Ref: Ro J Neurol. 2022;21(1)
DOI: 10.37897/RJN.2022.1.13

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy presenting as severe herniated nucleus pulposus: A case report

Chung-Yong Yang[1,2], Hyun Young Park[3], Jisu Yang[4], YoungSeo Kim[3], Li-Qun Zhang[1]

[1] Department of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine, Baltimore, USA
[2] Department of Physical Medicine and Rehabilitation, The SEUM Hospital, South Korea
[3] Department of Neurology, Wonkwang University School of Medicine and Hospital, South Korea
[4] Department of Neuroscience and Behavioral Biology, Emory University College of Arts and Sciences, Atlanta, USA

ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common inherited cerebral microangiopathy. Its clinical features include recurrent central nervous system symptoms—including lacunar stroke, migraine, psychiatric disturbance, acute reversible encephalopathy, and cognitive impairment. We report a case of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in a patient presenting with severe low back pain and a herniated nucleus pulposus. A 45-year-old female patient with a prior history of right-sided sciatic pain, hypoesthesia, and paresthesia in the right S1 sensory dermatome was referred after back surgery because of persistent low back pain and a spastic gait abnormality. Imaging revealed a right protruding disc herniation of L5/S1 with right S1 nerve root compression and right posterior disc bulging at L4/5 with foraminal stenosis and disc degeneration, for which she underwent surgery. After surgery, she experienced mild sciatica, an antalgic limping gait with foot-dragging, and progressive motor weakness. Her family history was significant for a parent and sibling affected by stroke. The diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy was established by polymerase chain reaction sequencing, which showed a mutated exon 11 of *NOTCH3* on chromosome 19. Clinicians should assess patients with non-specific extra-central nervous system symptoms or atypical courses for potential underlying diseases.

Keywords: CADASIL, CARASIL, herniated disc, low back pain, spondylosis deformans

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common dominantly inherited cerebral small vessel disease [1,2]. CADASIL is caused by pathogenic mutations clustered in exons 2–23 of the *NOTCH3* gene on chromosome 19 and has four distinct cardinal manifestations: stroke, migraine headache with aura, psychiatric disturbance and cognitive decline [1,3]. However, central nervous system (CNS) and peripheral neurological symptoms and neuromuscular involvement have been reported in patients with CADASIL [2–5], but not herniated lumbar discs accompanied by severe low back pain. Here, we describe the case of a 45-year-old female with confirmed CADASIL who presented with low back pain and disc herniation which were manifest as extra-CNS manifestations.

CASE PRESENTATION

A 45-year-old female patient presented with an 8-year history of right-sided sciatic pain, hypoesthe-

Corresponding author:
Hyun Young Park
E-mail: hypppark@gmail.com

Article history:
Received: 23 February 2022
Accepted: 3 March 2022

sia and paresthesia in the right S1 sensory dermatome. She was referred to our service for persistent low back pain and gradual development of a spastic gait abnormality after back surgery. Lumbar magnetic resonance imaging (MRI) revealed right protruding disc herniation of L5/S1 with right S1 nerve root compression and right posterior disc bulging at L4/5 with foraminal stenosis and disc degeneration (Figure 1).

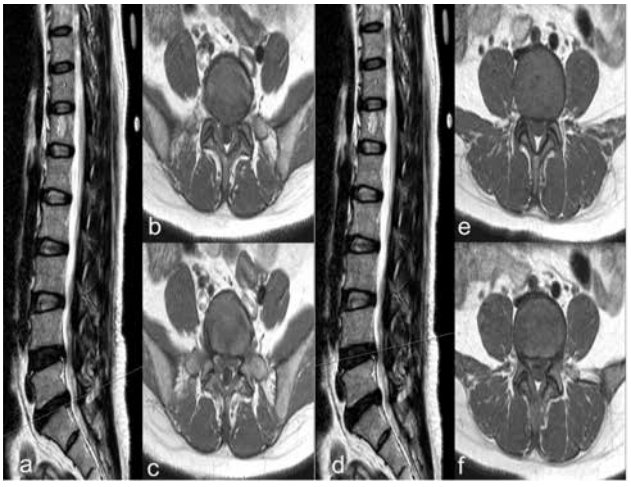

FIGURE 1. Lumbar magnetic resonance imaging reveals mild focal protruding disc herniation with mild inferior migration at the right posterolateral side of L5/S1, causing (a-c) right S1 nerve root compression and (d-f) posterior disc bulging at L4/5.

