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Letter to the Editor

A case of progressive frontal lobe syndrome in a sporadic form of Cerebral Amyloid Angiopathy: A singular overlap with fronto-temporal dementia?



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Fronto-temporal dementia (FTD)
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Akinetic mutism
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1. Introduction

Cerebral Amyloid Angiopathy (CAA) is a clinicopathological condition resulting from the deposition of β -amyloid within leptomeningeal and cortical arteries, arterioles, capillaries, and rarely veins [1]. The term β -amyloid refers to any amorphous, eosinophilic, extracellular protein deposit with specific staining characteristics, such as Congo red binding and birefringence with polarized light. CAA mostly occurs as a sporadic disease and it raises dramatically with age, rarely being present before the age of 50 and increasing in prevalence to more than 50% in people over 90. The most frequent feature of CAA in older people is the primary intracerebral haemorrhage (PICH) and subsequent cognitive impairment [2].

2. Case report

We describe the case of a 67-year-old man who at the age of 64 presented a sudden onset of postural instability and consciousness impairment. Imaging revealed a cerebellar haemorrhage. In the next year he presented another episode of postural instability due to a left nucleo-capsular haemorrhage. In this period it was also noticed an insidious onset of a behavioural disorder characterized by apathy, loss of empathy and social withdrawal. At our first visit, when the patient was already 67, neurological examination showed marked apathy, slow and effortful speech, spatial and temporal disorientation, left pyramidal hemi-syndrome, frontal lobe signs (bilateral grasping, Epstein sign), urinary incontinence. Laboratory analyses excluded blood dyscrasia and coagulopathy. Neuropsychological examination revealed behavioural disorders of inhibited type (loss of environmentstimulated initiative, spontaneous ideas, curiosity and emotion), executive dysfunction, constructive and ideo-motor apraxia. Neuropsychological assessment for aphasia showed a marked disorder of verbal comprehension and production, with relative sparing of repetition, reading and writing which was compatible with transcortical motor aphasia. Afterward this clinical condition progressed to a clear akinetic mutism. A sister of the patient presented a fairly identical pattern of cognitive impairment, beginning in the seventh decade of life, characterized by language impairment, apathy, frontal lobe signs and evolving up to akinetic mutism. Brain ¹⁸FDG-PET evidenced asymmetrical frontotemporal hypometabolism. Also a brother of our patient was referred to be cognitively impaired with aggressive behaviour, but he has not come to our observation. The two other siblings were not demented and their parents' medical history was uninformative. An extensive instrumental examination was performed in our patient. Brain MR scan (T2*GRE MR with T2*-weighted images) showed a relatively unexpected association of multiple cortico-subcortical brain haemorrhages, a haemorrhage in left middle cerebellar peduncle together with ischemic lesions (lacunas) and marked fronto-temporal cortico-subcortical atrophy prevalent on the left side (Fig. 1A-F). Brain MR-angiography did not reveal any vascular malformation. Brain ¹⁸FDG-PET demonstrated a significant hypometabolism in left fronto-temporal, bilateral anterior cingulate cortex and superior parietal areas (Fig. 1 G). Analysis of cerebro-spinal fluid revealed normal level of total tau and a low level of amyloid β -42 (525 pg/ml; n.v. 682–1063). Genetic analyses of amyloid- β protein precursor (AβPP) (exons 16 and 17), Presenilin1 (PSEN1) (exons 3–12) and Presenilin2 (PSEN2) (exons 3-12) genes were normal. Plasma progranulin level was normal (77 ng/ml; n.v. ≥61.55) [3], and analyses of progranulin gene (GRN), microtubule-associated protein tau gene (MAPT) (exons expressed in central nervous system: 1–5,7,9–13) and expanded region of C90RF72 gene were unrevealing. We also performed the analysis of Integral Membrane Protein 2B (ITM2B) gene (exons 1-6), which was normal. Taking into account our patient's age, the presence of a cerebellar haemorrhage without supporting risk factors and the coexistence of multiple ischemic and haemorrhagic lesions evidenced by MR scans, he received the diagnosis of probable CAA, according to Boston Criteria [4]. Nonetheless functional imaging data (involvement of parietal posterior areas) and CSF biomarkers (low amyloid β -42 value), more than clinical history, point toward an amyloidopathy. In addition the lack of motor and verbal initiative appears to be consistent with behavioural variant of fronto-temporal dementia (bv-FTD) of apathetic type [5].

