Unusual presentation of more common disease/injury

An unusual cause of bilateral ophthalmoplegia

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Summary

The authors present a case of a histologically confirmed giant cell arteritis that presented unusually with bilateral and multiple cranial nerve palsies and resolved following treatment with pulsed cyclophosphamide. The aetiology of the presenting features and the treatment choices are discussed.

BACKGROUND

The case emphasises the need for physicians to promptly recognise and treat giant cell arteritis (GCA) to avoid long-term complications. In addition, we urge that GCA is considered as a diagnosis even when faced with uncommon presenting features.

CASE PRESENTATION

A 72-year-old, independent, Caucasian woman, with no significant medical history, was admitted with a 3-day history of severe frontal headache and vomiting. She had no visual or speech disturbance, limb weakness, neck stiffness or rash; nor did she have any scalp tenderness, palpable temporal arteries or jaw claudication. Physical examination was unremarkable. Neurological examination was unremarkable with normal motor and sensory systems and intact cranial nerve function.

Initial blood tests and CT of the brain were normal apart from a raised C reactive protein (CRP) of 28 g/dl. Ophthalmology and ear, nose and throat reviews did not reveal any significant abnormalities or a cause for her symptoms.

By day 4 the headache remained constant and unresponsive to analgesia. The patient now complained of horizontal diplopia. Neurology review confirmed a complete left-sided ptosis, bilateral adduction palsy with left-sided paresis of cranial nerves III (pupil sparing), IV and VI, and horizontal gaze palsy of the right eye (figure 1). Optic nerves remained fully intact. Her speech became slightly slurred and she developed a tender, palpable, left temporal artery.

INVESTIGATIONS

MRI of the brain and lumbar puncture were normal. However, CRP had risen to 158 g/dl. A diagnosis of temporal arteritis (TA) was considered and the patient was started on a 5-day course of intravenous methylprednisolone (1 g/day).

After 5 days of intravenous steroid treatment, the intensity of the headache had reduced and the CRP had dropped to 30 mg/dl. However, the complete left-sided ptosis with

cranial nerve palsies of III, IV and VI persisted. A chest x-ray was performed to aid exclusion of a paraneoplastic syndrome. Following rheumatology review, a diagnosis of TA was raised again and a temporal artery biopsy was performed. Histology returned a florid positive result for TA (figure 2).

TREATMENT

While awaiting a histology result, oral prednisolone was started: 100 mg/day reducing to 50 mg/day after 7 days. Within 5 days of starting oral steroid, the headaches had resolved. The patient was more energetic, her appetite improved and the CRP had normalised. Following 7 days of oral steroid, she had regained a full range of eye movements on the right, had normal left eye abduction and no longer complained of horizontal diplopia. However, almost complete left eye ptosis and horizontal gaze palsy persisted.

In view of the persistent ophthalmoplegia palsies and the considerable impact of the complete left-sided ptosis, additional treatment for her vasculitis was considered. Further immune suppression was thought to be of benefit in reversing the left-sided ptosis and residual palsy. After consulting the literature she was started on weekly intravenous cyclophosphamide infusions (St Thomas' Regime).

OUTCOME AND FOLLOW-UP

Following treatment with cyclophosphamide the patient has made a complete recovery. She is maintained on a reducing dose of oral steroid and has follow-up with rheumatology.

DISCUSSION

Multiple bilateral cranial nerve palsy in TA is an uncommon presentation and the authors could find only two documented cases.^{1 2} In 1959, Fisher¹ reported the first case of bilateral oculomotor nerve palsy in TA and suggested that this was due to ischaemia of the vasa nervorum of the third nerve following cerebral artery inflammation. In 2005, Lazaridis *et al*² published a case report documenting bilateral third nerve palsy caused by TA. Our patient clearly was

Figure 1 The patient at day 4, with complete left-sided ptosis, bilateral adduction palsy with left-sided paresis of cranial nerves III, IV and VI, and horizontal gaze palsy of the right eye.

affected by bilateral ophthalmoplegia in the absence of diabetes with mainly left eye involvement of multiple cranial nerves, but in addition she also developed right horizontal gaze palsy. To the best of our knowledge there is no documented case of such widespread ophthalmic involvement in biopsy proven TA.

