Neuroleptic Malignant Syndrome Associated with Refractory Acute Disseminated Encephalomyelitis

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Key Words

Acute disseminated encephalomyelitis · Neuroleptic malignant syndrome · Central nervous system demyelinating disease

Abstract

We present the case of a young man who was transferred to our hospital with worsening acute disseminated encephalomyelitis (ADEM) despite treatment with intravenous methylprednisolone, intravenous immunoglobulin and plasma exchange. He developed neuroleptic malignant syndrome (NMS) without the use of dopamine-modulating drugs. His progressive clinical improvement started after treatment with intravenous cyclophosphamide and methylprednisolone. In our patient, acute demyelination with severe bilateral inflammation of the basal ganglia could have caused a state of central dopamine depletion, creating proper conditions for the development of NMS. Significant clinical improvement of our case after treatment with intravenous cyclophosphamide and steroids provides further evidence for a possible role of the inflammatory lesions in the pathogenesis of NMS in association with ADEM.

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Introduction

Neuroleptic malignant syndrome (NMS) is a rare but serious condition usually associated with neuroleptic drug therapy [1]. It is characterized by hyperthermia, muscle rigidity, altered mental status, and increased serum creatine kinase [2]. NMS may result from acute central dopamine depletion or a functional dopamine-deficiency state from dopamine receptor blockade [1, 2]. Other triggering factors such as an imbalance between dopamine and

other neurotransmitters, genetic factors, dehydration, and stress may be necessary in its pathogenesis [3]. Recent evidence suggests that pro-inflammatory cytokines released by activated macrophages could contribute to the pathogenesis of NMS [4]. Acute inflammation and macrophage infiltration is characteristic of the pathology of acute disseminated encephalomyelitis (ADEM), and basal ganglia involvement is common; however, occurrence of NMS in ADEM is rare. A review of the literature did not identify any previous reports of NMS in association with ADEM. We speculate on mechanisms of possible co-occurrence of these two disorders, which is distinctly unusual.

Case Report

A 22-year-old previously healthy male was admitted to a community hospital with new-onset numbness and weakness of the right face, arm and leg with slurred speech. One week earlier, he was treated with antibiotics for a presumed urinary tract infection. Initial workup including lupus panel, ANA, erythrocyte sedimentation rate, angiotensin converting enzyme levels, NMO-IgG, HTLV I/II antibodies was negative. Cerebrospinal fluid (CSF) showed RBC 26, WBC 24, glucose 97 mg/dl, protein 78 mg/dl, positive oligoclonal bands, normal IgG index and cytology. CSF VDRL was nonreactive. Brain MRI showed large gadolinium-enhancing white matter lesions. A diagnosis of ADEM was made after exclusion of infectious encephalitis. He continued worsening clinically and radiologically after treatment with intravenous (IV) methylprednisolone, IVIg and plasmapheresis. Three weeks later, he was transferred to our hospital for further care.

On arrival, he was awake and mute, with a dense right hemiplegia including the face, and dystonic posturing of the right upper extremity (flexed at elbow, fingers in clenched fist). Generalized bilateral rigidity was evident with sustained right patella and ankle clonus. Spinal fluid showed lymphocytic pleocytosis (14 lymphocytes), normal glucose, protein 65 mg/dl, normal IgG index and three oligoclonal bands. Myelin basic protein (MBP) was elevated at 8.7 µg/l (range 0–4.0). Cytology and flow cytometry were negative for malignant cells. CSF viral panel including CMV, EBV, HSV1/2, JCV, VZV DNA were negative by PCR. HIV and aquaporin serology was negative. Brain MRI showed multiple bilateral ring-enhancing white matter lesions involving temporal, parietal, and frontal lobes, basal ganglia, brain stem, and the splenium of the corpus callosum (fig 1).

His mental status declined and he became febrile at 39.5°C with diaphoresis, tachycardia and hypertension. Infectious cause for the fever was not evident. Propranolol was given for autonomic storming. He worsened with persistent fever, hypernatremia and elevated serum creatine kinase from 15,000 U/l to 90,000 U/l. He developed myoglobinuria and acute tubular necrosis with renal failure that responded to IV hydration. The clinical diagnosis of NMS was established and bromocriptine and amantadine were added to his management. After supportive care, assisted ventilation, and three courses of IV methylprednisolone, his clinical status stabilized but he remained unresponsive with recurrent episodes of oculogyric spasms. EEG showed generalized theta slowing.

