

Sporadic Cerebral Amyloid Angiopathy With Cortical Occipital Calcifications in the Elderly

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Cerebral amyloid angiopathy (CAA) is a common condition affecting the elderly and is associated with leukoencephalopathy and recurrent hemorrhagic strokes, including lobar microhematomas and macrohematomas and subarachnoid bleedings (for review, see the work of Biffi and Greenberg¹). Although a definite diagnosis can only be reached after a postmortem examination, the diagnosis of probable CAA can be made using clinical and neuroimaging arguments, according to the Boston revised criteria.² Very rare families exhibit autosomal dominant CAA due to a mutation in the *APP* gene, with an early onset (before 65 y). A minority of them exhibit cortical calcifications on computed tomographic (CT)-scan. Only 2 *APP* mutations have been reported to be associated with cortical calcifications and CAA, namely the Iowa (p.Asp694Asn, in 5/6 families) and the Italian mutation (p.Glu693Lys, in 1/5 families) (reviewed in the work of Sellal et al³). These calcifications, affecting mainly the occipital cortex, are considered to be very specific to these 2 rare mutations in the context of early-onset CAA. We report here the case of a woman presenting with similar calcifications in the context of sporadic late-onset CAA.

CASE REPORT

An 81-year-old woman suffered from sudden aphasia and right upper limb paresis revealing a left parietal lobe hematoma. Fifteen days later, she presented a recurrence affecting the right perirolandic region (Fig. 1A). She had no family history of any neurological or psychiatric disorder. Her main medical history was high blood pressure and a pacemaker implantation for sinus dysfunction diagnosed after 1 fall without loss of consciousness. She was diagnosed with major neurocognitive disorder 1 year before; the Mini-Mental State Examination scored 9/30. This cognitive decline was concomitant to several transient ischemic attacks and accompanied by probable progressive cognitive decline, suggesting a

combination of vascular and degenerative processes. Upon examination, the patient presented severe aphasia precluding the assessment of Mini-Mental State Examination and tetrapyramidal syndrome with spasticity. On top of lobar hematomas, CT-scans revealed periventricular hypodensities suggesting leukoencephalopathy, bilenticular calcifications (Fig. 1B), and calcifications of the occipital cortex (Figs. 1B and C). Probable CAA was diagnosed following revised Boston criteria². Blood phosphocalcic parameters assessment showed a normal level of calcium (2.47 mM), phosphorus (0.94), and parathormone (32 ng/L, N=5 to 40), whereas 25-OH vitamin D was slightly decreased (18 nM, N>30). *APP* sequencing (exons 16, 17), performed with informed written consent and in the context of a study approved by Paris Ile de France II ethics committee, revealed no pathogenic variant, which is consistent with the diagnosis of sporadic CAA of the elderly. Her *APOE* genotype was E3-E4, a common risk factor for CAA.

DISCUSSION

Occipital calcifications have been reported in a few conditions in adults, either in the context of CAA due to an Italian or an Iowa *APP* mutation, or independently from CAA. In primary familial brain calcification, phosphocalcic metabolism disorders, and diffuse neurofibrillary tangles with calcification, cortical calcifications are accompanied by moderate to severe calcifications in other areas (among pallidum, striatum, thalamus, white matter, and cerebellum), which was not the case here.^{4–6} Of note, the patient presented basal ganglia calcifications. However, the grade of severity in our patient was within the same ranges as what is commonly observed after the age of 60 years without clinical significance.⁴ In celiac disease, the calcifications appear with a coarser aspect than what is observed in Iowa and Italian *APP* mutation carriers and in phosphocalcic metabolism disorders.⁷ In Sturge-Weber syndrome, leptomeningeal angiomatosis is frequently calcified.⁸ Here, the clinical and imaging pictures were not suggestive of this diagnosis. Vascular malformations can also be calcified.⁹ It appears however very unlikely that vascular malformations would follow the cerebral sulci with such a homogeneous and serpentine aspect and respect the rest of the brain. Other conditions have been described as being potentially associated with cortical calcifications, with a different aspect on CT (for review, see the work of Ayrignac et al⁶ and Livingston et al¹⁰). The neuroimaging picture of our patient, including recurrent hemorrhagic strokes, leukoencephalopathy, and cortical calcifications, is very similar to the one observed in patients with early-onset CAA due to the Iowa or Italian *APP* mutations.^{3,11,12} Brain magnetic resonance imaging could have helped identify stigmata of subarachnoid hemorrhages and superficial siderosis,² but we could not propose such imaging in our patient because of the incompatibility of her pacemaker with magnetic resonance imaging. The negative family history and the late age of onset did not suggest a genetic cause. This was confirmed by the negative screen of the *APP* gene. We could conclude that our patient suffered from probable CAA in its common sporadic form affecting the elderly. It has been

