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ORIGINAL RESEARCH ARTICLE

A CLINICAL APPROACH TO OCULAR MYASTHENIA GRAVIS

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ABSTRACT

Myasthenia gravis is a common disorder of the neuromuscular junction characterized clinically by muscle weakness and fatigability. Ocular myasthenia is often misdiagnosed in the initial stages due to the fluctuating nature of ptosis and diplopia. Here, we describe the clinical characteristics of ocular myasthenia gravis along with the diagnostic difficulties in a tertiary eye care center in Nepal. We retrospectively reviewed the charts of the patients diagnosed as ocular myasthenia gravis in Neuro-ophthalmology clinic, BPKLCOS, from 2010 to 2013. The diagnosis of ocular myasthenia was based on the association of typical history and signs together with at least one of these features: unequivocal improvement of ocular signs after injection of neostigmine, positive response to electrophysiological tests and detection of serum antibodies to acetylcholine receptors. There were 24 cases of diagnosed ocular myasthenia gravis during the 3 years. Among them 11 cases (45.8%) were males and 13 cases (54.1%) were females. The mean age was 32.04±19.56 years with the age range from 9 years to 68 years. The most common symptoms among patients were drooping of the lids (45.8%, n=11), followed by both double vision and drooping of the lids (37.5%, n=9) and only intermittent double vision in16.6% (n=4). In two patients (9.09%) CT-scan findings were suggestive of thymoma. The symptoms were resolved with anticholinesterases alone in 66.6% (n=16) and anticholinesterases were supplemented with immunosuppressive drugs in 33.3% (n=8) patients. Ocular myasthenia is often misdiagnosed in the initial stages due to its fluctuating nature. With a high index of clinical suspicion simple clinical tests accompanied by pharmacological tests can be useful in diagnosing the condition.

Key Words: *Acetylcholine receptor antibody, anticholinesterase drugs, neostigmine test, ocular myasthenia gravist.*

INTRODUCTION

Myasthenia gravis is an autoimmune disease characterized clinically by muscle weakness and fatigability, caused by a reduction in the number of available acetylcholine receptors at neuromuscular junctions. The prevalence of myasthenia is 150 to 200 per million. [1] Incidence in female to male subjects is in 3:2 ratio. However, the greatest incidence in women is in the third decade in life whereas in men it is in the sixth or seventh decade. Onset may be at any age from birth to the ninth decade. [2] Ocular myasthenia accounts for 15% of all cases. Two thirds of those with initial ocular involvement develop systemic symptoms within 2 years.[3]

Ocular myasthenia gravis (OMG) causes ptosis, diplopia, and extraocular muscle and orbicularis oculi weakness without dysfunction of other muscles. The weakness of muscles occurs in a vague and fluctuating pattern leading to variable ptosis often alternating from one eye to another. The occurrence of intermittent diplopia can be confusing not only to the patients but also to the unsuspecting physician and may be misinterpreted as having a psychogenic origin.

The tests used to diagnose myasthenia gravis include clinical tests like ice pack test or sleep test, assays for circulating antibodies to components of the neuromuscular junction like acetylcholine receptor (AChR) and/or muscle specific tyrosine kinase (MuSK) antibodies, pharmacologic tests like Edrophonium or Neostigmine test and electrophysiological tests like repetitive nerve stimulation (RNS), and single-fiber electromyography tests. In addition, chest computed tomography (CT) or magnetic resonance imaging (MRI) with contrast should be performed in all myasthenia gravis patients to look for a thymoma. The important differential diagnoses for ocular myasthenia are mitochondrial myopathy like chronic progressive external ophthalmoplegia, oculopharyngeal dystrophy and restrictive thyroid ophthalmopathy. [4]

Although acetylcholinesterase inhibitors have been time-tested and used as a first line of therapy in cases of generalized myasthenia, they are not considered generally effective in cases of ocular myasthenia. Moreover, the treatment is controversial. [5] Recent studies have highlighted the role of immunomodulators like prednisolone to restore visual function in OMG. [6]

Here we report a study of the patients diagnosed with ocular myasthenia gravis along with the diagnostic difficulties in a tertiary eye care centre in Nepal.

