SHORT REPORT

Eyelid ptosis from sympathetic nerve dysfunction mistaken as myopathy: a simple test to identify this condition

G Tomelleri, G Vattermi, M Filosto, P Tonin

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Acquired isolated unilateral or bilateral blepharoptosis has many aetiologies. When the pupils are normal, a myasthenic syndrome or myopathy has to be ruled out. If the tests for myasthenia gravis are negative, the next step is to perform a muscle biopsy to establish a diagnosis. Muscle examination may show a mitochondrial disorder, non-specific abnormalities or be quite normal. We identified three patients, who had previously undergone various investigations, including a muscle biopsy, whose lid ptosis disappeared using eye drops containing naphazoline nitrate, a sympathomimetic drug, thus suggesting partial Horner's syndrome. We emphasise the usefulness of this simple and cheap test before performing more traumatic and expensive investigations.

Blepharoptosis is the downward displacement of the upper eyelid caused by a dysfunction of the eyelid elevator. Drooping of the eyelids has many aetiologies: it may be due to a lesion at the supranuclear level, or involve the oculomotor complex, the oculosympathetic system or the neuromuscular junction; it may be caused by myopathy; or it may be caused by an anatomical lid abnormality.¹ Unilateral or bilateral eyelid drop can be the first sign of a myopathic disorder, frequently a mitochondrial myopathy. For this reason, a patient who develops eyelid ptosis in the absence of abnormalities of the pupils, with a negative Tensilon test, no acetylcholine receptor (AChR) antibodies and a normal repetitive nerve stimulation or single fibre electromyography (EMG), often undergoes a muscle biopsy to determine the diagnosis. We report on three patients affected by mono-bilateral eyelid ptosis who first received a diagnosis of probable myopathy or ocular myasthenia. Subsequently, the response to an eyewash containing a sympathomimetic drug shifted the cause of the ptosis to a dysfunction of the sympathetic innervation. We emphasise the practical clinical implications of this test.

PATIENTS

Case No 1

A 52-year-old woman had mild right eyelid ptosis for 3 years with no fluctuation or worsening. She had no history of head trauma or diplopia or headache, and was not receiving any medication. Ocular movements, diameter of the pupils and light reflex were normal. Neurological examination was otherwise normal. AChR antibodies were absent. EMG, in the limb girdle muscles, showed abnormally increased polyphasic motor unit potentials that also had a short duration and low amplitude. Repetitive nerve stimulation was normal. A biopsy of the right deltoid muscle showed type 1 fibre predominance and a few atrophic fibres.

Case No 2

This 40-year-old woman from Sri Lanka was referred with bilateral eyelid ptosis of 15 months' duration and fatigability on daily activities. The ptosis was more evident on the left side and

was stable during the day. Ocular movements, diameter of the pupils and light reflex were normal. No other neurological abnormalities were present. The eyelid ptosis did not improve after the orbital ice test and the Tensilon test. Creatine kinase and thyroid function were normal. Antibodies to AChR, thyroglobulin, thyroid peroxidase and thyroid stimulation hormone receptor were negative. Chest CT scan did not show thymus enlargement. Brain MRI, electrocardiography, EMG and repetitive stimulation were normal. Biopsy of the vastus lateralis muscle showed only a few atrophic type 1 and type 2B fibres.

Case No 3

A 66-year-old man came to our attention with a left, steady eyelid ptosis and episodic diplopia from the age of 64 years. At that time, ophthalmic examination revealed only a left eyelid ptosis; brain MRI showed a small meningioma of the falx cerebri. EMG and repetitive stimulation of the ulnar, facial and accessory spinal nerve were normal. Creatine kinase, lactate and thyroid function were also normal. AChR antibodies were not detected. The Tensilon test was negative. Chest CT scan did not show enlargement of the thymus. Despite the absence of serological and electrophysiological signs of myasthenia gravis, the patient was treated with pyridostigmine tablets 60 mg three times a day and prednisone 25 mg/day without improvement. Biopsy of the vastus lateralis muscle, performed more than 1 year after the onset of the symptoms, showed only a few non-specific abnormalities. When the patient was 66 years old, the left eyelid ptosis was unchanged, as were pupil diameter and the light reflex. Diplopia was occasionally referred. Neurological examination showed slow saccades on lateral gaze, mild impairment of accommodative vergence movements, some difficulty in getting up from the chair, imbalance in turning around and a slight increase in muscle tone, all signs that suggested an extrapyramidal disorder.

In all of these three patients, instillation into the conjunctival sac of one or two drops (better results were obtained with two drops) of naphazoline nitrate 1 mg/ml (equivalent to 770 µg of naphazoline), an α -adrenergic eyewash commonly used in Italy as a decongestant, caused complete opening of the eyelids within 2–3 min that was not associated with enlargement of the pupil (fig 1A). This effect lasted for 5–7 h. The test was negative in five patients with lid ptosis caused by a genetically proven mitochondrial myopathy, in two patients with ocular-distal myopathy and rimmed vacuoles on muscle biopsy and in two patients with myasthenia gravis. In a 74-year-old man, affected with a mild axonal sensory-motor neuropathy of unknown cause, who had surgical correction for a left lid ptosis 2 years previously, the response to this test was positive on the right lid ptosis that had appeared 1 year before. A positive response was also found in a healthy 56-year-old man who had suffered from a right lid ptosis for several years. The test was also performed in a 73-year-old man affected with left Horner's syndrome of 6 years' duration due to

