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Patients with ocular symptoms referred for electrodiagnosis: how many of them suffer from myasthenia gravis?

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Abstract The aim of this study was the diagnosis of patients with isolated ocular manifestations (ptosis and/or diplopia) referred for electrophysiological evaluation to the electrodiagnostic laboratory of a University Neurological Department. Examination was performed either in inpatient status or in outpatient basis. We analyzed the clinical, electrophysiological and other laboratory data in 79 subjects. Myasthenia gravis (MG) was diagnosed in 38 %, 45.6 % in other diseases (Graves disease, blepharospasm, IIId cranial verve palsy, multiple sclerosis, stroke, etc.), while in 16.5 %, the cause remained unidentified. Symptoms fluctuation was significantly more frequent in the myasthenic patients, compared to patients with other diseases. The presence of both diplopia and ptosis are more likely due to MG rather than other pathology.

Keywords Ptosis · Diplopia · Myasthenia gravis

Introduction

Ocular symptoms, ptosis and diplopia, are common symptoms in subjects referred for electrodiagnosis (EDX). These symptoms may be the manifestations of different diseases. The most frequent causes of ocular symptoms are myasthenia gravis (MG), cranial nerve palsies (inflammations, aneurysms, trauma, diabetes mellitus, Miller Fisher syndrome, Horner's syndrome), multiple sclerosis, stroke

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and Grave's disease. Other causes include mitochondrial myopathies, dystonia (blepharospasm) [1–3] and ophthalmologic conditions (Heterotopia, levator dehiscence, exotropia, etc.) [4, 5]. Ocular signs and symptoms are the presenting symptom in more than half of the patients with myasthenia gravis [6, 7]. In contrast with generalized myasthenia gravis, the diagnosis of ocular myasthenia (OMG) is often difficult, given that it is often seronegative and can be confused with various other diseases, neurologic and ophthalmologic [5]. A non negligible number of patients with ocular symptoms remain undiagnosed [2, 5, 8, 9]. The aim of our study was to assess the diagnosis of patients with isolated ocular manifestations referred for electrophysiological evaluation, to the electrodiagnostic laboratory of a University Neurological Department.

Methods

We performed a mixed, retrospective and prospective study of all patients with isolated ocular symptoms only referred to the electromyographic laboratory of a University hospital over a two and half year period (from May 2009 to December 2012). From May 2009 to July 2010, the patients were studied retrospectively (15 patients) and from August 2009 to December 2012, prospectively. When all data could not be retrieved from medical records, or when patients were lost in follow up, they were contacted by telephone for final diagnosis.

The patients included in the study suffered from diplopia and/or ptosis without other manifestations (bulbar and/or limb symptoms) as referred by the patient in the medical history, or revealed during physical examination. The diagnosis of MG was made when the patients presented diurnal variation of symptoms and also fulfilled one of the

three following criteria: (1) Positive Acetylcholine receptor antibodies (AchR) or Muscle-specific receptor Tyrosine kinase antibodies (anti-MuSK). (2) Abnormal RNS and/or SFEMG. (3) Positive response to anticholinesterase treatment.

The demographic and other patient data including age, sex, specialty of referring physician, symptom duration, comorbidities and final diagnosis were assessed. Some patients were evaluated more than once with RNS and/or SFEMG until diagnosis was obtained.

All patients underwent RNS in the Orbicularis oculi (OO) and the recommendations of AAEM for RNS [10] were followed. SFEMG in OO was performed in the patients with normal RNS. Examination was performed either in inpatient status or in outpatient basis. For SFEMG, concentric needle and voluntary contraction were used.

Results

A total of 93 patients were studied. In 14 of them, no complete data were available or the patients were lost in follow up and could not be contacted by telephone. The remaining 79 patients were included in the study. There were 38 male and 41 female subjects of median age 51.7 ± 17 years (20–88). 50 were inpatients and 29 outpatients. Patients were referred from neurologists in 74 cases, general practitioners in two cases and ophthalmologists in three cases. The presenting symptom was ptosis in 26 patients, diplopia in 21 and both in 32 patients. Average duration of symptoms was 34.9 months (0.2–348 months). The long interval between symptoms onset and electrophysiological study in this group of patients is due to the fact that some of them were already diagnosed and some had long term spontaneous remissions. The median values are also influenced from four outliers. In fact, although the duration of symptoms were 6 days to 8 years in majority of the patients, there were four patients with symptoms duration 180–348 months. Daily variation of symptoms, as referred from the patients, occurred in 37 patients: 25 OMG (83.3 %) and 12 (24.5 %) non-OMG patients ($p = 0.002$).

