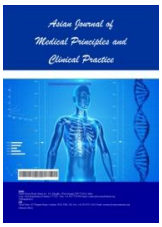

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Myasthenia Gravis at Presentation: A 14 Year Institutional Review of a Rare Disorder in Calabar, Southern Nigeria

Sidney K. Oparah[1*] and Affiong Ibanga[2]

[1]Neurology Unit, Department of Internal Medicine, University of Calabar Teaching Hospital, Nigeria.
[2]Department of Ophthalmology, University of Calabar Teaching Hospital, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Authors SKO and AI conceived, designed, wrote the protocol and collected the data for the study. Author SKO performed the literature search, statistical analysis and wrote the first draft of the manuscript. Both the authors reviewed, read and approved the final manuscript.

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ABSTRACT

Aim: Spurred on by the prevailing dearth of data from Nigeria and West Africa, in the context of reports suggesting racially influenced phenotypic variation in the manifestation of myasthenia gravis, this study explored the clinical presentation of patients with myasthenia gravis at a tertiary health facility in Calabar, Nigeria.
Study Design: We employed a cross-sectional study design.
Place and Duration of Study: This study was conducted at the University of Calabar Teaching Hospital, Nigeria. The period under review spanned from January 2006 to December 2019.
Methods: We obtained relevant demographic and clinical data from those who presented with myasthenia gravis from June 2017 to December 2019, and retrospectively extracted demographic and clinical information at presentation, from the records of patients diagnosed with myasthenia gravis at the outpatient neurology and ophthalmology clinics of the hospital from January 2006 to

**Corresponding author: E-mail: sidkele@yahoo.com;*

May 2017. Data analysis was done with version 22 of the statistical package for social sciences software.

Results: 26 patients with myasthenia gravis comprising 11 males and 15 females, with an overall mean age of 36.7 ± 18.79 years, presented at the clinics over 14 years; giving a male: female ratio of 1:1.4, and a prevalence of 26.3 per 100,000. Ocular and generalized forms of myasthenia gravis each constituted half of the number of cases.18.4%, 65.4% and 19.2% of the patients presented with juvenile-onset, early-onset, and late-onset myasthenia gravis, respectively. Ptosis (88.5%), diplopia (84.6%) and limb weakness (42.3%) were the top three presenting features. None of the patients had co-existing thymic enlargement at the time of the first presentation.

Conclusion: The majority of the cases had early-onset myasthenia gravis, with females more affected than males. Ocular symptoms comprise the predominant clinical features at initial presentation and there was no co-existing thymic enlargement.

Keywords: Myasthenia gravis; ocular; generalized; muscle weakness; Nigeria.

1. INTRODUCTION

Myasthenia gravis is an uncommon autoimmune-mediated chronic disorder affecting the neuromuscular junction of skeletal muscle in which there is the presence of autoantibodies against neuromuscular junction proteins available at the postsynaptic membrane, manifesting as fluctuating weakness and fatigability of skeletal muscles worsening with repetitive usage, and improving with rest [1-4]. Females are more affected than males before the age of forty years, with a reversal of sex predominance after the age of fifty years [5-7]. The global prevalence is estimated to be between 50 to 100 million people, and there are indications that the global incidence has increased over the past few decades [7-9].

Based on clinical manifestation, MG is classified into ocular MG, in which the weakness is restricted to the involvement of the extrinsic eye muscles and eyelids resulting to predominantly ocular symptoms such as ptosis and diplopia; and the generalized type, in which the muscle weakness is generalized [10]. Reports exist suggesting the occurrence of racially influenced phenotypic variations in myasthenia gravis manifestations [10-12]. However, the contribution to global literature on myasthenia gravis, from the African region is sparse as not much has been documented regarding MG in Africa; especially the sub-Sahara African region. Some have postulated possible explanations for the dearth of literature on myasthenia gravis from the region, including; under-recognition of the disorder by health professionals, lack of interest, and constraints of diagnostic difficulty [13]. The fluctuating nature of the symptoms of myasthenia gravis may pose some diagnostic challenges for clinicians with little experience of the uncommon disorder. Myasthenia gravis may be unrecognized in some settings in which the patient presents with ocular and unconvincing serology and electrophysiological results [14]. The outcome of myasthenia gravis treatment is encouraging; hence, prompt recognition and management of the disease is desirable, to avoid worsening of the symptoms and the risk of myasthenia crises [15]. A high index of suspicion is required on the part of clinicians to avoid needless delays in the diagnosis and commencement of treatment [16].

