# Ophthalmoplegia: when the tests are all negative, where next?

Gashirai K Mbizvo ,[1,2,3,4] Anna Visca,[5] Ian Marsh,[5] Mark Radon,[6] Dinesh Damodaran,[4] Andrew J Larner [7]

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[1]Liverpool Interdisciplinary Neuroscience Centre, University of Liverpool, Liverpool, UK
[2]Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK
[3]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK
[4]Neurology Department, The Walton Centre NHS Foundation Trust, Liverpool, UK
[5]Ophthalmology Department, Liverpool University Hospitals NHS Foundation Trust, Liverpool, England, UK
[6]Neuroradiology Department, The Walton Centre NHS Foundation Trust, Liverpool, UK
[7]Department of Translational Neuroscience & Stroke, University College London Queen Square Institute of Neurology, London, UK

**Correspondence to**
Dr Gashirai K Mbizvo;
Gashirai.Mbizvo@liverpool.ac.uk

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## ABSTRACT

When persistent neurological symptoms and signs defy diagnostic explanation despite repeated rounds of investigation, how should the clinician proceed? We present a case of this type with an eventual and unusual diagnosis. As well as being an exercise in awareness raising, the case serves as a prelude to considering what practical management strategies might be adopted in the face of persistent diagnostic uncertainty with its consequent frustrations for patient, significant others and physicians. We consider these approaches first with respect to the specific finding of ophthalmoplegia, the principal feature in this case, and second with respect to any neurological diagnosis.

## CASE

A previously healthy 44-year-old man presented with painless drooping of his right eyelid evolving over a few days, but with no diurnal variation in the degree of eyelid closure or other neurological symptoms. He had no headache, balance issues, weight loss or constitutional symptoms. He was a non-smoker and his travel history was unremarkable. He had been treated in primary care for presumptive eye infection, but the symptoms had progressed with the development of diplopia and then complete ptosis of the right eyelid.

Examination in the ophthalmology clinic identified complete paresis of the right external ocular muscles and no levator palpebrae function. The right pupil was dilated and unreactive to light. It constricted with dilute pilocarpine (0.125%), consistent with postganglionic parasympathetic denervation. There was no proptosis. Visual acuity, colour vision and funduscopy were normal, as was optic coherence tomography. The following neuroanatomical syndromes were considered:

1. *Orbital apex syndrome:* involving the right oculomotor (III), trochlear (IV) and abducens (VI) nerves, with possible early sparing of the optic nerve. The risk of subsequent optic nerve involvement and irreversible visual loss makes this a neuro-ophthalmic emergency.
2. *Cavernous sinus syndrome:* produces a similar pattern of cranial nerve dysfunction but typically spares the optic nerve, so usually there is no visual loss.
3. *Superior orbital fissure syndrome:* affects cranial nerves III, IV, VI and the ophthalmic division of the trigeminal nerve ($V_1$), again without optic nerve involvement.

Contrast-enhanced MR scan of brain and orbits was normal (figure 1A, B), as were CT cerebral angiography and venography, showing no mass lesion or vascular abnormality to explain the presentation.

The patient's symptoms and signs remained unchanged over the next 12 months of ophthalmological follow-up. They continued to markedly impair his day-to-day social interactions, and he was referred for consideration of ptosis lift repair surgery. The oculoplastic surgeon was concerned about intractable diplopia following the procedure and also questioned whether there might be an otherwise treatable neurological cause underlying the presentation, particularly given the normal MR scan of the orbits. Surgical plans were held, and a neurology opinion was requested.

Neurological assessment confirmed the previous examination findings of complete right eye ptosis and ophthalmoplegia, with a fixed dilated and unreactive pupil (online supplemental video 1). The rest of the neurological examination was normal, as was the general medical examination. We remained concerned about a problem in one of the three areas listed above. The underlying causes for lesions in these areas include *inflammatory* (idiopathic orbital inflammation,

