Expert Consensus on Clinical Diagnostic Criteria for Fatal Familial Insomnia

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Introduction

Fatal familial insomnia (FFI) is a serious and rare prion disease, which was first reported by Lugaresi *et al.* in 1986.[1] Early diagnosis of FFI might be important for early and sufficient counseling of patients and their relatives, also concerning the risk of inheritance, and potentially also for treatment studies. However, the diagnosis of FFI might be difficult because of the heterogeneity of clinical features, low sensitivity of diagnostic tests, and absence of family history. The aim of the present study was to develop a clinical scheme and diagnostic criteria for FFI based on our research and expert consensus.

Epidemiology of Fatal Familial Insomnia

Up until 2016, more than hundred FFI cases from 50 families carrying the gene for FFI in the world have been reported. The majority of the cases reported were from Europe, specifically Italy, Spain, and Germany.[2,3] Although familial aggregation is robust in FFI, nine sporadic cases have been reported.[2] It is speculated that the annual incidence of FFI worldwide is about one out of a million people.[2] There are no gender differences among FFI patients. The mean age at onset of FFI is approximately 50 years (range, 21–62 years), and the duration of FFI ranges from 7 to 25 months.[3] In recent years, more and more FFI cases have been reported worldwide, more specifically in China. The first Chinese case was reported in a patient who emigrated from Hong Kong to Canada in 2004,[4] and the second case was reported from the Hubei province in 2005.[5] A higher number of cases have been reported since the China Creutzfeldt–Jakob disease (CJD) surveillance program was initiated in 2006. A total of 13 cases from 13 Chinese families have been documented from 2006 to 2017.[6-13] Among Chinese patients, the age at onset ranges from 21 to 68 years. The average age at onset of FFI is similar to those reported in other countries, with a mean age of 46.5 years.[14] The clinical duration of FFI among the Chinese cases ranges from 6 to 38 months, which seems much longer than that for European patients.[15] Furthermore, it was reported that FFI is the most frequently identified genetic prion disease in China.[16]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.235115

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Received: 27-02-2018 **Edited by:** Peng Lyu
How to cite this article: Wu LY, Zhan SQ, Huang ZY, Zhang B, Wang T, Liu CF, Lu H, Dong XP, Wu ZY, Zhang JW, Zhang JH, Zhao ZX, Han F, Huang Y, Lu J, Gauthier S, Jia JP, Wang YP. Expert Consensus on Clinical Diagnostic Criteria for Fatal Familial Insomnia. Chin Med J 2018;131:1613-7.

It is worth noting that more FFI cases have been reported in China than those in any other Asian regions (three cases were reported in Japan and one case in Korea),[3] suggesting a genetic susceptibility among the Han population. Because FFI is a rare disease and most information is from case reports, its prevalence and associated factors need to be clarified by more studies.

Etiology and Pathogenesis

FFI is a genetic prion disease transmitted in an autosomal dominant pattern. It is associated with a missense GAC to AAC mutation at codon 178 of the prion protein (*PRNP*) gene located on chromosome 20, which leads to a substitution of asparagine for aspartic acid (D178N).[17,18] This mutation is always associated with methionine at the polymorphic position 129 of the mutant allele in FFI.[19]

Although highly expressed in brain tissues, the physiological function of the prion protein (PrP) remains enigmatic. The pathogenesis of FFI is considered to be due to the loss of the natural function of the PrP. This results in PrP that becomes more susceptible to transformation into an abnormal misfolded form, triggering a selective loss of neurons in the limbic thalamus and corticolimbic regions.[20] The highly selective neuronal loss is partly due to the binding of FFI toxic PrP or proteinase K-resistant prion protein (PrPres) to specific receptors, such as the limbic system-associated membrane protein (LAMP) receptor on thalamolimbic neurons.[21]

Pathologically, FFI is characterized by severe and selective thalamic degeneration, especially in the mediodorsal and anterior ventral nuclei,[1,17] in which more than 50% of the magnocellular and parvocellular neurons are lost as observed during autopsy. In some cases, almost 80% neuronal loss was observed.[17] The other thalamic nuclei are less consistently and less severely involved. Other histopathological changes, including reactive astrogliosis in thalamic nuclei, the cerebral and cerebellar cortices, and the olives, are also found. Spongiosis of the cerebral cortex is observed in some cases, but is either moderate or sometimes absent, especially in cases with a short disease course.[20] Parchi *et al*.[22] reported that patients with disease duration shorter than 18 months only have minimal cortical cerebral astrogliosis and focal spongiosis in the entorhinal cortex, whereas patients with a disease duration longer than 18 months have cortical spongiosis and astrogliosis that are more widespread. Moderate atrophy of the cortex and basal ganglia has also been previously observed in FFI cases, while abnormalities are rarely detected in the spinal cord.[23]

