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Cephalalgic syndrome in autosomal dominant cerebral arteriopathy with subcortical infarctions and leucoencephalopathy

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Abstract

Background: Autosomal Dominant Cerebral Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is caused by mutations in NOTCH3 gene, classic symptoms include migraine with aura, ischemic strokes, apathy, depression and dementia. Headache is usually the first symptom, characterized by recurrent attacks of migraine with typical, hemiplegic or prolonged aura with unusual frequency.
Material and methods: All the data were picked from the patient's medical recordings. The patient had undergone a complete clinical exam, a contrast enhanced MRI-scan and a genetic test. Then a literature review was done based on the peculiarities of the case.
Results: A 43-year-old woman presented with pulsatile, alternating, severe headache, accompanied by phono, and photophobia, nausea and vomiting, with an onset at 35 years and a frequency of 12/30, triggered by menstruation and stress, preceded by a day by a visual aura lasting 5-6 minutes. Family history revealed cases of stroke and migraine. Neurologic examination was normal, but a contrast enhanced MRI showed diffuse polymorph confluent subcortical white matter lesions, involving external capsule and anterior poles of the temporal lobes. NOTCH3 gene sequencing revealed the presence of a heterozygote missense c.421C>T mutation, localized in the 4thexone. After establishing the diagnosis, the patient was prescribed a symptomatic treatment.
Conclusions: Headache in CADASIL patients has well-defined diagnostic criteria in the International Classification of Headache Disorders, is being considered a secondary headache which may resemble or not migraine with aura. The patient presented a migraine-with-aura-like headache but with some peculiarities.
Key words: CADASIL, NOTCH3, migraine with aura.

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Introduction

This article presents a rare clinical case of secondary migraine-like headache attributed to Autosomal Dominant Cerebral Arteriopathy and Leukoencephalopathy. This type of headache is described in the International Classification of Headache Disorders, 3rd ed., section "Headache attributed to cerebral and/or cervical vascular diseases", subchapter 6.8 "Headache and/or migraine-like aura attributed to chronic intracranial vasculopathy", form 6.8.1 "Headache attributed to CADASIL" [1].

Headache is one of the 5 major symptoms of Autosomal Dominant Cerebral Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. The prevalence of headache in CADASIL patients according to the data of different studies, ranges between 14% and 72% [2-6], being higher in women than in men. The pattern of migraine differs from that observed in the general population, with migraine with aura being dominant [7]. The vast majority of patients report the presence of migraine with aura (80-90%) [3, 8]. The aura is typical in 44%, while 56% of patients show atypical aura – aura without headache, hemiplegic aura, basilar or prolonged aura [5, 9]. Imaging changes do not differ between patients with migraine with aura and those without aura [9].

Autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common cause of hereditary cerebral infarcts in adults [10, 11]. Clinically, it is manifested by migraine with aura, depression, apathy, dementia and recurrent ischemic strokes [12]. CADASIL is caused by mutations in the NOTCH3 gene on chromosome 19q12 [13], a transmembrane receptor located on cerebral vascular smooth myocytes, the mutation of which produces thickening and fibrosis of the vascular wall, changes responsible for the production of subcortical cerebral infarcts [10].

According to the International Classification of Headache Disorders, headache associated with CADASIL has the following criteria [1]:

A. Recurrent migraine attacks with typical aura, hemiplegic, or prolonged aura, fulfilling criterion C.

B. The existence of CADASIL has been demonstrated[1].

C. One or both of the following:

1. Migraine with aura is the earliest manifestation of CADASIL

2. Migraine attacks with aura improve with the appearance of other manifestations of CADASIL (ischemic strokes, affective disorders or cognitive disorders)

D. Not explained by another diagnosis from the International Classification of Headache Disorders.

Note:

1. Diagnosis is made by screening for the NOTCH3 mutation, by a simple skin biopsy with anti-NOTCH3 antibody immunofixation, or by electron microscopy to assess osmophilic granular extracellular material (GON) in the medial arterial wall.

The results of studies on the epidemiology of headache in CADASIL are controversial [6, 14-21]. Moreover, little is known about what the correct therapeutic approach would be and whether its management should be different from the management of migraine in the general population [22-26]. Although migraine with aura has been shown to be a risk factor for stroke in the general population [26-30], it is unclear whether migraine with aura in CADASIL is a predictive factor for infarction cerebral or for a more aggressive phenotype.

The purpose of the research was to analyze the characteristics of headache in CADASIL patient.

