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Case Report

An Uncommon Presentation of Cerebral Amyloid Angiopathy

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Abstract

The most frequent manifestation of Cerebral Amyloid Angiopathy (CAA) is symptomatic, spontaneous Intracerebral Hemorrhage (ICH), preferentially affecting lobar regions. It is the second most common cause of ICH after hypertensive angiopathy in the general population. Other common manifestations are ischemic episodes, transient focal neurological episodes, subarachnoid hemorrhage and cognitive decline. Here, we describe an interesting case of a patient with a clinical picture of a rapidly progressive dementia caused by CAA, to highlight the heterogeneous clinical variability of this condition. The diagnosis and, in particular, the management and therapy of patients affected by CAA or any inflammatory form is often challenging. Our case report shows that CAA without inflammation should be included among the possible cause of rapidly progressive dementia.

Keywords: Cerebral amyloid angiopathy; Stroke; Cerebral hemorrhage; Microbleeds; Dementia; Rapidly progressive dementia

Case Presentation

We describe the clinical case of an eighty-one-year-old man, with 15 years of education, who has been accompanied to our memory clinic, to investigate a cognitive decline which started 4 months earlier. The past medical history was characterized by a recently diagnosed diabetes mellitus, arterial hypertension and an endovascular procedure for an abdominal aneurysm. Both the diabetes mellitus and the arterial hypertension were well managed with pharmacotherapy. There was no family history of neurological diseases and, in particular, there was no history of dementia. He was a non-smoker and non-alcohol drinker. He did not suffer of any allergies. In December 2019 his wife and son noticed a beginning of a memory loss, especially regarding short term memory. The memory impairment worsened rapidly and, two months after, he couldn't even remember his age, if he had lunch and he began to neglect his medication. Besides the memory loss, behavioral changes were noticed, with verbal and physical aggressiveness, and delusional ideas directed also towards his family members. The day of the clinical evaluation, the family also referred episodes of urinary incontinence, gait abnormalities with a high risk of fall and the need to be helped while walking. At the time of the first evaluation, no seizure, myoclonus or hallucinations were reported, and the patient was nearly totally dependent on others for his daily activities.

As per advice of his general practitioner, he performed an enhanced total body CT scan that was normal. Due to the rapid progression of the clinical signs and symptoms the patient was hospitalized to perform the necessary investigations as soon as possible.

Upon entering the ward, the neurological examination showed: patient alert, disoriented in time and space, only partially oriented towards family members (at first, he did not recognize his son and he had difficulties remembering how old his wife

was), disoriented about autobiographic information, poorly collaborative. He tended to confabulate and a mild dysarthia was noticed. He was clearly aphasic with many semantic and phonetic paraphasias, and had also anomie for objects of common use. His score at the Mini Mental State Examination was 7 out of 30, revealing a severe dementia. We also observed a right slight hemiparesis with ipsilateral hemianopia.

The blood test showed only a high glucose level, congruous with his history of diabetes mellitus, and slightly high total cholesterol. Vitamin B12 and folic acid were in the range of normality. The antibody titers against thyroglobulin and peroxidase were absent. Syphilis screening was normal, as normal were also erythrocyte sedimentation rate, rheumatoid factor, anti-SS antibodies, HIV and hepatitis B and C, Anti-Neutrophil Cytoplasmatic Antibodies (ANCA), antibodies against Borrellia Burgdorferi, copper, ceruloplasmin, coagulation profile, homocysteine, glutamic acid decarboxylase. Paraneoplastic and autoimmune antibodies, performed on blood serum, were normal. Nasopharingeal test for COVID-19 was negative.

To investigate other conditions, we decided to perform a lumbar puncture; normal opening pressure, normal cellularity, slightly increased level of proteins 70 mg/dL (NV 15-45 in our lab), no abnormal 14-3-3 protein and no oligoclonal bands were detected.

The electroencephalogram showed only a generalized slowdown of the electrical brain activities without paroxysm or elements characterizing prion disease.

The brain Magnetic Resonance Imaging (MRI) on a 1.5 Tesla MR unit is shown in Figure 1 and Figure 2. The T2* weighted GRE sequences show multiple small hypointense foci that are suggestive and typical for hemosiderin deposits, as well as a lobar haemorrhage in the left parietal lobe. FLAIR images showed a hyper intense lesion in the supratentorial regions, expression of gliosis and/or microleukoangiopathy. All these radiological findings suggested a diagnosis of Cerebral Amyloid Angiopathy.

