Clinical Features Of Ocular Myasthenia Gravis In Adult Patients: Diplopia and Ophthalmoplegia

Junjie Tang
Jinan University First Affiliated Hospital
Fangyuan Chen
Jinan University First Affiliated Hospital
Xiaoyong Liu
Jinan University First Affiliated Hospital
Jian Chen
Jinan University First Affiliated Hospital
Qing Zhou (Kerryzh@163.com)
https://orcid.org/0000-0002-5234-6383

Research article

Keywords: Ocular myasthenia gravis, Diplopia, Extraocular muscle, Ophthalmoplegia, Adult

Posted Date: February 11th, 2020

DOI: https://doi.org/10.21203/rs.2.23102/v1

Abstract

Background: The diagnosis of ocular myasthenia gravis (OMG) in adult patients remained challenged and the characteristics of diplopia and ophthalmoplegia in OMG is unclear.

Methods: Retrospective case series study of medical records of 40 adult patients diagnosed with OMG at The First Affiliated Hospital of Jinan University from June, 2016 to December, 2019, was performed to analyze the clinical features, diagnostic tests and preferential affected extraocular muscles of OMG.

Results: 40 adult patients with OMG were involved and men represented 20 (50%) of cases. Mean age (±SD) among men was 49 ± 21 years (range: 19-81 years) and 40 ± 15 years (range: 21-65 years) among women. 18 patients (45.0%) were 18 to 39 years old, 12 patients (30.0%) were 40 to 59 years old, 9 patients (22.5%) were 60 to 79 years old, 1 patients (2.5%) over 80 years old. The median course of the disease among all the patients was 6 months (ranged: 1 month to 10 years). Neostigmine test was positive in 32 of 40 patients (80.0%), acetycholine receptors antibodies assay was positive in 4 of 40 patients (10.0%), Thymus CT showed abnormal findings in 5 of 40 patients (12.5%). At the first visit, 27 patients (67.5%) showed diplopia only, 9 patients (22.5%) showed ptosis only, 4 patients (10.0%) showed diplopia with ptosis. The most paralytic EOM, determined through light reflection, cover-uncover test and red glass test for patients presented with diplopia only (n=27) and diplopia with ptosis (n=9), was lateral rectus (51.6%), superior rectus (19.4%), medial rectus (12.9%), inferior rectus (9.8%), superior oblique (3.2%), inferior oblique (3.2%) in order.

Conclusions: OMG mainly affected adults at the working ages. Diplopia serves as initial symptom in most adult patients with OMG and lateral rectus is most susceptible.

Background

Myasthenia gravis (MG) is regarded as an autoimmune disease, with antibodies against acetycholine receptors (AchR) at the neuromuscular junction (NMJ), causing faulty transmission of impulses and consequently leading to muscle weakness[1, 2]. Ocular myasthenia gravis (OMG) is defined as MG symptoms and signs restricted to extraocular muscle (EOM), levator palpebrae superioris and orbicularis oculi[1]. The clinical manifestations of OMG include pupil sparing ophthalmoplegia, with or without ptosis, which can mimic isolated cranial nerve palsies, thyroid eye disease and internuclear ophthalmoplegia[3]. Diplopia and ptosis are classic findings in OMG and these ocular symptoms are variable and fluctuant, easily leading to misdiagnose. Several researches had mentioned the mechanism of the susceptibility of ocular muscles in OMG[4, 5], but there was few study discussed the characteristics of diplopia and ophthalmoplegia in OMG. In this study, we reviewed the medical records of 40 adult patients with OMG and summarized the clinical features of OMG in adult patients and the characteristics of diplopia and ophthalmoplegia in OMG.

Methods

The medical records of 40 adult patients diagnosed with OMG at The First Affiliated Hospital of Jinan University from June, 2016 to October, 2019 were reviewed. The study was approved by the Ethics Committee of The First Affiliated Hospital of Jinan University and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

All patients followed the diagnostic criteria of OMG: the variable and fluctuant ocular muscle weakness and fatigability, which is the hallmark of the disease, with one of the positive results of neostigmine testing, antibodies examination, electrophysiologic testing, thyroid function and thymus CT[6, 7]. Patients who showed extra symptoms or signs of GMG or less than 18 years old were excluded. The general information of the patients including age, gender and the course of the disease were collected. The positive results of the diagnostic testing including neostigmine test, acetylcholine receptor antibodies (AChR-ab) assay, thymus CT were collected. To manifest the occurrence rate of diploia in OMG, patients were divided into three phenotype according to ocular manifestation: diplopia only, ptosis only and diplopia with ptosis.

