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Case Report

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An Unsuspecting Recurrent Cryptogenic Stroke: A Case Report

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ABSTRACT

Cerebral Autosomal Dominant Arteriopathy with Sub-Cortical Infarcts and Leukoencephalopathy (CADASIL) is a rare autosomal genetic disorder that affects the brain's small vessels. It is recognized among the leading causes of stroke in the young.

This is a case report of a 35-year-old female with underlying migraine with auras who presented with recurrent cryptogenic strokes. She presented no vascular risk factors or any family history of neurological disease. An investigation into her presentation leads us to a diagnosis of CADASIL following typical subcortical and deep white matter changes seen on her Magnetic Resonance Imaging (MRI).

Introduction

Cerebral Autosomal Dominant Arteriopathy with Sub-Cortical Infarcts and Leukoencephalopathy (CADASIL) is a rare autosomal genetic disorder that affects the brain's small vessels. This hereditary disease is assumed to be due to various mutations of the NOTCH3 gene situated on chromosome 19q12; it codes for a transmembrane receptor protein located on the surface of the smooth muscle cells that surround an artery. An accumulation of the pathologic NOTCH3 receptor proteins in small and medium-sized cerebral arteries is thought to be responsible for CADASIL's pathogenesis and phenotypic presentation [1]. CADASIL often initiates with migraine attacks with aura during the third decade, followed by ischemic events around 10 years later, dementia approximately 20 years after onset, and death during the sixth decade. Family history is invariably always present.

Case Presentation

A 35-year-old female of Chinese origin with underlying young hypertension and a history of migraines

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with aura presented recurrent cryptogenic strokes. Before her cerebrovascular event, she lived a healthy lifestyle. She did not smoke or consume alcohol, exercised regularly, and performed well as an accountant at work. There was no significant family history. She was diagnosed with hypertension at 30 on a routine medical examination and was prescribed an ace inhibitor by her family physician. Apart from migraines triggered by particular food and irregular sleep, she did not complain.

Her first stroke occurred at 33 years of age, following a severe migraine-like headache. She woke up that morning with an acute left-sided hemiparesis. A Compute Tomography (CT) brain scan revealed multifocal infarcts affecting the right putamen, right thalamic, and left parietal regions. She recovered fairly well without residual weakness and was started on aspirin and a high-intensity statin. She was compliant with her medication and followed a strict dietary regime. The patient was worked up for possible causes for a young stroke, and the test came back normal. The patient's blood parameters were within normal limits, and the Antiphospholipid (APLS) and thrombophilia screen were negative. An ultrasound of her carotids was normal, and a transcranial ultrasound did not suggest any intracranial stenosis. A complete cardiac assessment was also performed, which included an Electrocardiogram (ECG), Transthoracic Echocardiogram (TTE), Transoesophageal Echocardiogram (TOE), and a 48-hour Holter, which revealed no significant finding.

Following this, the patient did report 2 other brief episodes of weakness, the first involving her entire right side, which lasted for a few hours, and she fully recovered. A second episode involved mild weakness on the same side but lasted less than 15 minutes. She never sought any form of treatment for those episodes and from further retrospective history obtained, her symptoms were strongly suggestive of transient ischaemic attacks.

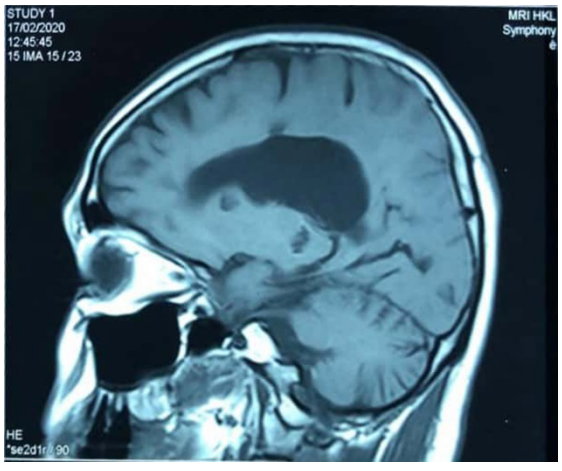

Figure 1. MRI T1W coronal plane showing periventricular hypointensities

The patient had a second major stroke in 2018, and this time presented with a dense right hemiparesis, dysarthria, aphasia, neglect, and visual agnosia. Routine blood investigations and an electrocardiogram were all normal.

