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Ocular palsies in the absence of other neurological or ocular symptoms: analysis of 105 cases

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Abstract We studied prospectively 105 unselected patients complaining of ptosis and/or diplopia due to extrinsic ophthalmic muscle palsies without other neurological signs. All patients underwent the same diagnostic protocol. The presenting symptoms were: ptosis, 35 patients (33%); diplopia, 27 patients (26%); ptosis and diplopia, 43 patients (41%). The oculomotor nerve was most frequently involved, followed by the abducens nerve. The final diagnoses were: ocular myasthenia, intracranial and/or orbital pathology, thyroid ophthalmopathy, diabetic ophthalmoplegia, mitochondrial myopathy, oculopharyngeal muscular dystrophy. In 26 patients (25%) the cause remained undetermined. Our study confirms the difficulty of establishing an aetiological diagnosis in patients with isolated ocular palsies.

Key words Ocular palsies · Ptosis · Diplopia · Ocular myasthenia

Introduction

Ocular palsies are frequently observed in neurological practice. They may be a symptom of generalized disease or occur in isolation.

Previous studies have shown that it is often difficult to establish the aetiology of these symptoms so that more than 25% of cases remain undiagnosed [16–19], the chances of making a diagnosis being higher in patients with associated neurological findings or multiple ocular palsies [16].

Starting with our clinical experiences, we established a diagnostic protocol for patients with isolated ocular palsies. Here, we report the results of this prospective study.

Patients and methods

We studied consecutive patients seen in our clinic between January 1992 and December 1994, who were affected by ptosis, diplopia, or both, with or without pupil involvement. All patients underwent both neurological and ophthalmological examinations. We excluded patients with accompanying neurological signs, orbital pain or headaches, ocular diseases and congenital cases. A Hess screen test was performed in all patients complaining of diplopia.

According to the established protocol, all patients were submitted to the following diagnostic tests:

1. Carbohydrate metabolism study: fasting glucose plasma concentration, oral glucose tolerance test.
2. Thyroid function tests: thyroxine, tri-iodothyronine, free thyroxine (FT4) and free tri-iodothyronine (FT 3), thyroid-stimulating hormone (TSH), anti-thyroid antibodies (anti-thyroglobulin, anti-microsomal) serum concentrations.
3. Anti-acetylcholine receptor (anti-AChR) antibody titration, according to Lindstrom [10], with minor modifications [1].
4. Edrophonium test.
5. Computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and orbits.
6. Conventional electromyography (EMG); low-rate supra-maximal repetitive nerve stimulation (SRNS) of limb muscles (deltoid and abductor digiti minimi) and/or single fibre study (SF-EMG) of the orbicular muscle. The low-rate SRNS test was considered positive for neuromuscular junction (NMJ) disorder when an abnormal decrement (> 11%) of the 3th–5th compound muscle action potential (CMAP) was evident. SF-EMG

was considered positive for NMJ disorder when jitter was increased in more than 4 of 20 single fibre pairs.

In addition, muscle biopsy was performed: (1) in both sporadic and familial progressive ptosis, whether or not associated with ophthalmoparesis; (2) in patients with myopathic findings on their EMG; and (3) in some patients in whom all the other diagnostic tests were negative. The deltoid or biceps muscle was selected for muscle biopsy and routine morphological and histochemical analysis was performed [5]. In cases with ragged red fibres on muscle biopsy, total DNA was isolated from 10–150 mg of frozen muscle [28], preparation of mitochondrial DNA (*mtDNA*) probes and Southern blot analysis were performed as described by Zeviani et al. [29].

Table 1 Clinical diagnoses (*CPEO* chronic progressive external ophthalmoplegia, *OPMD* oculopharyngeal muscular dystrophy)

Diagnosis	Patients	
	(*n*)	(%)
Ocular myasthenia	43	41
Intracranial pathology	11	10.5
Thyroid ophthalmopathy	10	9.5
Diabetic ophthalmoplegia	9	8.5
CPEO	5	4.8
OPMD	1	0.9
Undiagnosed cases	26	24.8
Total	105	100

Results

We observed 130 patients with ocular palsies, of which 25 were excluded because we had insufficient clinical data. Of the 105 cases studied, 55 patients (52%) were male and 50 (48%) were female, aged between 7 and 81 years (mean 47.2).

The presenting symptoms were: uni- or bilateral ptosis, 35 patients (33%); diplopia, 27 patients (26%); ptosis and diplopia, 43 patients (41%). The pupils were normal in all patients but one.

