Inherited prion disease with A117V mutation of the prion protein gene: a novel Hungarian family

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Abstract
Three members of a family with inherited prion disease are reported. One additional family member had a progressive neurological disease without details. Two developed symptoms of ataxia, dementia, myoclonus, rigidity, and hemiparesis, and one had a different phenotype with the combination of lower motor neuron deficit, parkinsonism, intellectual decline, and ataxia. In this last patient cell loss of the anterior horn motor neurons and chronic neurogenic muscle atrophy was evident. Immunostaining for the prion protein disclosed unicentric and multicentric plaques, and coarse and fine granular positivity. Genetic analysis of the prion protein gene of the propositus showed a 117 codon alanine to valine mutation and homozygous 129 valine/valine genotype.

Keywords: prion diseases; amyloid plaque; A117V mutation

Human prion diseases are mostly sporadic and rarely acquired, but about 10% are inherited.1 There are three human hereditary disease types: familial Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia.1 Point mutations and insertions within the prion protein gene (PRNP) form the genetic background, but polymorphisms are also described.2 The best known polymorphism at codon 129 (methionine/valine) is a susceptibility factor and influences the clinicopathological presentation.2,3 Recently, pathogenic mutations in four different genes (including PRNP) were found in patients with familial early onset dementia, and further PRNP mutations and polymorphisms are also registered.4,5 Here we present a Hungarian family with the rarely reported alanine to valine mutation at PRNP codon 117, including one case with a distinct clinicopathological phenotype.

Methods
PEDIGREE
The pedigree, provided by the propositus’ mother, is shown in figure 1.
ACTTTGTGCAGCAGTCGTCGA. Sequencing reactions were analysed on an ALF Express DNA analysis system (Amerham Pharmacia Biotech).

NEUROPATHOLOGY

Postmortem was carried out 24 hours after death. Formalin fixed, paraffin embedded blocks of the spinal cord and several regions of the brain, brainstem, and cerebellum of patient II/1 were investigated. Sections were stained using haematoxylin and eosin, Klüver-Barrera, PAS, and Congo red methods. Prion protein (PrP) immunocytochemistry after a consensus pretreatment protocol was performed using five monoclonal antibodies (3F4/epitope: amino acids 109–112, 1:300, SENETEK, Maryland Heights, MO, USA; 6H4/epitope: amino acids 144–152, 1:500, Prionics, Zürich, Switzerland; 12F10/epitope: amino acids 142–

Figure 2 (A) Coronal T1 weighted cranial MRI of the propositus showing atrophy of the right hemisphere. (B) Fluorodeoxyglucose positron emission tomography (PET) of the propositus showing reduced metabolism in the right hemisphere. (C) Loss of motor neurons and intraneuronal vacuolation (arrowhead, enlarged in the right upper corner) in the anterior horn (*) of the cervical spinal cord (Klüver-Barrera, originally×10 and ×40). (D) Multicentric amyloid plaque in the white matter of the cerebellum (immunocytochemistry for prion protein with 12F10, originally×20). (E) Diffuse granulofilbrillar depositions in the subcortical region with immunostaining for prion protein with 3F4 (originally×10). (F) Prion protein deposition adjacent to a vessel in the striatum (immunocytochemistry for prion protein with 3F4, originally×20). (G) Immunopositivity for the prion protein around the same vessel as seen on F is weaker using 6H4 antibody (originally×20). (H) Overview of the cerebellum: plaques are seen in the white matter, and along the surface in the molecular layer (immunocytochemistry for prion protein with 3F4, originally×10).
In the propositus (III/2) an alanine to valine mutation was found at PRNP codon 117, with valine homozygosity at codon 129.

RESULTS

CASE REPORTS

The propositus (III/2) developed depression at the age of 29 years. At the age of 32, progressive ataxia and left sided weakness appeared. Now at the age of 35, left sided hemiparesis, exaggerated tendon reflexes, pyramidal signs, rigidity, dysdiadochokinetics, limb and gait ataxia, myoclonus in all limbs, and intellectual decline were seen. Repeated cranial MRI showed progressive atrophy of predominantly the right hemisphere (fig 2 A). An EEG showed a reduced alpha activity and increased theta activity over the right side. Transcranial magnetic stimulation demonstrated a mild activity over the right side. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed chronic neurogenic atrophy. 

Achilles areflexia. Fasciculation, but not Babinski’s sign, was seen. An EMG was not performed. Chronic neurogenic atrophy was seen in an anterior tibial muscle biopsy. An EEG showed diffuse slowing, later sharp waves in the right-frontocentral region.

The propositus’ paternal grandfather (I/1) died at the age of 45 after a progressive neurological illness. No further clinical or neuropathological data are available.

Discussion

We describe three members of a Hungarian family with the A117V PRNP mutation. According to the dominant inheritance of a neurological disease, the PRNP mutation in one affected member, and the presence of multicentric plaques in the brain of another, the diagnosis of familial prion disease, Gerstmann-Sträussler-Scheinker disease type, was made.7

Previously one British-Irish, two French-Alsatian, and two American (one with German descent) families were described with this genotype.6,12 In these, the age at onset varied between 20 and 64 years, the duration of illness 1 to 11 years; our patients were similar. Hsiao et al reported on two members of a family with intellectual decline in one, and with dementia, rigidity, myoclonus, and dysarthria in the other. The cerebellum was preserved; thus the term telencephalic variant was used.14 In the other patient, the central clinical syndrome was progressive dementia and varying degrees of cerebellar ataxia, parkinsonian features, pyramidal signs, myoclonus, pseudobulbar...
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