Emotion processing in the minimally conscious state

As a newly described condition distinct from coma or the vegetative state, minimally conscious state (MCS) is characterised by a threshold level of consciousness, and diagnostic criteria have recently been proposed. In MCS, cognitively mediated behaviour occurs inconsistently, but is reproducible or sustained enough to be differentiated from reflexive behaviour. It is clinically essential to distinguish this condition from persistent vegetative state (PVS), due to a potentially more favourable outcome. So far, whether patients in MCS can process emotion is unknown.

Cortical processing has been described in PVS using auditory and visual functional paradigms with positron emission tomography. However, to date hardly any functional imaging studies are available in patients in MCS. We used fMRI to assess brain activity induced by an emotional stimulus in a patient in MCS. A 17 year old man was riding his bicycle when he was hit by a train. The accident resulted in head trauma and immediate coma, progressing to MCS over the course of 4 months, when he was admitted to our institution. This research protocol was approved by the Institutional Ethics Committee. At the time of the fMRI study, 5 months after the accident, the patient localised noxious stimuli, had spontaneous eye opening, detectable sleep/wake cycles, sustained visual fixation, and contingent smiling, thus meeting criteria for MCS. A structural MRI study showed mild cortical atrophy and dilated ventricles. Auditory evoked potentials showed decreased conduction velocities at brainstem level. The patient increased his level of awareness 2.5 months after the functional study was conducted. Auditory evoked potentials after recovery were within normal range, while MRI showed much less ventricle dilatation. Six months after recovering full consciousness, he was able to chat normally and feed himself. Currently we are retesting the patient with the same paradigm.

Non-familiar voice v silence and mother’s voice v non-familiar voice recognition were tested in an fMRI block design with 30 seconds per epoch. The patient listened to his mother reading a story, followed 30 seconds later by an age matched voice reading the same story, for 30 seconds with silence epochs in between. Blood oxygen level dependent images were acquired using a T2 weighted gradient echo planar sequence on a General Electric Signa CVI, 1.5T system with real time image processing of multislice and multi-slice images during patient stimulation and rest periods. The Medx 3.4 Sensor System was used to carry out fMRI post-processing, including motion correction and Gaussian smoothing. An uncorrected significance threshold of P<0.001 was used because amygdala and insula activation was expected, owing to emotional voice processing. Activated clusters were localised following co-registration with an anatomical T1-IR volume.

Subtraction of the phrases read by the age matched voice from silence was the control experiment, showing a significant focus of activation in the transverse and superior temporal gyrus, which spread to the planum temporale; more anterior activation was found in the superior (right) and inferior (left) insula (fig 1A). The subtraction of the mother’s phrases from the age matched voice disclosed a strong activation of the amygdala and insula spreading to the inferior frontal gyrus; there was also weaker activation of the transverse temporal gyrus, temporal operculum, and planum temporale (fig 1B,C). Activation was lower on the right hemisphere in both comparisons, non-familiar voice v silence and familiar voice v non-familiar.

To the best of our knowledge, our results provide for the first time anatomical evidence for the response of an MCS patient to a familiar voice, in which both amygdala and insula appear to play a major role.

The activation pattern of the control experiment agrees with previous studies. Our results showed that the mother’s voice activates the extended amygdala, an emotionally related structure, and a directly connected area such as the insula, perhaps acting jointly as limbic integration cortex. Although residual cerebral activity was unequivocal in our case, representing fragmentary cognitive processing, it should not be assumed that it depicts a fully integrated system required for normal levels of awareness; however, our findings highlight the legal and ethical implications of careless bedside chatter. Whether functional imaging represents a reliable method to evaluate neural processing in MCS patients, in whom cognitive output is extremely difficult to assess, remains to be seen.

References

Figure 1 Brain areas of activation produced by non-familiar voice subtracted from silence in coronal view (control experiment, A). Brain areas of activation produced by mother’s voice subtracted from non-familiar voice in coronal view (B), and in axial view (C).
Neurosyphilis presenting with gummatous oculomotor nerve palsy

Although epidemiological studies suggest that the incidence of primary syphilis is rising, 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 light. The right eye evolved a 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 meningial 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) 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.

Discussion

Neurosyphilis is known to cause oculomotor nerve palsies either in the meningovascular phase, due to small vessel vasculitis with resultant nerve infarction, 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 al1 reported a case of oculomotor nerve palsy associated with MR findings similar to ours that also resolved with penicillin treatment. Standaert et al2 described an enhancing penicillin-responsive lesion based in the interpeduncular cistern that compressed the ventral midbrain. The oculomotor nerve lesion in our patient was insonant to adjacent brain on T1 and T2 sequences, with brisk enhancement after intravenous injection of gadolinium contrast. We believe the lesion was a manifestation of meningal 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.

