Letters

Clinical and Familial Characteristics of Ten Chinese Patients with Fatal Family Insomnia*

SHI Qi[1], CHEN Cao[1], GAO Chen[1], TIAN Chan[1], ZHOU Wei[1], ZHANG BaoYun[1], HAN Jun[1], and DONG Xiao Ping[1,2,#]

1.State Key Laboratory for Infectious Disease Prevention and Control, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China; 2. Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China

Abstract

Objective Fatal familial insomnia (FFI) is an autosomal dominant prion disease characterized clinically by inattention, sleep loss, dysautonomia, and motor signs. This study is aimed to investigate clinical and familial characteristics of ten Chinese Patients with FFI.

Methods We identified ten FFI cases from the surveillance network for Creutafeldt- Jakob disease (CJD) in China.Final diagnosis of FFI cases was made in accordance with the WHO criteria for CJD.The main clinical features and family histories of these ten FFI cases were analyzed.

Results The median age of ten cases at onset was 38 years (from 19 to 55). The foremost symptoms seemed to be various, including sleep disturbances, vision disorder, dizziness and anorexia. Sleep disturbances appeared in all cases and lasted in the whole clinical courses. Progressive sympathetic symptoms, memory loss, movement disturbances, myoclonus and hypertension were also frequently observed. The median duration of the disease was 9.5 months. EEG and MRI did not figure out special abnormality. 14-3-3 protein in CSF was positive in five out of eight tested patients. Clear family histories were identified in 8 patients.

Conclusion The data from our study confirm that the Chinese FFI cases have similar clinical characteristics as that of the Caucasian cases. Compared with other genetic CJD associated mutations, the genetic frequencies of D178N in *PRNP* are apparently high among the Chinese cases.

Key words: Fatal family insomnia; D178N, *PRNP*; Creutzfeldt-Jakob disease, CJD

Biomed Environ Sci, 2012; 25(4):471-475 doi: 10.3967/0895-3988.2012.04.013 ISSN:0895-3988

www.besjournal.com(full text) CN: 11-2816/Q

INTRODUCTION

Fatal familial insomnia (FFI) as well as familial Creutzfeldt-Jakob disease (fCJD) and Gerstmann-Sträussler-Scheinker diseases (GSS) are subtypes of human genetic spongiform encephalopathies[1]. FFI is an autosomal dominant heredopathy, characterized clinically by a disordered sleep-wake cycle, dysautonomia and motor signs. Pathologically, the hallmark is characterized by

*This work was supported by China Mega-Project for Infectious Disease (2009ZX10004-101, 2008ZX), SKLID Development Grant (2008SKLID102, 2011SKLID211) National Basic Research Program of China (973 Program) (2007CB310505). The Project was sponsored by the Young Scholar Scientific Research Foundation of China CDC (2012A102), Chinese National Natural Science Foundation Grants 30771914 and 30800975 and Institution Technique R&D Grant (2008EG150300).

#Corresponding should be addressed to DONG Xiao Ping, Tel and Fax: 86-10-58900815. E-mail: dongxp238@ sina.com

Biographical note of the first author: SHI Qi, female, born in 1976, Ph.D, associate professor, majoring in pathogenesis of prion disease.

Recevied: December 6, 2011; Accepted: April 24, 2012

predominance of lesions in the thalamus[2]. Genetically, FFI is linked to a GAC to AAC point mutation (aspartic acid to asparagines substitution) at codon 178 of the prion protein gene (*PRNP*) on chromosome 20 in conjunction with methionine at the polymorphic position 129 of the mutant allele[3].

In 2006, a surveillance network for CJD based in China CDC was established. More than twenty genetic CJD (gCJD) cases were reported and diagnosed genetically since then. Among them, 10 FFI cases were identified. In this study, the detailed clinical features, family history data and genetic evidences of these ten FFI cases from different provinces in China were comparably analyzed.

METHODS

Ten FFI cases were identified and enrolled from the surveillance network for CJD (CNSNC) from 2006 to 2010.in China. Final diagnosis of FFI cases was made in accordance with the WHO criteria for CJD[4]. The specimens from ten cases, including blood and cerebrospinal fluid (CSF), were collected and postm ortem brains were dissected. 14-3-3 protein in CSF, neuropathological changes and PrP^{Sc} in brains and *PRNP* sequencing in blood cells were detected as described previously[5].

