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Characterization of Patients with Juvenile Myasthenia Gravis from a Reference University Hospital in Colombia

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Abstract

Introduction: Juvenile myasthenia gravis (JGM) is a rare entity, about which there is not enough information. This pathology has its own characteristics and a recognized demographic variability. The consequences of not being diagnosed and treated in time can be serious and its treatment is based on what has been observed in adults.

Objective: To characterize sociodemographically and clinically the population of children diagnosed with MGJ in a reference university hospital in Colombia.

Methodology: Retrospective observational study, in which the medical records of hospitalized patients at the Hospital Universitario San Vicente Fundación (HUSVF) in the city of Medellín, Colombia, from January 2011 to December 2017 were analyzed.

Results: The medical records of 23 patients (14 women) were included. The mean age of onset was 9.1 years. 15 (65.2%) were in the prepubertal period. The type of ocular myasthenia was the most frequent, mainly in prepubertal patients. The myasthenic crisis (MC) occurred in 5 patients (21.7%), predominantly in post pubertal patients. A significant difference was found between the age group and the type of presentation; and a tendency to present psychiatric disorders according to sex and age.

Conclusions: For the authors' knowledge, this is the first characterization study of patients with MGJ in Colombia. The diagnosis was made mainly in prepubertal patients, and the female sex was more affected in both age groups. Similar to what was found in other latitudes, the ocular type appeared more frequently. The proportion of patients with MC was higher than reported. In this study, it was found that belonging to the prepubescent group can increase the risk of presenting MGO. Autoimmune comorbidity was not frequent, and the performance of the different diagnostic aids is good. The guidelines and management lines conform to the recommendations given, however more studies and a sample size of more significant drugs are needed.

Keywords: Acetylcholine; immunosuppressant; autoimmune disease; neuromuscular disease; myasthenia gravis; thymectomy

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Introduction

Myasthenia gravis (MG) is an autoimmune disease that affects the neuromuscular junction and has been considered the most common of its kind, can cause significant disability and mortality if left untreated [1, 2]. It can occur at any age. In children under 18 years of age, JGM is divided into neonatal, prepubertal and post pubertal MG [2].

The most common type of presentation is the ocular. However, it can progress to the generalized form (3), and be accompanied by other autoimmune disorders [2]. Its diagnosis is mainly clinical. Although, it can be supported by electrophysiological studies and the presence of antibodies; mainly those directed against acetylcholine receptors (AntiAChR), muscle-specific kinase receptors (AntiMuSK), and low-density lipoprotein receptor-related protein 4 (AntiLRP4) [4]. Despite this, a strong index of suspicion is required to diagnose it in a timely manner [5].

For its treatment, the most used drugs have been, pyridostigmine

and steroids [2, 6], likewise, intravenous immunoglobulin (IVIG) and plasmapheric, in case of crisis [7, 8]. Thymectomy is also a therapeutic option in selected patients [9].

JGM represents 11% - 24% of all patients with MG [10], with an incidence of 1.6/million per year [2]. In this regard, different studies have been published, especially in Asia and Europe. In Latin American countries, such as Cuba, Brazil and Chile, it has been possible to report, in part, the behavior of this disease in their populations [11-13].

In Colombia, a study on MG in adults was published in 2002 [14]. However, to date there are no publications on MGJ. It is not known if there is predominance by female sex, age, main form of presentation and its initial symptoms; nor about the use of different diagnostic tools, nor the treatment trends. That is why this study aims to describe for the first time in Colombia the Sociodemographic, clinical, para clinical characteristics and their management, in children diagnosed with MGJ in a reference university hospital.

Materials and Methods

A retrospective observational study was carried out of the registration of the medical records of patients evaluated in the HUSVF of Medellín, Colombia (fourth level reference hospital), with diagnosis of MGJ according to clinical manifestations, the presence of antibodies, alterations in electromyography, response to drug administration and clinical tests, from January 1, 2011 to December 31, 2017.

