PRION DISEASES

Site of prion disease brain injury uncovered

New research indicates that a thalamostriatal network is involved in the pathogenesis of human prion diseases such as Creutzfeldt–Jakob disease (CJD). The study by Hedok Lee and colleagues provides new insights into the disease processes in CJD.

> “These data suggest that the thalamostriatal network is affected early in the onset of prion disease”

Human prion diseases are difficult to study, owing to their rarity, virulent course, and uncertain diagnosis at early stages of the disease. The initial site of cerebral injury, resulting from prion protein accumulation in the brain, and the associated pathophysiology are poorly understood. Patients with CJD who can be studied at the early stages of disease are needed to investigate the initial loci of injury in the human brain, explains principal investigator Isak Prohovnik of the Mount Sinai School of Medicine, New York. A familial variant of hereditary CJD with a Glu200Lys mutation on the prion protein gene has been found to be clinically similar to the sporadic form of CJD. Lee *et al.* studied differences in the brain before and during progression of the disease in a group of individuals carrying the Glu200Lys mutation.

A total of 54 participants were enrolled in the study; 14 patients with the familial genetic form of CJD, 20 healthy carriers of the Glu200Lys mutation (asymptomatic for CJD), and 20 healthy controls (negative for the mutation) recruited from the same families. All participants underwent whole-brain imaging with MRI. “Our primary tool was diffusion-weighted imaging, an advanced MRI technique that measures the mobility of water in the brain, and thus reveals the microstructure of tissue,” Prohovnik describes. The diffusion was quantified by the apparent diffusion coefficient and analyzed at the voxel level.

The researchers found that patients with CJD had abnormalities in the thalamostriatal network, which consists of the putamen and the mediodorsal, ventrolateral and pulvinar thalamic nuclei (structures known to be involved in motor and cognitive activity, typically disrupted in CJD). Prohovnik noted that “this same network was already affected in the brains of healthy subjects who carry the E200K [Glu200Lys] mutation.” No such abnormalities were observed in the control group.

The researchers comment that, following onset of disease, carriers of the Glu200Lys mutation display around a 10% further reduction in diffusivity in structures within the thalamostriatal network. These data suggest that the thalamostriatal network is affected early in the onset of prion disease. Future work could reveal why “certain brain areas, but not others, are vulnerable to prion-associated degeneration,” Prohovnik concludes.

Lisa Richards

Original article Lee, H. *et al.* Thalamo-striatal diffusion reductions precede disease onset in prion mutation carriers. *Brain* doi:10.1093/brain/awp064