Clinical Neurology and Neurosurgery 114 (2012) 402–404

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case report

Anti-*N*-methyl D-aspartate-type glutamate receptor antibody-positive limbic encephalitis in a patient with multiple sclerosis

Akiyuki Uzawa[a,*], Masahiro Mori[a], Yukitoshi Takahashi[b], Yoshitsugu Ogawa[a], Tomoyuki Uchiyama[a], Satoshi Kuwabara[a]

[a] Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan
[b] Department of Research, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

ARTICLE INFO

Article history:
Received 30 June 2011
Received in revised form 26 October 2011
Accepted 29 October 2011
Available online 5 December 2011

Keywords:
Multiple sclerosis
Anti-*N*-methyl D-aspartate (NMDA) receptor antibody
Anti-glutamate receptor antibody
Encephalitis
Psychosis

1. Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system. Although it often coexists with other autoimmune diseases, its association with anti-*N*-methyl D-aspartate receptor (NMDAR) antibody-positive encephalitis, which is characterized by fulminant prominent neuropsychiatric manifestations, seizures, dyskinesias and autonomic instability [1], is rare. In this study, we describe the case of a Japanese female MS patient who developed with anti-NMDA type glutamate receptor (GluR) antibody-positive limbic encephalitis. The simultaneous manifestation of both diseases has never been reported to the best of our knowledge.

2. Case report

A 33-year-old Japanese woman developed left optic neuritis (ON) at the age of 30. She experienced some demyelinating inflammatory episodes, including the development of 2 left optic nerve lesions, 3 different spinal cord lesions and 1 brainstem lesion between the ages of 31 and 33 years. Intravenous high-dose methylprednisolone pulse (IVMP) therapy was effective for treating the acute inflammatory episodes. The patient's relapses, in addition to the observation of clinical lesions on magnetic resonance images (MRI), led to the diagnosis of MS according to 2005 McDonald's criteria.

At age 33, the patient developed fatigue and fever. Three weeks after manifestation of prodromal symptoms, she developed epileptic seizures and lost consciousness following psychobehavioral symptoms; she was then admitted to our hospital for further investigation. Upon admission, she was conscious and responsive, but presented with mild cognitive deficits (verbal and performance IQ of 88 and 78, respectively, as determined by the Wechsler Adult Intelligence Scale-R), manic, persecution complex and over-interfering to others. Neurological examination revealed loss of visual acuity, left abductor muscle weakness, mild left hemiparesis and left hypoesthesia below the C4 and T7 dermatomal areas. Cerebrospinal fluid (CSF) parameters on admission were as follows: cell count, 3 cells/mm^3; protein level, 35 mg/dl; immunoglobulin G index, 0.700; positive for oligoclonal bands and no evidence of any active viral infections. Laboratory findings were unremarkable and negative for antinuclear, anti-SS-A/B, anti-thyroid peroxidase or anti-aquaporin-4 antibodies. Brain MRI demonstrated hyperintensity of the bilateral medial temporal lobes, some periventricular ovoids on FLAIR images and multifocal white matter lesions with gadolinium enhancement (Fig. 1). Spinal cord MRI revealed a solitary C2 lesion. Epileptic discharges were not noted on some times of electroencephalograms. She was diagnosed with limbic encephalitis instead of an MS exacerbation and was treated with IVMP (1 g/day for 3 days) followed by oral prednisolone (30 mg/day). The aetiology of the patient's psychobehavioral symptoms and seizures was further examined, and it was determined that antibodies against the GluRε2 subunit were in her CSF, but not the serum. Systemic computed tomography/MRI/ultrasonography did not detect any tumours. Although she presented with epileptic seizures and required ventilatory support 2 months after admission, her symptoms were ceased not immediately but slowly. She was discharged without neurological deficits, psychobehavioral symptoms or epileptic seizures 6 months later.

* Corresponding author at: Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan. Tel.: +81 43 226 2129; fax: +81 43 226 2160.
E-mail address: a-uzimp1204@graduate.chiba-u.jp (A. Uzawa).

