Cerebral Amyloid Angiopathy, Hemorrhages and Superficial Siderosis

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In this issue of Stroke, Feldman and coworkers describe 3 subjects with clinically somewhat atypical Alzheimer Disease (AD) and with a radiologically verified superficial siderosis (SS). In 2 of these patients, a neuropathological examination confirmed AD with concomitant cerebral amyloid angiopathy (CAA) and a premortem diagnosis of SS. Thus, a linkage was made between CAA, SS and atypical AD. This report highlights 3 issues of major interest. First, are chronic hemorrhages due to CAA and SS factors to be taken into account when dealing with subjects with AD or vascular cognitive impairment (VCI) due to CAA. Secondly, should we consider conducting imaging analysis in demented subjects displaying a somewhat atypical clinical phenotype of AD and/or VCI. Finally, can gradient-recalled echo (GRE) T2*-weighted MRI be exploited as a tool to identify those individuals with severe CAA?

Superficial siderosis is defined as a condition where hemosiderin is deposited in the subpial layer of the central nervous system with the symptoms developing after chronic repeated subarachnoidal hemorrhages (SAH). Already in 1960, Iwanowski and Olszewski were able to experimentally reproduce SS in dogs by repeated subarachnoidal injections of blood. In the review article from 1995 by Fearnly and colleagues, one can find a comprehensive summary of the issues regarding clinical, radiological and pathological findings observed in this entity. In a more recent case report including a fine review of the literature, Levy and colleagues summarized the findings of the worldwide published reports (ie, 270 SS cases) and concluded that in only 3% of all reported SS cases was the etiology considered to be related to CAA. This would be in line with findings of a necropsy study from 1993 by Yamada and colleagues, reporting that CAA was never found to be the cause of SAH in their 15 subjects. It is noteworthy, however, that in their material when intracerebral hemorrhage (ICH) had ruptured into the subarachnoidal space, ie, secondary SAH, in half of the cases the etiology was attributed to CAA. Thus, the claim that the percentage of CAA being responsible for SS is a mere 3% of the reported cases is surprisingly low, bearing in mind that CAA is a common finding (Figure) in the aged affecting vessels both in the leptomeninges and in the superficial cortex and, particularly, as this vascular alteration is known to predispose to hemorrhaging.

Thus, one has to ask are all cases of SS being identified? In 2007, Simeoni and colleagues stated in their Case Report of a subject with SS that “clinical symptoms of SS are unlikely to be familiar to clinicians because SS is rare and unusual”, and thus, cases with SS might easily be overlooked by clinicians. Furthermore, in conjugation with AD, the percentage of identified SS might be low as the clinical symptoms can be obscured as was the case in the 3 cases described by Feldman and his colleagues in this issue. Another potential explanation for the low percentage might be the neuropathological assessment. In a case with AD and severe CAA, as well as in CAA cases with acute bleedings, the signs of SS might be overlooked. Moreover, in general, all over the world the percentage of autopsies, and thus, neuropathological investigations on aged and demented individuals and particularly on subjects suffering hemorrhages are alarmingly low, and thus, the recorded percentages of SS might be underestimated.

Another possible explanation for the reported low percentages would be that in fact hemorrhages and particularly microbleeds and chronic hemorrhages are not that common in subjects with CAA. Already in 1987, Yamada and colleagues reported that neuropathologically verified CAA was seen in 57% of aged subjects (average 83 years at death) and later in 2006, Tanskanen and colleagues reported a prevalence of 44% of CAA in very old individuals, ≥95 years at death. Thus, CAA is indeed a common age-related vascular change and in an excellent review on CAA from 1987, Vinter stated that CAA accounted for 5% to 10% of primary nontraumatic brain hemorrhages. In that review, he also speculated that CAA as an etiologic factor in primary nontraumatic brain hemorrhage would likely increase with the greying of the population. Surprisingly, in the recent study by Attems and colleagues which examined a total of 2060 elderly subjects with a mean age at death 78.5 years, CAA was seen in as many as 73.2% of cases, whereas spontaneous ICH (excluding microbleeds) were seen in only 5.6% of the total cohort, thus indicating that no major increase in nontraumatic brain hemorrhaging had occurred during the past 20 years.

CAA develops over time, not overnight, and it could be anticipated that in subjects with CAA in addition to spontaneous grossly notable ICH, some microbleeds should be observed. Imaging studies have explored this issue and in 2002, Nakata and colleagues reported that they could detect microbleeds using GRE T2*-weighted MRI. These microbleeds were demarcated...
as low intensity spots corresponding to focal deposition of hemosiderin within macrophages and these lesions were seen in cortical/subcortical area in 18.4% of AD cases. Later, Nakata-Kudo and colleagues refined the study material to include only pure AD cases excluding all those with clinically observed cardiovascular disease (CVD), history of CVD or detectable infarcts on MRI but still observed radiologically detectable microbleeds in 7 (17%) of their 42 AD patients. However, in none of their cases did they report any signs of SS. In the review by Fearnley, SS was radiologically defined as a marginal hypointensity seen in GRE T2*-weighted MRI that neuropathologically corresponded to deposition of hemosiderin up to depth of 3 mm. The three AD subjects described by Feldman and colleagues displayed SS as defined above. It is probable, however, that some of the cases in the study by Nakato-Kudo with cortical signal loss in T2*-weighted images also displayed hemosiderin deposits in the superficial molecular layer and thus would have fulfilled the radiological and neuropathological criteria for SS.

In conclusion, based on the first neuropathological report published in this issue by Feldman and colleagues observing SS, ie, hemosiderin deposits within macrophages in subpial region in association with CAA in AD subjects and based on the imaging studies particularly those conducted by Nakata-Kudo indicating microbleeds in the superficial cortex in as many as 16.7% of AD subjects, one is inclined to suspect that SS in AD with CAA is an overlooked complication that should be acknowledged, and thus, its presence should be sought particularly in subjects with an unusual clinical phenotype. It is also noteworthy that in subjects with VCI, dementia suspected to be primarily of vascular origin, CAA has been cited as one significant culprit both by Kalaria and colleagues and by Hachinski and colleagues, and thus, the significance of microbleeds with potential complication such as SS might also be of importance in these patients. Thus, the interesting report by Feldman and colleagues published in this issue combined with our current knowledge regarding CAA and particularly microbleeds give rise to some speculation. The GRE T2*-weighted MRI of demented subjects either being suspected of suffering AD or VaD, might reveal SS to be a more common alteration than previously believed, especially in subjects with an unusual or unique clinical presentation. One could even make a more radical speculation regarding the future imaging practice of demented subjects. If economical restrictions were not an issue, one could recommend an initial imaging of β-amyloid (βA) aggregation in the brain by applying Pittsburgh Compound B (PIB) PET followed by regular controls applying GRE T2*-weighted MRIs. This would allow an assessment of the severity of CAA and related complications, in particular in those subjects prone for microbleeds, ie, patients receiving anticoagulative therapy.

Disclosures
None.

References

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