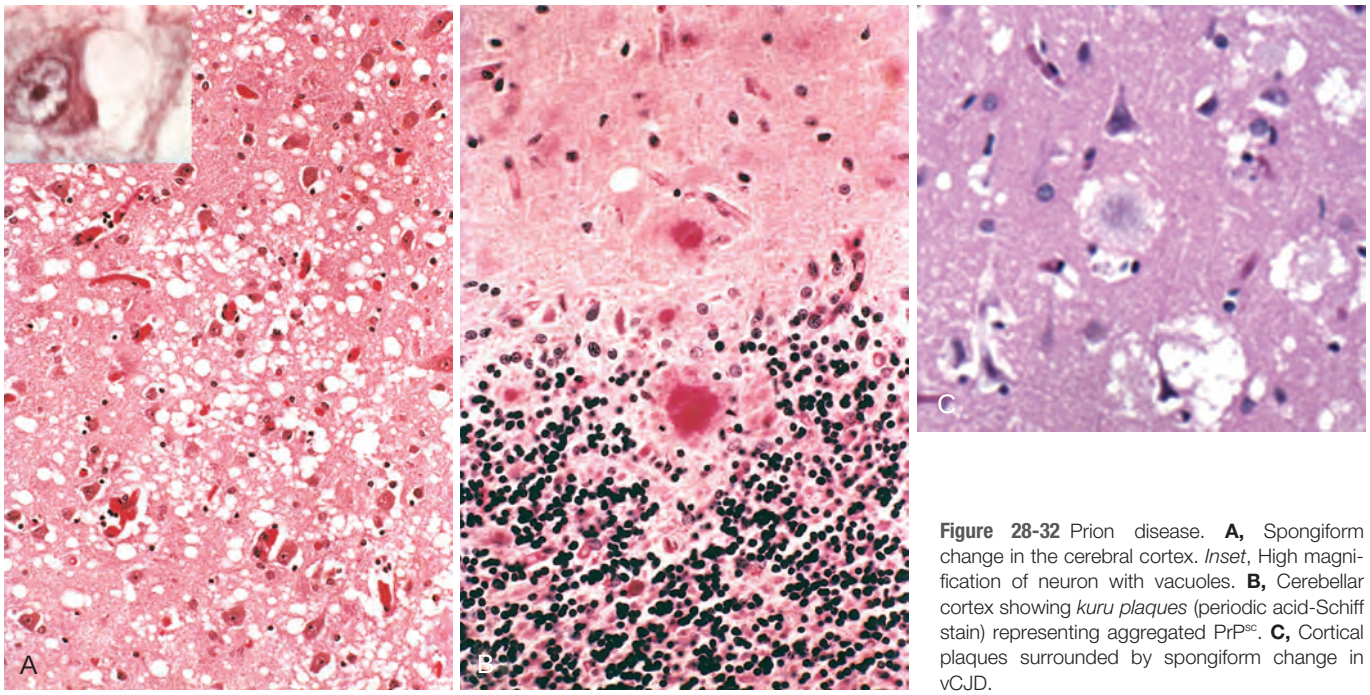

Figure 28-32 Prion disease. **A,** Spongiform change in the cerebral cortex. *Inset*, High magnification of neuron with vacuoles. **B,** Cerebellar cortex showing *kuru plaques* (periodic acid-Schiff stain) representing aggregated PrP^{sc}. **C,** Cortical plaques surrounded by spongiform change in vCJD.

caused by a specific mutation in the *PRNP* gene. The mutation, which leads to an aspartate substitution for asparagine at residue 178 of PrP^{c}, results in FFI when it occurs in a *PRNP* allele encoding methionine at codon 129, but causes CJD when present in tandem with a valine at this position. How these amino acids influence disease phenotype is not understood. In the course of the illness, which typically lasts fewer than 3 years, affected individuals develop other neurologic signs, such as ataxia, autonomic disturbances, stupor, and finally coma. A noninherited form of the disorder (fatal sporadic insomnia) has also been described.

MORPHOLOGY

Unlike other prion diseases, FFI does not show spongiform pathology. Instead, the most striking alteration is neuronal loss and reactive gliosis in the anterior ventral and dorsomedial nuclei of the thalamus; neuronal loss is also prominent in the inferior olivary nuclei. Proteinase K-resistant PrP^{sc} can be detected by immunostaining or western blotting.

KEY CONCEPTS

Prion Diseases

- Prion diseases may be sporadic, familial or transmissible (infectious). The disease is driven by the conversion of a normal cellular protein (PrP^{c}) into an abnormal conformation (PrP^{sc}), with the acquisition of distinct characteristics including relative resistance to protease digestion, self-propagation, and the ability to spread..
- Familial forms of these diseases are linked to mutations in the gene encoding PrP^{c} (*PRNP*). A polymorphic locus in *PRNP* (codon 129 may be either Met or Val) determines disease phenotype, with homozygosity at this site increasing risk of sporadic disease.
- Disease phenotypes include Creutzfeldt-Jakob disease (rapidly progressive dementia), Gerstmann-Sträussler-Scheinker syndrome (progressive cerebellar ataxia) and fatal familial insomnia.

Demyelinating Diseases

Demyelinating diseases of the CNS are acquired conditions characterized by preferential damage to myelin with relative preservation of axons. The clinical deficits are due to the effect of myelin loss on the transmission of electrical impulses along axons. The natural history of demyelinating diseases is determined, in part, by the limited capacity of the CNS to regenerate normal myelin and by the degree of secondary damage to axons that occurs as the disease runs its course.

Several pathologic processes can cause loss of myelin. These include immune-mediated destruction of myelin, as in multiple sclerosis, and infections. In progressive multifocal leukoencephalopathy, JC virus infection of oligodendrocytes results in loss of myelin (described earlier). In addition, inherited disorders may affect synthesis or turnover of myelin components; these are termed *leukodystrophies* and are discussed with metabolic disorders.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space. It is the most common of the demyelinating disorders, having a prevalence of