Current overview of myasthenia gravis and experience in China

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ABSTRACT

Myasthenia gravis (MG) is an acquired autoimmune disease affecting synaptic transmission via the neuromuscular junction mainly due to the presence of auto-antibodies targeting acetylcholine receptors. Ocular or generalized MG is clinically diagnosed when the extra-ocular muscles or other muscle groups beyond the extra-ocular muscles are involved. MG occurs in both sexes at any ages from all races but shows a wide variability in incidence and prevalence. Differences in clinical phenotypes of MG patients between West and East countries have been observed. Herein, we review the current concept on epidemiology, classification, and generalized progression in MG, mainly focusing on the differential features from mainland China.

Key words: Classification, epidemiology, generalization, myasthenia gravis

INTRODUCTION

Myasthenia gravis (MG) is known as an autoimmune disease mainly mediated by auto-antibodies against the acetylcholine receptors (AChR) between the synaptic space of the skeletal muscles, leading to an impairment of the neuromuscular transmission and corresponding clinical symptoms such as fluctuating muscle weakness and fatigability.[1] According to clinical symptoms, MG is divided into ocular MG and generalized MG. Secondary generalization of clinical symptoms is common in MG, resulting in a poor prognosis for patients and a tremendous burden for families and society.[2] Although epidemiological studies have shown that all the races worldwide can be affected, differences between Caucasian and Asian patients were found in relation to clinical phenotypes.[3-5] In this mini-review, we address the current concepts of MG, including epidemiology, classification of clinical subtypes, and secondary generalization. We also focus on the different clinical features of MG in China.

EPIDEMIOLOGY

It is well known that MG occurs worldwide affecting both males and females at any ages as shown in an epidemiological study with a large sample size.[6] However, the incidence and prevalence of MG are characterized by marked variation, depending on the time and/or the location of studies. A national epidemiological study in Australia has shown that the annual crude incidence and prevalence rates of MG were 24.9 and 117.1/million, respectively.[7] Other two population-based studies have been conducted in Taiwan and Norway. The reported annual incidence and prevalence of MG were 21 and 84-140/million in Taiwan,[8] and 16 and 131/million in Norway.[9] Moreover, the estimated annual incidence rate of MG is 30/million in central London,[10] 24/million in Ferrara province of Italy,[11] and 21.3/1 million in Barcelona of Spain.[12] Unfortunately, no national population-based epidemiological studies of MG have been conducted in mainland China. To obtain pooled data from a larger sample, Carr *et al.*[6] have collated 55 studies performed between 1950 and 2007, representing 1.7 billion population-years. By utilizing the meta-analysis, they have estimated that the annual incidence and prevalence rates of MG were 5.3 (range: 1.7-21.3) and 77.7/million (15-179), respectively.

The onset of MG may be influenced by sex and age. Regardless of age, the crude incidences of females

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and males in Australia are 27.9 and 21.9/1 million, respectively, with a female predominance.[6] A similar tendency was shown in Taiwan where the incidence ratio of males to females is 0.68.[8] However, three studies with large sample sizes showed a nearly equal incidence for both sexes in mainland China.[13-15] Considering age and sex, the occurrence of MG exhibits a bimodal fashion. Below 40 years of age, the ratio of female to male is nearly 3:1; however, during puberty and between 40 and 50 years, the incidence rate is roughly equal. Over 50 years, MG is more common in males, with a ratio of 3:2.[16] Osserman and Genkins have observed two peaks of incidence in MG, with the first one at 20-40 years old and the second one at 40-60 years old,[17] but in another study, the second peak of incidence was determined at ages of 60-80 years.[18] Childhood MG (onset < 15 years) is not common in North America and Europe, comprising 10-15% of MG cases.[19] However, MG occurs during childhood in up to 50% of Chinese patients, mainly with pure ocular symptoms.[5,13]

CLASSIFICATION OF MYASTHENIA GRAVIS

Myasthenia gravis is a heterogeneous disorder with variable clinical symptoms because of the different location of involved neuromuscular junction. Up to now, the most widely accepted classification is the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification,[20] a Task Force that was formed by the Medical Scientific Advisory Board of MGFA since 1997. It was designed to identify subtypes of MG patients with distinct clinical features or severity of disease indicating different prognosis or treatment response, but it is not used to evaluate the outcome. According to MGFA, MG can be divided into 5 main classes and several subclasses [Table 1].

