Case report

Seronegative neuromyelitis optica presenting with life-threatening respiratory failure

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Context: Dyspnea has rarely been reported as a presenting symptom in patients with neuromyelitis optica (NMO). We report an unusual case of NMO relapse presenting with rapidly progressive respiratory failure and briefly discuss the possible pathophysiological mechanisms of this potential life-threatening complication of NMO.

Findings: The 58-year-old woman with a history of bilateral optic neuritis presented to the emergency department with rapidly worsening dyspnea. Cervical spine magnetic resonance imaging showed extensive abnormal signal with involvement of the medulla oblongata.

Since in our patient chest radiography failed to disclose a diaphragmatic palsy that is commonly observed in patients with phrenic nerve involvement, this acute manifestation of the disease may be attributed to brainstem involvement instead of cervical myelitis.

Conclusion/clinical relevance: Clinicians should be aware of this atypical presentation of NMO, which needs to be promptly recognized and aggressively treated.

Keywords: Neuromyelitis optica, Respiratory failure, Cervical spine, Brainstem, Anti-aquaporin-4 antibodies

Introduction

Neuromyelitis optica (NMO) is an autoimmune inflammatory demyelinating relapsing disease of the CNS in which a disease-specific circulating autoantibody (NMO-immunoglobulin G [IgG]) binds to the aquaporin-4 (AQP4) water channel.^{1–3}

We report the case of an AQP4-antibody-negative NMO patient whose initial presenting symptom of a NMO relapse was an acute respiratory failure requiring mechanical ventilation. We briefly review the literature, and discuss the possible pathophysiological mechanisms of this life-threatening complication of NMO.

Case report

A 58-year-old woman with a history of bilateral optic neuritis (eight months before) presented to the emergency department with rapidly worsening of shortness of breath, approximately 30 minutes after beginning of the

symptomatology. The patient did not present any other brain stem symptoms or signs, such vomiting or hiccups, as a premonitory event. Respiratory failure rapidly ensued and the patient was intubated, supported with mechanical ventilation, and transferred to the ICU. The patient was unable to walk at presentation; bilateral upper extremities weakness was also noted, but, due to rapid clinical deterioration, a thorough neurological examination was unfortunately not possible before intubation in the emergency room.

Cervical spine magnetic resonance imaging showed extensive abnormal signal with involvement of the medulla oblongata (Figure 1 A,B,C). Notably, the characteristics of the spinal cord MRI are NMO spectrum disorders (NMOSD) compatible, in particular the central location in cross-sectional axis of the cord showed by the T1 axial imaging. Brain magnetic resonance imaging did not disclose other signal abnormalities.

Laboratory investigations, including ANA, pANCA and cANCA, anti-ENA, anti-dsDNA, anti-SSA/Ro and anti-SSB/La antibodies, rheumatoid factor, antiphospholipid antibodies, levels of soluble IL-2R, onconeural

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Figure 1. Sagittal T2-weighted (A) and T1-weighted non-enhanced (B) magnetic resonance images of the cervical spine show abnormal T2 signal and expansion of the spinal cord from the level of the pontomedullary junction through the T2 level including involvement at the cervico-medullary junction (arrows). Contrast-enhanced T1-weighted image (C) reveals extensive cord enhancement across these levels.

antibodies, ceruloplasmin, copper and vitamin B12, were normal. Cerebrospinal fluid examination was also unremarkable: cell count, protein, IgG index were within the normal limits, oligoclonal bands were absent, NMO/AQP4-IgG ELISA was < 1.6 U/mL (reference range: < 1.6). Also polymerase chain reaction (PCR) for Herpesvirus (*herpes simplex*, *varicella zoster virus*, *cytomegalovirus*, Epstein-Barr virus), HIV, HTLV-1, *Treponema pallidum*, *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Borrelia burgdorferi* were negative.

She received a 5-day course of high-dose methylprednisolone, plasma exchange, and a single dose of rituximab with partial response. Extubation was possible after 5 days and at that time a tetraparesis more marked at the lower limbs persisted. After extubation pulmonary function testing was within normal limits.

Although NMO/AQP4-IgG was not found in the CSF and anti-aquaporin 4 receptor antibodies were not found in the blood, based on the revised diagnostic criteria for NMO the patient otherwise fulfilled criteria for an NMO diagnosis.⁴ However, a cell-based assay for serum aquaporin-4 antibodies, which is the current reference standard for NMOSD,⁴ had not been performed.

