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Case Report

Long-standing neuromyelitis optica with leukodystrophy-like asymptomatic MRI changes ☆,☆☆

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ABSTRACT

Patients with neuromyelitis optica (NMO) are unlikely to develop clinically silent lesions on brain magnetic resonance imaging (MRI), unlike patients with multiple sclerosis (MS). We encountered a patient with NMO who showed radiological progression and leukodystrophy-like changes on MRI during a long-standing, clinically asymptomatic period.

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Introduction

Neuromyelitis optica (NMO) is characterized by selective involvement of the optic nerve and spinal cord and is distinguished from multiple sclerosis (MS) by normal brain magnetic resonance imaging (MRI) [1]. After a disease-specific autoantibody was identified and incorporated into the diagnostic criteria, the clinical and radiological spectrum of NMO expanded [1]. Currently, symptomatic cerebral syndrome, diencephalon syndrome, and area postrema syndrome with typical brain lesions are well identified in patients with NMO, in addition to optic nerve and spinal cord lesions [1].

Nevertheless, asymptomatic and progressive brain lesions in clinically stable aquaporin-4(AQP4)-antibody-seropositive patients with NMO are rarely observed, and even in such cases, brain lesions are usually non-specific deep white matter changes [2].

Herein, we report the case of a patient with serologically and clinically typical, but radiologically atypical, NMO with silent extensive white matter hyperintensities (WMH) mimicking leukodystrophy and review previous literature.

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Case presentation

A 61-year-old woman who had a history of recurrent optic neuritis and myelitis attacks was diagnosed with NMOSD by confirming the presence of serum AQP-4-IgG antibody. She had 3 episodes of myelitis at the ages of 41, 44, and 47 years, respectively, without sequelae. She had fourth episode of bilateral optic neuritis (ON) at the age of 49 years, with good visual recovery. And she had fifth episode of longitudinally extensive transverse myelitis (LETM) (Fig. 1), with the presence of serum AQP-4-IgG (fixed cell-based assay, Euroimmun, Lübeck, Germany) at the age of 61 years. She had never had symptoms consistent with cerebral syndrome such as hemiparesis or encephalopathy. Furthermore, she remained stable and free of relapse for 12 years which was between bilateral optic neuritis (fourth attack) and LETM (fifth attack), even though she had not received any disease modifying treatment such as low dose steroid, azathioprine, mycophenolate mofetil, or rituximab.

However, brain magnetic resonance imaging (MRI) scans obtained on fourth ON attack and fifth LETM attack showed striking alterations, including extensive symmetric T2-weighted hyperintensities involving the subcortical and deep white matter, external capsules, deep gray matter, anterior temporal lobe, and pons, without contrast enhancement irrespective of her clinical stability (Fig. 2). On the fifth acute demyelinating attack, she was treated with intravenous methylprednisolone (1 g per day, 5 consecutive days) followed by oral prednisolone and started on azathioprine. She recovered fully ambulatory, except for mild limb paresthesia. Subsequent spinal cord MRI after treatment showed decreased extent of the T2-hyperintensity with enhancement. However, she experienced a sixth episode of LETM (Fig. 3) involving the C1–5 and T3–5 vertebral levels at 63 years of age. Follow-up brain MRI revealed more progressed white matter changes on T2-weighed image compared to the MRI obtained 2 years ago (Fig. 4) and several new microbleeds on T2*-weighted images (Fig. 5). These MRI features mimicked leukodystrophy including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The authors could not conduct genetic mutation test which is associated with CADASIL (*NOTCH3*) nor other inherited disease. However, she never presented clinical manifestation suggesting CADASIL nor had risk factors eliciting such white matter changes: the patient was a nonsmoker and nondrinker with no history of migraine, seizure, stroke, diabetes mellitus, or hypertension; the patient had no family history of inherited diseases, stroke, or dementia; the patient exhibited normal cognition and was underweight. After steroid pulse therapy, her neurological symptoms improved, MRI revealed resolution of spinal cord lesions, and no further progression of the neurological deficits was observed. The patient has still visited our hospital regularly and the expanded disability status scale (EDSS) was 1.0 at the last follow-up.

