Case Report

Cad asil syndrome: A case report with a literature review

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A R T I C L E   I N F O

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A B S T R A C T

“CADASIL” is a genetic microangiopathy with autosomal dominant inheritance. Its epidemiology and physiopathogenesis are poorly specified, but it is proven that this disease is due to a mutation of the NOTCH3 gene resulting in a loss of elasticity of the media of the affected vessels. The clinical expression is variable, dominated by migraine attacks with aura, ischemic vascular accidents and psychiatric disorders, in particular depression. MRI is essential for diagnosis even in the pre-symptomatic phase. It shows signal abnormalities in the basal ganglia and white matter, characteristic especially when located in the anterior part of the temporal lobes. The management of CADASIL is multidisciplinary, psychological for the most part without specificity of a particular treatment.

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Clinical case

This is a 51-year-old patient with no notable medical history who has complained for 4 years of recurrent episodes of migraine attack, most often accompanied by scintillating scotoma-type aura and cheiro-oral paresthesias sometimes extending to the upper limb. The patient did not show signs of intracranial hypertension or extra-neurological signs, particularly of the skin or joints.

The course of symptoms was characterized by the resurgence of migraine attacks becoming increasingly intense and resistant to the usual analgesics (Acetaminophen). Neurological examination did not find any focal signs. Head CT did not show any abnormality and a brain MRI revealed a marked leukoencephalopathy in the frontal lobes with sev-
infarcts

Cerebral researchers consequently antiepileptics. Level and family, unable. Negative Doppler (Doppler).

A lumbar puncture was normal, and a cardiovascular workup (TTE, Holter ECG and supra-aortic trunk echo-Doppler) did not reveal any abnormality. HIV serology was negative and the rest of the blood work was also unremarkable. Family history revealed extensive similar cases in the family, prompting the evaluation of arteriopathy of the small vessels. Genetic studies were positive for a mutation in the NOTCH3 gene. The patient was placed on Anti-platelet agents and began symptomatic treatment of migraine attacks with level 2 analgesics, as well as background treatment with antiepileptics. The number and severity of these attacks subsequently decreased (Figs. 3, 4).

Discussion

The term CADASIL was proposed in 1993 by French researchers to designate the disease. This is an acronym for "Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy". This genetic disease affects the small blood vessels in the brain and results in poor blood supply to certain areas of the brain, resulting in multiple ischemic lesions and variable symptoms based on the location of the lesions. The prevalence of CADASIL is not well understood, but affects approximately 1 in 24,000 people although it is probably underestimated. The sex ratio is 1:1. Symptoms begin in adulthood, usually between the ages of 30 and 40. The disease is linked to a mutation in the NOTCH3 gene, carried on the short arm of chromosome 19. This gene is involved in several functions during the development of the fetus, in particular the genesis of the media of the arteries.

Following an anomaly of the NOTCH3 gene, the muscular layer of the arteries is of lower quality leading to its progressive degradation. The lining of the arteries then loses elasticity, which hinders blood flow. Although the arterioles of all organs can be affected, the repercussions are mainly cerebral. Areas of the brain supplied by these arterioles are deprived of oxygen, resulting in the occurrence of multiple infarctions. The repetition of these small cerebral infarctions therefore causes the symptoms and their progressive aggravation.

The first clinical manifestation of CADASIL in young adults is most often episodes of migraine. Later on, recurrent sub-

Fig 1 – (a,b,c): Axial images of brain MRI in T2 Flair weighted sequences, showing confluent hyperintense lesions in the periventricular and subcortical white matter related to leukoaraiosis and sequelae of ischemic lacunar lesions in the supra and infratentorial white matter.

Fig. 2 – (a, b, c): The B-1000 Diffusion weighted sequence shows no abnormality (a) associated to the absence of enhancement on T1 post contrast images, (b, c) confirming the chronic ischemic nature.
cortical ischemic attacks lead to neurological deterioration, frontal-type dementia and depressive-type psychiatric disorders.

MRI Signal abnormalities are always present in symptomatic subjects. The onset of clinical manifestations may be preceded by a shorter or longer interval during which brain imaging is abnormal [2,3]. MRI shows punctate or nodular foci of hyposignal in T1- and hypersignal in T2-weighted sequences in the basal ganglia and white matter, with often confluent areas within the white matter. These hypersignals are usually symmetrical, predominant in the periventricular regions and the centrum semiovale, showing an aspect of more or less extensive leukoencephalopathy associated with lacunar infarcts of the basal ganglia and brainstem and sometimes microscopic bleeding on the gradient-echo sequences. The involvement of the anterior poles of the temporal lobes is particularly suggestive [4].

However, distinguishing on MRI between CADASIL and leukoaraiosis may be difficult in a patient with multiple infarctions and subcortical dementia, especially in the absence of a family history. During these two pathologies, the lesions observed are those of a microangiopathy. In both cases, white matter anomalies, mainly in the supratentorial and in the periventricular regions, are observed on the T2 sequences. Vascular lesions, which can be demonstrated by a skin biopsy, sit on small arteries, the media of which are thickened by granular osmiophilic material (GOM). However, the skin biopsy is currently only performed for diagnostic purposes in cases of persistent doubt after sequencing of the NOTCH3 gene. This gene, which codes for a transmembrane protein, is found mutated in these patients, resulting in the accumulation of the protein in the media during CADASIL, which is the cause of a probable defect in the reactivity of the vascular wall. The inheritance of the mutation is autosomal dominant. The fam-

Fig. 3 – (a, b): Brain MRI performed at 18 months following diagnosis, T2 (a) and T2 FLAIR (b) weighted sequences show an extension of leukoaraiosis lesions, with the development of other supratentorial white matter and mesencephalic lesions.

Fig. 4 – (a, b, c): A brain MRI performed within 3 hours of an intense headache at- tack occurring 36 hours diagnosis, showing a focal restriction of diffusion in the midbrain without imaging translation on FLAIR sequences (b), and without an abnormality on 3DTOF (c) weighted sequence, suggesting an acute ischemic injury.
ily investigation should include MRI, which may show extensive white matter lesions in a patient who is asymptomatic or whose symptoms reduce to migraines or depression [1].

No specific treatment has been proven to date in CADASIL. Some authors suggest the use of antiplatelet agents in patients who have had ischemic manifestations of the brain, based on data on the prevention of ischemic strokes associated with atherosclerosis. The recommendations are not to use anticoagulants, because of the risk of hemorrhage in the brain (symptomatic intracerebral hemorrhages reported in a few cases and frequency of microbleeds within the brain tissue), and to avoid all vasoconstrictor treatments to treat the symptoms of migraine attacks during the disease, due to the potential ischemia-inducing risk of these molecules. The medical and psychological care of the patient and his or her family is crucial in this pathology as soon as the diagnosis is announced. An organization for the support of families participates in improving the medical and social care of the patients concerned by CADASIL [5].

The medical care of patients must be carried out in multi-disciplinary and specialized structures.

**Conclusion**

"CADASIL" is a genetically caused microangiopathy of the cerebral vessels. The symptomatology is dominated by migraines with aura, transient ischemic attacks, and progressive cognitive deterioration in the context of a family history of dementia and / or ischemia. The final diagnosis is based on the sequencing of the NOTCH3 gene, the mutation of which is responsible for the pathology, but MRI plays a key role through revealing the characteristic abnormalities that it highlights even in pre-symptomatic disease. Treatment is nonspecific and psychological support is a cornerstone in the management of this disease.

**Patient consent**

This piece of the submission is being sent via mail.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2021.08.023.

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