On the other hand, the other potential differential diagnoses had been considered and excluded: neoplastic etiology such as B-cell lymphoma, ependymoma and astrocytoma (MRI findings and absence of extraspinal manifestations); autoimmune diseases, in particular systemic lupus erythematosus, Sjögren syndrome, sarcoidosis (see the above-mentioned laboratory examinations);

Behçet disease (no signs of involvement of other organs, such as mouth and genital sores, uveitis or arthropathy, superficial or deep vein thrombosis); infectious viral, bacterial and parasites diseases (specific antibodies in serum, culture and PCR of CSF negative, MRI findings); a paraneoplastic manifestation, and a nutritional etiology (especially vitamin B12 and copper deficiency).

Discussion

Due to its rarity, evidence-based guidelines for NMO treatment are lacking.⁵ Although NMO is characterized by involvement of the optic nerves and spinal cord,^{4,6} demyelinating lesions in the brainstem, and especially in the medulla oblongata and area postrema, are frequently observed in NMO.^{7,8} In a recent population-based and descriptive study, brain stem lesions were observed in 25 patients out of 35 patients with NMO, 18 of them in medulla oblongata.⁹ Lesions were symptomatic in medulla oblongata and pons, asymptomatic in mesencephalon and diencephalon. Interestingly, unlike our case, brain stem lesions were observed significantly more often in anti-AQP4 antibody-positive than in seronegative patients. In fact, the distribution of NMO-characteristic brain lesions correspond to the sites of high AQP4 expression, adjacent to the ventricular system at any level, including third and fourth ventricle.¹⁰

Respiratory failure can also be observed in NMO patients, although cases with respiratory weakness at the beginning of an attack/relapse have been rarely reported. Whitham and Brey first reviewed the literature

in 1985 (43 cases) and reported its occurrence in 22% of the cases.¹¹ Wingerchuk and colleagues in a review of 71 patients with NMO evaluated at the Mayo Clinic found respiratory failure, which was attributed to the acute cervical myelitis, in 33% of the relapsing patients and in 9% of the monophasic patients.¹² Fifteen of the 16 relapsing patients (93%) with respiratory failure died. In a retrospective study of 28 Brazilian patients with NMO, four patients died due to respiratory failure.

Recently, Dembiski *et al.* reported the case of a 13-year-old girl affected by severe NMO presenting with ascending paralysis and respiratory failure in coincidence with a weaning of steroid treatment.¹³ A small percentage of children diagnosed with acute transverse myelitis later are diagnosed with other demyelinating diseases, especially NMO or multiple sclerosis.¹⁴ Correct diagnosis is important for prognosis and treatment, which should begin with intensive surveillance for acute life-threatening respiratory or autonomic complications.

A possible explanation for the acute respiratory failure in our patient could be the extensive spinal cord involvement. However, chest radiography failed to disclose a diaphragmatic palsy that is commonly observed in patients with phrenic nerve involvement due to high cervical spinal cord injury. In fact, diaphragmatic palsy usually manifests as elevation at chest radiography.¹⁵ Even if this finding is of little value in the diagnosis of diaphragm paralysis, the condition is unlikely if diaphragm elevation is absent.¹⁶ Therefore, it cannot be excluded that ventilation failure was secondary to dysfunction of the brainstem neuronal network that controls activity of the motoneurons innervating the respiratory muscles. This network includes the dorsal and ventral respiratory groups in the medulla, which contain neurons that are activated during inspiration, post-inspiration, or expiration.^{17,18} Moreover, in the medulla exist important interactions between the respiratory and cardiovascular control networks.

This case report study has some important limitations, which should be recognized and avoid in future studies. In fact, phrenic nerve conduction studies¹⁹ and needle EMG examination²⁰ should have been performed bilaterally to exclude loss of motor axons in the phrenic nerves, C3–C5 roots, or C3–C5 cord segments. In addition, it should be considered that fluoroscopic examination of the diaphragm combined with stimulation of phrenic nerves is more useful in assessing diaphragmatic function than plain films of the chest, particularly in patients with high spinal cord injury.^{21,22}

Conclusion

This case report indicates that NMO may present with severe respiratory failure due to cervical cord or

brainstem involvement, which needs to be promptly recognized and aggressively treated.

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