Multiple ocular nerve palsies were present in 26 cases (25%); in the other 79 patients, the oculomotor nerve was affected most frequently (61%), followed by the abducens nerve (9%). The trochlear nerve was the least commonly involved (5%).

An aetiological diagnosis was made in 79 patients (75%); 26 cases (25%) remained undiagnosed.

Table 1 shows the clinical diagnoses. Clinical symptoms and cranial nerves that supply extraocular muscles involved in the different diseases are shown in Tables 2 and 3, respectively.

A diagnosis of ocular myasthenia was made in 43 patients (41%), 21 male and 22 female, aged between 7 and 81 years (mean 44.1). The diagnosis of ocular myasthenia was made on the basis of typical history and symptoms associated with at least two of the following criteria: unequivocal improvement after edrophonium injection, pos-

Table 2 Presenting symptoms in different diseases

Diagnosis	Patients (*n*)	Clinical symptoms		
		Ptosis	Diplopia	Ptosis + Diplopia
Ocular myasthenia	43	14	7	22
Intracranial pathology	11	0	6	5
Thyroid ophthalmopathy	10	6	4	0
Diabetic ophthalmoplegia	9	0	4	5
CPEO	5	4	0	1
OPMD	1	0	0	1
Undiagnosed cases	26	11	6	9
Total	105	35	27	43

Table 3 Nerves supplying the extraocular muscles involved in the different diseases

Diagnosis	Patients (*n*)	Nerves					
		III	VI	IV	III, VI	III, IV	III, IV, VI
Ocular myastenia	43	27	0	1	12	2	1
Intracranial pathology	11	5	2	2	1	1	0
Thyroid ophthalmopathy	10	8	1	0	1	0	0
Diabetic ophthalmoplegia	9	5	4	0	0	0	0
CPEO	5	4	0	0	0	0	1
OPMD	1	0	0	0	0	0	1
Undiagnosed cases	26	16	2	2	5	1	0
Total	105	65	9	5	19	4	3

Table 4 Final diagnoses, symptoms and affected nerves in patients with intracranial pathology. *SF-EMG* single fibre electromyography

Diagnosis	Patients (*n*)	Clinical symptoms			Affected nerves				
		Ptosis	Diplopia	Ptosis + Diplopia	III	VI	IV	III, VI	III, IV
Encephalopathy with multi-infarcts	4	0	3	1	3	1	0	0	0
Post-traumatic diplopia	2[a]	0	2	0	0	1	1	0	0
Frontal sinus mucocele	1[a, b]	0	0	1	0	0	0	0	1
Carotid cavernous sinus fistula	1[a]	0	0	1	1	0	0	0	0
Midbrain haemorrhage	1[c]	0	0	1	1	0	0	0	0
Basal meningitis	1	0	1	0	0	0	1	0	0
Cerebral tumour	1	0	0	1	0	0	0	1	0
Total	11	0	6	5	5	2	2	1	1

[a] Positive SF-EMG
[b] Diabetes mellitus
[c] Pupil involvement

itive serum anti-AChR antibody result, signs of NMJ disorder on SRNS and/or SF-EMG. Symptoms were fluctuating and consisted of ptosis in 14 patients (33%), diplopia in 7 (16%) and ptosis and diplopia in 22 (51%). The orbicularis oculi muscle was involved in 20 of the 43 cases (46.5%); this sign was not appreciated by any of the patients. The edrophonium test was performed in 39 patients and was positive in all of them; in four cases it was not performed on account of symptoms being too subtle and fluctuating. Anti-AChR antibody results were positive in 21 of the 43 patients (49%). Electrophysiological tests were performed in 42 cases and were positive in 40 of these (95%): SRNS was positive in 14 of 34 patients (41%) and SF-EMG in 34 of 36 (94%) cases. Only 2 patients (5%), in whom both the edrophonium test and the anti-AChR antibody assay were positive, showed a normal result of SRNS and SF-EMG. Two patients also suffered from non-insulin-dependent diabetes mellitus; a thyroid disorder was present in 1 case.

Ocular palsy was related to intracranial or orbital pathologies in 11 cases: 9 males and 2 females aged between 8 and 67 years (mean 53). Clinical symptoms, affected nerves and final diagnoses are shown in Table 4. In 9 of 11 cases, a clinical diagnosis was made on the basis of CT or MRI findings; in two patients with post-traumatic diplopia, results from neuroimaging were negative. Fluctuating ptosis and/or diplopia were present in three patients affected by basal meningitis, cerebral tumour and frontal sinus mucocele respectively. This last patient had a positive SF-EMG result. SF-EMG also produced positive results in the two cases affected by post-traumatic diplopia and in the patient with carotid cavernous sinus fistula. Anti-AChR antibody and edrophonium tests were negative in all of these cases.

