

PAPER

Clinical and serological study of myasthenia gravis in HuBei Province, China

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Background: Ocular and childhood myasthenia gravis (MG) cases seem relatively more common in Oriental than in Caucasian populations, but there have been no comprehensive serological studies on patients from mainland China.

Methods: 391 unselected patients with MG attending Tongji Hospital in WuHan (the largest hospital in the province of HuBei, China) were studied during a 15-month period; most had already received treatment for their condition.

Results: The male to female ratio was 0.8. 50% of the patients were children (<15 years), and age at onset showed a single peak at between 5 and 10 years of age. 64% of the children and 66% of the adults were positive for acetylcholine receptor (AChR) antibodies but the antibody titres were lower than in similar Caucasian studies, although this was partly due to the high incidence of ocular MG. Of the 43 patients with generalised MG without AChR antibodies, only 1 had muscle-specific kinase antibodies (2.5%) and 2 had voltage-gated calcium channel antibodies indicating probable Lambert–Eaton myasthenic syndrome. 75% of the children, compared with only 28% of the adults, had ocular MG. Thymoma was evident by MRI in 1.5% of children and in 20% of adults. Despite most patients having received prednisone, very few had obtained full clinical remission.

Conclusion: This study emphasises the frequency of early childhood onset with ocular symptoms and shows that many of these patients have AChR antibodies. By contrast, patients presenting in later age seem to be very uncommon in comparison with recent studies in Caucasian populations.

Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. Acetylcholine receptor (AChR) antibodies are present in sera from 80% to 90% of patients with generalised MG, about 50% from those with pure ocular MG and infrequently in healthy people.¹ The remaining 10–20% of generalised patients with MG are AChR antibody negative (seronegative MG, SNMG). IgG autoantibodies to the muscle-specific kinase (MuSK) were first identified in 70% of patients with generalised SNMG.² However, subsequent reports have found a variable prevalence in different countries, with a low proportion of MuSK antibody-positive MG in one study from Taiwan³ (reviewed in Vincent and Liete⁴).

A number of studies indicate that MG in Oriental populations may be clinically different from that in Caucasians.^{5–8} In particular, paediatric cases are frequent in China, Taiwan and Japan and purely ocular MG is relatively common in children. Since there are also differences in human leucocyte antigen associations between Japanese, Chinese and Caucasian populations,^{9–12} these observations may provide clues to the immunopathogenesis of MG.

However, there have been no comprehensive studies of AChR and MuSK antibodies in patients from mainland China. Here, we studied the histories and serology of 391 Chinese patients attending a major hospital in WuHan, China.

PATIENTS AND METHODS

During a 15-month period (September 2004–December 2005), all 600 patients with a diagnosis of MG presenting to the Tongji Hospital, WuHan, China, were invited to participate, and 391 consented to give serum for antibody studies. A total of 324 patients had been monitored regularly in our hospital over periods from <1 to 27 years, and 67 were attending for the first

time. The diagnosis of MG was made on the basis of the clinical history of fatiguable weakness, neostigmine test and the response to acetylcholinesterase therapy. Electromyography was only performed in 2 children and 10 adults. The severity was described according to the Myasthenia Gravis Foundation of America (MGFA) classification¹³ (for quantitative purposes, grades I–V were changed to 1–5). Thymic pathology was deduced from MRI scans, but thymectomy was only performed in 44 patients.

AChR antibodies and MuSK antibodies were measured using radioimmunoprecipitation assays (RSR, Cardiff, UK). AChR antibody values >2.5 nM were re-assayed with 1 µl of serum to provide a more accurate titre. Voltage-gated calcium channel (VGCC) antibodies were measured as described previously.¹⁴ Serum from 20 healthy individuals and 80 patients with other diseases were used as controls.

RESULTS

Demographic and serological features of all patients with MG

The most striking feature was the large number of children with MG, many aged <5 years at the first recognition of symptoms (fig 1A). In all, 50% (197/391) of the patients presented as children aged <14 years and 50% (194/391) as adolescents or adults; only 6 patients were aged >60 years (fig 1A). The male-to-female ratio was 0.8, with no clear difference in sex distribution at any age (fig 1A).