The MRI investigation didn't show any radiological signs of inflammation related to CAA. In addition, there were no signs related to a possible prion disease, such as pulvinar sign, or other cortical hyperintensities both in T2 sequences and DWI.

Following the Boston Criteria [1-4] and its development (Table 1) we concluded for a probable Cerebral Amyloid Angiopathy (CAA), the highest level of suspicion for CAA, without the support of pathology.

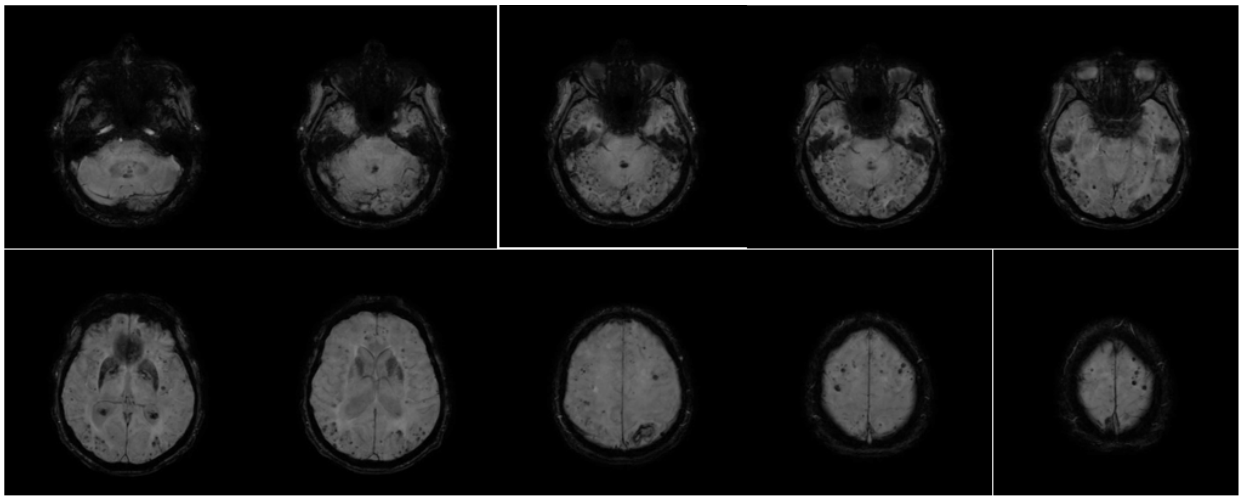

Figure 1: T2* MRI showing the multiple hypointense lesions typically distributed at the cortical-sotto cortical junction. The left parietal hemorrhage is also visible.

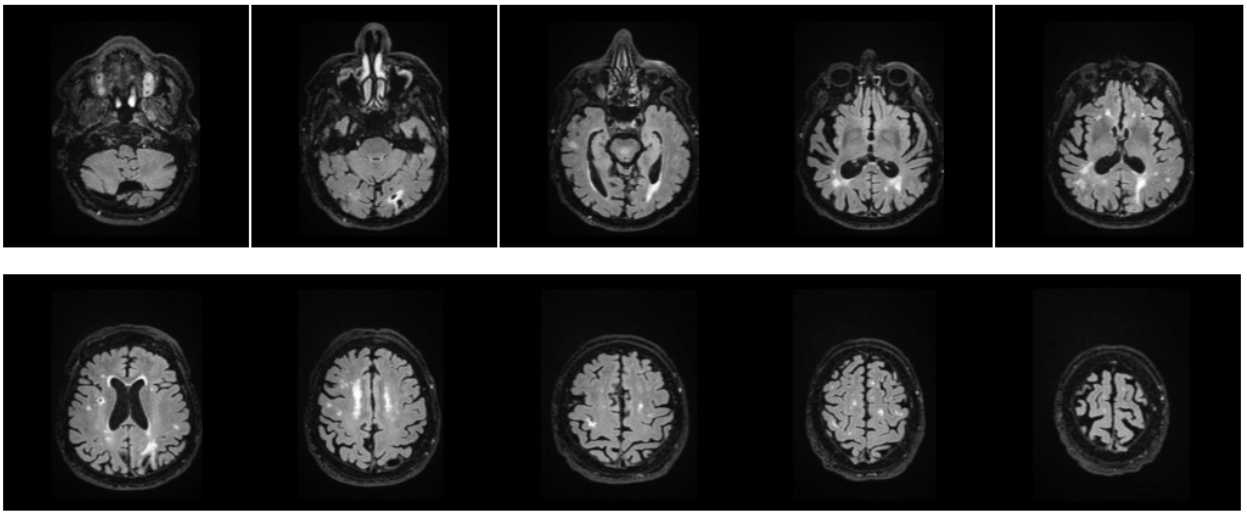

Figure 2: Axial Flair images showing ventricular and sulcal enlargement with some hyperintense lesions.