METHODS

We retrospectively reviewed the charts of the patients diagnosed as ocular myasthenia gravis in our Neuro-ophthalmology clinic from 2010 to 2013. The diagnosis of ocular myasthenia was based on the association of typical history and signs together with at least one of these features: unequivocal improvement of ocular signs after injection of Tensilon test, positive response to Electromyography tests, detection of serum antibodies to AChR[5]. We excluded all patients who had symptoms of difficulty in swallowing or chewing, fatigue, limb weakness or respiratory muscle weakness which suggested features of generalized myasthenia gravis (GMG) at the onset of disease. Other exclusion criteria were restrictive muscle pathology, chronic progressive external ophthalmoplegia, congenital ptosis and Duane's retraction syndrome.

Neostigmine test was done in all our patients suspected of myasthenia gravis. The patient was kept in observation and atropine 0.6mg was administered intramuscularly 15 minutes before neostigmine. Injection neostigmine (1.5-2.5mg) was administered intramuscularly monitoring cardiac status and pulse rate. The ptosis or deviation was measured before medication. After medication it was measured every 5 minutes for 15 minutes, then every 10 minutes for 30 minutes and later half hourly until 2 hours. Any improvement in ptosis or ocular deviation was noted as positive response.

Patients once diagnosed as myasthenia gravis were advised for computed tomography(CT) of the chest to rule out thymoma, serum Acetylcholine Receptor antibody (AChR antibody) and thyroid function tests. Besides, rheumatoid factor and anti-nuclear antibody tests were also sent to rule out other associated autoimmune diseases. For patients who could not afford all these expensive investigations priority was given to CT-chest. MRI of the brain and orbit was done in some patients where other intracranial pathology was suspected.

All the patients with ocular myasthenia gravis were started with oral pyridostigmine tablets 180mg daily in three divided doses in adults and half the dose in children. The dose was increased up to maximum of 240mg daily if there was no improvement in symptoms. Patients who were not responding well with this treatment were supplemented with oral neostigmine, oral steroids and/or oral azathioprine. Only those patients who had at least one follow up after starting medications were included to see the response to the medication.

RESULTS

There were 24 cases of diagnosed ocular myasthenia gravis in the 3 years from 2010 to 2013.

Among them 11 cases (45.8%) were males and 13 cases (54.1%) were females. The mean age was 32.04 ±19.56 year with the age range being from 9 years to 68 years. The mean age for the males was 29.5±21.33 years and the mean age for females was 34.0 ±18.73 years.

The most common symptoms among patients were drooping of the lids (45.8%, n=11), followed by occasional double vision along with drooping of the lids (37.5%, n=9) and intermittent double vision (16.6%, n=4). Most of the patients (83.3%, n= 20) reported diurnal fluctuation or variability of symptoms. The duration of symptoms at presentation varied from as early as 5 days to 6 years. Out of 24 patients, 83.3% had visual acuity 6/6. Only 16.6% had visual acuity 6/18 or less.

Most of the patients in our study group (45.9%) had right eye involvement. Left eye involvement was seen in 29.1% and both eyes showed weakness in 25% of the cases. The most commonly involved muscle was levator palpebrae superioris alone (45.8%, n=11), followed by orbicularis oculi, medial rectus, superior rectus, inferior oblique, lateral rectus and inferior rectus in various combinations. There were two cases of isolated medial rectus weakness, one case each of isolated superior rectus and lateral rectus paresis. Among the 13 patients with ocular deviation combined horizontal and vertical ocular misalignment was most frequent (46.1%,n=6) followed by horizontal (30.7%,n=4) and vertical (23%,n=3) deviations.

