Neurosyphilis presenting with gummatous oculomotor nerve palsy

Although epidemiological studies suggest that the incidence of primary syphilis is rising,[1] neurosyphilis remains an uncommon manifestation of *Treponema pallidum* infection. In addition, the MRI appearances of this treatable neurological condition are not well known. Many patients with neurosyphilis are asymptomatic, but manifestations include subacute basal meningitis, a meningovascular syndrome of small deep cerebral and cranial nerve infarctions, chronic gummatous inflammation with focal intracranial mass lesions, chronic comportmental dementia of general paresis, and chronic sensory-ataxic myelopathy of tabes dorsalis. We report a case in which a meningeal form of neurosyphilis presented with rapid evolution of a pupil-involving oculomotor nerve palsy to highlight the clinical, CSF, and MRI features and good response to treatment.

Case report

The patient was a 54 year old right handed homosexual man with a history of syphilis of unknown stage, treated with penicillin 25 years previously. He was well until 6 weeks prior to evaluation when he sustained minor head trauma in an automobile accident, followed by intermittent headaches, fatigue, photophobia, and anorexia. Four days before admission he developed worsening and persistent drooping of the right eyelid and double vision. On examination, his mental status was remarkable only for psychomotor slowing. The right pupil was round but enlarged at 6 mm and sluggishly constricted to 5 mm with direct and consensual light stimulation as well as near vision. The left pupil was round and 4 mm and constricted briskly to 2 mm to light. The right eye showed moderate ptosis of the upper lid, and the globe was deviated laterally in primary gaze with markedly impaired adduction and elevation. In the left eye, ptosis was absent and ocular motility was normal. Other cranial nerve, sensory, motor, and reflex functions and gait were normal with the exception of a slight decrease in vibration and position sense in the feet. There were no signs of meningeal irritation. Head computed tomography (CT) and CT angiography revealed neither blood in the subarachnoid space nor evidence of intracranial aneurysm. MRI of the head (fig 1) showed a spheroid contrast-enhancing lesion at the root of the right oculomotor nerve, which extended towards the cavernous sinus. Incidentally noted were right cerebellar and right frontal developmental venous anomalies. CSF examination revealed normal opening pressure at lumbar puncture, 344 white blood cells (WBCs) (95% lymphocytes), 14 red blood cells (RBCs), protein of 167 mg%, and glucose of 39 mg%. CSF Venereal Disease Research Laboratory test (VDRL) was positive at 1:8 whereas serum Rapid Plasma Reagin (RPR) was positive at 1:64. HIV testing was negative. Treatment with intravenous penicillin G (4 million Units every 6 hours) was administered for 2 weeks. By treatment day 4, the adduction and elevation of the right eye were improving. At 1 month follow up, mild fatigue persisted. There was trace right ptosis. Elevation and adduction of the right eye had improved to nearly normal, but the pupil remained 6 mm and sluggishly responsive to light. Repeat CSF examination showed seven WBCs (97% lymphocytes), protein of 86 mg%, and glucose of 71 mg%. CSF VDRL and serum RPR titres were unchanged. At 6 months, no additional improvement in oculomotor nerve functions was seen but fatigue had subsided. Repeat MRI 7 months after hospital admission showed complete resolution of the oculomotor nerve abnormality.