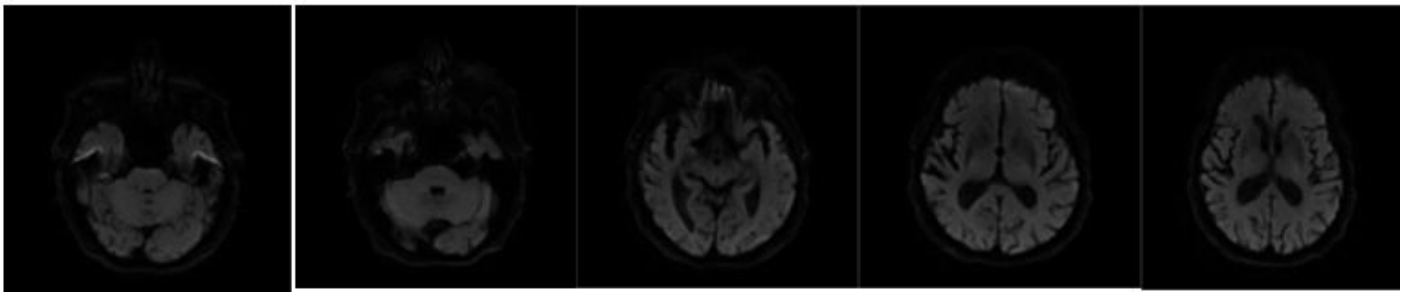

Figure 3: DWI b1000 images showing no signal abnormalities related to acute ischemia or other signs.

Modified Boston Criteria for Cerebral Amyloid Angiopathy			
Definite CAA	Probable CAA with pathology	Probable CAA	Possible CAA
Full post-mortem examination	Clinical data and pathological tissue demonstrating:	Clinical data and MRI or CT demonstrating:	Clinical data and MRI or CT demonstrating:
Lobar, cortical or sub-cortical hemorrhage	Lobar, cortical or cortical-subcortical hemorrhage	Multiple haemorrhages restricted to lobal, cortical or cortical-subcortical regions	Single lobar, cortical or cortical-subcortical hemorrhage or microbleeds or cortical siderosis
Severe CAA vasculopathy	Some degree of CAA in specimen	Age ≥ 55y	Age ≥ 55y
Absence of other diagnostic lesions	Absence of other diagnostic lesions	Absence of other causes of hemorrhage (see text)	Absence of other causes of hemorrhage (see text)

Table 1: Modified Boston criteria for cerebral amyloid angiopathy [1].

We suggested to our patient and his family to perform a cerebral biopsy, in order to obtain a histological diagnosis, however they did not accept. Our patient didn't have other evident causes for atypical cerebral haemorrhage, as he had not suffered an antecedent head trauma, didn't use warfarin or other anticoagulant agent, didn't suffer of vasculitis, haemorrhagic brain tumor, ateriovenous malformation or ischemic stroke with hemorrhagic transformation, that are all considered as the principal potential causes of atypical cerebral haemorrhage. Also, the MRI examination excluded the inflammatory form of CAA.

After the discharge from our Neurological department, the cognitive and clinical picture of the patient continued to worsen rapidly, until he couldn't walk, even aided, and talk, due to both a severe aphasia but also dysarthria. He also developed dysphagia, at first only for liquids and later also for solid foods. A nasogastric tube has been placed to guarantee the correct intake of calories, proteins, water and all the other necessary nutrients. Despite this, in the following months the patient developed pressure ulcers both on his heels and in the sacral region. He was then institutionalized because his total inability to attend every aspect of life and the family wasn't able to take care of all the needs of the patients.

Discussion

Rapidly Progressive Dementias (RPDs) are very challenging clinical cases. Differently from the other more common type of dementias, that usually have a clinical course that last many years, RPDs are characterized by a very rapid progression of symptoms, that usually develop over a period of months, weeks or even days until death [1-2]. Since some diseases leading to RPDs are treatable, an accurate diagnosis of these conditions is crucial for the correct management of these patients.