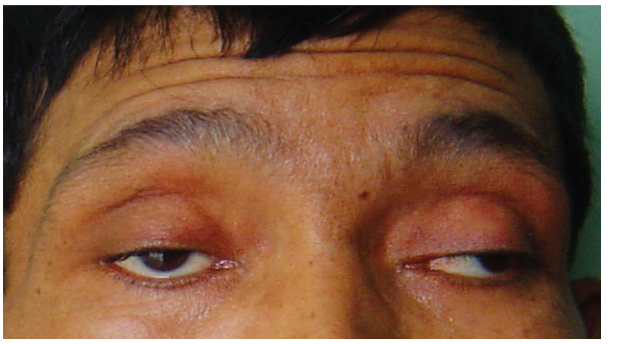

Figure1: Bilateral ptosis in ocular myasthenia

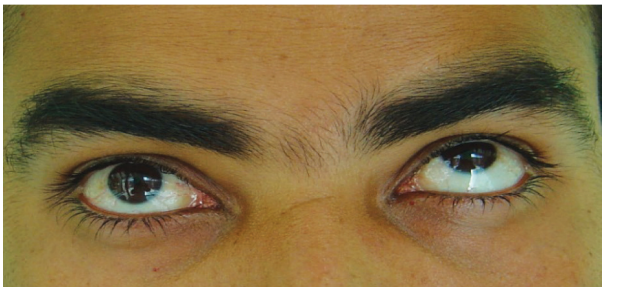

Figure 2: Restricted upgaze in ocular myasthenia

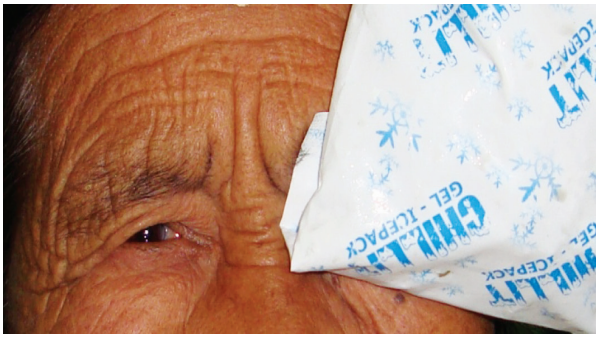

Figure 3: Icepack test being performed in a patient

Icepack test was positive in 18 patients (75%). Neostigmine test was positive in 20 patients (83.3%). Out of the 15 patients with serum AChR antibody reports 66.6% (n=10) had negative reports, 20% (n=3) had positive and 13.3% (n=2) had equivocal results.

Table 1: Diagnostic sensitivity of clinical and laboratory tests in ocular myasthenia

Diagnostic test	Total no of cases	No. of positive cases	Sensitivity
Ice pack test	24	18	75%
Neostigmine test	24	20	83.3%
AchR antibodies	15	2	20%

Out of the 24 patients, 22 patients (91.6%) had CT-chest reports available. Nineteen out of 22 patients (86.3%) had normal chest CT. In two patients (9.09%) CT-scan findings were suggestive of thymoma out of which one case followed up after surgery and biopsy reports confirmed the finding as thymoma. In rest 1 case (4.5%) the finding was suggestive as thymic hyperplasia.
The thyroid function test reports were available of 13 patients which showed normal results in 76.9% (n=10), hypothyroidism in 15.3% (n=2) and hyperthyroidism in 7.6% (n=1).
Magnetic resonance imaging (MRI) of the brain was done in 8 cases (33.3%) in patients where the diagnosis was not clear initially and to rule out any intracranial pathology. However, the reports in all cases were within normal limits.

The symptoms were resolved with anticholinesterases alone in 66.6% (n=16) and anticholinesterases were supplemented with immunosuppressive drugs in 33.3% (n=8) patients. Among the eight patients who received immunosuppressive drugs all eight received oral prednisolone and two others received oral azathioprine in addition. The prednisolone dose was started with 10mg/day initially and dose was increased by 10mg to a final dose of 50-60mg/day. Two patients (8.3%) later stopped anticholinesterase treatment due to intolerable muscarinic side effects.

Two patients during follow up developed generalization of the symptoms both of which occurred within a year of onset of disease.

DISCUSSION

The diagnosis of ocular myasthenia gravis is mainly based on typical clinical history of fluctuating symptoms. Often there may be no obvious signs evident in mildly affected patients at first examination unless we specifically look for fatigable weakness of ocular muscles with repeated provocative clinical tests. Hence there may be delay in the diagnosis. Two of the patients in our study were initially misdiagnosed; one case as a case of migraine headache with intermittent diplopia. She later developed frank ptosis and further tests proved it to be a case of OMG. The other case was initially treated with oral steroids for lateral rectus palsy which resolved. Later there was fatigable ptosis and the diagnosis was reconfirmed as OMG after further tests.
There was no significant difference in sex in our study with males being 45.8% and females being 54.1%, however there was male predominance among OMG patients in a major study.[2] For all cases of myasthenia gravis including ocular myasthenia the incidence in female to male subjects is in the ratio of 3:2. In the same study the bimodal age distribution was evident with the incidence in women being in the third decade in life and in the sixth or seventh decade in life for men. [2] Due to the small number of patients in our study, no specific distribution pattern of age and sex was evident.