Material and methods

The case is reported of a patient diagnosed with CADASIL, who phenotypically presented migraine-like headaches, but with some particularities, and the literature review is presented regarding the particularities of the headache syndrome in CADASIL. The patient's medical data were extracted from the medical record with her consent. The creation of the literature review was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. 380 articles in the PubMed database published between 1993 and 2023 dedicated to the headache syndrome in CADASIL were identified. Keywords to identify references were: *CADASIL, headache, migraine*. Articles reporting clinical cases and articles referring to basic research were excluded, as a result, 14 studies on the epidemiological, clinical and treatment features of headache syndrome in CADASIL were included.

Results

A 42-year-old female patient presents with generalized, pulsatile alternating hemicrania that gradually increases in intensity to 9/10 SVA on the first 2 days, then 8/10 SVA on the 3rd day, then 5-6/10 SVA on the 4th day, with a frequency of 12/30 days, duration – 72 hours, triggered by menstruation and psycho-emotional stress, relieved by the administration of analgetics, which started at 35 years old, accompanied by nausea, vomiting, phono- and photophobia, visual aura lasting 5-6 minutes, which appears a day before the headache and sensitive aura – numbness in the left hand, history of eredo-collaterals – paternal aunt suffers from migraines. Neurological examination was unremarkable.

When collecting the anamnesis, the patient revealed that the paternal grandmother suffered a stroke, as a result of which she was paralyzed, the patient's father died of a cerebral infarction at the age of 49, and the paternal aunt suffers from migraines. Figure 1 shows the genealogical tree of the family, which outlines a pathology with autosomal dominant transmission.

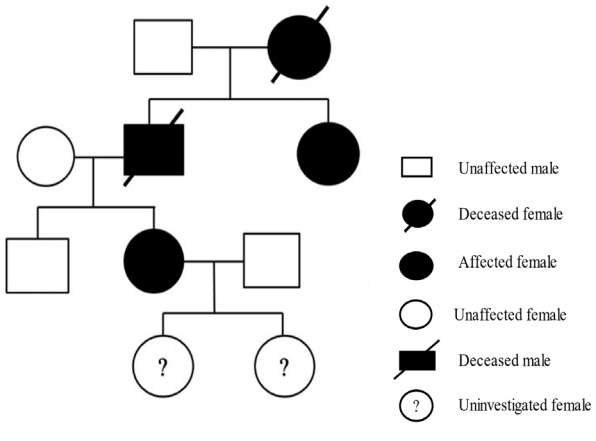

Fig. 1. The genealogical tree of the family
Family history showed that her paternal grandmother and her father, aged 49, died both from a stroke, whilst her paternal aunt has migraines. The family pedigree revealed an autosomal dominant type inheritance.

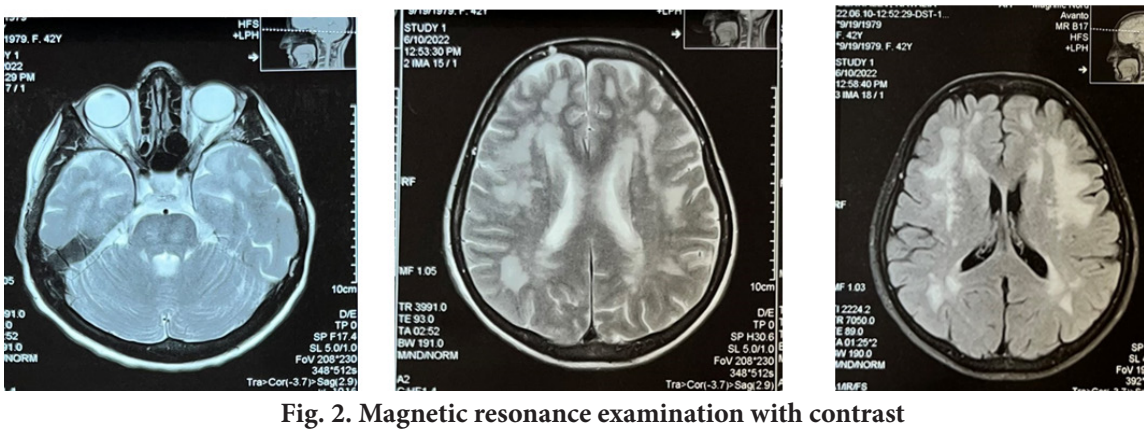

Fig. 2. Magnetic resonance examination with contrast

Figure 2 shows images of the 1.5T cerebral Magnetic Resonance examination with contrast which revealed the existence of multiple confluent polymorphous lesions in the subcortical, bihemispherical periventricular and infratentorial cerebral white matter at the level of the pons of Varolio bilaterally, the anterior poles of the temporal lobes bilaterally, the external capsule. Lacunar focus <4mm in the frontal subcortical white matter on the right.

