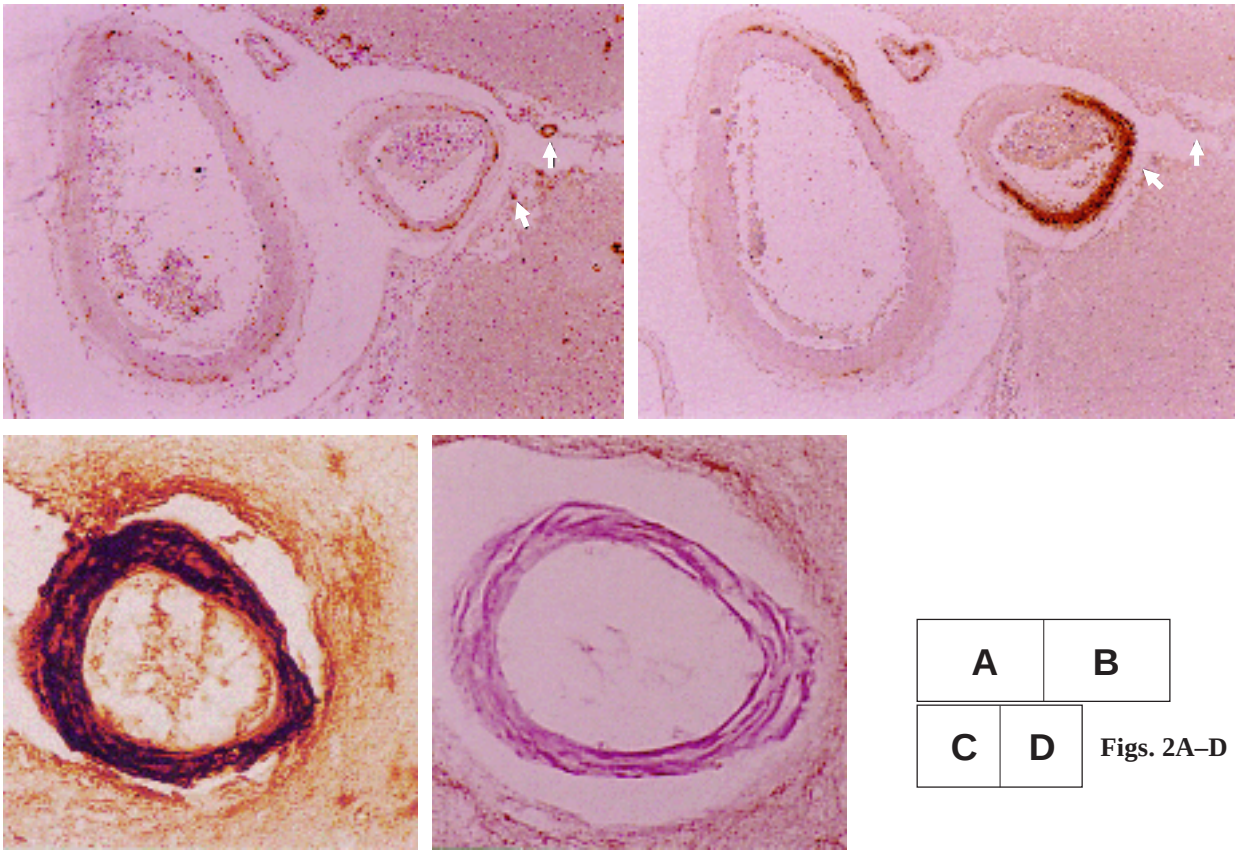

Fig. 2A–D. Immunohistochemistry of cerebral amyloid angiopathies (CAAs).
A: Immunostaining for amyloid β42 (Aβ42). In larger meningeal arteries, small positive areas are limited to the media adjacent to the adventitia but smaller cortical arteries are intensely stained in their whole walls (arrows). The occipital cortex in Alzheimer's disease (AD) (Patient 2).
B: An adjacent section immunostained with Aβ40. Positive areas are larger than Aβ42 but smaller cortical arteries are negative (arrows). **A, B:** original magnification, × 40.
C: Immunostaining for Aβ40 of an artery in the occipital cortex, showing complete replacement of the wall by Aβ40. The occipital cortex from AD (Patient 3).
D: An adjacent section to **C**, showing complete abscence of α-smooth muscle actin immunoreactivity in the media. **C, D:** original magnification, × 100.

adventitia as well. As the amount of amyloid deposition increased, the deposits extended more to part of the media and eventually to the whole vessel wall, which were clearly demonstrated as absence of smooth muscle actin immunoreactivity in the media (Figs. 2C and D). Early small amyloid deposits were never observed in the vicinity of the endothelium or the internal elastic lamina.