The most paralytic extraocular muscle was idnetified in patients presented with diplopia through light reflection, cover-uncover test, red glass test and Maddox rod test[8, 9]. Firstly, objective assessment of ocular alignment was tested by corneal light reflex and cover-uncover test. Then the double vision was determined and interpreted by the result of Maddox rod test. There are two responses in patients with diplopia. Vertical diplopia is indicated when the horizontal line is above or below the light and horizontal diplopia is indicated when the vertical line is to the left or to the right of the light. The most paralytic extraocular muscle is determined by the red glass test. In the red glass test, patient held a red glass in front of the deviated eye (or right eye if no obvious deviation) and looked at the light point with both eyes in six cardinal positions. The position with a maximum distance of double vision indicates the associated muscles are paralyzed.

Results

A total of 40 patients with OMG met the inclusion criteria. Men represented 20 (50%) of cases. Mean age (± SD) among men was 49 ± 21 years (range: 19–81 years) and 40 ± 15 years (range: 21–65 years) among women. 18 patients (45.0%) were 18 to 39 years old, 12 patients (30.0%) were 40 to 59 years old, 9 patients (22.5%) were 60 to 79 years old, 1 patients (2.5%) over 80 years old (Table 1). The median course of the disease among all the patients was 6 months (ranged: 1 month to 10 years). For the positive results of diagnostic tests, the neostigmine test was positive in 32 of 40 patients (80.0%), AChR-ab assay was positive in 4 of 40 patients (10.0%), Thymus CT showed abnormal findings in 5 of 40 patients (12.5%) (Table 2). At the first visit, 27 patients (67.5%) showed diplopia only, 9 patients (22.5%) showed ptosis only, 4 patients (10.0%) showed diplopia with ptosis. Phenotype and age distribution were shown in Table 3. The most paralytic EOM, determined through light reflection, cover-uncover test and red glass test for patients presented with diplopia only and diplopia with ptosis, was lateral rectus (51.6%), superior rectus (19.4%), medial rectus (12.9%), inferior rectus (9.8%), superior oblique (3.2%), inferior oblique (3.2%) in order (Table 4).

Table 1

Age and gender distribution of 40 adult patients with ocular myasthenia gravis

Age groups (years)	Total		Male		Female	
	Number	%	Number	%	Number	%
18–39	18	45.0	8	20.0	10	25.0
40–59	12	30.0	5	12.5	7	17.5
60–79	9	22.5	6	15.0	3	7.5
≥ 80	1	2.5	1	2.5	0	0
Total	40	100.0	20	50.0	20	50.0

Table 2

Results of diagnostic testing in 40 patients with OMG

Diagnostic Testing	Positive results	
	Number	%
Neostigmine test	32	80.0
AChR-Ab assay	4	10.0
Thymus CT	5	12.5
OMG: ocular myasthenia gravis AChR-Ab: acetylcholine receptor antibody		
CT: computed tomography		

Table 3

Phenotype and age distribution of 40 adult patients with ocular myasthenia gravis

Phenotype	Patients		Age (years)			
	Number	%	18–39	40–59	60–79	≥ 80
Diplopia only	27	67.5	15	6	5	1
Ptosis only	9	22.5	4	3	2	0
Diplopia with ptosis	4	10.0	1	1	2	0
Total	40	100.0	20	10	9	1
OMG: ocular myasthenia gravis						

Table 4
The most paralytic EOM in patients presented with diplopia only and diplopia with ptosis

EOM	Patients (n = 36)	
	Number	%
LR	16	51.6
SR	6	19.4
MR	4	12.9
IR	3	9.8
SO	1	3.2
IO	1	3.2
EOM: extraocular muscle MR: medial rectus LR: lateral rectus SR: superior rectus		
IR: inferior rectus SO: superior oblique IO: inferior oblique		

Discussion

In this study, we found that the peaking age of OMG ranged from 18 to 39 years both in men and women. The age and gender distribution showed a diminishing distribution with age increased in both male and female. The distribution pattern was different from the results of previous studies. It was reported that there was a bimodal distribution in female and unimodal distribution in male[10]. However, patients involved in those studies were mainly Caucasian and non-Caucasian patients diagnosed with OMG tended to be younger than Caucasian patients for nearly 2 decade, especially the Asian patients[10–12]. Patients in this study were all Chinese, which might explain the younger diagnostic age. Previous studies reported that more patients presented with initial symptoms of ptosis only, in which the children were involved[13, 14]. In this study, most patients presented with diplopia only, which may be related to the age composition, because there was no child was involved in this study and diplopia alone was less common in childhood OMG[15]. The median course of OMG in this study was 6 months and the course ranged from 1 month to 10 years. The long and fluctuant course of disease was a feature of OMG, because most patients came to the first visit at the time when they could not endure the variable discomfort anymore. To summarize the characteristics of the age, phenotype distribution and course of OMG in this study, we could find that OMG mainly affected adult at the working ages and most of them had a long course and presented with diplopia only, which would definitely cause significant socioeconomic impact.

