

# Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy with spinal cord lesion: A case report and literature review

\*<sup>1</sup>Heqian Du, \*<sup>1</sup>Xinyuan Li, \*<sup>1</sup>Hongmei Meng, <sup>1</sup>Ziwen Lu, <sup>2</sup>Lijun Zhu, <sup>1</sup>Shaokuan Fang

\*These three authors contributed equally to this work

<sup>1</sup>Department of Neurology, Neuroscience Centre, the First Teaching Hospital of Jilin University, Changchun; <sup>2</sup>The Third Teaching Hospital of Jilin University, Changchun, China

## Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a common hereditary disease caused by NOTCH3 gene. The major clinical manifestations include recurrent small-vessel ischaemic events, migraine, dementia and mood disturbance. Herein, we report a 32-years-old male presented with right leg weakness and persistent migraine. We carried out neurological exams, genetic testing, blood and cerebrospinal fluid analysis (CSF) as well as magnetic resonance imaging (MRI) for the brain and spinal cord. There were no anti-aquaporin-4 antibodies and oligoclonal bands in the CSF and blood investigations were within the normal range. MRI scans revealed multiple hyperintense regions in the brain and longitudinally hyperintense signal in spinal cord. Further, we identified a c.383G>A(p.Cys128Tyr) mutation in NOTCH3 gene. Therefore, the patient was diagnosed with CADASIL concurrent with spinal cord lesion. The patient's condition slightly improved after two weeks treatment with daily dosage of 0.5 g citicoline and 75 mg clopidogrel.

**Keywords:** CADASIL; spinal cord lesion; NOTCH3 gene

## INTRODUCTION

CADASIL is a rare hereditary autosomal dominant cerebral small vessel disease caused by mutations in NOTCH3 gene.<sup>1</sup> Migraine, mood disorders, cognitive decline, dementia and recurrent strokes without arterial risk factors are the most prominent clinical manifestations of CADASIL.<sup>2</sup> CADASIL patients usually develop migraine as the earliest clinical feature followed by more severe manifestations like cognitive decline, dementia and recurrent strokes. CADASIL diagnosis is mainly based on magnetic resonance imaging (MRI) and NOTCH3 mutation analysis.<sup>3,4</sup> Multiple hyperintense lesions in the subcortical areas especially the periventricular white matter as well as lacunar infarcts, and cerebral microbleeds are the major MRI findings.<sup>5</sup> Concurrent hyperintense lesions in the brain and spinal cord are rarely observed in CADASIL cases. In this study, we report a rare case of CADASIL with concurrent spinal cord lesion.

## CASE REPORT

A 32-year-old male patient was admitted to the

Department of Neurology, The First Teaching Hospital, Jilin University in March, 2017. The patient complained from right leg weakness from December 2016 that persisted during the last three months and he suffered from migraine for the past 5 years without hypertension. His mother experienced migraine for 10 years and died two years earlier. The patient did not have prior history of neurological or psychiatric illness. At the time of admission, his blood pressure was 128/87 mmHg, heart rate was 68 beats/min and body temperature was 36.7°C. Upon examination, the muscle power according to Medical Research Council (MRC) muscle strength scores were grade 5 in the upper limbs, and grade 3 in the proximal right lower limb. The muscle tone of his extremities was normal while, the deep tendon reflexes of all extremities were increased. The cranial nerve examination was normal and there were no deficits in the superficial sensation, while he had decreased vibratory sensation in the bilateral toes and ankles. Babinski and Chaddock signs were bilaterally negative. Next, the patient underwent MRI brain scans that revealed multiple hyperintense lesions in the periventricular white

Address correspondence to: Professor Shaokuan Fang, Department of Neurology, Neuroscience Centre, the First Teaching Hospital of Jilin University, No. 71 Xinmin Street, Changchun, Jilin, 130021 China. E-mail: fang20063536@sina.com

