Agrypnia excitata and obstructive apnea in a patient with fatal familial insomnia from China

A case report

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Abstract

Rationale: Fatal familial insomnia (FFI) linked to a D178N/129M haplotype mutation in the PRNP gene is the most common genetic prion disease in the Han Chinese population. Here, we describe a Han Chinese patient with FFI who exhibited agrypnia excitata and obstructive apnea.

Patient concerns: A 46-year-old man displayed involuntary movements during sleep time, snoring, autonomic nervous system dysfunction, cognitive deficit, brainstem symptoms, myoclonus and ataxia in order within 8 months. The electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI) revealed abnormal changes but without the typical prion disease signs.

Diagnoses: After the conduction of Polysomnogram (PSG) and gene detection of PRNP, the patient was diagnosed as FFI. Three others exhibiting the same clinical manifestations were observed in the large family.

Interventions: The patient responded temporarily well to drugs that strengthening the function of mitochondria.

Outcomes: Sudden death occurred after 3 month ever since the diagnoses. The total disease course was 11 months.

Lessons: The insomnia in FFI is complex, agrypnia excitata and obstructive apnea can also be indicators for FFI. Polysomnogram is necessary for recognizing the sleep loss when the symptom of insomnia is not typical. Improving energy metabolism may be a potential treatment for it.

Abbreviations: CN = cranial nerves, CSF = cerebrospinal fluid, DWI = diffusion-weighted magnetic resonance imaging, EEG = electroencephalogram, FFI = fatal familial insomnia, gCJD = genetic Jakob–Creutzfeldt disease, GSS = Gerstmann–Sträussler–Scheinker, MRI = magnetic resonance imaging, PRNP = prion protein, PSG = polysomnogram, sCJD = sporadic Jakob–Creutzfeldt disease.

Keywords: agrypnia excitata, fatal familial insomnia, obstructive apnea

1. Introduction

Fatal familial insomnia (FFI) is a very rare genetic human prion disease with D178N-129M mutation in prion protein gene (PRNP, OMIM #176640). Gene mutations contribute to a cellular prion protein more susceptible to transformation into an abnormal misfolded pathological form, which caused fatal neurodegenerative disorders. The disease mostly occurs in patients over the age of 40 years with insidious and progressive insomnia accompanied by vivid dreams initially, then syndromes caused by dysfunction of autonomic nervous system emerged, such as hyperhidrosis, palpatation, sexual impotence, and constipation. As the disease progresses, motor and cognitive symptoms appeared, for example, memory descent, hallucination, double vision, slurred speech, difficulty in swallowing, and disturbances of gait. Typical signs such as subcortical dementia states, nystagmus, dysarthria, ataxia, and myoclonus would be observed in the later stages of the disease. Total duration of disease is about 12 to 16 months.[1]

Agrypnia excitata is a clinical syndrome characterized by an inability to generate slow wave sleep associated with motor agitation and autonomic hyperactivity. Polysomnography test confirms that patients are in a permanent state of subwakfulness with complete absence of spindle and delta sleep. Meanwhile, motor overactivation (such as chewing, grasping, pulling, and winding nonexistent objects) and sympathetic overactivation (such as increased heart rate, blood pressure, and body temperature) persist day and night without any circadian. A few cases presenting the symptom have been noted from FFI, sporadic Creutzfeldt–Jakob disease, Morvan syndrome, delirium tremens, and corticobasal degeneration.[2] Obstructive sleep apnea is a common sleep disorder characterized by repetitive upper airway collapse with apnea; it results in fragmented sleep and hypoxemia.[3]
and tried to deduce the mechanism of the particular insomnia characteristics of a patient with FFI from a Chinese kindred and to deduce the mechanism of the particular insomnia characteristics of a patient with FFI from a Chinese kindred.

2. Case report

A 46-year-old man who served as a government official first visited our hospital with complaints of 8-month history of involuntary movements during sleep time, and 3-month history of slow response and walking unsteady. He had begun feeling depressed without a known cause 8 months ago. At almost the same time, he had started to engage in involuntary movement such as kicks and grasps during nighttime sleep, with snoring and sleep apnea. He took diazepam tablets, but it did not work. Afterwards, he noticed excessive sweating and felt hot and cold waves. His maximum body temperature was 37.2°C; after he used nimesulide, the temperature dropped to 35.0°C and was subsequently increased, with difficulty. Moreover, he got terrible constipation at that point. He visited mental health centers and was diagnosed with “mild depression” without auxiliary examinations or treatment 4 months ago. About 3 months ago, his family noticed that he had lost approximately 20kg in weight, choked when drinking, and exhibited slow response, visual hallucinations, and walking unsteady. He got frequent drops from bed during sleeping due to his substantial actions; meanwhile, gasping breath and sleep apnea fragmented his sleep. Eventually, he spoke seldom and seemed to be blunt with shuffling gait.

