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Letter to the Editor

Recurrent rhombencephalomyelitis associated with allergen immunotherapy by mite antigen sublingual tablets

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Dear Editor,

Rhombencephalomyelitis is a rare disorder involving the spinal cord, medulla oblongata, pons and cerebellum. Monophasic rhombencephalomyelitis is associated with infections, such as varicella zoster virus [1], enterovirus 71 [2], and cytomegalovirus [3], while recurrent rhombencephalomyelitis may be associated with neuromyelitis optica spectrum disorders (NMOSD) [4]. Here, we report a case with recurrent rhombencephalomyelitis associated with allergen immunotherapy by mite antigen sublingual tablets for allergic rhinitis.

1. Case report

A 19-year-old man who had atopic dermatitis since the age of 2 and allergic rhinitis since the age of 8, developed right lower limb numbness and weakness 3 weeks after initiation of mite antigen sublingual tablets for allergen immunotherapy against allergic rhinitis. These symptoms extended to the left lower limb over the following two months, even though sublingual tablets were discontinued. On admission to our hospital, neurological examination revealed right side-dominant spastic paraparesis with hyper-reflexia and an extensor plantar response, all sensory impairment below the Th12 segment, dysuria and constipation. No mucosal ulcers or skin lesions were found and needle reaction was negative. Magnetic resonance imaging (MRI) showed T2-hyperintense lesions with some gadolinium enhancement disseminated in the midbrain, pons, cerebellar peduncles, and spinal cord but not in the supratentorial region (Fig. 1A–H). Cerebrospinal fluid (CSF) examination revealed an increased total protein level (52 mg/dL) and cell counts (33/mm^3, 76.5% mononuclear cells and 23.5% polymorphonuclear cells). Serum anti-aquaporin-4 (AQP4; ELISA and cell-based assay), anti-myelin oligodendrocyte glycoprotein (MOG; cell-based assay), anti-nuclear antigen, anti-SS-A/SS-B, myeloperoxidase- and proteinase 3-anti-neutorphil cytoplasmic antibodies, other systemic autoantibodies, and anti-human T lymphotropic virus type 1 antibodies were all negative. Angiotensin-converting enzyme (ACE; 8.9 IU/L), and soluble interleukin 2 receptor (IL2R; 282 U/mL) levels were normal. IgE was elevated to 1018 IU/mL and specific IgE against *Dermatophagoides pteronyssinus* and *D. farinae* were both class 5-positive. His human leukocyte antigen (HLA) genotype was *HLA-A*24/31*, *-B*07/15*, *-DRB1*01:01/04:06*, *-DPB1*05:01/04:02:01*. Whole body CT was normal. Three courses of methylprednisolone (mPSL) pulse therapy (1000 mg/day for 3 consecutive days) followed by oral prednisolone (30 mg/day) with gradual taper alleviated his symptoms and reduced all hyperintense T2-lesion sizes.

Thirteen months later, he noticed left side-dominant lower limb weakness and sensory impairment and dysuria following exacerbation of allergic rhinitis. Neurologically, left side-dominant spastic paraparesis with hyper-reflexia and an extensor plantar response, all sensory impairment below the Th12 segment, and sphincter disturbance were found. On MRI, new T2-hyperintense lesions without gadolinium enhancement appeared in the dorsal pons and cervical spinal cord, whereas no supratentorial lesions were detected (Fig. 1I-L). CSF showed a mild pleocytosis, while oligoclonal IgG bands (OCBs) were negative. Serum and CSF anti-AQP4 antibodies were again negative. Two courses of IVMP followed by oral prednisolone improved his symptoms and reduced MRI lesions.

2. Discussion

The present case demonstrated recurrent myelitis with disseminated cervical and upper thoracic cord MRI lesions. Although he showed no obvious brainstem and cerebellar signs, MRI revealed multiple lesions affecting the medulla oblongata, pons and cerebellar peduncles at the onset and at relapse, in the absence of supratentorial lesions. Therefore, we diagnosed him as having recurrent rhombencephalomyelitis. As for the cause of rhombencephalomyelitis, absence of supratentorial lesions at the onset and relapse, as well as negative OCBs, indicate a diagnosis of multiple sclerosis (MS) less likely, although careful long-term follow-up is required to completely rule out MS. Absence of anti-AQP4 and anti-MOG antibodies exclude NMOSD with AQP4 IgG and MOG antibody disease. Close examination of the spinal cord lesions of the present case disclosed these lesions to be a conglomeration of short spinal cord lesions that occupied less than half of the spinal cord cross-sectional area. Together with the absence of characteristic brain MRI lesions, it suggests NMOSD without AQP4 IgG to be less likely [5]. Furthermore, absence of systemic symptoms and general autoantibodies, normal ACE