Discussion

Neuromyelitis optica spectrum disorder (NMOSD) is one of inflammatory demyelinating disease of central nervous system. Its pathomechanism is known to be highly relevant with serum autoantibodies (AQP-4-IgG) against the aquaporin-4 water channel which is primarily expressed at the end-feet process of astrocyte throughout the brain and spinal cord [4]. It had been characterized with simultaneous or successive ON and transverse myelitis (TM) and some were relapsing, therefore, it had been regarded as opticospinal form of multiple sclerosis formerly. However, its exceedingly selective and

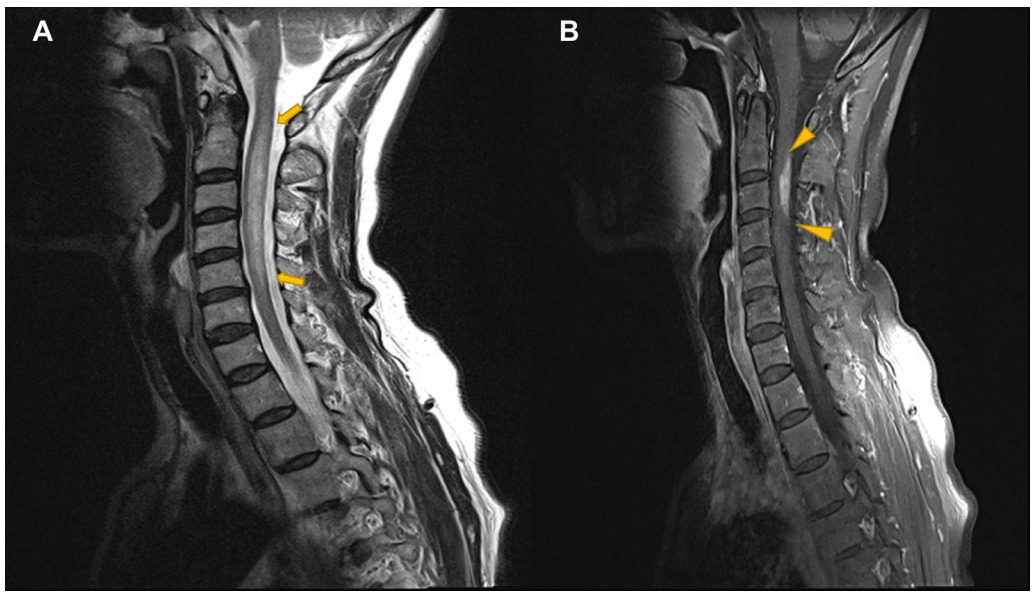

Fig. 1 – Magnetic resonance imaging (MRI) of the cervical and upper thoracic spine of the patient after the fifth attack. The T2-weighted sagittal scan (A) and its corresponding T1 post-contrast scan (B) showed longitudinally extensive transverse myelitis (arrows) with partial gadolinium enhancement (arrowheads) involving C1–C5.