0303-8467/$ – see front matter
doi:10.1016/j.clineuro.2011.10.047

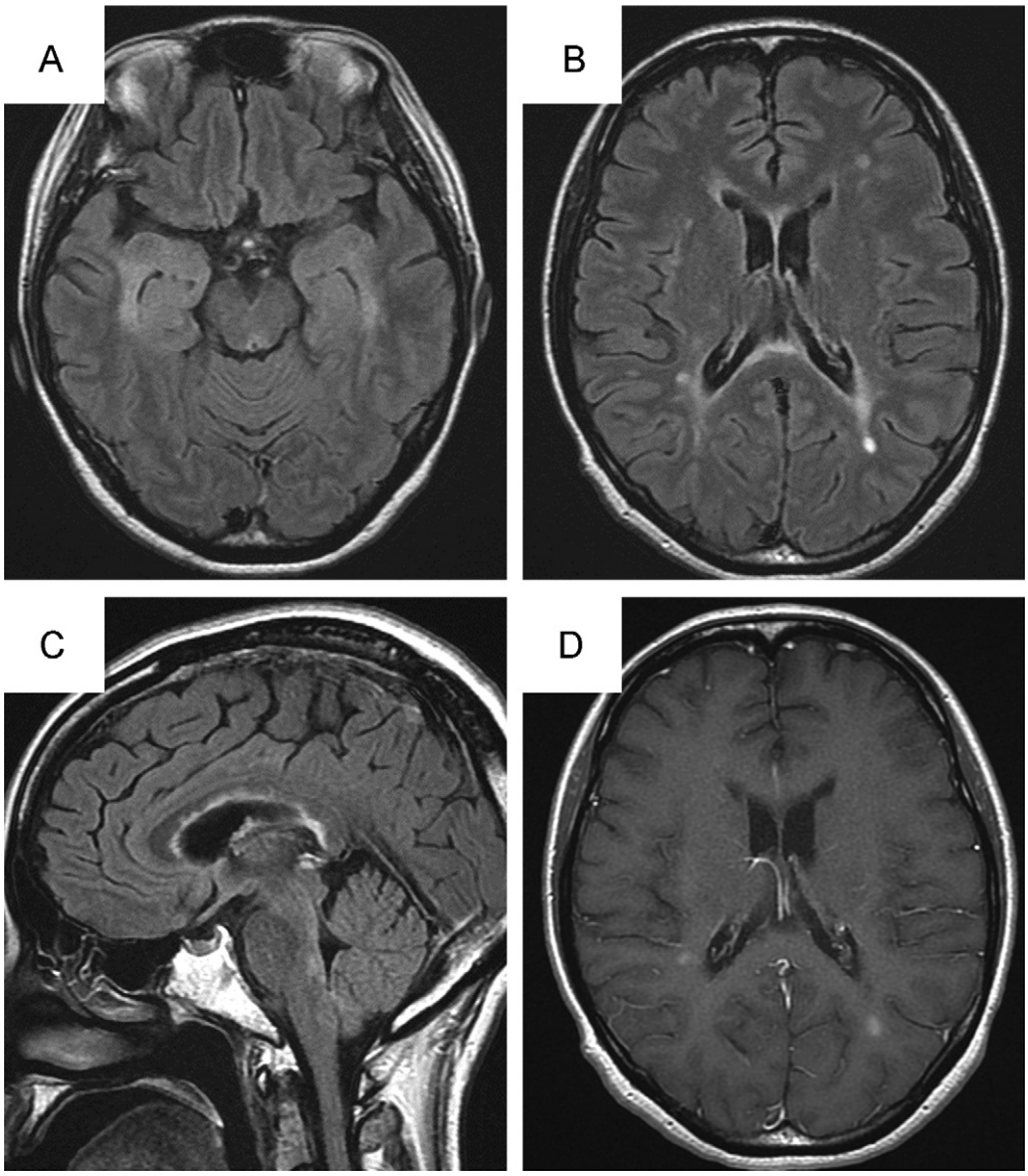

Fig. 1. Brain MRI performed on admission showing a high-intensity lesion on FLAIR images of the bilateral medial temporal lobes (A); some MS plaques (ovoid lesions) are noted around the lateral ventricle (B and C); an image obtained with gadolinium enhancement (D) is also shown.

3. Literature review

The coexistence of ON or neuromyelitis optica (NMO) with anti-NMDAR or anti-GluR antibody positive encephalitis has attracted attention recently. Four previously reported cases [2–5] and the present case are summarized in Table 1. Among these 5 patients, 2 were diagnosed with NMO, 2 with ON and 1 with MS. All 5 patients were female, and this predominance fits the clinical characteristics of their respective diseases. In all cases, anti-NMDAR or anti-GluR antibodies were detected in the CSF. The symptoms of the 3 patients with ON or MS preceded the development of anti-NMDAR encephalitis. Interestingly, no patient developed tumours and showed poor clinical prognoses.

