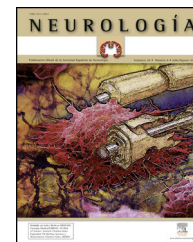




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LETTERS TO THE EDITOR

Isolated diplopia as a form of presentation of CADASIL: Presentation of a case[☆]

Diplopía aislada como forma de presentación de CADASIL: a propósito de un caso

Dear Editor

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an inherited adult-onset disorder characterised by migraine with or without aura, recurrent episodes of cerebral ischaemia without the typical cardiovascular risk factors, subcortical dementia, and neuropsychiatric disorders.^{1,2} Although this disease is underdiagnosed, it is considered the most frequent hereditary cause of ischaemic stroke.³

Doctors should suspect CADASIL in patients younger than 50 presenting typical symptoms, with a family history of similar entities, and whose brain MRI shows typical findings.^{3–5}

We would like to present a new clinical case characterised by atypical presentation and absence of family history.

The patient was a 65-year-old woman with a history of transient and recurrent diplopia evolving over 30 years. In 1986, she was examined in another hospital, where lumbar puncture yielded normal biochemical and cytological findings and cranial CT revealed anomalies in the white matter. In the preceding 8 months, she had been experiencing symptoms of progressive apathy and amnesia. One month before the visit, she was referred to the neurology department due to a new episode of transient diplopia whose clinical characteristics were similar to those of prior episodes. Neurological examination yielded no relevant findings at that time and could not provide more information about the episodes, except that they always had the same presentation. Forty-eight hours before our consultation, she presented language difficulties, mental confusion, retropulsion when walking, and loss of sphincter control. Her personal history included dyslipidaemia, right-sided mixed hypoacusia, and left-sided

neurosensory hypoacusia that required use of a hearing aid. The patient's parents had no history of stroke, migraine, or cognitive impairment. Examination showed the patient to be afebrile with a blood pressure of 130/70 mm Hg. Orientation was limited to recognising people, and speech was halting and reduced to stereotyped word use. Comprehension was limited to simple commands and object naming; reading and writing abilities were impaired. Gait was characterised by retropulsion and wide-based stance accompanied by inability to walk unaided. Cranial nerves were spared and the confrontation visual field test was normal. Diplopia was not detected during the hospital stay. Physical examination revealed no other abnormalities. Blood test including a haemogram and basic biochemical assessment yielded normal results. Serum levels of calcium, thyroid hormones, vitamin B₁₂, and folic acid were normal. Serology tests for HIV and syphilis were negative, as were results for antiphospholipid and antinuclear antibodies, and a thrombophilia study. Cranial CT displayed multiple ischaemic small-vessel lesions. CSF study showed normal results (1 cell, spinal fluid glucose concentration 70 mg/dL, protein concentration 45 mg/dL). Cranial MRI revealed extensive damage to bilateral supratentorial white matter, basal ganglia, and the bulbopontine region with presence of multiple ischaemic infarcts in basal ganglia (Fig. 1). MR angiography ruled out vascular malformations. The electroencephalogram, electromyogram, and visual evoked potentials were all normal. The ophthalmoscopy and carotid Doppler ultrasonography revealed no alterations.

Given the absence of alternative diagnoses that could justify these findings, doctors performed a skin biopsy and a genetic study to rule out CADASIL, even though the patient did not meet classic criteria for this disease. Electron microscopy of the skin biopsy revealed granular electron-dense deposits. Typical of CADASIL, these deposits were located between smooth muscle cells, in cell indentations, or within the basement membrane (Fig. 2). The genetic study revealed a heterozygous sequence change (C > T) at position c.397 on the Notch3 gene which led to a p.Arg133Cys (A133c) amino acid variant. The patient was treated with acetylsalicylic acid and galantamine.

Doctors interviewed the patient's 3 asymptomatic children (2 daughters aged 34 and 41 years, and a 44-year-old son). None of her children had a history of migraines or other clinical manifestations compatible with their mother's diagnosis. MRI scans from the 2 daughters showed extensive damage to periventricular white matter and multiple

