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LETTER TO THE EDITORS

CADASIL with spinal cord involvement: a case report and literature review

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Dear Sirs,

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare small-vessel disease caused by mutations in the NOTCH3 gene. The main clinical features of CADASIL are stroke, dementia, migraine with aura and mood disturbances [1]. However, spinal cord is rarely involved. Here, we report a case of CADASIL with cervical cord infarction.

A 35-year-old male presented with the history of recurrent weakness in both legs for 1 year past, with weakness lasting for few seconds to minutes. He was unable to walk for the last 7 days, due to worsening of the symptoms and, thus, was brought to the medical care. He complained that he had difficulties in using chopsticks and writing. On neurological examination, the tendon reflexes in the lower limbs were very brisk, bilateral Babinski's signs and Hoffman's sign were positive, with muscle strength of 4/5 in his upper limbs and the power in the lower extremities was of the grade 3/5 on the medical research council (MRC) scale, and bowel and bladder control were preserved. He had a positive history of migraine for more than 5 years. His mother died at the age of 51, due to stroke and had developed dementia in her later years. He had no history of hypertension, diabetes mellitus, smoking, and alcohol consumption. T2-weighted MRI images of the brain revealed extensive white matter changes, with involvement of the temporal lobe. T2-weighted MRI images of the spinal cord demonstrated cervical hyperintensity from C2 to C6 (Fig. 1). He was initially suspected as a case of inflammatory demyelinating process such as MS or NMO. However, examination of the blood and cerebrospinal fluid (CSF) revealed values within normal range without oligoclonal bands and anti-aquaporin-4 antibodies, and there was no fever before and during the onset of the disease. Other investigations, including routine blood test, routine urine test, coagulation routine, glycosylated hemoglobin, serum lipid, uric acid, homocystein, high-sensitivity C-reactive protein, B12 vitamin, folate, fasting blood glucose, erythrocyte sedimentation rate (ESR), HIV serology, syphilis serology, serum lactate, anti-nuclear antibody, body mass index (BMI), renal function, and liver function were all normal or negative. In addition, no abnormalities were found in carotid artery color ultrasound, TCD, ECG, color Doppler echocardiography, foaming test, microemboli monitoring, and visual evoked potentials. Based on neuroimaging data and personal history, he was also suspected to have developed CADASIL. NOTCH3 gene analysis confirmed the diagnosis of CADASIL by validating the c.383G > A mutation at exon 3. The patient could walk by himself after 3 week treatment with daily dose of 100 mg aspirin and 60 mg edaravone as well as 0.5 g citicoline. After discharge, the patient continued to take aspirin with daily dose

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of 100 mg. Repeat MRI approximately after 3 months of his treatment showed the spinal cord lesion improved much (Fig. 2).

We report a case of CADASIL with an unusual finding of cervical cord lesion. The patient presented with a relapsing and remitting weakness of both the legs for past 1 year, lasting for seconds to minutes, and no abnormalities of the lower extremity were detected by color Doppler ultrasound. We considered the transient lower limbs weakness as a spinal cord TIA. The fact that he was acutely unable to walk for the last 7 days and the lesions occurred longitudinally, mainly in the anterio-median part of the spinal cord, indicated the tendency of cervical cord infarction. The pathological feature of CADASIL is specific arteriopathy, mainly affecting the small penetrating cerebral arteries [1]. Although clinical manifestations of CADASIL were only cerebral, an apparent exception was myocardial infarction reported in ten of 41 Dutch patients [2]. Pathologic examination of myocardial