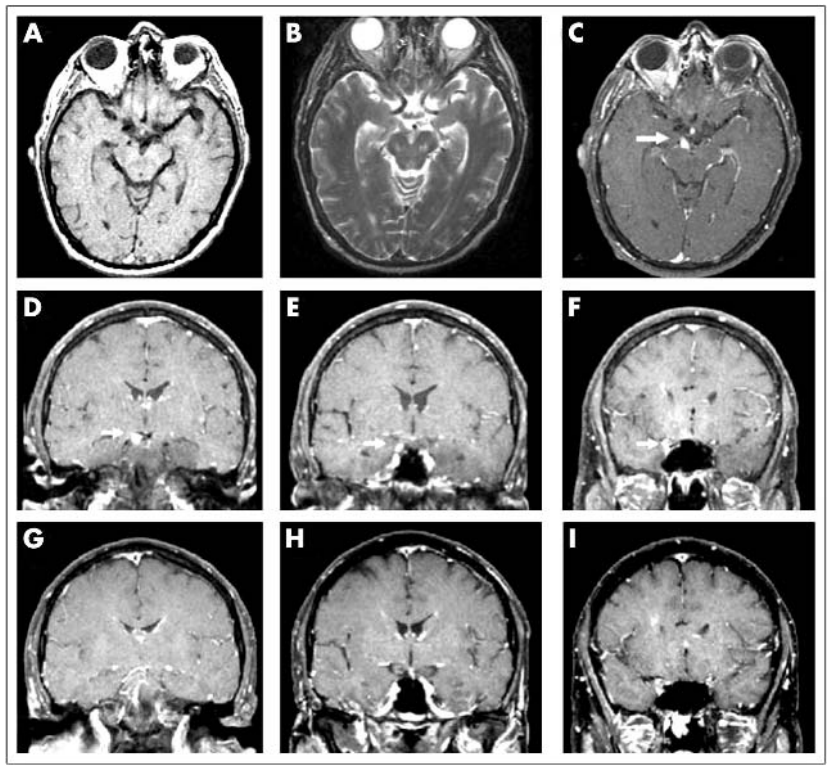

Figure 1 Head MRI showing the 8 mm (antero-posterior) × 6 mm (left to right) × 6 mm (rostro-caudal) tapering spheroid lesion at the base of the right midbrain, tracing the course of the oculomotor nerve forward into the cavernous sinus (panels A–F). The lesion is isointense to adjacent brain on T1 and T2 sequences (panels A and B) and enhances on a T1 sequence after gadolinium contrast (panel C). Pre-treatment (D–F) and post-treatment (G–I) coronal images demonstrate complete resolution at 7 months.

Discussion

Neurosyphilis is known to cause oculomotor nerve palsies either in the meningovascular phase, due to small vessel vasculitis with resultant nerve infarction,[2] or in granulomatous basal meningitis, due to inflammation of the nerve or its investiture; however, the literature on syphilitic mass lesions around the oculomotor nerve is sparse. Vogl *et al*[3] reported a case of oculomotor nerve palsy associated with MR findings similar to ours that also resolved with penicillin treatment. Standaert *et al*[4] described an enhancing penicillin-responsive lesion based in the interpeduncular cistern that compressed the ventral midbrain. The oculomotor nerve lesion in our patient was isointense to adjacent brain on T1 and T2 MR sequences, with brisk enhancement after intravenous injection of gadolinium contrast. We believe the lesion was a manifestation of meningeal syphilis in the form of an oculomotor nerve gumma. A gumma is a focally accentuated, exuberant granulomatous response of the meninges, typically with sparse treponemal organisms. Nonetheless, treatment of the underlying infection quiets the inflammatory process and can, as in our patient, lead to significant reversal of neurological deficit. We add our case to the growing literature on MR correlates of neurosyphilis and encourage a search for neurosyphilis when an unexplained mass lesion is present in the basal subarachnoid space. Neurosyphilis, albeit rare, still deserves inclusion among eminently treatable causes of a rapidly developing oculomotor nerve palsy.

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High dose cyclophosphamide for severe refractory myasthenia gravis

Myasthenia gravis (MG) exemplifies autoimmune disease. Most patients require immunomodulating treatment, including steroids, chemotherapy, or intravenous immunoglobulin (Ig), in addition to anticholinesterase

treatment. Drachman *et al*[1] published the beneficial effects of high dose cyclophosphamide in three patients with severe refractory myasthenia. We recount our experience of three myasthenic patients treated in a similar way.

Materials and methods

All patients participated in studies approved by the Drexel University College of Medicine and signed informed consent. These three patients with severe (class IVb) refractory MG includes all patients treated. Patients received cyclophosphamide 50 mg/kg (adjusted ideal body weight)/day over four consecutive days. Patients received antibacterial, antiviral, and antifungal prophylaxis. Haemorrhagic cystitis prophylaxis included Mesna and forced diuresis. Packed red cells and platelets were transfused to maintain haemoglobin ⩾8.5 g/dL and platelets ⩾10×10^9/L, respectively. Patients received filgrastim (G-CSF) (5 μg/kg/day) starting day 10 until their absolute neutrophil count (ANC) reached 10×10^9/L for two consecutive days.

Results

Patient 1 was diagnosed with seronegative MG at 30 years of age by a positive tensilon test and a decremental response on repetitive stimulation. Initial treatment included pyridostigine and plasmapheresis, but worsening symptoms prompted thymectomies at 12 and 18 months later. Her thymic pathology revealed thymic hyperplasia. Additional treatment with only transient responses included low dose oral cyclophosphamide, intravenous Ig, azathioprine, methylprednisolone, and continued pyridostigine with plasmapheresis. She required 27 intubations between initial diagnosis and immunoablative treatment at 41 years of age.