Taking into account the presence of the clinical picture of migraine with atypical aura and the suggestive imaging changes, the patient was recommended to perform the genetic test that identified the mutation c.421C>T (p. Arg141Cys) at the level of exon 4 of the NOTCH3 gene in a heterozygous state. This change is reported in the specialized literature as having clinical pathological significance. Interpretation: the patient is affected by CADASIL syndrome as a result of the heterozygous c.421C>T mutation in exon 4 of the NOTCH3 gene. The clinical diagnosis was established – Autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy. Over 3 months, the patient reported a decrease in both headache intensity to 4/10 SAV and frequency – 4/30.

Discussion

The diagnosis of primary headache is established only on the basis of clinical criteria, according to the International Classification of Headache Disorders, 3rd edition, but it is imperative to initially exclude the causes of secondary headaches, especially treatable ones.

This case meets the criteria of the International Classification of Cephalalgic Disorders. Criterion A – the patient suffers from migraine attacks with atypical aura. Criterion B – the existence of CADASIL has been demonstrated. Criterion C – Migraine with aura is the earliest clinical manifestation of CADASIL.

In the case of this patient, the first clinical symptom was a migraine-like headache, which is, by the way, the most frequent and typical manifestation, but cases with atypical onset are described in the literature, such as migrainous status [7], hemiplegic migraine sporadic [8], acute confusional migraine [9], progressive asymmetric parkinsonism [10], generalized epileptic seizures [11] or recurrent intracerebral hemorrhage [12].

Headache in CADASIL is not a constant symptom, studies report different results, thus the study by Guey et al., which included 378 patients, reported a migraine incidence of 54.4%, of which with aura – 45.8% [6], Bianchi et al. (229 patients) report a migraine incidence of 42%, migraine with aura – about half [14], Paraskevas et al. (54 patients) report the incidence of migraine with aura – 39% [15], Tan et al. (52 patients), of which 39.58% suffer from migraine [16], Liao et al. (112 patients) report a very low incidence of migraine, only 2.7% [17], Chen et al. (169 patients) – 32.2% of patients have migraine [21], in the study by Ince et al. (25 patients) – 52% have migraine [20], Hawkes et al. (13 patients) report an incidence of 38.5% [19], and Nogueira et al. in the study that included 26 patients, 1/3 patients suffer from migraine [18].

Although CADASIL has diverse clinical presentation, even within the same family, 5 core symptoms are characteristic: migraine with aura, subcortical ischemia, affective disturbances, apathy, and cognitive impairment. These symptoms vary in frequency depending on age and duration of illness [3, 12, 31, 32].

There are several theories regarding the pathogenetic mechanisms of the headache syndrome in CADASIL. The first theory suggests that migraine with aura is the result of episodic ischemia caused by decreased blood circulation and cerebrovascular reactivity, which corresponds to the classical vascular theory of migraine [5]. The second theory claims that in CADASIL there is an increased susceptibility for the expansion of cerebral depression, which is caused by chronic vascular cerebral lesions or acute episodes of hypoperfusion [33], a mechanism already demonstrated in animal models [5, 34, 35]. Functional MRI studies have shown that in migraineurs with aura, areas located in the dorsal pons are excessively activated [36-39], at the same time, pontine lesions are often observed in patients with CADASIL [39, 40], thus, hypothetically these lesions could lead directly or indirectly to the occurrence of migraine with aura [5].

The most used preparations for the acute treatment of headache belong to the following groups: non-steroidal anti-inflammatory drugs, opioids, triptans, and for prophylactic treatment: calcium channel blockers, beta-blockers, anticonvulsants, and from other groups. Beta-blockers, although effective for the prophylactic treatment of migraine, in CADASIL headache patients report frequent side effects (fatigue and nightmares) [41]. Several small studies demonstrate that acetazolamide may be effective as a prophylactic treatment for CADASIL headache [22-24]. CGRP inhibitors would be potential drugs for the prophylactic treatment of CADASIL headache [42], but other authors argue that their use should be limited due to adverse effects (exacerbation of ischemia and psychiatric effects) [43].

Conclusions

1. Headache in CADASIL has well-defined criteria in the International Classification of Headache Disorders, being similar or not to migraine with aura.

2. The given patient presented a headache similar to migraine with aura, but with certain peculiarities (onset at 35 years, atypical visual aura and family history), suggesting that it is a secondary headache.

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Authors' contribution
CG, OG designed the research, did statistics and interpreted the data; LR, GC, SO drafted the manuscript; IM revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The research protocol was approved by the Research Ethic Board of the *Diomid Gherman* Institute of Neurology and Neurosurgery and the tests have been done according to the contemporary principles in biological standardization of experiences and Declaration of Helsinki with further amendments (Somerset West Amendment, 1996).

Conflict of interests
No competing interests were disclosed.