LETTER TO THE EDITOR

To the Editor

Optic Neuritis in Guillain-Barre Syndrome

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In Guillain-Barre syndrome (GBS) the underlying antibody-mediated attack against peripheral nerves and/or myelin generally spares the central nervous system (CNS), as CNS myelin is produced by oligodendrocytes, not Schwann cells, and expresses different antigenic epitopes from peripheral myelin. The optic nerve, a part of the CNS, can nevertheless occasionally develop inflammatory demyelination – optic neuritis (ON) – in variants of GBS.

A 19 year old previously healthy female presented one week after an upper respiratory infection with a two-day history of mild blurry vision, ascending paresthesias, and rapidly progressive generalized weakness. On initial examination her right pupil was 7 mm and non-reactive; her left pupil was 6 mm and reactive. She had mild ophthalmoparesis that did not localize to a particular cranial nerve. Optic discs and fundi were normal. She was areflexic, had lower more than upper extremity weakness, and had decreased proprioception and vibration at the toes, with intact pain and temperature sensation throughout. She did not have limb ataxia.

Initial investigations were normal, including MRI brain and CSF analysis. Anti-GQ1b antibody testing was negative. She was diagnosed clinically with GBS and was started on IV immunoglobulin (IVIg) 2 g/kg (divided over three days).

The next day she developed a rapid deterioration in bulbar function and required intubation. Electrodiagnostic studies performed 72 hours after symptom onset showed a motor predominant process characterized by profoundly reduced compound motor action potential (CMAP) in the upper and lower extremities, without clear evidence of demyelination, conduction block, or temporal dispersion. Motor point stimulation did not demonstrate distal conduction block. Sensory nerve action potentials (SNAP) from the extremities were normal. Electromyography (EMG) of the first dorsal interossei, biceps, and tibialis anterior revealed no recruitable motor units and no spontaneous EMG activity.

She deteriorated further over the next week, developing facial diplegia and flaccid quadriplegia. Her visual acuity dropped to hand motion on the right and 20/25 on the left. There was a right relative afferent pupillary light defect (RAPD) and near-complete ophthalmoplegia with optic disc edema bilaterally. Unfortunately, she could not be transported out of the ICU for fundus photography or visual evoked potentials (VEPs), given her unstable clinical status.

Repeat CSF analysis on day nine of admission revealed 19 x10^6/L leukocytes and a strikingly elevated protein of 4191 mg/L. MRI brain revealed restricted diffusion in the optic nerves (right > left) and subtle enhancement of the right optic nerve (Figure 1).

Repeat electrodiagnostic studies ten days after onset continued to show a generalized reduction in CMAP amplitudes, now with profound reduction of SNAP amplitudes but normal latencies and conduction velocities. Needle EMGs revealed reduced to absent recruitment in multiple muscles, without any changes in motor unit morphology. There continued to be no evidence of acute denervation (i.e. fibrillations or positive sharp waves).

Two weeks after admission she began to recover strength. By four weeks she had recovered nearly full power, and her reflexes had returned. Her studies showed significant improvement in CMAP and, to a lesser degree, SNAP amplitudes throughout. EMG studies of multiple limb muscles were essentially normal. The SNAPs normalized over the next three months. Overall, we thought her electrophysiological findings were best interpreted as very distal conduction block, accounting for the lack of acute denervation, the initial motor greater than sensory changes, and the overall clinical phenomenology with the patient's rapid response to IVIg.

Her visual acuity gradually recovered to 20/25 in the right eye and 20/20 in the left eye, with resolution of the optic disc edema in both eyes, but persistently absent colour vision in the right eye and a right RAPD. Five months later colour vision had normalized and she had only a very mild residual right optic neuropathy, detectable as a small RAPD with subtle central visual field depression.

Optic neuritis is an uncommon feature of GBS. In our patient the rapid and profound deterioration in vision, followed by prompt and nearly complete recovery, suggested demyelination rather than ischemia of the optic nerve, despite the diffusion restriction seen on MRI.[1,2] Visual evoked potentials would likely have provided further supportive evidence for optic nerve demyelination, but could not be obtained acutely (because of the patient's unstable status in the ICU) and were not deemed necessary in isolation during the convalescent period (when she had already achieved her dramatic visual recovery).

Our patient's remarkable improvement stands in contrast to most previously published reports of combined optic neuritis and GBS. Biotti et al. enumerated thirteen cases published prior to 2012 of combined optic neuritis and GBS,[3] only four cases of which had recovery of visual acuity to 20/25 or better in the affected eye.[4-7] The combination of optic neuritis and GBS is a subtype of combined central and peripheral demyelination (CCPD) that can be post-infectious[8] (e.g., from *Mycoplasma pneumoniae*, CMV, or EBV), autoimmune[9] (e.g., from neuromyelitis optica (NMO) or anti-ganglioside antibodies), or idiopathic.[3] Although our patient had acute and nearly simultaneous central and peripheral demyelination, CCPD may also include chronic and relapsing forms of central or peripheral demyelination, such as a multiple-sclerosis-like illness and chronic inflammatory demyelinating polyneuropathy (CIDP).[10] Data from a retrospective cohort of 31 patients with CCPD showed heterogenous features, common post-infectious or post-vaccination onset (65%), a monophasic or chronic clinical course, poor response to immunotherapy, and a generally poor outcome.[11] This cohort was characterized, however, by a large number of patients with multifocal brain and spinal cord lesions and electrophysiological findings in keeping with CIDP, and therefore had much more extensive and chronic disease than our patient, perhaps explaining their worse overall outcome.

