Fatal Familial Insomnia

The First Account in a Family of Chinese Descent

Sian D. Spacey, MD; Manuela Pastore, PhD; Barbara McGillivray, MD; Jonathan Fleming, MD; Pierluigi Gambetti, MD; Howard Feldman, MD

Background: Fatal familial insomnia (FFI) is an autosomal dominant disease linked to a mutation in the prion protein gene. Fatal familial insomnia is characterized by sleep disturbance and loss of neurons, with gliosis in the thalamic nuclei.

Objective: To describe the clinical, neurophysiological, radiological, and neuropathological data in a Chinese family with FFI.

Setting: Tertiary referral university hospital setting.

Patients: Patient 1 was a 36-year-old man who presented with insomnia and myoclonus. In the subsequent 9 months, he developed ataxia and dementia, followed by death. Patient 2 was the aunt of patient 1, and presented at the age of 47 years with insomnia, myoclonus, and dementia; her condition declined during a 12-month period. Genetic analysis was performed, followed by neuropathological and biochemical analysis of the disease-associated form of the prion protein PrPSc on the postmortem brain specimen.

Results: Molecular analysis demonstrated an aspartic acid to asparagine mutation at codon 178 and homozygosity for methionine at codon 129. Both patients showed severe neuronal loss and prominent gliosis in the thalamus and brainstem involvement, with evidence of astroglisis in the inferior olivary nucleus. Patient 1 also had neuronal loss and astroglisis in the region of the superior colliculus and in the periaqueductal region. PrPSc was detected on Western blot analysis, and had a wide distribution. The strongest signals were present in the amygdala, hypothalamus, caudate, parahippocampal gyrus, periaqueductal gray matter, and mediodorsal thalamus.

Conclusions: To our knowledge, this is the first report of FFI in a family of Chinese descent. This supports the worldwide distribution of FFI, and despite differences in genetic background, the clinical and pathological findings are similar to those found in white patients with FFI.

Arch Neurol. 2004;61:122-125

From the Division of Neurology, the Department of Medicine (Drs Spacey and Feldman), and the Department of Psychiatry (Dr Fleming), The University of British Columbia, Vancouver; National Prion Disease Pathology Surveillance Center, Institute of Pathology, Case Western Reserve University, Cleveland, Ohio (Drs Pastore and Gambetti); and the Department of Medical Genetics, B. C. Children's Hospital, Vancouver (Dr McGillivray).

FFI is a prion disease characterized by progressive sleep impairment, dysautonomia, and motor dysfunction, with onset in adulthood. The pathological abnormalities are primarily in the thalamus, with relative sparing of the cerebellum and brainstem. Fatal familial insomnia has an autosomal dominant mode of inheritance, with unknown penetrance.1

Fatal familial insomnia and familial Creutzfeldt-Jakob disease (CJD) result from a substitution of asparagine for aspartic acid at codon 178 of the prion protein gene (PRNP).2 The methionine or valine polymorphism at codon 129 of the mutated allele determines whether the phenotype is FFI (methionine) or CJD (valine).1

We present clinical, neurophysiological, radiological, and neuropathological data observed in the first description of FFI, to our knowledge, in a 4-generation family of Chinese descent.

METHODS

GENETIC ANALYSIS

DNA was extracted from frozen organ tissue, and the PRNP open reading frame was amplified by a polymerase chain reaction using primers and conditions described previously.3 The coding region of PRNP was studied by direct sequencing.

NEUROPATHOLOGICAL FEATURES

Tissue samples from the neocortex, caudate nucleus, putamen, thalamus, mesencephalon, pons, medulla, and cerebellum were fixed and stained, as previously described.3
BIOCHEMICAL ANALYSIS OF PrPSc

Biochemical analysis of the disease-associated form of the prion protein PrPSc was performed by Western blot analysis of protein extracted from homogenized brain tissue, as previously described.6

RESULTS

The family is of Chinese descent. Family members IV:12 and III:11 (Figure 1) emigrated from Hong Kong to Canada, where they came to neurological attention.