RESULTS

Since 2006, ten FFI cases have been identified one after another in CNSNC, with definitely genetic confirmation of D178N mutation and M129M in *PRNP*. Except that the first two reported cases are an uncle and his niece from Henan Province, the rest eight cases were sporadically identified in different cities without kinship. Five patients were males and the other five were females. The median age of ten cases at onset was 38 years old (19 years old to 55 years old), one younger than 20 years old, three between 20 and 29 years old, one between 30 and 39 years old, two between 40 and 49 years old and three between 50 and 59 years old. The age distribution of the ten FFI cases is summarized in Table 1. As to the professions they were farmers, teachers, workers or office clerks.

Table 1. Age Distribution of the Ten FFI Cases

	Age Distribution					Range	Mean	Median
	<20	20-29	30-39	40-49	50-59			
Number	1	3	1	2	3	19-55	37.5±13.76	38

A summary of the main clinical features is showed in Table 2. Among the foremost symptoms, sleep disturbances, including insomnia and hypersomnia, appeared in five of the cases (5/10). Vision disorders, e.g. diplopia, were observed in three cases. In addition, two cases complained of dizziness and anorexia was also present in one case. Some of the patients (3/10) were accompanied with psychologicalmanifestations, e.g. anxiety and emotional lability and others. Along with the progression of the disease, other symptoms and signs gradually appeared, and among them, sleep disturbances appeared in all the ten cases and lasted in the whole clinical courses. Progressive sympathetic symptoms, including excessive sweating, salivation and minor evening pyrexia, were noticed in almost all of the cases from early to the late of clinical course . Memory loss (8/10) and movement disturbances (9/10) were also observed. Neurological examinations revealed myoclonus in eight patients (8/10) and pathologic reflexes in five patients, including Babinski sign and Chaddock sign were also revealed. Six patients showed hypertension and two had borderline hypertension (diastolic pressure above 90 mmHg). EEG examinations recorded different abnormalities, but none of the patients showed periodic sharp-waves (PSW). MRI did not figure out special abnormality, showing only mild brain atrophy in three cases and broadening ventricle in one case. CSF biochemical tests of all cases were normal. 14-3-3 protein in CSF was positive in five out of eight tested patients. All patients showed asarcia and significant weight loss at their terminus. The durations of illness after onset varied from 7 to 30 months, mostly (8 cases) being 7 to 10 months, with median duration of 9.5 months.

Three autopsies were performed, two of them (Case 1 and 2) had been described previously. Generally, severe gliosis was seen in the thalamus and cortex regions, while no spongiform degeneration was observed. Positive, but weak, PrP^{Sc} signals were detected in the brains, which were remarkably

Table 2. Comparison of the Main Clinical Features of Ten FFI Cases

Case No.	Gender	Age at Onset (y)	Family History	Foremost Symptoms	Other Signs and Symptoms	Blood Pressure (mmHg)	Progressive Sympathetic Symptoms				CSF 14-3-3	EEG (PSW*)	MRI	Time of Diagnosis after Onset (m)	Duration of Illness (m)
							Excessive Sweating	Salivation	Minor Evening Pyrexia	Weight Loss					
1	M	45	Yes	Sleep disturbance, sympathetic symptoms	Insomnia,dysautonomia, motor abnormalities	145/95	Yes	Yes	Yes	Yes	ND	-	Normal	2	10
2	F	26	Yes	Sleep disturbance	Insomnia, dysautonomia, myoclonus	142/98	Yes	Yes	Yes	Yes	ND	-	Normal	1	14
3	M	53	Yes	Sleep disturbance, apathy	Insomnia, progressive dementia, myoclonus, ataxia	105/70	Yes	No	No	Yes	+	-	Slight brain atrophy	1	10
4	F	24	No	Diplopia	Insomnia, memory loss, ataxia, myoclonus, pyramidalism	120/90	Yes	Yes	Yes	Yes	-	-	Normal	2	30
5	F	19	Yes	Diplopia diaphoresis	Sleep disturbance, diplopia, memory loss, ataxia	130/90	Yes	Yes	Yes	Yes	-	-	Broadening ventricle	2	9
6	M	25	Yes	Dizziness, ache in right knee joint	Hypersomnia, memory loss, tremor, pyramidalism	140/100	Yes	No	Yes	Yes	+	-	Normal	1	8
7	M	55	Yes	Sleep disturbance, fidget	Insomnia, diaphoresis, hyperthermia, memory loss	145/95	Yes	Yes	No	Yes	+	-	Normal	2	8
8	F	47	No	Dizziness, diplopia	Apathy, memory loss, ataxia, tremor, hyperthermia	140/76	Yes	No	Yes	Yes	+	-	Normal	1.5	10
9	F	50	Yes	Insomnia, anxiety	Memory loss, ataxia, tremor, abnormal motor behavior	120/60	Yes	Yes	Yes	Yes	-	-	Slight brain atrophy	1	8
10	M	31	Yes	Hypersomnia, anorexia	Acousma, memory loss, aprosexia, pyramidalism	126/96	Yes	No	No	Yes	+	-	Slight brain atrophy	1.5	7

