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【 CASE REPORT 】

Reversible Periventricular Hyperintensity Lesions in Cerebral Amyloid Angiopathy: A Case Mimicking Cerebral Amyloid Angiopathy-related Inflammation

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Abstract:
A 59-year-old man with progressive cognitive decline and mood disturbances was admitted to the hospital. Brain magnetic resonance imaging revealed marked white matter hyperintensity (WMH) and widespread lobar cerebral microbleeds. Because he had untreated hypertension, we started antihypertensive treatment and found a significantly improved cognitive function and WMH regression. We diagnosed him with cerebral amyloid angiopathy (CAA) based on the modified Boston Criteria with the rare apolipoprotein E (ApoE) ε2/ε4 genotype. The mechanism underlying reversible leukoencephalopathy in CAA may be related to the loss of autoregulation of brain circulation: cerebrovascular amyloid β deposits damaged the blood-brain barrier of the capillaries, which led to vasogenic edema induced by blood pressure surges.

Key words: amyloid β, cerebral amyloid angiopathy, leukoencephalopathy, white matter hyperintensity

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Introduction

Cerebral amyloid angiopathy (CAA) is characterized by amyloid β (Aβ) deposits in the leptomeningeal and cortical arteries. Patients with CAA may present with a wide spectrum of clinical symptoms, including intracerebral hemorrhage transient focal neurological deficits, and dementia (1). Patients with CAA also rarely develop CAA-related inflammation (CAA-ri), which manifests as reversible encephalopathy and demonstrates a favorable response to immunosuppressive treatment (2). Symmetric or asymmetric white matter hyperintensity (WMH) lesions in the cortex and subcortical white matter, together with subacute neurobehavioral symptoms, headache, and seizures, strongly indicate the presence of CAA-ri (3).

In a rare case of CAA with asymmetric WMH lesions that reportedly mimicked CAA-ri, increased blood pressure presumably accounted for the clinical worsening, and antihypertensive agents proved to be an effective treatment. However, because of the dearth of publications related to this disorder, the clinical and radiological features of such cases remain unclear.

We herein report a patient with CAA who had progressive dementia and marked leukoencephalopathy, which suggested CAA-ri, and in whom we achieved clinical and radiological improvements using antihypertensive treatment. We also discuss the underlying mechanism of reversible WMH in CAA, including the relationship with apolipoprotein E (ApoE) genotypes.

Case Report

A 59-year-old man was admitted to the hospital because of a progressive cognitive decline and mood disturbances that had persisted for the past 8 months, with occasional apathy or irritability that had worsened in the previous 1 month. The symptoms impaired his social activities, and he resigned from his job. He exhibited a postural tremor in the bilateral upper limbs. The Mini-Mental State Examination

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(MMSE) score was 18, and the Japanese version of the Montreal Cognitive Assessment (MoCA-J) score was 21. His score on Raven's Colored Progressive Matrices (RCPM) was 18; his time for the Trail Making Test (TMT)-A was 93 s, and that for the TMT-B was 321 s.

The patient was then transferred to our department for a continued examination and treatment. He was afebrile, his electrocardiogram revealed sinus rhythm, and he had a heart rate of 86 beats per minute and a blood pressure of 165/107 mmHg. The neurological examination revealed normal muscle strength, sensation, and reflexes in all limbs. Although we noted some improvement in the MMSE score, to 24, compared with the score on admission, and the MoCA-J score was 23, his mood disturbances and postural tremor persisted.

Brain magnetic resonance imaging (MRI) revealed bilaterally widespread WMH lesions on T2-weighted spin echo sequences (Figure A-C) and numerous, widespread lobar microbleeds on susceptibility-weighted imaging (Figure D-F). An old asymptomatic hematoma was also seen in the left cerebellum. Hyperintense lesions were not detected by diffusion-weighted imaging (Figure G-I), but an apparent diffusion coefficient (ADC) map revealed high-intensity lesions, which suggested vasogenic edema (Figure J-L). Post-gadolinium T1-weighted imaging revealed no enhancement. Blood tests, including antinuclear, anti-DNA, anti-SS-A and SS-B, and anti-thyroid autoantibodies and anti-cardiolipin antibodies, demonstrated no abnormalities. A cerebrospinal fluid analysis showed a slightly elevated protein level of 51 mg/dL with a normal pressure, normal cell count, normal IgG index, and negative oligoclonal band. An electroencephalogram showed generalized slowing of background activity without epileptiform discharges. Angiography of cerebral arteries produced unremarkable results except for a small, saccular aneurysm in the left vertebral artery.