Abbreviations: AChR, acetylcholine receptor; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; SNMG, seronegative myasthenia gravis; VGCC, voltage-gated calcium channel

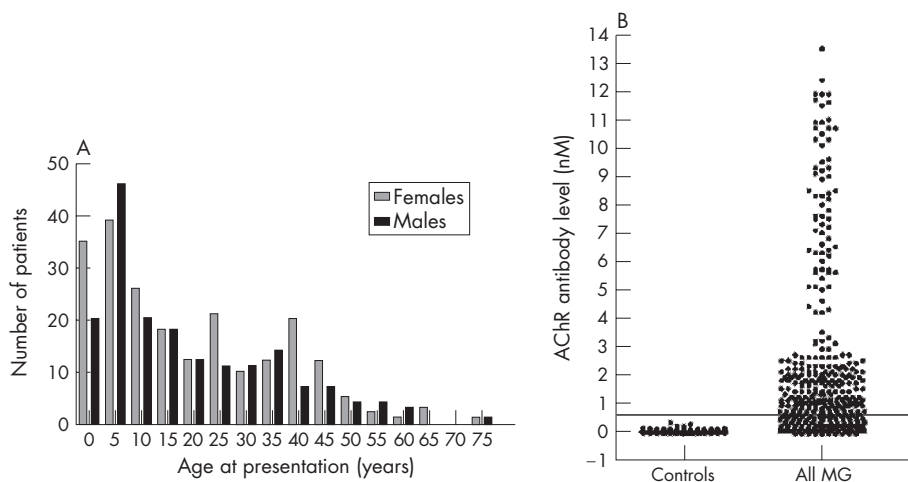


Figure 1 (A) Frequency histograms of age at presentation for male and female Chinese patients with myasthenia gravis (MG). (B) Acetylcholine receptor (AChR) antibody levels in 100 Chinese controls and in 391 patients with MG. The line is drawn at 0.5 nM, which is the cut-off used in the Oxford laboratory where the assays were performed.

AChR antibodies were tested in all 391 sera, although many of the patients had had MG for many years (range 1–45 years) at the time of sampling. After subtraction of the mean of three healthy Chinese sera, the Chinese control values ranged from -0.1 to 0.35 nM. A conservative value of 0.5 nM was used to distinguish AChR antibody-positive from AChR antibody-negative patients (as used in the Oxford laboratory). AChR antibodies were positive in only 65% (254/391) of the Chinese patients with MG (fig 1B). Overall, the AChR antibody levels were lower than they are in typical AChR antibody-positive Caucasian patients with MG (data not shown), and there was no clear demarcation between positive and negative values within the patient population.

Three cases of familial MG were present among the cohort (approximately 1%): a father and son, a father and daughter, and a mother and son. In all cases, both individuals were positive for AChR antibodies. A mother with AChR antibodies and her newborn baby were both positive. Seven healthy siblings of patients with MG were all negative for AChR antibodies.

Only 1 of the 43 (2.5%) AChR antibodies-negative patients with generalised MG was positive for MuSK antibody, and none of the patients with ocular MG was positive for MuSK antibodies (see below). MuSK antibodies were also not detected in 65 patients with AChR antibodies. Two patients were positive for VGCC antibodies. All three patients with MuSK or VGCC antibodies were excluded from further analysis, but their histories are summarised below.

Clinical features

The presenting symptoms were ocular motor disturbance in 73%, oropharyngeal weakness in 18% and limb weakness in 9%. Only 16% (62/388) of the patients had progressive weakness that involved oropharyngeal and limb muscles. We used the patients' records to assign MGFA scores at onset, maximum weakness and at the last clinic visit. At the time of serum sampling, positivity for AChR antibody was 65% in all patients, with 59% in purely ocular MG, and 85% in patients with grades $\geq 2a$ (fig 2).

The duration of MG at the time of study ranged widely, from <1 to 45 years (median 3 years). One-way analysis of variance showed some influence of disease duration on MGFA grade ($p = 0.02$ for adults and $p = 0.04$ for children), but post-testing showed that only the grades in adult patients with >10 years of disease duration were significantly different from the presenting MGFA grade ($p < 0.05$). We therefore ignored duration of disease in further analyses.