The peculiarity of CAA is the accumulation of amyloid proteins, with the [beta]-amyloid type being the most common, in the leptomeningeal vessels and cortical arterioles [3]. This accumulation leads to a vessel stiffening and a subsequent possible rupture of its walls [4-6]. It is responsible for cerebrovascular disease, especially for symptomatic lobar haemorrhage, microbleeds and cortical siderosis. The most frequent manifestation of CAA during life is symptomatic, spontaneous Intracerebral Haemorrhage (ICH), preferentially affecting lobar regions with a prevalence in the occipital and posterior temporal lobes [7-9]. Ischemic episodes, transient focal neurological manifestations due to transient ischemic attack or also caused by focal seizure, gait instability in the elderly, subarachnoid haemorrhage and cognitive decline are common manifestations [9].

MRI with Gradient Echo (GRE) sequence enables us to evaluate many aspects of CAA radiology. Firstly, the exact location of the bleeding, showing the typical cortical-subcortical distribution: this is due to the anatomic distribution of the vessels containing [beta]amyloid [10], then the signs of previous cerebral haemorrhages which may have been asymptomatic. MRI shows also microhaemorrhages, defined as petechial lesions with a diameter less than 5 mm that are generally asymptomatic and located at the cortical-subcortical junction predominantly located in the posterior half of the brain: this distribution pattern is considered to be characteristic for CAA [11]. Cerebellar superficial siderosis has been considered a novel marker for CAA [12]. Other MRI findings of patients affected by CAA are leukoencephalopathy and ischemic lesions.

In the last years, a new entity has arisen: the inflammatory form of CAA, also known as Cerebral Amyloid Angiopathy-Related Inflammation (CAARI). CAARI is widely recognized as a quite rare and aggressive form of CAA. This variant has characteristic clinical and radiological findings [13]. This is a syndrome of reversible encephalopathy found in patients with CAA. It is characterized by neurobehavioral symptoms, seizures, headache, and stroke-like focal signs in contrast with the classical sign of CAA [14]. Acute or subacute onset of cognitive impairment or behavioural problems are the most common signs of CAARI [15].

The MRI findings of this condition are large and confluent T2/FLAIR hyper intense areas in the cortex and sub-cortical white matter that could be symmetrical or mostly asymmetrical [16] and could extend to the cortex with a mass effect showing hyper intensity in apparent diffusion coefficient as for vasogenic oedema [17], plus scattered strictly lobar microbleeds on gradient echo sequences.

Our case report describes an uncommon presentation of CAA. Indeed, there are few similar cases in the literature available. In the clinical case described by Takada et al [18], the patient had a rapidly progressive dementia that, after the investigations, they diagnosed as CAA causing RPD. As in our case, they found a slightly increased level of CSF protein, whilst every other parameter in cerebrospinal fluid was normal. The increase of CSF protein is not common in CAA. In the paper by Greenberg et al., they found an increase in CSF protein in two of seven patients, and one of these two patients had a rapidly progressive dementia [19]. Probably, more studies are needed to evaluate if this increase in the level of the CSF protein in patients with CAA could be a marker of possible development of rapidly progressive cognitive decline. In these cases myoclonus that is generally thought as the most common sign in prion diseases was not described in the clinical pictures of the patients, as for ours. In all these cases MRI was the instrumental investigation that led to the diagnosis of CAA and ruled out most of the differential diagnoses. The duration of the disease is variable in literature, ranging from days or weeks, up to about 2 years, and there isn't a clinical or instrumental marker that can suggest how long the disease will last. Today, it is difficult to say if there is a gender preference in RPD caused by CAA, and the literature describes 4 cases in men and 2 in women. According to the epidemiology of CAA, also the CAA patients with RPD are generally old, with the majority above 75 years and only one below 60 years.

Our study has some limitations, one of them being a follow up of imaging and the fact that we didn't perform a RT-QuIC test or brain biopsy, since the family of the patient didn't allow it. We have also considered the surprisingly low diagnostic accuracy of the brain biopsy in the diagnosis of prion diseases [20]. The clinical picture, unfortunately, worsened so rapidly that for the family it was nearly impossible to move the patient to undergo other tests and an MRI investigation would have needed a sedation, owing to his inability to collaborate. We didn't perform the RT-QuIC test on CSF due to some considerations: in that period our laboratory didn't carry out this kind of test and we would have had to send the sample to another laboratory, so we decided to follow the Center for Disease Control and Prevention diagnostic criteria for the diagnosis of sCJD [21], that suggests how to diagnose a probable sCJD without the RT-QuIC test on CSF or other tissues. We also considered that the time of onset, the clinical picture and all the results of the instrumental investigations could be sufficient to exclude a prion disease like CJD.