We suspected CAA-ri based on the clinical features, asymmetric WMH lesions, and multiple microbleeds (4). The patient had untreated hypertension with a systolic blood pressure of more than 170 mmHg after admission, at which point we started antihypertensive treatment with 40 mg of nifedipine, 50 mg of losartan, and 12.5 mg of hydrochlorothiazide before treatment with immunosuppressants. Along with the reduction in systolic blood pressure to 130 mmHg, he became oriented to time and less apathetic and irritable. His performance on the RCPM (30), TMT-A (57 s), and TMT-B (162 s) also improved.

Brain MRI three weeks later (i.e. nine months from the symptom onset) revealed a significant regression of the WMH lesions (Figure M-O) and a partial normalization of the ADC values. In addition, the MMSE score improved to 29, the MoCA-J score was 29, and the postural tremor decreased and showed a reduced amplitude. We also found that the patient had the ApoE ε2/ε4 genotype. Ten months after the symptom onset, at his latest visit to the outpatient clinic, his cognitive function had continued to improve, his MMSE score was 30, and his MoCA-J score was 29. We used no immunosuppressants throughout the course of medical treatment.

Discussion

This case is the second unique case of CAA-related reversible leukoencephalopathy, in which antihypertensive treatment contributed to improved cognitive function and reduced WMH lesions. Sarazin et al. (5) reported biopsy-proven CAA with leukoencephalopathy. In that report, antihypertensive therapy led to improved neuropsychological symptoms that had progressed for the previous four months and regression of WMH lesions. The reduction in WMH lesions after antihypertensive treatment and lack of use of immunosuppressants indicated the irrelevance of hypoperfusion and inflammation. The excellent response to antihypertensive treatment in our case and that of Sarazin et al. also reminds us of hypertensive encephalopathy, which rarely demonstrates a prolonged course (6).

We propose, as a possible explanation, that the WMH in the present case was in fact an indication of reversible vasogenic edema caused by vascular leakage that resulted from superimposed hypertension with reduced autoregulation. Although cerebrovascular autoregulation maintains cerebral blood flow independent of changes in systemic arterial pressure, when the blood-brain barrier is disrupted by Aβ (7), hyperperfusion may easily result from increased blood pressure, similar to the mechanism underlying hypertensive encephalopathy (8). Posterior reversible encephalopathy syndrome (PRES) is also characterized by vasogenic edema over the parieto-occipital white matter and a good response to antihypertensive therapy (9). However, the chronic onset over eight months in our case seems markedly different from the typical course in PRES patients with a subacute onset involving headache, seizures, or changes in the consciousness level.

We also found that the patient had the rare ApoE ε2/ε4 genotype, which makes individuals prone to develop CAA at an early age (10). In addition, ApoE ε2 itself is associated with fibrinoid necrosis in CAA (11), which may increase the loss of autoregulation via damage to smooth muscle cells or the endothelium. Hendricks et al. (12) reported a biopsy-proven CAA case with cognitive deterioration that occurred over several months. The blood pressure on admission was 200/100 mmHg; no information about treatment or follow-up data were available.

The present case emphasizes the importance of realizing that extensive subcortical WMH in CAA is sometimes reversible, in that blood pressure reduction alone may contribute to dramatic improvement in the symptoms. Although recent progress in neuroradiological techniques has made the clinical diagnosis of CAA safer and easier to confirm, distinguishing between hypertensive CAA-related leukoencephalopathy and CAA-ri is still difficult. Therefore, when we suspect CAA-ri from radiological findings, we should include in the differential diagnosis a CAA-ri mimic, in which