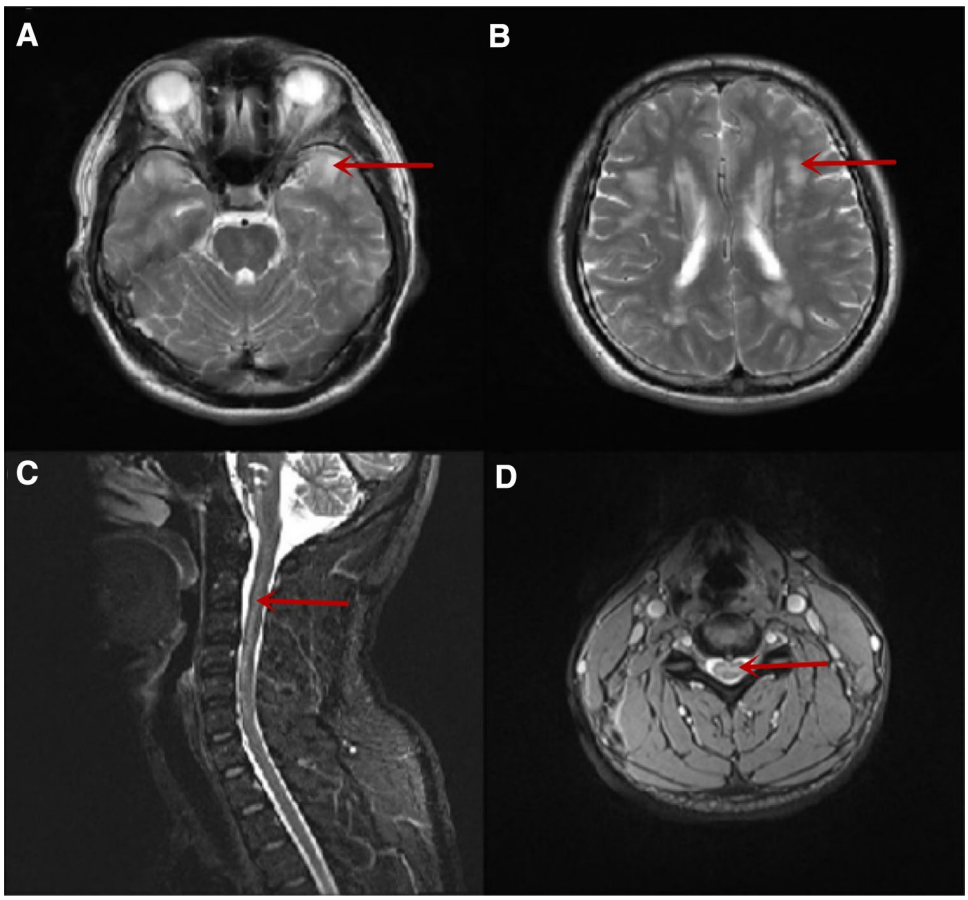

Fig. 1 MRI images of the brain and spinal cord of the patient. **a**, **b** Axial T2-weighted images of the brain showing extensive confluent white matter lesions, global atrophy, and deep white matter changes in temporal lobes. **c** Sagittal T2-weighted image of the spinal cord showing cervical hyperintensity, mainly located in the anterior spinal cord from C2 to C6. **d** Axial T2-weighted image of the spinal cord highlighting the anterior nature of the signal change