Although most patients presented with ocular MG (MGFA grade 1), many adult patients with AChR antibodies had generalised disease at onset (fig 2) or progressed to generalised

weakness. Thus, at maximal severity, only 70/191 adults had ocular MG compared with 157/197 of the children (table 1; Fischer's exact test, $p = 0.002$). Most patients with generalised symptoms had relatively mild disease, although there were some with MGFA grade $\geq 3b$ (table 1). Interestingly, the overall proportion of AChR antibody-positive childhood cases (127/197; 64%) was similar to that of the adults (127/191; 66%), but the AChR antibody positivity in the children with ocular symptoms at the time of study (103/154; 66%) was higher than that in the equivalent adult cases (31/70; 44%; $p = 0.003$).

Pure ocular MG, defined as weakness restricted to the ocular muscles for >2 years, was present in 118/205 (58%) of all cases, including 94/126 (75%) children and 24/85 (28%) adults. Similar to the overall data, 72% of the children and only 50% of the adults with pure ocular MG were positive for AChR antibodies.

Thymus pathology

All the patients had MRI scans to look for thymic pathology; the results were classified as normal for age, thymitis or thymoma. Most children had a normal thymus but a proportion had thymitis evident on scans (fig 3); only 15 patients with thymitis (aged 3–52 years) underwent a thymectomy. Overall, 42 patients (11%) had thymoma detected on scans; 3 of these were AChR antibody-positive children. In all, 39/191 (20%) adult patients had thymomas, 4 of these were negative for AChR antibodies. In the 28 patients with thymoma who underwent thymectomy, the pathology was confirmed by histology. None have had a thymoma recurrence during a follow-up period of a median of 3 years.

Response to treatments

Most patients were given acetylcholinesterase inhibitors (pyridostigmine bromide) at doses between 120 and 180 mg/day. Most patients also received prednisone at doses starting at 30 mg/day, reducing to 10–15 mg/day within a few weeks if there was improvement. These doses were then maintained for 6 months to 1 year, after which they were reduced to 5 mg/day. Patients who did not show or report clinical benefit received azathioprine and intravenous immunoglobulin, and occasionally plasma exchange. Most patients improved to some extent with prednisone, but it was usually difficult to reduce this dose beyond 5 mg/day.

Despite the prednisone treatments, many of the adults with AChR antibodies still had generalised disease and no patients were in complete clinical remission (MGFA grade 0) at the time of the study. Using the post-interventional scoring system, only one patient was known to have died, 11 were worse, 151 were unchanged and 225 had improved. The final MGFA grades were

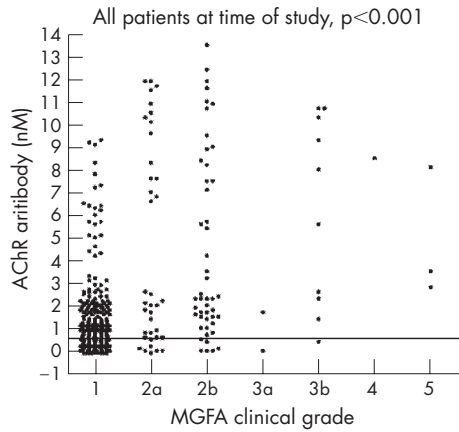


Figure 2 Acetylcholine receptor (AChR) antibody levels in Chinese patients plotted against Myasthenia Gravis Foundation of America (MGFA) clinical grades at the time of sampling (given as 1–5, corresponding to I–V). Most of the AChR antibody-negative samples were from patients with MGFA grade 1. Some of these patients had had higher grades at maximum severity (table 1).

significantly lower than the grades at maximum severity for both children and adults, but the greatest change was in adults who underwent thymectomy (fig 4).