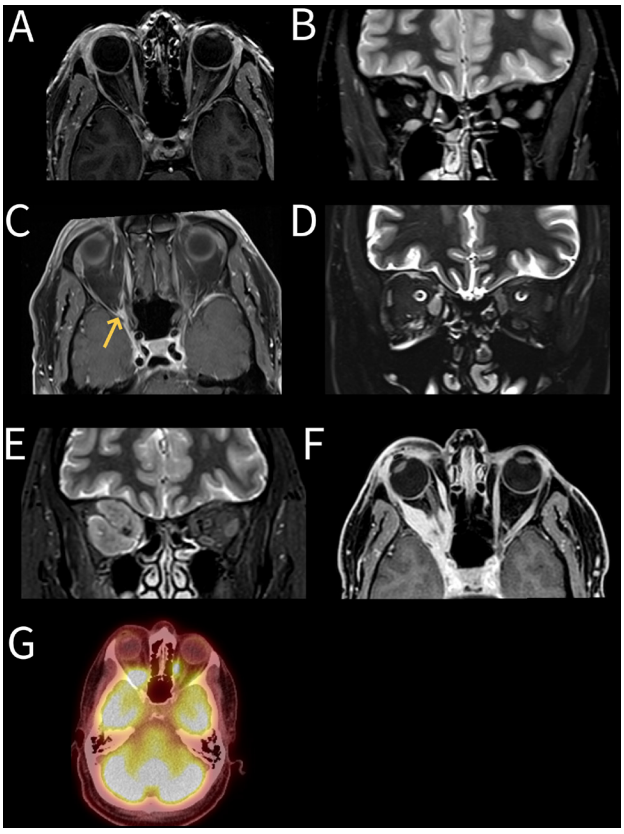


**Figure 1** **(A, B)** Initial MR scan of orbits (**A**=axial T1-weighted postcontrast; **B**=coronal T2-weighted) showing no abnormality of the extraocular muscles or orbital apex. Even with the benefit of hindsight and specialist neuroradiological review, the imaging was considered normal despite the marked clinical signs. (**C, D)** Second MR scan of orbits (**C**=axial T1-weighted postcontrast; **D**=coronal STIR) showing swelling of the right medial and inferior recti, with subtle enhancement at the right orbital apex (arrow). On retrospective review, there is an asymmetric signal abnormality suggestive of oedema involving all the right extraocular muscles. In the context of negative investigations for inflammatory orbital pathology at this stage, such a pattern should have raised a red flag for widespread muscle denervation, which would typically be due to proximal structural pathology (ie, at the orbital apex, cavernous sinus or superior orbital fissure). (**E, F)** Fourth MR scan of orbits (**E**=coronal T2-weighted**; F**=axial T1-weighted postcontrast) showing dramatic progression of extraocular muscle enlargement and enhancement, together with an enhancing mass at the right orbital apex. (**G)**18F-FDG PET-CT showing increased metabolic uptake corresponding to the right orbital apex mass.

thyroid eye disease, Tolosa-Hunt syndrome, sarcoidosis, IgG4-related disease), *infective* (bacterial sinusitis with orbital extension, invasive fungal sinusitis such as mucormycosis or aspergillosis), *neoplastic* (lymphoma, meningioma, metastatic disease), *vascular* (cavernous sinus thrombosis, carotid-cavernous fistula) and *traumatic causes*.[1] A second contrast-enhanced MR scan of the brain and orbits was performed, now 18 months since presentation. This showed subtle thickening and enhancement of the right medial and inferior rectus muscles extending to the right orbital apex, with no mass lesion (figure 1C, D). These changes were considered non-specific and perhaps indicated the previously outlined inflammatory causes. However, the painless nature of the presentation was not in keeping with Tolosa-Hunt syndrome, and full blood count, inflammatory markers, serum ACE, thyroid function, thyroid peroxidase antibodies and IgG4 subclass levels were all normal or negative, making the remaining inflammatory considerations less likely. Therefore, further investigations included acetylcholine receptor and MuSK antibody testing, which were negative. A neurophysiological study showed normal electromyography findings of the right frontalis and orbicularis oculi, with normal voluntary jitter findings in the right orbicularis oculi, hence no electrodiagnostic evidence to support a myopathy or disorder of the neuromuscular junction. Cerebrospinal fluid examination was normal, including normal ACE levels. Renal profile, HbA1c and HIV testing were also normal.

We gave a therapeutic trial of pyridostigmine to help exclude seronegative myasthenia gravis, but with no clinical benefit. This was followed by immunosuppression with intravenous methylprednisolone (500 mg daily for 3 days), then oral prednisolone 60 mg daily with a gradual taper of 10 mg every 2 weeks. This was given to cover the range of potential inflammatory causes under consideration. However, again there was no clinical response. Repeat contrast-enhanced MR scan of the brain and orbits at 21 months showed no interval improvement following steroid treatment (not shown). We became increasingly concerned about malignancy and arranged CT imaging of the chest, abdomen and pelvis, which was unremarkable. We then attempted to obtain a tissue diagnosis. Two separate biopsies were taken from the enhancing extraocular muscles. The initial sample, from the medial rectus muscle, showed only a non-specific pattern of inflammation. Due to its inconclusive nature, we arranged a second biopsy. Histology from this second specimen identified both inflammation and muscle atrophy, which were neither specific nor diagnostic. Intraoperatively, the surgical team noticed a severely congested orbit, which, with the initial biopsy result in mind, reinforced the suspicion of non-specific orbital inflammation. Therefore, we attempted a second therapeutic trial of immunosuppression, this time with mycophenolate mofetil at 500 mg two times a day for 4 weeks, then 1000 mg two times a day, which continued for 6 months. The patient did not improve.

