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Case Report

Persistent aura and status migrainosus in CADASIL syndrome: A case report[☆]

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy characterized by a genetic predisposition to small arteries of the brain. It is produced by a mutation in the NOTCH3 gene and concerns adults. The symptomatology is diversified including migraines with or without aura, subcortical ischemic events, and cognitive impairment. The diagnosis of CADASIL is suspected by neuroimaging and confirmed by genetic testing. Treatment of the disease remains preventive. We report a case of CADASIL manifesting as status migrainosus with persistent aura.

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic vasculopathy caused by a NOTCH3 gene mutation.

It affects middle-aged people and manifests as diversified clinical symptomatology, including subcortical ischemic events, migraines with or without aura, and cognitive impairment [1]. The overall prevalence of CADASIL is unknown because it is rare and often misdiagnosed. A study from Scotland estimates that the prevalence of the disease is 4.15 cases per 100,000 [2].

CADASIL could be diagnosed by several methods, including MRI, genetic testing, and skin biopsy. The characteristic ra-

diological findings of the disease are signal abnormalities involving the anterior temporal lobes and the external capsule. Genetic testing revealed a mutation in the NOTCH3 gene on chromosome 19 [3]. A granular osmiophilic material (GOM) is found in the smooth muscle cells. We present an uncommon case of CADASIL with a prolonged aura and status migrainosus.

Clinical case

A 38-year-old female patient who has no significant medical history was admitted to the emergency department after 6 days of continuous, unilateral, pulsatile, and severe

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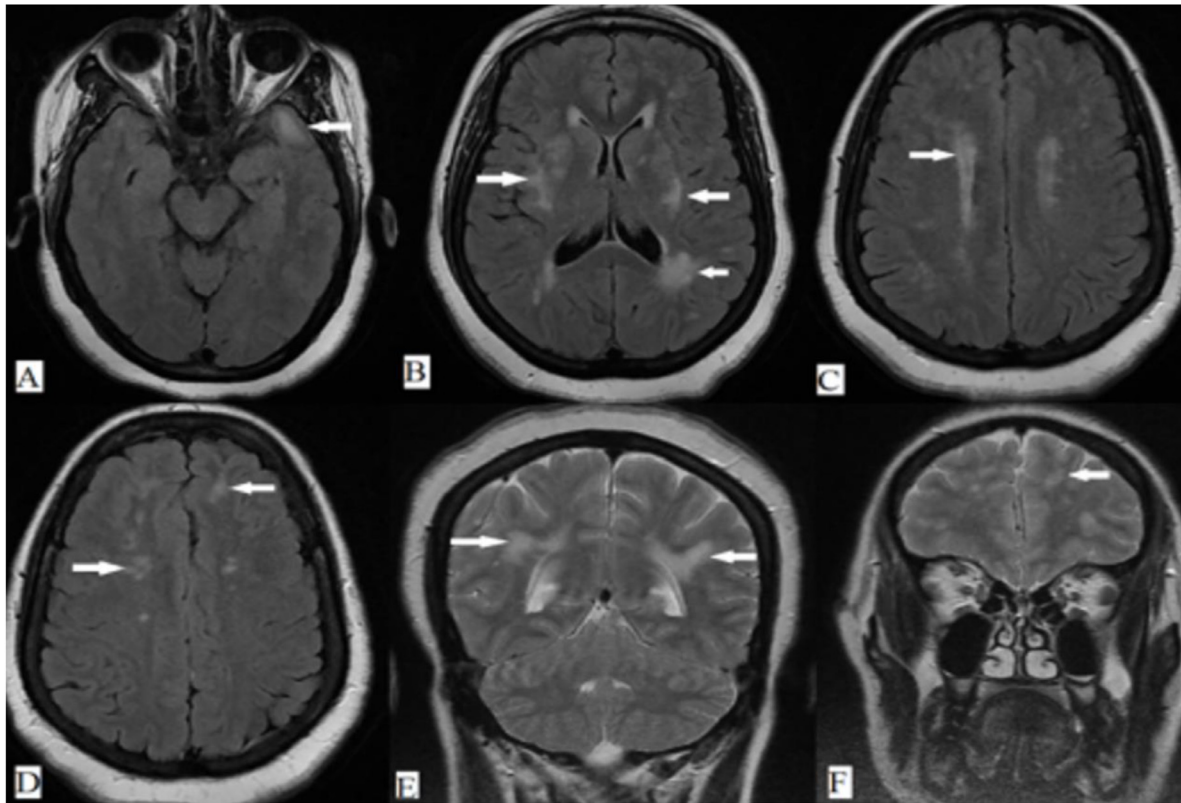


Fig. 1 – Cranial MRI on axial FLAIR sequence (A to D) and coronal T2 weighted sequence (E and F) showing increased signal intensity interesting the left temporal lobe, the periventricular regions, the subcortical areas, and the external capsules.

headaches. Twelve hours before admission, the patient had scintillating scotoma in the left visual field with left arm paresthesias. The patient has complained about recurrent episodes of migraine attack with typical visual aura for 2 years. She did not see a doctor because her symptoms resolved spontaneously. She reported a family history of ischemic stroke at age 45.

The patient was afebrile with normal blood pressure. A neurological examination revealed a confused patient with psychomotor slowness. She had difficulty in speech and paresthesias on the left upper limb. Examination of muscle strength, sensitivity, and motor coordination was normal. The deep tendon reflexes were brisk with a normal plantar response. There was a peripheral scotoma in the left visual field. The cranial nerves were intact. The examination of other extra neurological systems was unremarkable.