Currently, OMG remains a clinical diagnosis, but various diagnostic testing can help in determining the diagnosis. Edrophonium is a short-acting acetylcholinesterase (AChE) inhibitor, which was commonly used in clinic to diagnose MG. The sensitivity of the edrophonium test for diagnosing OMG was 88–97%

[6, 16, 17]. Neostigmine, an alternative to edrophonium for pharmacological testing, is a long-acting AChE, making it more suited in the examination of ocular motility and diplopia testing[1]. The sensitivity of neostigmine test in this study was 80.0%, indicating that neostigmine test is also available in diagnosing OMG. Serological tests for AchR antibodies, antimuscle specific tyrosine kinase (MuSK) and LDL-related receptor-related protein 4 (LRP4) were used in diagnosing MG[6]. Detection of AChR antibodies remained the most common method for the diagnosis of OMG so far, but elevated level of AchR antibodies were found in only on half of patients with OMG, especially in older age, male sex, and progression to GMG[18, 19]. Thymic assessment like chest computed tomography (CT) should be done in every patients with MG symptoms to determine the presence of thymoma or thymus hyperplasia, because about 10% of patients with MG are correlated with thymus disorders[20]. The results of the serological test and thymic CT were similar to the previous reports, though the positive results were not found in most patients, it remained necessary examination for OMG.

Ophthalmoplegia can be found in different kinds of diseases and bring huge disturbance for patients in daily life. Ophthalmoplegia in OMG can range from involvement of a single EOM to multiple EOMs even the complete ophthalmoparesis[3, 21]. Previous research had demonstrated that the preferential susceptibility of ocular muscles in MG might be explained by the unique physiological properties of EOM synapses[4, 5, 22]. However, whether there is any different susceptibility within the six EOMs in OMG remained unclear. Clinical findings suggested that there might be differences within the EOMs. For example, inferior rectus and medial rectus are more susceptible in thyroid eye disease[23]. In this study, the most paralytic EOM was determined through light reflection, cover-uncover test, red glass test and Maddox rod test. The results demonstrated that lateral rectus was the most susceptible, followed by superior rectus and medial rectus. The mechanisms underlying why different EOM show different susceptibility remain unclear. Lateral rectus, innervated by abducent nerve, was studied in animal researchs but seldom studies compared lateral rectus with other EOMs[24]. When lateral rectus was affected in patients with OMG, esotropia was found and patients would complained a horizontal double vision, which was aggravated when gazed laterally.

This case series was limited by the retrospective nature and the small samples of the study. However, to our best knowledge, this is the first study to report the susceptibility differences of EOMs in OMG. In order to certain the diagnosis of OMG in early period and prevent it convert into GMG, more cases should be collected to further study the characteristics of diplopia and ophthalmoplegia in adult patients with OMG.

Conclusion

This study revealed that OMG mainly affected adults at the working ages. Diplopia serves as initial symptom in most adult patients with OMG and lateral rectus is most susceptible.

Abbreviations

OMG: Ocular Myasthenia Gravis; MG: Myasthenia gravis; AchR: Acetycholine receptors; NMJ: Neuromuscular Junction; EOM: Extraocular Muscle.

Declarations

Acknowledgements

We would like to thank all the patients involved in this study. This work was supported by the Department of Ophthalmology, The First Affiliated Hospital of Jinan University, Guangzhou, China.

Authors' contributions

JJT collected the medical records and wrote the first draft of the manuscript and figures. FYC managed and analyzed the data. XYL contributed to the design of the study the study and the preparation of the manuscript. JC and QZ were involved in critical revision of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported in part by grants from Guangzhou Research Collaborative Innovation Projects (201803040011). The funding organization had no role in designing or conducting of this study.

Availability of data and materials

All data generated or analysed during this study have been presented within the manuscript and in the form of charts.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Jinan University and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Consent for publication

Written informed consent was obtained from all patients for the publication of this report.

Competing interests

The authors declare that they have no competing interests.

Author details

The Department of Ophthalmology, The First Affiliated Hospital of Jinan University, No. 613, Huangpu Avenue, Tianhe District, Guangzhou, Guangdong Province, China.

