Cerebral Amyloid Angiopathy, Hemorrhages and Superficial Siderosis

Irina Alafuzoff, MD, PhD

See related article, pages 2894–2897.

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 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 of cases, whereas spontaneous ICH (excluding microbleeds) were seen in only 5.6% of the total cohort, thus indicating 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 Nakato-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 us an increased awareness of the potential significance of SS in subjects with AD. See*.

References


Key Words: amyloid angiography imaging
Cerebral Amyloid Angiopathy, Hemorrhages and Superficial Siderosis

Irina Alafuzoff

*Stroke.* 2008;39:2699-2700; originally published online July 17, 2008;
doi: 10.1161/STROKEAHA.108.516955

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/39/10/2699