Myasthenia gravis presenting with isolated ptosis: a poorly studied subgroup

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Investigation into the cause of one isolated symptom or sign can be challenging if that particular sign may be caused by a variety of pathological processes, affecting different tissues, and presenting to different specialties. Unilateral ptosis is a case in point with a prevalence of 11.5%, in the over 50s [1]. It may reflect disorders of the neurological and muscular systems, as well as local mechanical causes. The investigator's task is not made easier if one cause is fairly common, and others relatively rare, with no one test to clearly differentiate between the various types.

Myasthenia gravis (MG) is not commonly considered in the differential diagnosis of isolated ptosis by ophthalmologists. It is an autoimmune disorder causing characteristic fluctuating muscle weakness that can affect any skeletal muscle, in any combination [2].

However, 15% have a form of MG that is permanently restricted to the ocular muscle [2]. Ocular muscle is more susceptible to fatigability due to increasing firing frequency and rapid contraction kinetics [3]. Compared to limb muscle, it has fewer Acetylcholine Receptors (AChR) and less Acetylcholine (ACh) released at the neuromuscular junction so increased vulnerability to MG. Small changes in the function of ocular muscle causing ptosis or diplopia are symptomatic [3].

We felt that isolated ptosis was probably under investigated and its true nature misdiagnosed. However, diagnosis can be difficult, because investigations may well be negative.

These tests include AChR antibodies (by radioimmunoassay) and single fibre electromyography (SFEMG) preferably utilising the peri-ocular or frontalis muscle. Whereas a positive result would confirm a diagnosis of myasthenia, a negative result will not necessarily exclude it.

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The results of Tensilon testing are regarded as being less reliable, as a positive response can be difficult to objectively verify. The associated risks, including fatality, make this a less palatable option [4,5].

Other suggested tests, including the use of heat to accentuate a ptosis and the sleep test and ice to improve a ptosis, are useful only as an adjunct in people who have ptosis in known cases of MG [6,7,8].

Bilateral, asymmetrical ptosis which is variable usually improving with rest, fatigability with episodes of remission [9], is typical of MG but various other presentations are seen. These would include unilateral ptosis as an isolated symptom and sign.

Apart from the inherent benefit of diagnostic precision per se it is important to establish the correct diagnosis to prevent mislabelling as a commoner condition, such as levator aponeurosis dehiscence which may lead to inappropriate surgery [1], with the risk of corneal exposure when the underlying MG is treated medically. There are also the rare risks associated with generalisation of the undiagnosed MG (i.e. myasthenic crisis).

Table 1: Additional investigations carried out on patients to aid diagnosis of myasthenia gravis.

Investigations	Carried out	Negative	Abnormal results
MuSK ab	17	16	1
SMab	22	20	2
CT mediastinum	9	8	1 (small thymoma)
Thyroid function tests	23	22	1 (pt with 1y* hyperthyroidism due to thyroid malig-nancy
Ab to thyroid peroxidase and thyroglobulin	23	21	2**
Tensilon test	7	2	5

*Results show low TSH and raised T4 and normal T3.
**One patient with primary hypothyroidism, Crohn's disease and Pernicious Anaemia, the other patient with no autoimmune disorder.

We performed a retrospective study to characterise MG presenting as isolated ptosis, which we would contend, from a subgroup of patients with ocular myasthenia gravis (OMG). We found that ptosis can remain the only feature of OMG in some MG patients. This study cannot give epidemiological information as the study group is biased.

Material and methods

Ethical approval was given by the Sefton Research Ethics committee. A retrospective case study was carried out on patients referred to a specialist MG clinic between 1998 and 2002 with isolated ptosis. We were able to obtain full information on 138/162 (86%) patients.

Patients who presented to a specialist MG clinic with either bilateral or unilateral ptosis were included. Follow-up was 14 months to 11 years (mean = four years and four months).

Patients were excluded if they presented with any extra or intraocular muscle weakness other than isolated ptosis, if the information regarding referral or subsequent follow-up was incomplete or any another pathology was found.

From this group with complete records we found 23/138(17%) were eligible for the study.

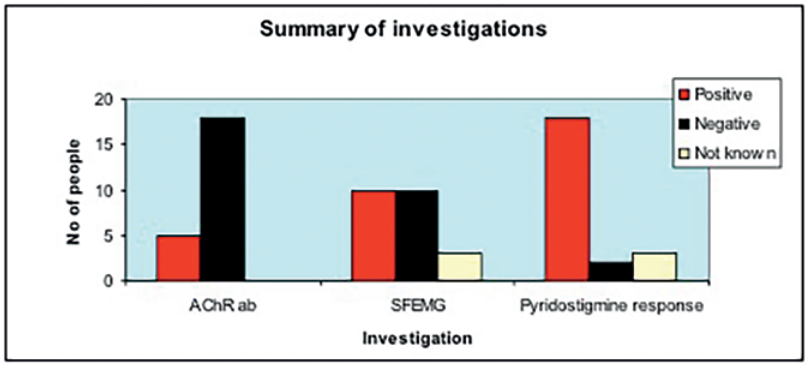
Of 23 patients in the study group 14 patients were referred by ophthalmologists, three by general practitioners, two by paediatric neurologists who had already diagnosed MG, two by general physicians, one by a neurosurgeon and one not known.