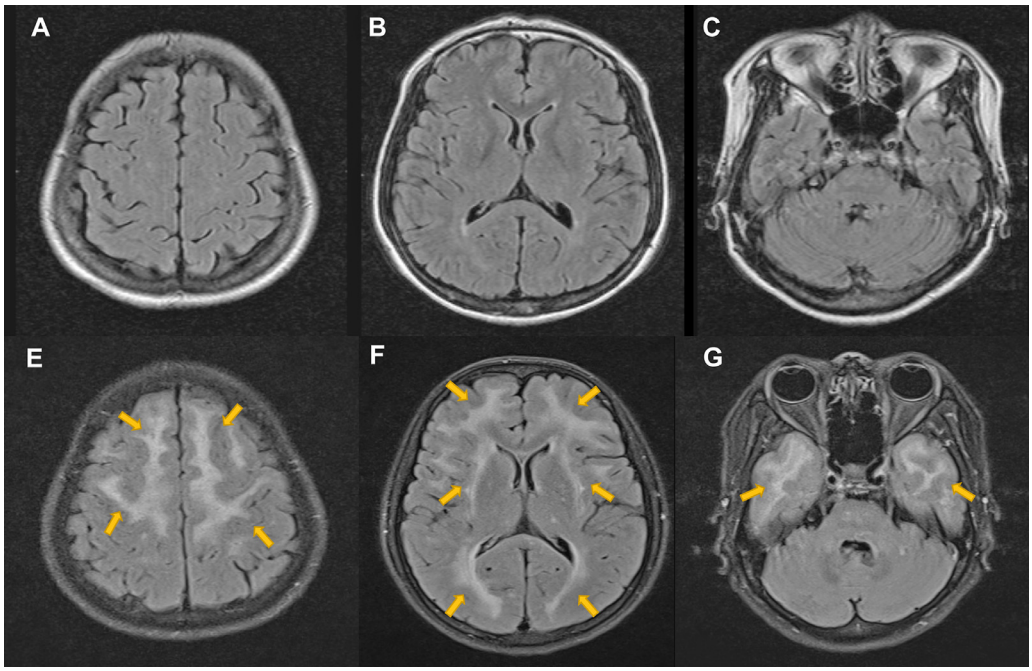

Fig. 2 – Comparison of the brain MRI obtained between the fourth (A–C) and fifth attacks (D–F), with an asymptomatic twelve-year interval, revealed striking white matter hyperintensities involving the subcortical and deep white matter, external capsules, deep gray matter, anterior temporal lobe, and pons (arrows).

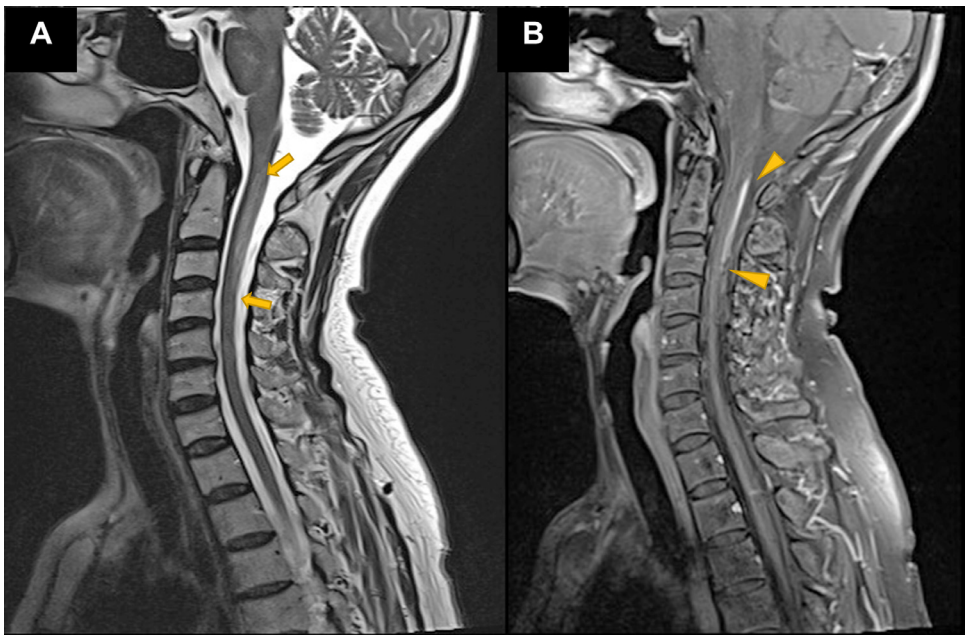

Fig. 3 – MRI of the cervical and upper thoracic spine obtained after the sixth attack, presenting recurrent myelitis. The T2-weighted sagittal scan (A) and its corresponding T1 post-contrast scan (B) showed a different location of T2 hyperintensity (arrows) and partial gadolinium enhancement (arrowheads). Thoracic myelitis involving T3–T5 was concurrent (MRI not shown).