Imaging findings

MRI data revealed multifocal lacunar infarcts of varying ages in regions supplied by anterior and posterior circulations. An acute right occipital lacunar infarct was noted with microhemorrhages and evidence of leukoencephalopathy. Multiple periventricular hypointensities were noted on a T1W coronal planesed (Figure 1). The T2W axial plane, on the other hand, showed temporal and periventricular hyperintensity (Figure 2). In the FLAIR sequence on the axial plane (Figure 3), there were confluent hyperintensities over bilateral periventricular and deep white matter, corona radiata, external capsule, and centrum semi ovale with leucoencephalopathy. Multiple lacunar infarcts were also noted in the basal ganglia. Using Gradient Echo sequences (GRE), microbleeds (hypointense foci) mainly over the left thalamus were visible (Figure 4).

MRA 3D TOF of Willis arteries MCAs, ACAs, PCAs, and the vertebrobasilar system showed normal flow signals without significant stenosis. There was no evidence of aneurysmal dilatation or arteriovenous malformation.

Making a diagnosis

Upon reviewing these MRI findings coupled with this patient's clinical presentation, we suspected CADASIL. Genetic analysis demonstrated a typical NOTCH3 mutation that confirmed our suspicion.

Progress

The patient was an only child, and she did not report any family history of strokes. Her antiplatelet agent was switched to clopidogrel from aspirin. She was started on an ACE inhibitor that provided adequate control for her blood pressure. Her migraines with auras initially remained frequent though they responded well to NSAIDs in the acute phase; however, we decided to start her on additional acetazolamide (250 mg daily), which proved beneficial in reducing the frequency of the attacks. She was referred to the stroke rehabilitation team and is currently progressing well.

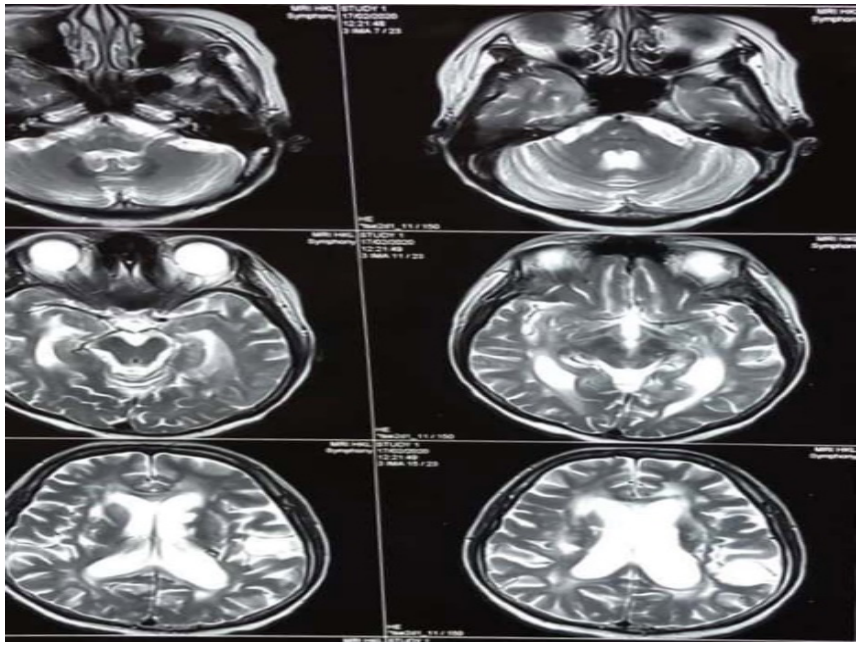

Figure 2. MRI T2W Axial plane showing symmetric white matter hyperintensities with leukoencephalopathy

Discussion

Epidemiology

CADASIL has an autosomal dominant trait, with patients typically becoming symptomatic in adulthood (30-50 years). Based on most regional databases, the estimated prevalence of carriers harboring pathogenic variants in NOTCH3 from earlier studies was 0.8 to 5 per 100,000 individuals [1].