Patients with MuSK or VGCC antibodies

Only 1 of 44 generalised patients with SNMG (2.5%) was positive for MuSK antibody. This patient was a 45-year-old woman who developed transient ptosis and diplopia followed by progressive dysphagia, dysarthria and limb weakness. No thymic abnormalities were identified on MRI scan. The patient did not respond well to pyridostigmine. She developed severe dyspnoea requiring ventilatory support. Because of progressive dyspnoea, the patient underwent three sessions of immunoadsorption, with a dramatic response. During the 1-year follow-up period, she was much improved and led a normal life when she was maintained on pyridostigmine 180 mg/day and prednisone 15 mg/day.

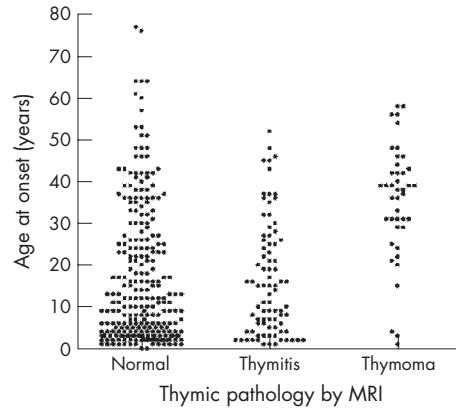


Figure 3 Age at onset plotted against thymic pathology. MRI was used to define the thymic pathology since many patients were not thymectomised.

The patients with VGCC antibodies were both men, aged 40 and 49 years at onset. Both had relatively mild generalised disease for 7 years and 1 year, with no evidence of lung cancer on CT scan of the thoraces. Only one received prednisone, and both are unchanged at present.

Factors that might influence the clinical expression of MG in China

A total of 21 of the children had hyperthyroidism (diagnosed on the basis of FT3, FT4 and thyroid-stimulating hormone levels), 16 of whom were AChR antibody positive (76%). In addition, 33 of the adults had hyperthyroidism, of whom 50% were AChR antibody positive at the time of study. There were no other relevant disease associations in the patients. To look at the demographics of MG in China, we compared the total MG cases with the demographics of the total population in HuBei Province (table 2). The prevalence of MG in children (14/million) was higher than that in adults (4.5/million), although this might partly reflect the self-referral patterns to different hospitals in the province.

The patients described above include 67 newly referred patients who had not received treatment before, and we added a further 40 patients seen in 2006. In HuBei Province, 40% (24

Table 1 Summary of clinical features and disease associations

	Total	Children		Adults	
		AChR Ab-positive*	AChR Ab-negative*	AChR Ab-positive*	AChR Ab-negative*
Total		127	70	127	64
F:M		76:51	29:41	76:51	34:30
Maximum MGFA grade, n					
1	227	103	54	31	39
2a	50	11	10	19	10
2b	53	10	2	30	11
3a	5	0	1	3	1
3b	34	3	2	26	3
4a	4	0	1	3	0
4b	6	0	0	6	0
5	9	0	0	9	0
Thymic pathology (MRI), n					
Normal†		98	52	63	48
Thymitis		26	18	29	12
Thymoma		3	0	35	4
Hyperthyroidism					
		16	5	16	17

Ab, antibody; AChR, acetylcholine receptor; F, female; M, male; MGFA, Myasthenia Gravis Foundation of America. *Most of the AChR antibodies were not measured at the time of maximum disease severity. †Normal refers to normal for age at the time of MRI; this would include adults with thymic atrophy.

