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Case report

Unusual cortical involvement in aquaporin-4 antibody-positive patients: An analysis with double inversion recovery and phase-sensitive inversion recovery imaging



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ARTICLE INFO	A B S T R A C T
Keywords: Neuromyelitis optica Cortical lesion Double inversion recovery Phase-sensitive inversion recovery	Background: : Previous studies strongly suggested the absence of cortical involvement in neuromyelitis optica spectrum disorder. Methods: : We describe two patients with anti-aquaporin-4 antibody and cortical lesions. Results: : A 58-year-old and a 61-year-old woman presented with status epilepticus and right leg numbness, respectively. Double inversion recovery (DIR) and phase-sensitive inversion recovery (PSIR) imaging, magnetic resonance imaging sequences that enable the clear delineation of gray matter, revealed intracortical lesions and lesions located across the cortex and subcortex. Conclusion: : Although rare, cortical involvement may exist in aquaporin-4 antibody-positive patients. DIR and
	PSIR MRI can help to determine the exact location of the lesion.

1. Introduction

In contrast to multiple sclerosis (MS), where cortical lesions are frequently observed, previous magnetic resonance imaging (MRI) or neuropathologic studies strongly suggested the absence of cortical involvement in neuromyelitis optica spectrum disorder (NMOSD) (Calabrese et al., 2012). In fact, cortical lesions are regarded as an MRI feature that differentiates MS from NMOSD (Kim et al., 2015). While a few studies recently demonstrated cortical and leptomeningeal involvement in patients with NMOSD (Kim et al., 2016; Tahara et al., 2012), the precise location of the lesions was not evaluated by MRI protocols that clearly delineate gray matter.

Here, we report two patients with anti-aquaporin-4 (AQP4) antibody suspected to have cortical lesions on conventional MRI, suggesting the possibility of cortical involvement in such patients.

2. Methods

Brain imaging was acquired on a 3T MR scanner equipped with a 32-channel head coil. PSIR images were generated using a synthetic MRI protocol. 3D DIR images were acquired with a volumetric fast spin echo sequence with variable flip angle sweep (VFA-3D FSE), at an

isotropic resolution of 1.0 mm (TR/TI1/TI12/TE: 7000/2863/545/90). 2D T2 FLAIR images in follow-up MRI for case 1 and initial MRI for case 2 were acquired conventionally (TR/TI/TE: 11000/2800/125). 3D T2 FLAIR images in initial MRI for case 1 and follow-up MRI for case 2 were acquired with VFA-3D FSE with fat suppression, at an isotropic resolution of 1.0 mm (TR/TI/TE: 4800/1345/116). Post gadolinium T1weighted images were acquired with a T1 FLAIR sequence after injection of a single dose of contrast agent (TR/TI/TE: 2000/10/1000).

3. Case reports

3.1. Case 1

A 58-year-old woman who had two previous attacks of longitudinally extensive transverse myelitis (Supplementary Fig. 1) and was positive for anti-AQP4 antibody presented with status epilepticus. Seizures initially manifested as left eyeball deviation and tonic left arm flexion, and were secondarily generalized. The patient experienced six generalized tonic-clonic seizures without recovery of consciousness between episodes. Brain MRI showed multiple T2 hyperintense lesions in the brain stem, cerebellar peduncle, internal capsule, and subcortical and deep white matter without contrast enhancement. DIR and PSIR

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https://doi.org/10.1016/j.msard.2019.01.020

Received 16 November 2018; Received in revised form 15 December 2018; Accepted 6 January 2019 2211-0348/ © 2019 Published by Elsevier B.V.





Fig. 1. Brain MRI of case 1 (A–D) and case 2 (E–H). (A) Axial fluid attenuated inversion recovery (FLAIR) image showing increased cortical signal in the right frontal cortex (arrowhead). (B) Axial reformatted image of 3D double inversion recovery (DIR) and (C) phase sensitive inversion recovery (PSIR) images clearly revealing intracortical lesions (arrowhead). (D) Axial post gadolinium T1-weighted image showing no definite contrast enhancement. (E) Axial T2 FLAIR image demonstrating increased cortical signal in the left medial frontoparietal lobe (arrow). (F) Axial reformatted 3D DIR and (G) PSIR images well delineating the mixed gray-white matter lesions (arrow). (H) Axial post gadolinium T1-weighted image showing leptomeningeal enhancement.

imaging revealed the lesion in the right frontal area to be intra- and subcortical (Fig. 1A-D). Cerebrospinal fluid (CSF) analysis showed clear and acellular fluid with elevated protein (52.9 mg/dl) and negative CSF cytology results. No oligoclonal bands were detected. Autoimmune work-up revealed positive results for antinuclear antibody (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA). Results for anti-DNA, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), rheumatoid factor, viral serologies (human T-lymphotropic virus-I/II, human immunodeficiency virus), and venereal disease research laboratory (VDRL) were negative. Chest computed tomography revealed no evidence of mass lesions or hilar adenopathy. Seizures were controlled by anti-epileptic medication, and the patient was further treated with corticosteroids, plasma exchange, and rituximab. The mental status of the patient nevertheless deteriorated to a stuporous state, and mechanical ventilation was applied. Follow-up MRI revealed newly developed T2 hyperintense lesions in the right temporal area and the bilateral thalami (Supplementary Fig. 2). Two months after admission, the mental status of the patient started to improve; she started to communicate and began an oral diet 5 months after admission.