The registration and collection of information included: review of the histories of newborn patients and less than 18 years of age, with a diagnosis of JGM according to the ICD 10 nomenclature [15], the identification and assessment was made by pediatricians, and the validation by pediatric neurologists, who established the treatment and evaluated the clinical evolution during hospitalization.

Characterization of the population: From the medical histories were obtained: sex, age of onset of the disease, origin. Individuals were classified into the prepubertal and post pubertal groups [16]. As well as all information regarding neurological examination; initial symptoms and signs, type of presentation, severity of disease according to the modified Osserman scale (EOM) [17], personal history. Likewise, antibody result using the radioimmunoassay (RIA) technique. Electrophysiological studies and computed axial mediastina tomography (CT) scan. The results of clinical and pharmacological diagnostic tests were also evaluated. Similarly the histopathological report of thymus. The frequency of medications used, lines of treatment and surgical management were evaluated.

Absolute and relative frequencies of categorical variables, and measures of central tendency (mean and median) and dispersion (standard deviation and range) were determined for quantitative variables. Unless otherwise indicated, the values are expressed as: absolute quantity and percentage in the case of qualitative variables, and mean ± standard deviation for quantitative variables. Comparisons of categorical variables between groups were made using Fisher's exact test. A p-value < 0.05 was considered statistically significant.

This study was approved by the ethics committees of the HUSVH and the faculty of medicine of the University of Antioquia, framed under the research standards of the Ministry of Health of Colombia [18].

Results

In the verification of medical records, 23 patients met the criteria for the diagnosis of MGJ. The mean age at diagnosis was 9.1 years (± 5.96), ranging from 6 months to 17 years. According to the distribution by age group, 65.2% were in the prepubertal group.

60.9% of the population was female. The ratio, woman - man, was 1.5: 1. Most of the patients resided in the department of Antioquia, mainly in the city of Medellín, and 30% came from other departments of the country. No statistical significance was found in terms of the presence of CGM, sex and age group.

The most frequent type of presentation was ocular, and the most common clinical findings were ptosis and diplopia. The generalized form occurred in 47.8% of cases, of which three evolved from MGO; while CM occurred in 21.7% (n 5), of these, 60% were found in the post pubertal group. Table 1 details the Sociodemographic and clinical characteristics of patients, including severity. Five patients were not classified according to the EOM, however, pediatric neurologists, based on clinical presentation, and classified them as MGO or MGG. When evaluating age group and type of presentation with Fisher's exact test, a significant difference was found (p <0.0214), with OR of 9, in prepubertal patients to present MGO and in post pubertal patients to present MGG **(Table 1)**.

Case associated with another autoimmune pathology was found. Likewise, psychiatric disorders were presented, observing a non-significant trend (p 0.29) where post pubertal men presented such disorders.

In the antibody detection assay, two patients were reported positive and four negative for antiAchR, and one case negative for AntiMusK. Five patient outcomes were not reported for AntiAchR or AntiMusK.

The electrophysiological study showed good performance to detect alteration of the neuromuscular junction, especially the single fiber electromyography, and the repetitive stimulus test. The tests with anticholinesterases were performed in 3 patients, in all of them an improvement in muscle strength was evidenced after its administration. The ice test was performed on five patients, it was positive in four cases. Mediastina CT were performed on 19 patients. Three reported thymus hyperplasia the same for thymoma. T summarizes the diagnostic tests performed and their result **(Table 2)**.

