

Early intravenous immunoglobulin (IVIG) may be effective in severe brainstem-spinal encephalomyelopathy refractory to steroid suggestive of neuromyelitis optica spectrum disorders

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Abstract

We present five cases of severe brainstem-spinal encephalomyelopathy suggestive of neuromyelitis optica (NMO) spectrum disorders treated with or without intravenous immunoglobulin (IVIG). The result shows that early IVIG is probably effective in preserving neurological function in cases with severe brainstem-spinal encephalomyelopathy suggestive of NMO spectrum disorders.

INTRODUCTION

The efficacy of intravenous immunoglobulin (IVIG) in treatment of neuromyelitis optica (NMO) and its spectrum has not been well established by randomized controlled trials. However, only few reports investigated the effect of IVIG in the treatment of multiple sclerosis (MS) and related disorders.¹ We present here five cases of severe brainstem-spinal encephalomyelopathy suggestive of NMO spectrum disorders treated with or without IVIG. The results show that early IVIG intervention may be effective in preserving neurological function in cases with severe brainstem-spinal encephalomyelopathy suggestive of NMO spectrum disorders.

CASE REPORTS

From 2009 to 2010 five patients with brainstem-spinal encephalomyelopathy were admitted to the Neurology ward of Taipei Veterans General Hospital. All patients had radiological evidences of either brainstem or long cervical cord involvement (greater than three vertebral segments) with abnormal high T2 signal intensity lesions on MRI, their clinical data and treatments were retrospectively analyzed (Figure 1).

All the patients were excluded for autoimmune diseases, i.e., systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, and antiphospholipid syndrome, by evaluation of autoantibodies SSA, SSB, SCL-70, antiphospholipid Ab-IgG, cardiolipin-IgG, aTG,

aTPO, ANA, ANA, DS-DNA, ENA, C-ANCA, P-ANCA, JO-1

The CSF analysis, serum aquaporin-4 (AQP-4) autoantibody survey, global functional assessment of neurological condition, and the Expanded Disability Status Scale (EDSS) were done for all the patients. VDRL, virus IgG/M antibody titer for CMV, HSV, VZV, HIV were negative in all the patients. (Table 1)

Three cases (Patient 1 to 3, Group A) received IVIG (0.4gm/kg/day for five days) as rescue therapy, and the other two (Patient 4 and 5, Group B) did not. In Group A, all patients received intravenous pulse methylprednisolone (1000mg qd for five days) between 1 day to 8 days after the onset of clinical symptoms and signs. Since the high dose steroid did not result in clinical improvement, IVIG was initiated at 5 days, 15 days, and 30 days respectively after the onset of illness. Two patients developed respiratory failure and received intubation with mechanical ventilation before or during IVIG administration. After the IVIG treatment, there was no worsening of the paralysis. The respiratory insufficiency also gradually resolved with successful extubation. One patient received plasmapheresis between corticosteroid and IVIG administration and also had improvement in muscle power.

As for the patients in Group B who received only intravenous methylprednisolone pulse therapy and plasmapheresis during acute attack, no or partial improvement in muscle power was observed. Both patients finally progressed to