Clinical Characteristics of the Fatal Familial Insomnia

FFI is a hereditary autosomal dominant prion disease, which is mainly characterized by prominent sleep impairment accompanied by a series of neuropsychiatric disorders, dysautonomia, motor dysfunction, and episodes of peculiar oneiric behaviors (oneiric stupor).[24] Irregular breathing, hypnic jerks, propriospinal myoclonus at the wake-sleep transition, and quasi-purposeful limb gestures are considered to be core features of FFI. Homozygous FFI might be different from heterozygous FFI in terms of clinical severity.[17]

The most prominent clinical manifestation is sleep disturbance, which includes insomnia, laryngeal stridor, sleep breath disturbance, oneiric or stuporous episodes with hallucinations and confusion, and sleep-related involuntary movements (such as hypnic jerks, restless sleep with frequent changes in body position, and twitchy nonpurposeful movement of limbs). However, FFI symptoms are variable and some FFI cases may not present with clinically significant insomnia.[25,26]

Rapidly progressive dementia (RPD) along with psychiatric symptoms occurs in all patients. Patients might have cognitive/amnestic deficits, spatial disorientation, and visual hallucinations. They may also display personality changes, depression, anxiety, aggressiveness, disinhibition, and listlessness.[27]

The symptoms and signs of sympathetic hyperactivity (such as evening pyrexia, hypertension, increased sweating and tearing, tachycardia/tachypnea, and impotence) and somatomotor abnormalities (including pyramidal signs, myoclonus, dysarthria/dysphagia, and gait dysfunctions) occur with variable latency and worsen progressively. The prominent motor impairment is a gait dysfunction, and its severity and features may be related to duration and genotype.[28] Furthermore, husky voice was reported in 22% of FFI patients in Germany.[27]

The main clinical and neurological features of FFI are summarized in Table 1.

Diagnostic Studies

For diagnosis of FFI, the main tests with high diagnostic value include genetic analysis, brain magnetic resonance imaging (MRI), electroencephalograms (EEG), polysomnography (PSG), positron emission tomography (PET), single-photon emission tomography (SPECT), biochemical cerebrospinal fluid (CSF) analysis, and autopsy.

Genetic analysis

Genetically, FFI is associated with a GAC to AAC point mutation at codon 178 of *PRNP* resulting in the D178N substitution in combination with methionine (*Met*) at codon 129 in the mutated allele of *PRNP* (D178N-129M haplotype).[29]

Brain magnetic resonance imaging

Routine brain MRI (T1- and T2-weighted imaging) usually reveals nonspecific features including mild cerebral cortical atrophy and enlarged ventricles. The mean apparent diffusion coefficient value could increase in the thalamus.[30]

Hyperintense signals could be detected by diffusion-weighted image (DWI) in the basal ganglia and other gray matter areas.[31]

Table 1: Clinical characteristics of the FFI patients

Parameters	Rare	Frequent	Common
Cluster A-sleep-related symptoms			
Insomnia			+
Sleep-related involuntary movements			+
Sleep-related dyspnea			+
Laryngeal stridor			+
Cluster B-neuropsychiatric symptoms			
RPD			+
Psychiatric symptoms		+	
Ataxia		+	
Pyramidal sign		+	
Parkinsonism	+		
Cluster C-progressive sympathetic symptoms			
Hypertension		+	
Sweating		+	
Tachycardia	+		
Irregular breathing	+		

FFI: Fatal familial insomnia; RPD: Rapidly progressive dementia. "+" : The frequency of the symptom.

Electroencephalograms

EEG usually demonstrates a diffusive excess of theta (θ) and delta (δ) frequencies. Periodic spike discharges are not found in most cases of FFI, but patients with long disease duration can transiently show periodic EEG activities in latter stages.[32]

Polysomnography

A key early polysomnographic sign of the disease onset is the loss of sleep spindles and K-complexes. Other polysomnographic findings include progressively shortened total sleep time, significantly reduced durations of rapid eye movement sleep and slow-wave sleep, abnormal behaviors, complex hallucinations, vivid dreams during sleep, and laryngeal sounds during sleep.[24]

Positron emission tomography and single-photon emission tomography

PET study typically indicated hypometabolism predominantly in the thalamus and cingulate cortex in FFI.[33] SPECT imaging showed reduced blood flow perfusion in bilateral temporal lobes, basal ganglia, and thalamus.[13]

Cerebrospinal fluid analysis

CSF biochemical test could be normal or show a mildly elevated protein concentration. The CSF is usually negative for 14-3-3 protein in FFI.

