Recurrent ptosis due to myopathy of the levator palpaebrae superioris

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Abstract

Here we report the 10–year follow–up of a case with a recurrent ptosis affecting both eyelids independently. The histology of the levator palpaebrae superioris and Müller's muscle were consistent with a localised myopathic process. A therapeutic response to acetazolamide suggests that ion–channel dysfunction may be the underlying cause for this new myopathy.

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A recurrent ptosis is an not uncommon finding in a general neurological clinic. In a number of cases the aetiology remains unknown, despite an intensive diagnostic workup. Only rarely is a biopsy of the levator palpaebrae superioris (LPS) muscle taken. Here we present the 10–year follow–up of a 49–year old woman with alternanting recurrent ptosis who underwent a bilateral LPS biopsy. Our first report described the situation four years following the onset of symptoms (1). The present report extends a subsquent discussion in the Journal of Neurology, Neurosurgery and Psychiatry as to whether the phenotype in the present case, in a second case seen by us and in two cases reported by Sieb and Hartmann (2) could be due to local pathology of the lid surface anatomy (3) or represent sympatic nerve dysfunction due to a “partial” Horner’s syndrome. We are now able to present the findings of a biopsy of the levator muscle and the successful treatment of the disorder with acetazolamide.

Case report

A now 49–year old woman developed a recurrent right ptosis at the age of 36 years. Each attack would follow a sterotyped pattern. The ptosis would develop over about 24 hours and last for up to 10 days. The initial attack frequency of 3–6 months slowly increased over 4 years. After our first description (1), she started to develop similar attack on the left side. These paroxysmal episodes of recurrent ptosis began to occur monthly alternating between the left and right lid. At occasions such an attack would be preceeded by nonspecific symptoms such as fatigue, mood changes and loss of appetite. There have never been any other associated features such as

diplopia, swallowing problems or limb weakness or headache. LPS function is normal between attacks. At the height of an attack LPS function is abolished with evidence of Müller muscle involvement also (1) (see Figure 1). In our case, adrenergic stimulation with phenylephrine 10% did not show any muscular activity (1). The attack frequency decreased after a treatment trial with acetazolamide 250 mg three times daily. She remained attack–free for over one year at the 10–year follow–up visit.

During one attack of a left ptosis on of us (JROC) undertook a vertically orientated biopsy extending from Whitnall's ligament to Müller's muscle from both lids (Figure 2). There were no complications and she made a complete recovery from this procedure. For comparison the LPS of a healthy control is presented (Figure 2A). The healthy muscle shows homogenous staining, no central nucleoli and no fibre splitting. The quality of the lid biopsy from our patient was good (Figure 2B). At higher magnification the heterogenous staining of the affected muscle fibres, frequent fibre splitting and some central nucleoli become clearly visible (Figure 2C, E & F). This is also a feature of the right LPS in which a recurrent ptosis was present for 8 years, but which was not affected at time of biopsy (Figure 2D).

To investigate whether this could be due to a mitochondrial problem we isolated mitochondrial DNA (mtDNA) from the LPS. No mutation was detected in mtDNA. In particular there was no evidence for the A3243G mutation, no large–scale rearrangements, no single or multiple deletions and no duplications.

Discussion

The biopsy findings are suggestive of a bilateral LPS myopathy. The differential diagnosis thus includes myopathic conditions such as a mitochondrial cytopathies due to a nuclear mutation or a channelopathy. We could not detect any infiltration and no inflammatory cells as seen in myositis. An autoimmune mediated mechanism seems inprobable for the same reason and the failure to respond to immunosuppresion. Also antibody negative myasthenia gravis is unlikely as the patient did not show any signs of impairment of the neuromuscular junction on neurophysiological assessment, nor did she responded to a prolonged treatment trial with pyridostigmine (1).

The observation of a recurrent complete ptosis without involvement of the extraocular muscles is not uncommon. It is therefore surprising to find only five recently published cases including the present case and another seen by ourselves (Table 1).

In a healthy person a small crease in the skin over the lid can be observed on complete downgaze with the eyes shut. This lid crease is caused by activity of Müller's muscle alone, because the LPS is inhibited in complete down–gaze. There is photographic evidence that in none of the published cases such a lid–crease was present on the affected side, whilst clearly visible in the non–affected one (1; 2; 4). This suggests that both the LPS and Müller's muscle have been involved. An absent lid–crease in complete down-gaze which re-appears on lid elevation in a patient with a small (1–2 mm) ptosis is seen in Horner Syndrome. Whilst the presence of a lid–crease in complete downgaze in a patient with ptosis suggests pathology

affecting the LPS or it's neuronal pathways, sparing Müller's muscle. Thus patients with myasthenia gravis typically have a preserved lid–crease. The lid–crease sign is of no value in patients where the lid crease is absent from birth due to an additional layer of adipose tissue between the aponeurosis and the skin.

