

The Importance of Establishing a Certain Diagnosis of Focal Neurologic Deficits: CADASIL Family Case Misdiagnosed Like Multiple Sclerosis

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Abstract

The differential diagnosis between many types of vascular and demyelinating diseases is sometimes difficult. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common genetic cause of ischemic strokes, but its diagnosis is sometimes difficult and requires time and molecular tests.

The aim of this case report is to present a misdiagnosed family in which three male patients were treated with interferon 1β due to clinical and imaging manifestations suggestive of multiple sclerosis, but in the end, CADASIL was diagnosed.

A 48-years-old male presented an episode of central right facial palsy and progressive ipsilateral hemiparesis with the familiar antecedent of a non-specific central nervous system illness present in a brother and in a cousin. Under the diagnosis of multiple sclerosis, the patient was managed with interferon 1β , yet, he presented a new focal deficit despite treatment. After realizing the familiar pattern among the patients, and reconsidering the clinical and imaging characteristics, the multiple sclerosis diagnosis was unlikely, so the brother and cousin were re-evaluated, and a Notch 3 gene mutation was found, so that finally, the correct diagnosis of CADASIL was made.

This case report shows the importance of a familial approach when diagnosis seems to be unclear and there is no improvement in the control of the disease. Also, shows a familial approach in a very rare and misdiagnosed disease.

Introduction

The differential diagnosis between many types of vascular and demyelinating diseases is sometimes difficult and requires molecular and laboratory tests that require time and may retard the specific medical treatment. The clinical approach in patients between the 3rd and 6th decades of life with a medical history of a headache, acute and recurrent neurological deficit, mood changes and cognitive decline with MRI abnormalities, it is mandatory to discard demyelinating and vascular diseases. Clinicians should consider the epidemiology, familiar history of neurological diseases, common cardiovascular risk factors, previous episodes, and complete imaging and laboratory tests.

In the group of demyelinating diseases, Multiple Sclerosis (MS) is a relatively common disease that course similar to the previous description, although the familial history of neurologic diseases is infrequent, and also, females of reproductive age are more affected. To determine MS diagnosis, diffuse white matter changes in MRI and Cerebrospinal Fluid (CSF) evidence of Oligoclonal Bands (OCB's) or increased IgG index (or both) needs to be present [1].

On the other hand, patients with a significant familiar history of permanent neurological deficits in more than one member of different generations, especially males, other causes besides MS should be taken into consideration. Genetic causes like Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) must be ruled out. The prevalence of CADASIL has been estimated as more than 4 per 100,000 adults [2]. Its clinical characteristics include migraine episodes with aura, and the ischemic stroke is the most frequent finding. About

85% of symptomatic CADASIL patients present lacunar syndromes [3] and neuropsychological changes, which can later progress to dementia. There is no evidence of spinal cord lesions in MRI and lacks OCB's in CSF [4].

The aim of this case report is to present a misdiagnosed family in which three male patients were treated with interferon 1β due to clinical and imaging manifestations suggestive of MS but finally, CADASIL was diagnosed.

Case presentation

Case 1

A 48-year-old male was evaluated in a neurological medical office, his family history is relevant because of a 50-year-old cousin with acquired non-specific motor disorders, three uncles with nonspecific central nervous system disease patients with motor deficit, and two siblings, a 36 years old male with diagnosis of MS, and the other male with language and learning disorder. His medical history included hypertension treated with amlodipine. In 2012, the patient presented an episode of right central facial paralysis and progressive ipsilateral hemiparesis, he sought multiple medical cares, being diagnosed with MS after neurological evaluation. Two years later, he arrived at the neurology clinic with a new complaint of weakness of his right leg although he followed the Interferon 1β treatment. During the neurological examination, we found central right facial paralysis and mild right spastic hemiparesis with hyperreflexia, Achilles tendon clonus, Hoffman, Trömner and Babinski signs were present on the right side. CBOs were absent from the CSF. There were multiple sub-cortical lesions on MRI (Figure 1). Due to family history, we decided to reevaluate the patient's cousin (Case 2) and brother (Case 3) even though they were receiving medical care for MS in other institution.

Case 2

A 50-year-old male patient with a history of close relatives with a motor deficit, a medical history of systemic arterial hypertension. Symptoms began in December 2013 with progressive left hemiparesis and episodic dizziness. In that year, his neurologist observed

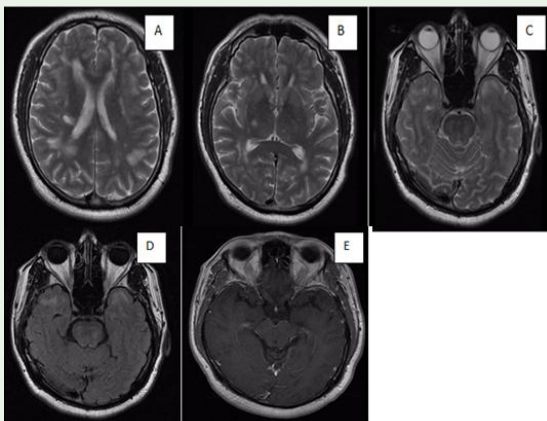


Figure 1: MRI of the brain. Multiple subcortical hyper intensities localized in corona radiata, temporal lobes, thalamus, putamen and midbrain and pons corresponding to ischemic strokes in T2 (A, B and C) and T2 FLAIR (D) weighted images. In contrasted T1 images (E) no increased signal intensity was noted.