It was now two and a half years since symptom onset. The patient had lost vision in his right eye in addition to the complete ptosis and ophthalmoplegia. Contrast-enhanced MR scan of the brain and orbits was repeated a fourth time and now showed an enhancing mass in the right orbital apex, alongside progression in the thickened right extraocular muscle appearances (figure 1E, F). A repeat CT of the chest, abdomen and pelvis was normal. Nevertheless, with ongoing concern

for a primary malignancy or metastatic disease, we arranged whole-body PET CT imaging. This showed a metabolically active soft tissue mass at the right orbital apex (figure 1G), without evidence of a metabolically active primary malignancy or distant metastases. The orbital mass was biopsied. An initial histopathological report of metastatic carcinoma was returned, but with no clue as to the primary source. However, further characterisation of the histopathological findings led to diagnostic revision to skin adnexal carcinoma (specifically, the biopsy was negative for CK7, CK20, positive for the cytokeratin marker, AE1/AE3, with focal weak positivity for TTF-1 and showed diffuse expression of p63 and D2-40). Skin adnexal carcinoma, also known as sclerosing sweat duct carcinoma or microcystic adnexal carcinoma, may be either a primary periorbital lesion or an extension from an eyelid primary (although this patient never had an eyelid lesion). Hence, a final pathological diagnosis was reached more than 3 years after symptom onset.

The patient was treated with fractionated radiotherapy to the right orbit (30 Gy/10#) over 2 months with no change in symptoms. Follow-up PET CT showed no convincing residual disease, but ongoing monitoring for recurrence using this imaging modality was recommended.

## DISCUSSION

Microcystic adnexal carcinoma of the eyelid and orbit is very unusual and, like us, most neurologists and ophthalmologists will not be familiar with it. First described in 1982,[2] this condition has appeared under various names including sclerosing sweat duct carcinoma, malignant syringoma, sweat gland carcinoma with syringomatous features, eccrine epithelioma and syringoid eccrine carcinoma. A narrative literature review published in 2023 identified only 36 cases involving the eyelid and orbit, but it was not entirely clear how many of these had sufficient orbital involvement to cause ophthalmoparesis or ophthalmoplegia. Perineural invasion often occurs as a feature of tumour behaviour, likewise recurrence, although metastasis is rare. Perineural invasion could explain why this patient had an unreactive, dilated pupil despite normal imaging. The parasympathetic fibres controlling pupillary constriction run on the superficial surface of the oculomotor nerve and are particularly susceptible to infiltrative processes. Perineural invasion could therefore selectively damage these fibres, leaving unopposed sympathetic activity and producing mydriasis, without generating imaging-visible structural change. Delayed diagnosis was evident in the published cases, even in those with evident eyelid tumour. Follow-up was not always recorded in these cases, so ultimate prognosis was not clear.[3]

In view of this rarity, it is difficult to make the case that all neurologists and ophthalmologists should be aware of microcystic adnexal carcinoma: it is likely that most will never see a patient with this condition. However, it should be included in textbook accounts of the differential diagnosis of unilateral ptosis with or without ophthalmoparesis and a fixed unreactive pupil, particularly when the imaging is normal. From the practical point of view, the more pressing issue in the case reported here related to management: specifically, how best to manage a patient with persistent, disabling neurological symptoms and signs in whom repeated investigations over years have failed to lead to a diagnosis.

We first consider the particular situation of 'Ophthalmoplegia: when all the tests are negative'.[4] In a review of clinical and imaging clues to the diagnosis of ptosis and ophthalmoparesis, Keene *et al*[1] devised a flow diagram that would suggest that asymmetrical ptosis and ophthalmoparesis without symptom fluctuation implies nerve disease, either hereditary (pain rare) or acquired (pain often), whereas acquired muscle disease correlates with absence of ptosis, asymmetrical ophthalmoparesis and no fluctuation. Following this suggested pathway of clinical reasoning may not therefore have facilitated diagnosis in this patient, who presented with asymmetrical ptosis and ophthalmoparesis with no fluctuation. The absence of pain and proptosis would also be an argument against acquired muscle disease, although the MRI changes (eventually) pointed to an inflammatory process in this diagnostic category.[1]

In situations of diagnostic uncertainty, it can be very helpful to reinforce what is known. In this case, the evidence against myasthenia gravis was compelling on clinical grounds, including persistently unilateral ptosis, lack of fluctuation and a fixed pupil, as well as on neurophysiological and neuroimmunological testing. Although a trial of pyridostigmine was unlikely to cause harm, it may nevertheless have served as a diagnostic distraction. Similarly, the complete absence of both clinical and radiological response to corticosteroids might reasonably have argued against escalation to mycophenolate, given that most inflammatory orbital disorders show at least partial steroid responsiveness. This case therefore highlights a broader lesson: when strong clinical signs coexist with repeatedly normal or non-specific investigation findings, the understandable urge to 'do something' can risk overshadowing established clinical reasoning. Recognising and moderating this instinct is essential and represented an important learning point for us.

