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RACIAL DIFFERENCES IN MYASTHENIA GRAVIS IN ALABAMA

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Abstract

Demographic, clinical, and laboratory features were compared in 235 white and African-American (AA) patients with myasthenia gravis (MG) at the University of Alabama at Birmingham Neuromuscular Disease Clinic from May 2003 to January 2008. Seventy nine percent of patients were white. Acetylcholine receptor antibody was positive in 71% of white patients and in 59% of AA. In patients with seronegative generalized MG, the rate of positive muscle-specific tyrosine kinase antibody (MuSK-Ab) was significantly higher in AA than it was in whites (50% in AA vs. 17% in whites). Ocular MG was seronegative in 75% of AA patients. In AA, MG occurred earlier and more frequently in females, whereas, in whites, disease onset was later and more common in males. Another significant difference was a higher percentage of abnormality on repetitive nerve stimulation in AA. There was also a tendency for more severe forms of MG in AA. There are racial differences in MG between whites and AA in Alabama. These racial differences highlight the need to study biological factors in the pathogenesis of MG and to assess different approaches in diagnosis and treatment.

Keywords

MuSK antibody; myasthenia gravis; racial differences

In myasthenia gravis (MG), racial differences among patients have not been emphasized historically. The acetylcholine receptor antibody (AChR-Ab) has been known to be positive in 66–90% of myasthenia gravis (MG) cases without regard to race.^{6,10,12,20} With regard to the presence of muscle-specific tyrosine kinase antibody (MuSK-Ab), however, data have been accumulating in the past few years that there is a vast regional or racial difference: 0% in Norway to 49% in Turkey.^{7,16} This finding led us to study the racial differences in clinical, laboratory, and therapeutic features between African-American (AA) and white patients at our institution.

METHODS

We analyzed all clinical, laboratory, and electrophysiological data from 235 MG patients evaluated at the Neuromuscular Disease Clinic, University of Alabama at Birmingham (UAB), between May 2003 and January 1, 2008.

A diagnosis of MG was made when there was fluctuating muscle weakness with at least one of the following four tests being abnormal: AChR-Ab, MuSK-Ab, repetitive nerve stimulation (RNS), and single-fiber electromyography (SFEMG).¹⁴ MuSK-Ab testing was done for all AChR-Ab-negative (seronegative) patients. The RNS test was performed routinely in four

muscles: abductor digiti quinti (ADQ), flexor carpi ulnaris (FCU), orbicularis oris (OO), and trapezius muscles, following the protocol of Oh et al.^{13,14} SFEMG was usually performed in the extensor digitorum communis (EDC) muscle, or in the frontalis or OO muscle in a few patients when it was normal in the EDC muscle.

Information collected included demographic data, 13 symptoms, and 11 signs. The Myasthenia Gravis Foundation of America (MGFA) classification of disease was used for severity of disease at the initial visit, at disease nadir, and at the last follow-up visit.¹¹ Ocular MG was defined when ocular findings persisted for at least 2 years and were the only clinical manifestation at the last examination. Laboratory data included AChR-Ab and MuSK-Ab tests, RNS test, and SFEMG. Treatment modes and patient responses were also recorded. Non-responsiveness to anticholinesterase included hypersensitivity or worsening of MG symptoms, intolerance of side-effects, or lack of clinical response. Severity level of symptoms and signs was graded as normal (N), mild (+), moderate (++), or severe (+++). With regard to limb muscle strength, the Medical Research Council (MRC) scale was used for grading: mild, 4 to 5⁻; moderate, 3; and severe, 0–2. The MGFA classification was determined on the basis of overall assessment of the severity of symptoms and signs, as just noted. To evaluate treatment response and long-term (≥ 3 years) outcome, we used MGFA post-intervention status.¹¹ An “improved” (I) status was defined as an improvement to normal (MGFA 0 class), “remission” (R), or “minimal manifestation” (MM) status, or at least a two-class improvement in MGFA classification. Any improvement less than I was considered “minimally improved” (MI).