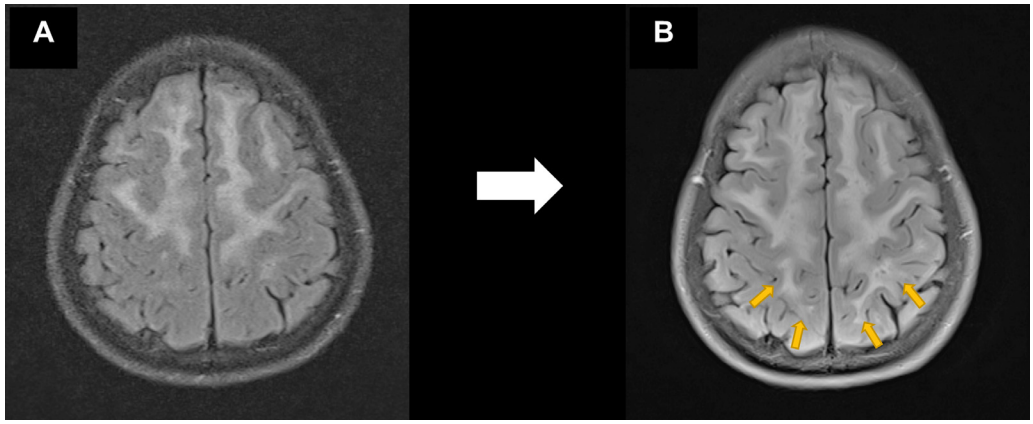

Fig. 4 – Comparison of the brain MRI obtained between the fifth (A) and sixth attacks (B), with a two-year interval, revealed further progressive T2 white matter hyperintensity behind the central sulcus (arrows).