Another classification of MG is based on clinical symptoms, age of onset, auto-antibody profile and thymic histology.[21-24] Briefly, MG patients are divided into six subtypes: ocular MG, early-onset MG, late-onset MG, thymoma-associated MG, muscle-specific tyrosine kinase (MuSK) antibody-associated MG and seronegative MG.[25,26] Early-onset patients have several clinical characteristics such as female predominance, generalized involvement, no evidence of thymoma and presence of anti-AChR antibodies. A predominance of thymic hyperplasia is observed in this subtype. However, late-onset MG patients are more common among males. These patients have generalized symptoms, and usually have normal or atrophic thymus.[27] The titer of anti-AChR antibodies is usually lower in late-onset subtype than that in the early-onset subtype, and antibodies against titin

and ryanodine receptor are detected in about 50% of such patients.[23] Thymoma-associated MG involves MG patients with thymoma regardless of the extent of muscular involvement, accounting for about 10-15% of all MG patients. Male and female patients are equally common in this subtype, and MG occurs at any age with a peak onset age of 50 years.[28,29] In seronegative MG patients, anti-AChR and anti-MuSK antibodies are undetectable. Clinical features such as variable age of onset, lack of thymoma and variable extent and severity of muscular involvement are also found.[30] The detailed characteristics of all subtypes are listed in Table 2.

Table 1: MG foundation of America clinical classification	
Type	**Characteristics**
Class I	Any ocular muscle weakness, possible ptosis, no evidence of muscle weakness elsewhere
Class II	Ocular muscle weakness of any severity, mild weakness of other muscles
Class IIa	Predominantly limb and/or axial muscles weakness, possible lesser involvement of bulbar muscles
Class IIb	Predominantly bulbar and/or respiratory muscles weakness, possible lesser or equal involvement of limb and/or axial muscles
Class III	Ocular muscle weakness of any severity, moderate weakness of other muscles
Class IIIa	Predominantly limb and/or axial muscles weakness, possible lesser involvement of bulbar muscles
Class IIIb	Predominantly bulbar and/or respiratory muscles weakness, possible lesser or equal involvement of limb and/or axial muscles
Class IV	Ocular muscle weakness of any severity, severe weakness of other muscles
Class IVa	Predominantly limb and/or axial muscles weakness, possible lesser involvement of bulbar muscles
Class IVb	Predominantly bulbar and/or respiratory muscles weakness, possible lesser or equal involvement of limb and/or axial muscles
Class V	Intubation with or without mechanical ventilation except when employed during routine postoperative management, the use of feeding tube without intubation places the patient in class IVb

MG: myasthenia gravis

Table 2: Clinical subtypes of MG	
Subtypes	**Characteristics**
Ocular MG	Purely ocular symptoms, no evidence of thymoma, adult in America and Europe, childhood in Asia, anti-AChR antibody positive in 50%
Early-onset MG	Age of onset < 50 years, thymic hyperplasia, usually females, antibodies against AChR
Late-onset MG	Age of onset > 50 years, normal or atrophic thymus, mainly males, presence of antibodies against AChR, titin, RyR
Thymoma-associated MG	Age of onset between 40 and 60 years, thymic neoplasia, antibodies against AChR, titin, RyR and voltage-gated K+channel subfamily A member 4 (KCNA4)
MuSK antibody-associated MG	Onset age < 40 years in most patients, normal thymus, antibodies against MuSK
Seronegative MG	Variable muscular involvement and severity, variable age of onset, thymic hyperplasia in some patients, no detectable antibodies against AChR and MuSK

MG: myasthenia gravis; MuSK: muscle-specific tyrosine kinase; AChR: acetylcholine receptors; RyR: ryanodine receptor

Modified osserman classification is also commonly used to distinguish subtype of MG patients and indicates the different prognosis and treatment response. This classification has been frequently recommended and widely used over the past several decades in China. Although the modified Osserman classification is based on clinical symptoms, impact on work and daily life, course of disease and treatment response, it is extremely challenging to take into account the prognosis and disability of patients. Moreover, this classification does not contain MG-associated auto-antibodies and low-frequency repetitive nerve stimulation (RNS) tests.

