LETTERS TO
THE EDITOR

Familial Pick’s disease and dementia in frontal lobe degeneration of non-Alzheimer type are not variants of prion disease

The prion diseases are a group of neurodegenerative conditions affecting both humans and animals. They are transmissible after inoculation, have long incubation periods, and have been known as the spongiform encephalopathies, slow virus diseases, or transmissible spongiform encephalopathy. The human diseases include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and kuru. They are associated with the deposition in the brain of an abnormal, partially protease resistant, isoform of the prion protein (PrP). An impressive body of experimental evidence now argues persuasively that this abnormal isoform of PrP is the central and conceivably the sole component of the transmissible agent of these diseases. Human prion diseases have inherited, sporadic, and acquired forms and the inherited types are associated with coding mutations in the PrP gene. This availability of diagnostic genetic markers has enabled molecular diagnosis in patients not previously thought to be suffering from CJD or GSS and who carried clinical diagnoses including Alzheimer’s disease, Pick’s disease, and Huntington’s disease. A wider phenotypic range of these disorders at the histological level has also been revealed after molecular diagnosis, with the identification of cases entirely lacking the usual pathological features of these conditions. This finding has led to a realisation that CJD and GSS are parts of a spectrum of what may be more appropriately called prion diseases. The recent classification of fatal familial insomnias as an inherited prion disease further emphasises the need to search out their full phenotypic range. A similar, molecular subclassification is now beginning, based on the identification of mutations in the amyloid β protein in familial Alzheimer’s disease and other familial neurodegenerative conditions such as hereditary cerebral haemorrhage with amyloidosis (Dutch type). For this reason we considered the hypothesis that both Pick’s disease (PD) and dementia in frontal lobe degeneration of non-Alzheimer type (FLD) could be variants of prion disease. As with prion diseases, most cases occur sporadically but families showing an autosomal dominant pattern of inheritance are known. Pronounced frontal lobe features have been documented in at least one type of inherited prion disease; Pick type cells have been reported in CJD; spongiform change is seen in spongiform encephalopathy. The familial forms of these conditions for the presence of either known or novel mutations in the PrP gene and also by attempting to show the presence of the disease related isoform of PrP. We studied well characterised families with these conditions that met both classical clinical and histological criteria and in which the disease segregation shows an autosomal dominant pattern. All families have been documented previously. We studied a Dutch family with PD one case presented with mental impairment at age 45, becoming apathetic and inactive. At age 45 she was completely dependent. Both her mother and two brothers had presented dementia. Postmortem examination of her mother had shown lobar atrophy and Pick bodies. The second Dutch family with PD was characterised by onset in their 40s of behaviour disturbances and inactivity. There was confirmation of Pick’s disease at necropsy. In a Swedish family with FLD 10 members in three generations were affected similarly with deterioration in personality and behaviour, lack of concern, and disinhibition. Later there were changes in speech with stereotyped phrases and echolalia. Three neuropathologically studied cases showed gross frontal atrophy with neuronal loss and splitting of the superficial frontal cortices.

DNA was extracted from either blood or frozen brain tissue from an affected case from each family by common techniques (using category 3 level microbial biological containment to handle the brain tissue). The polymerase chain reaction (PCR) was used to amplify the PrP gene open reading frame and the PCR product was directly sequenced by the chain termination method.

Frozen brain tissue was only available (from two cases) from the FLD kindred. A 10% brain homogenate with histologically most affected area (frontal cortex) was prepared under microbiological containment level 3 conditions. Homogenate (4 µl) was spotted in duplicate on to nitrocellulose membranes and one filter of the pair was treated with protease K to digest the normal cellular isoform of PrP. The filters were then treated with the prion protein polyclonal antiserum 2H4 (provided by Dr Prusiner) and detection of bound primary antibody was with horseradish peroxidase conjugated goat anti-rabbit antisemir/ enhanced chemiluminescence (Amersham). (KCL Sidle et al, in preparation). Each filter included both positive (histologically confirmed CJD) and negative controls (both histologically confirmed Alzheimer’s disease and normal brain (provided by MRC Brain Bank, Institute of Psychiatry). With the exception of the known common polymorphic variation at codon 129 no mutation was identified in either allele in any of the kindreds. Immunoblotting showed no evidence for the presence of the disease related isoform of PrP in the FLD cases studied.

These well documented cases of PD and FLD are not associated with PrP mutations. In the case at least of FLD no protease resistant PrP was detectable by immunoblotting. It seems likely therefore that PD and FLD are diseases with different underlying mechanisms, and variants of prion disease. It remains possible, however, that a proportion of less well defined cases and in particular those without neuropathological confirmation or in which neuropathology is equivocal may turn out to be further examples of inherited prion diseases. Screening by PrP gene analysis and immunoblotting may be helpful diagnostically in these cases.

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Acute neuromuscular respiratory paralysis

In their article on respiratory failure Hughes and Bhan1 make the point that forced vital capacity (FVC) and not peak expiratory flow (PEF) should be used in the assessment of declining respiratory function. The FVC has been shown to have predictive value for the need for ventilatory assistance in patients with myasthenia gravis and Guillain-Barré syndrome.2 We report a case that shows the need to measure FVC and also the results of a survey indicating the non-availability of such facilities. A 65-year-old woman with myasthenia gravis, affecting mainly eye movement, bulbar function, facial expression, and neck strength was treated with pyridostigmine and later started on 75 mg prednisolone daily. As may have been predicted, after six days of the steroid her clinical condition worsened. At this point serial measurements of both FVC and PEF were measured (figure). An increased dose of pyridostigmine was prescribed and neostigmine added. During the