References


High dose cyclophosphamide for severe refractory myasthenia gravis

Myasthenia gravis (MG) exemplifies autoimmune disease. Most patients require immuno-modulating treatment, including steroids, chemotherapy, or intravenous immunoglobulin (IVIg), in addition to anticholinesterase...
treatment. Drachman et al. 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, antifungal, 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 x 10^9/L. Patients received filgrastim (G-CSF) (5 μg/kg/day) starting day 10 until their absolute neutrophil count (ANC) reached 10 x 10^9/L, for two consecutive days.

Results
Patient 1 was diagnosed with seronegative MG at 30 years of age by a positive tension test and a decremental response on repetitive stimulation. Initial treatment included pyridostigmine 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 pyridostigmine. She required 27 intubations between initial diagnosis and immunomodulatory treatment at 41 years of age.

Patient 2, previously reported, suffered from both seronegative MG and chronic inflammatory demyelinating polyneuropathy (CIDP). He presented at 47 years of age with myasthenia and the mean disease duration of 10.3 years. In comparison, in the three patients described here, two had antibody negative myasthenia and the mean disease duration was 16.3 years (range: 9–29) years. All required multiple intubations: 27, 2, and 11, and our median follow up was 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 pa tients even after 2 years. This suggests that long term remissions in MG may be possible even without achieving complete immunosuppression. 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 treatment effect and time to maximum benefit. High dose cyclophosphamide treatment warrants further study as a treatment for severe refractory MG.

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 2 required 27 intubations before treatment and only once since, and who in the past 6 months stopped oral cyclophosphamide, may yet to enjoy the maximum benefit of this treatment. Patient 2, 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. 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. This suggests that long term remissions in MG may be possible even without achieving complete immunosuppression. High dose cyclophosphamide has the potential to significantly reduce symptoms and increase quality of life among people with MG refractory compared to conventional treatment. Long term follow up is necessary to evaluate the treatment effect and time to maximum benefit. High dose cyclophosphamide treatment warrants further study as a treatment for severe refractory MG.

Table 1 Patient characteristics before high dose cyclophosphamide treatment

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Patient 1 41/female</th>
<th>Patient 2 56/male</th>
<th>Patient 3 41/female</th>
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</thead>
<tbody>
<tr>
<td>Duration of MG (y)</td>
<td>11</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>MG severity class</td>
<td>IVb</td>
<td>IVb</td>
<td>IVb</td>
</tr>
<tr>
<td>AChR positivity</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Detectable</td>
</tr>
<tr>
<td>Previous treatment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Thymectomy (ies)</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>iv Ig (no of infusions)</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>10–100 mg qd, duration 3 years</td>
<td>40–100 mg qd, duration 7 years</td>
<td>10–60 mg qd, duration 4 years</td>
</tr>
<tr>
<td>Plasmapheresis (no. of procedures)</td>
<td>2/7</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50 mg/d, duration 7 months limited by nausea/vomiting</td>
<td>200 mg qd, duration 2 months limited by nausea/vomiting</td>
<td>50–150 mg qd, duration 15 months</td>
</tr>
<tr>
<td>Oral cyclophosphamide</td>
<td>100 mg qd, duration 28 months</td>
<td>50–125 mg bid, duration 6 months</td>
<td>250–500 mg qd, duration 7 months</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cellcept</td>
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</tr>
</tbody>
</table>

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

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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 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 C4/5, which did not change with neck flexion, but were otherwise unchanged. He remained neurologically intact but complained of progressive use of the upper limb and, after 2 months, was found to be neurologically intact. He remained neurologically intact after 2 months. x Rays showed that the sublaminar wires at C5 had eroding through the skin, necessitating a redo procedure.

In view of patient A’s course and the evidence in patient B of acute denervation that might recover, patient B was managed expectantly, although support 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 drop. This was removed after 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 drop.

Patient C, a 54 year old man, was similar to patient B. He suffered a whiplash injury in an RTA and developed head drop and angulation at C5/6 on cervical x rays 2 weeks later. Investigation and management mirrored those in patient B. He had evidence of denervation 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 in this patient.

There are several reports of head drop in conditions predominantly affecting neural rather than muscular elements. 3 Umapathi et al 4 cite Braun et al 5, who treat refractory torticollis by the excision 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 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 insertions 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 the muscle. 6 There is some evidence for similar architecture in human neck extensors: they receive innervation from several cervical dorsal rami 7 and have tendinous insertions producing several at least partially serial compartments. 8 Denervation of one compartment bilaterally would produce significant weakness and fatigueability in such compartmentalised muscles. Additionally, the deeper muscles only traverse one motion segment and are innervated by one primary ramus. Segmental denervation of either type of muscle would lead to angulation at a motion segment, limited by intact joints, ligaments, and disc space.