Patients had a full neurological history and examination by the neurologist (IH).

All 23 patients in the study were tested for serum AChR antibodies (AChR ab) and 22 for striated muscle antibody (MuSk ab). Of those who were AChR ab negative, 17 were tested for MuSk ab. Twenty patients had SFEMG of the frontalis muscles, while seven patients had a Tensilon test performed. Additional investigations were performed if clinically indicated for the patient's management and exclude other / coexisting pathologies. Table 1 summarises all the investigations and results.

A clinical diagnosis of MG was made if history and examination were consistent with no other explanation found on investigation.

Those patients who tested negative for AChR ab, with SFEMG findings atypical for MG, more suggestive of myopathy and who were unresponsive or inadequately responsive to pyridostigmine, had a muscle biopsy.



Graph 1: Summarises the investigations and clinical methods that were used to diagnose myasthenia gravis.

Results

One hundred and thirty-eight patients attended the myasthenia gravis clinic. Of these, 23/138(17%) patients had isolated ptosis; 14 were unilateral, six were bilateral and in three, laterality could not be determined from the records.

Nine (39%) were men and 14 (61%) women. The average age of onset was 51 years (range 7-67years). However, when two paediatric onset patients were excluded, this rose to 54. The mean age was higher in women at 56.4 years (range 34-81) than in men 43.7 (range 7-77).

Duration of the isolated ptosis at presentation ranged from five days to 61 years, a mean duration of 9.7 years. The duration of the ptosis was at least three years in 20/23 (87%) of our patients and follow-up was at least three years in 16/23 (70%).

Graph 1 gives an outline of the three tests/clinical methods used to diagnose MG and the outcome of these investigations.

We divided the groups depending on the response to the laboratory based investigations or response to pyridostigmine. We have designated our group with isolated ptosis ocMG. The first group (laboratory confirmed ocMG) were those with at least one objective finding of MG. Twelve out of 23 (52%) patients had AChR abs and / or an abnormal SFEMG suggestive of MG. Within this group, three patients had both AChR abs and an abnormal SFEMG, and two people had AChR abs and declined SFEMG and seven people had an abnormal SFEMG only.

The second group (clinically probable ocMG) was defined by a typical history and examination, variable ptosis +/- fatigability who showed improvement with pyridostigmine. There were 8/23 (35%) patients in this group.

The third group (working diagnosis of ocMG) were defined by history and examination suggestive of MG and with no evidence of another neurological disorder on investigation but without objective test evidence of MG and who declined treatment or did not respond to pyridostigmine. There were 3/23 (13%) patients in this group.

MG in our patients typically followed a benign course with 14/23 (56.5%) having ptosis as their only problem during the follow-up of at least 1.2 years (mean four years and four months). Six (30%) developed diplopia. Three (13%) developed generalised MG – all within two years of presentation (two patients at six months and one patient at two years). When these three patients with a working diagnosis of ocMG were excluded, 10/20 (50%) continued to have isolated ptosis over the follow-up period without developing any other clinical signs of other muscle (extraocular or somatic) involvement.

We also looked at the outcomes of our patients in relation to the results of their MG investigations (see Table 2). The 13 patients with isolated ptosis at the end of follow-up tended to have negative MG investigations. Interestingly one patient who developed generalised MG had a negative SFEMG and was AChR ab negative.

There was variability in the way isolated ptosis in ocMG presented. Unilateral presentations were the most common and were seen in 14/20 patients, of which eight were fatiguable. Whereas 6/20 showed bilateral ptosis, of which five were asymmetric and four were fatigable.

Table 2: Categorisation of investigations and the result in combination with progression of myasthenia gravis in our patients.

1. SFEMG testing with results	2. Ach R antibody testing with results (absence / presence of antibodies)	3. Response to pyridostigmine	Progression of oMG with development of other features
3 people unable to carry out testing	2 positive antibodies 1 had absent antibodies	All 3 responded	2 developed diplopia 1 continued with ptosis only
10 people had abnormal response	Of these 3 people were positive for antibodies	1 responded 1 not known	1 developed diplopia 1 developed generalised MG
		1 no response	1 developed diplopia
	Of these 7 people absent antibodies	7 responded	1 diplopia 5 had ptosis only 1 developed generalised MG
10 people had normal response	All 10 absent antibodies	2 responded	1 developed generalised MG 1 developed diplopia
		5 responded 1 no response 2 not responded	8 people continued with ptosis only

Discussion

There are limitations to our study. The numbers are small. It is retrospective. However, ptosis, as an isolated feature is not an uncommon presentation in MG. This group of patients (ocMG) with ptosis and myasthenic features probably represents a subgroup of OMG, that has not been specifically looked at in the literature.