The relationship of PPs to SPs and CAAs

In AD patients, there were many mature plaques not only in the neuropil but also around blood vessels or adjacent to PPs, but diffuse plaques were not associated with blood vessels. There was no correlation between the number of PPs and that of SPs, but a good correlation was noted between the number of PPs and CAAs in AD and CAA patients (Table 2).

Discussion

Uematsu (1923) first described PPs as a perivascular form of SPs. Thereafter Scholz (1938) described PPs as *drusige Entartung* in German, SP-like angiopathy in English. He reported the small argyrophilic material resembling SPs initially deposits at the outer part of the media of the cortical arteries, extends to the adventitia and then eventually to the perivascular brain tissues. After Scholz, there have been few studies focusing on PPs and the neuropathological significance of PPs has not yet been elucidated.

In this immunohistochemical study, we found PPs were also a common form of Aβ deposits like SPs and CAAs in AD and CAA patients. They were always immunostained with Aβ42 and Aβ40, but their positive-staining areas were always larger in Aβ42 staining. In addition, they were always associated with AT8-positive, degenerated neurites and also with GFAP-positive astrocytes and astrocytic fibers within and around them. All of these immunohistochemical features are the same as mature SPs, indicating that PPs are another form of mature plaque.

PPs were much more frequent in CAA, particularly in CAA-D in which CAAs were remarkably numerous but the number of both NFTs and SPs was within range of physiological aging. Furthermore, our semiquantitative analysis revealed no correlation between the number of PPs and that of SPs but a good correlation between the number of PPs and that of CAAs. These findings suggest that PPs may play an important role in the pathogenesis of dementia, especially in CAA-D, and that there is a close relationship between the formation of PPs and the development of CAAs.

Neither the exact origin of Aβ in PPs and CAAs nor the mechanism by which it is deposited has as yet been resolved. Mandypur (1975) described that amyloid appeared in the neuropil along arterioles or in the Virchow-Robin spaces in the cerebral cortex, but the vessel wall itself was not necessarily involved. Some recent studies raised the hypothesis that Aβ was deposited initially in periarterial interstitial fluid drainage pathways of the cerebral cortex and contributed to CAAs in AD (Weller et al., 1998, 2000; Yow et al., 2002). Our results support this hypothesis from 2 aspects. First, PPs were also found around non-CAA arteries in AD and CAA patients, although they were frequently seen around varying degrees of CAAs. This finding suggests that the formation of PPs precedes the development of CAAs. Second, the main component of Aβ in PPs was Aβ42, and the early Aβ deposits in the vascular wall was also Aβ42, suggesting that Aβ in the vascular wall came from PPs, which was subsequently followed by Aβ40. Yamaguchi et al. (1992) also reported the same results in an immunoelectron microscopic study. In addition, Frautschy et al. (1992) also supported the hypothesis from their observations in animal experiments where direct injection into rat brains of isolated amyloid plaque cores had migrated to vessel walls and ventricular linings, implying that the distribution of injected amyloid is not necessarily comparable to the initial site of its deposition. Our 2 findings, together with other previous reports, were consistent with the Aβ deposit pathway described by Weller et al. (1998, 2000).

In summary, the present study demonstrated some immunohistochemical characteristics of PPs: they are immunopositive for Aβ42 and Aβ40, predominant for Aβ42, and always associated with degenerated neurites and reactive astrocytosis. These findings suggest that PPs were another form of mature plaque and that they may contribute to the development of dementia, particularly in CAA-D, and to the formation of CAAs.

Acknowledgments: The authors thank Professor Kenji Nakashima, Department of Neurology, Institute of Neurological Sciences, and Professor Ryuzo Kawahara, Division of Neuropsychiatry, Department of Multidisciplinary Internal Medicine, School of Medicine, Tottori University Faculty of Medicine, for their critical reading of the manuscript.

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Received January 7, 2003; accepted January 8, 2003

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