Noncontrast computed tomography (CT) was normal. The patient was started on a 50 mg dose of oral sumatriptan with 400 mg of oral ibuprofen in the emergency department. The pain was slightly improved but the visual disturbance remained unchanged. A few minutes later, the patient exhibited a sudden generalized seizure lasting 3 minutes. She received 2 mg of IV lorazepam before being hospitalized.

Cranial MRI demonstrated on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences, high-signal intensity in the periventricular areas and subcortical regions with confluent lesions in the external capsules and the left anterior temporal lobe (Fig. 1).

Lumbar puncture was normal. Fundoscopy revealed retinal cotton-wool spots. Cardiovascular workup (Holter ECG, Transthoracic echocardiography, and supraaortic trunk echodoppler) was normal. A Venereal Disease Research Laboratory test was normal. Standard laboratory tests were negative. Gene mutation screening revealed a mutation in NOTCH3 at exon 3.

As a symptomatic therapy for migraine attacks, the patient was given antiplatelet drugs and conventional analgesics, with antiepileptics as a background medication. The impact and frequency of migraine episodes considerably improved after few weeks.

Discussion

CADASIL is a hereditary arteriopathy affecting the brain's white matter. It was described for the first time in 1955. Since that, various cases of vascular disorders with vascular dementia have been documented [4]. The disease's clinical symptomatology differs between individuals.

The characteristic clinical symptoms are migraine with aura, cognitive impairment, transient cerebral ischemic attack, and mood disorders. The frequency of clinical symptoms varies with the duration of the disease and age. Around 20%–40% of patients with CADASIL have presented with different types of migraine [5,6].

A study by Guey et al. [7] conducted in 378 patients with CADASIL using a standardized questionnaire of migraine demonstrated that 54.5% of the patients had a history of migraine. 84% of these patients had aural symptoms with migraine, and 62% were female.

The clinical diagnostic criteria for status migrainosus and prolonged aura without infarction were met by our patient [8]. Cases of CADASIL presenting as a status migrainosus (migraine attacks lasting longer than 72 hours) have already been reported.

Our patient presented with status migrainosus and prolonged aura, which is unusual. Another intriguing discovery was that our patient had an epileptic seizure while suffering from status migrainosus and after taking sumatriptan. This triptan drug may have triggered an aberrant vasoconstrictor reaction, which resulted in the generalized epileptic seizure. This hypothesis needs to be confirmed.

MRI is important in the diagnosis of CADASIL. The MRI abnormalities first show at the age of 30 and are evident in all patients beyond the age of 35 [9]. CT scan did not show the early finding but could exclude acute bleeding.

The earliest abnormalities in MRI are a punctiform or nodular high signal intensity on FLAIR and T2-weighted images predominating in the periventricular regions. These abnormalities eventually become extensive and symmetrical, mostly in the front temporal lobes and the external capsule, which is strongly indicative of CADASIL [10]. A novel noninvasive and effective approach for detecting early signs of CADASIL is optical coherence tomography angiography [11].

CADASIL is diagnosed by genetic testing. Genetic mutations of the NOTCH3 gene were discovered in 1996 [12]. NOTCH3 is a transmembrane receptor found in smooth muscle cells. The genetic mutations generate protein misfolding and defects in the reactivity of the vascular wall, which obstruct blood flow in small vessels and cause subcortical ischemic events [13]. Exons 2–24 encode 34 epidermal growth factor repeats in the receptor's extracellular region. All CADASIL mutations are found in exons 2–24, with exons 3 and 4 showing the most grouping [14].

Microscopic investigations in CADASIL show a specific arteriopathy characterized by a nonamyloid GOM within the media associated with morphological changes in smooth muscle cells [15]. In the case of a negative molecular test in a patient with clinoradiological characteristics indicative of CADASIL, skin biopsy is recommended.

Presently, there is no therapy for CADASIL that is effective. The treatment of migraine with aura is based on prophylactic drugs such as β -blockers or antiepileptic drugs. For migraine attacks, conventional analgesics are preferred to vasoconstrictors such as triptans and ergot derivatives, which should be avoided [16].

Antihypertensive drugs, statins, treatment of vascular risk factors, and antiplatelet agents are the main preventive measures of ischemic attacks. Several factors, including the genotype, hypertension, gender, diabetes, and intercurrent infections could reduce the life expectancy of patients with CADASIL [3]. In this chronic and severe condition, nursing care, psychological support, and rehabilitation are critical.

Conclusion

CADASIL is a genetic microangiopathy that has received attention in the last decade as the most frequent form of ischemic cerebral small artery disease. The main clinical symptoms are migraine with aura, cerebrovascular accident and impaired cognition. A mutation in the NOTCH3 gene is related to CADASIL. MRI can reveal the characteristic abnormalities of the disease. Skin biopsy is restricted to patients with a negative molecular test. The management of the disease is based on the control of vascular risk factors, antiplatelet agents, rehabilitation, and psychological support.

Patient's consent

I qualify as the corresponding author to this manuscript warrant that I have informed the patient of this scientific manuscript and I confirm that I obtained his written and informed consent for the publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.radcr.2022.07.050](https://doi.org/10.1016/j.radcr.2022.07.050).

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