EDITORIAL

Inflammation Complicates an 'Age-Related' Cerebral Microangiopathy

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The cerebral microvascular lesion described by the terms cerebral amyloid (Congophilic) angiopathy (CAA) or cerebrovascular amyloidosis is recognized as having a variety of clinicopathologic manifestations.[1,2] There are also numerous biochemically distinctive forms of CAA, many of them quite rare, usually inherited as autosomal dominant traits, and found in specific geographic regions. An example of a familial form of CAA (fCAA) is Hereditary Cystatin C amyloid angiopathy (HCCAA), related to a point mutation in the gene that encodes cystatin C, a cysteine protease inhibitor. This disorder exists only in Iceland or in individuals of Icelandic origin.[3]

By far the most common form of CAA is that resulting from progressive ABeta deposition in the walls of cerebral meningeal and cortical arteries/arterioles, a process that occurs with advancing age.[4] ABeta CAA is commonly associated with brain aging and especially Alzheimer disease (AD), though there appears to be a subset of individuals who harbor severe CAA in the absence of a significant 'load' of other neuropathologic lesions associated with AD. However, the precise or specific role of ABeta CAA in the pathogenesis and progression of the cognitive decline associated with AD remains unclear. Though CAA is found, to some extent, in the vast majority of brains of AD patients who undergo autopsy (arguably 85-90%+), this microangiopathy is severe in only a small minority of affected individuals—probably no more than 5-10%. Unfortunately, many of the feared neurologic complications of CAA occur in this comparatively small subset of patients—and even more unfortunately, absent a brain biopsy there is no way for a clinician to know with certainty which elderly patient has severe CAA. Recently, it has been shown by several groups that there is a strong association between cerebral microinfarcts and severe CAA, suggesting that this microvascular lesion may actually present with a clinical picture resembling ischemic-vascular dementia.[5-7]

Though the diagnosis of "definite CAA" can only be established by postmortem examination, the Boston Cerebral Amyloid Angiopathy Group has outlined criteria for "probable CAA with supporting pathological evidence" (requiring examination of evacuated clot material and/or a brain biopsy) and "probable" or "possible" CAA—the diagnosis of 'probable' CAA being made when clinical data and magnetic resonance imaging (MRI) findings indicate a patient at least 60 years-of-age, with multiple cerebral lobar, cortical or corticosubcortical hemorrhages, and absence of another etiology for intraparenchymal hemorrhage.[8] Of interest, the Boston CAA Group has also published studies suggesting that Pittsburgh Compound B (PiB) in conjunction with positron emission tomographic (PET) scanning may be used to provide evidence in support of the clinical diagnosis of CAA.[9,10] Unfortunately, there are no cerebrospinal fluid (CSF) markers that reliably predict the presence of CAA itself, or amyloid beta-related angiitis (ABRA), the subject of an interesting report in this issue of the CJNS. One could, however, envision a scenario whereby the 'Boston criteria' are used to predict the likelihood of a given patient's having CAA, amyloid imaging in conjunction with PET may then provide further evidence for severe CAA, and CSF markers of inflammation are assessed to support the likelihood of associated vasculitis (such a study has yet to be done). The size of vessels affected by ABRA is too small to allow for their accurate assessment by angiography and, as Rigby et al indicate, MRI findings are variable among affected patients.[11]

In this issue of the Canadian Journal of Neurological Sciences (CJNS), Rigby et al add significantly to our knowledge of the clinicopathologic spectrum of ABeta-related (cerebral) angiitis, or what could also be described as CAA-associated angiitis.[11] The association of angiitis (often with a granulomatous component) with ABeta deposition in cerebral vessel walls has been recognized almost since the first ABeta antibodies became available.[12] The clinical presentation of such patients is variable, but commonly includes intractable seizures and focal neurologic deficits, as in this small series. The MRI abnormalities vary among patients, and examples of these are nicely illustrated in this paper. The diagnosis of ABRA, though suspected clinically, can only be made with certainty by a brain biopsy, as it was in these three cases. As well, the authors of this series have characterized the immunophenotype of inflammatory cells infiltrating affected vessel walls. [The Neurosurgeon performing a biopsy for suspected ABRA should be instructed to provide a generous tissue fragment including leptomeninges, since (as with all vasculitides) the greater the number of vessels available for examination, the easier it becomes to confirm the diagnosis of a vasculitis].

Of interest, all three patients in the report were treated with immunosuppressive medications, including high dose prednisone. This resulted in substantial neurologic improvement, sometimes even a return to 'baseline' function. The authors make the point that ABRA is not associated with AD. However, this lack of an association may be the result of most cases of ABRA (in this series and prior studies) being diagnosed on brain biopsy, which by definition allows for examination of only small brain fragments, usually of neocortex and overlying meninges. The relative absence of ABeta-immunoreactive senile plaques and tau-immunoreactive neurofibrillary tangles and neuropil threads in such a small fragment does not rule out fairly advanced Alzheimer disease changes elsewhere in the brain. All three patients in this report showed cognitive impairment, though in one patient this was probably at least in part on the basis of ischemic brain lesions. Nevertheless, it is possible that their brains were significantly 'Alzheimerized', even though this was not seen in the brain biopsies performed.