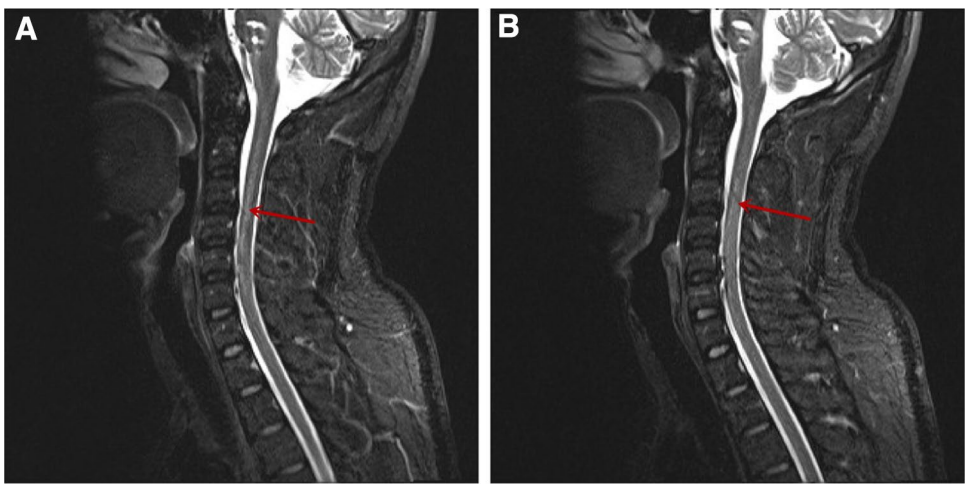

Fig. 2 MRI images of spinal cord of the patient. (**a** March 16, 2017) Sagittal T2-weighted image of the spinal cord when the patient first admitted to the hospital. (**b** June 12, 2017) Repeat MRI approximately after 3 months of his treatment showed the spinal cord lesion improved much

tissue revealed typical CADASIL arteriopathic changes of the coronary microvasculature. Microscopic and ultrastructural investigations of CADASIL showed a specific arteriopathy affecting mainly the small penetrating cerebral arteries. Arteriopathy was also present in other organs, such as the spleen, liver, kidneys, muscle, aorta, and skin [3–6]. In 2016, Sangle et al. reported a case of CADASIL with multi-organ involvement confirmed by a complete autopsy examination, microscopic examination also found that similar granular material within the walls of paraspinal blood vessels, though the spinal cord tissue was unremarkable [7]. It can be presumed that NOTCH3 mutation carriers may be at risk of ischemic spinal vascular diseases. The spinal cord is perfused by one anterior and two posterior spinal arteries. Anterior spinal artery (ASA) is the principal vascular supply to the spinal cord, arising from the vertebral artery and descends the entire length of the spinal cord. The spinal cord supplied by ASA is vulnerable to ischemia, as the vertical connectivity of ASA is poor. The terminal penetrating extensions of ASA are the left and right sulcocommissural arteries, which supply the anterior two-thirds of the spinal cord [8]. It can be presumed that the sulcocommissural artery might be more susceptible to CADASIL vasculopathy, and thus, we speculate that the chronic small-artery diseases are responsible for the cervical cord infarction. Symptom relief after receiving antithrombotic drugs and neurotrophic factor therapy supports our diagnosis.

Involvement of spinal cord in CADASIL is rarely reported in the literature. Bentley et al. first reported the cases of two sisters with a novel NOTCH3 mutation and a spinal cord lesion confined to the postero-median part of spinal cord. The lesions were speculated as a small-vessel ischemia or an inflammatory demyelinating process [9]. Collongues et al. reported a case of a 53-year-old woman with a high intensity signal in the thoracic spinal cord on T2-weighted MRI image, and the corticosteroid therapy was effective in the patient [10]. Hinze et al. reported a case of CADASIL in a patient who presented with a rapidly progressive spastic paraparesis and was found to have a posterior spinal cord infarction [11]. Recently, Schiess et al. reported a patient with an NOTCH3 heterozygous mutation, 10 oligoclonal bands in the CSF, and MRI revealed new lesions in the cervical spinal cord [12]. This case raised the question—whether inflammatory demyelinating process and CADASIL are two independent diseases found coincidentally in the same patient or a variant of CADASIL with inflammatory characteristics?

To our knowledge, although transient ischemic attacks and stroke were reported in approximately 85% of CADASIL individuals, transient ischemic attacks (TIAs) of the spinal cord have not been documented as an initial symptom of CADASIL. Moreover, T2-weighted MRI images revealing cervical hyperintensity in the anterio-median part of the cervical cord in patients of CADASIL have also not been reported in the literature. In conclusion, compared to the already published cases about CADASIL with spinal cord involvement, we reported a novel case of CADASIL with an anterio-median infarct of cervical spinal cord, first presented as spinal TIA. Although clinical manifestations of CADASIL are mainly restricted to the brain, arteriopathy may occur in other part of the central nervous system. Thus, we contend that spinal artery might be susceptible to CADASIL, particularly ASA, and spinal TIAs might be one of the initial syndromes of CADASIL.

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Compliance with ethical standards

We have obtained the patient's permission and informed consent for the publishing of his information and images.

Conflicts of interest The authors declare that they have no conflict of interest.

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