Eight months before presentation, she underwent partial hemilaminectomy, ligamentum flavectomy, foraminotomy at the right L5/S1 and L4/5 levels, and a discectomy at the right L5/S1 level. During surgery, a thecal sac, S1 root compression caused by rupture of L5/S1 disc (non-traumatic), and canal stenosis due to hypertrophy of the L4/5 ligamentum flavum were noted. Her pain, numbness, and hypoesthesia in the right anterior thigh improved after surgery. However, she experienced mild sciatica, an antalgic limping gait with foot-dragging, progressive motor weakness (Medical Research Council grade 4), and spastic gait disturbance in the right leg.

She was being administered antihypertensive medication (amlodipine 5 mg once per day) for 11 years, and her blood pressure was normal. Her family history revealed a brother who sustained a minor stroke with slurred speech at age 41. Her mother died of a major stroke at age 56. The patient had no history of migraine, baldness, epileptic seizure, cognitive impairment (Korean version of Mini-Mental Status Examination: 30/30) [6], or major psychiatric problems. The results of routine blood tests and autoimmune markers as anticardiolipin, lupus anticoagulant, and anti-neutrophil cytoplastic antibody were within normal limits. Electrodiagnostic studies revealed right lower lumbar and lumbosacral radiculopathy. A brain MRI revealed multiple chronic infarctions and severe chronic periventricular ischemic white matter changes (Figure 2), while the results of magnetic resonance angiography were normal. She and her brother showed the same missense mutation c.1819C>T (pArg607Cys, heterozygote) on exon 11 of *NOTCH3* on chromosome 19 (19p13.2-p13.1) on polymerase chain reaction sequencing studies and were diagnosed with CADASIL. After receiving neural block intervention and prescription antiplatelets (clopidogrel 75 mg per day), antidepressants (escitalopram oxalate 10 mg per day), antispastic medica-

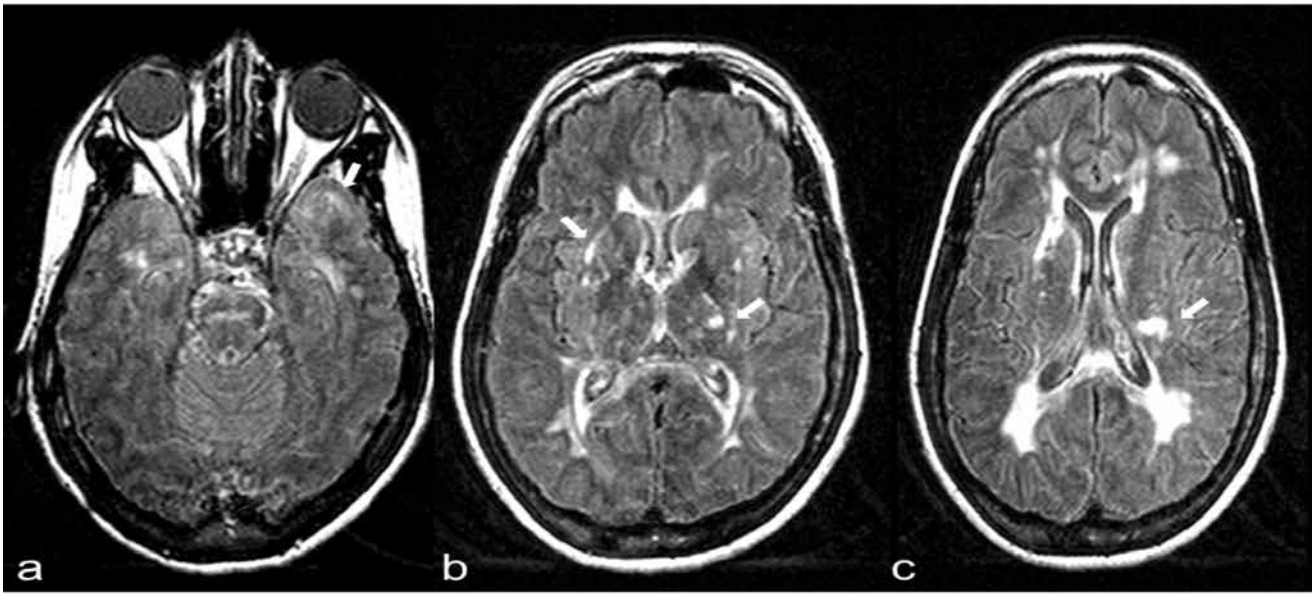

FIGURE 2. (a-c) Brain magnetic resonance imaging reveals high-signal-intensity lesions (arrows) with lacunar lesions in the anterior temporal lobe, both periventricular and subcortical white matter, corpus callosum, thalamus, and basal ganglia on axial FLAIR, concomitant with mild deep cerebral white matter atrophy. FLAIR: fluid attenuated inversion recovery.