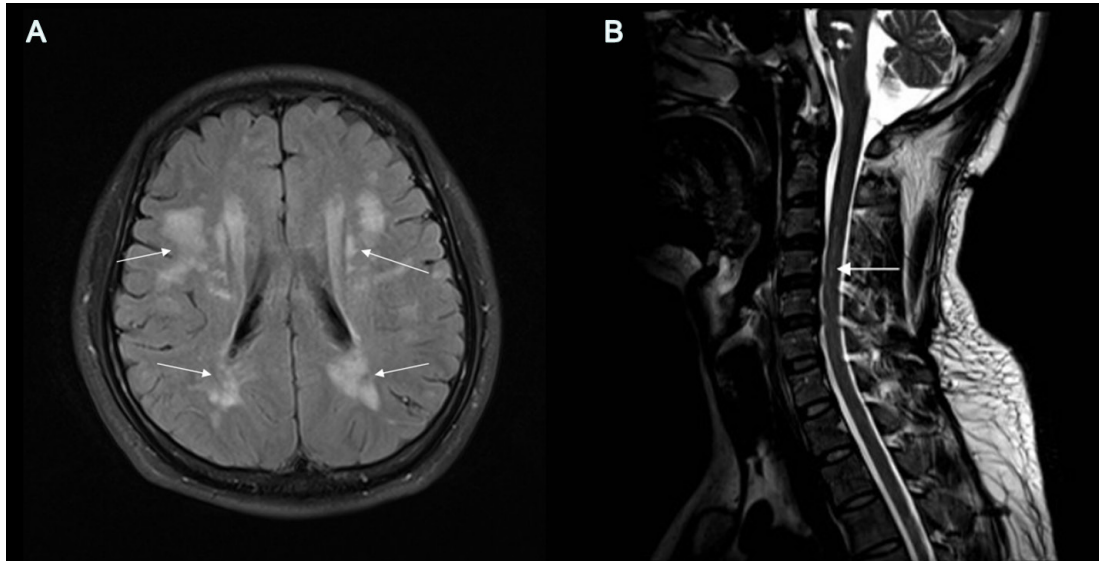


Figure 1. MRI of the brain and cervical cord. A. Axial FLAIR images showed multiple hyperintensities in the periventricular white matter and corona radiate. B. Sagittal T2-weighted images showed longitudinally hyperintensities that were not enhanced by contrast. (white arrows)  
MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery.

matter, corona radiate (Figure 1A). Further, the spinal cord MRI demonstrated longitudinally hyperintensities confined to the cervical cord and the lesions were not enhanced by contrast (Figure 1.B). The results of routine blood test were within the normal range. The anticardiolipin and lupus anticoagulant, extractable nuclear antigen (ENA), anti-neutrophil cytoplasmic antibody (ANCA), serology for syphilis, HIV-1, anti-aquaporin-4 antibodies as well as the serum oligoclonal bands were all negative. Lumbar puncture showed a cerebrospinal fluid (CSF) pressure of 160 mmH<sub>2</sub>O. The biochemical and cytological examinations of the CSF were normal; i.e, acellular fluid, with normal protein, glucose and the brucellosis PCR assay was also negative. Additionally, there were no anti-aquaporin-4 antibodies and oligoclonal

bands in the CSF. Genetic testing identified a heterozygous missense mutation in c.383G>A (p.Cys128Tyr) (Figure 2). Taken together, the MRI findings and the result of genetic testing indicated a CADASIL case with possible infarction in the spinal cord. The patient was treated with citicoline (0.5 g once daily) for nerve nutrition and clopidogrel (75 mg once daily) for two weeks. At the four months' follow up visit, the patient showed worsening symptoms of memory loss.

### DISCUSSION

In this study, we reported a CADASIL case that co-existed with cervical cord lesion. CADASIL cases with cord lesions are documented but extremely rare. Hutchinson et al reported