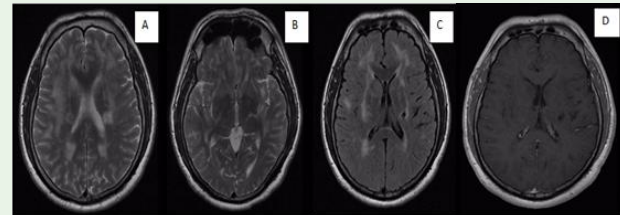


Figure 2: MRI of the brain. Multiple subcortical hyper intensities with localization in corona radiata, temporal lobes, thalamus and putamen corresponding to ischemic strokes in T2 (A and B) and T2 FLAIR (C) weighted images. In contrasted T1 images (D) no increased signal intensity was noted.

images suggestive of MS by MRI analysis and began his treatment with interferon 1β. Neurological exploration with left central facial paralysis, ipsilateral hemiparesis with hyperreflexia and Hoffman's sign was present, left hemihypaesthesia was evident. The rest of the cranial nerves and cerebellar examination were normal. CBOs were absent from the CSF. There were multiple sub-cortical lesions on MRI (Figure 2).

Case 3

A 57-year-old patient with a family history of a neurological disease (cases 1,2) and history of heavy smoking for eight years. His symptoms began at 45 years-old with episodes of vertigo lasting a few seconds and acute loss of vision of about one hour with total recovery. In May 2014 his family noticed dysarthria but comprehension was preserved; at the neurological examination, dysarthria was found without other motor deficits. CBOs were absent from the CSF, there were multiple sub-cortical lesions on MRI (Figure 3). The diagnosis of MS was made and interferon 1β was prescribed by a neurologist.

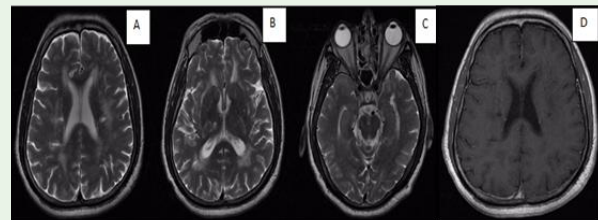


Figure 3: MRI of the brain. Multiple subcortical hyper intensities with predominant periventricular localization, corona radiata, temporal lobes, thalamus and putamen corresponding to ischemic strokes in T2 (A, B and C) In contrasted T1 images (D) no increased signal intensity was noted.

With the knowledge of the clinical course of the three patients and the family bond, CADASIL was probably the definitive diagnosis. To perform the CADASIL diagnosis, serum samples from the three patients were sent to the molecular biology laboratory to determine Notch 3 gene mutation. The reported mutation was Notch3 NM_000435.2: C505C> T in the 3 patients and the offspring were evaluated for the mutation. Finally, the diagnosis was made four years after the first patient had the first symptom.

Discussion

CADASIL is a heritable disease with high penetrance, which results in occlusion of brain arterioles leading to small deep infarcts

and progressive accumulation of demyelination areas that manifest like the recurrent headache of migraine pattern, focal deficits secondary to brain infarction, and in later stages, neuropsychiatric disorders including dementia [1].

In the present case, the three male patients of the same family, between 45 and 60 years – old, were treated with immunomodulatory therapy because of misdiagnosis of MS, and no other diagnosis was suspected although the familiar relation within them was considered relevant. We must pay close attention to the relatives of affected patients, in order to detect neurological and psychiatric manifestations that might lead to an earlier diagnosis. This group of patients had a positive familiar history of motor deficits in first degree relatives (five uncles of both genders) by a no identified cause. This injury or harm pattern keeps an autosomal dominant form of inheritance [5].

Dichgans et al. and other studies reported that a migraine usually with aura is the initial symptom present in 22 to 40% of the patients with a first attack before 20 years of age; nevertheless, the commonest manifestations are cerebrovascular injuries [6]. Our patients only developed changes associated with typical lacunar syndromes as isolated unilateral motor and sensory deficits being the first manifestation around 45 years – old, which is the frequent age of the beginning of the CADASIL disease. Other abnormalities were found, like visual-loss in one patient that could be associated with a Transient Ischemic Attack because of its recurrence, acute beginning, and total recovery after one hour. Vestibular symptomatology was present in this patient too.

The raising of ischemic lesions probably contributes to the presence of cognitive manifestations with slow evolution to dementia at age of 60 years or more. Cognitive impairment and dementia are the second most common manifestations after cerebrovascular injury [1]. In these patients, there is no objective evidence of cognitive symptoms but their families refer mood changes in the three cases without any significant impact on their life activities.

MRI at earlier stages of CADASIL may comprise only White Matter Hyper intensities (WMHs), similar to those found in MS,

and this may also have a similar clinical presentation as CADASIL. MRI images of young patients with CADASIL revealed a significantly higher load of WMHs and a higher prevalence of WMHs in anterior temporal lobe, external and internal capsule. The temporal lobe is useful as a radiological hallmark to differentiate CADASIL from MS in younger patients [7], as we have found in our cases (Figures 1b, 2b, 3b).

In conclusion, we present a family case report of CADASIL with an important delay in diagnosis and treatment (4 years). Epidemiologic, familiar and imaging data were of great value to suspect the diagnosis that posterior was confirmed by molecular biology test. This case report shows the importance of a familial approach when the diagnosis is unclear and there is no improvement in the control of the disease, and also shows a familiar approach in a very rare and frequently misdiagnosed disease.

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