Patient 2, previously reported, suffered from both seronegative MG and chronic inflammatory demyelinating polyneuropathy (CIDP).[2] He presented at 47 years of age with fluctuating double vision, ptosis, dysphagia, arm weakness, and breathing difficulties. Testing revealed a decremental response on repetitive stimulation. Pyridostigine was initiated. Thymectomy revealed a 75 g lipoma. His MG resulted in two intubations. After thymectomy, to control symptoms, prednisone (25–40 mg daily) was required. At 54 years of age, CIDP was diagnosed. Despite steroids (plasmapheresis, intravenous Ig, azathioprine, and pyridostigmine) he continued with symptoms of double vision, dysphonia, and dysphasia with a continued decremental response to repetitive stimulation. At 56 years of age, he underwent high dose cyclophosphamide without stem cell rescue.

Patient 3 was diagnosed with antibody positive MG at 12 years of age, initially treated with pyridostigine. She received her first thymectomy at age 18 years and continued on pyridostigine and occasional steroids. By 36 years of age, she was steroid dependent. Between ages 38 and 41 years she required 11 intubations and only transiently responded to intravenous Ig and plasmapheresis. A second thymectomy was performed at age 39 and cyclosporine (CsA) was initiated. She continued on prednisone 25 mg qod, scheduled intravenous Ig every 3–4 weeks, and intermittent plasmapheresis. The CsA and Cellcept were maintained but poorly tolerated. At 41 years of age, she underwent high dose cyclophosphamide without stem cell rescue.

Treatment course

Patient 1 had 13 days of neutropenia, required three units of packed red cells and three platelet transfusions. Patient 2 had 9 days of neutropenia, required two units of packed red cells, and three platelet transfusions. Patient 3 had 11 days of neutropenia, required five units of packed red cells, and two platelet transfusions. Patients 1 and 3 experienced MG flares requiring intravenous Ig and plasmapheresis, but neither required intubation.

Neurological follow up

Patient 1, intubated 27 times before treatment, required a single intubation during 48 months of follow up. To control less severe exacerbations, during the first 40 months after immunoablative treatment, oral cyclophosphamide was necessary. She continues scheduled plasmapheresis and pyridostigmine. No other immunomodulatory medications are prescribed.

Patient 2 had myasthenic symptoms of dysphagia and diplopia. Seven months after treatment pyridostigmine was stopped and after 12 months prednisone was stopped. Twenty five months after treatment, his MG is in full remission.

Patient 3 experienced five flares at 1, 6, 11, 19, and 30 weeks following treatment. The exacerbations at 1, 6, and 11 weeks required intravenous Ig and steroids; exacerbations at 1, 19, and 30 weeks required plasmapheresis. Her last exacerbation necessitated intubation. Between exacerbations her functional ability consistently improved. She stopped steroids at 50 weeks. At 52 weeks, a slow pyridostigine taper began. Her serum AChr levels did not correlate with disease activity during the follow up periods.

Table 1 Patient characteristics before high dose cyclophosphamide treatment

Age/sex	Patient 1 41/female	Patient 2 56/male	Patient 3 41/female
Duration of MG (y)	11	9	29
MG severity class	IVb	IVb	IVb
AChr antibody	Undetectable	Undetectable	Detectable
Previous treatment			
Pyridostigine	X	X	X
Thymectomy(ies)	2	1	2
iv Ig (no of infusions)	1	1	62
Prednisone	10–100 mg qd, duration 3 years	40–100 mg qd, duration 7 years	10–60 mg qd, duration 4 years
Plasmapheresis (no. of procedures)	217	14	16
Azathioprine	50 mg/d, duration 7 months limited by nausea/vomiting	200 mg qd, duration 2 months limited by nausea/vomiting	50–150 mg qd, duration 15 months
Oral cyclophosphamide	100 mg qd, 28 months		
Cyclosporine			50–125 mg bid, duration 39 months
Cellcept			250–500 mg qd, duration 7 months

MG, myasthenia gravis; iv, intravenous; Ig, immunoglobulin; qd, four times daily; bid, twice daily

Discussion

The patients discussed have all suffered from severe refractory MG, which requires multiple intubations. All underwent thymectomy: patients 1 and 3 repeat thymectomies. Patient 2 had an early and sustained response to treatment. Patients 1 and 3 had multiple exacerbations. As this treatment targets IgG production, exacerbations following treatment are expected. Patient 1, who required 27 intubations before treatment and only once since, and who has in the past 6 months stopped oral cyclophosphamide, may yet to enjoy the maximum benefit of this treatment. Patient 3, one year after treatment, has an improving activity level. The intervals between exacerbations are increasing: 5, 8, and 11 weeks. It is 26 weeks since her last exacerbation.

