Early and Progressive Cognitive Disorder Imposes CADASIL Syndrome in the Diagnostic Assumption

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Abstract

The case presented is a diagnostic challenge considering the family and medical history of the 65-year-old patient with family history of migraine depression, emotional lability and gait disorders manifested at his grandmother, his mother and his sister. After multiple hospitalizations for the described symptoms and multiple treatments with questionable results, the diagnosis was imposed by the appearance described by brain MRI to which were added the data from the patient's family and personal history. Of course, a full confirmation of the diagnosis would have required skin biopsies and genetic testing that the patient refused to perform. However, due to its peculiarities, the presented case tries to offer a diagnostic orientation path for practitioners in situations where previous diagnoses and treatments are not sufficiently conclusive either due to the impossibility of performing specific tests at that time or either because of the patient's indifference to his state of health.

Keywords: Cognitive disorders; Diagnostic assumption, CADASIL, NOTCH3, Skin biopsy.

Introduction

Disorders of cognition are mental health impairments including amnesia, dementia, delirium and cognitive disorders not otherwise specified (excessive use of alcohol drugs, by or from physical trauma) that primarily affect perception, problem solving, learning and memory. The case that we describe in the following, illustrates a 65-year-old woman with family history of migraine depression, emotional liability and gait disorders manifested at his grandmother, his mother and his sister, each of them with multiple consultations and treatments performed in neurology and psychiatry clinics.
Although, in this case, we did not have all the necessary tests to confirm the diagnosis, we present it as an assumed diagnostic case being at the same time the best diagnosis received by the patient so far as a case to come in the support of medical practitioners in the moments when they have to decide a diagnosis in such conditions.

**Case Presentations**

The onset of the disease is difficult to detect in time and poorly defined as clinical manifestations, but relatives and neighbors describe this woman’s family as well as her as having a reduced social presence and inclinations towards isolation from the community. However, the history of the last 10 years reveals multiple neurological and psychiatric consultations, hospitalizations in neurology and psychiatry clinics for clinical manifestations as headaches with characteristics of migraine, cognitive disorders, depression, anxiety, emotional lability and transient weakness and long-term treatments with valproate sodium, venlafaxinum or sertralinum. The effectiveness of treatment in recent years has been relatively low. In the last 2-3 years, to the symptoms described above were added, balance disorders, gait disorders, cognitive decline with dementia manifestations, and urinary disturbances with features of neurogenic bladder. Because, the patient was also known to have high blood pressure and non-alcoholic liver steatosis was admitted for evaluation in an Internal Medicine clinic.

During hospitalization, the patient describes episodes of persistent headache and gait and balance disorders. Because daily assessment of the patient during hospitalization by clinical examination, biological tests and strict monitoring of blood pressure values did not justify this symptom, and considering the patient’s family and personal history as well as the fact that he never performed the imaging examination of the skull, we resorted to performing a cranial MRI. After MRI examination of skull with gadolinium contrast was described, contoured diffuse areas symmetrically located in the white matter at the level of the anterior temporal lobes and at the level of the bilateral internal capsule with demyelinating substrate; round-oval areas with a diameter between 1 and 10 mm located in the white matter frontal, parietal and occipital bilateral with degenerative microangiopathic substrate; leukoaraisis. Aspects described in the MRI examination of the brain have advocated for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (Figure 1).

The psychiatric consultation confirmed cognitive disorder with features of dementia syndrome and the recommended treatment for the patient was with Pramiracetam, Cebrium and gastro-resistant Acidum acetyl salicilicum. In the present case, the diagnosis was difficult both in the early stages and subsequently without the MRI examination of the brain. In the subsequent exploration of this case, the genetic test is required to confirm the genetic abnormality of the Notch 3 gene and skin biopsy with microscopic examination to detect changes of the smooth muscle cells in the small and medium-sized penetrating arteries. The genetic test to identify NOTCH gene mutations is currently unavailable in our country and the skin biopsy for microscopic examination was refused by the patient.
Under these conditions, the only possibility to provide a diagnosis was by assuming it based on the changes described in the MRI examination of the skull corroborated with the personal and family history of the patient as well as with the current symptoms.

**Figure 1:** Diffused areas outlined in T2 FLAIR hypersignal, moderately T1 hyposignal, without gadophilia in white matter to the level of anterior temporal lobes and at the level of the bilateral internal capsule with demyelinating appearance. a) Axial section. b) Sagittal section. c) Coronal section.