3.2. Case 2

A 61-year-old woman presented with weakness and sensory change in her right leg that had progressed over the preceding 10 days. The patient denied any history of visual or neurological symptoms prior to the onset of her leg weakness. Brain MRI showed T2 hyperintensity lesions with blurred margins in the left medial fronto-parietal lobes and leptomeningeal enhancement (Supplementary Fig. 3). DIR and PSIR sequences displayed lesions across the cortex and subcortical white matter in the left medial fronto-parietal area (Fig. 1E-H). No abnormal spinal cord lesion was observed on spine MRI. Cerebrospinal fluid analysis showed pleocytosis (37 white blood cells/mm³), elevated protein (53.5 mg/dl), and negative CSF cytology results. No oligoclonal bands were detected. Serological investigations including autoimmune work-up (ANA, ANCA, rheumatoid factor), viral serologies (cytomegalovirus, human immunodeficiency, herpes simplex, and varicella zoster virus), and VDRL were within the normal or negative range. Chest x-ray revealed no mass lesions or hilar adenopathy. Serum anti-AQP4 antibody analyses were positive. Repeated serum anti-AQP4 analysis 8 days after the initial test showed positive results. Visual evoked potentials revealed normal P100 latencies without significant interocular latency differences. Median somatosensory evoked potentials were within normal limits. Tibial somatosensory evoked potentials demonstrated increased interpeak latencies between spinal and cortical responses, suggesting a defect in bilateral somatosensory pathways. The patient was treated with a high dose (1 g) of intravenous methylprednisolone for 5 days, followed by oral prednisolone and azathioprine, and reported a gradual improvement of her symptoms. Brain MRI obtained 5 months after onset demonstrated an improvement of sulcal hyper-intensities and leptomeningeal enhancement (Supplementary Fig. 4). The patient is currently on oral corticosteroids and azathioprine and experienced no relapse.

4. Discussion

DIR and PSIR MRI have demonstrated their usefulness in providing superior gray-white matter contrast and discriminating intracortical, subcortical, and mixed gray-white matter lesions in MS (Nelson et al., 2007). In contrast, lesions in NMOSD were rarely evaluated using these sequences. A previous study analyzed 30 patients with NMOSD using DIR and found no evidence of cortical lesions (Calabrese et al., 2012). However, this study was based on a small number of patients, and it is uncertain whether the MRI was taken during the clinical attack or during remission. Cortical lesions in NMOSD may be difficult to detect as they are rare and may vanish after clinical remission. Here, we performed DIR and PSIR MRI during the clinical attack and found evidence of cortical involvement.

The characteristics of the lesions observed here are consistent with previous reports. The patient of the first case had longitudinally extensive transverse myelitis and brain lesions in the corpus callosum and along the corticospinal tract, a known pattern of brain involvement in NMOSD (Kim et al., 2015). The characteristics of the lesions of the second patient, which showed blurry margins with leptomeningeal enhancement, are also in line with previous reports (Kim et al., 2016; Tahara et al., 2012). Kim et al. reported that 3.1% of patients with NMOSD had cortical lesions that were frequently located in the frontal and posterior parietal lobes and had blurry margins with leptomeningeal enhancement (Kim et al., 2016). Tahara et al. also described three patients with NMOSD with blurry cortical lesions and leptomeningeal enhancement (Tahara et al., 2012).

The second patient presented with isolated leptomeningeal and cortical manifestations. Although previous studies reported some leptomeningeal and cortical involvement in patients with NMOSD (Kim et al., 2016; Tahara et al., 2012), none of them had isolated leptomeningeal/cortical lesions. The present case does not meet the diagnostic criteria for NMOSD, due to the absence of both core clinical characteristic and NMOSD-typical brain lesions. However, the common MRI features between this and previous cases, the patient's response to immunotherapy, and the positive anti-AQP4 antibody results suggest the NMOSD diagnosis.

Although anti-AQP4 antibody was detected in both cases and MRI features correspond to previous reports, an alternative diagnosis is still possible. In case 1, anti-N-methyl-D-aspartate receptor (NMDAR) antibodies were not evaluated, and there might be an overlap between NMOSD and anti-NMDA receptor encephalitis. Furthermore, although there was no clinical evidence of vasculitis or systemic lupus erythematosus except for positive results for ANA and P-ANCA, an overlap with systemic lupus erythematosus or ANCA vasculitis involving the central nervous system cannot be excluded. Similarly, in the second case, other diseases that mimic NMOSD cannot be completely excluded.

In conclusion, cortical involvement may exist in aquaporin-4 antibody-positive patients. In such cases, DIR and PSIR MRI can help determining the exact lesion location.

Declarations of interest

None.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors report no financial conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.01.020.

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