Brain biopsy was performed because of concerns for lymphoma and his unresponsiveness to all standard treatments. Brain biopsy identified demyelination with reactive astrocytes and macrophage infiltration, consistent with inflammatory demyelinating disorder. His status continued to decline and 9 weeks from symptom onset, treatment was initiated with IV cyclophosphamide at 500 mg/m² for 3 days and the fourth course of IV methylprednisolone. Nadir WBC count was $0.2 \times 10^3/\mu\text{l}$ 1 week after cyclophosphamide treatment and brain MRI showed improvement with minimal gadolinium enhancement 4 weeks later.

Three months from symptom onset, and 3 weeks after cyclophosphamide, his mentation, motor strength, and speech began improving gradually and he was transferred to inpatient rehabilitation. Brain MRI showed no new or enhancing lesions 7 months from onset and EEG was normal 2 months later.

The patient has continued improving and his last evaluation 2 years after the beginning of his symptoms showed normal cognition and speech. All cranial nerves were normal including vision. Weakness in both legs and the right arm has persisted. His sensations and coordination were normal. He manifested a right circumduction gait with stand-by assistance, a cane, and bilateral AFO.

Discussion

We report the case of a young man that developed an acute onset of a central nervous system demyelinating disorder. MRI of brain showed multiple, large ring-enhancing white matter lesions. Infectious or autoimmune causes were excluded. CSF IgG index was normal, but it showed three oligoclonal IgG bands and increased MBP. The presence of oligoclonal bands in the CSF would favor a diagnosis of multiple sclerosis (MS), but his lesions were very atypical, disseminated and more suggestive of ADEM, and unlike tumefactive MS, which is often a solitary lesion with edema and mass effect. His condition was refractory to standard treatments and he required several courses of IV steroids for clinical stabilization but there was no clear improvement. He developed NMS, a rare condition not previously reported in association with demyelinating disorders without the use of neuroleptic or dopamine-modulating drugs. After treatment with IV cyclophosphamide, his clinical condition started improving progressively. Follow-up for 2 years did not reveal the development of new or enlarged brain demyelinating lesions. His disease course appears monophasic and suggestive of ADEM and very unlikely for tumefactive MS. In this patient, acute demyelination with severe bilateral inflammation of the basal ganglia and particularly caudate and putamen could have caused a state of central dopamine depletion, creating conditions conducive to the occurrence of NMS (fig. 2).

Supporting evidence has shown that IV steroid therapy is beneficial to reduce the disease duration and improve the clinical symptoms of NMS in Parkinson's disease patients, suggesting that dopaminergic activity may be increased by glucocorticoids [5]. Additional benefits of steroid therapy may also help reduce inflammation in ADEM, and decrease the release of pro-inflammatory cytokines, also implicated in the development of NMS [4].

Conclusion

NMS is an uncommon but severe disorder that could occur in association with demyelinating disorders like ADEM without the use of dopamine-modulating drugs. Early diagnosis and proper treatment are essential for improved clinical outcome. Combination therapy with IV cyclophosphamide and methylprednisolone could be an effective treatment alternative for refractory cases of central nervous system demyelinating disorders.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

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Fig. 1. Brain MRI with and without contrast performed on arrival to our hospital. **A** Axial FLAIR images show multiple, extensive and bilateral areas of abnormal signal intensity in the white matter. **B** Axial T₁ post-gadolinium images show numerous large, confluent, and patchy ring-enhancing lesions.

Delgado et al.: Neuroleptic Malignant Syndrome Associated with Refractory Acute Disseminated Encephalomyelitis

Fig. 2. Brain MRI with and without contrast obtained on arrival to our hospital. **A** Coronal FLAIR images show large, confluent lesions involving basal ganglia bilaterally (caudate and putamen). **B** Coronal T1 post-gadolinium images show areas of patchy and ring-like enhancement consistent with active demyelinating lesions.