For statistical analysis, we used the unpaired *t*-test for age comparison and Pearson’s chi-square test for others. $P < 0.05$ was considered statistically significant.

RESULTS

Among 235 patients, 186 (79%) were white and 49 (21%) were AA (Table 1). The male:female ratio was 1:1 in whites and 2:1 in AA ($P = 0.0165$). There were more female patients with onset at 10–19 years of age for both races (Fig. 1); however, there was male predominance among whites only after 50 years of age. The number of patients with onset before 40 years of age was significantly higher in AA, whereas the number of patients with onset at beyond age 40 years was significantly higher in whites. The mean age of onset in AA was significantly lower than in whites by 18 years ($P < 0.0001$). In whites, the mean age of onset was greater in males than females by one decade ($P < 0.0001$). However, in AA, the mean age of onset between males and females was not very different. Figure 1 shows that, in whites, there was a gradual increase in the number of patients in each decade up to the seventh, whereas in AA there was a gradual decrease in the number of patients in each decade after the fourth. The frequency of ocular MG in AA and whites was not different.

The rate of positive AChR-Ab was comparable between the two groups: 71% in whites and 59% in AA. However, 75% of AA ocular MG patients were seronegative, whereas 68% of white ocular MG patient were seropositive ($P = 0.04$). The overall rate of positive MuSK-Ab was significantly higher in AA than it was in white MG patients (14% vs. 4%; $P = 0.0063$). In seronegative generalized MG, this difference was even more striking: 50.0% in AA and 16.7% in whites ($P = 0.0147$). MG tended to be more severe at onset (MGFA classification $\geq$ III) in AA compared with whites ($P = 0.051$). The rates of occurrence of the bulbar form, MG crisis, and thymoma were comparable between the two groups.

The edrophonium test was positive in 91% of tested cases with comparable rates in AA and white patients. The RNS test was abnormal in 72% of 223 tested cases. However, the rate of

abnormality was significantly higher in AA than it was in whites (89% vs. 68%; $P = 0.0096$). SFEMG was abnormal in 89% of white MG patients and in 80% of AA MG patients.

There was no difference in the rates of anticholinesterase nonresponsiveness between whites and AA or in the rates of achieving I status with anticholinesterase treatment. There was no difference in the rate of I status with all modes of treatment between whites and AA (Table 1). Thymectomy was performed in 58 white patients and 21 AA patients. The rates of R and MM status in long-term follow-up after thymectomy were not different between the two races.

More than 3-year follow-up was achieved in 117 patients (Table 1). Mean duration of follow-up was 9.3 years in whites and 10.1 years in AA. In this long-term outcome, R or MM status was achieved in 34 of 83 (41%) white patients and in 20 of 34 (39%) AA patients, suggesting a tendency toward a better outcome in AA. There was no difference in I, MI, or U status between the two races.

DISCUSSION

This study is based on an analysis of data from MG patients at the UAB Neuromuscular Disease Clinic, Birmingham, Alabama. This is not an epidemiological study and thus has some inherent limitations. The data are biased by factors related to an institutional referral practice. However, considering that UAB is the only major tertiary-care institution in the state of Alabama and that African-Americans comprise 37.3% of the Alabama population, we are in an excellent position to study racial differences in MG in the USA. Our study has shown some notable differences in the demographic and laboratory features and outcome of MG between whites and AA patients in Alabama. We suggest that these findings may be applicable to a larger population as well. Further study is needed to determine whether these racial differences exist in other regions of the USA.

In the present study, AA represented 21% of MG patients. This ratio is lower than the 37.3% of AA in the 2005 Alabama census.⁵ Thus, our data do not seem to suggest a higher occurrence of MG in AA. Phillips et al. reported a somewhat higher incidence and prevalence of MG for AA of both genders in an epidemiological study in Virginia.¹⁵ Because we did not do an epidemiological study, we cannot make a firm judgment with regard to incidence or prevalence rate.

