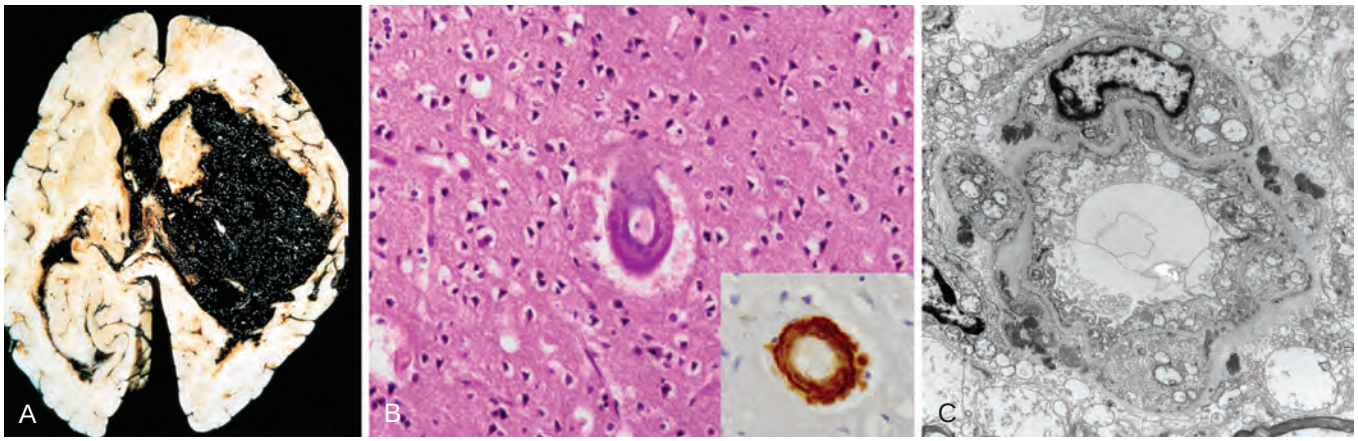

Figure 28-18 **A,** Massive hypertensive hemorrhage rupturing into a lateral ventricle. **B,** Amyloid deposition in a cortical arteriole in cerebral amyloid angiopathy; *inset*, immunohistochemical staining for Aβ shows the deposited material in the vessel wall. **C,** Electron micrograph shows granular osmophilic material in a case of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).

Cerebral amyloid angiopathy (CAA) is the risk factor most commonly associated with lobar hemorrhages. In CAA, amyloidogenic peptides, usually the same ones found in Alzheimer disease ($A\beta_{40}$; see later), are deposited in the walls of medium- and small-caliber meningeal and cortical vessels. This deposition can weaken the vessel wall and lead to hemorrhage. Many individuals with CAA have evidence of numerous small hemorrhages within the brain ("microbleeds"), which can be visualized by various imaging methods. As with Alzheimer disease, in which there is a relationship between a polymorphism in the gene that encodes apolipoprotein E (ApoE) and risk of disease, there is an effect of the ApoE genotype on the risk of recurrence of hemorrhage from sporadic CAA. The presence of either an ε2 or ε4 allele increases the risk of repeat bleeding. While some mutations in the precursor protein for the Aβ peptide (amyloid precursor protein, APP) cause familial Alzheimer disease, others result in autosomal dominant forms of CAA.

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The underlying vascular abnormality of CAA is typically restricted to the leptomeningeal and cerebral cortical arterioles and capillaries, although involvement of the molecular layer of the cerebellum can be observed as well. Involved vessels are rigid, and as a result fail to collapse during tissue processing and sectioning. Unlike with arteriolar sclerosis, there is no fibrosis; rather, dense and uniform deposits of amyloid are present (Fig. 28-18*B*).

Other forms of hereditary small-vessel diseases of the CNS have been identified recently. *Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL) is an autosomal dominant disorder caused by mutations in the *NOTCH3* gene that lead to misfolding of the extracellular domain of the NOTCH3 receptor. NOTCH3 is preferentially expressed in vascular smooth muscle, and mice engineered to express NOTCH3 receptors bearing CADASIL mutations recapitulate features of the human disease, indicating that the disease is caused by vascular smooth muscle dysfunction.

The disease is characterized clinically by recurrent strokes (usually infarcts, less often hemorrhages) and dementia. Imaging studies show that the first detectable changes are in white matter, usually by around the age of 35 years, whereas infarcts typically occur 10-15 years later. Arteries in the CNS and in other tissues such as skin show concentric thickening of the media and adventitia, loss of smooth muscle cells, and the presence of basophilic, PAS-positive deposits. These appear as osmiophilic compact granular material by electron microscopy and are consistently detected in the walls of affected vessels (Fig. 28-18*C*). The characteristic deposits contain the misfolded NOTCH3 protein. How these deposits relate to the disease is not understood. The diagnosis is made through the identification of these deposits in the walls of vessels in biopsies of other tissues, such as skin or muscle, or by sequencing of *NOTCH3*.

Other forms of the heritable small vessel diseases include a disorder associated with mutations in the gene for COL4A1, a component of the vascular basement membrane.

Clinical Features. Intracerebral hemorrhage, independent of cause, can be clinically devastating if it affects large portions of the brain and extends into the ventricular system, but it can affect small regions and either be clinically silent or evolve like an infarct. Over weeks or months there is a gradual resolution of the hematoma, sometimes with considerable clinical improvement. Again, the location of the hemorrhage determines the clinical manifestations.

Subarachnoid Hemorrhage and Ruptured Saccular Aneurysms

The most frequent cause of clinically significant subarachnoid hemorrhage is rupture of a saccular ("berry") aneurysm in a cerebral artery. Subarachnoid hemorrhage may also result from extension of a traumatic hematoma, rupture of a hypertensive intracerebral hemorrhage into