INDIVIDUAL IV:12 (PATIENT 1)

The proband was a 36-year-old previously healthy man who presented with myoclonus and insomnia refractory to traditional hypnotic agents. He experienced witnessed apneic spells, somniloquism, and dream enactment.

In the first 6 months of his illness, he developed intermittent horizontal diplopia and progressive dysphagia. His speech was initially hypophonic and became progressively dysarthric. He developed progressive ataxia and moderate to severe dementia over 9 months. He lost 9 kg, and developed dysautonomic features, including constipation, urinary retention, and profuse sweating. His insomnia evolved into a state of hypersomnia, and he slept up to 18 h/d in the last 3 months of the disease. He died of pneumonia after a 12-month course.

Clinical Investigations

Magnetic resonance imaging performed at 8 months revealed mild cerebral cortical atrophy. Serial electroencephalograms demonstrated a diffuse excess of θ and δ frequencies; there was no electrographic correlation with myoclonic activity and there were no periodic sharp waves. Polysomnography at 6 months demonstrated marked insomnia, atypical periodic limb movements, apneic periods, dream enactment, and whole body myoclonic jerking. The cerebrospinal fluid at 9 months was normal, and the opening pressure was unremarkable.

Molecular analysis demonstrated an aspartic acid to asparagine mutation at codon 178. The patient was homozygous for methionine at codon 129.

Neuropathological Studies

Severe neuronal loss and prominent gliosis occurred in the thalamus, chiefly in the ventral anterior, medial dorsal, lateral dorsal, and pulvinar nuclei; the lateral anterior and lateral posterior nuclei were relatively preserved. There was astroglisis in the region of the superior colliculus, the periaqueductal region, and the inferior olivary nucleus. In the cerebellum, there was mild Purkinje cell loss with a moderate number of axonal “torpedoes” (Figure 2).

Western Blot Analysis

PrPSc from subject IV:12 includes 2 major fragments (28 and 26 kDa) and a minor fragment (19 kDa). The 3 fragments have been shown to correspond to different glycosylated prion protein isoforms or glycoforms, the 19-kDa fragment being unglycosylated.6 The relative percentage of the 3 isoforms was calculated on Western blot analyses from 11 brain areas. The mean ± SD distribution of the high, middle, and low molecular weight was as follows: 63.0% ± 4.0%, 31.5% ± 6.0%, and 5.0% ± 2.0%, respectively (Figure 3). Within the mediodorsal area from the thalamus, the calculated percentages for the 3 forms of PrPSc (diglycosylated, monoglycosylated, and unglycosylated) were as follows: 63.5% ± 7.0%, 29.3% ± 4.0%, and 7.1% ± 5.0%, respectively.

PrPSc Distribution

PrPSc was widely distributed. The strongest signals were present in the amygdala, hypothalamus, caudate, parahippocampal gyrus, periaqueductal gray matter, and mediodorsal thalamus. A milder signal was present in the ventrolateral thalamus and the cortices (frontal, tempo-
ral, cingulate, and occipital); there was no signal in the cerebellum.

INDIVIDUAL III:11 (PATIENT 2)

The paternal aunt of patient 1 was previously well and presented at the age of 47 years with insomnia, rapid weight loss, nervousness, and a generalized headache. She developed diplopia and a rapidly progressive dementia. She had myoclonic jerks in all of her limbs, mixed flaccid and spastic tone, and extensor plantar responses. She had experienced progressive dysphagia and weight loss. She died 12 months after the onset of disease.

Clinical Investigations

The results of cerebrospinal fluid tests and repeat computed tomographic scans were normal. An electroencephalogram demonstrated diffuse slowing without evidence of epileptiform activity. There were no periodic complexes.

Neuropathological Studies

There was mild, diffuse, cerebral cortical atrophy, sparing the occipital and temporal regions. There was some spongiform degeneration in the superficial frontal and temporal cortices, particularly in the second cortical layer. The thalamus revealed severe neuronal loss and gliosis in the medial dorsal nucleus. Focal mild or minimal spongiform degeneration was seen in the cingulated gyrus, entorhinal cortex, and putamen, while the oliva showed severe neuronal loss and astrogliosis. Scattered torpedoes were seen in the cerebellum (Figure 2B).