Thyroid-associated eye disease was diagnosed in 10 patients, 5 males and 5 females, aged between 26 and 61 years (mean 45). Five patients, two with mild fluctuating unilateral ptosis and three with diplopia, had a history of hyperthyroidism (Graves' disease). At the time of examination, thyroid hormone levels were raised in three and normal in two cases. Autoimmune thyroid disorder was diagnosed in one patient with unilateral ptosis on the basis of raised anti-thyroid (anti-thyroglobulin, anti-microsomal) antibodies. Three patients with ptosis were undergoing treatment for primary hypothyroidism; one of them had myopathic findings at EMG, but a muscle biopsy of the deltoid muscle did not show any myopathic changes. Double vision with vertically separated images was present in one patient with both normal thyroid function and antithyroid antibodies. In this case, ultrasonography and MRI of the orbits showed an enlargement of the left inferior rectus muscle. This finding was considered typical for subclinical Graves' hyperthyroidism. MR images are shown in Fig. 1.

Diabetic ophthalmoplegia was diagnosed in nine patients, five males and four females, aged between 43 and 80 years (mean 63). All of these patients had been suffering from diabetes mellitus for many years and were undergoing treatment with insulin or oral hypoglycemic agents. All patients demonstrated acute onset of symptoms; five patients showed ptosis and diplopia due to oculomotor nerve involvement, four had diplopia due to abducens nerve palsy. A peripheral neuropathy was present in one case. Brain CT showed an encephalopathy with multiinfarcts in one patient and a frontal hygroma in another.

A diagnosis of chronic progressive external ophthalmoplegia (CPEO) was made in five patients (four with progressive ptosis and one with fluctuating ptosis and diplopia) on the basis of muscle biopsy findings of ragged red fibres and cytochrome c oxidase (COX)-deficient fibres. The patients were two males and three females, aged between 56 and 71 years (mean 62.4). A positive

