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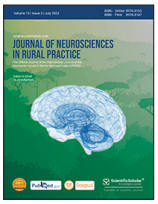

*Case Report*

# Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: Atypical clinical presentation with isolated frontotemporal dementia

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## ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary syndrome caused by heterozygous mutations in the *NOTCH3* gene that manifests in adulthood and is characterized by recurrent transient ischemic attacks and strokes, migraine-like headaches, psychiatric disturbance, and progressive dementia. The current study reports an interesting case of CADASIL in a Saudi patient with a heterozygous mutation in exon 18 of the *NOTCH3* gene presenting only with cognitive decline without migraine or stroke. The diagnosis was suspected mainly because of the typical brain magnetic resonance imaging (MRI) features that led to performing genetic testing to confirm the diagnosis. This illustrates the importance of brain MRI in the diagnosis of CADASIL. Increased awareness of neurologists and neuroradiologists about the typical MRI features of CADASIL is of paramount importance to reach the diagnosis in a timely manner. Awareness of the atypical presentations of CADASIL will lead to identifying more CADASIL cases.

**Keywords:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *NOTCH3*, Autosomal dominant, Dementia, Migraine, Stroke

## INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) a hereditary syndrome caused by heterozygous mutations in the *NOTCH3* gene that manifests in adulthood and is characterized by recurrent transient ischemic attacks and strokes, migraine-like headaches, psychiatric disturbance, and progressive dementia.[1] Dementia is most often diagnosed at the end stage of the disease and is associated with motor impairment, pseudobulbar palsy, and sphincter incontinence. Cognitive impairment is usually uncommon at an early stage of CADISAL without evidence of a previous stroke. However, there are some case reports that revealed cognitive impairment as the sole manifestation of CADASIL.[2] A study on CADASIL suggested that cognitive impairment can occur without any major vascular event. Therefore, despite the lack of a history of migraine headaches and stroke, CADASIL cannot be excluded.[3] A thorough literature review identified only one case of CADASIL reported from Saudi Arabia in exon 19 of the *NOTCH3* gene.[4] The present study reports an interesting case of CADASIL in a Saudi patient with a heterozygous mutation in exon 18 of the *NOTCH3* gene presenting only with cognitive decline without migraine or stroke.

## CASE REPORT

A 55-year-old male came to the neurology clinic complaining of a progressive cognitive decline over 6 years, including a gradual onset of forgetfulness with memory, executive, and visuospatial dysfunction. In addition, he had urine incontinence, mood symptoms, and seizures. He denied a history of migraine or strokes. The medical history of the patient included hypertension, diabetes mellitus, and dyslipidemia. There was no previous history of trauma, drug abuse, toxins, smoking, or alcohol intake. Family history was negative for young-onset stroke or dementia. Montreal cognitive assessment score was 18 out of 30. He scored zero on the visuospatial and executive questions. Tandem gait was

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difficult to perform. Routine biochemical and hematological examinations were significant for protein C deficiency and elevated erythrocyte sedimentation rate. Magnetic resonance imaging (MRI) of the brain showed bilateral extensive discrete and confluent T2 and fluid attenuated inversion recovery hyper-intensities involving the periventricular deep white matter of both cerebral hemispheres and centrum semiovale with a few other small cortical leukomalacia changes affecting both frontal and parietal lobes associated with extensive supra and infratentorial white matter changes with multiple old small cortical infarctions [Figure 1]. Electroencephalography showed evidence of mild diffuse encephalopathy with a right temporal cerebral dysfunction. Genetic testing using whole-exome sequencing revealed a heterozygous missense variant c.2989T>C, p.Cys997Arg in exon 18 of the *NOTCH3* gene (NM_000435). We started the patient on aspirin, atorvastatin, rivastigmine, and memantine. We counseled the patient and advised early medical retirement.