Abbreviations: AChR, acetylcholine receptor; EMG, electromyography

Figure 1 (A) Right eyelid ptosis with normal pupils in patient No 1 (top). Instillation into the conjunctival sac of two drops of naphazoline nitrate caused complete resolution of the ptosis (bottom). (B) Left eyelid ptosis in a patient affected with Horner's syndrome (top). Two drops of naphazoline nitrate caused mydriasis of the left pupil and resolution of the ptosis (bottom). Informed consent was obtained for publication of this figure.

dissection of the internal carotid artery beginning 3 cm above the common carotid artery bifurcation. Two drops of naphazoline nitrate caused mydriasis of the left pupil and reversed the lid ptosis after 15 min (fig 1B). Two years after the first observation, the lid drooping in patient No 1 was unchanged and limited to the right eye; two drops of naphazoline nitrate were still effective in resolving the ptosis for approximately 6 h. The patient is now using these drops only for some public engagements. Patient No 2 was still responsive to naphazoline 1 year after the first examination. We lost contact with patient No 3.

DISCUSSION

Our three patients had non-fluctuating unilateral or bilateral eyelid ptosis with normal pupils and light reflex. In the first patient, the EMG recording was myopathic and the muscle biopsy showed signs of a non-specific myopathy but these abnormalities were probably of no pathological significance as the patient was symptomless 2 years after the first examination. The second patient complained of asthenia and muscle fatigability; however, a myopathy and myasthenia gravis were ruled out by appropriate investigations for the two diseases. The third patient was referred with diplopia that suggested myasthenia gravis as the first diagnosis, although AchR antibodies were absent, as well as the typical decrease in compound muscle action potentials on

repetitive nerve stimulation. It is known that repetitive stimulation can be normal in ocular myasthenia and AchR antibodies are not detectable in approximately 15% of patients with generalised myasthenia and in about 45% of patients with ocular myasthenia.² Nevertheless, the lack of any response to the drugs commonly used to treat this disorder prompted us to search for an alternative cause for the lid ptosis. Also, the muscle biopsy was normal in this patient. Acquired unilateral or bilateral eyelid drop in adult patients, in the absence of abnormalities of the pupil or the use of topical steroids, suggests a myasthenic syndrome or other neuromuscular diseases, more frequently a mitochondrial myopathy.¹ In non-myasthenic old patients, an isolated ptosis can be caused by disinsertion or dehiscence of the levator aponeurosis, and thus can be regarded as senile ptosis; local infiltration, microvascular pathology or other conditions can be considered in the differential diagnosis.³ In patients not fulfilling the diagnostic criteria of myasthenia gravis, a diagnostic workup becomes necessary to locate the lesion, to clarify the underlying pathological process and to choose the appropriate treatment strategy.

In our patients, the response to naphazoline nitrate, a sympathomimetic drug, indicated that the eyelid ptosis was due to denervation of Muller's muscle that receives tonic sympathetic innervation and is responsible for palpebral width. Cannon's law, or the phenomenon of denervation hypersensitivity, justifies the response.⁴ The positive response to the test obtained in the patient with Horner's syndrome as a result of dissection of the internal carotid artery, a postganglionic sympathetic syndrome, strengthens our hypothesis. The diagnosis of Horner's syndrome is usually made on the basis of ptosis and miosis. Anhydrosis, the third feature of the classic triad of oculosympathetic paresis, is an inconstant sign. In clinical practice, when miosis is absent it is difficult to suspect Horner's syndrome. A "partial" Horner's syndrome, characterised by the presence of either miosis or ptosis, without anhydrosis, was described in some patients with cluster headache and in chronic paroxysmal hemicrania.⁵⁻⁶ A relapsing alternating ptosis, never associated with miosis, was reported in two sisters with no history of migraine or cluster headache⁷; in the authors' opinion, the symptoms were caused by an intermittent sympathetic dysfunction causing a partial Horner's syndrome. Commonly, an oculosympathetic paresis results in the upper eyelid ptosis of 1–2 mm⁸; contraction of Muller's muscle alone raises the upper eyelid by about 1.5 mm.⁹ However, it was reported that in some patients with Horner's syndrome due to carotid artery dissection, the ptosis was more evident.¹⁰ In bright light both pupils may appear almost equal in Horner's syndrome while in dim light there is anisocoria. It is therefore possible that we were unable to observe miosis in the setting of the neurological examination although our ophthalmologists did not describe miosis even in a more appropriate setting. Nevertheless, from a practical point of view, as a patient with only upper lid ptosis and no evident miosis is usually not considered to have Horner's syndrome, we emphasise that the instillation of two drops of naphazoline nitrate into the eye is a simple, cheap and safe test that should be performed before starting more complex, traumatic, expensive and time consuming investigations. A positive test solves the diagnostic dilemma in a few minutes. We have added this test to our routine clinical examination before carrying out other investigations in patients presenting with non-fluctuating lid ptosis.

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Authors' affiliations

G Tomelleri, G Vattemi, P Tonin, Department of Neurological Sciences, Section of Clinical Neurology, University of Verona, Verona, Italy

M Filosto, Department of Medical and Surgical Sciences, Clinical Neurology, University and Hospital "Spedali Civili", Brescia, Italy
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Correspondence to: Dr Giuliano Tomelleri, Department of Neurological Sciences and Vision, Section of Clinical Neurology, Piazzale L.A. Scuro 10, 37134 Verona, Italy; giuliano.tomelleri@univr.it

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