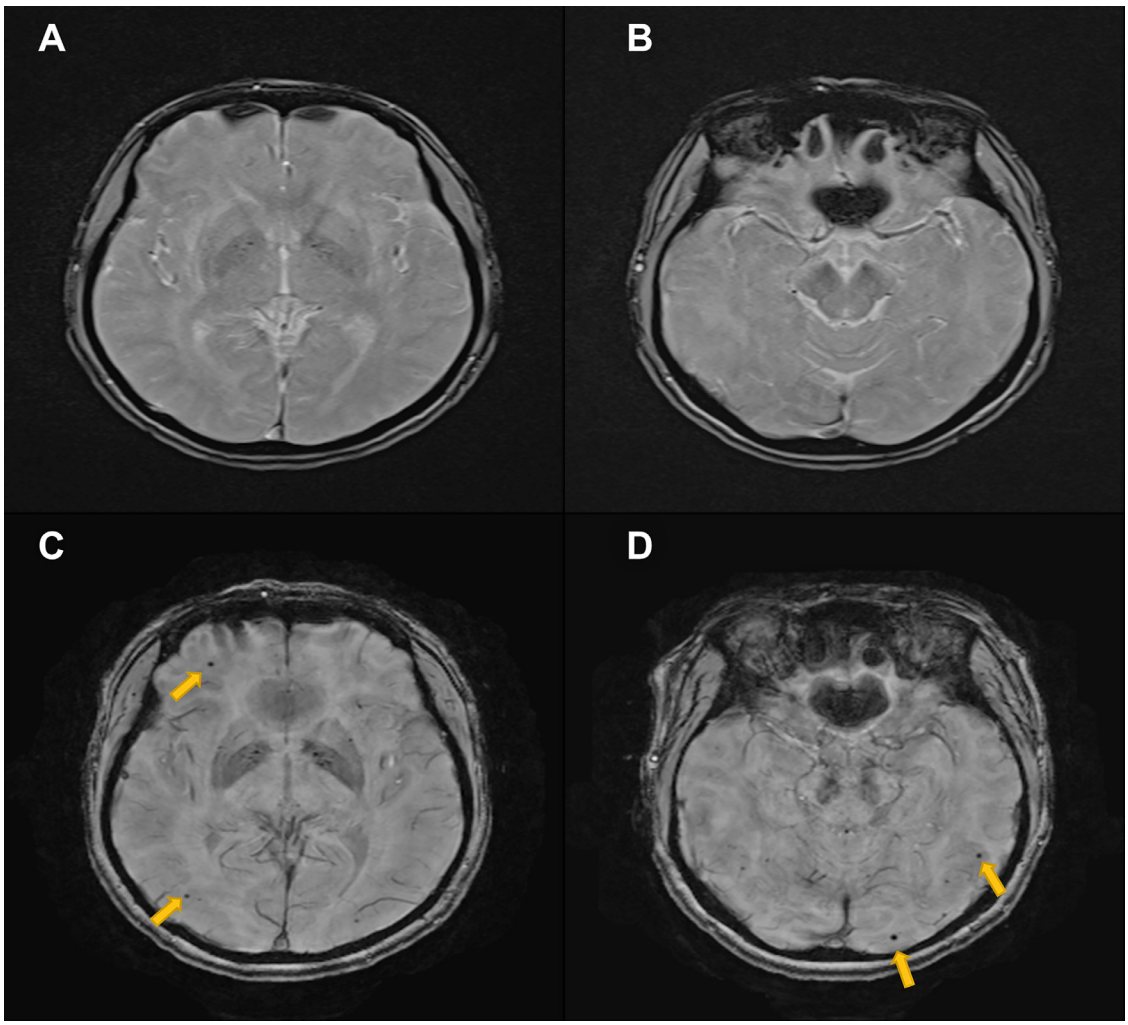

Fig. 5 – Comparison of susceptibility weighted imaging obtained between the fifth (A) and sixth attacks (B), with a two-year interval, revealed several new microbleeds (arrows).

Table 1 – Clinical and radiological presentation of previously reported cases of extensive white matter hyperintensities in patient with clinically silent, long standing neuromyelitis optica spectrum disorders.

Reference	Number of cases	Disease duration	Number of attack prior to the brain MRI alteration	Interval between the baseline and first abnormal brain MRI	Lesion involvement	Gadolinium enhancement	Co-morbidity
[10]	1	20 years	24	15 years	Symmetric, subcortical and deep WM, external capsules, anterior temporal lobe, cerebellum	None	Not identified
[11]	1	26 years	15	9 years	Symmetric, subcortical and deep WM, external capsules, anterior temporal lobe, cerebellum	None	Not identified
[12]	1	9 years	1	9 years	Symmetric, subcortical and deep WM, external capsules, anterior temporal lobe, pons, cerebellum	None	Sjogren's syndrome (positive antibody, Schirmer's test, salivary gland scintigraphy)
[13]	2	Maybe 15 years	Maybe 2	First brain MRI was abnormal, follow-up MRI taken 6 months revealed enlargement of the lesion without clinical attacks	Symmetric, subcortical and deep WM external capsules, anterior temporal lobe,	None	Not identified
		5 years	1	5 years	Symmetric, subcortical and deep WM external capsules, anterior temporal lobe,	None	Presence of anti-SSA, anti-SSB antibody
Present case	1	20 years	4	12 years	Symmetric, subcortical and deep WM, external capsules, anterior temporal lobe	None	Not identified

WM, white matter.

