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

Methods

PEDIGREE The pedigree, provided by the propositus' mother, is shown in figure 1.
ACTTTGTGCAGACTGCGTCA. 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–

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 granulofibrillar depositions in the subiculum 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).
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 2 A). An EEG showed a reduced alpha activity and increased theta activity over the right side. Transcranial magnetic stimulation demonstrated a mild hypometabolic area with a reduced tracer uptake (PET) showed reduced tracer uptake over the right side. An EMG was not performed.

The propositus’ father (II/2) died at the age of 45. For 3 years, he had been a contralateral cerebellar diaschisis. At postmortem his brain weight was 1140 g. Marked cortical atrophy with right sided accentuation was described, but histological examination was not performed.

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, was abstinent. Her symptoms started at the age of 53 with impairments in social behaviour, disordered gait was reported. Rigidity, hypokinesia, and cerebellar signs were also noted. She developed atrophy in the interosseal, shoulder girdle, thigh, and tibial muscles, and increased upper limb tendon reflexes, but there was 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.

Neuropathological data are available. The propositus’ paternal aunt 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, disordered gait was reported. Rigidity, hypokinesia, and cerebellar signs were also noted. She developed atrophy in the interosseal, shoulder girdle, thigh, and tibial muscles, and increased upper limb tendon reflexes, but there was 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.
syndrome, and dysarthria, but behavioural, personality, and mood disturbance were also noted. In the Alsatian family progressive hemiparesis was mentioned 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. Preceding 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.

This study is part of the European Union Biomed-2 Concerted Actions Human Transmissible Spongiform Encephalopathies (prion diseases): The Neuropathology Network (PRIONET) and European Centralised Facility for Human TSEs (TSFEC-FAC) (project leader H Budka). We acknowledge the support of the Austrian-Hungarian Foundation (Stiftung Aktion Österreich-Ungarn, project number 990ub). We are indebted to the Debrecen University PET Centre for performing the PET examination. The help of Johannes A Hausfeller in preparing the illustrations is also acknowledged.

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 and H Budka

*J Neurol Neurosurg Psychiatry* 2001 70: 802-805
doi: 10.1136/jnnp.70.6.802