The most striking difference between whites and AA was a higher frequency of MuSK-Ab positivity in AA. This difference is seen in MG as a whole as well as in seronegative generalized MG. None of the ocular MG cases, regardless of race, had a positive MuSK-Ab test in our series. Stickler et al. were the first to report a higher MuSK-Ab rate among AA in North Carolina.¹⁹ Among 19 AA patients with generalized MG, 8 (42%) had a positive AChR-Ab; among 11 seronegative patients, 10 (91%) had a positive MuSK-Ab. On the other hand, among 95 white patients with generalized MG, 62 (65%) had a positive AChR-Ab; among 33 white patients with seronegative generalized MG, 10 (30%) had a positive MuSK-Ab. Compared with Stickler's series, the most prominent differences in our study were a higher rate of AChR-Ab and a lower rate of MuSK-Ab in AA patients. It is not clear whether this difference is due to the small number of AA in Stickler's series. A higher MuSK-Ab rate and a positive AChR-Ab rate comparable to that for whites observed in AA were also confirmed at the University of Texas at Southwest Medical Center and at the University of Virginia.⁴ Thus, this racial difference in MuSK-Ab positivity in the USA seems to be genuine, and there may be a different biological contribution in the pathogenesis of MuSK-Ab MG.

Other striking differences between MG in whites and AA are the female predominance and earlier onset of disease in AA and the male predominance in older whites. In a 1981 study in the USA, two peaks of frequency were identified in MG: young females and old males.⁹ In

more recent studies on whites in the USA and Europe, an upsurge of MG was noted in older patients, especially males, whereas female predominance was maintained in young patients.^{1,3,8,15,17} Our study shows that this trend could be observed in whites but not in AA. In fact, there was a decrease in the number of patients with a late age onset and no male predominance in the older group in AA. We compared our data with the 2005 population data from Alabama and found that there was a parallel reduction in the number of patients with late-onset MG and the population of older AA citizens (Fig. 1).⁵ In contrast, in whites, there was an upsurge of MG in older patients despite a general reduction in the population of older whites. A low frequency of late-onset MG was also reported in South African blacks and in Chinese and Turkish MG patients.^{7,10,21}

Our study found a predominance of seronegative ocular MG in AA. In ocular MG, the AChR-Ab-positive rate was usually lower and its titer lower compared with generalized MG.¹² In order to determine whether our finding of a predominant seronegative ocular MG in AA was due to a sampling error, we surveyed all ocular MG cases in our patient database since 1980 and found a similar trend, and thus our finding seems to be genuine. However, it is possible that this may be due to a referral bias. We recommend further study to resolve this issue.

Our study showed that MG tended to be more severe in AA compared with whites at the time of presentation and that the RNS test showed a higher rate of abnormality in AA. It is possible that AA patients do not consult a physician until they are sicker. It has been known that the diagnostic sensitivity of RNS increases with severity of disease.^{13,14} This finding indicates that it is easier to confirm the diagnosis of MG in seronegative cases by the RNS test in AA than in whites.

A racial difference in therapeutic response in MG has been reported in juvenile MG in North Carolina.² Andrews et al. did not observe any difference in incidence, disease severity, or gender ratio between 29 AA and 86 white juvenile MG patients in North Carolina, but they observed that spontaneous or treatment-induced remission was infrequent in AA but common in whites. The investigators reported a different response to early thymectomy; there was a higher remission rate in whites compared with AA in postpubertal juvenile MG. In a South African study, blacks were more likely to develop treatment-resistant complete ophthalmoplegia and ptosis, and whites were more likely to develop generalized MG that was poorly responsive to therapy.¹⁰ Our data suggest that there is no real racial difference in therapeutic responses to various modes of treatment in MG, including thymectomy.

In the long-term outcome analysis, remission and minimal manifestation status tended to be achieved less often in whites than in AA. The age of onset may be an important factor in this regard. A poor outcome in whites may be due to the predominant late onset of MG. Older patients have, in general, a greater chance of developing side-effects from various treatments because of other coexisting systemic diseases. In late-onset MG, there are some data to suggest that treatment can be difficult, because the disease may be more severe. There are also higher rates of thymoma, higher titin antibody titers, and more frequent complications with steroid therapy.^{1,8,18}

Our study has shown some racial differences in MG between whites and AA. These findings highlight the need to study biological factors in different subgroups in the pathogenesis of MG and suggest different approaches with regard to diagnosis and treatment.