Few reports on myasthenia gravis have been documented from Nigeria, especially from the south-western, eastern, and northern regions [17,18]. We are not aware of any prior reports of such studies from our parts of southern Nigeria, adjoining the oil-rich Niger Delta region of the country.

The scarcity of data regarding MG in Nigeria and our locality, in particular, necessitated this study which set out with the aim to review the clinical presentation of patients diagnosed with myasthenia gravis at the University of Calabar Teaching Hospital in Nigeria, over fourteen years spanning from January 2006 to December 2019.

2. METHODOLOGY

2.1 Study Site

This study was conducted at the University of Calabar Teaching Hospital located in Calabar, Nigeria. Calabar; a major tourist destination city in Nigeria is situated in the transition zone from the Niger delta to the tropical rain forest belt of southern Nigeria, at latitude 4° 57' 0.4248'' North and longitude 8° 23' 35.9088'' East. The last nationwide population census in Nigeria put the

population of the city at 184,415 for the female inhabitants and 186,607 for males [19]. The hospital, which is the only federal government-owned health facility that offers multi-specialty clinical services in the city of Calabar, predominantly serves the population in the city and other parts of the state; it also receives patients from the neighbouring states of Akwalbom, Benue, Abia, and Ebonyi. Besides, patients come from communities in the neighbouring countries of Equatorial Guinea and Cameroon.

2.2 Study Design

This was a cross-sectional study.

2.3 Study Population

The participants were drawn from patients who presented at the ophthalmology and medical outpatient clinics of the aforementioned teaching hospital who met the eligibility criteria for the study. Those who presented with myasthenia gravis at the outpatient clinics, within the period of the study, were considered eligible.

2.4 Sampling Technique

The study recruited all those who were diagnosed to have myasthenia gravis during clinic visits within the period of interest; from January 2006 to December 2019.

2.5 Data Collection

Patients who presented with myasthenia gravis from June 2017 to December 2019 had their demographics and clinical features obtained during their time of initial presentation cum diagnosis by the participating ophthalmologist and neurologist at the ophthalmology and medical outpatient clinics, respectively; whereas, information on the demographic and clinical features at initial presentation, for those who had presented from January 2006 to May 2017 were extracted from their case records.

The diagnosis of MG was based on clinical evaluation of the patients by the attending specialist physicians, supported with positive responses to Ice pack and Tensilon`s tests. The American Myasthenia Gravis Foundation classification was used to grade the severity of symptoms [20]. The results of thoracic-inlet imaging reports were reviewed to identify the presence of co-existing enlargement of the thymus gland suggestive of thymic hyperplasia or thymoma.

2.6 Data Analysis

The analysis of data was done with version 22 of the statistical package for social sciences software (SPSS Inc., Chicago, Illinois, USA). Categorical variables were reported as proportions, whereas continuous variables were presented as means and standard deviations, and median values reported for variables with nonparametric distributions. Chi-square test was used to compare proportions between groups. The age at presentation, age at onset, and duration of illness were found to lack a normal distribution; although the pattern of distribution was similar between the male and female sex groups. Mann-Whitney U test was used to compare the median values of the continuous variables lacking a normal distribution, between the male and female sex groups. Two-tailed P values were computed, with the level of statistical significance set at *P*-value <.05.

3. RESULTS AND DISCUSSION

3.1 Results

26 out of 98,675 patients who presented at the ophthalmology and medical outpatient clinics of the hospital during the 14 years under review were diagnosed with myasthenia gravis, yielding a prevalence rate of 26.3 per 100,000 persons seen at the neurology and ophthalmology outpatient clinics of the hospital. Fifteen females presented with MG out of 52,430 female patients seen during the period reviewed, giving a sex-specific hospital prevalence of 28.6 per 100,000 females; whereas, 11 out of 46,245 males who presented within the same period, were diagnosed with MG, with a sex-specific prevalence of 23.7 per 100,000 males.