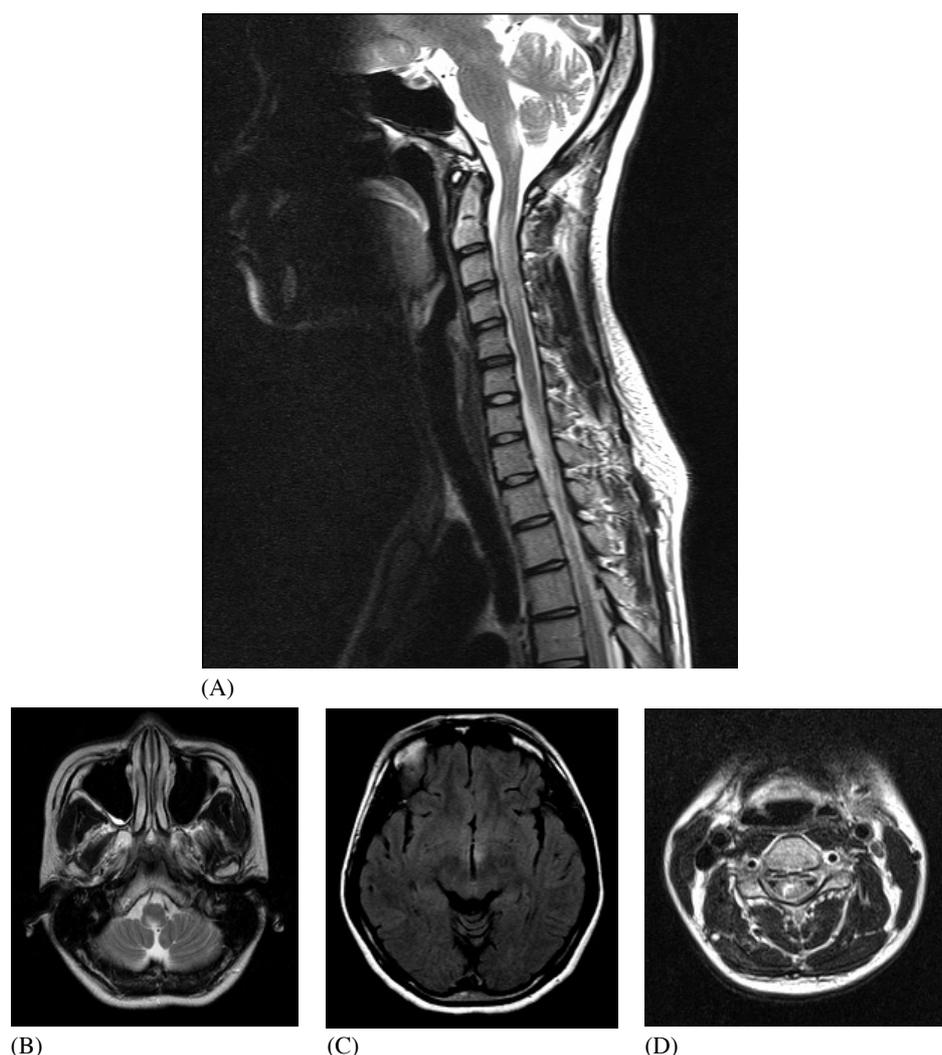


Figure 1. MRI of Patient 1, (A) T2WI showing hyperintense lesions longer than 3 vertebral segments in medulla and high cervical spine; (B) Axial view of T2WI in medulla, (C) FLAIR image in hypothalamus, (D) T2WI in cervical spine, showing central lesions.

tetraplegia, difficulty weaning with continuous ventilation support, failure of Foley catheter removal, constipation, pneumonia, or complex partial seizure.

DISCUSSION

Brainstem-spinal encephalomyelopathy which is usually identified by T2 hyperintense lesions on cranial and spinal MRI could be attributed to central nervous system (CNS) infection, multiple sclerosis, autoimmune diseases, malignancy, acute disseminated encephalomyelitis (ADEM), and NMO spectrum disorders. We do not believe that our patients had ADEM. ADEM seldom spare supratentorial territory. Typically, ADEM shows large, symmetric subcortical brain lesions. These typical findings were not observed in our

patients. Non-specific and variable spinal cord lesions have been found in ADEM. However, three of our patients presented with typical NMO spectrum disorder spinal cord finding which were longitudinal involvement of more than 3 vertebral segments (Patient 1, 4, and 5), instead of the usual ADEM spinal cord lesions.²⁻⁴

We believe that our patients have NMO spectrum disorder, as we have excluded other possible causes. Three of our patients also had longitudinally extensive lesions (Patient 1, 4, and 5), and two others were atypical for MS (Patient 2 and 3), with severe disease refractory to steroid. Although AQP4 autoantibody were all negative in our patients, we do not think it is against our diagnosis as the seropositivity of AQP4 is only seen in 40%-70% of NMO patients.⁵⁻⁶

Table 1: Details of patients data

	<i>Patient 1 (25/ F)</i>	<i>Patient 2 (39/ M)</i>	<i>Patient 3 (55/ M)</i>	<i>Patient 4 (61/ F)</i>	<i>Patient 5 (40/ F)</i>
CSF	WBC/RBC/Prot/Glu 35 (Lymph 95%) /0/56.8/52 IgG index : 0.807	WBC/RBC/Prot/Glu 2/180/47.8/140 IgG index : 0.95	WBC/RBC/Prot/Glu 2/180/47.8/140 IgG index : 0.95	WBC/RBC/Prot/Glu 2/54/60.7/43 IgG index : 0.58	*WBC/RBC/Prot/Glu 5/7/68.5/82 *IgG index : 0.76
MRI of brain (High SI T2WI)	Left dorsal medulla Left hypothalamus	Left medulla enhancement (+), peripheral, incomplete)	Left medulla enhancement (+), peripheral, incomplete)	Normal brain MRI	Bil. pons and medulla (left predominant)
MRI of spine (High SI T2WI)	Long segmental swelling lesions at C1-C5 & T4-L1 ; Enhancement (+)	High cervical lesions extended from medulla C1-2 Enhancement (+)	High cervical lesions extended from medulla C1-3 Enhancement (+)	Long segmental swelling lesions at C spinal cord, C1-5 Enhancement (-),	High cervical lesions extended from medulla C1-2 Enhancement (+)
R.F.	+	+	+	+	+
Steroid	+	+	+	+	+
P. P.	-	-	+	+	+
IVIG	+	+	+	-	-
AQP-4 Ab	-	-	-	-	-
EDSS At Disease onset	8	8.5	7.5	7.5	8.5
EDSS 6 months later	2.5	4.5	3.0	8.0	8.5
Result	Paraparesis, recovering	Paraparesis, recovering	Paraparesis, recovering	Tetraplegia	Tetraplegia MV- dependent

R.F.=respiratory failure, P.P.=plasmapheresis, MV=mechanical ventilation

* The patient and her CSF analysis data was transferred from another medical center.

In NMO and its spectrum disorders, cases with medullary centers of neuromuscular respiration control involvement are at very high risk of neurogenic respiratory failure.⁷ Since death may occur, initiation of therapy with high dose methylprednisolone (1 g for 3-5 consecutive days) and early initiation of plasmapheresis in steroid-unresponsive patients are commonly practiced. It should be noted however, that there have been no controlled therapeutic trials to evaluate the effectiveness of steroid in NMO.⁸

Our patients suggest that IVIG may have a beneficial role in severe brainstem-spinal encephalomyelopathy refractory to steroid, in patients suggestive of neuromyelitis optica spectrum disorders. However, a prospective and

randomized controlled trials is necessary to prove the efficacy of IVIG. Until now, IVIG is only used as monthly infusion to prevent relapses and promote neurological recovery documented in case reports.⁹ It is seldom been used in patients who are refractory to corticosteroid and plasmapheresis in NMO spectrum disorders.¹⁰ It may be relevant to note here that IVIG has also been reported to be beneficial in severe steroid-resistant post-infectious encephalomyelitis, especially on motor dysfunction.¹¹

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