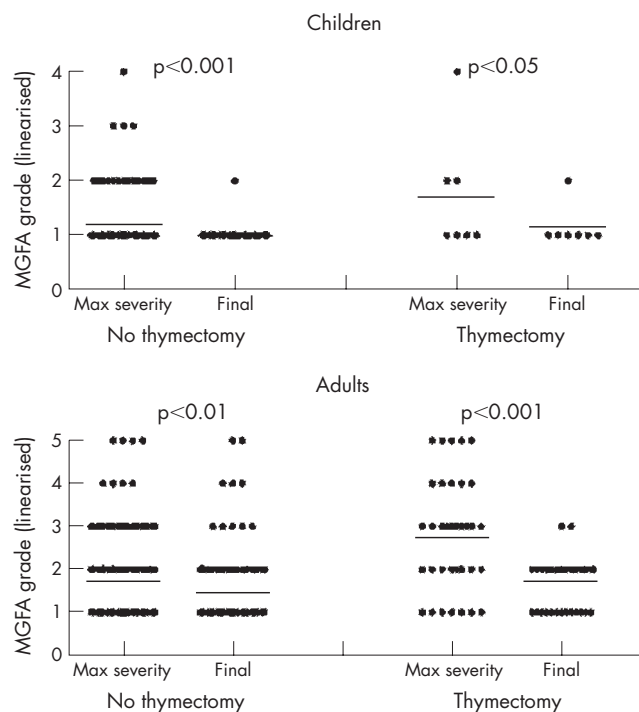


Figure 4 The Myasthenia Gravis Foundation of America (MGFA) grades (given as 1–5, corresponding to I–V) are shown at maximum (max) severity and final follow-up in patients without or with thymectomy.

million) of the 60 million population lives in rural villages (table 3). We found that among the 107 newly presenting patients at the Tongji Hospital, 54% came from rural communities and 46% from urban communities, both children and adults. Striking, however, was the time between onset of symptoms and the first visit to the clinic in many cases, with a suggestion of longer time intervals in females. The longest duration from the onset to the first clinic was in a rural woman who had symptoms for 47 years.

DISCUSSION

MG occurs worldwide,¹⁵ but differences in the clinical expression of MG have been observed, principally between Caucasian and Oriental patients. This was the first large clinical/serological study of unselected patients with MG attending a clinic in mainland China. The most striking result is the high proportion of childhood cases, mostly with purely ocular MG. In contrast with most Caucasian studies, there were few patients aged >40 years presenting to the clinic and no marked gender bias, which differs from that in Caucasians.^{15–18} AChR antibodies were found in >60% of the patients with ocular MG, both children and adults, and in 85% of those with generalised disease at the time of sampling. Thus, we confirm that MG in mainland China differs from that in Caucasian populations by the high incidence of childhood ocular MG, and show that a high proportion of these childhood cases are AChR antibody positive.

Despite the high positivity in ocular MG cases, overall, 35% of the patients were AChR antibody negative, which is higher than the previous results (13%) of the Chinese patients in Taiwan.⁵ However, that study only performed AChR antibody titres on 67 untreated patients, rather than the full cohort of 388 patients with MG studied here, and it was not clear whether they were adult or childhood cases. Moreover, many of our patients had a long disease duration and were not at maximal severity at the time of serum sampling. Alternatively,

Table 2 Number of patients with myasthenia gravis related to the population of HuBei Province

	Total patients with MG	HuBei Province* (millions)	Patients with MG (per million)
Total population	388	60	6.47
Male	173	31	5.58
Female	15	28	7.68
Age (years)			
0–14	197	14	14.07
15–64	189	42	4.50
≥65	2	3.7	0.54

MG, myasthenia gravis.
*These data are based on the website of the National Bureau of Statistics of China.

one could argue that the seronegative cases may not have had MG, since electromyography is not carried out routinely at our hospital, and was performed in only 12 patients. Moreover, the neostigmine test is unlikely to have the sensitivity or specificity profile of the AChR antibody.¹⁹ The high incidence of ocular MG cases will confound this problem as they are known to have lower positivity on all tests. Nevertheless, here, only three cases were found to have other neuromuscular junction disorders on serological testing of the patients with generalised AChR antibody-negative MG, and the proportion of AChR antibody positivity among the ocular cases is similar or higher than that found in Western studies²⁰. Therefore, most of the AChR antibody-negative cases are likely to have had myasthenia. On the other hand, it is possible that some of those cases designated as ocular MG had mild generalised weakness that was unrecognised; this possibility requires further study.