Male and female patients comprised 42.3% and 57.7% of the patients who presented with MG, respectively; with a male to female ratio of about 1: 1.4. The mean age of those who presented with MG was 36.7 ± 18.79 years. The mean and median duration of illness were 18.1 ± 18.19 months and 12 months, respectively; with sex-specific mean and median durations of 21.6 ± 20.49 months; 24 months and 16.1 ± 17.33 months; 9 months, for the male and female patients, respectively (*P* = .71). Table 1 shows the characteristics of the patients at the time of presentation with MG.

Table 1. Background characteristics of the patients who presented with MG within the reviewed period

Variables	Males (n = 11)	Females (n = 15)	Total (N = 26)	*P* –value
Age at presentation (in years)				
Mean age (SD)	40.8 (19.0)	31.9 (18.35)	35.7 (18.79)	
Age range	10 to 71	9 to 68	9 to 71	0.24
Median age	38.0	25	31.5	
Residence				
Rural (%)	1(9.1)	4 (26.7)	5 (19.2)	0.36
Urban (%)	10 (90.9)	11 (73.3)	21 (80.8)	
Education (%)				
Primary	1 (9.1)	2 (13.3)	3 (11.5)	
Secondary	0 (0)	3 (20)	3 (11.5)	.39
Tertiary	5 (45.5)	4 (26.7)	9 934.6)	
Unknown	5 (45.5)	6 (40)	11 (42.3)	
Age at onset (in years)				
Mean age at onset (SD)	27.7 (11.06)	28 (18.02)	27.9 (15.47)	
Age range	6 to 40	4 to 62	4 to 62	.84
Median age at onset	28	19.5	27	
MGFA grade at presentation (%)				
I	5 (45.5)	8 (53.3)	13 (50)	
II	5 (45.5)	6 (40)	11 (42.3)	.92
III	1 (9.1)	1 (6.7)	2 (7.7)	
IV	-	-	-	
V	-	-	-	

SD = Standard Deviation
MGFA = Myasthenia Gravis Foundation of America

Table 2. Proportion of symptoms at presentation by the patients with MG

Symptoms	Frequency (n = 26)	%
Ptosis	23	88.5
Diplopia	22	84.6
Limb weakness	11	42.3
Difficulty chewing	9	34.6
Dysphagia	5	19.2
Dysarthria	5	19.2

Four (18.4%), 17 (65.4%), and five (19.2%) of the patients presented with juvenile, early-onset, and late-onset myasthenia gravis, respectively. 13 (50%) presented with ocular MG, and 13 (50%) had generalized MG. None of the patients had co-existing thymic hyperplasia or thymoma. Ptosis (88.5%) was the most common presenting symptom among patients with MG. Table 2 shows the proportion of presenting symptoms as reported by the patients diagnosed with MG.

3.2 Discussion

The rarity of myasthenia gravis in our locality was evidenced by few numbers of affected persons seen at the hospital throughout 14 years; with a prevalence rate of 26.3 per 100,000 patients seen at the medical and ophthalmology outpatient clinics of the health facility. A hospital-based retrospective study conducted in the northern part of Nigeria, over a decade and a half ago, identified only four cases of MG among patients seen at a tertiary health facility over the preceding period of 10 years; whereas, 27 cases were seen over five years in a study reported from the south-western part of the country [17,18]. Although MG is generally regarded to be an uncommon autoimmune disease, the prevalence appears to be relatively higher among Caucasians compared to those living in the tropics. Some have suggested a link between the rarity of autoimmune diseases in the tropics, to the influence of frequent parasitic infestations believed to suppress autoimmunity [21,22]. This influence is attributed to the impact of parasitic infestations on the immunologic balance between

TH1/TH7 (T_H1/ T_H2) and TH2 responses associated with autoimmunity and bacterial infections, and parasitic infestations, respectively. Parasitic infestations stimulate TH2 response and inhibit TH1 response, with consequent suppression of autoimmunity [23].

Our study showed a female preponderance among the affected persons, with a male to female ratio of 1: 1.4; corroborating the outcome of a similar study in the West African region which documented a male to female ratio of 1:1.3 [24]. Myasthenia gravis is reported to be influenced by sex in a pattern dependent on age; with females predominating under the age of 40 years, and males more affected beyond 50 years of age [6]. Thus, the female preponderance observed in our study did not surprise us; as the majority of the patients had early-onset myasthenia gravis. Sex hormones have been suggested to play some role in myasthenia gravis; especially estrogen which has been fingered as a mediator of the disorder [25,26].