COMMENT

Fatal familial insomnia was first described in the European population and was subsequently described in families in the United States, Australia, and Japan.7 To our knowledge, FFI has not previously been described in the Chinese population, which is genetically distinct from the Japanese population.8,9 Fatal familial insomnia is molecularly distinguished from CJD because of a polymorphism at codon 129 on the mutated allele; a methionine polymorphism predicts an FFI phenotype and a valine polymorphism predicts a CJD phenotype. A Chinese study10 found the distribution of the polymorphism at PRNP codon 129 in the Han Chinese population to be as follows: 97% methionine/methionine, 3% methionine/valine, and 0% valine/valine (methionine is 0.985, and valine is 0.015). According to these data, the finding of a valine haplotype in patients with prion disease seems improbable and the occurrence of the FFI phenotype seems forcedly favored compared with the CJD phenotype once the mutation at codon 178 occurs.10

The Japanese report11 of FFI documented the absence of clinical insomnia. Insomnia was observed in this Chinese family, and the clinical features seen in the 2 Chinese patients described herein are similar to those seen in white patients with FFI.
The primary site of pathological abnormalities in white patients with FFI is the thalamus.\(^2\) This was observed in both of the Chinese patients; however, brainstem involvement was also documented. Both patients described herein have features compatible with brainstem involvement. Patient 1 experienced apnea, diplopia, dysarthria, and dysphagia, and pathological studies demonstrated astrogliosis in the superior colliculus, periaqueductal gray area, and olivary nucleus. PrP\(_{Sc}\) was also present in the periaqueductal gray matter. Patient 2 experienced diplopia, dysarthria, and dysphagia, and postmortem studies showed severe neuronal loss and astrogliosis of the oliva and degeneration of the vagal nuclei. Neuronal loss and gliosis have been reported in the brainstem in the olivary nuclei in white FFI patients.\(^5\) Significant amounts of PrP\(_{Sc}\) have been demonstrated in several brainstem regions, including the locus coeruleus, periaqueductal gray matter, and olivary nuclei.\(^6\) It has been speculated that apnea, observed in several FFI patients, may be due to the pathological features of the brainstem.\(^12\) All patients previously described as having respiratory dysfunction who underwent genotyping were homozygous for methionine in the 129 codon. This was also observed in patient 1.

Western blot analysis demonstrated that the calculated percentages of the 3 isoforms of PrP\(_{Sc}\) (diglycosylated, monoglycosylated, and unglycosylated) from the medial dorsal thalamus and from 11 areas of the brain were comparable to those found in similar brain regions in white FFI patients.\(^6\)

In summary, to our knowledge, this is the first description of a Chinese family with FFI. This supports the worldwide distribution of FFI, and despite differences in genetic background, the clinical and pathological findings were similar to those found in white FFI patients.

Accepted for publication September 16, 2003.

Author contributions: Study concept and design (Drs Spacey, Pastore, Gambetti, and Feldman); acquisition of data (Drs Spacey, Pastore, McGillivray, Fleming, Gambetti, and Feldman); analysis and interpretation of data (Drs Spacey, Pastore, McGillivray, Fleming, Gambetti, and Feldman); drafting of the manuscript (Drs Spacey and Feldman); critical revision of the manuscript for important intellectual content (Drs Pastore, McGillivray, Fleming, Gambetti, and Feldman); administrative, technical, and material support (Drs Spacey, Pastore, Fleming, Gambetti, and Feldman); study supervision (Drs Gambetti and Feldman).

Corresponding author and reprints: Howard Feldman, MD, Division of Neurology, The University of British Columbia, S192-2211 Wesbrook Mall, Vancouver, British Columbia V6T 1Z8 (e-mail: hfeldman@interchange.ubc.ca).

REFERENCES