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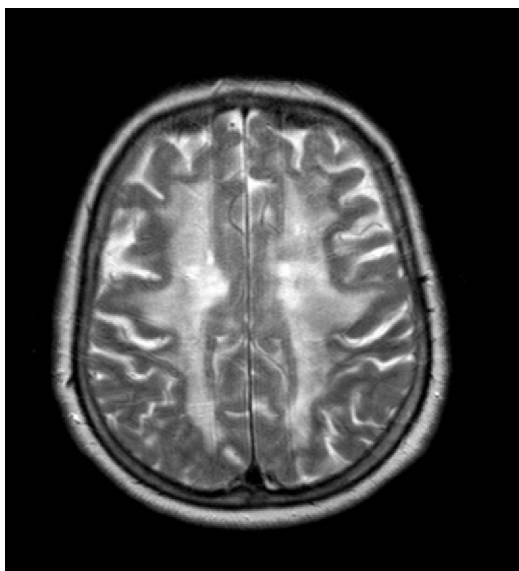


Figure 1 T2-weighted MRI sequence: generalised signal alteration in the basal ganglia, brainstem, and supratentorial white matter (callosum, external capsule, corona radiata).

subcortical infarcts; MRI in the son revealed only changes compatible with leukoaraiosis. Genetic tests and functional studies to confirm or rule out CADASIL are still pending. Genetic counselling was offered to the patient and cardiovascular risk factors were closely monitored.

CADASIL is a disease with various clinical manifestations and forms of presentation; this situation contributes to diagnostic difficulties and delays.^{6,7} The literature includes descriptions of visual disorders, especially amaurosis fugax, as initial manifestations of the disease.^{8,9} Likewise, researchers have published cases of early visual



Figure 2 Electron microscopy showing electron-dense deposits marked with a circle.

disorders that were detected by electrophysiological studies in asymptomatic patients with Cys146Tyr mutations.¹⁰ Diplopia is rare as a form of presentation of CADASIL. It has been mentioned as a manifestation of the brainstem impairment caused by the disease.⁴ However, the literature includes few clinical cases describing this symptom. Gurumukhani et al. published the case of a woman aged 52 who presented permanent diplopia in late stages of the disease. This was related to extensive white-matter damage.¹¹ Blanco-Menendez et al. mentioned diplopia as the form of presentation of a transient ischaemic attack in the course of CADASIL.¹² Lastly, Marrero-Falcon et al. described the case of a 55-year-old woman who, 10 years before, had begun experiencing recurrent episodes of vertigo and diplopia that were interpreted as transient ischaemia of the vertebrobasilar territory.¹³ In our case, diplopia appeared as the only symptom in similar recurrent and self-limiting episodes which she experienced over the years; between episodes, the patient's vision disorders resolved completely. This is unlikely to reflect transient ischaemic events in the posterior region of the brain, since such events are usually accompanied by other neurological deficits.^{14,15} Diplopia manifesting as a migraine aura is rare, but it has been described in the literature.¹⁶ This seems to be a case of aura without headache, since the patient has no history of headaches. According to the International Headache Society (IHS) classification, this is a subtype of migraine with aura.¹⁷ In spite of the fact that aura without headache has been described as a manifestation of CADASIL,¹⁸ no publications mention diplopia as an expression of that migraine subtype in this disease.

Regarding absence of family history of CADASIL, we should highlight that even if a positive family history supports the diagnosis of the disease, the absence of this background does not rule out this condition. *De novo* mutations may occur, and in such cases, there would be no detectable genetic alterations in the patient's ancestors. However, the mutation would be transmittable to the patient's descendants.^{19,20} Another relevant finding in our case was that diagnostic criteria (Table 1) showed low sensitivity, since they were unable to establish even a possible diagnosis for the patient. The decision to request tests to confirm CADASIL was based on typical MRI findings in the absence of an alternative aetiological diagnosis. We should also discuss the use of galantamine treatment in this case. Although no treatments have been shown to modify the course of the disease, some authors suggest that there may be a neuronal cholinergic deficit and that cholinomimetic drugs may be useful for the underlying cognitive decline. However, no randomised and controlled trials have explored this topic.^{21–23}

Lastly, the diagnosis may be confirmed in a patient's asymptomatic family members by means of a genetic study. This approach is frequently necessary in order to maximise preventive measures when cardiovascular risk factors are present and also to offer proper genetic counselling, given that the inheritance pattern is autosomal dominant. Although genetic study is the procedure of choice in asymptomatic patients, neuroimaging tests (especially MRI) play an important role since all carriers will develop the disease before the age of 60 and present typical imaging changes

Table 1 Diagnostic criteria for CADASIL.*Probable CADASIL*

1. Age at onset <50 years
2. At least 2 of the following clinical findings:
 - Stroke-like episodes with permanent neurological signs
 - Migraine
 - Major affective disorders
 - Subcortical dementia
3. Absence of cardiovascular risk factors aetiologically related to the deficit
4. Evidence of an autosomal dominant inheritance pattern
5. MRI showing white matter damage without cortical infarcts

Confirmed CADASIL

Criteria for probable CADASIL + discovery of Notch3 mutation and/or pathological findings showing small-vessel arteriopathy with granular osmiophilic material (GOM) deposits.