Recently an association has been discovered between CCPD and antibodies against neurofascin-155, an adhesion molecule found at the nodes of Ranvier and paranodes in both the CNS and PNS.[12,13] In one Japanese survey, 75% of patients with CCPD had

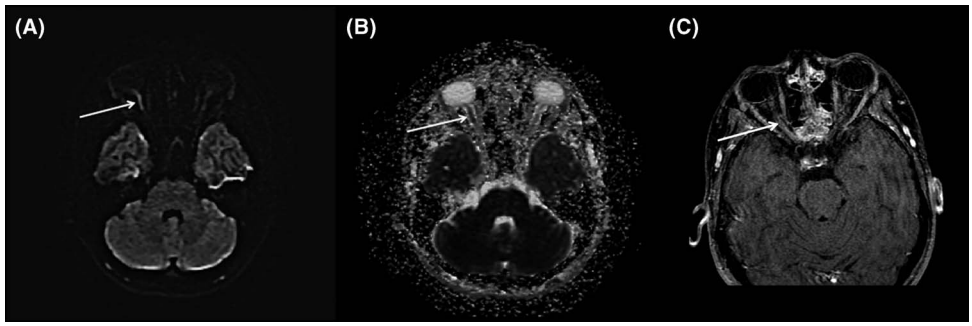

Figure 1: *MRI of the optic nerves. (A) Axial diffusion weighted imaging shows increased restriction in the optic nerves, right (arrow) more than left; (B) Axial apparent diffusion coefficient map showing a corresponding dark appearance (arrow), in keeping with true diffusion restriction; (C) Axial gadolinium-enhanced fat-suppressed T1-weighted imaging showing subtle contrast enhancement of the right optic nerve (arrow), consistent with inflammation.*

optic nerve involvement and responded well to immunotherapy.[13] Our patient was not tested for anti-neurofascin-155 antibodies because she presented in 2012, before the association of CCPD with these antibodies was widely recognized.

The pathophysiology underlying antibody-mediated optic nerve demyelination in GBS likely relates to optic nerve myelin sharing a common antigenic epitope with peripheral nerve axons or myelin.[3] One such reported antigenic epitope is the GQ1b ganglioside, most often targeted by autoantibodies in the Miller Fisher variant of GBS and found in relatively high concentrations in the optic nerve.[14,15] Antibodies against another ganglioside, GM1, have been detected in severe axonal forms of GBS, and portend a poorer prognosis, but are not associated with ON.[16] Although we did not test for anti-GM1 antibodies in our patient, her subsequent excellent recovery was not compatible with an anti-GM1 syndrome. The rapid clinical recovery and pattern of abnormalities on electrophysiological studies could argue for reversible impairment of conduction across the nodes of Ranvier as a possible pathogenic mechanism; this phenomenon is characteristic of other anti-ganglioside antibody-mediated neuropathies and is sometimes termed a "nodo-paranodopathy."[17]

Mycoplasma pneumonia may precede GBS in 5% of cases, and there has even been a report of NMO-spectrum-disorder-associated polyneuropathy following a *Mycoplasma* infection.[18] (Our patient was not tested for *Mycoplasma pneumonia* due to centre-specific lab restrictions surrounding the low sensitivity and specificity of this test.) Similarly, NMO has been described in a small number of cases in patients presenting with post infectious inflammatory polyneuropathy and optic neuritis.[19] Our patient had a negative MRI brain and spinal cord initially and made a complete recovery; these features essentially exclude NMO, and we did not test for anti-NMO antibodies in our patient.

Reports of patients with optic neuritis in the setting of anti-GQ1b-*negative* GBS are scarce in the literature; one patient, described by Biotti et al., had a rapid loss of motor and sensory function associated with bilateral optic neuritis but did not regain useful vision despite a full recovery of motor function.[3]

Our patient had fulminant GBS, culminating in complete flaccid quadriplegia and facial diplegia, with bilateral optic disc edema and a unilateral severe optic neuropathy consistent with optic neuritis. Her bilateral optic disc edema was likely due to undocumented high intracranial pressure, an uncommon but reported complication of GBS in the setting of very high CSF protein.[20] Her optic neuritis was presumably due to the optic nerve sharing an actively antigenic non-GQ1b epitope with the peripheral nerves. Despite the strikingly aggressive nature of her GBS she made a remarkably rapid and complete recovery in all respects after treatment with IVIg, including near-complete return of vision in the affected eye.

Disclosures

Anita Dayal, Kurt Kimpinski, and J. Alexander Fraser do not have anything to disclose.

Statement of Authorship

Anita Dayal, Kurt Kimpinski, and J. Alexander Fraser each contributed substantially to the conception, design, acquisition, analysis, and interpretation of data; they drafted the manuscript together and revised it critically for important intellectual content; they each gave final approval of the version to be published.

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