We detected MuSK antibodies in only 1 of 44 (2.5%) of our Chinese patients with generalised SNMG, which is similar to the result (4%) reported previously in Taiwan.⁵ This frequency is much lower than the 40–70% frequency reported in most Caucasian studies,^{21–24} although a recent study from Norway found no MuSK antibody-positive patients.²⁵ This regional variation, therefore, applies to both Western and Eastern populations⁴ (Avincent, unpublished results, 2006). Like many previously reported Caucasian MuSK antibody-positive patients,^{21–24} our Chinese MuSK antibody-positive patient was an adult women with marked bulbar weakness. We also found two patients with VGCC antibodies which were diagnostic for Lambert–Eaton myasthenic syndrome. This syndrome has not been widely considered in the differential diagnosis of neuromuscular weakness in China, and had not been diagnosed clinically. Fortunately, neither patient has developed lung cancer.

Table 3 Demographics of 107 patients at first presentation

	Rural	Urban
Total population in HuBei Province (millions)	24	36
Females with MG, n	27	27
Males with MG, n	30	23
Age at onset		
0–14 years, n	25	20
>14 years, n	32	30
Duration from onset to first clinic		
<1 year, n	33 (F:13; M:20)	30 (F:13; M:17)
1–3 years, n	17 (F:9; M:8)	15 (F:11; M:4)
>3 years, n	7 (F:5; M:2)	5 (F:3; M:2)
Hyperthyroidism, n	9	6

The thymic pathology was assessed by MRI, and for economic reasons thymectomy was only performed in a proportion of patients, even those with thymitis or thymoma. In all those who underwent thymectomy, the pathology was confirmed by histology. However, since no cases with "normal" pathology on MRI were treated surgically, we cannot assess the sensitivity of the MRI. Although, unusually, four of the patients with a history of MRI-diagnosed thymomas (three confirmed by histology) were negative for AChR antibodies; sera from the time of diagnosis were not available.

Apart from the study from Taiwan,⁵ the closest is that of 470 Japanese patients.⁸ Previous reports have indicated a high frequency of human leucocyte antigen class II allele-DR9 in both Chinese and Japanese patients,⁹⁻¹² compared with DR3¹⁸ in Caucasians, so one might expect the clinical expression to be similar. The Japanese patients were recruited from 19 Japanese tertiary medical centres and included both childhood and adult cases, but the median age at onset was in adulthood, differing from that shown here. In addition, they found fewer patients with purely ocular MG and most of the Japanese patients achieved remission, with 30% of the patients achieving complete remission (MGFA grade 0), whereas this was not the case in our patients. One of the reasons could be that more of their patients underwent thymectomy (68% in Japan, 11.25% in China), since we found here that there was greater improvement in patients who had undergone thymectomy than those who had not (fig 4), although these results are confounded by the use of prednisone in most patients. Another reason for the difference in clinical response may be that the Chinese patients were younger than the Japanese. Childhood MG is so rare in Caucasian societies that the optimal treatment for childhood MG is not well studied. In China, many children receive prednisone, but the lack of clear clinical remission in our patients suggests that this treatment is not optimal. Moreover, it could stunt growth, which must be considered when starting treatment.

It is difficult to comment on the overall prevalence of MG in China from these and previous studies.^{7, 26} Previous studies found a high prevalence of childhood and ocular MG cases (around 1:16 000) as we did, but did not use standard assays for antibody detection. However, despite the fact that our hospital is one of the five largest hospitals in WuHan where patients can attend a neurology clinic, the numbers of patients is likely to be an underestimate. The relatively high proportion of males compared with females at all ages, and the long duration of symptoms in a high proportion of the patients at first clinic, may reflect the fact that attendance at the neurology clinic depends on self-referral and financial situation rather than necessarily on clinical need.

Finally, these data not only indicate a need for more studies of MG and its treatment in Chinese children, but also raise interesting questions on the aetiology of this disease. The relatively high prevalence of MG in children compares strikingly with the situation in Caucasian populations¹⁶ and this suggests that the disease might follow a common childhood infection or other environmental factors. However, there was no evidence for MG segregating with rural or urban communities, making this less likely. Genetic factors, as mentioned above, may contribute to the differences in aetiology, clinical expression and susceptibility between Caucasian and Oriental races. It will, therefore, be interesting to compare the relative numbers of Chinese childhood and adult cases in other parts of the world where Chinese people reside.

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Competing interests: The Department of Clinical Neurology in Oxford receives payments and royalties from AChR and MuSK antibody tests.

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