tions (baclofen 20 mg, twice a day), and rehabilitation therapy, she could walk comfortably with decreased spasticity and pain.

DISCUSSION

We report an unusual case of CADASIL in a patient presenting with severe low back pain and herniated nucleus pulposus following an atypical post-surgical course and without a classic CADASIL symptom profile. While recent studies have reported an extra-CNS involvement in CADASIL [2–5], no reports have demonstrated an association of CADASIL with severe low back pain, spondylosis or disc herniation, or nodular thickening of the posterior longitudinal ligament. One case reported an association with back pain and alopecia [7].

The possibility of CADASIL with extra-CNS symptoms is low, and its pathogenic interpretation difficult. The classic symptoms seen in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). CARASIL is a less-common, inherited, cerebral, small-vessel disease. It has characteristic extra-CNS symptoms, including premature baldness/alopecia (90% of patients), low back pain (80% by age 20–40 years), and spondylosis deformans; these factors distinguish it from CADASIL [8]. However, genetic heterogeneity through altered NOTCH signaling may be a possible mechanism-of-action. NOTCH signaling comprises an important cascade pathway in somitogenesis; NOTCH signaling abnormalities such as DLL3, MESP2, LNFG, NOTCH2, and JAGGED1 can cause diverse extra-CNS symptoms [9]. Such symptoms were observed in our patient—including vertebral disc herniation, severe low back pain and mild spondylosis deformans. Although these genes have different chromosome locations, the NOTCH signaling pathway can enlarge the clinical spectrum because different proteins—and their related signaling systems—influence each other through interactions.

Although the HTRA1 gene study for CARASIL was not performed in this patient, diagnosis of CADASIL was possible based on brain MRI, NOTCH 3 gene analysis, and family history of stroke. In conclusion, we should pay special attention when evaluating lumbar radiculopathy or when we encounter patients with unusual courses and non-specific extra-CNS symptoms; an underlying disease like CADASIL is a possibility.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Tikka S, Baumann M, Siitonen M, et al. CADASIL and CARASIL. *Brain Pathol*. 2014; 24(5):525–44.
2. Sakiyama Y, Matsuura E, Maki Y, et al. Peripheral neuropathy in a case with CADASIL: a case report. *BMC Neurol*. 2018; 18(1):1–4.
3. Jing XZ, Jiang W, Gan L et al. Demyelinating Disease Study Group. CADASIL with spinal cord involvement: a case report and literature review. *J Neurol*. 2019; 266:2330–3.
4. Bentley P, Wang T, Malik O et al. CADASIL with cord involvement associated with a novel and atypical NOTCH3 mutation. *J Neurol Neurosurg Psychiatry*. 2011; 82(8):855–60.
5. Schröder JM, Züchner S, Dichgans M et al. Peripheral nerve and skeletal muscle involvement in CADASIL. *Acta Neuropathol*. 2005; 110(6):587–99.
6. Oh EA, Kang YW, Shin JH, Yeon BK. A validity study of K-MMSE as a screening test for dementia: comparison against a comprehensive neuropsychological evaluation. *Dement Neurocogn Disord*. 2010; 9(1):8-12.
7. Yamada H, Yasuda T, Kotorii S et al. Report of a patient with CADASIL having a novel missense mutation of the Notch 3 gene--association with alopecia and lumbar herniated disk. *Rinsho Shinkeigaku*. 2001; 41(2-3):144–6.
8. Mancuso M, Arnold M, Bersano A et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol*. 2020; 27(6):909–27.
9. Turnpenny PD, Alman B, Cornier AS et al. Abnormal vertebral segmentation and the notch signaling pathway in man. *Dev Dyn*. 2007; 236(6):1456–74.