In our study most of the patients had ptosis (45.8%), followed by both ptosis and diplopia (37.5%) and diplopia alone was present in 16.6% of cases. This is different from a previous study [6] where majority of the cases had both diplopia and ptosis. Combined horizontal and vertical ocular misalignment was most frequent (46.1%) followed by horizontal (30.7%) and vertical (23%) deviations which was similar to a previous study. [6] Like other reports, LPS was the most commonly affected muscle followed by orbicularis oculi. [5]

The use of local cooling in a patient with ptosis who is suspected of having myasthenia is a rapid, simple, and inexpensive test with a high degree of specificity and sensitivity. [7, 8] A transient improvement of symptoms after injection of edrophonium (Tensilon test) is generally considered fundamental in the diagnosis of MG. Because of the transient nature of the ocular (and systemic) changes in muscle strength that occur following the administration of edrophonium, the neostigmine bromide test remains an exceptionally valuable method of diagnosing MG, particularly in patients with diplopia but without ptosis. The longer duration of the effects of this drug is sufficient to permit repeated testing of muscle strength and evaluation of ocular motility. [9] In addition edrophonium is expensive and is not available in our setting. Besides, reports have suggested positive diagnostic response to neostigmine in 70-94% cases of myasthenia cases. [10,11] One report shows similar sensitivity to the test for both generalized and ocular myasthenia gravis. [11] Our report of positive neostigmine test (83.3%) is similar to these previous reports.

AChR Antibodies were positive in 20% of our patients which is lower than that of previous studies.[5, 2,13] It has been reported that patients who are negative for AChR antibody at the onset of the disease, seroconversion may occur later during the course. Hence repeated testing 6-12 months later may detect AChR antibodies in approximately 15% of patients who were seronegative. [14] Due to the short duration of our study and limited follow up visits we could not repeat serum AChR antibody test which may have led to the above results. Besides, this test is not available in our country and the blood samples had to be sent abroad. It is an expensive test and along with the cost of CT-chest, many patients could not afford to do both the tests. So in such patients we gave priority to CT-chest as AchR antibodies does not change the prognosis in diagnosed myasthenia patients. In our patients thymoma was found in 9% cases and thymic hyperplasia in 4.5% (1 case) and all three were in young patients. Similar reports were noted in previous studies. [11,15]

Repetitive nerve stimulation(RNS) studies use a slow rate (2–5 Hz) of repetitive electrical stimulation. The study is positive if the motor response declines by more than 10%. RNS in distal muscles are positive in about 75% patients of GMG and in 30%

with OMG. [16] Due to technical problems we were not able to do RNS in ocular muscles, hence it was done only in cases of GMG. Single fibre EMG which is technically more demanding is positive in 95% of GMG and in 85-90% of OMG cases, however it is not available in our country at present.

In our study most of the patients were treated with acetylcholinesterase inhibitors alone with significant improvement in 66.6% cases and immunosuppressives were added in 33.3% cases. Immunosuppressives used were prednisolone alone in 8 cases and in 2 cases it was supplemented with azathioprine. This is in contrast to previous reports where most patients required steroids for remission and to maintain binocular single vision.[5,6] This may have occurred because most patients in our study had ptosis and it has been seen that pyridostigmine alleviates ptosis but may be ineffective in resolving diplopia. [17] Side-effects requiring discontinuation of acetylcholinesterase were noted in 2 cases (8.3%) whereas no side effect severe enough to require discontinuation were present when steroids were given. This may be due to dietary counseling done in all patients to reduce weight gain, use of proton pump inhibitors, calcium and vitamin D, using low maintenance doses, and also maybe due to the short duration of follow up in our study. Prednisolone is the most commonly used immunomodulator, which leads to remission or marked improvement in 70-80% patients with OMG/GMG. [18] It may also reduce the progression of OMG to GMG. [19] Moderate dose (50–60 mg) daily prednisone, tapered over 6 weeks, followed by 10 mg or less daily, resolves diplopia in primary and downward gaze more frequently than with pyridostigmine alone. [6] Although azathioprine appears to be effective, it can take 6 months to improve the ocular motor dysfunction and is less practical for patients needing a rapid response. [20] Azathioprine or other immunosuppressive agents like mycophenolate mofetil could be considered for patients who fail prednisolone.

