Bickerstaff brainstem encephalitis in a patient with ankylosing spondylitis on tumour necrosis factor-alpha inhibitor

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TNF-alpha inhibitors effectively reduce disease activity and spinal pain in ankylosing spondylitis (AS) (1). However, demyelination disorders such as autoimmune encephalitis may develop following TNF-alpha inhibitor treatment (2-4). Bickerstaff brainstem encephalitis (BBE) is an autoimmune encephalitis characterised by ophthalmoplegia, ataxia, and altered consciousness (5). BBE in patients being treated with TNF-alpha inhibitors has not been reported. Here, we report a 30-year-old woman who developed BBE while using adalimumab.

She visited our hospital due to general weakness and dizziness. She had been diagnosed with AS and was being treated with adalimumab for the past two years. She had no antecedent infections and her AS was well controlled (Ankylosing Spondylitis Disease Activity Score=1.6). Results of physical and neurological examinations were unremarkable except for a non-whirling type of dizziness. Results of laboratory tests and cultures of blood, sputum, and urine for detection of viral and bacterial pathogens including CMV, HSV, EBV, VZV, and Japanese-B encephalitis virus antibody were all negative. CT scans of the chest and abdomen were confirmed negative for infections or neoplasms. The cerebrospinal fluid test showed no evidence of meningitis (leukocytes: 0 cells/mm^3; erythrocytes: 1 cell/mm^3; glucose concentration: 58 mg/dL; and protein levels: 21.3 mg/dL). Brain magnetic resonance imaging and angiography also found no evidence of meningitis or encephalitis (Fig. 1A-B).

On the fourth day of admission, the patient developed limb ataxia, spasticity, acute ophthalmoplegia, hyperreflexia, and disturbed consciousness (drowsiness). Results of a nerve conduction study, electromyogram, and assessment of evoked potentials were normal. We suspected autoimmune encephalitis; therefore, we measured levels of GM1, Hu, Ri, Yo, NMO, NMDAR, AMPA1, LGI1, CASPR2, GABAB, Ma2, CV2/CRMP5, SXO1 and GQ1b antibodies and initiated treatment with an anti-viral agent, methylprednisolone, and intravenous gamma globulin (IVIg). After the sixth day, the patient was still experiencing ophthalmoplegia, spasticity, and altered mentation. Treatment was continued with glucocorticoid and rituximab. After treatment, her mental status and ophthalmoplegia improved. An immunologic test conducted a few days later was positive for anti-GQ1b antibodies at 1:200 and negative for other antibodies. Finally, she was diagnosed with BBE based on the symptoms (ophthalmoplegia, ataxia, and impaired consciousness) and the antibody test.

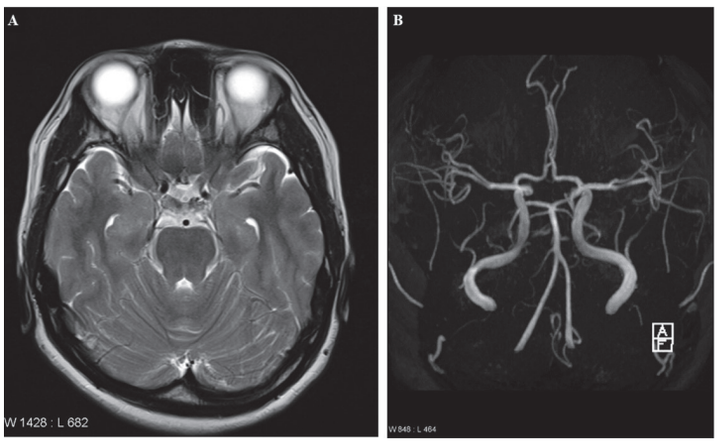

Fig 1. The brain magnetic resonance imaging (**A**) and angiography (**B**) showed that there was no abnormality which causing decreased mentation such as meningitis or encephalitis

Guillain-Barré syndrome (GBS), Miller Fisher syndrome (MFS), and BBE represent a continuous spectrum of demyelinating disorders, however, there are several manifestations and serologic finding that allow clinicians to distinguish BBE from GBS and MFS. GBS is characterised by flaccid paralysis without ophthalmoplegia or altered mentation. MFS and BBE present with ataxia, ophthalmoplegia, and humoral factors, including the presence of anti-GQ1b antibodies. However, drowsiness is only present in BBE (5, 6). Our patient had progressive ataxia and ophthalmoplegia; therefore, we could rule out GBS. In addition, she developed drowsiness, a semeiotic feature of BBE, and was positive for anti-GQ1b antibodies. Therefore, we diagnosed her with BBE.

Plasma exchange, IVIG, or glucocorticoids may be effective treatment options for BBE (6). Since the GQ1b antibody binds to presynaptic motor nerve endings causing complement activation and membrane attack complex formation (7), rituximab might be effective for BBE by blocking antibodies and complement-dependent immune responses (8).

Although the role of anti-TNF alpha inhibitors in the development of demyelinating disorders remains unclear, a lack of TNF alpha may augment or prolong the myelin-specific T cell response and increase the risk of developing or prolonging an immune-mediated neuropathy (2-4). Therefore, we believe that BBE in our patient may be related to TNF-alpha inhibitors through augmentation of the number of activated peripheral T cells or disturbance in the intrinsic balance between TNF-alpha and its receptors, even though a causal relationship between BBE and TNF-alpha inhibitors is difficult to prove.

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