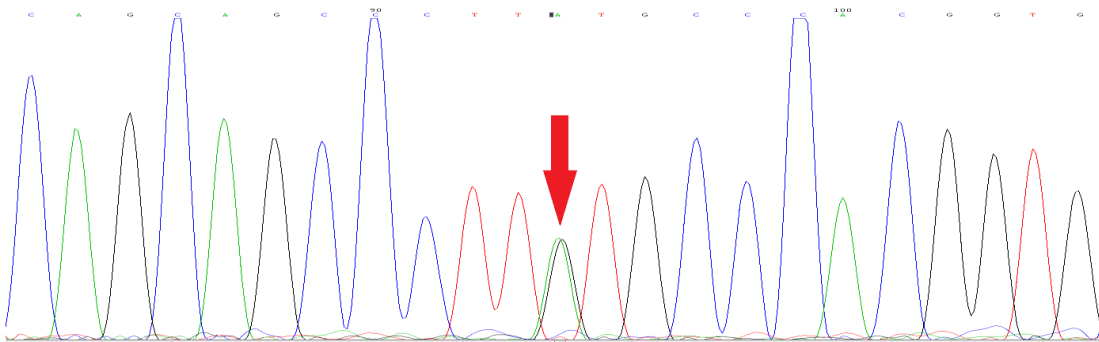


Figure 2. A c.383G>A mutation, indicated by an arrow, was observed in the patient's NOTCH3 gene.

the clinical manifestation suggestive of a CADASIL case with spinal infarction in an Irish patient.<sup>6</sup> Additionally, Hinze *et al.* described longitudinally posterior spinal cord infarction with CADASIL.<sup>7</sup> Moreover, Rocca *et al.* study found that CADASIL patients had reduced peak height of the magnetization transfer ratio (MTR) in the cervical cord, reflecting cord lesion.<sup>1</sup> In addition, Bentley *et al.* reported two CADASIL patients both manifested a distinctive pattern of cord lesions.<sup>8</sup> Skowrońska *et al.* presented a case of CADASIL co-existing spinal canal tumors.<sup>9</sup>

Migraine is the earliest feature of CADASIL in one third of patients and it generally occur between 30 and 50 years old.<sup>10</sup> Migraine is usually followed by more severe manifestations including cognitive decline, dementia and recurrent strokes.<sup>3</sup> However, CADASIL can be diagnosed before the first clinical stroke based on the MRI findings. The diagnosis can also be confirmed by genetic testing for *NOTCH3* mutations as well as skin biopsy to examine the small blood vessels.<sup>9</sup> CADASIL is inherited in an autosomal dominant manner, therefore, we screened the patient's father for mutations in *NOTCH3* gene and no abnormalities were observed. However, the patient's mother died two years earlier and therefore, we could not confirm possible *NOTCH3* mutations.

In the current report, the patient had a 5-year-history of migraine and the brain MRI revealed the typical features for CADASIL that included multiple infarctions in the periventricular white matter, basal ganglia, thalamus and pons. Furthermore, DNA sequencing identified a missense c.383G>A (p.Cys128Tyr) mutation within *NOTCH3* gene.<sup>10</sup> These findings confirmed the diagnosis of CADASIL. In addition, the MRI of the spinal cord disclosed longitudinal lesions in the cervical cord and anti-aquaporin-4 antibodies and oligoclonal bands were negative in both blood and CSF. The morphology as well as the fact that it was not enhanced by contrast indicated that this could be infarction in the small perforating arteries.

In adults, *NOTCH3* gene is expressed in the vascular smooth muscle cells (VSMC) of arterial vessels and it plays a vital role in the balance of VSMC growth and apoptosis. *NOTCH3* mutations leads to the destruction of VSMC and a gradual auto-regulation failure of blood flow.<sup>11</sup> Consequently, this leads to progressive wall thickening, fibrosis and luminal narrowing in small perforating arteries.<sup>12</sup> It is noteworthy that the frequency of the lesion depends on the length of perforating arteries and longer arteries

are usually more affected than shorter ones.<sup>13</sup> These pathological changes have been previously documented in all organs of CADASIL patients. However, clinical manifestations and imaging generally appear to be limited to the brain lesion. With regard to the cervical cord lesion, we suggest a possible explanation that the spinal cord owns long perforating arteries and is considered to be perforating arteries ischemia, parallel with the cerebral lesions.<sup>8</sup>

In conclusion, the current report highlights a rare case of CADASIL concurrent with spinal cord lesion. It provides new insights for possible co-existence of cord infarction along with brain damage in CADASIL patients. Future studies should explore the specific mutations associated with spinal cord infarction and the underlying pathophysiology.

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## DISCLOSURE

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Conflict of interest: None

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