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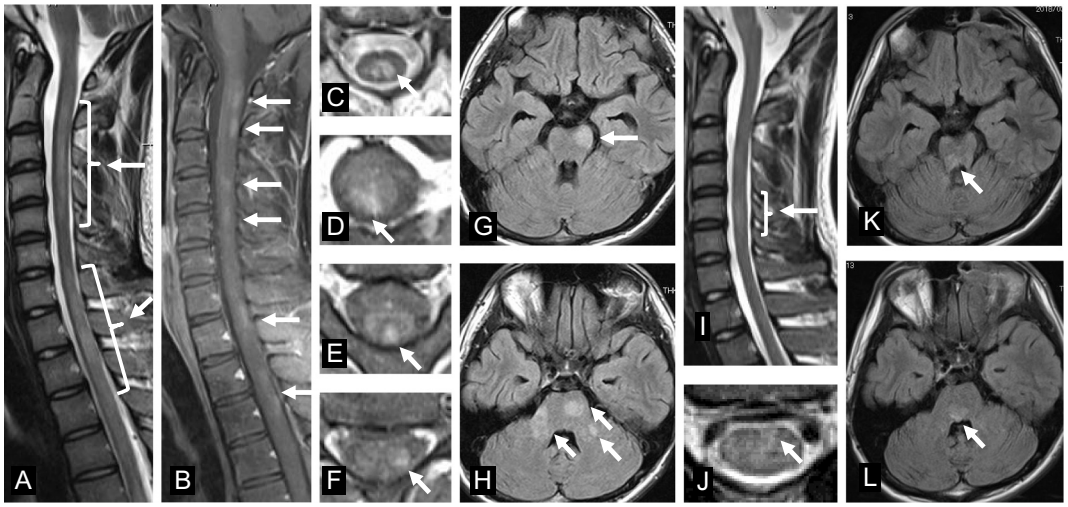

Fig. 1. Brain and spinal cord magnetic resonance imaging.
(A) T2-weighted images on admission (sagittal: 1.5 T, TR 1760 ms, TE 106 ms, FA 180°). (B) T1-weighted images with gadolinium enhancement on admission (sagittal: 1.5 T, TR 745 ms, TE 12 ms, FA 180°). (C) T2-weighted images on admission (axial at C3 spinal level: 1.5 T, TR 2000 ms, TE 113 ms, FA 170°). (D) T1-weighted images with gadolinium enhancement on admission (axial at C5 spinal level: 1.5 T, TR 644 ms, TE 11 ms, FA 170°). (E) T1-weighted images with gadolinium enhancement on admission (axial at C7 spinal level: 1.5 T, TR 644 ms, TE 11 ms, FA 170°). (F) T1-weighted images with gadolinium enhancement on admission (axial at Th4 spinal level: 1.5 T, TR 644 ms, TE 11 ms, FA 170°). (G, H) Fluid attenuation inversion recovery images on admission (head: 1.5 T, TR 8000 ms, TE 95 ms, FA 170°). (I) T2-weighted images at 13 months after onset (sagittal: 1.5 T, TR 1760 ms, TE 105 ms, FA 180°). (J) T2-weighted images 13 months after onset (axial at C5 spinal level: 1.5 T, TR 2000 ms, TE 113 ms, FA 170°). (K, L) Fluid attenuation inversion recovery images at 13 months after onset (head: 1.5 T, TR 8000 ms, TE 102 ms, FA 170°). Lesions are indicated by arrows. At onset, the lesions were in the midbrain, pons, cerebellar peduncle, and spinal cord. In transverse imaging, the lesions were located in the central intermediate substance, lateral funiculus, and posterior funiculus, and parts of some lesions exhibited gadolinium enhancement (A–H). At the time of recurrence, there were new lesions in the dorsal pons and C5 spinal cord (I–L).

and IL2R levels, and normal body CT excluded collagen-vascular diseases.

Therefore, we finally considered the possibility that his rhombencephalomyelitis was associated with atopic/allergic diseases and the allergen immunotherapy by mite antigen sublingual tablets. Coexistence of atopic dermatitis and allergic rhinitis, hyper-IgEaemia, and mite antigen-specific IgE in the absence of MS-like supratentorial lesions and OCBs suggest atopic myelitis, predominantly found in Japanese and Koreans [6,7], based on the proposed criteria [8]. Because atopic myelitis occurs and recurs preferentially in association with exacerbation of atopic/allergic diseases [6], the relapse of the present case may have been triggered by exacerbation of pre-existing atopic/allergic diseases. However, occurrence of multiple brainstem and cerebellar peduncle lesions and extensive spinal cord lesions without predilection to the posterior column seems to preclude the possibility of typical atopic myelitis. The beneficial effects of allergen immunotherapy by sublingual tablets are mediated by induced IgG4 that blocks IgE and induces regulatory T cells, which emerge a few months after the initiation of the therapy [9]. Mite antigens in the sublingual tablets can initially stimulate allergic inflammation [10]. Therefore, allergen immunotherapy by itself may have triggered rhombencephalomyelitis through allergic stimulation in the present case. As allergen immunotherapy using sublingual tables is becoming popular in clinical practice, neurologists should be aware of the development of rhombencephalomyelitis as a rare complication.

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