It is difficult to make a long–term prognosis, but the increasing frequency of the attacks in the five reported cases suggests that this may turn out to be a chronic condition. Whether the LPS is permanently affected and will eventually lose it's function we are unable to tell. The finding that the histopathological appearance of the right side which had been affected for 8 years was not noticably worse compared to the left side which had been affected for 4 years suggests that over this time muscular function is preserved. Additionally our patient remained attack free over one year following regular treatment with acetazolamide.

Other treatment options such as acetylcholine esterase inhibitors and immuno–suppresion have been tried by us and others without success. The younger patient of Sieb and Hartmann showed a mild and transient response to the serotonin antagonist pizotifen (2). Whether this was due to peripheral anti–muscarinic or a central mechanisms remains unknown. The response to the carbonic anhydrase inhibitor acetazolamide suggests that the underlying cause for this new recurrent myopathic disorder may be due to a channelopathy probably affecting the distal neuronal pathways, the neuromuscular junction or the myocytic membrane within the eyelid musculature.

References

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[3] A. Petzold, G. Plant, Recurrent Ptosis, J Neurol Neurosurg Psychiatry 70 (2001) 819–820.

[4] D. Stidham, I. Butler, Recurrent isolated ptosis in presumed ophthalmoplegic migraine of childhood, Ophthalmology 107 (2000) 1476–1478.

Table 1: *Literature review on cases presenting with recurrent ptosis without involvement of the extraocular muscles. d = day, w = week, m = month, y = year, — = not available.*

Reference	Age	Sex	Age of	Characteristics of ptosis				Diagnosis
			onset	Duration	Frequency	Side	lid-crease [1]	
(1)	41	F	36	≈10d	2-4/y [2]	R [3]	no	myopathy?
(2)	46	F	39	3–14	>1/m	R+L	no	"partial" Horner
(2)	47	F	—	—	—	R+L	—	"partial" Horner
(4)	8	F	3	6w	1-2/y	R	no	Ophthalmic migraine
(3)	62	M	59	7-10d	1-2/y	R	no	myopathy?

[1] Our interpretation of the published photographs

[2] The attack frequency increased subsequently to about 1/month.

[3] At the age of 40 the L side became involved as well.