Possible CADASIL

1. Late-onset (>45 years)
 - Stroke-like episodes without permanent signs
 - Minor affective disorder
 - Global dementia
3. Minor VRF: mild HTN, mild hyperlipidaemia, smoking, oral contraceptives
4. Unknown or incomplete family history
5. MRI with atypical changes in white matter

Exclusion criteria

1. Age at onset >70 years
2. Severe or complicated HTN with cardiac or systemic disease
3. Absence of cases in a well-documented family tree
4. Normal MRI at >35 years of age

Modified from Davous.⁴

before the age of 40. If the brain MRI remains normal beyond this age, the subject is highly unlikely to develop the disease.⁵

In summary, CADASIL is a rare disease with a wide spectrum of clinical manifestations that have probably not yet been fully described. CADASIL should be considered in patients with recurrent episodes of diplopia and MR images that are typical of the disease. In addition, absence of family history is no reason to rule out this entity and not order tests that could confirm the diagnosis.

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Contrast uptake by anterior roots in acute motor axonal neuropathy[☆]

Captación de raíces anteriores en la neuropatía aguda motora axonal

Dear Editor:

Guillaume–Barré syndrome (GBS) is an acute immune-mediated disease affecting the peripheral nervous system. It can be divided into different subtypes according to clinical, immunological, neurophysiological, and pathological criteria.¹

GBS includes at least 3 patterns: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy/acute motor-sensory axonal neuropathy (AMAN and AMSAN), and Miller Fisher syndrome.

AMAN is a pure motor form of GBS which is frequently associated with the presence of certain anti-ganglioside antibodies and preceded by an infection with *Campylobacter jejuni*. This clinical form may present clinical characteristics that delay diagnosis.

We present the case of a man, aged 29, who came to the emergency department due to acute tetraparesis predominantly affecting the upper limbs and associated with back pain. The patient reported having had diarrhoea one week before. He claimed not to have experienced autonomic dysfunctions or sensory disorders. The neurological examination revealed normal reflexes and asymmetric tetraparesis predominantly affecting right-sided distal regions and the upper limbs.

Contrast-enhanced MR imaging of the spinal cord revealed enhancement limited to the anterior nerve roots (Figs. 1 and 2).

The patient's Achilles reflex subsequently disappeared. The CSF study showed albuminocytological dissociation.

The neurophysiological study revealed a decrease in motor evoked potential amplitude with no changes in velocity or latencies and normal sensory nerve conduction. Conduction block was not detected. F-waves displayed normal persistence and latency in the upper and lower limbs. The needle study showed abundant spontaneous muscle activity in proximal and distal muscles of the upper and lower limbs with a reduced recruitment pattern. These neurological findings were compatible with exclusively motor and axonal impairment. Serology tests for *C. jejuni* were positive (1/1000). Tests were negative for anti-ganglioside antibodies GM1, GM2, GD1a, GT1B, and GQ1b. The patient was diagnosed with AMAN and treated with immunoglobulins (2 g/kg body weight), after which symptoms improved.

Three months after onset of symptoms, he presented distal weakness predominantly affecting the upper limbs (4/5 on the Medical Research Council scale).

AMAN is a form of GBS that exclusively affects motor function of the peripheral nervous system and causes axonal impairment while sparing myelin.¹ It seems that there is a relationship between AMAN and a prior infection with *C. jejuni*. This bacterial species has surface lipooligosaccharides that work as antigens and possess structures similar to those of some peripheral nerve gangliosides.² In these cases, neurophysiological studies show motor impairment with signs of axonal damage. However, some authors, such as Berciano et al., have shown that the pathological basis of this disease is demyelination even if neurophysiological studies are unable to demonstrate this finding in some cases. Demyelination is primarily radicular with secondary wallerian degeneration.³

Different studies have shown contrast uptake by nerve roots in acute polyradiculoneuropathies^{4–8} or even by cranial nerves.⁴ This uptake seems to be due to the absence of perineurium in preforaminal nerve roots and to a compromised blood–nerve barrier.⁹ It has been suggested that this uptake is related to more severe pain and a poorer prognosis. Doctors decided to perform an MRI scan due to the initial asymmetry of the symptoms and because reflexes that were initially present disappeared during the course of the disease. The presence of normal reflexes or even hyperreflexia has been described in other patients with AMAN.¹⁰ Although

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