Whiplash injury can cause neurapraxia of cranial nerve XI, XII, and branches of the cervical plexus, 9 10 and there are other reports of traction neurapraxia in the neck. Most studies of 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.

References


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We report a case of acute disseminated encephalomyelitis (ADEM) temporally associated with *Campylobacter* gastroenteritis. The association of *Campylobacter* infection and Guillain-Barré syndrome is well recognised.

The paucity of reported cases of ADEM associated with *Campylobacter jejuni* infection may be due to the patient's presentation with non-specific symptoms and signs of ADEM, and the lack of awareness among clinicians that ADEM can present as an acute, multifocal, inflammatory disease of the central nervous system. It is an uncommon but a serious condition with mortality rates estimated between 10–30%.

In a majority of cases, ADEM develops after systemic viral infections most commonly measles, mumps, rubella, influenza A and B, herpes simplex, Epstein-Barr virus, varicella, and vaccinia. It has also been reported following bacterial infection with *Mycoplasma pneumoniae*, *Chlamydia, Legionella*, and *Streptococcus*, or following immunisations for rables, diphtheria/tetanus/pertussis, smallpox, measles and Japanese B encephalitis.

The pathogenesis of ADEM is not fully understood. However, the evidence suggests that activated T cells, which recognise amino acid sequences shared between microbial epitopes and myelin antigens, attack central nervous system structures alone or in synergy with antibodies. Viral or bacterial superantigens could likewise trigger autoreactive T cells with similar results.

The diagnosis of ADEM is usually made clinically with the aid of MRI scanning. Lumbar puncture findings or electroneuromy- 

ology studies. MRI scanning reveals multiple areas of increased signal on T2 weighted images in the white matter throughout the central nervous system, most being located in the subcortical white matter of both hemispheres, which are often quite extensive and enhance with contrast. CSF findings include mononuclear pleocytosis and mild protein elevation. There are few data on evidence based treatment regimens, but treatment is usually instituted with high dose glucocorticoids. Plasmapheresis and intravenous immunoglobulin have also been used.

*Campylobacter* gastroenteritis is the most common cause of acute gastroenteritis in the UK, accounting for over 56 000 cases in 2000. Its incidence has risen progressively over the past 2 decades. In the majority of cases, the illness self terminates within a few days with no long term consequences. It is estimated that approximately 1/1000 reported campylobacteriosis cases lead to Guillain-Barré syndrome, and around 33% of Guillain- Barré syndrome cases in children may be triggered by campylobacteriosis. Huber et al reported a case of combined ADEM and acute motor axonal neuropathy following *Campylobacter jejuni* infection and hepatitis A immunisation. A case of *Campylobacter jejuni* infection and cranial MRI scanning showed a slight enhancement in the left cerebral peduncle that disappeared when the study was repeated a week later. Nasralla et al reported a case of postinfectious encephalomyelitis a year after *Campylobacter jejuni* enteritis. Cranial MRI scanning showed a combination of predomi- nant grey matter involvement with concomi- tant foci of involvement in the subcortical white matter lesions with no pathognomonic features which the authors felt to be different from the pattern of signal abnormalities seen in patients with ADEM. The MRI abnormalities in our case were in keeping with ADEM although, as with the case reported by Huber et al, the amount of enhancement was minimal, indicating that the majority of the lesions were not acute. The paucity of reported cases of ADEM following *Campylobacter* infection is surprising given the high incidence of *Campylobacter jejuni* infection and Guillain-Barré syndrome and the pathogen- 

esis of the latter. In these cases, *Campylobacter jejuni* induces humoral and cellular immune responses due to molecules specific lipopolysaccharide epitopes on the infecting agent and target epitopes on the

**References**


**Acute disseminated encephalomyelitis temporally associated with Campylobacter gastroenteritis.**

The association of *Campylobacter* infection and Guillain-Barré syndrome is well recognised.
surface components of the peripheral nerves, resulting in myelin destruction and axonal degeneration.\textsuperscript{7} Furthermore, patients with ADEM often have peripheral nervous system involvement and there have been occasional cases of ADEM associated with Guillain-Barré syndrome. Our patient did not have any clinical features suggestive of peripheral nervous system involvement. However, nerve conduction studies were not performed and a degree of sub-clinical neuropathy cannot therefore be excluded.

We describe the first identifiable case of ADEM temporally associated with \textit{Campylobacter} gastroenteritis alone. Our patient made an excellent recovery associated with therapy with high dose methylprednisolone.

**Acknowledgements**

We are most grateful to Dr D Connolly for reviewing the MRI imaging.

**References**


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**Figure 1** Axial T2 weighted image showing supra- and infra-tentorial high signals in both hemispheres, and coronal T1 weighted images showing peri-trigonal white matter lesions with slight enhancement following intravenous gadolinium DTPA injection in keeping with ADEM.