Conclusion

Our report describes a clinical case of RPD that was initially suspected to be a prion disease, but that the investigations and the ancillary tests were not supportive for this diagnosis or for other conditions that could lead to a RPD, whilst they revealed a CAA without inflammation. In fact, the MRI examination showed a diffuse damage due to microbleeds, a previous lobar haemorrhage, but not inflammatory lesions. This condition is rarely referred as a possible cause of RPD. One may question whether or not CAA was the only cause of RPD in our patient. Accordingly to all the investigations performed, we think that our case report suggests that even CAA without inflammation should be included among the possible cause of RPD and we suggest considering this diagnosis when approaching a patient with a clinical picture of RPD.

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References:

1. Geschwind MD (2016) Rapidly Progressive Dementia. Continuum (Minneap Minn). 22(2 Dementia):510-37.
2. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL (2008) Rapidly progressive dementia. Ann Neurol. 64:97-108.
3. Kozberg MG, Perosa V, Gurol ME, van Veluw SJ (2021) A practical approach to the management of cerebral amyloid angiopathy. Int J Stroke. 16:356-369.
4. McLauchlan D, Malik GA, Robertson NP (2017) Cerebral amyloid angiopathy: subtypes, treatment and role in cognitive impairment. J Neurol. 264:2184-2186.
5. Maia LF, Mackenzie IR, Feldman HH (2007) Clinical phenotypes of Cerebral Amyloid Angiopathy. J Neurol Sci. 257:23-30.
6. Yamada M (2000) Cerebral amyloid angiopathy: an overview. Neuropathology. 20:8-22.
7. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, et al. (2005) Greenberg SM. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol. 58:459-62.
8. Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, et al. (2017) Emerging concepts in sporadic cerebral amyloid angiopathy. Brain. 140:1829-1850.
9. Wermer MJH, Greenberg SM (2018) The growing clinical spectrum of cerebral amyloid angiopathy. Curr Opin Neurol. 31:28-35.
10. Chao CP, Kotsenas AL, Broderick DF (2006) Cerebral amyloid angiopathy: CT and MR imaging findings. Radiographics. 26:1517-31.
11. Tachibana N, Ishii K, Ikeda S. (2016) Cerebral Amyloid Angiopathy-related Microbleeds: Radiology versus Pathology. Intern Med. 55:1235-6.

12. Koemans EA, Voigt S, Rasing I, van Harten TW, Jolink WMT, et al. (2021) Cerebellar Superficial Siderosis in Cerebral Amyloid Angiopathy. Stroke.

13. Wu JJ, Yao M, Ni J (2021) Cerebral amyloid angiopathy-related inflammation: current status and future implications. Chin Med J (Engl). 134:646-654.

14. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM (2004) Clinical manifestations of cerebral amyloid angiopathy-related inflammation. Ann Neurol. 55:250-6.

15. Ronsin S, Deiana G, Geraldo AF, Durand-Dubief F, Thomas-Maisonneuve L, et al. (2016) Pseudotumoral presentation of cerebral amyloid angiopathy-related inflammation. Neurology. 86:912-9.

16. Kirshner HS, Bradshaw M (2015) The Inflammatory Form of Cerebral Amyloid Angiopathy or "Cerebral Amyloid Angiopathy-Related Inflammation" (CAARI). Curr Neurol Neurosci Rep. 15:54.

17. Raghavan P, Looby S, Bourne TD, Wintermark M (2016) Cerebral amyloid angiopathy-related inflammation: A potentially reversible cause of dementia with characteristic imaging findings. J Neuroradiol. 43:11-7.

18. Takada LT, Camiz P, Grinberg LT, Leite CDC (2009) Non-inflammatory cerebral amyloid angiopathy as a cause of rapidly progressive dementia: A case study. Dement Neuropsychol. 3:352-357.

19. Greenberg SM, Vonsattel JP, Stakes JW, Gruber M, Finklestein SP (1993) The clinical spectrum of cerebral amyloid angiopathy. Neurology. 43:2073-2079.

20. Manix M, Kalakoti P, Henry M, Thakur J, and Menger R, et al. (2015) Creutzfeldt - Jakob disease: updated diagnostic criteria, treatment algorithm, and the utility of brain biopsy. Neurosurg Focus. 39:E2.

21. https://www.cdc.gov/prions/cjd/diagnostic-criteria.html