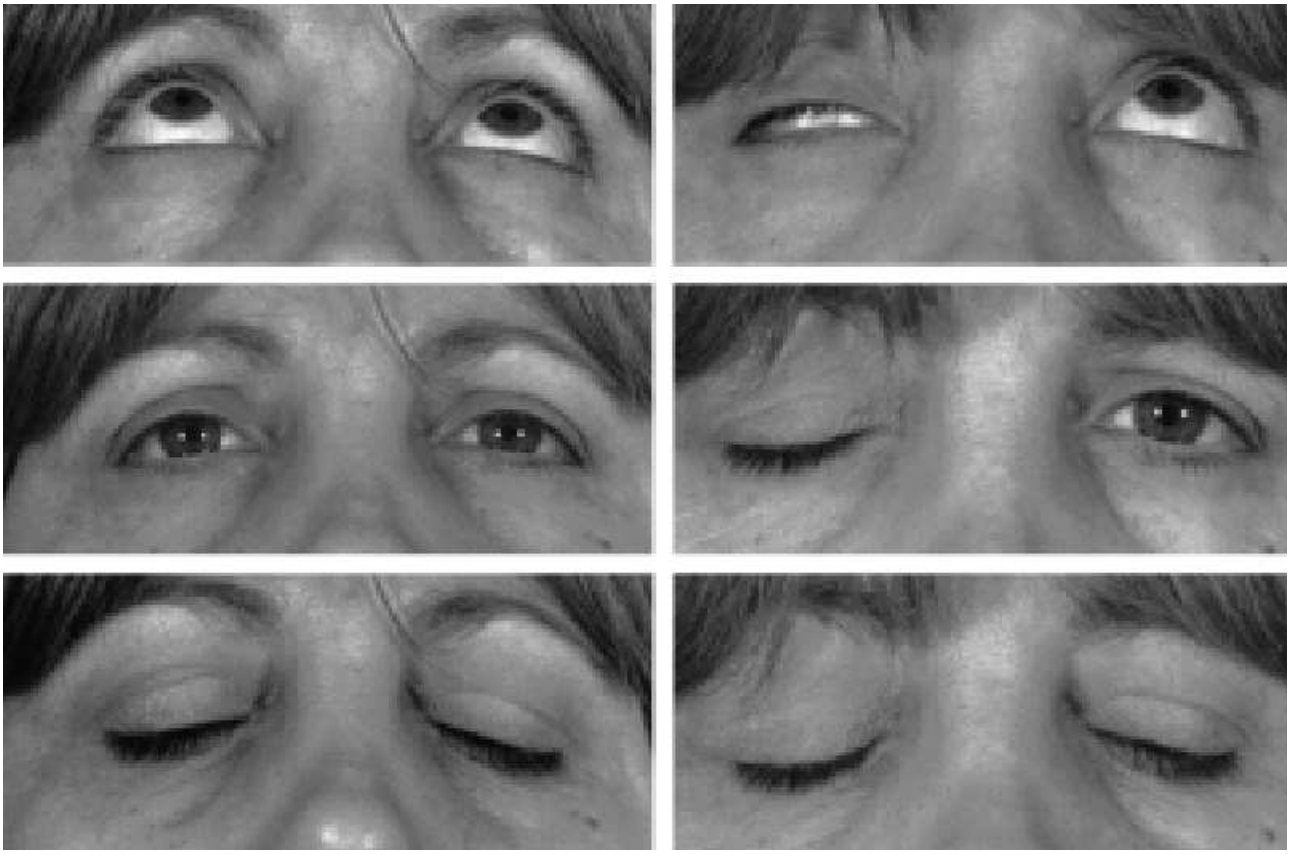

Figure 1. *A 41 year old patient with recurrent right sided ptosis. On the right the patient is shown during an attack and on the left during recovery. On the top row the patient is shown in upgaze, in the middle row in primary position and on the bottom row in downgaze. Note the missing crease on the upper tarsal part of the eyelid indicating loss of function of Müller's muscle as well as the levator palpebrae superioris. There is no "upside-down ptosis" of the lower lid. Also the fact that the right lid is lower in extreme downgaze indicates involvement of the Müller's muscle. In top right image frontalis has not been disabled and the small amount of lid movement is entirely due to frontalis activation. (Figure reprinted with permission from reference (1)).*

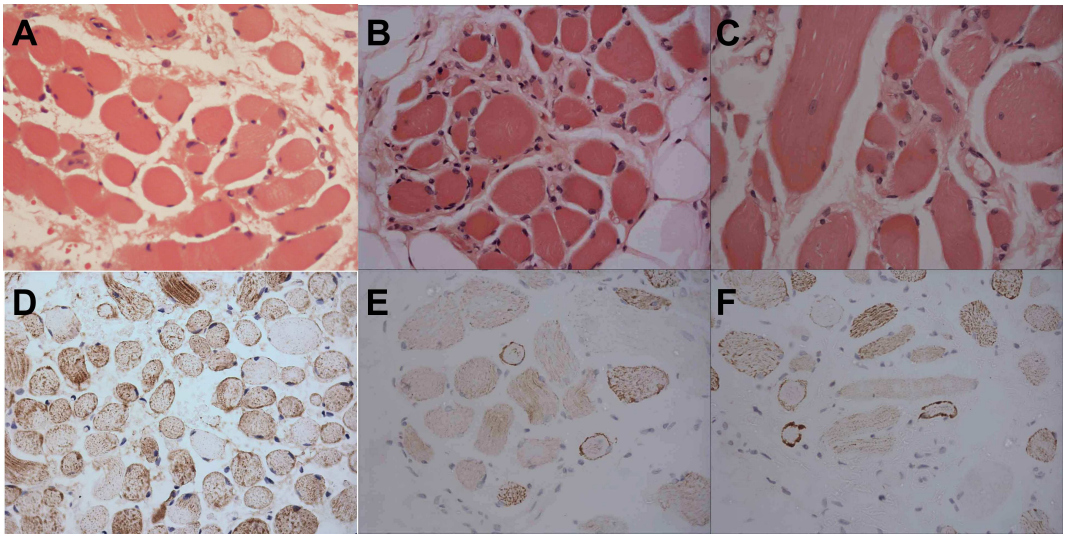

Figure 2. *Myopathy of the levator palpaebrae superioris (LPS). (A) a normal control LPS (x40), (B) the patients left LPS, including part of the aponeurosis and Müller's muscle (x10), (C) the left LPS (x20) demonstrating inhomogenous staining, split fibres and some central nuclei, (D) the right LPS (x20) showing the same features as noted for the left side, (E) the left LPS at higher resolution (x40) and (F) a central nucleus in the left LPS (x100, HE).*