3 details the lines of treatment used, according to the type of presentation and severity. The drugs used according to frequency were, in the first place, pyridostigmine (78.2%), followed by the use of steroids (65.2%), and in third place azathioprine (26%). In the combination of drugs, pyridostigmine plus steroids and pyridostigmine plus steroids, plus azathioprine were used with the same frequency (26%). Regarding the management of CM

Table 1. Sociodemographic and clinical characteristics of patients with MGJ in the HUSVF Of Medellín, Colombia. Duren the years 2011-2017.

sex	Woman	14(60,9)
	man	9(39,1)
Age at diagnosis	Stocking	9,1
	Infant (0-2 years)	4 (17.4)
	Preschool (2-5 years)	4 (17,4)
	School (6-10 years)	3(13.0)
	Adolescent (10-18 years)	12 (52.2)
Age group	Pre-puber – (M:H)	15 (65,2)-(9:6)
	Post-tuber- (M:H)	8 (34.8)- (5:3)
origin	Medellin	9(39.2)
	Antioquia	7 (30.4)
	other	7 (30,4)
type of myasthenia	Ocular	12 (52.2)
	Generalized	11 (44.8)
	Both	3 (13.0)
	Average age (years)MGO	7,4
	Average age (years)MGG	12,6
gravity according to Osseman scale modifiesda	I	10 (43.5)
	IIA	1(4.3)
	IIB	3 (13.0)
	III	2 (8.7)
	IV	2 (8,7)
	another classification	5 (21.7)
symptoms presented	Ptosis	13(56.5)
	Diplopia	10(43.5)
	difficulty swallowing/chewing	
	fatigue	9 (39.1)
	dyspnea	6 (26.1)
		3 (13.0)
Findings: Physical Examination	ptosis unilateral	9(39.1)
	ptosis bilateral	4 (17.4)
	cervical weakness	9(39.1)
	facial weakness	5(21.7)
	misathenic crisis	5(21,7)
	generalized weakness	4 (17.4)
	shoulder girdle weakness	3(13,0)
	pelvic girdle weakness	4 (17,4)
	paralysis extra ocular muscles	2 (2.8)
	dysarthria	
	hypotonia	2 (2,8)
		1(4.3)
associated diseases	autoimmune Vasculitis	1(4,3)
	thyroid disease, DM, SLE	0
	depression	
	anxiety disorder	2 (8,7)
	sleep disorder	2 (8,7)
	psychogenic crises	1 (4,3)
	consumption of psychotropic	1 (4,3)
	pulmonary tuberculosis	1 (4,3)
	sickle cell disease	1 (4,3)
	chronic malnutrition	1 (4,3)
		1 (4,3)
Thiectomy	Women	4 (17,4)
	Men	4 (17,4)
	Pre-pubertal	4 (17,4)
	post pubertal	4 (17,4)

Table 2. Diagnostic support test used in the series of 23 patients withMGJ at the HUSVF in Medellin, Colombia. During the years 2011-2017.

Diagnostic aids	Made	Positive	Negative	No result
Antibodies:				
AntiAchR	11(47.8)	2(18)	4(36)	5 (45)
AntiMusK	6(26.1)	-	1(17)	5(83)
Electrophysiology:				
Single Fiber EMG				
repetitive stimulus test	14(60.8)	12(86)	1 (7)	1 (7)
EMG and neuro conduction				
	3(13)	3(100)	-	-
	6(26)	-	3(50)	3(50)
Pharmacology:				
neostigmine tests	2 (8.6)	2 (100)	-	-
pridostigmine test				
Tests with	1(4.3)	1 (100)	-	-
tension				
	1 (4.3)	1(100)	-	-
Clinic:				
ice pack test	5 (21.7)	4 (80)	1(20)	-
Imaging:				
CT scan of mediastinum	19(82.6)	6(30)	11(55)	2(10.5)
thymus biopsy	8 (34.8)	3(37.5)	-	5 (62.5)

(n 5), four required management with plasmapheresis, although two of them had previously received IVIG; one patient responded to treatment with first-line medications, and two underwent thymectomy (34.7%). -who are included in the total number of patients who required surgical management **(Table 3)**.

Discussion

Knowing the characteristics of CGM in a population is of paramount importance, due to the disability and mortality that can occur if not treated promptly [2, 19]. In this lies the importance of avoiding delays in diagnosis and treatment, especially in children [6]. In this study, a higher presentation was observed in the prepubertal group. The average age at diagnosis was 9.1 years, which is consistent with other studies (13.20). Women were more affected in both age groups; which is in accordance with previous publications [19, 21, 22]. However, among affected women, the predominance was greater in those under 12 years of age, which differs from other research, where a greater affectation of post-pubertal women has been described (23). This female predominance could be related to the higher prevalence of autoimmune diseases in them [24, 25].