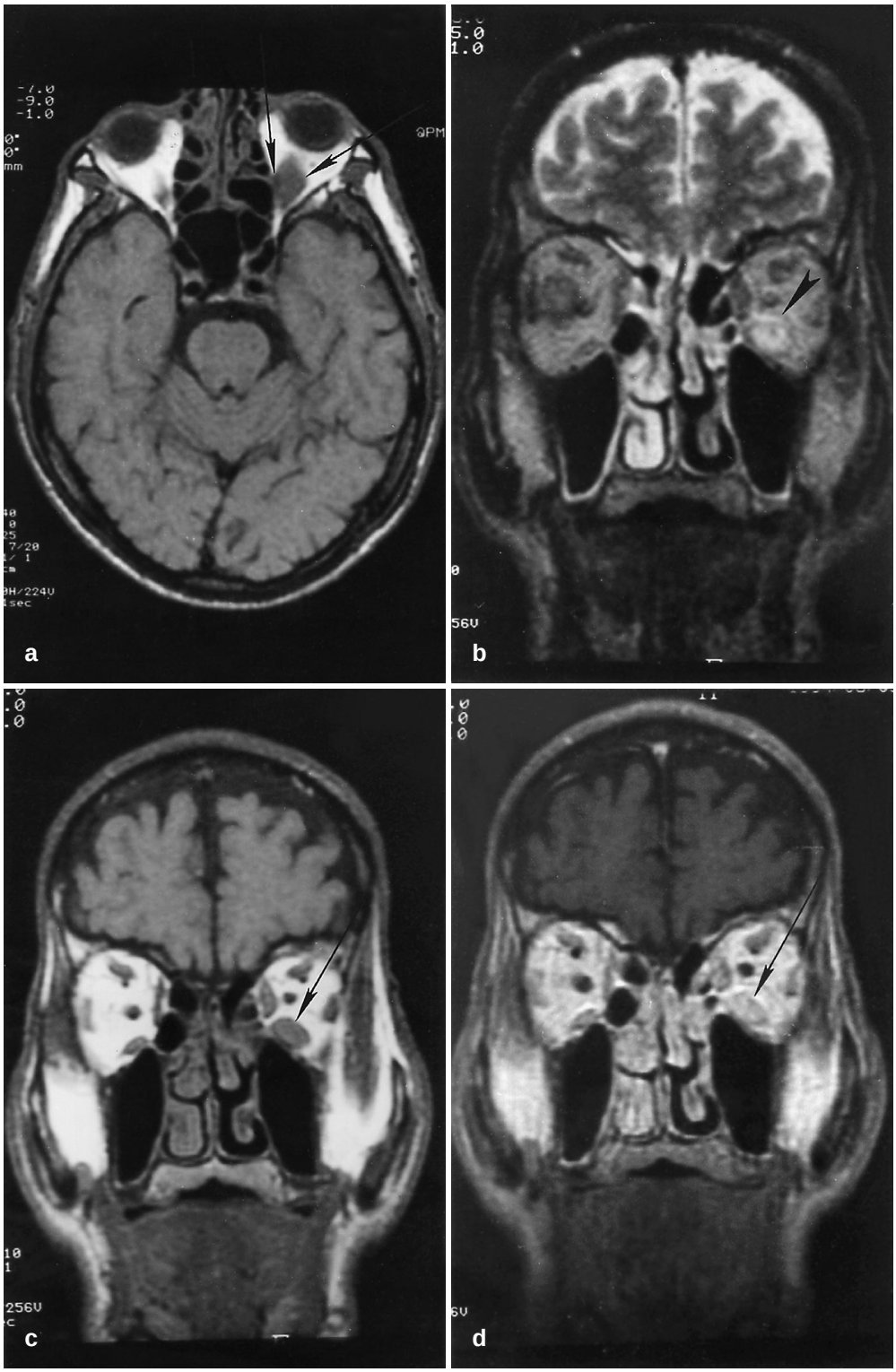

Fig. 1 a–d MRI of a patient with subclinical Graves' disease: **a** axial spin-echo (SE) T_1-weighted image; **b** coronal fast-spin-echo (FSE) T_2-weighted image; **c** coronal SE T_1-weighted image; **d** enhanced coronal SE T_1-weighted image. The left inferior rectus muscle is enlarged *(black arrows)*, showing evident hyperintensity in the T_2-weighted image *(arrowhead)* and enhancement after contrast administration owing to inflammatory changes

family history was present in three cases with progressive ptosis: inheritance was autosomal dominant in two cases and autosomal dominant or maternal (no transmitting male was available) in the other. Southern blot analysis for *mtDNA* showed several bands due to the presence of multiple *mtDNA* deletions in one case and a normal 16.6 band in the other two. Two cases were sporadic; Southern blot analysis for *mtDNA* showed a normal 16.6 kb band in

one patient and an additional band due to a deleted population of *mtDNA* genomes in the other. SF-EMG was positive in one of these patients.

Oculopharyngeal muscular dystrophy (OPMD) was diagnosed in one 63-year-old woman with a family history of ptosis, suffering from progressive bilateral ptosis and ophthalmoplegia; dysphagia was absent at that time. She had a myopathic pattern at EMG in limb muscles; muscle biopsy showed myopathic changes in typical "rimmed vacuoles" within the muscle fibres. Electron microscope examination showed characteristic intranuclear tubular filaments.

No definite diagnosis was established in 26 cases, 13 males and 13 females, aged between 14 and 72 years (mean 41). Unilateral or bilateral fluctuating ptosis was present in six patients (23%), unilateral or bilateral progressive ptosis in five (19%), diplopia in six (23%), and ptosis and diplopia in nine (35%). In all of these patients, diplopia was accompanied by extraocular muscle palsies. Three female patients with progressive ptosis had a family history of ptosis. Oral glucose tolerance test, thyroid function tests, anti-AChR antibody tests and CT or MRI of the brain were negative in all 26 patients. The edrophonium test was negative in 22 patients; it was not performed in four cases that demonstrated signs that were too subtle and fluctuating at the time of examination. SF-EMG was positive in seven cases: two with diplopia, two with ptosis and diplopia and three with unilateral fluctuating ptosis. None of these patients demonstrated a positive edrophonium test or responded to long-term pyridostigmine therapy. One of these patients with unilateral fluctuating ptosis had been wearing hard contact lenses for a long time. Myopathic findings at EMG were found in two patients, one with mild non-fluctuating ptosis and the other with ptosis and diplopia. The five patients with progressive ptosis and the two with myopathic findings at EMG underwent both muscle biopsy and Southern blot analysis for *mtDNA*, which produced normal results.