Recently, Drachman *et al*[1] published a single institution case series of three patients with refractory MG who were also treated with high dose cyclophosphamide. In this series, one patient had AChR antibody negative MuSK antibody positive myasthenia. Their mean disease duration was 10.3 (range: 3–15) years; one required intubation and median follow up was 24 (range: 7–40) months. In comparison, in the three patients described here, two had antibody negative myasthenia and the mean disease duration was 16.3 (range: 9–29) years. All required multiple intubations: 27, 2, and 11, and our median follow up is 25 (range: 13–48) months. During follow up, patient 3's serum AChr levels remained detectable and did not correlate with her clinical course. Drachman *et al* reported a decline in antibody levels in their patients treated in a similar way, although AChr antibody titres and MuSK antibodies persisted in their patients even after 2 years.[1] This suggests that long term remissions in MG may be possible even without achieving complete immunoablation. High dose cyclophosphamide has the potential to significantly reduce symptoms and increase life quality among people with MG refractory compared to conventional treatment. Long term follow up is necessary to evaluate the duration effect and time to maximum benefit. High dose cyclophosphamide treatment warrants further study as a treatment for severe refractory MG.

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Acute head drop after cervical hyperflexion injury

Head drop is familiar to neurologists, but not widely appreciated by neurosurgeons. There are multiple causes of this condition[1] in which the patient is unable to hold their head up because of weakness of the neck extensor musculature. It predominantly results from primary muscle pathologies in the neck extensor muscles, with occasional evidence supporting a neurogenic aetiology.[1 2] I describe three patients in whom acute head drop closely followed cervical hyperflexion injury, and suggest that the cause is bilateral traction neurapraxia of one or more cervical dorsal rami.

Patient A was an 84 year old man who enjoyed excellent health prior to falling backwards, striking his occiput on a wall and sustaining forced flexion of the cervical spine. He complained of posterior cervical pain but, when seen in casualty for closure of an occipital laceration, was found to be neurologically intact. Cervical *x* rays showed only degenerative disease in the mid-lower cervical spine and loss of lordosis. Over 2 weeks the pain in his neck resolved, but he became aware of a difficulty holding his head up as the day progressed and, later, of aching in his neck extensor muscles. He was referred to neurosurgery as a possible case of delayed instability. Cervical *x* rays demonstrated 5° of forward angulation at C4/C5, which did not change with neck flexion, but were otherwise unchanged. He remained neurologically intact but, fearing progression of the angulation and development of neural injury, posterior segmental fixation at C4/5 with a Hartshill rectangle and sublaminar wiring was advised. Surgery was remarkable only for the absence of significant ligamentous injury or abnormal mobility. Unfortunately, his head ptosis recurred after 2 months. *x* Rays showed that the sublaminar wires at C5 had ''cheese-wired'' through the bone and allowed recurrence of angulation. He remained neurologically intact. After some discussion, he submitted to extended fixation from C3–C7, producing good alignment, albeit with restricted neck movements. However, he had ongoing problems with neck pain because of prominence of the metalwork due to profound atrophy of the paraspinal muscles. Three months later, he again developed head drop because of ''cheese-wiring'', and the Hartshill rectangle was eroding through the skin, necessitating a third procedure to remove it. At this stage, a muscle biopsy was performed showing end-stage atrophy and fibrosis although no comment could be made as to aetiology. The patient declined further investigation or surgery and was managed in a Philadelphia collar in the long term. Despite all the above, the malalignment at C4/5 never progressed, nor did any neurological deficits develop.

Patient B was a fit 72 year old man who sustained a flexion/extension whiplash injury during a road traffic accident (RTA). In casualty, he had minor neck pain but was neurologically intact and had cervical *x* rays showing only minor degenerative changes and loss of lordosis. He was managed with analgesics and a rigid collar. Ten days later he returned to casualty complaining of aching in his neck and progressive difficulty in holding up his head throughout the day. Neurological examination remained normal. Cervical *x* rays showed angulation into 7° of flexion at C5/6, but were otherwise unchanged. He was referred to neurosurgery and at review was strikingly reminiscent of patient A. He had to hold his chin up with a hand to look ahead, had pain in the back of his neck, which developed over the day unless he used his collar, and was neurologically normal, including in the cervical dermatomes. Magnetic resonance imaging (MRI) of his neck revealed normal soft tissue anatomy. A neurological opinion confirmed the normal examination, other than head ptosis. There was no evidence of inflammatory, autoimmune, or endocrine disease clinically or biochemically, the Tensilon test was negative, and serum creatine kinase was normal. There were no features of Parkinson's disease or amyotrophic lateral sclerosis (ALS). Electroneuromyography (EMG) studies of the neck muscles performed 3 weeks after injury were normal in the ventral muscles, but there were typical features of acute partial denervation in the neck extensors bilaterally, particularly in a band in the mid-to-low cervical spine with more normal EMGs above and below this. However, electrophysiological examination of the limbs was abnormal also and consistent with an asymptomatic peripheral neuropathy. The patient declined muscle or nerve biopsy.