MG was diagnosed in 30 patients (38 %) and other diagnoses in 36 patients (45.6 %). The cause was not identified in 13 subjects (16.5 %). The demographic characteristics of the two groups, MG and non-MG patients, are shown in Table 1. Median age of the patients and sex did not differ in the two groups. Diplopia was present in 24 out of the 30 patients with MG, and 29 out of 49 in the non-MG group ($p = 0.6$). Ptosis was present in 25 patients of the MG group and in 33 of the non-MG ($p = 0.7$). Both diplopia and ptosis were present in 19 and 13 patients, respectively ($p = 0.1$, Fisher's exact test).

Daily variation of symptoms was observed in 25 MG and 12 non-MG patients ($p = 0.002$). RNS was abnormal in half and SFEMG in 76 % of the tested MG patients. SFEMG was also abnormal in two other patients, in whom the final diagnosis was different to that of MG: Myopathy was diagnosed in one (clearly myopathic needle EMG in orbicularis oculi and Biceps brachii) and blepharospasm in another patient. AchR antibodies were present in 13 patients, anti-MuSK in seven and LRP4 in one patient. Overall, 70 %.of the MG patients were seropositive. The five patients with no clear daily variation of symptoms were included in the group of OMG because two of them had positive RNS and SFEMG, two others had abnormal SFEMG and positive response to anticholinesterase treatment, and one was seronegative with normal RNS and SFEMG, but had a positive response to anticholinesterase treatment.

MG and the other diagnosis are shown in Table 2. Ophthalmologic disease was the most frequent other cause, diagnosed in nine patients (blepharospasm, levator dehiscence, idiopathic ptosis). Other neurological diseases included III cranial nerve palsy (6 patients), thyroid dysfunction, stroke, and more rarely myopathy, trauma, multiple sclerosis, hemicrania. In two patients who were referred for ptosis, was not observed during the examination. The cause was unidentified in eight patients with diplopia, four with ptosis and one with both diplopia and ptosis.

Discussion

In this study, MG was diagnosed in 38 % of the patients. Other diseases were diagnosed in 45.6 %, while 16.5 % patients remained undiagnosed.

The diagnosis of MG is based on clinical examination, the detection of circulating antibodies (AchR and anti-MuSK) and electrophysiological study: RNS and SFEMG. Given that the mentioned antibodies are present in 80–92 % of patients with generalized MG [7, 11], but only in 30–60 % of those with OMG [12], the role of electrophysiological study is crucial in the evaluation of such patients, although RNS is diagnostic in OMG in 30–60 % [12, 13]. SFEMG on the contrary has a sensitivity of 89–99 % but lower specificity [13, 14]. In this study, SFEMG was abnormal in 76 % of OMG patients. In the study of Mercelis and Merckaert [15], a low sensitivity (80 %) was also found, and Benatar [16] cast a doubt on the high sensitivity of SFEMG in OMG, claiming that it is probably overestimated. Ptosis and/or diplopia are the presenting symptom in about 75 % of the MG patients, and nearly all of them will present ocular symptoms in the course of the disease [17]. Given the above limitations regarding the low sensitivity of RNS in OMG and also the fact that these patients are

Table 1 Baseline characteristics of patients with ocular symptoms

N = 79	OMG group (N = 30)	Non-OMG group (N = 49)	p, Fisher's exact test
Sex F/M	15/15	26/23	
Age (median, range)	53 (20–80)	52.9 (18–84)	
In:out-patients (N)	15:15	27:21	
Starting age (median, range)	45 (9–80)	49.5 (5–82)	
Symptoms duration (median, range)	4 (1–336)	6 (0.2–348)	
Diplopia (N, %)	24 (80)	29 (59.2)	0.6
Ptosis (N, %)	25 (83.3)	33 (68.7)	0.7
Ptosis + diplopia (N, %)	19 (63.3)	13 (26.5)	0.1
Daily variation (N, %)	25 (83.3)	12 (24.5)	0.002
RNS (N, %)	14/28 (50)	0/49 (0 %)	
SFEMG (N, %)	19/24 (76)	2/23 (8.7)	
ACHRAbs (N, %)	13 (43.3)		
MuSK	7 (23.3)		
LRP4	1 (3.3)		