According to the type of presentation, the most frequent was the ocular. Similar to what was reported in other investigations [2, 3, 26, 27]. Diplopia and ptosis -unilateral-, were the most frequent clinical findings, which also agrees with other publications [2, 5, 28].

A finding found in this study identifies that belonging to the prepubertal group may increase the risk of developing ocular MGJ. Likewise, being post pubescent can increase it to present the generalized type.

The transformation of MGO to the generalized form was observed

Table 3. Details the lines of treatment used, according to the type of presentation and severity. The drugs used according to frequency were, in the first place, pyridostigmine (78.2%), followed by the use of steroids (65.2%), and in third place azathioprine (26%). In the combination of drugs, pyridostigmine plus steroids and pyridostigmine plus steroids, plus azathioprine were used with the same frequency (26%). Regarding the management of CM (n 5), four required management with plasmapheresis, although two of them had previously received IVIG; one patient responded to treatment with first-line medications, and two underwent thymectomy (34.7%). who are included in the total number of patients who required surgical management.

Table 3. Lines of treatment according to the type of presentation and severity.

Schemes	All	Modified Osserman					Another classification		
		n (%)					n (%)		
		I	IIA	IIB	III	IV	MGO	MGG	CM
	23%	10	1	3	2	2	2	3	5
First lineto									
Only tigmine pyrids	6 (26,1)	3 (30,0)	0 (0,0)	1 (33,3)	0 (0,0)	0 (0,0)	1 (50,0)	1 (33,3)	-
Steroids only	3 (13,0)	3 (30,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	-
Tigmine Pyridos + Steroids	6 (26,1)	2 (20,0)	1 (100,0)	0 (0,0)	0 (0,0)	1 (50,0)	1 (50,0)	1 (33,3)	1(20)
Second line									
Pyridos tigmine + steroids + azathioprine	6 (26,1)	1(10,0)	0 (0,0)	2 (66,7)	2(100,0)	0 (0,0)	0 (0,0)	1 (33,3)	-
IVIG	5 (21,7)	1(10,0)	-	1 (33,3)	2(100,0)	0 (0,0)	0 (0,0)	1 (33,3)	2(40)
Plasmapheresis	5 (21,7)	0 (0,0)	1(100,0)	0 (0,0)	2(100,0)	2(100,0)	0 (0,0)	0 (0,0)	4(80)
Plasmapheresis post-IVIG	2 (8,7)	0 (0,0)	0 (0,0)	0 (0,0)	2(100,0)	0 (0,0)	0 (0,0)	0 (0,0)	2(40)
Surgery									
Timectomia pos 1st line	1 (4,3)	0 (0,0)	0 (0,0)	0 (0,0)	1 (50,0)	0 (0,0)	0 (0,0)	0 (0,0)	2(40)
Timectomia pos 2nd line	7 (30,4)	1(10,0)	1(100,0)	2 (66,7)	2(100,0)	0 (0,0)	0 (0,0)	1 (33,3)	

MGO: Ocular myasthenia gravis, MGG: Generalized myasthenia gravis, CM: My asthenic crisis. Five patients were not classified according to the Osserman scale. Five patients presented CM being previously classified according to this scale.

in 13%, mainly in the post-pubertal group. Different from what is described in other studies, where this evolution can occur in 30% - 50%, and prepubertal patients are the most affected [2, 3]. It is described that, in most cases, this transformation occurs in the first six months from the onset of symptoms [2, 29].

According to our results, it has been reported that the degree of severity, for the most part, corresponds to grade I [22, 30]. On the other hand, cases of CM evolved from grades III and IV, and occurred more frequently than reported (2). This allows us to reaffirm that MGJ is not a benign pathology and its outcomes can be serious [31, 32].