In 1997, Wang *et al.*[31] proposed a new clinical absolute and relative score system for MG in Chinese patients. The absolute scoring system consists of 8 items: ptosis, palpebra superior fatigability, disability of ocular motion, fatigability of the upper and lower extremity muscles, disability of facial muscles, chewing difficulties, dysphagia and disability of respiratory muscles, with a score of each item ranging from 0 (normal) to 4 (severe dysfunction). The relative scores are obtained by subtracting the pretreatment scores from the posttreatment scores and then dividing the results by the pretreatment scores. Several studies have proven that the clinical absolute and relative scoring system has good reliability and sensitivity to evaluate the disabilities in MG patients[31,32] and the clinical absolute and relative system is officially recommended by the Consensus of Chinese Experts in the Diagnosis and Treatment for Myasthenia Gravis.[33]

SECONDARY GENERALIZATION

Generalization of clinical symptoms is an important hallmark of MG patients. Ocular MG is termed when weakness is only limited to the extra-ocular muscles for > 2 years,[34,35] while generalized MG is defined as an extension of weakness beyond ocular muscles. The involvement of muscles is confirmed mainly by clinical presentations. Due to the different involvement of muscle groups, clinical presentation varies from fluctuating extra-ocular muscular weakness to respiratory failure. Secondary generalization mainly occurs during the first 2 years[16,36] and sometimes leads to the deterioration of prognosis including death.

It is well-known that ocular muscle weakness is the most common initial symptoms of MG, occurring in approximately 85% of patients. About 50% of these ocular MG patients may progress to generalized MG within 6 months after onset, 80% of patients within 1-year, and 90% of patients after 3 years. Only 10% of MG patients do not progress to secondary generalization throughout lifetime.[2] Another published study has reported that up to 65% of MG patients initially show

ocular muscle involvements, and generalization of symptoms occur in only 44% of patients within 2 years.[37] In a follow-up study including 96 Thai patients with ocular MG, only 15 patients (15.6%) developed generalized symptoms within 2 years from the initial diagnosis.[38] It is to be noted that about 50% of Chinese MG patients present with pure ocular manifestations during their entire lifetime,[5] with a relatively lower rate of generalization. Recently, Jing *et al.*[39] have also reported that only 26% of Chinese patients with ocular MG develop into generalized MG during a 13-year follow-up period. These differences in the rate of secondary generalization might be attributed to the difference in race, severity of disease and early treatment with immunosuppressive drugs, especially corticosteroids.[38,40]

Given the poor prognosis of generalized MG, it is important to detect the risk factors of secondary generalization in those MG patients with initial ocular presentations. Previous studies have revealed that onset age > 15 years, presence of thymoma, early corticosteroids therapy and abnormal RNS results on stimulating proximal limb muscles are predictors for the development of generalized MG.[39,41-43] Our recent study has shown that disease onset during adulthood and RNS abnormality of the facial nerve predict the progression from ocular to generalized MG while course of the disease is inversely correlated with secondary generalization (unpublished data). In a senior population, the ocular MG patients with anti-AChR antibodies, antistriated muscle antibodies, abnormal RNS findings and abnormal single fiber electromyography tend to develop generalized MG.[44] However, other studies have demonstrated that none of these factors significantly predict development of generalized MG in younger populations.[2,45,46] Although similar results have been obtained in some studies, there are also some limitations such as the use of retrospective methodology, incomplete clinical data, small sample size and single hospital or center. Larger-sample, multi-center, prospective studies are needed to obtain more convincing risk factors for generalization of ocular MG.

ACKNOWLEDGMENTS

REFERENCES

1. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet* 2001;357:2122-8.
2. Bever CT Jr, Aquino AV, Penn AS, Lovelace RE, Rowland LP. Prognosis of ocular myasthenia. *Ann Neurol* 1983;14:516-9.

3. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. *Neuroepidemiology* 2010;34:171-83.

4. Kawaguchi N, Kuwabara S, Nemoto Y, Fukutake T, Satomura Y, Arimura K, Osame M, Hattori T. Treatment and outcome of myasthenia gravis: retrospective multi-center analysis of 470 Japanese patients, 1999-2000. *J Neurol Sci* 2004;224:43-7.

5. Zhang X, Yang M, Xu J, Zhang M, Lang B, Wang W, Vincent A. Clinical and serological study of myasthenia gravis in HuBei Province, China. *J Neurol Neurosurg Psychiatry* 2007;78:386-90.

6. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. *BMC Neurol* 2010;10:46.

7. Gattellari M, Goumas C, Worthington JM. A national epidemiological study of myasthenia gravis in Australia. *Eur J Neurol* 2012;19:1413-20.

8. Lai CH, Tseng HF. Nationwide population-based epidemiological study of myasthenia gravis in Taiwan. *Neuroepidemiology* 2010;35:66-71.

9. Andersen JB, Engeland A, Owe JF, Gilhus NE. Myasthenia gravis requiring pyridostigmine treatment in a national population cohort. *Eur J Neurol* 2010;17:1445-50.

10. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;123:665-76.

11. Casetta I, Groppo E, De Gennaro R, Cesnik E, Piccolo L, Volpato S, Granieri E. Myasthenia gravis: a changing pattern of incidence. *J Neurol* 2010;257:2015-9.

12. Aragonès JM, Bolíbar I, Bonfill X, Bufill E, Mummany A, Alonso F, Illa I. Myasthenia gravis: a higher than expected incidence in the elderly. *Neurology* 2003;60:1024-6.

13. Liu WB, Men LN, He XT, Xia Q, Huang RX. Clinical analysis on 1520 patients with myasthenia gravis in southern China. *Chin J Neuroimmunol Neurol* 2006;13:326-30.

14. Xu JZ, Yang MS, Li BH, Jiang HP, Zhang RX, Xu SB. Myasthenia gravis: clinical study in 2385 patients. *Chin J Neurol* 1999;32:347-50.

15. Wang W, Chen YP, Wang ZK, Wei DN, Yin L. A cohort study on myasthenia gravis patients in China. *Neurol Sci* 2013;34:1759-64.

16. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141-9.

17. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. *Mt Sinai J Med* 1971;38:497-537.

18. Thanvi BR, Lo TC. Update on myasthenia gravis. *Postgrad Med J* 2004;80:690-700.

19. Phillips LH 2nd. The epidemiology of myasthenia gravis. *Ann N Y Acad Sci* 2003;998:407-12.

20. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55:16-23.

21. Compston DA, Vincent A, Newsom-Davis J, Batchelor JR. Clinical, pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain* 1980;103:579-601.

22. Kuks JB, Limburg PC, Horst G, Oosterhuis HJ. Antibodies to skeletal muscle in myasthenia gravis. Part 2. Prevalence in non-thymoma patients. *J Neurol Sci* 1993;120:78-81.

23. Romi F, Skeie GO, Aarli JA, Gilhus NE. Muscle autoantibodies in subgroups of myasthenia gravis patients. *J Neurol* 2000;247:369-75.

24. Agius MA, Richman DP, Fairclough RH, Aarli J, Gilhus NE, Romi F. Three forms of immune myasthenia. *Ann N Y Acad Sci* 2003;998:453-6.

25. Gilhus NE, Owe JF, Hoff JM, Romi F, Skeie GO, Aarli JA. Myasthenia gravis: a review of available treatment approaches. *Autoimmune Dis* 2011;2011:847393.

26. Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: a review. *Autoimmune Dis* 2012;2012:874680.

27. Myking AO, Skeie GO,Varhaug JE, Andersen KS, Gilhus NE, Aarli JA. The histomorphology of the thymus in late onset, non-thymoma myasthenia gravis. *Eur J Neurol* 1998;5:401-5.