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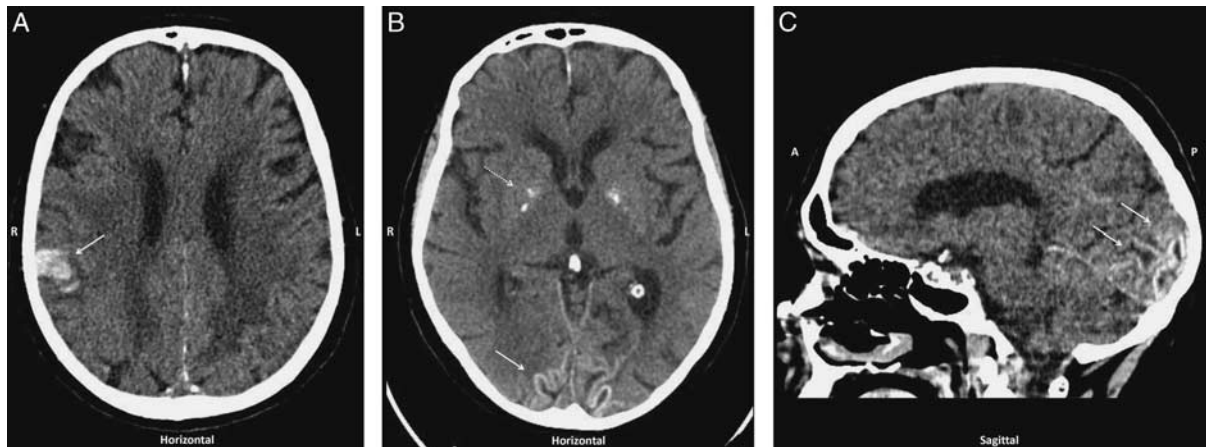


FIGURE 1. Cerebral CT-scan revealing cortical calcifications in a patient with sporadic probable cerebral amyloid angiopathy. Spontaneous right perirolandic hematoma (A, horizontal view, full arrow). Calcifications affecting the occipital cortex (B, horizontal view, full arrow) and (C, sagittal view, full arrows). Note the presence of basal ganglia calcifications (B, dotted arrow), the extension of which was comparable with what is observed during uncomplicated aging suggesting a coincidence.

suggested before that cortical calcifications could affect elderly patients with CAA.¹¹ However, we could not find a case description in the literature, suggesting that this remains rare. The mechanisms leading to these calcifications remain obscure, even in the patients with an *APP* mutation, which is a clue to the understanding of the mechanisms. In a neuropathologic point of view, CAA is defined by the deposition of an amyloidogenic peptide in the walls of cortical and leptomeningeal vessels. The causal peptide is the A β peptide in common CAA as well as in CAA due to *APP* mutations. To the best of our knowledge, there is no evidence of a direct link between calcifications and brain hemorrhage in the literature of CAA but this hypothesis would deserve to be assessed. Of note, patients with mutations in the *TTR* gene causing transthyretin-related CAA, can also present cortical calcifications,^{13,14} suggesting that this phenomenon is not specific to the A β peptide.

We conclude that probable CAA in its most common form, that is, affecting the elderly without Mendelian inheritance, can also be associated with cortical calcifications as is the case for exceptional families with autosomal dominant early-onset CAA.

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