In view of patient A's course and the evidence in patient B of acute denervation that might recover, patient B was managed expectantly. Physiotherapy was used to maintain range of neck movement and encourage use of the neck extensor muscles. He was given a Philadelphia collar, which was worn by day once he became aware of head ptosis. With this regime he recovered to normal over 4 months, including recovery of the spinal alignment at C5/6, and the Philadelphia collar was withdrawn. There has been no recurrence of head ptosis.

Patient C, a 54 year old man, was similar to patient B. He suffered a whiplash injury in an RTA and developed head ptosis and angulation at C5/6 on cervical *x* rays 2 weeks later. Investigation and management mirrored patient B. He also had focal abnormality of his neck extensor muscle EMG, which suggests partial denervation, but otherwise was normal clinically, biochemically, and electrophysiologically. We did not suggest muscle or nerve biopsy as it was clear he would be managed conservatively. With physiotherapy and external bracing, patient C made a complete recovery in 2 months, including recovery of spinal alignment at C5/6. There was no recurrence of head ptosis at last contact.

Although there are reports of head drop in conditions predominantly affecting neural rather than muscular elements,[3] Umapathi *et al*[1] cite Braun *et al*,[4] who treat refractory torticollis by section of multiple cervical dorsal rami without generating significant functional deficits, as evidence that focal denervation of neck extensor muscles is unlikely to cause head ptosis. This surgical denervation, however, is unilateral and the denervated muscles are also likely to be grossly abnormal because of secondary changes resulting from the underlying condition. The cat neck extensor muscle biventer cervicis (analogous to human semispinalis capitis) has tendinous inscriptions defining serially arranged compartments, each receiving segmental innervation from a cervical dorsal ramus. The muscle only generates useful tension if all compartments are co-stimulated; unstimulated compartments act as weak springs in series and dissipate tension within the muscle.[5] There is some evidence for similar architecture in human neck extensors: they receive innervation from several cervical dorsal rami[6] and have tendinous inscriptions producing several at least partially serial compartments.[7] Denervation of one compartment bilaterally would produce significant weakness and fatigability in such compartmentalised muscles. Additionally, the deeper muscles only traverse one motion segment and are innervated by one posterior primary ramus. Segmental denervation of either type of muscle would lead to angulation at a motion segment, limited in degree by intact joints, ligaments, and disc space.

Whiplash injury can cause neurapraxia of cranial nerve XI,[8] XII,[9] and branches of the cervical plexus,[10] and there are other reports of traction neuropathies in the neck.[11 12] In the present cases, the close temporal relationship of the head drop to a forced flexion injury and the EMG findings suggesting acute denervation of neck extensor muscles are consistent with a neurogenic mechanism. Although dystonia of neck flexor muscles can produce head drop, these patients could easily lift their chins and there was no evidence of ventral muscle hypertonia on clinical examination. In addition, in patients B and C, there were normal EMG findings in the ventral neck muscles but abnormal findings in the neck extensors.

Neurapraxia of dorsal primary rami would be expected to recover in time, as happened in patients B and C. Equally, muscle tearing would recover in time, but it is inconceivable that sufficient fibres would have been torn to produce head drop without also producing soft tissue abnormalities on MRI scanning. This is not the case. Only two of the cases were investigated to exclude primary neuromuscular disorders. These were excluded in patient C. Although patient B had evidence of a pre-existing peripheral neuropathy, this may simply have made him more prone to traction neurapraxia after whiplash and his eventual recovery is consistent with the proposed mechanism.

It is unclear why this syndrome has not been described before. Perhaps most whiplash injuries produce insufficient neurapraxia to provoke head drop unless patient factors adversely affect the transmission of forces to the nerves or their susceptibility to injury. In non-predisposed individuals, sufficiently severe injuries might instead produce fractures/dislocations, whose management masks signs of a concomitant neurapraxia. Lesser injuries might produce mild head drop, which is either not recognised or recovers quickly and never requires secondary referral. Furthermore, although motor deficits may be rare after whiplash, sensory symptoms may be common, presenting as the patient's symptoms in a case of ''typical'' whiplash syndrome. There is support for this