Nuclear abnormalities as a manifestation of mitotic instability of vascular myocytes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a stroke and dementia syndrome with degeneration and loss of vascular smooth muscle cells (VSMC). The disease is associated with mutations in the *NOTCH3* gene playing a role in VSMC differentiation, proliferation and apoptosis. Since one of the possible pathomechanism of CADASIL may involve alterations in cell proliferation that are governed by the activity of the Notch-3 receptor-signaling pathway, to verify that hypothesis we performed morphological studies of VSMC. Material and methods: In autopsy and skin-muscle biopsy material of patients with CADASIL diagnosis, assessment of VSMC in arterial vessels at the level of light and electron microscopy was performed. Proliferative activity of VSMC was evaluated in immune reactions to proliferative markers: PCNA, and cyclins B1 and D. Results: In CADASIL, a part of VSMC revealed abnormal nuclear morphology. The affected myocytes showed variability in nuclear size, irregularity in nuclear shape, and abnormal chromatin appearance. Frequently, double nuclei of equal size or micronuclei were observed. Sometimes, even multinucleated myocytes were found. In some VSMC nuclei the immune reactions to PCNA and studied cyclins were positive. Conclusions: Aberrant structure and number of VSCM nuclei as well as their immunoreactivity to proliferative markers suggest mitotic instability of vascular myocytes in CADASIL. Mutated *NOTCH 3* gene which is unable to control properly VSMC proliferation, may be responsible for their premature or inappropriate entry of into mitosis, irreversible arrest of the cell cycle, senescence or degeneration and loss.