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

G G Kovács, C Ertsey, C Majtényi, I Jelencsik, L László, H Flicker, L Strain, I Szirmai, H Budka

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

PRION PROTEIN GENE ANALYSIS
This was done with written permission. High molecular weight genomic DNA was prepared from peripheral blood cells of the propositus (III/2). The PRNP open reading frame was amplified by polymerase chain reaction (PCR) in 50 µl reactions containing 100 ng DNA, 200 µM each dNTP, 15 mM MgCl2, 50 mM KCl, 10 mM TrisCl (pH 8.3), 1 U Taq polymerase, and 0.1 µM of primers (forward primer: TGA-TACCATTGCTATGCACTCATTC, reverse primer: GACACCACCACTAAAGGCTGCAG). Cycling conditions were 35 cycles of 94°C for 1 minute, 60°C for 1 minute, 72°C for 1 minute, with a final step at 72°C for 10 minutes. The amplified product (956 bp) was sequenced using a ThermoSequenase dye primer 7-deaza cycle sequencing kit (Amersham Pharmacia Biotech) in four overlapping segments using the fluorescently labelled (5'FAM) primers CTATGCACTCATTCAT- TATG, GCAGCCCTGGAGGCAACCGC, AGGTGGCACCCATCGT, and and

Methods
PEDIGREE
The pedigree, provided by the propositus’ mother, is shown in figure 1.

Figure 1  Pedigree of the family. Generations are indicated with Roman, the family members with arabic numerals. NA=data not available.
ACTTTGTGCACGACTGCGTCA. Sequencing reactions were analysed on an ALF Express DNA analysis system (Amersham 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 protocol6 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 142–152/, 1:500, Prionics, Zürich, Switzerland; 3F4/epitope: amino acids 109–112/) 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 142–152/, 1:500, Prionics, Zürich, Switzerland).
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, dysdiadochokinesis, 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 2A). An EEG showed a reduced alpha activity and increased theta activity over the right side. Transcranial magnetic stimulation demonstrated a mild lesion of the right-sided motor pathways. Fluorodeoxyglucose positron emission tomography (PET) showed reduced tracer uptake in the right-frontocentral region.

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, dysdiadochokinesis, 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 2A). An EEG showed a reduced alpha activity and increased theta activity over the right side. Transcranial magnetic stimulation demonstrated a mild lesion of the right-sided motor pathways. Fluorodeoxyglucose positron emission tomography (PET) showed reduced tracer uptake over the whole right hemisphere (fig 2B), with contralateral cerebellar diaschisis.

The propositus’ father (II/2) died at the age of 45. For 3 years, he had been affected by progressive left-sided hemiparesis, exaggerated tendon reflexes, pyramidal signs, rigidity, dysdiadochokinesis, limb and gait ataxia, myoclonus in all limbs, and intellectual decline. Repeated cranial MRI showed progressive atrophy of predominantly the right hemisphere (fig 2A). An EEG showed a reduced alpha activity and increased theta activity over the right side. Transcranial magnetic stimulation demonstrated a mild lesion of the right-sided motor pathways. Fluorodeoxyglucose positron emission tomography (PET) showed reduced tracer uptake over the whole right hemisphere (fig 2B), with contralateral cerebellar diaschisis.

The propositus’ paternal aunt (II/1) died at the age of 55 in 1974. She had been a heavy drinker for years, but for the last 6 years she was abstinent. Her symptoms started at the age of 53 with impairments in social behaviour, lack of initiative, memory failure, and personality change. Six months before her death, disordered gait was reported. Rigidity, hypokinesia, and cerebellar signs were also noted. She developed atrophy in the interosseous, shoulder girdle, thigh, and tibial muscles, and increased upper limb tendon reflexes, but there was no 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.6,14 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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Inherited prion disease with A117V mutation of the prion protein gene was mentioned. In the Alsatian family progressive hemiparesis was as well.

In our patients, where detailed clinical data were available, intellectual decline, rigidity, and cerebellar signs were seen in all patients, whereas two (II/2 and III/2) had progressive hemiparesis (and unilateral cerebral atrophy in patient III/2). The clinical picture of patient II/1, consisting of motor neuron disease associated with dementia, parkinsonism, and ataxia, resembled frontotemporal dementia-parkinsonism-motor neuron disease. Previsously this combination of symptoms was not emphasised in A117V patients, although fasciculation and atrophy were mentioned.

Loss and intraneuronal vacuolation of spinal cord motor neurons in combination with neurogenic atrophy of muscle tissue were not described previously. Neuropathological investigation disclosed widespread accumulation of prion protein immunopositive plaques, as in earlier findings.

The codon 129 polymorphism might account for the heterogeneity between reported cases. The genotype of our propositus showed valine on the mutated allele, as in previous cases. As genetic information was available in only one of our patients, other causes for the motor symptoms might be also considered. However, the role of alcohol intake in the symptoms of patient II/1 is unlikely as she was abstinent for the past 6 years.

Prion immunocytochemistry of the plaques supports the notion that the amyloid core is strongly visible, with antibodies recognising the mid-region of the prion protein molecule, and that prion positive depositions might contain distinct prion protein fragments. It was already demonstrated that A117V Gerstmann-Sträussler-Scheinker disease shows western blot patterns different from those seen in Creutzfeldt-Jakob disease.

In conclusion, one of our patients showed a distinct clinical phenotype with loss and vacuolation of lower motor neurons (motor neuron disease type). In other respects (genotype, clinical course of other patients), our family is in accordance with earlier reports. Our finding widens the range of familial prion disease phenotypes and further emphasises the need for detailed analysis of the prion protein gene in atypical familial neurodegenerative conditions.

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