Ophthalmoplegia in TA is commonly attributed to neuronal damage. There has been debate among authors whether ocular muscle ischaemia or nerve involvement is the primary pathological cause of the ophthalmoparesis.^{2–4} The complete recovery of ophthalmoplegia, as seen in our patient, would suggest that permanent neuronal damage has not occurred. Interestingly, the only autopsy proven case of ophthalmoplegia in TA showed necrosis of multiple extra-ocular muscles, but no pathological involvement of oculomotor nerves was identified.⁵ We did not perform imaging to prove such a theory. The topic continues to be an area for further research and discussion.

It remains uncertain whether our patient recovered as a result of continued oral steroid after initial intravenous pulsed steroid, cyclophosphamide infusion or a combination of both agents. Conventionally, TA is treated with glucocorticoids to swiftly alleviate symptoms and preclude ischaemic complications.⁶ There is no clear consensus on the best treatment regime and duration, but an initial dose of 40–60 mg daily of prednisolone is thought to be sufficient in the vast majority of cases⁷ with tapering of the drug according to symptoms and inflammatory markers.

Interestingly, the patient in this case did not show a marked response to 5 days of intravenous methylprednisolone treatment. Higher dose glucocorticoid pulse treatment has been supported for patients experiencing visual disturbance; however, its use is controversial. A 2003 randomised controlled trial (RCT) of 164 patients⁸ showed no evidence that pulsed glucocorticoid treatment was more effective than oral treatment in improving vision or preventing visual

Figure 2 Florid positive result for temporal arteritis on temporal artery biopsy.

deterioration due to GCA. Conversely, a 2006 RCT⁹ showed that pulsed methylprednisolone given at onset of TA allowed for quicker tapering of oral steroid and, in the long-term, a higher proportion of patients maintained remission of disease after glucocorticoid treatment was withdrawn.

The adverse effects of long-term glucocorticoid treatment are well-documented and rapid tapering to alleviate these side-effects often results in relapse of GCA. Consequently, steroid-sparing agents are increasingly of interest in GCA treatment. Methotrexate, azathioprine and infliximab are the only steroid-sparing agents that have undergone formal RCT/meta-analysis testing for their efficiency in GCA with results being particularly disappointing. A 2006 meta-analysis of three RCTs on the use of methotrexate in GCA¹⁰ concluded that it was useful in preventing relapses, but did not decrease steroid-related side-effects and was not fast acting. Similarly, a double-blind, placebo-controlled study on the use of azathioprine in GCA and polymyalgia rheumatica (PMR)¹¹ concluded its benefit was not remarkable and, again, was of late onset. The use of other biological agents (including tumour necrosis factor α inhibitors) and aspirin are currently under investigation.

The patient in this case review was successfully treated with a combination of oral glucocorticoid and pulses of intravenous low-dose cyclophosphamide (St Thomas' Regime). Evidence behind the use of cyclophosphamide is limited. However, experience in treating other large vessel vasculitis such as TA and small vessel vasculitis (eg, rheumatoid arthritis) suggests it can still be a very useful and effective agent. The low dose St Thomas' Regime has been used successfully and safely for many years.¹² Using lower dose weekly pulses for rapid effect was a particularly attractive therapeutic option for this patient. In keeping with this

approach, a study of four female patients published in 1992 reported a rapid clinical and laboratory response to three weekly pulses of 0.5 mg cyclophosphamide.¹³ Various case studies, such as our own, have also described successful cyclophosphamide use in GCA.¹⁴

Learning points

- It is important to consider the diagnosis of GCA even with an unusual presentation.
- Rapid initiation of steroids is needed in TA to prevent permanent ophthalmoplegia and blindness, with oral treatment being as efficacious as intravenous.
- Further immunosuppression with steroid sparing agents may be required in refractory cases and remains an area for further research.

Competing interests None.

Patient consent Obtained.

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