## DISCUSSION

The typical manifestations of CADASIL start in the third decade of life with attacks of migraine with aura followed by subcortical ischemic infarctions leading to psychiatric symptoms and dementia.[5] The disease is characterized by striking phenotypic heterogeneity in several features such as age at onset, clinical syndromes, and disease progression. For instance, the disease duration in CADASIL can range from 3 to 43 years.[6] It is likely that even within a family, the clinical syndromes may vary considerably, and no evidence has been found of interfamilial clustering of particular phenotypes.[7]

Early-onset dementia (onset before age 65) is a challenging condition with many possible causes, including early-onset familial Alzheimer's disease, frontotemporal lobar degeneration, Parkinson's dementia, Lewy body dementia, disorders of amino acid and organic acid metabolism, leukodystrophies, lysosomal storage diseases, disorders of metal metabolism, and mitochondrial diseases.[8] In our patient, the history, physical examination, laboratory investigations, and neuroimaging were not suggestive of these causes and prompted the search for a rare etiology.

The most common MRI finding associated with CADASIL is basal ganglia and white matter hyperintensities in T2-weighted sequences that start as punctate or nodular foci and then often become confluent, extensive, and usually symmetrical, mainly in the periventricular region, anterior temporal pole, external capsule, the centrum semiovale, and frontal and parietal areas.[9] The diagnosis in our case was mainly suspected based on the MRI findings that made CADASIL a very likely diagnosis and prompted performing genetic testing. This indicates the importance of recognizing the MRI pattern and considering the atypical presentation of CADASIL to score the diagnosis in a timely manner.

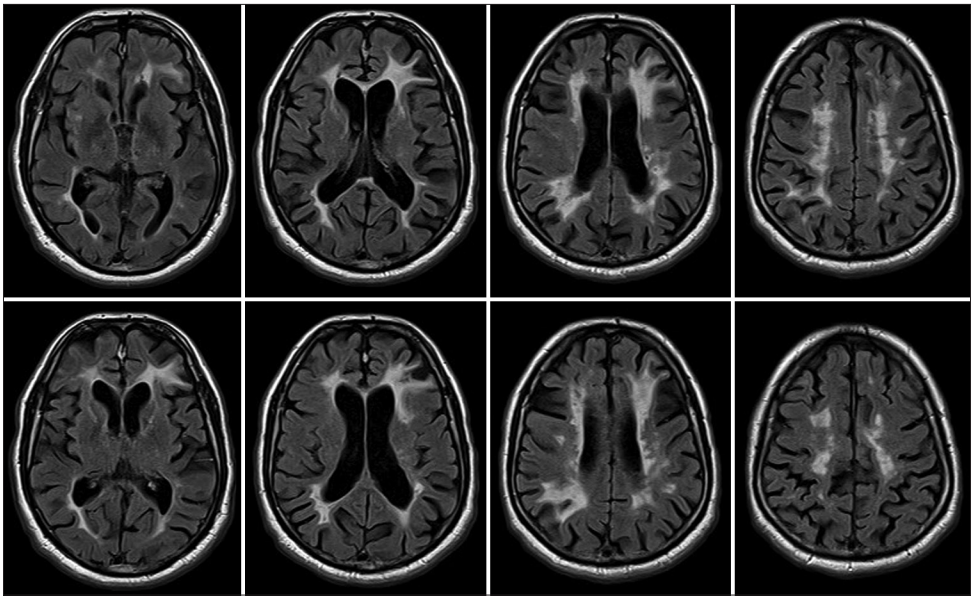

**Figure 1:** Axial magnetic resonance imaging of the brain showing bilateral extensive discrete and confluent fluid attenuated inversion recovery hyper-intensities involving the periventricular deep white matter of both cerebral hemispheres and centrum semiovale with a few other small cortical leukomalacia changes affecting both frontal and parietal lobes associated with extensive supra and infratentorial white matter changes with multiple old small cortical infarctions.

## CONCLUSION

This article reported an interesting case of CADASIL from Saudi Arabia who had an atypical clinical presentation in the form of isolated frontotemporal dementia. The diagnosis was suspected mainly because of the typical brain MRI features that led to performing genetic testing to confirm the diagnosis. This illustrates the importance of brain MRI in the diagnosis of CADASIL. Increased awareness of neurologists and neuroradiologists about the typical MRI features of CADASIL is of paramount importance to reach the diagnosis in a timely manner. Awareness of the atypical presentations of CADASIL will lead to identifying more CADASIL cases. Multidisciplinary care of patients with CADASIL should be carried out in specialized centers.

### Declaration of patient consent

Institutional review board (IRB) permission obtained for the study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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