The patients with MG in our study were evenly distributed between the ocular and generalized types; an observation akin to the reports by Bakari and Onyemelukwe who observed equal proportions of ocular and generalized variants among patients diagnosed with MG in the north-western part of the country; over 10 years [17]. The same pattern of the presentation was obtained by Ojini et al. who documented each type of MG (ocular and generalized) to account for 50% of cases they found in Lagos, south-western Nigeria [18]. It is relevant to note that the determination of the type of MG among the patients in our study was based on their clinical features at the time of the initial presentation. A high proportion of patients with ocular MG at the initial stages progresses to develop a generalized form of the disease [27]. It is reported that the use of immune modulators such as steroids and azathioprine mitigates progression from ocular to generalized forms of MG in up to three-quarters of patients [28].

The study identified ptosis and diplopia to be the most common presenting clinical features of myasthenia gravis among the patients seen in our hospital. This mirrors documented report that majority of the patients with Myasthenia gravis present with involvement of the extrinsic ocular muscles as the initial symptom [29]. Furthermore, the outcome of a multi-racial study, conducted in South Africa, demonstrated an increased proportion of ophthalmoplegia and ptosis among myasthenicnegroid patients compared with Caucasians [13].

The explanation for early involvement of extrinsic ocular muscles is not clear; considering that these muscles are known to have high mitochondrial density, with high blood flow and metabolic rates that should mitigate susceptibility to fatigue [30]. However, they possess small-sized motor units with high firing frequencies, rendering them prone to fatigue, and multiple neuro-muscular junctions in which end-plate potentials, instead of action potentials, directly activate contractile apparatus; resulting to a direct impact on the strength of muscle contraction in the presence of any reduction in end-plate potentials [1]. Furthermore, these muscles are known to have reduced expression of regulators of complements; a situation that could predispose them to complement-mediated injuries [31].

We did not find evidence of enlargement of the thymus gland suggesting the absence of thymic hyperplasia or thymoma among the patients seen in our locality within the 14 years. A previous study from the West African country of Burkina Faso reported the presence of a thymic abnormality in ten of the fourteen MG patients in their study, and detected the presence of antibodies to acetylcholine receptor and muscle-specific tyrosine kinase (MuSK) antibodies in the serum of six and three of their patients, respectively [24]. Bakari and Onyemelukwe also did not observe thymus gland enlargement among the cases of MG they reported from the northern part of Nigeria [17]. Absence of thymus gland abnormality can be seen in certain persons with MG who lack antibodies to acetylcholine receptor antibodies and may possess antibodies to muscle-specific tyrosine kinase (MuSK) and other post-synaptic neuromuscular junction proteins. They are more likely to present with female predominance, and an atypical pattern manifesting as prominent muscle atrophy, selective weakness of the facial, neck, bulbar and respiratory muscles, and relative sparing of ocular muscles [32]. On the other hand, thymoma associated MG usually have detectable antibodies to acetylcholine receptors, other striational antibodies, and antibodies linked with paraneoplastic conditions such as anti-Hu, anti-dihydropyrimidinase-related protein 5 and anti-glutamic acid decarboxylase antibodies [33-35]. However, the patients in our study presented with predominant ocular symptoms despite the absence of thymic enlargement. We recommend

further local studies on MG incorporating immunoassay techniques to help elucidate such uncertain aspects of MG in our region.

We acknowledge that the hospital-based nature of our study is fraught with the challenges of selection bias occasioning exaggeration of actual prevalence rates in comparison to community-based studies.

4. CONCLUSION

We conclude that majority of the patients who presented at our facility with myasthenia gravis during the 14 year period of our study had early-onset myasthenia gravis, with females more affected than males. There were equal proportions of ocular and generalized types at presentation. Ocular symptoms comprise the predominant clinical features at initial presentation and there was no co-morbid thymus gland abnormality.

CONSENT AND ETHICAL APPROVAL

This study was conducted after obtaining the approval of the study protocol and it was carried out in compliance with the Helsinki declaration of 1975, which was revised in 1983 and 2013. We ensured the preservation of the confidentiality of patients` records and identity. Consent was obtained from the patients recruited at the clinics during the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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