28. Skeie GO, Romi F. Paraneoplastic myasthenia gravis: immunological and clinical aspects. *Eur J Neurol* 2008;15:1029-33.

29. Evoli A, Minisci C, Di Schino C, Marsili F, Punzi C, Batocchi AP, Tonali PA, Doglietto GB, Granone P, Trodella L, Cassano A, Lauriola L. Thymoma in patients with MG: characteristics and long-term outcome. *Neurology* 2002;59:1844-50.

30. Romi F, Aarli JA, Gilhus NE. Seronegative myasthenia gravis: disease severity and prognosis. *Eur J Neurol* 2005;12:413-8.

31. Wang SY, Xu XH, Sun H, Han X, Zhang H, Guo H. A clinical absolute and relative score system for myasthenia gravis. *Chin J Neurol* 1997;30:87-90.

32. Chen P, Wang YP, Liu JJ, Dang GX. Application of clinical absolute and relative score system in diagnosis for myasthenia gravis. *J Fourth Mil Med Univ* 2008;29:566-8.

33. Li ZY, Hu XQ, Neuroimmunology Branch of Chinese Society for Immunology; Neuroimmunology Branch, Chinese Society of Neurology, Chinese Medical Association. Consensus of Chinese experts in the diagnosis and treatment for myasthenia gravis. *Chin J Neuroimmunol Neurol* 2012;19:401-8.

34. Beekman R, Kuks JB, Oosterhuis HJ. Myasthenia gravis: diagnosis and follow-up of 100 consecutive patients. *J Neurol* 1997;244:112-8.

35. Keesey JC. Clinical evaluation and management of myasthenia gravis. *Muscle Nerve* 2004;29:484-505.

36. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. *Arch Neurol* 2003;60:243-8.

37. Schlezinger NS, Fairfax WA. Evaluation of ocular signs and symptoms in myasthenia gravis. *Arch Ophthalmol* 1959;62:985-90.

38. Leeamornsiri S, Chirapapaisan N, Chuenkongkaew W. Clinical profiles of Thai patients with ocular myasthenia gravis in Siriraj Hospital. *J Med Assoc Thai* 2011;94:1117-21.

39. Jing J, Zhang XJ, Yu L, Chen RL, Qin NN, Ma S. Factors affecting the progression from ocular to generalized myasthenia gravis. *Chin J Neurol* 2014;47:21-5.

40. Yang ZX, Xiong H, Zhang YH, Bao XH, Jiang YW, Wu Y, Wang S, Chang XZ, Qin J, Lin Q, Wu XR. Clinical characteristics and follow-up management of 135 children with myasthenia gravis. *Beijing Da Xue Xue Bao* 2011;43:455-9.

41. Hong YH, Kwon SB, Kim BJ, Kim BJ, Kim SH, Kim JK, Park KS, Park KJ, Sung JJ, Sohn EH, Lee YB, Jeong D, Joo IS, Choi BO, Choi YC, Korean Research Group for Neuromuscular D. Prognosis of ocular myasthenia in Korea: a retrospective multicenter analysis of 202 patients. *J Neurol Sci* 2008;273:10-4.

42. Kupersmith MJ. Ocular myasthenia gravis: treatment successes and failures in patients with long-term follow-up. *J Neurol* 2009;256:1314-20.

43. Guan YZ, Cui LY, Liu MS, Wang H, Zhang JB, Li YF. Progression from ocular to generalized myasthenia gravis in adults. *Chin J Neurol* 2012;45:866-8.

44. Allen JA, Scala S, Jones HR. Ocular myasthenia gravis in a senior population: diagnosis, therapy, and prognosis. *Muscle Nerve* 2010;41:379-84.

45. Sommer N, Sigg B, Melms A, Weller M, Schepelmann K, Herzau V, Dichgans J. Ocular myasthenia gravis: response to long-term immunosuppressive treatment. *J Neurol Neurosurg Psychiatry* 1997;62:156-62.

46. Weinberg DH, Rizzo JF 3rd, Hayes MT, Kneeland MD, Kelly JJ Jr. Ocular myasthenia gravis: predictive value of single-fiber electromyography. *Muscle Nerve* 1999;22:1222-7.