Note. PSW*: Periodic Sharp-Waves.

enhanced by the protocols of precipitation of sodium phosphotungstic acid[6]. The PrP^{Sc} profile in the brains showed a predominant diglycosylated PrP^{Sc} pattern, which was more like that of typical sporadic CJD type 2B with M129M homozygote.

Clinical investigations by interviewing the family members during hospitalization and during sampling on-field revealed clear family disease-associated histories in 8 patients, including the first two cases from one family that was described already[6]. Case 3 was a 53 year-old farmer. His father died at the age of 80 with cardiovascular disease and his mother was 86 years old at the time and is still in good health conditions. His elder sister died with hepatocirrhosis at 50 years old. The son of this case's uncle was described to be dementia at about 30 years old without definite diagnosis and is still alive now. Case 7's elder brother died with similar symptoms in 2009 with about 1 year duration. Case 7's father died at 73 with lung cancer and his mother is 83 years old and is still in good health conditions. The son of the case 7 is 31 years old and is still in health conditions. Case 9's father died at the age of 70 with stoke and his mother is still alive. His elder sister developed the similar symptoms at the age of 47, including sleeping disturbances, dementia and spasm, and died half year later. Case 10's father had similar clinical manifestations since the onset and died 9 months later without definite diagnosis. The family members of Case 4 and Case 8 denied or did not remember whether having similar neurological disease in their three- generation relatives or not.

Blood samples from the family members of some patients were collected with informed consents. In spite of *PRNP* data of the first two cases described elsewhere, several cases with FFI-related mutations were also identified. *PRNP* tests of fourteen family members of Case 3 including his brothers and their off-springs did not identify any mutation, though his cousin died of unknown neurological disorder. Five family members of Case 5 were tested, including the patient's parents and her maternal uncle and aunties. Her mother contained D178N mutation with M129M, but remained healthy. Thirteen blood samples were taken from the family members and relatives of Case 6. His mother contained D178N mutation but is still alive, and his father and brothers were normal. No such mutation was detected in the rest relatives, including his maternal grand-mother and uncles. Eleven family members of Case 7 were screened for *PRNP*. D178N mutations were observed in his second elder brother and the son of this brother who was still healthy. The rest families of the patients refused to the genetic analysis.

DISCUSSION

Three main clinical and pathological phenotypes have been differentiated in human familial prion diseases: familial CJD, Gertsmann-Straussler-Sheinker disease (GSS) and FFI. FFI is described as being associated with the D178N mutation when the allele encodes methionine in the polymorphism of codon 129, whereas the encoding of valine by the mutant allele would produce the CJD phenotype.

The importance of the thalamus in sleep physiology is first reported by Hess[7]. Being similar as the clinical characteristics of inattention, sleep loss, dysautonomia, and motor signs and pathologically characterized by a preferential thalamic degeneration in Caucasian FFI cases[8], sleep disturbances are the most common early symptom of the Chinese FFI cases, including the change of sleep rhythm and course, the behavior modification when falling asleep, insomnia and hypersomnia. Diplopia and dizziness also appear as foremost symptoms. Furthermore, sleep disturbances appear sooner or later in all ten patients and persist in the whole clinical course of disease. Coincidently, sympathetic hyperactivities, e.g. excessive sweating, salivation, minor evening pyrexia and weight loss are present in nearly all of the cases. Hypertension has been frequently detected. These special clinical manifestations may be related to the selective involvement of the AV and MD thalamic nuclei [9]. Severe and consistent atrophy of these nuclei is the common pathological abnormality among FFI cases, which distinguishes from other prion diseases and results in a unique clinical phenotype.

