Case Report

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Vascular Parkinsonism and Cognitive Impairment without Lobar Hemorrhage related to Cerebral Amyloid Angiopathy

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Abstract

Clinical recognition of Cerebral Amyloid Angiopathy is difficult due to clinical and imagiological heterogeneity. The Modified Boston Criteria for diagnosis of 'probable Cerebral Amyloid Angiopathy' pathologically validated in 2010 had an increase in sensitivity with only a modest decrease in specificity. Following case illustrates a diagnostic challenge to an elderly patient with vascular risk factors, neurodegenerative symptomatology with multiple cerebral vascular lesions (ischemic and hemorrhagic, without lobar hemorrhage). The use of a non-invasive amyloid marker would be useful in atypical clinical courses of patients with Cerebral Amyloid Angiopathy.

Keywords: Vascular parkinsonism, Cognitive impairment, Microbleeds, Hemorrhages, Magnetic resonance imaging, Amyloid PET, Cerebral amyloid angiopathy

Abbreviations: CAA: Cerebral Amyloid Angiopathy; CMBs: Microbleeds; CVD: Cerebrovascular Disease; GM: Gray Matter; HTN: Hypertension; TFNEs: Transitory Focal Neurological Episodes; VFR: Vascular Risk Factors; WM: White Matter

Introduction

Cerebral Amyloid Angiopathy (CAA) is an entity of unknown origin that it is characterized by the deposition of material amyloid in the walls of the cerebral vessels and leptomeninges. Although the most common clinical presentation is recurrent lobar hemorrhage and dementia, at present, there is a clinical and imagiological heterogeneity with medical care and the progress of neuroimaging. The Modified Boston Criteria for diagnosis of 'probable CAA' pathologically validated in 2010 had an increase in sensitivity to 94.7% with only a modest decrease in specificity to 81.2% [1]. The use of a non-invasive amyloid marker would be useful in atypical clinical courses of patients with CAA.

Case Presentation

A 73-year-old male was admitted to the emergency room for gait instability and falling with urinary incontinence, without cranial trauma or autonomic complaints.

Medical history: 4 years of schooling, hypertension (HTN), old cerebral infarction and alcoholism (polyneuropathy and brain atrophy, abandoned alcohol consumption 9 months ago). I was on treatment with acetylsalicylic acid 100 mg a day and folate 5 mg a day. On admission, his blood pressure was 131/74 mmHg, and his pulse was regular at 78 beats/min. His physical examination was normal.

Neurological examination: Disoriented in time, not in space, dysarthria sequela, without other neurological signs. Blood tests (included reactive protein C, erythrocyte sedimentation rate) were normal. A thoracic x-ray, electrocardiogram and ecocardiogram were normal. A cranial computed tomogram revealed lacunar infarcts (in base nuclei, radiata crowns and thalami) and bilateral cerebellar infarcts, of right predominance, these to be better characterized by cerebral MRI. Moderate leucoaraiosis and cortico-subcortical atrophy.

He was medicated with betahistine 24 mg 2 times per day and was sent to a neurology outpatient consult. Two months after admission, the patient had a fracture on the right patella and was referred to rehabilitation. During a session he developed freezing of gait with falls. At the third month, he was observed in the neurology consult. A dysarthria sequela was observed, without aphasia or cognitive decline. The pupils were normoreactive isochoric and examination of the cranial nerves was normal. Muscle strength and sensitivity were preserved. Deep tendon reflexes were grade 1 bilaterally and plantar responses were indifferent. A hyperextension of the knees was perceptible. It was not revealed dysmetria. Right akinesia and rigidity in the right upper extremity and in the lower extremities were noted. Decreased right arm swing with pseudo-dystonia in the right hand was also observed without tremor. Upright posture during standing and unsteady gait was also found.