severe involvement of the optic nerve and spinal cord, the term 'neuromyelitis optica(NMO)' was coined in 1894 by Eugene Devic [1]. Since Wingerchuk et al [5] proposed a strict diagnostic criteria for NMO in 1999 and Lennon et al [6] discovered the AQP-4-IgG pathogenicity in patients with NMO in 2004, highly specific clinical manifestation, MRI features, and seropositive of AQP-4-IgG status incorporated into revised diagnostic criteria in 2006 [7]. After revealing of disease-specific autoantibodies, reports of interesting clinical and radiological features in addition to the ON and TM have begun to accumulate in patients with the presence of serum AQP-4-IgG. It includes area postrema syndrome, brainstem syndrome, diencephalon syndrome, and cerebral syndrome which coincides with explainable MRI lesions. These broaden the boundaries of the disease and brought out the newer term "neuromyelitis optica spectrum disorders" and newer diagnostic criteria in 2015 by the International Panel for NMO Diagnosis(IPND) [3]. Our case patient met all requirements of the 2015 IPND criteria.

What's the interesting point in this case patient is that asymptomatic, progressive, severe brain white matter hyperintensities. Extensive and symmetric white matter hyperintensities on brain MRI have a variety of differential diagnoses, i.e., a vasculopathic, toxic-metabolic, infectious (e.g., HIV encephalopathy and progressive multifocal leukoencephalopathy), inflammatory demyelinating, traumatic, and radiogenic etiology, as well as adult-onset leukodystrophy, which is very rare [8]. The age of the patients, the progression of the disease, the clinical and neurological findings, previous illnesses, family history, laboratory findings, and various characteristic lesion patterns on MRI should be considered in the diagnosis of this condition. Particularly, clinical and radiological pattern recognition could aid to narrow the type of leukodystrophy [9]. Specific involvement of the anterior temporal pole and external capsule white matter hyperintensities on T2-weighted sequences and microbleeds, as seen our case, has been described in CADASIL, although the case patient did not manifest symptoms nor signs consistent with CADASIL.

The literature reports several similar cases of NMOSD mimicking CADASIL or leukodystrophy (Table 1) [10–13]. These cases of asymptomatic, inter-attack MRI finding progression shared several features: the patients were all positive for the anti-AQP4-antibody in the serum and had a longer disease duration, of at least 5 years. Moreover, they showed a favorable response to corticosteroids in most relapses, did not require plasma exchange, and did not exhibit aggravation or high scores on the EDSS, despite the presence of significant brain lesions. In addition, compared with severe WMH, brain atrophy seemed to rarely progress in these patients, as assessed by visual inspection of MRI. Although we cannot exclude the possibility of CADASIL because of the lack of genetic testing, the absence of a family history of, and the absence of clinical features related to CADASIL reduce the likelihood of this diagnosis. To date, the concomitant presence of the anti-AQP4 antibody in the serum and of a *NOTCH3* genetic mutation has not been reported.

Extensive WMH can also be observed in patients with progressive multiple sclerosis (PMS) and long-standing MS. In contrast with our case and previous cases, patients with PMS usually show progressive WMH and brain volume loss in longitudinal MRI studies, independent of acute attack and associated with higher disability accumulation [14]. A higher T2 lesion volume at the baseline and lesion accumulation was associated with higher rates of loss of total brain volume, accelerated ventricular enlargement, and worse prognosis [15]. However, our patient and previous cases exhibited clinically stable or asymptomatic state regardless of extensive WMH and the brain volume was preserved.

Unlike MS, patients with NMOSD are considered to exhibit attack-dependent disability, T2 lesion volume, and neurodegeneration. Although some recent studies reported that silent progression of brain atrophy was observed in AQP4-antibody-seropositive NMOSD [16,17], the silent progression of extensive WMH and its clinical significance in patients with long-standing NMOSD have not been reported. The present and previous cases indicated that asymptomatic leukodystrophy-like MRI findings can be present in NMOSD and not related to a poor prognosis, although further investigations are necessary to confirm this conclusion.

Statement of ethics

Ethical approval is not required for this study in accordance with local or national guidelines.

Patient consent

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. No identifying information is included in the manuscript and is otherwise securely held.

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