Table 2 Causes of ocular symptoms in the 79 patients

Myasthenia (N, %)	30 (38)
Other causes (N, %)	36 (45.6)
Hyperthyroidism	5 (6.3)
III cranial nerve palsy	6 (7.6)
VI cranial nerve palsy	3 (3.8)
IV cranial nerve palsy	2 (2.5)
Stroke	3 (3.8)
Traumatic	1 (1.3)
Hemicrania	2 (2.5)
Tumor	1 (1.3)
Multiple sclerosis	2 (2.5)
Blepharospasm	3 (3.8)
Levator dehiscence	2 (2.5)
Idiopathic	4 (5.1)
No ptosis, edema	2 (2.5)
Unidentified causes (N, %)	13 (16.5)

frequently seronegative, ocular symptoms can be confused with various other neurologic and ophthalmologic conditions and nonrarely remain undiagnosed.

In OMG group, seven MuSK positive patients (23.3 %) are included. It is obviously a coincidence and this number does not reflect the incidence of MuSK antibodies in OMG which on the contrary is very low. On the other hand, ocular are the presenting symptoms in many of the MuSK positive MG patients, which is a generalized disease and quite all of them generalize. Our patients had 10 months mean duration of symptoms. In six of them, the duration ranged from 1 to 9 months and in only one, the duration was 36 months. So, we think that quite all of them will be transformed in generalized myasthenia granis (GMG) within 2–3 years.

Fluctuation of ptosis and diplopia is common in MG [4], although present and in other causes [2, 4, 9]. In this study was significantly more frequent in the MG patients. Mean age of the patients and female-to-male ratio seem also not to differ in the two groups (OMG and non-OMG).

The presence of both diplopia and ptosis, although not statistically significant, is more likely to be due to MG. In this study this significance ($p = 0.1$) is very close to $p = 0.05$, and more higher of that for the two symptoms separately. The presence of only one of these symptoms, although more frequently observed in MG, may be due to either MG or other neurologic or ophthalmologic diseases. Mittal et al. [5] performed a retrospective study of 138 patients referred to a neuro-ophthalmology clinic for ocular symptoms (ptosis and/or diplopia). OMG was the most common cause, being diagnosed in 49 % of the patients. Patients with OMG who were transformed to GMG were those with both diplopia and ptosis, and no one with isolated ptosis or diplopia. Padua et al. [9] reported 40 % of their patients having OMG and Batocchi et al. [2] 41 %.

The higher percentage of OMG diagnosed in the study of Mittal et al. [5] in comparison with our study is probably due to the sample selection. The lower percentage of MG patients in this study is probably due to the fact that the hospitalized patients in a neurology department, as well as those examined in an outpatient basis present a wider spectrum of neurological symptoms and diseases, and are referred for electrodiagnosis not only to confirm but also to exclude MG. EDX is also frequently performed before MRI and the other paraclinical investigation. The fact that our sample was included patients already diagnosed did not

influence the percentage of OMG patients because it is composed of all consecutive patients referred for electro-diagnosis. Moreover, the percentage of OMG patients found is lower than that reported in earlier studies [2, 5, 9].

The percentage of patients with ocular symptoms who remain undiagnosed is not negligible [5, 8, 10]. In this study, 16.5 % of patients remained undiagnosed. In the study of Padua et al. [9], the undiagnosed cases were 50 % and in that of Mittal et al. [5] undiagnosed remained 27 % of the patients with diplopia, 36 % of those with ptosis and 28 % of those with both ptosis and diplopia. Batocchi et al. [2] also reported that 25 % of their patients with pure ocular symptoms remained undiagnosed.

One limitation of the present study was the fact that our patients were referred to the EMG laboratory by neu-rologists and most of them were inpatients and as such, our group is probably not quite representative of the whole population of patients with ocular symptoms, given that many of them are referred to ophthalmologists. Accord-ingly, our findings are similar to those of previous studies from neurology departments [2, 9] and slightly different from population referred to Neuro-Ophthalmology clinic [5]. Some of our undiagnosed patients to be diagnosed as MG in the future cannot also be excluded.

In conclusion, MG is diagnosed in 38 % of patients with isolated ocular symptoms referred for electrodiagnosis from neurologists. The main clinical symptom indicative of MG is fluctuation of ocular symptoms. The presence of both diplopia and ptosis is more likely to be due to MG rather than other diseases. Extensive paraclinical study, including biochemical and endocrinological investigation, CT and MRI of the orbits and brain, electromyogram of the orbicularis oculi and eventually, muscle biopsy is required in cases of non-OMG.

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