The occurrence of ABRA, an unusual but not a rare entity, suggests that there may be examples of more subtle

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inflammation in CAA-affected arteries. In a large experience of autopsies on AD patients, we have occasionally encountered examples of severe CAA in which macrophages and even a few multinucleated giant cells are present in or adjacent to arteries/arterioles involved by pronounced CAA. ABeta related angiitis occurs only with severe CAA, and multinucleated giant cells sometimes appear to be 'ingesting' ABeta-immunoreactive material in or adjacent to the vessel wall, suggesting that in some way the beta-amyloid is triggering a classic foreign body giant cell reaction.[13] Unusually severe ABeta CAA is found in an autosomal dominant form of stroke observed in coastal regions of the Netherlands (Hereditary Cerebral Hemorrhage with Amyloidosis, Dutch type, HCHWA-D). This disease results from an APP codon 693 point mutation, resulting in an overwhelming CAA burden within the brain, with numerous associated ischemic and hemorrhagic lesions.[14,15] In HCHWA-D, multinucleated giant cells are frequently encountered around the extensive ABeta deposits in vessel walls.[16] It is possible that pathogenesis of inflammatory changes associated with the HCHWA-D form of fCAA will provide clues to the etiology of sporadic ABRA.

The report in this issue by Rigby et al re-emphasizes the value of careful clinicopathologic assessment of unique patients in attempting to discover novel mechanisms of neurologic impairment in patients—even when the neuropathologic features of a given lesion are ones not commonly encountered.

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References

1. Vinters HV. Cerebral amyloid angiopathy—a critical review. Stroke. 1987; 18: 311-24.
2. Vinters HV, Wang ZZ, Secor DL. Brain parenchymal and microvascular amyloid in Alzheimer's disease. Brain Pathol. 1996; 6: 179-95.
3. Palsdottir A, Snorradottir AO, Thorsteinsson L. Hereditary Cystatin C Amyloid Angiopathy: Genetic, clinical, and pathological aspects. Brain Pathol. 2006; 16: 55-9.
4. Zhang-Nunes SX, Maat-Schieman MLC, van Duinen SG, Roos RAC, Frosch MP, Greenberg SM. The cerebral beta-amyloid angiopathies: Hereditary and sporadic. Brain Pathol. 2006; 16: 30-9.
5. Haglund M, Sjobeck M, Englund E. Severe cerebral amyloid angiopathy characterizes an underestimated variant of vascular dementia. Dement Geriatr Cogn Disord. 2004; 18: 132-7.
6. Soontornniyomkij V, Lynch MD, Mermash S, Pomakian J, Badkoobehi Clare R, Vinters HV. Cerebral microinfarcts associated with severe cerebral beta-amyloid angiopathy. Brain Pathol. 2010; 20: 459-67.
7. Selnes OA, Vinters HV. Vascular cognitive impairment. Nature Clinical Practice Neurology. 2006; 2: 538-47.
8. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston Criteria. Neurology. 2001; 56: 537-9.
9. Johnson KA, Gregas M, Becker JA, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol. 2007; 62: 229-34.
10. Vinters HV. Imaging cerebral microvascular amyloid. Ann Neurol. 2007; 62: 209-12.
11. Rigby H, Easton A, Bhan V. Amyloid β-related angiitis of the central nervous system: report of 3 cases. Can J Neurol Sci. 2011; 38(4): 626-30.
12. Gray F, Vinters HV, Le Noan H, Salama J, Delaporte P, Poirier J. Cerebral amyloid angiopathy and granulomatous angiitis: Immunohistochemical study using antibodies to the Alzheimer A4 peptide. Human Pathol. 1990; 21: 1290-3.
13. Anders KH, Wang ZZ, Kornfeld M, et al. Giant cell arteritis in association with cerebral amyloid angiopathy: Immunohistochemical and molecular studies. Human Pathol. 1997; 28: 1237-46 [erratum pub'd in vol. 29:205-206].
14. Maat-Schieman J, Roos R, van Duinen S. Hereditary cerebral hemorrhage with amyloidosis—Dutch type. Neuropathology. 2005; 25: 288-97.
15. Natte R, Vinters HV, Maat-Schieman MLC, et al. Microvasculopathy is associated with the number of cerebrovascular lesions in hereditary cerebral hemorrhage with amyloidosis, Dutch type. Stroke. 1998; 29: 1588-94.
16. Vinters HV, Natte R, Maat-Schieman MLC, et al. Secondary microvascular degeneration in amyloid angiopathy of patients with hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D). Acta Neuropathol. 1998; 95: 235-44.

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