Atypical Fulminant Seronegative *Neuromyelitis Optica* in a Post-renal Transplant Patient

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Introduction

Neuromyelitis Optica (NMO) has generated significant interest in recent years as a severely disabling antibody-mediated autoimmune disease of the central nervous system (CNS). It preferentially targets optic nerves and the spinal cord, and in many cases is associated with autoantibodies to aquaporin-4 (AQP4 Ab)water channels. Few case reports have highlighted NMO involving the entire cervicothoracic spinal cord. Moreover, until recently NMO has been thought to exclusively affect the CNS, sparing the peripheral nervous system (PNS). Here in, we report a renal transplant patient who developed severe, rapidly progressive AQP4 Ab negative, clinically definite NMO, resulting in quadriparesis and blindness. In our patient, neurophysiologic studies were suggestive of concomitant involvement of the PNS in the context of NMO.

Case report

A 51 year old Hispanic female, status post renal transplant one year ago, on tapering dose of tacrolimus, with post transplant course complicated by cytomegalovirus infection, presented with sudden onset lower extremity numbness. Presenting symptoms progressed to complete paraplegia and sensory loss over 24 hours. The following day, she developed weakness and numbness in bilateral upper extremities, T3-T4 sensory level, and complete vision loss. MRI at presentation revealed contrast enhancement of the pre-chiasmatic optic nerves (Figure 1 A-C) as well as T2 hyperintensity involving the entire cervicothoracic spinal cord (Figure 2 A-B). Cerebrospinal fluid analysis documented elevated protein with neutrophilic pleocytosis. Nerve conduction studies (NCS) showed severe reduction in compound motor action potential amplitudes (CMAP), most pronounced in lower extremities (Figure 3 A-B). Slowing motor conduction velocities and slowing of distal latencies and F- wave latencies were also seen. Needle examination (EMG) showed active denervation without reinnervation in sciatic/peroneal nerve innervated muscles. Serum AQP4 Ab was negative. At presentation, high dose intravenous (IV) methylprednisone closely followed by five sessions of plasmapheresis (PLEX) were administered. Subsequently, weekly cycles of IV rituximab therapy (X4) were given. At discharge, the patient had significant improvement in muscle strength and sensation in upper extremities. However, she remained paraplegic despite repeat MRI showing near complete resolution of the previously seen lesions (Figure 2 C-D). Repeat AQP4 Ab at the time of discharge was negative. Follow up in 6 months demonstrated 5/5 strength in her upper extremities with improved strength in her lower extremities. Patient was was able to stand and use a walker. Furthermore, patient regained considerable vision in her right eye. Repeat NCS/EMG at 6 months revealed improvement in CMAP amplitude, with return to normal parameters in median, ulnar, peroneal and tibial nerves (Figure 3C-D).

Results

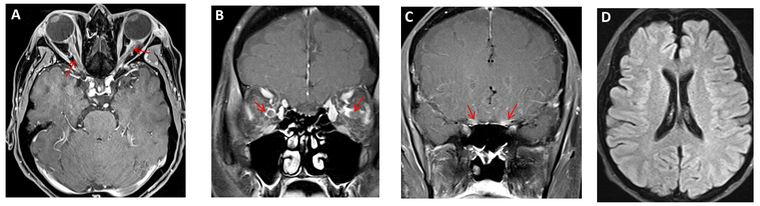

Figure 1. Brain MRI at presentation. (A) Axial T1 post contrast MRI showing enlarged prechiasmatic optic nerves with diffuse contrast enhancement consistent with bilateral optic neuritis (arrows). (B) Coronal T1 post contrast MRI showing diffuse enhancement of the optic nerves compatible (arrows). (C) Coronal T1 post contrast MRI demonstrating enhancement of the optic nerves, crossing the optic canal (arrows). (D) Axial FLAIR MRI did not reveal periventricular or subcortical white matter lesions that meets multiple sclerosis imaging criteria.