Abbreviations

AA	African-American
AChR	acetylcholine receptor

AChR-Ab	acetylcholine receptor antibody
ADQ	abductor digiti quinti
EDC	extensor digitorum communis
FCU	flexor carpi ulnaris
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of American
MM	minimal manifestation
MRC	Medical Research Council
MuSK-Ab	muscle-specific tyrosine kinase antibody
OO	orbicularis oculi
RNS	repetitive nerve stimulation

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FIGURE 1.

(A) Number of patients (Y) vs. age of onset per decade according to gender and race. (B) Number of Alabamians (Y) vs. age per decade according to gender and race. W M, white male; W F, white female; AA M, African-American male; AA F, African-American female.

Table 1

Clinical and laboratory features in myasthenia gravis.

	White (n = 186)	African-American (n = 49)	P-value
Gender (female:male)	89:97 (48:52%)	33:16 (67:33%)	0.0165
Onset age (<40:≥40 y)	49:137 (26:74%)	32:17 (65:35%)	<0.001
Mean age (y)	51.84 ± 17.68	33.49 ± 16.02	<0.0001
Female	46.35 ± 18.45	31.27 ± 17.07	<0.0001
Male	56.66 ± 15.51	38.06 ± 12.89	<0.0001
MG type			
Ocular	19	8	
Generalized	167 (89%)	41 (84%)	
Seropositive	132 (71%)	29 (59%)	
Ocular	13 (68%)	2 (25%)	0.0381
Generalized	119	27	
Seronegative	54 (29%)	20 (41%)	
Ocular	6	6	
Generalized	48	14	
MuSK-Ab ⁺	8 (17%)	7 (50%)	0.0147
MGFA class at presentation			
I	40	10	
II (a:b)	92 (66:26)	18 (13:5)	
III (a:b)	34 (6:28)	14 (7:7)	
IV (a:b)	10 (2:8)	3 (0:3)	
V	10	4	
≥III	54 (29%)	21 (43%)	0.0514
Bulbar classification	62 (33%)	15 (31%)	
Crisis	33 (18%)	12 (24%)	
Thymoma	30 (16%)	9 (18%)	
Positive edrophonium test	62/70 [†] (89%)	25/26 (96%)	
RNS abnormalities	120/176 (68%)	41/47 (89%)	0.0096
ADQ muscle	52/158	18/42	
FCU muscle	55/150	19/42	
Facial muscle	77/150	23/37	
Trapezius muscle	65/145	23/38	
SFEMG abnormalities	127/142 (89%)	28/35 (80%)	
AChE non-responsiveness	33 (18%)	10 (20%)	
Therapeutic improvement (I) [‡]			
Pyridostigmine	69/177	18/49	
Steroid	53/132	20/40	
Immunosuppressants	42/109	7/24	
Intravenous globulin	17/55	3/14	
Plasma exchange	21/40	6/19	

	White (n = 186)	African-American (n = 49)	P-value
Thymectomy	58 (31%)	21 (43%)	
R, MM	23	10	
Long-term outcome [§]	83	34	
R, MM	34 (41%)	20 (59%)	
CSR	5	0	
PR	11	7	
MM	22	17	
Improved (I)	50	24	
Minimally improved (MI)	15	6	
Unchanged (U)	18	4	
Death	12	2	

MGFA, Myasthenia Gravis Foundation of America; RNS, repetitive nerve stimulation; ADQ, abductor digiti quinti; FCU, flexor carpi ulnaris; SFEMG, single-fiber electromyography; AChE, anticholinesterase; R, remission; MM, minimal manifestation; PR, pharmacologic remission; CSR, complete stable remission.

* At presentation.

[†] Sixty-two of 70, edrophonium positive in 62 among 70.

[‡] Improved.

[§] Follow-up period ≥ 3 years; mean follow-up period: 9.3 years in white vs. 10.1 years in AA.