Autopsy

No FFI case involving brain biopsy case has been reported. At autopsy, severe thalamic neuronal loss and gliosis are characteristically seen in postmortem brains of FFI patients, usually without a concomitant spongiform change. The most seriously affected thalamic nuclei are the anteroventral, mediodorsal nuclei, and pulvinar.[34,35]

Diagnosis

Central clinical presentations in FFI patients can be divided into three categories [Table 1]: Cluster A – organic sleep disturbance, including insomnia, laryngeal stridor, sleep-related dyspnea, and sleep-related involuntary movements; Cluster B – RPD, with or without ataxia, pyramidal or extrapyramidal symptoms/signs, and psychiatric symptoms; and Cluster C – progressive sympathetic symptoms, including hypertension, sweating, tachycardia, irregular breathing, and dysarthria.

Based on the above clinical classification, family history, and laboratory tests, we propose the following clinical diagnostic criteria algorithm for the diagnosis of FFI: (1) possible FFI, (2) probable FFI, and (3) definitive FFI.

Core clinical features and possible fatal familial insomnia

The organic sleep-related abnormalities (a) in addition to one or two other core features (b/c) are essential for a diagnosis of possible FFI.

a. Organic sleep-related symptoms: Insomnia, lack of deep sleep, sleep fragmentation and reduction or loss of REM sleep, laryngeal stridor, sleep breath disturbance, and involuntary movements
b. RPD: The presence or absence of ataxia, pyramidal or extrapyramidal symptoms or signs, and psychiatric symptoms
c. Progressive sympathetic symptoms: Hypertension, sweating, tachycardia, and irregular breathing.

Suggestive features and probable fatal familial insomnia

If one or more of these suggestive features and two or more core features above are present, a diagnosis of probable FFI can be made.

a. Positive family history of RPD and insomnia
b. Organic insomnia, sleep-related apnea, laryngeal stridor, and involuntary movements revealed by PSG
c. Low glucose uptake in the thalamus demonstrated by SPECT or PET imaging.

Diagnostic features and definitive fatal familial insomnia

If the *PRNP* gene test is positive, a diagnosis of definitive FFI can be confirmed.

PRNP gene sequencing revealed D178N mutation with methionine polymorphism at codon 129.

Differential Diagnosis

Patients affected by CJD usually present with RPD, myoclonus, visual abnormalities, cerebellar dysfunction, pyramidal and extrapyramidal dysfunction, and akinetic mutism. DWI or fluid-attenuated inversion recovery (FLAIR) MRI shows a hyperintense signal in the caudate nucleus and putamen or at least two cortical regions. Although FFI patients may have any of these CJD symptoms, they do not fulfill the established diagnostic criteria for CJD.[18-20] FFI patients are more likely to have longer disease durations,

and severe insomnia and dysautonomia, and are less likely to have typical CJD-like cortical ribboning in DWI. D178N point mutation with biallelic codon 129 M on *PRNP* gene is the only causative mutation for FFI, while familial CJD may be caused by 22 types of point mutations, or by insertional mutations.[36] Neuropathological findings of FFI and CJD are quite different: selective thalamic gliosis and neuronal loss are core features of FFI while typical neuropathological findings of CJD include neuronal loss, gliosis, and vacuolation (or spongiform changes).[37]

Gerstmann Sträussler Scheinker disease (GSS) is another prion disease that shares similar clinical manifestations with FFI. It typically presents as a subacute progressive ataxic and/or parkinsonian disorder with a later onset of cognitive impairment. The mean disease duration is around 5 years, ranging from 3 to more than 8 years. GSS has been associated with many different point mutations or insertional mutations of octapeptide repeats, and D178N has not been identified in GSS.[36] Limbic DWI or FLAIR hyperintensities can be found in up to 50% of cases.[38]

Paraneoplastic and nonparaneoplastic limbic encephalitis can also present with RPD and behavior and movement disturbances. Unlike FFI, patients with paraneoplastic and nonparaneoplastic limbic encephalitis have acute/subacute onsets, and symptoms peak within days to weeks; CSF tests usually show pleocytosis and an increased protein level. The main MRI findings that allow the differentiation of encephalitis from FFI are cortical swelling, petechial hemorrhages, and patchy enhancement postcontrast agent administration in the subacute stage.[39] Antibody testing in both CSF and serum is especially crucial.

Conclusion

We attempted to establish easily applicable and reliable clinical diagnostic criteria for FFI based on our own research and the literature review. The scheme would also enable the clinical diagnosis in cases with/without available diagnostic testing. We hope that these criteria might improve the early recognition of this peculiar and rare prion disease.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (No. 81470074), and the Clinical funding from Beijing Municipal Science and Technology Committee (No.Z141107002514117).

Conflicts of interest

There are no conflicts of interest.

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