In support of this assumed diagnosis, we also bring the MRI examination of the skull performed recently. The recent MRI (contrast with gadolinium) of the skull (August 2021), two years after the first examination of this kind, allows the maintenance of the previously formulated diagnosis because it describes the same lesions on the T2 sequences (TIRM). At the level of the cerebral hemispheres, multiple focal lesions of variable dimensions are described, without contrast intakes, with the appearance of chronic nonspecific demyelination of ischemic etiology by affecting the small vessels. The conclusion of these descriptions was: multiple small ischemic strokes and multiple demyelination of microangiopathic ischemic etiology in the cerebral hemispheres.

**Discussion**

It is interesting that from the discussions with the patient’s relatives, it seems that her daughter also presents maladaptation at work, tendency to isolation and long periods of lack of verbal communication with the husband; these are probably early manifestations of CADASIL syndrome.

For this case it should be mentioned that the diagnosis of CADASIL syndrome would have been difficult to prove for the patient’s grandmother or mother due to the impossibility of performing high performance imaging or genetic test during that period.

However, even in the case of the patient, the diagnosis was rather late due to the fact that in approximately 10-15 from the beginning until the cerebral MRI the symptomatology was permanently attributed to a depressive syndrome. The necessity of performing cerebral MRI was dictated by the occurrence of urinary incontinence, cognitive deficiency as well as walking and balance disorders.
Subsequently, to strengthen the diagnosis, the patient was recommended to perform the genetic test and skin biopsy. It was also recommended to perform brain MRI, genetic test and skin biopsy for his descendants. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) are inherited vascular disease with autosomal dominant transmission in which the genetic abnormality is small deletions or simple mutations in the Notch3 gene on chromosome 19. The Notch3 encoding a transmembrane receptor and his mutation lead decrease production in vascular smooth muscle cells [1,2].

Microscopic examination of skin biopsy samples collected from patients with CADASIL syndrome shows changes in the small and medium penetrating arteries consisting of parietal thickening, reduction of vascular diameter, alteration of smooth muscles in the vascular wall and fibrosis [3]. Angiopathy occurs in the capillaries and small cerebral arteries as a result of the accumulation of eosinophilic protein deposits; this angiopathy is generalized but predominates in the cerebral vessels having as clinical expression the loss of consciousness and repetitive vacuoles [1].

The clinical picture begins in people in the 4th decade of life with symptoms and clinical signs such as strokes with or without clinical expression, migraine with aura or seizures. The most common symptoms are emotional lability, gait disorders, depression, spasms of striated muscles. Impairment of the frontal lobe is progressive leading to subcortical dementia and deficient memory. The lesions are visualized by MRI and consist of lacunar infarctions as a result of ischemic lesions of the gray and white subcortical substance in the basal ganglia, temporal lobes and internal capsule. A subtype of migraine known as familial hemiplegic migraine and characterized by transient weakness or frank paralysis during the aura has also been mapped close to the CADASIL locus. The newer acronym, CADASILM (cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, and migraine), refers to a subvariety of CADASIL characterized by the high frequency of migraine [1,2].

The differential diagnosis includes amyloid angiopathy, homocystinuria, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and, Binswanger disease [1]. Computed tomography (CT), magnetic resonance imaging (MRI), genetic test and skin biopsy are extremely useful tests in diagnosis and evaluating patients with CADASIL disease [4]. In this case, confirming the diagnosis allowed a retrospective look at the patient’s family history, raising the assumption that the patient’s grandmother and mother probably had CADASIL syndrome.

**Conclusion**

The case presented proves once again, if necessary, that the diagnosis of rare diseases, with long evolution, can be accidental and in totally unexpected circumstances. Although the patient had multiple hospitalizations in neurology and psychiatric clinics, the most appropriate diagnosis to explain these hospitalizations was made in an internal medicine clinic. Of course, in the current era of medicine, patients have multiple investigations, which do not prove anything
and among these investigations, the imaging ones are the most frequent. The diagnosis established for this patient is a diagnosis imposed by the aspect described on MRI corroborated with her family and personal history and represents the best and most explicable diagnosis in this context, being supported by the substantially improved evolution after adapting the treatment to this diagnosis.

Thus, an investigation done by chance or on the basis of minimum criteria to impose it can bring you closer to the diagnosis than the multitude of hospitalizations or medical consultations from which the essential investigation is missing and this approach to medicine is only practiced by doctors. - The so-called medical flair or "sixth sense".

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Conflict of interest

The authors have no conflict to disclose

References