Of the autoimmune pathologies related to MGJ, thyroid disorders are the most observed [2, 33]. In our study there was one case associated with autoimmune vasculitis. Likewise, there were cases associated with psychiatric pathologies, especially depressive disorder and anxiety disorder, among others; where a non-significant trend of greater affectation was observed in post pubertal men. There were also cases associated with: pulmonary tuberculosis, sickle cell anemia and malnutrition; pathologies with certain prevalence in our region. Consequently, we could recommend a more active search for these pathologies and investigate more thoroughly about the quality of life of these patients.

Regarding the diagnosis, a low percentage of patients with positive antibodies was found, similar to what was demonstrated by other research, where it has been observed that those with ocular JGM may have the lowest levels [2, 27, 34]. Therefore, serial monitoring of antibodies is recommended, especially if they are prepubertal [2, 35]. It has been reported that patients with clinical suggestive of MGJ but with negative antibodies for antiAChR and antiMuSK, could be positive for LRP-4 [36]. Therefore, it is appropriate to emphasize that, although the presence of antibodies is important to support the diagnosis of immune MGJ, a negative result does not rule it out, and that the ethnicity of patients influences the serum level of these [37].

In this study, it was found that both the single fiber EMG and the repetitive stimulus test were positive in percentages similar to what was reported in the literature [38], despite the difficulty involved in performing them in children [39].

Cases where pharmacological tests were used to support the diagnosis were completely positive. The most commonly used drug was neostigmine, which offers the advantage of observing positive signs for longer periods [40]. Pyridostigmine and edrophonium were also used. With the latter, there is an increased risk of complications [41].

The ice test reflected a good performance to detect ocular MGJ, similar to what was previously documented, where its advantages have also been highlighted [42, 43].

In the CT scan of the thymus, findings compatible with thymoma and thymus hyperplasia were reported in equal proportion. However, and according to previous research, the histological study was positive for hyperplasia in all reported cases [22, 44].

Treatment, it was observed that all patients received pharmacological management and approximately one third of them required additional surgical management. The first line of management was given mainly to patients with ocular symptoms, and in some who presented greater severity, in order to achieve their stabilization; in these cases it was necessary to establish second-line drugs, as recommended by consensus on the management of MGJ published in 2020 [45]. According to other publications, the use of IVIG and plasmapheresis was indicated mainly in patients who presented more severe symptoms and in those who presented CM [46]. In this sense, it has been shown that plasmapheresis, compared to IVIG, can improve strength in a few days, although it is limited by difficult venous access in young children [47].

Treatment with another class of drugs, such as rituximab, of which there is recent evidence suggesting its use especially in patients with AntiMuSK, was not observed, and can be considered as second-line therapy in MGJ [45, 48].

On the other hand, thymectomy was performed in a percentage similar to that reported in previous research [9, 22]. All patients received medical management prior to surgery. Those with CM were stabilized with IVIG and plasmapheresis, according to the recommendations of the management guidelines [45]. No deaths were recorded in this study.

Study Limitations

They are inherent in a retrospective investigation, based on clinical history reports and the failure to obtain some data; which despite its nature provides important information that increases the understanding of FGM in the country and the region.

Conclusions

In our study it was observed that the average age of presentation was 9 years. The female sex was the most affected both in the prepubertal and post-pubertal groups. The type of ocular presentation manifested itself more frequently than the generalized type. There may be an increased risk of MGO in the prepubertal and MGG in the post pubertal. Different from what was published, a significant proportion of CM was presented. Comorbidity with autoimmune entities was not common; but yes, with mental pathologies, especially in post pubertal men, which despite being a finding without statistical significance, is a component that, due to its importance, should be evaluated in future research. Neurophysiological studies and testing with the ice pack showed good performance to support the diagnosis. Pyridostigmine and steroids were the most commonly used drugs, according to the recommendations. Thymectomy was performed on a considerable number of patients.

Conflicts of Interest

The authors stated that they had no conflicts of interest.

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