4. Discussion

The early clinical course of this patient was typical of MS and the later course was compatible with anti-NMDAR encephalitis. The patient's fulminant neuropsychiatric manifestations and seizures, including the lesions that were present in the bilateral medial temporal lobes on MRI and positivity for the anti-GluRε2 antibody in the CSF, are atypical of MS, which encouraged the diagnosis of anti-NMDAR encephalitis with overlapping MS. GluRε2 (NR2B) is a subunit of NMDAR that is predominantly expressed in the hippocampus and forebrain and is involved in memory function. The mild cognitive impairment of the present case appears to have been caused by lesions in these areas.

Antibodies against NR1/NR2B heteromers are specific to NMDAR-associated encephalitis, with or without ovarian teratoma, whereas GluRε2 antibodies are also found in some other disorders, such as Rasmussen's encephalitis and progressive epilepsia partialis continua, and may lack syndrome specificity. Hence, the detection of anti-GluRε2 antibodies in the present patient's CSF may be related to her epilepsy or the destruction of her central nervous system. However, an activated autoimmune system in such patients may be related to the production of anti-NMDA antibodies; previous cases [4,5] and present case have manifested ON or

Table 1
Characteristics of patients with presenting with NMO, ON or MS with anti-NMDA or anti-GluR receptor antibody positive encephalitis.

Authors	Age/sex	Disease	Onset	Anti-NMDAR Ab in CSF	Epilepsy	NMO-IgG/ anti-AQP4 Ab	Spinal lesion	Optic nerve lesion	Tumour	Prognosis
Honda [2]	39 years/F	NMOSD	NA	Anti-GluRε2	Absent	Anti-AQP4 Ab (+)	+ (>3VL)	–	–	Good
Kruer [3]	15 years/F	NMO	NMDA → NMO	Anti-NMDAR	Present	NMO-IgG (–)	+ (>3VL)	+	–	Good
Motoyama [4]	10 years/F	ON	ON → NMDA	Anti-NMDAR	Present	Anti-AQP4 Ab (–)	–	+	NA	Good
Ishikawa [5]	12 years/F	ON	ON → NMDA	Anti-GluRε2	Present	NA	–	+	NA	Good
Our case	34 years/F	MS	MS → NMDA	Anti-GluRε2	Present	Anti-AQP4 Ab (–)	+ (<3VL)	+	–	Good

NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; MS: multiple sclerosis; ON: optic neuritis; NMDAR: *N*-methyl D-aspartate receptor; GluR: glutamate receptor; Ab: antibody; AQP4: aquaporin 4; NA: not available; VL: vertebral segments in length.

MS before the development of anti-NMDAR encephalitis. A previous review reported that 59% of anti-NMDAR encephalitis patients have tumours and 36% of patients without tumours showed severe deficits or died [1]. Most noteworthy were the facts that all reported cases [2–5] and present case who presented with ON, NMO or MS with anti-NMDAR encephalitis did not present with tumours, and that those cases demonstrated good recoveries. Positive outcomes may be possible following the use of intensive immune-modulating therapies.

5. Conclusion

We reported the first case of a patient who developed anti-NMDA glutamate receptor antibody-positive encephalitis with good recovery during the course of MS. There may be a possible linkage between these diseases, and concurrent autoimmune responses may be important for the development of autoimmune encephalitis. Anti-NMDAR encephalitis should be recognized as a rare manifestation that can occur in MS patients who develop psychiatric symptoms and seizures. However, further investigation of patients with related disorders and analysis is needed.

References

[1] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[2] Honda K, Yuasa T. A case of anti-aquaporin-4 and anti-glutamate receptor antibodies positive myelitis presented with modest clinical signs. Magn Reson Med Sci 2008;7:55–8.
[3] Kruer MC, Koch TK, Bourdette DN, Chabas D, Waubant E, Mueller S, et al. NMDA receptor encephalitis mimicking seronegative neuromyelitis optica. Neurology 2010;74:1473–5.
[4] Motoyama R, Shiraishi K, Tanaka K, Kinoshita M, Tanaka M. Anti-NMDA receptor antibody encephalitis with recurrent optic neuritis and epilepsy. Rinsho Shinkeigaku (in Japanese) 2010;50:585–8.
[5] Ishikawa N, Tajima G, Hyodo S, Takahashi Y, Kobayashi M. Detection of autoantibodies against NMDA-type glutamate receptor in a patient with recurrent optic neuritis and transient cerebral lesions. Neuropediatrics 2007;38:257–60.