CADASIL: Intracytoplasmic Granular Osmiophilic Material Deposits Are Pseudoinclusions

We read with interest the recent study by Yamamoto et al (1) in which the authors demonstrated the specificity of anti-NOTCH3 ectodomain antibodies in CADASIL patients and confirmed the predominant localization of NOTCH3 ectodomain in granular osmiophilic material (GOM) deposits. The authors also documented widespread accumulation and distribution of NOTCH3 ectodomain in the meninges and cerebral microcirculation, particularly in capillaries. In particular, Figure 7B shows a perivascular cell that was interpreted as a phagocyte-appearing cell (Ph), which seems to engulf GOM deposits; the feature around the intracytoplasmic GOM is a bilayer membrane. Figures 7C and D show the same GOM-containing cells labeled with immunogold NOTCH3 particles.

We would like to advance a different interpretation of this autopsy material. It is our opinion that the cells depicted in Figure 7 are vascular smooth muscle cells, as borne out by the fact that they are surrounded by basal lamina (a characteristic ultrastructural feature of this cell type), and that they are degenerating cells, as demonstrated by the clumped chromatin. We also feel that the electron-dense structures inside the cells are GOM-containing pseudoinclusions, as supported by the basal lamina surrounding them (Fig. 7B). The basal lamina around the intracytoplasmic GOM deposits is replicated, like the one surrounding the cell in Figure 7B. In practice, the membrane invagination containing GOM in the longitudinal section will appear as a pseudoinclusion in the transverse section. We recently described GOM-containing pseudoinclusions in a homozygous CADASIL patient and we believe it to be related to the irregularity of the cell membrane of arterial smooth muscle cells (2, 3). The Figure depicts some cytoplasmic pseudoinclusions containing GOM found in a smooth muscle cell from our CADASIL patient.

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REFERENCES

Authors’ Reply

We read the correspondence from Drs Morroni and Lorenzi with much interest and thank them for taking interest in our report. As they reason, it is possible that the intracytoplasmic deposits of granular osmiophilic material (GOM) we report in phagocyte type of cells are “pseudoinclusions” in vascular smooth muscle cells (VSMCs). Electron microscopy sections are 50 to 70 nm thick and hence represent only a snapshot of the structural depth of the tissue; this often makes interpretation difficult. We should first note that the image provided by Dr Morroni is from a skin biopsy whereas we are assessing the brain. Moreover, the evidence we present is from the leptomeninges covering the cortex, and it is likely that the mobilization of GOM in the brain is different given that it has barriers between blood and CNS tissue.