CONCLUSION

Although myasthenia gravis is one of the common disorders of the neuromuscular junction, ocular myasthenia is often misdiagnosed in the initial stages due to its fluctuating nature. With a high index of clinical suspicion, simple clinical tests accompanied by pharmacological tests can be useful in diagnosing the condition. In developing countries like ours, where sophisticated investigations are not available and cost factor is one of the major drawbacks utilizing clinical acumen becomes all the more important.

List of abbreviations

1. AChR : acetylcholine receptor
2. CT : computed tomography
3. EMG : elctromyography
4. GMG : generalized myasthenia gravis
5. MG : myasthenia gravis
6. MRI : magnetic resonance imaging
7. MuSK : muscle specific tyrosine kinase
8. OMG : ocular myasthenia gravis

REFERENCES

1. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle & nerve. 2004;29(4):484-505.
2. Perlo VP, Poskanzer DC, Schwab RS, Viets HR, Osserman KE, Genkins G. Myasthenia gravis: evaluation of treatment in 1,355 patients. Neurology. 1966;16(5):431-9.
3. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. Archives of neurology. 2003;60(2):243-8.
4. Li Y, Arora Y, Levin K. Myasthenia gravis: newer therapies offer sustained improvement. Cleveland Clinic journal of medicine. 2013;80(11):711-21.
5. Evoli A, Tonali P, Bartoccioni E, Lo Monaco M. Ocular myasthenia: diagnostic and therapeutic problems. Acta neurologica Scandinavica. 1988;77(1):31-5.
6. Kupersmith MJ, Ying G. Ocular motor dysfunction and ptosis in ocular myasthenia gravis: effects of treatment. The British journal of ophthalmology. 2005;89(10):1330-4.
7. Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. Neurology. 1987;37(8):1383.
8. Ertaş M, Araç N, Kumral K, Tunçbay T. Ice test as a simple diagnostic aid for myasthenia gravis. Acta neurologica Scandinavica. 1994;89(3):227-9.
9. Viets HR, Schwab RS. Prostigmin in the Diagnosis of Myasthenia Gravis. New England Journal of Medicine. 1935;213(26):1280-3.
10. Miller NR, Morris JE, Maquire M. Combined use of neostigmine and ocular motility measurements in the diagnosis of myasthenia gravis. Archives of ophthalmology. 1982;100(5):761-3.
11. Hsu SY, Tsai RK, Wang HZ, Su MY. A comparative study of ocular and generalized myasthenia gravis. The Kaohsiung journal of medical sciences. 2002;18(2):62-9.
12. Vincent A, Newsom Davis J. Anti-acetylcholine receptor antibodies. Journal of neurology, neurosurgery, and psychiatry. 1980;43(7):590-600.
13. Oda K, Ito Y. Myasthenia gravis: antibodies to acetylcholine receptor in ocular myasthenia gravis. Journal of neurology. 1981;225(4):251-8.
14. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. Muscle & nerve. 2007;36(5):651-8.
15. Kaye AD, Janssen R, Arger PH, Lisak R, Coleman BG, Gefter W, et al. Mediastinal computed tomography in myasthenia gravis. The Journal of computed tomography. 1983;7(3):273-9.
16. Oh SJ, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D. Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle & nerve. 1992;15(6):720-4.
17. Schlezinger NS, Fairfax WA. Evaluation of ocular signs and symptoms in myasthenia gravis. Archives of ophthalmology. 1959;62:985-90.
18. Pascuzzi RM, Coslett H, Johns T. Long-term corticosteriod treatment of myasthenia gravis: Report of 116 Patients. Annals of neurology. 1984;15(3):291-8.
19. Monsul NT, Patwa HS, Knorr AM, Lesser RL, Goldstein JM. The effect of prednisone on the progression from ocular to generalized myasthenia gravis. Journal of the neurological sciences. 2004;217(2):131-3.
20. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology. 1998;50(6):1778-83.