A subsequent analysis showed normal results in the lipid and thyroid profiles, folic acid, vitamin B12, proteinogram, ceruloplasmin, copper and autoimmunity. Serologies were negative for *Treponema pallidum*, *Borrellia*, *Toxoplasma*, *Epstein-Barr virus*, *Herpes simplex virus-1* and *-2*, *Cytomegalovirus*, *Brucella* and *Human immunodeficiency virus*. The Holter was normal.

Three months after the clinical picture, the patient performed a brain MRI (Figure 1) that revealed multiple lacunar infarcts of white matter (WM) and gray matter (GM) in both cerebral hemispheres and brainstem, and infarction of the right posterior-inferior cerebellar artery. Yuxtacortical microbleeds (CMBs) in the left hemisphere mainly at the left parietal region, subcortical CMBs and cortico-subcortical cerebellar bilateral hemorrhages. Ischemic leucoaraiosis and cerebral atrophy.

MRI Conclusion: Severe cerebrovascular disease (CVD) with coexistence of CAA.

Figure 1: MRI scan.

A-D: Axial T2 MRI.

A: Presence of bi-hemispherical periventricular WM lesions of left predominance. Bilateral frontal subdural hygroma and in the left hemisphere. Generalized and bi-frontal atrophy.

B-C: Multiple lacunar infarcts in both cerebral hemispheres and in the brain stem.

D: Inferior right cortico-subcortical cerebellar infarct.

E-G: Axial T2*-weighted gradient-echo.

E: Cortico-subcortical cerebellar bilateral hemorrhages.

F: Yuxta-cortical microhemorrhages in the left hemisphere mainly at the parietal region.

G: Subcortical and midline microhemorrhages.

H: Axial FLAIR: Periventricular and subcortical WM lesions.

A sonographic examination revealed mild-moderate vertebral artery stenosis. It was decided to suspend aspirin because of the risk of brain bleeding (HAS-Bleed 5). Levodopa was also tested without improvement, later the patient received 2 mg of rotigotine and 30 days later 4 mg showing a slight overall improvement mainly in akinesia and locomotion.

Six months after the clinical debut, episodes of several min (3-4) of duration were observed at home with ocular deviation, facial pallor, drooling, without involuntary movements of limbs, remaining inanimate, without urinary incontinence. He had a Mini-Mental State Examination score suggesting mild cognitive impairment (score 26: orientation 9, registration 3, attention and calculation 5, recall 2, language 6 and construction 1), without hallucinatory activity or behavior alteration. She was treated with lamotrigine 25 mg, 2 times per day and neuralex® [folic acid 200 mcg, vitamin B12 1.25 mcg, vitamin B6 0.7 mg, and omega-3 fatty acids (docosahexaenoic acid 450 mg and eicosapentaenoic 90 mg)], 2 time per day.

An EEG of vigil and sleep was requested and the results were normal. A neuropsychological study (Scale of intelligence and memory of Wechsler, Wisconsin Card Sorting Test and verbal Fluency) showed alterations in the following functions: deferred memory, retention and recovery of information and auditory memory. Also in visual attention, working memory, processing speed, psychomotor speed and mental flexibility. The QI was 83 (normative interval 90-109), there being a large clinically significant difference between verbal (medium level) and manipulative (lower level) competencies. He needed light support in some instrumental activities of daily living.

The study was completed with DaT-SCAN (Figure 2) and PET-PIB Amyloid (Figure 3). The DaT-SCAN showed pre-synaptic dopaminergic deficit of left predominance. In the PET-PIB Amyloid, a moderate uptake of the radiopharmaceutical at cortical level was observed, mainly in the frontal lobes, parietal/precuneus, posterior cingulate cortex and lateral portion of the temporal lobes. In the occipital cortex a marked uptake was observed.

Figure 2: DaT-SCAN. In the left basal ganglia was observed a marked reduction of radiopharmaceutical uptake in the putamen and a discrete decrease in the caudate. On the right side preserved uptake was observed in the caudate and discrete decrease in the putamen.