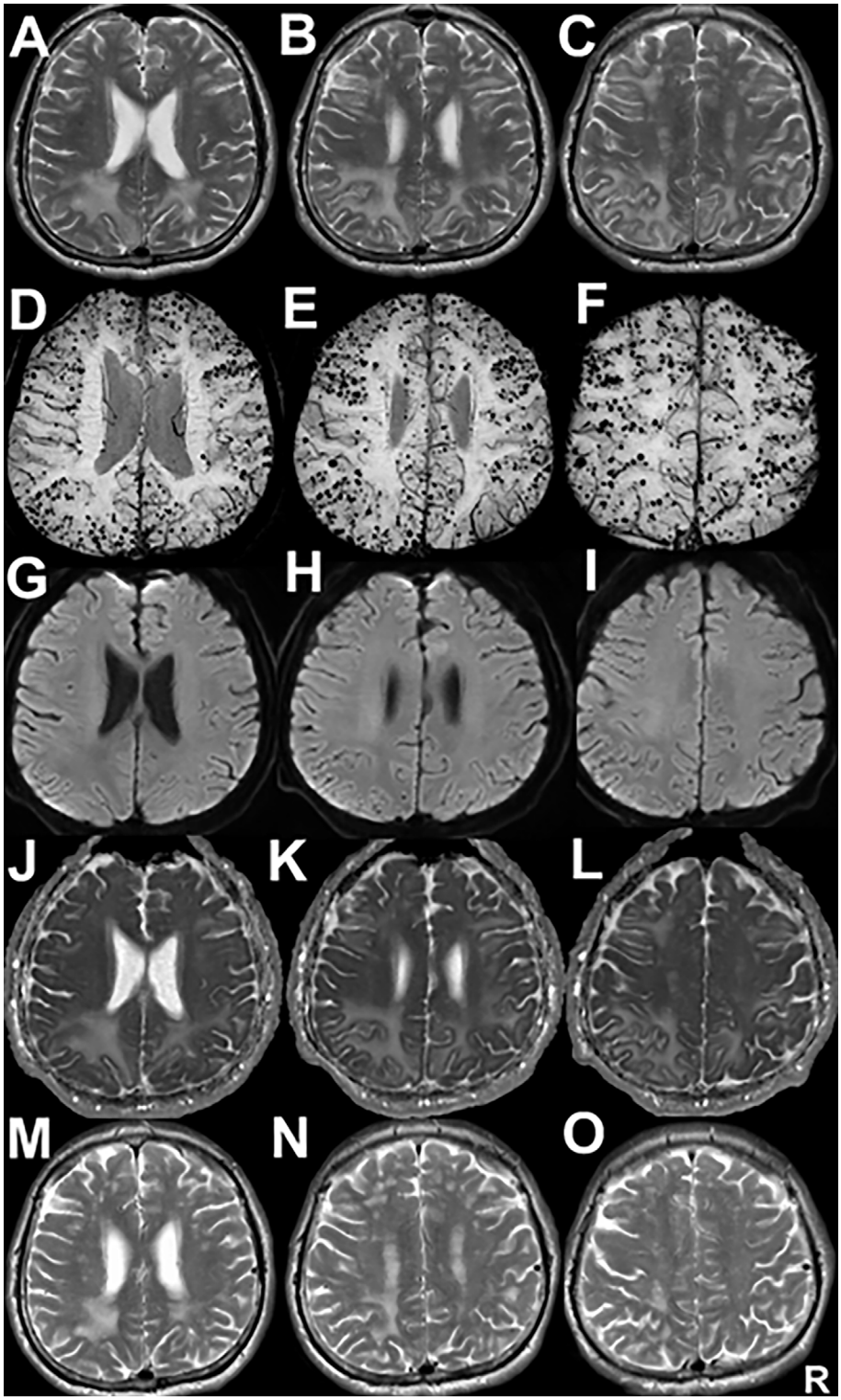

Figure. **(A-C) Axial T2-weighted spin echo sequences of the brain on admission, with images that show a bilateral high-intensity signal that involve the subcortical white matter of the temporo-occipital lobes. (D-F) Axial susceptibility-weighted imaging on admission, with images that reveal a widespread strictly lobar distribution of microbleeds. (G-I) Axial diffusion-weighted MRI on admission, with images that demonstrate no high-intensity signals. (J-L) Axial ADC map on admission that shows increased ADC values in the bilateral subcortical white matter of the temporo-occipital lobes. (M-O) Axial T2-weighted MRI obtained after three weeks of follow-up, with images that demonstrate drastically reduced subcortical white matter involvement.**

underlying hypertension may exist as related to CAA-related leukoencephalopathy.

The authors state that they have no Conflict of Interest (COI).

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