades, as shown in **Figure 1**. No congenital myasthenia patients were reported in our study. Four Generalized myasthenia patients (17.4%) went to Crisis for which mechanical intubation

was done. Association of hypothyroidism was found in 9 patients (39.1%), Hypertension in 4 (17.3%), Diabetes Mellitus in 1 (4.3%) and Hyperthyroidism in 1 (4.3%).

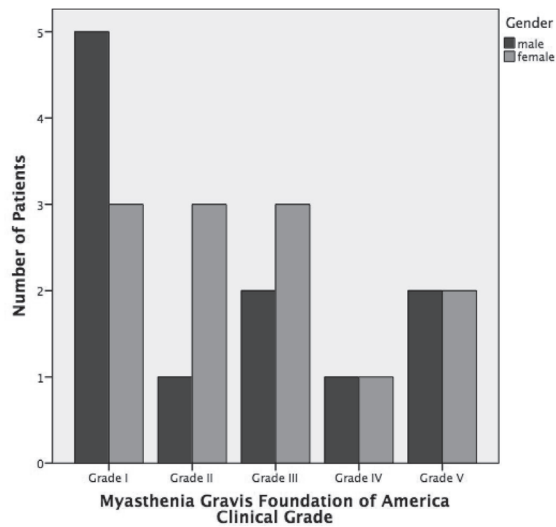


Figure 1: Clinical Grading of Myasthenia Gravis Foundation of America

Twenty-two patients (95.7%) have drooping to eyelids and diplopia, 20 patients (87%) had restricted eye movements, 14 patients (60.9%) had nasal voice, 11 patients had dysphagia (47.8%), 10 patients (43.5%) had limb weakness, 7 patients (30.4%) had headache, and 5 patients (21.7%) had shortness of breath.

Icepack test was found to be positive in 16 patients (69.6%), negative in 4 (17.4%) and not done in 3 (13%). Decremental pattern was reported in 11 patients (47.8%). Serological tests were done in all patients. Seventeen patients (73.9%) were acetylcholine receptor (AChR) antibodies positive, 9 males and 8 females ( $p=0.640$ ); 6 patients were AChR antibodies negative and one female patient (4.3%) with AChR antibody negative was found to be muscle specific kinase (MuSK) positive.

## Discussion

Clinical, serological and electrophysiological features of both ocular and generalized myasthenia were the focus of our study. Since ocular myasthenia can transform into generalized myasthenia within 1-2 years, careful examinations were done to look for any findings supporting generalized myasthenia. MG occurs worldwide affecting both sexes in all age-groups. Our study showed the equal distribution of MG between male and female. Male and female distribution had been found to be similar in a large cohort study in China.<sup>24</sup> Its prevalence in Australia was found to be 117.1 per million, predominant among female in age-group of 15-64, but male patients predominant after 65 years.<sup>6</sup> A Norwegian study reported female patients

were predominant in their study and prevalence was high among patients more than 50 years. Our study showed the increase tendency of male myasthenia patients above 40 years of age. Similarly, increased incidence among elderly people has been reported in Danish epidemiological study.<sup>23</sup> In contrast to these western studies, few Asian studies showed higher MG prevalence among adult populations.<sup>10, 24</sup>

Pure ocular myasthenia gravis was diagnosed in 34.8% of patients. Our result was similar to the studies of India, China, Sri Lanka.<sup>4,5,24,21</sup> Zang et al has reported 58% of ocular myasthenia in their study.<sup>24</sup> Our patients were only followed for few months after diagnosis. Usually 2-3 years is needed to see whether there is transformation to generalized myasthenia, as 50-70% of them can change to Generalized Myasthenia.<sup>4</sup> Mechanical intubation was needed in about 17.4% which is quite high, in comparison to other previous studies.<sup>5,21</sup>

Previous studies have shown the association of MG with autoimmune diseases of thyroid disorders, hyperthyroidism being common.<sup>3,5</sup> In contrast to this, our study showed hypothyroidism was common among MG patients (9 patients; 39.1%) whereas only 1 patient (4.3%) was found to have hyperthyroidism. A recent Chinese study showed that ocular myasthenia was more likely to be associated with thyroid dysfunction as compared to general myasthenia.<sup>17</sup> Although the association between MG and autoimmune thyroid disorders is still unclear, likelihood of genetic mechanism and sharing of similar epitopes have been postulated.<sup>3,16</sup> Some studies have postulated regarding the thyroid hormonal imbalance is likely in MG.<sup>11,12</sup>

Muscle weakness and fatigability are the features of MG. Ocular involvement is usually seen in about 70-90% MG patients.<sup>13,20</sup> In our study, about 95% patients had drooping of eyelids or diplopia and 87% had restricted eye movements. Similar to our study, bulbar involvement is another common finding in previous studies.<sup>5,15,21</sup> Lee et al reported that there is a high risk among generalized myasthenia patients to go into crisis.<sup>15</sup> Although there was no case of congenital myasthenia syndrome in our study, it is an important differential for congenital myopathies and autoimmune myasthenia gravis and can present even in adulthood.<sup>18</sup>

Icepack test was positive in about 70% of patients. It has a high sensitivity and specificity in myasthenia patients with ptosis and it is a useful diagnostic test even if edrophonium test is negative.<sup>14</sup> RNS study is relatively insensitive in ocular myasthenia and generalized myasthenia with mild weakness. Only 47.8% of MG patients showed the decremental response in RNS study whereas previous studies has reported about 75% of RNS

positive cases.<sup>21,24</sup> In our study, 74% of patients were AChR antibodies positive and 4.3% were MuSK positive which was similar to that of studies in India and China.<sup>8,21</sup>

### Conclusions

Equal gender distribution among MG patients was seen in our study. Ophthalmological findings are the most common presentation of MG patients. Icepack test is an easy diagnostic tool for outpatient department which has both high sensitivity and specificity. RNS and antibody tests are other supporting tests useful for diagnosis. Beside AChR and MuSK antibodies, further evaluation for other antibodies will help to understand whether the antibody profile of Nepalese population is similar to rest of the countries. So, a large number of patients with extensive investigations is needed for future studies.

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