Clinical presentations

Patients with CADASIL usually present with one or more of the following manifestations: ischemic events, cognitive impairment, migraines with aura, neuro-psychiatric symptoms, and acute reversible encephalopathy [2].

Diagnosis

CADASIL is suspected based on symptoms, family history, and brain MRI lesions compatible with the disease. An MRI may present typical features such as hyperintensities on T2-weighted imaging or FLAIR in the periventricular and deep white matter regions; a characteristic presence of isolated T2 hyperintensities involving the temporal poles, and microhaemorrhages. Although MRI can identify characteristic changes in the brains of individuals with CADASIL, such changes are not unique to CADASIL.

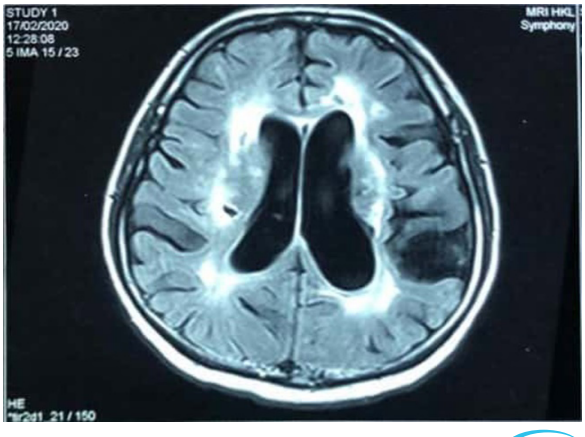

Figure 3. MRI FLAIR showing periventricular hyperintensities

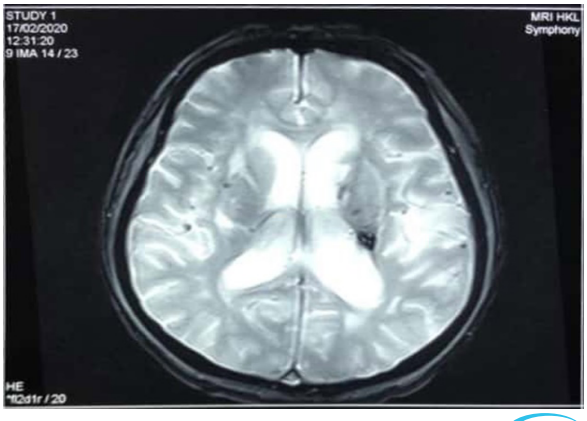

Figure 4. MRI Gradient Echo Sequences (GRE) sequence showing small hypointense foci represent microbleeds

More specific tests are usually required to make a confirmatory diagnosis. It was found that the deposition of a Granular Osmiophilic Material (GOM) in vascular smooth muscle cells, observed on electron microscopy from a skin biopsy, had shown to be an essential diagnostic tool, with a specificity of 100%, and a variable sensitivity which could be as low as 45% according to the different reports [3]. Given this, a negative test does not entirely rule out CADASIL.

In reason times, genetic testing has become a more popular diagnostic tool and when there is a clinical suspicion of CADASIL, a genetic analysis of NOTCH3 Sanger sequencing of EGFr encoding exons is the first choice for confirming the clinical diagnosis. It can be performed as a screening tool for asymptomatic family members.

Treatment

In CADASIL, ischemic manifestations, such as acute transient ischemic attack and acute stroke are managed following the general principles of stroke medicine. Other related symptoms need to be addressed and treated appropriately. These may include;

1) Migraines

2) Depression or anxiety

3) Cognitive difficulties

It is important to note that in a patient with CADASIL, physical and cognitive disability tends to be progressive, and in some cases, it may become quite severe. Given this, it is always important to frequently assess these patient's ability in performing activities of daily living, ambulation, and self-care. A rehabilitation regimen ideally should be prescribed for all these patients upon discharge [4].

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

The authors reported no conflict of interest.

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