We did not have positive investigations for all our patients. We relied on a consistent history and examination, in addition, comprehensive investigations to exclude other neurological causes. In 11 of our patients we did not have objective evidence of OMG. We justified OMG in the working diagnosis group of eight because of a positive response to pyridostigmine. Corroborating evidence that this criteria for identifying myasthenics was valid is shown by one patient who developed generalised weakness and one patient developing diplopia. In three patients, pyridostigmine was declined and we have relied on clinical information. We can concede that these patients may not have had OMG, but the same clinical criteria had been used for all groups. Ptosis in these patients remained stable for at least 13 years and our total follow-up was at least six years.

Our ocMG group of 12 had at least one objective finding of MG (AChR abs and/or abnormal SFEMG). AChR ab were present in 22% and SFEMG of the frontalis muscle was abnormal in 50%. We feel clinical criteria used to aid our diagnosis is robust because we demonstrated progression in nine patients in the whole group. Also four patients had other autoimmune conditions, a feature associated with myasthenic patients.

"As physicians we need to explain that detection of MG is important to be aware of the risk of generalisation."

MG in our patients typically followed a benign course with 13/23 (56.5%) having ptosis as their only problem during the follow-up of at least one year (mean 3.84 years). The percentage of OMG progressing to generalised MG varies between studies from 53-75% but 93% occur within three years of presentation [2,10]. The maximum weakness of the muscle is said to be reached at three years and after five years OMG tends to be stable [2]. However, when the ptosis is progressive, it needs further investigation with a muscle biopsy to exclude a mitochondrial cytopathy, ideally with the ocular muscle because this is where the disease is manifesting.

Generalised MG were 90% AChRab+ve. AChR abs were found in 53-75% of patients with all forms of OMG [2,4,5]. We found that AChR abs were present in 22% of our patients. Our figure may be lower because we considered OMG in patients who would not usually be seen by a neurologist in whom the disease was mild. It has been suggested that that our assaying technique may not be sensitive enough to pick up the lower levels of AChR ab serum titres in OMG [11]. Certainly AChR ab levels tend to be lower in ocular myasthenics compared to generalised myasthenics [4,12]. Given we had identified a highly select group of OMGs we can hypothesise that AChR ab levels could be even lower.

SFEMG is said to be positive in 100% of generalised MG [4,13]. SFEMG was abnormal in 50% of our patients using the frontalis muscle. By comparison, SFEMG is negative in 12-23% in OMG [12,13]. The sensitivity improves when a more proximal muscle is used. The most sensitive technique uses the most affected ocular muscles including levator palpebrae (LP) or the rectii muscles when detection rate approaches 100% [4,14]. This is not used routinely as it is technically difficult, time- consuming and riskier.

The subgroup of patients presenting with isolated ptosis appears to be different from OMG. There are various theories that explain why extraocular muscles are preferentially involved but not why ptosis can be an isolated feature except that levator palpebrae superioris (LPS) is subject to near constant neuronal stimulation and contains different proportions and types of muscle fibre compared to the other

extraocular muscles (EOMs) [15].

The EOMs operate at higher firing frequencies with shorter recovery time. They are more susceptible to blocking at the neuromuscular junction (NMJ) because the post synaptic units have less AChR and proportionately less acetycholine is released at the presynaptic junction for every action potential compared for limb muscles.

It has been shown that antigenicity of AChR of extraocular muscles is different to limb muscles [16]. Previously, the little known immune factors such as acetylcholinesterase antibody were found in higher concentrations in OMG and another contributing factor suggested is that these patients have reduced complement regulatory proteins found in the EOM so get complement mediated damage at the NMJ [17,18]. We can only postulate that LPS is somehow more antigenically vulnerable compared to the other EOMs.

There was a lower incidence of AChR ab positivity, reduced abnormal SFEMGs and a decreased conversion to generalised MG in this subgroup of ocMG. Conversely, in the nine patients who had diplopia and generalised symptoms of myasthenia gravis, which can be seen as a hallmark of the disease, two had normal electromyography (EMG) and five had no AchR ab, which illustrates the different nature of these patients compared to the OMG patients.

Isolated ptosis as the initial sign has been found to vary between 10-25% of OMG patients [17,19]. There are no studies to compare where ptosis remains the only symptom. In our select group, for over half (14/23), ptosis was the only symptom (range 3-22 years) with no other weakness which is commonly associated with MG. This is a group where investigation or treatment may be rejected by the patient due to mild, insignificant symptoms. As physicians we need to explain that detection of MG is important to be aware of the risk of generalisation. Also ptosis surgery on these patients increases the risk of corneal exposure with a greater chance of failure due to the fluctuating weakness.

A trial of pyridostigmine can be a valuable addition to our array of investigations, especially as conventional investigations tend to be negative.

A further prospective study looking at all patients presenting with ptosis to the eye clinic with a defined protocol is indicated to find out more about this poorly recognised and probably under diagnosed subgroup of ocular MG.

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