Figure 3: PET-PIB amyloid. Coronal (A), sagittal (B) and Axial (C). A moderate uptake of the radiopharmaceutical at cortical level was observed, mainly in the frontal lobes, parietal/precuneus, posterior cingulate cortex and lateral portion of the lobes. In the occipital cortex a marked uptake was observed.

The genetic study was negative for ApoE (Apolipoprotein E), PRNP (Prion Protein), APP (Amyloid beta (A4) Precursor Protein), CR1 (Complement receptor 1) and CST3 (Cystatin C (Amyloid Angiopathy and Cerebral Hemorrhage)). At this time, the patient remains stable.

Discussion

CAA is typical of elderly people, the average age of cerebral hemorrhage is the 7th decade, it is related to the ApoE and CR1 genes, it does not have sex predominance, and the risk factors of hemorrhage in the CAA are ischemic stroke previous, alcoholism and drugs (anticoagulants, thrombolytics and antiaggregants). On the other hand, the clinical spectrum is heterogeneous: asymptomatic, symptomatic cerebral hemorrhage, transient neurological symptoms, cognitive impairment and dementia, rapidly progressive cognitive and neurological impairment. The brain lesions can be lobar hemorrhage, microbleeds (these typically involve the union of the GM-WM, and usually respect the basal ganglia), subarachnoid haemorrhage (SAH), superficial cortical siderosis, cortico-subcortical microinfarcts and leukoaraiosis, according to Mateu AM, 2014.

Our patient is an old male with vascular risk factors (HTN and alcoholism), parkinsonism, "transitory focal neurological episodes" (TFNEs) and mild cognitive impairment, with ischemic cerebral infarcts, CMBs and cerebellar hemorrhages.

Parkinsonism could be of vascular cause, since our patient is an old male, clinical evolution of subacute onset, presence of vascular risk factors (VRF), small vessel disease in nuclei of the base and thalami, akinetic-rigid syndrome, freezing of gait [2-5], poor response to levodopa and improvement with rotigotine. In the literature it is not possible to correlate the asymmetric brain lesions with the side of the symptoms [6-7]. In a series of 13 patients with vascular parkinsonism, rotigotine produced significant motor and cognitive improvement [8].

In our case TFNEs were not the result of SAH in the convexity or electroencephalographic alterations, observed in the literature. Our patient remained with lamotrigine because it can reduce the frequency or severity of the TFNEs, these can also disappear spontaneously, there is a lack of data from controlled trials [9].

Cognitive impairment is related to lacunar infarcts, microbleeds, hemorrhages, leukoaraiosis and amyloid deposition.

In spite of our patient having VRF and not having a lobar hemorrhage, post-mortem histopathological studies of brains with CAA without cerebral hemorrhage have shown that CAA was less severe [10]. In addition,

Izumihara et al. reported that 15 of 37 patients with CAA-related hemorrhage (41%) had a history of HTN [11]; and HTN might be a contributing factor in causing hemorrhage in patients with CAA because different pathogenic mechanisms might be at work at same time [12]. Likewise, it is difficult, if not entirely impossible, to distinguish CAA-related hemorrhage from HTN-related hemorrhage on CT and MRI scans in cerebellar hemorrhages, although the multiplicity and bilaterality of hemorrhages suggest the diagnosis of CAA [12].

In this way, the most likely diagnostic hypothesis would be a sporadic CAA supported by age (over 55 years), parkinsonism [13] (this also described in the literature), TFNEs, cognitive impairment, presentation of bilateral cerebellar hemorrhages (especially superficial) [12] of unlikely hypertensive cause and PET-PIB with more marked deposition of cerebral amyloid material in the occipital region [14].

The last 5 years have seen ongoing progress in this area, thanks in part to the development of new technologies within the fields of MR, amyloid PET ligands and cerebrospinal fluid (CSF) biomarker analysis [15].

More and more authors are advocating a diagnosis based on a compatible clinical-radiological picture supported by some amyloid deposit marker [13].

Conflict of interests

The author declares that he has no conflicts of interest.

Patient's consent

The patient provided informed consent for this case.

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