Neuromyelitis optica spectrum disorder in a patient with spinocerebellar ataxia type 6

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Abstract

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant, late-onset, slowly progressive cerebellar ataxia due to a pathological CAG repeat expansion in CACNA1A. Inflammation may be involved in the pathogenesis and progression of the trinucleotide repeat expansion disorder. We report a rare case of a 59-year-old woman with SCA6 who developed neuromyelitis optica spectrum disorder (NMOSD). In our case, this combination is coincidental but suggests that an inflammatory response to an unstable CAG repeat may contribute to NMOSD pathogenesis.

Keywords: Spinocerebellar ataxia type 6, neuromyelitis optica spectrum disorder

INTRODUCTION

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant cerebellar ataxia caused by a small CAG repeat expansion in the coding region of the α1A subunit of the voltage dependent calcium gene (CACNA1A). Neuromyelitis optica spectrum disorder (NMOSD) is an idiopathic, autoimmune, inflammatory syndrome predominantly affecting the spinal cord and optic nerve. We report a rare case of a patient who developed NMOSD three years after symptom onset of SCA6.

CASE REPORT

A 59-year-old woman who was diagnosed three years ago with a transient ischemic attack admitted to another hospital with tingling sensation in the right hand, occipital neuralgic pain, and voiding difficulty. Brain and spinal magnetic resonance imaging showed lesion in the dorsal medulla and longitudinal extensive signal abnormalities from C1 to C6 (Figure 1a and 1b). Autoimmune antibody screening tests for angiotensin-converting enzyme, anti-nuclear antibody, double-stranded DNA, anti-Ro, anti-La, and anti-neutrophil cytoplasmic antibody were negative, but cell-based indirect immunofluorescence assay for aquaporin-4 antibody (AQP4-Ab) in the serum was positive. She was diagnosed with NMOSD and received intravenous high dose steroid and oral prednisolone, and the neuralgic pain and voiding difficulty improved. Two months after onset of symptoms, she was admitted to our hospital with dysarthria and painful tonic spasm in the right upper limb. The tonic spasm was restricted to the right upper limb, lasted for 2-3 minutes, and occurred several times a day. Neurological examination showed bilateral gaze-evoked horizontal nystagmus and mild weakness of grasp in the right hand (Medical research council grade IV). A follow-up MRI showed diffuse cerebellar atrophy and improvement of lesions in the brainstem and cervical spinal cord (Figure 1c). Her transient dysarthria and gait disturbance recurred, although the tonic spasms improved with topiramate. Genetic analysis revealed 21 CAG repeats in the CACNA1A gene, and she was diagnosed with SCA6 combined with NMOSD.

DISCUSSION

After the discovery of AQP4-Ab in the serum of neuromyelitis optica (NMO) patients, NMOSD was proposed for a broad clinical spectrum of AQP4-Ab-mediated diseases. Our patient showed lesion in the dorsal medullar area and longitudinal extensive transverse myelitis, which are specific for NMO. Although the patient did not have optic nerve disturbance, as AQP4-Ab was positive, the patient could be diagnosed with NMOSD according to the international consensus diagnostic criteria. SCA6 is hereditary neurodegenerative disease characterized by late onset, slowly progressive,
mostly pure cerebellar ataxia, sometimes preceded by an episodic dysarthria and vertigo\(^1\), resulting in our patient to be incorrectly diagnosed with transient ischemic attack at a local hospital. SCA6 is associated with short expansions of a polyglutamine stretch located in the cytoplasmic C-terminal tail of the protein.\(^3\) The other two mutation disorders of CACNA1A, episodic ataxia type 2 and familial hemiplegic migraine type 1, have clear molecular mechanisms, such as loss or gain of channel function.\(^4\,\,^5\) SCA6 has a more complex pathogenesis of the disease in addition to a simple dysfunction of channel due to affected pore, type and location of mutation.\(^6\) The common feature of most trinucleotide repeat expansion disorders is the loss of neurons in specific brain regions accompanied by reactive gliosis and astrocytosis, which may suggest involvement of inflammation in pathogenesis.\(^7\) Studies about the role of the immune response in the pathogenesis of polyglutamine diseases is incomplete and predominantly limited to spinocerebellar ataxia type 3.\(^8\) The previous report of SCA3 combined with multiple sclerosis suggested that neuronal injury by unstable CAG repeats trigger gene transcription of inflammatory mediator and stimulates microglia and astrocyte to antigen-presenting capacity and immune responsiveness.\(^9\) SCA31, which is an adult-onset autosomal dominant disorder caused by complex pentanucleotide repeats, was reported with NMOSD.\(^10\) Although this combination was considered to be a coincidence because there was no report on upregulated inflammation on SCA31, this report suggested that inflammatory process could be involved in the pathogenesis of NMOSD.

To our knowledge, the development of NMOSD in a patient with SCA6 has not been previously reported. The immune response in SCA6, activated by unstable CAG repeats, may be involved in the pathogenesis of NMOSD, although the role of the polyglutamine tract in immune response activation is still unclear.

**DISCLOSURE**

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**REFERENCES**