With the benefit of hindsight, it is also reasonable to question whether earlier use of PET-CT imaging, following initially normal and subsequently non-specific MRI findings and failed therapeutic trials, might have expedited detection of the orbital mass and allowed the definitive biopsy to occur earlier. Clearly, in this case, the non-specific enhancement of the extraocular muscles on the second MRI (figure 1C, D) acted as a neuroanatomical distractor. Isolated pathology

in these muscles could not have accounted for the patient's pupillary involvement, yet the surgeons were understandably reticent to biopsy the orbital apex without a discrete imaging target. This is because the procedure carries a high risk of injury to critical structures, including the optic nerve, ophthalmic artery and cavernous sinus, with an attendant risk of permanent visual loss or catastrophic haemorrhage.[5] Nevertheless, it is open to question whether repeating a biopsy of the non-specific extraocular muscle inflammation, yielding predictably non-diagnostic results, represented the optimal strategy when the clinical neuroanatomical picture pointed strongly to pathology at the orbital apex. Indeed, our retrospective review of the second MR scan identified asymmetric signal abnormality involving all the right extraocular muscles, likely representing oedema. If this were not attributable to an inflammatory process, it raises the possibility of widespread muscle denervation, which causes oedema by disrupting normal muscle tone and vascular regulation.[1] The diffuse distribution across multiple extraocular muscles, and hence across multiple cranial nerve territories, necessarily localises the lesion proximally to a site of neural convergence, such as the orbital apex, cavernous sinus or superior orbital fissure.[6] Recognising this pattern, and its implications, could have prompted earlier PET-CT once MRI had failed to show a sufficiently discrete proximal abnormality to justify a targeted biopsy of that location. PET-CT is probably underused in ophthalmology, particularly in apparently benign orbitopathy.[7]

Second, we consider the general situation where there are persistent neurological signs, but with no established diagnosis despite recurrent investigation. A management schema in such cases may be applicable more widely than in the current case. While the passage of time might be deemed an important element in neurological investigation—occult pathologies may eventually declare themselves on further or repeated investigation—this temporising approach may collide with the understandable frustrations of the patient, and likewise also family, friends and other physicians.

To our knowledge, there is no explicit guidance about how to manage this clinical dilemma, so we proffer a few suggestions that we hope may at least carry face validity. It may be helpful for the neurologist to acknowledge to the patient her/his own frustration with the diagnostic uncertainty and to promise continued follow-up and investigation of the problem at a time when only symptomatic treatment can be offered. Prior clinical or published experience of eventual diagnostic resolution may be used as reassurance. Seeking a second opinion or further consultation, either informally or through referral to a suitably qualified individual or multidisciplinary team, should also be pursued, alongside perhaps presentation to audiences at local or regional clinical meetings. Patients often appreciate the knowledge that their difficulties have prompted wider discussion. This may suggest other avenues of investigation, diagnostic possibilities or treatment. We presented this patient's case at the neurology grand round following the second non-specific muscle biopsy result. Drawing on colleagues' experience that relevant abnormalities may only declare themselves with time on imaging in similar cases, we were encouraged to continue interval MRI surveillance. This was helpful for this particular case, although time may be the ultimate arbiter of diagnosis in other cases, depending on the presentation. Therefore, in the absence of a definitive diagnosis, long-term follow-up and periodic re-evaluation may be a sensible approach.

## Key points

- When seeing unilateral ptosis and complete ophthalmoparesis, consider problems at the orbital apex, cavernous sinus or superior orbital fissure.
- The underlying cause may be inflammatory, infective, neoplastic, vascular or traumatic.
- Imaging should include MR of the brain and orbits with contrast—to be repeated periodically if negative—alongside consideration of early PET in MR-negative cases.
- In cases with marked multiple cranial nerve palsies but normal MRI, consider pathologies that cause perineural invasion.
- Microcystic adnexal carcinoma is a rare cause for this presentation.

## Further reading


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**ORCID iDs**
Gashirai K Mbizvo https://orcid.org/0000-0002-9588-2944
Andrew J Larner https://orcid.org/0000-0003-0128-8010

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