Likewise, clinical examinations and routine MRI failed to identify valuable abnormality in all Chinese FFI patients, except for slight brain atrophy in some cases. Although DWI sequence that is believed to be more sensitive in detecting cortical and basal ganglia hypersignals, none of the ten patients have undertaken that examination. No CJD typical pattern in EEG has been recorded in all FFI, which may indicate a FFI associated phenomenon. Relatively higher positive rate of CSF 14-3-3 protein has been observed in these Chinese FFI cases, but the diagnostic meaning remains to be further evaluated.

The Chinese FFI cases in this study reveal obvious dominate genetic phenomenon, of whom

eight patients have family histories and some of them have genetic evidence among their family members or relatives. In line with the previous observation[6], two FFI cases are confirmed genetically to have D178N mutation, but remain alive without any detectable related disorder. It suggests again that in addition to the specific mutation within *PRNP*, other unknown factors may be involved in clinical appearance of FFI. However, it was noticed that when the clinical symptoms appear, the progression of disease seems to be fairly quick. The average illness duration of the FFI patients in this study is even shorter than that of the sCJD cases notified in the past five years in China, but is similar with the FFI cases reported in other countries which are between 8 and 20 months[10].

Since the first case was identified in 1986, FFI have been reported worldwide that become one of the common human genetic prion diseases in different ethic groups. Compared with other types of gCJD, FFI seems to be more frequent in the Chinese population, especially in the Han Chinese. Of the 20 various gCJD cases that have been diagnosed by CNSNC since 2006, 10 are FFI cases. This phenomenon highlights a relatively high genetic frequency of D178N in *PRNP* among the Chinese. Meanwhile, M129M homozygote is highly predominant in the Han Chinese, and more than 93% of the Han Chinese have such polymorphism[11]. This genetic distribution may also most likely contribute to higher incidence of FFI in China.

ACKNOLEDGEMENTS

We sincerely thank all colleagues working for China CJD surveillance network based in China CDC, 12 provincial CDCs and sentinel hospitals for their kind support and cooperation in this study.

REFERENCES

1. Brown K, Mastrianni JA. The prion diseases. J Geriatr Psychiatry Neurol, 2010; 23, 277-98.
2. Ayuso Blanco T, Urriza Mena J, Caballero Martínez C, et al. Fatal familiar insomnia: clinical, neurophysiological and histopathological study of two cases. Neurologia, 2006; 21, 414-20.
3. Montagna P, Gambetti P, Cortelli P, et al. Familial and sporadic fatal insomnia. Lancet Neurol, 2003; 2, 167-76.
4. Global Surveillance. Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation. Geneva, Switzerland 9-11 February, 1998.
5. Shi Q, Gao C, Zhou W, et al. Surveillance for Creutzfeldt-Jakob disease in China from 2006 to 2007. BMC Public Health, 2008; 8, 360.
6. Shi XH, Han J, Zhang J, et al. Clinical, histopathological and genetic studies in a family with fatal familial insomnia. Infect Genet Evol, 2010; 10, 292-7.
7. Cortelli P, Gambetti P, Montagna P, et al. Fatal familial insomnia: clinical features and molecular genetics. J Sleep Res, 1999; 1, 23-9.
8. Friedrich M, Körte R, Portero C, et al. Fatal familial insomnia--a rare differential diagnosis in dementia. Fortschr Neurol Psychiatr, 2008; 76, 36-40.
9. Haïk S, Galanaud D, Linguraru MG, et al. *In vivo* detection of thalamic gliosis: a pathoradiologic demonstration in familial fatal insomnia. Arch Neurol, 2008; 65, 545-9.
10. Almer G, Hainfellner JA, Brücke T, et al. Fatal familial insomnia: a new Austrian family. Brain, 1999; 122, 5-16.
11. Hou XS, Gao C, Zhang BY, et al. Characteristics of polymorphism of 129th amino acid in PRNP among Han and Uighur Chinese. Zhong Hua Shi Yan He Lin Chuang Bing Du Xue Za Zhi, 2002; 16, 105-8. (In Chinese)