Discussion

The application of our diagnostic protocol allowed us to establish a definite diagnosis in 79 of 105 patients (75%). The age of onset of symptoms does not seem relevant in making an aetiological diagnosis: in our experience, ocular myasthenia, intracranial pathologies and thyroid-associated eye diseases can affect patients at any age; diabetes mellitus and vascular encephalopathy are more common in patients over 40 years of age in whom they may be associated with other causes of ocular palsies (ocular myasthenia, in our series). A diagnosis of mitochondrial myopathy was made only in patients over 50 years of age, but we cannot exclude this disease in some of the younger undiagnosed patients, not all of whom were submitted to muscle biopsy.

Our experience confirms that many different pathologies can cause palsy of extraocular muscles supplied by one or more ocular nerves. In the present series, only diabetic ophthalmoplegia was characterized by the involvement of a single ocular nerve.

In contrast to previous reports [18–19], in our series the muscles innervated by the third cranial nerve were affected most frequently; the pupil was involved in only one of 105 cases. A possible explanation is that, in our patients, ocular palsies were not associated with other neurological signs or pain.

With regard to the course of the disease, fluctuation of symptoms, although typical of myasthenia gravis [14], does not exclude other diagnoses, since it can be present in intracranial pathologies [12, 15, 24], thyroid-associated eye diseases and mitochondrial myopathies [9]. On the other hand, symptoms may be quite stable in some patients with long-term ocular myasthenia [3].

Ocular myasthenia was found to be the most common pathology in our series. This finding is likely to result from patient selection, as our clinic is a centre for myasthenia gravis. In making the diagnosis of ocular myasthenia, the edrophonium test proved sensitive and fairly specific, even if positive responses in other neurological diseases have been reported [4, 9, 13, 21]. Anti-AChR antibody assay was confirmed as being highly specific [14] although not very sensitive; on the other hand SF-EMG proved to be more sensitive, but less specific, as it was also positive in one patient with mitochondrial myopathy and in four cases with intracranial pathologies.

Ocular palsy was related to intracranial causes in 11 patients (10%). As previously reported, many different pathologies can be responsible [2, 11, 16–20, 25] and the course of the disease can be acute, progressive or even fluctuating. Given the possibility of false-positive results of other diagnostic tests, we recommend CT and/or MRI of the brain and orbits in all patients with non-familial ocular palsy.

Thyroid-associated eye disease was diagnosed in 10 patients. This diagnosis is a clinical one that may be supported by laboratory tests (altered levels of T3, T4, TSH, presence of autoantibodies) [27], a prior history of hyperthyroidism or, less often, of goitre or a family history of thyroid disease [6]. A "pseudoptosis" because of unappreciated contralateral eyelid retraction in the absence of exophthalmos and diplopia is quite a common symptom in thyroid-associated eye disease, and a true ptosis has also been described [7]; in other cases, diplopia is the initial symptom of the disease. Moreover, the ocular changes of Graves' disease may precede clinical or laboratory evidence of thyroid dysfunction by some months or years [27], as observed in one of our patients.

Diabetic ophthalmoplegia was diagnosed in nine patients with diabetes in whom the other diagnostic tests were negative. The oculomotor nerve was the most frequently affected; both pupil involvement and headaches were absent in all cases.

We found evidence of CPEO in five patients, two sporadic and three with a positive family history. Our data confirm that fluctuating ophthalmoparesis and even isolated ptosis may be the only symptoms of a mitochondrial disease [22, 23]. On the other hand, in our patient with OPMD, dysphagia was absent at the time of the first examination and diagnosis was possible only on the basis of muscle biopsy. From our experience, in the aetiological diagnosis of ophthalmopareses, a muscle biopsy should be performed whenever other diagnostic tests are negative.

Our diagnostic protocol failed to produce a definitive diagnosis in 26 patients (25%), confirming the difficulty in clarifying the aetiology of ocular palsies. Both progressive and fluctuating symptoms were present in these cases. SF-EMG results were positive in seven patients, but the other diagnostic tests have not yet confirmed the diagnosis of myasthenia gravis. In one of these cases with unilateral ptosis, symptoms could be related to long-term wearing of hard contact lenses as previously reported [26]. Two patients had myopathic signs at EMG, but no myopathic changes at muscle biopsy. Three patients with familial ptosis had normal muscle biopsy specimens; they could have a mild mitochondrial myopathy with no evidence of ragged red fibres on skeletal muscle biopsy [8, 22]. Lastly, in some of the other undiagnosed cases, symptoms might be related to a subclinical autoimmune thyroid disease that may require a longer follow-up to become evident [6].

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