References

1. Nair AG, Patil-Chhablani P, Venkatramani DV, Gandhi RA: Ocular myasthenia gravis: A review. Indian J Ophthalmol. 2014, 62(10):985-991.
2. Melzer N, Ruck T, Fuhr P, Gold R, Hohlfeld R, Marx A, Melms A, Tackenberg B, Schalke B, Schneider-Gold C *et al*: Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol. 2016, 263(8):1473-1494.
3. Smith SV, Lee AG: Update on Ocular Myasthenia Gravis. Neurol Clin. 2017, 35(1):115-123.
4. Soltys J, Gong B, Kaminski HJ, Zhou Y, Kusner LL: Extraocular muscle susceptibility to myasthenia gravis: unique immunological environment? Ann N Y Acad Sci. 2008, 1132:220-224.
5. Ubogu EE, Kaminski HJ: The preferential involvement of extraocular muscles by myasthenia gravis. Neuro-Ophthalmology. 2001, 25(4):219-227.
6. Fortin E, Cestari DM, Weinberg DH: Ocular myasthenia gravis: an update on diagnosis and treatment. Curr Opin Ophthalmol. 2018, 29(6):477-484.
7. Nils EG: Myasthenia Gravis. N Engl J Med. 2016, 375(26):2570-2581.
8. Danchaivijitr C, Kennard C: Diplopia and eye movement disorders. J Neurol Neurosurg Psychiatry. 2004, 75 Suppl 4:iv24-31.
9. Yoo HS, Park E, Rhiu S, Chang HJ, Kim K, Yoo J, Heo JH, Nam HS: A computerized red glass test for quantifying diplopia. BMC Ophthalmol. 2017, 17(1):71.
10. Peragallo JH, Bitrian E, Kupersmith MJ, Zimprich F, Whittaker TJ, Lee MS, Bruce BB: Relationship Between Age, Gender, and Race in Patients Presenting With Myasthenia Gravis With Only Ocular Manifestations. J Neuroophthalmol. 2016, 36(1):29-32.
11. Phillips LH, 2nd, Torner JC, Anderson MS, Cox GM: The epidemiology of myasthenia gravis in central and western Virginia. Neurology. 1992, 42(10):1888-1893.
12. Chiu HC, Vincent A, NewsomDavis J, Hsieh KH, Hung T: Myasthenia gravis: population differences in disease expression and acetylcholine receptor antibody titers between Chinese and Caucasians. Neurology. 1987, 37(12):1854.
13. Supinda L, Niphon C, Wanicha C: Clinical profiles of Thai patients with ocular myasthenia gravis in Siriraj Hospital. J Med Assoc Thai. 2011, 94(9):1117-1121.
14. Wang LL, Zhang Y, He ML: Clinical Features and Prognosis of Ocular Myasthenia Gravis Patients with Different Phenotypes. Chin Med J (Engl). 2015, 128(19):2682-2684.
15. Huang X, Li Y, Feng H, Chen P, Liu W: Clinical Characteristics of Juvenile Myasthenia Gravis in Southern China. Front Neurol. 2018, 9:77.
16. Mittal MK, Barohn RJ, Pasnoor M, McVey A, Herbelin L, Whittaker T, Dimachkie M: Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response. J Clin Neuromuscul Dis. 2011, 13(1):46-52.

17. Benatar M: A systematic review of diagnostic studies in myasthenia gravis. Neuromuscul Disord. 2006, 16(7):459-467.
18. Provenzano C, Marino M, Scuderi F, Evoli A, Bartoccioni E: Anti-acetylcholinesterase antibodies associate with ocular myasthenia gravis. J Neuroimmunol. 2010, 218(1-2):102-106.
19. Peeler CE, De Lott LB, Nagia L, Lemos J, Eggenberger ER, Cornblath WT: Clinical Utility of Acetylcholine Receptor Antibody Testing in Ocular Myasthenia Gravis. JAMA Neurol. 2015, 72(10):1170-1174.
20. Higuchi O, Hamuro J, Motomura M, Yamanashi Y: Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol. 2011, 69(2):418-422.
21. Weinberg DA, Lesser RL, Vollmer TL: Ocular myasthenia: a protean disorder. Surv Ophthalmol. 1994, 39(3):169-210.
22. Rautenbach RM, Pillay K, Murray ADN, Heckmann JM: Extraocular Muscle Findings in Myasthenia Gravis Associated Treatment-Resistant Ophthalmoplegia. J Neuroophthalmol. 2017, 37(4):414-417.
23. Dagi LR, Zoumalan CI, Konrad H, Trokel SL, Kazim M: Correlation Between Extraocular Muscle Size and Motility Restriction in Thyroid Eye Disease. Ophthal Plast Reconstr Surg. 2011, 27(2):102-110.
24. Bishop KN, McClung JR, Goldberg SJ, Shall MS: Anatomic and physiological characteristics of the ferret lateral rectus muscle and abducens nucleus. J Appl Physiol (1985). 2007, 103(5):1706-1714.