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

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Abstract

Introduction: Juvenile Myasthenia Gravis (MGJ) 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 is 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 patients hospitalized at the Hospital Universitario San Vicente Fundación (HUSVF) in the city of Medellin, Colombia, were analyzed from January 2011 to December 2017.

Results: 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 children. Myasthenic Crisis (MC) occurred in 5 patients (21.7%), predominantly postpubertal. 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: To the authors' knowledge, this is the first characterization study of patients with JMG in Colombia. The diagnosis occurred 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 BC was higher than reported. In this study it was found that belonging to the prepubertal group can increase the risk of presenting OMG. Autoimmune comorbidity was not frequent, and the performance of the different diagnostic aids is good. Medications and lines of management are adjusted to the recommendations given; however, more studies and a more significant sample size are needed.

Keywords: Acetylcholine; immunosuppressants; Autoimmune disease; Neuromuscular disease; Myasthenia gravis; Thymectomy

Introduction

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

The most common type of presentation is 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), against muscle-specific kinase receptors (AntiMuSK), and low-density lipoprotein receptor-related protein 4 (AntiLRP[4]) [4]. Despite this, a strong index of suspicion is required for timely diagnosis [5].

For its treatment, the most used medications have been pyridostigmine and steroids [2,6], as well as Intravenous Immunoglobulin (IGIV) and plasmapheris, in case of crisis [7,8]. Thymectomy is also a therapeutic option in selected patients [9].

JMG 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 unknown if there is a predominance by female sex, age, main form of presentation and its initial symptoms; nor about the use of different diagnostic tools, nor treatment trends. For this reason, this study intends to describe for the first time in Colombia the sociodemographic, clinical, and paraclinical characteristics and their management in children diagnosed with MGJ in a reference university hospital.

Materials and methods

A retrospective observational study was carried out, recording the medical records of patients assessed at the HUSVF in Medellín, Colombia (fourth level reference hospital), diagnosed with JMG according to clinical manifestations, the presence of antibodies, changes 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 records of newborns and patients under 18 years of age, diagnosed with JMG according to the ICD 10 nomenclature [15], identification and assessment was made by pediatricians, and validation by neurologists. Pediatricians, who established the treatment and evaluated the clinical evolution during hospitalization.

Characterization of the population

The following were obtained from the medical records: sex, age of onset of the disease, origin. Individuals were classified into prepubertal and postpubertal groups [16]. Like all the information regarding the neurological examination; initial symptoms and signs, type of presentation, severity of the disease according to the modified Osserman scale (MOE) [17], personal history. Likewise, the result of antibodies using the Radioimmunoassay technique (RIA). Electrophysiological studies and Computerized Axial Tomography of the mediastinum (CAT). The results of clinical and pharmacological diagnostic tests were also evaluated. Likewise, the histopathological report of the 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) for quantitative variables were determined. Unless otherwise indicated, values are expressed as: absolute amount 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 value of $p < 0.05$ was considered statistically significant.

This study was approved by the ethics committees of the HUSVH and that of the Faculty of Medicine of the University of Antioquia, framed under the research regulations of the Colombian Ministry of Health [18].

Results

On 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), with a range of 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 female-to-male ratio was 1.5:1. Most of the patients resided in the department of Antioquia, mainly in the city of Medellin, and 30% came from other departments of the country. No statistical significance was found regarding the presence of MGJ, gender and age group.

The most frequent type of presentation was ocular, and the most common clinical findings were ptosis and diplopia. The generalized form was presented in 47.8% of cases, of which three evolved from MGO; while BC was present in 21.7% (n 5), of these, 60% were found in the postpubertal group. Table 1 details the sociodemographic and clinical characteristics of the patients, including severity. Five patients were not classified according to 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 OMG and in postpubertal patients to present MGG.

One case was found associated with another autoimmune pathology. Likewise, psychiatric disorders were presented, observing a non-significant trend (p 0.29) where postpubertal men presented said disorders.

In the antibody detection assay, two positive and four negative patients were reported for antiAchR, and one negative case for AntiMusK. Results for five patients for AntiAchR and AntiMusK were not reported.

The electrophysiological study showed good performance to detect alteration of the neuromuscular junction, especially the single fiber electromyography, and the repetitive stimulus test. Tests with anticholinesterase agents were performed in 3 patients, in all of which an improvement in muscle strength was observed after their administration. The ice test was performed on five patients, it was positive in four cases. Mediastinal CT was performed in 19 patients. Thymus hyperplasia was reported in three; same for thymoma. Table 2 summarizes the diagnostic tests performed and their results.

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 drug combination, pyridostigmine plus steroids and pyridostigmine plus steroids plus azathioprine were used with equal frequency (26%). Regarding the management of MC (n 5), four required management with plasmapheresis, despite the fact that two of them had previously received IVIG; one patient responded to treatment with first-line drugs, and two underwent thymectomy (34.7%). -Who are included in the total number of patients who required surgical management-. Discussion

Knowing the characteristics of JMG in a population is extremely important, due to the disability and mortality that can occur if it is not treated in a timely manner [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 agreement with previous publications [19, 21,22]. However, within the affected women, the predominance was greater in those under 12 years of age, which differs from other investigations, 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 that 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 can increase the risk of presenting ocular MGJ. Likewise, being post-pubertal can increase it to present the generalized type. The transformation of MGO to the generalized form was observed in 13%, mainly in the postpubertal group. Different from what has been described in other studies, where this evolution can occur in 30% - 50%, and prepubertal children are the most affected [2,3]. It has been described that, in most cases, said transformation occurs in the first six months from the onset of symptoms [2,29].

In accordance with 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, the cases of BC 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 involvement in post-pubertal men was observed. Similarly, there were 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 further investigate the quality of life of these patients.

Regarding the diagnosis, a low percentage of patients with positive antibodies was found, similar to what has been shown by other investigations, where it has been observed that those who present ocular MGJ may present 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 symptoms suggestive of JMG but with negative antibodies for antiAChR and antiMuSK could be positive for LRP-4 [36]. Therefore, it is convenient to emphasize that, although the presence of antibodies is important to support the diagnosis of immune JMG, a negative result does not rule it out, and that the ethnic origin of the patients influences their serum level [37].

In this study, it was found that both the single fiber EMG and the repetitive stimulus test were positive in percentages similar to those reported in the literature [38], despite the difficulty involved in performing them in children [39]. The cases where pharmacological tests were used to support the diagnosis were all positive. The most 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 a higher risk of complications [41].

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

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

Regarding 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 the consensus on the management of JMG 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 BC [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, for which there is recent evidence suggesting its use especially in patients with AntiMuSK, and can be considered as second-line therapy in MGJ, was not observed [45,48].

On the other hand, thymectomy was performed in a percentage similar to that reported in previous investigations [9,22,49]. All patients received medical management prior to surgery. Those who presented BC 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 those inherent to a retrospective investigation, based on clinical history reports and the failure to obtain some data; despite its nature, it provides important information that increases the understanding of MGJ 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 group and in the postpubertal group. The ocular type of presentation was manifested more frequently than the generalized type. There may be an increased risk of MGO in prepubertal children and of MGG in postpubertal children. Different from what was published, a significant proportion of BC was presented. Comorbidity with autoimmune entities was not frequent; 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 the ice pack test showed good performance in supporting the diagnosis. Pyridostigmine and steroids were the most used drugs, according to the recommendations. Thymectomy was performed in a considerable number of patients.

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