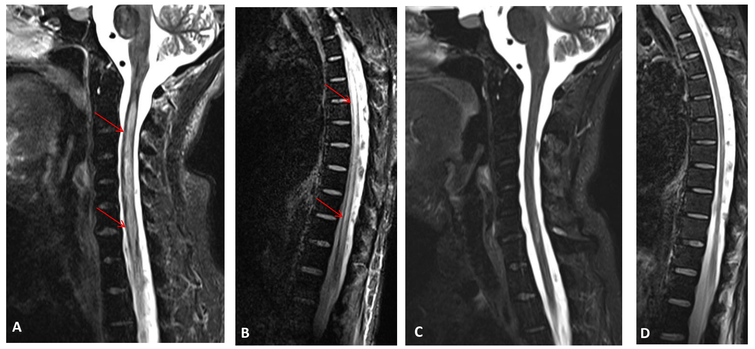

Figure 2. Spine MRI at presentation and post treatment. Sagittal T 2-weighted MRI of the cervical (A) and thoracic spine (B) at presentation showing increased T2/STIR signal throughout the cervical and thoracic spinal cord (arrows). Repeat Sagittal T2 weighted MRI of the cervical (C) and thoracic spine (D) at 3 weeks, following 1st cycle of IV Rituximab administration preceded by high dose methylprednisone closely followed by PLEX administration, demonstrating marked improvement in the appearance of the spinal cord.

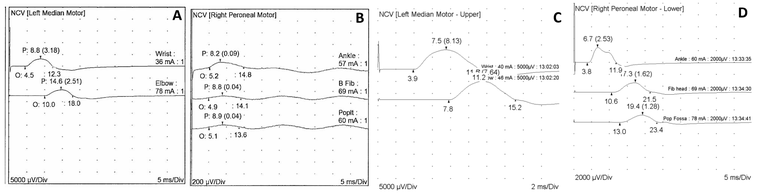

Figure 3. Neurography of the left median and right peroneal motor nerves at presentation and following initial and maintenance treatments. At presentation, left median nerve (A) and right peroneal NCS (B) yielded reduced CMAP. Repeat NCS of the left median motor (C) and right peroneal motor (D) at 6 months follow up showing significant improvement in CMAP.

Discussion

Recently Wingerchuk *et al.* has proposed revised diagnostic criteria for NMO. Our case described here meet the new criteria, although she lacked AQP4 Ab. AQP4 antibodies are undetectable in 10–40% of patients with the disease and AQP4 Ab seronegativity does not necessarily preclude a diagnosis of NMO. Interestingly, recent studies show that AQP4 Ab positive NMO differs clinically and epidemiologically from seronegative disease: strong predominance in women, more severe clinical attacks, higher spinal cord lesion load, and frequent association with coexisting autoimmunity.

NMO has been previously described as an inflammatory condition restricted to the CNS with no documentation of PNS involvement. In addition to lesions in the CNS, in our patient, NCS/EMG studies are suggestive of concomitant involvement of the PNS. To our knowledge only three cases of seropositive NMO with neurophysiologically documented lower motor neuron involvement have been described. In our patient, the persistence of sensory and motor symptoms despite the resolution of spinal cord lesions could suggest concomitant involvement of PNS at disease onset. Moreover, NCS/EMG demonstrating a reduction in CMAP and acute denervation with no signs of myopathy whereas MRI showing grey mater involvement suggests an involvement of the second motor neuron (PNS) in the context of NMO. On a pathophysiological level, it has been hypothesized that involvement of the PNS may be due to reduced local blood flow in consequence of severe inflammation, hypoxia, local blood–brain-barrier break down and tissue swelling.

Immunosuppressive agents such as azathioprine, rituximab, cyclophosphamide, and mycophenolate are the mainstay of NMO maintenance treatment. In our patient maintenance therapy with rituximab significantly improved neurologic deficits, radiologic disease burden as well as nerve conduction parameters .

Conclusions

- This report, an unusual case of NMO that involved the entire cervicothoracic spinal cord and PNS, further highlights the growing clinicopathological spectrum of NMO.
- Further studies are needed to elucidate the exact mechanism of PNS involvement in NMO and understand its significance in the prognosis and the recovery of patients with NMO.

References

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2. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology 2006; 66: 1485–89.*