3. Discussion and conclusions

CAA, characterized by the occurrence of both ischemic and haemorrhagic strokes due to the deposition of β -amyloid within the cerebral arteries' walls, leads to a progressive cognitive decline whose main features are memory impairment, speech disturbances, neuropsychiatric involvement and in the late stages gait disturbances and ataxia [1]. Fronto-temporal dementia (FTD) is a clinico-pathological entity which includes bv-FTD, semantic dementia (SD) and primary nonfluent aphasia (PNFA). It is associated with intraneuronal deposits of filamentous tau, insoluble TDP43 protein, or, more rarely, FUS-positive inclusions [6], in absence of β -amyloid. Recent clinico-pathological studies have investigated the relationship between cerebrovascular lesions and neurodegenerative dementias (AD, Dementia with Lewy Bodies, FTD). CAA was present in 57.8% of AD patients (taking into

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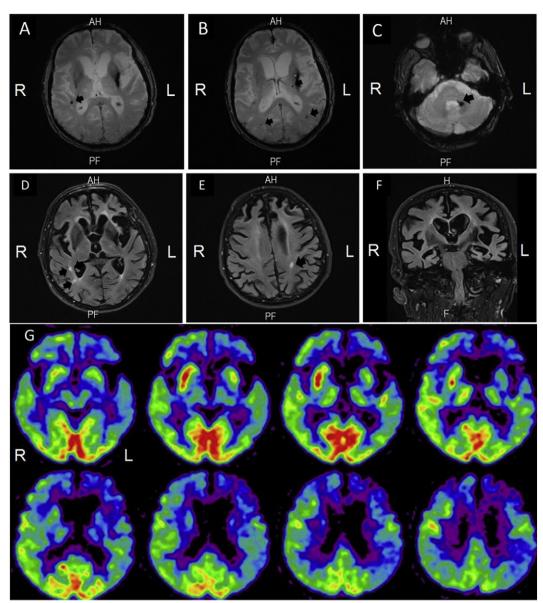


Fig. 1. Axial T2*GRE (Gradient echo) MR with T2*-weighted images revealed multiple sub-cortical haemorrhages (A, B) and a left cerebellar haemorrhage (C) (black arrows). Axial FLAIR (fluid attenuated inversion recovery) images demonstrated multiple lacunar infarctions (black arrows) (D, E). Coronal T1 image showed marked cortico-subcortical atrophy prevalent to bilateral fronto-temporal lobe (F). Brain FDG-PET showed a significant hypometabolism prevailing in left fronto-temporal, bilateral anterior cingulate cortex and superior parietal areas (G). R = right side, L = left side.

account in vivo MR scans and post mortem neuropathological analysis) and absent in nondemented individuals. In FTD patients on the contrary a similar relationship did not emerge, thus suggesting that CAA does not play any role in neuronal death in FTD [7]. Our patient presented a progressive cognitive and behavioural disorder whose main clinical features (early executive, behavioural and language disorders) were in favour of a diagnosis of probable FTD [5]. Moreover MRI evidenced several ischemic lesions and multiple hemosiderin deposits which is consistent with CAA criteria. Finally CSF biomarkers were in favour of an amyloidopathy. We focused on the research of the main mutations associated with FTD and CAA, considering the family history for cognitive impairment. The genes that can be associated with familial CAA and AD are APP (duplicated or mutated mainly in exons 16 or 17) [8], PSEN1 and PSEN2, whereas MAPT, GRN and C9ORF72 are mutated in familial FTD [6]. We also considered a possible, although very rare, involvement of ITM2B gene. However the results of genetic analyses were all negative. Though lacking neuropathological data, our case is indubitably singular because its onset, its clinical, neuropsychological and neuroimaging findings strongly suggest the diagnosis of FTD. However there is an increasing number of AD cases presenting with focal cortical syndromes not determining a prominent amnestic disorder (i.e., frontal or posterior variants). It is supposed that these focal dementias are related to AD pathology especially in younger patients [9]. In vivo diagnosis remains still uncertain, as we can only provide a singular clinical description of a case of FTD associated with CAA, whose exact nature may only be revealed by neuropathological assessment together with the analysis of additional genes involved in dementia, and possibly through a whole exome sequencing analysis [10].

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