The patient did not have any relevant medical history. He denied having history of trauma, prior blood transfusions, intravenous drug use, and alcohol abuse (Table 1).

The patient was the fourth individual in his large family to exhibit the same clinical manifestations. The other 3 members all died within a year after onset (Fig. 1, pedigree chart).

Eight months after the onset, he was taken to our hospital by his families. We did series of tests at that time.

2.1. Physical examination

The middle-aged man appeared dull. During check-up, he fell into “sleep” easily and soon was awakened in horror by his involuntary sleep movements or snoring. The skin and general examination were normal. Temperature: 36.5°C; respiratory rate 20/min, Blood pressure (lying): 165/109, Pulse: 115. Blood pressure (standing): 150/100 mm Hg, Pulse: 110. Weight: 77 kg. Height: 178 cm.

2.2. Neurological examination

2.2.1. Mental status. He exhibited severe cognitive impairments, particularly with respect to orientation, attention, calculation power, delayed memory, and visuospatial dysfunction (his Mini-Mental State Examination and Montreal Cognitive Assessment scores were 15/30 and 9/30, respectively).

2.2.2. Speech. He had slurred speech and dysarthria.

2.2.3. Cranial nerves. Cranial nerves (CNs) I-VIII and XI-XII revealed no deficits. CN IX and X showed slowness of bilateral gag reflex, and limited symmetrical elevation of soft palate to phonation.

2.2.4. Motor examination. Muscle tone was normal. Muscle strength was 5/5 for all groups tested. Spontaneous and evoked myoclonus was evident.

2.2.5. Reflexes. Bilateral biceps reflex and bilateral triceps reflex were 3/4, and bilateral patellar reflex and bilateral Achilles reflex were 4/4. Hoffman sign and Babinski sign were absent. Frontal lobe signs palmpmental and grasp were not elicited.

2.2.6. Sensory examination. Touch, pin, vibratory, and proprioception sensations were normal. Romberg test was negative.

2.2.7. Cerebellar examination. Coordination was inaccurate for finger/nose testing and heel/knee/shin testing; rapid alternating movements were clumsy.

2.2.8. Gait. Arm swing was absent. There was bradykinesia and postural instability. Rapidly progressive dementia, ataxia (dysarthria and gait instability), and myoclonus were typical signs in prion diseases.

Temperature monitoring revealed that the patient’s body temperature fluctuated from 36.0 to 37.8°C, and the loss of circadian rhythm was observed. Blood pressure monitoring indicated a steady high blood pressure of approximately 150/100 mm Hg and the loss of dipper-type blood pressure rhythm, with a heart rate that fluctuated approximately 100 beats per minute. A dynamic electrocardiogram revealed sinus rhythm with the incidental discovery of multifocal ventricular premature beat.

Blood examinations such as blood routine, coagulation function, liver and kidney function, electrolytes, myocardial enzyme, blood ammonia, homocysteine, folic acid, VitB12, microelement (calcium, cadmium, cobalt, chromium, copper, iron, lithium, magnesium, manganese, nickel, lead, thallium, zinc), thyroid function and antibodies, rheumatism biomarker, infection-related antibodies (hepatitis B virus, hepatitis C virus, syphilis, HIV), and tumor marker showed normal. Cerebrospinal

| Table 1 | Summary of our patient's clinical features. |
| --- | --- |
| Age at onset, y | Duration of illness | Phenotype | Endocrine | Electrophysiology | Polysomnogram | MRI | Gene mutation |
| 46 | 11 mo | Sleep disorder, excess sweating, constipation, weight loss, psychological symptoms, cognitive impairments, visual hallucination, bulbar paralysis, myoclonus, ataxia | Theromatous dysfunction, loss rhythm of circadian and blood pressure, abnormal secretory rhythmicity of prolactin and growth hormone | ECG: sinus rhythm with incidentally discovered multifocal ventricular premature beat | Deprivation of total sleep time, neither spindle nor slow wave sleep was detected during the patient snoring, mentalis relaxation and kicks. Sleep apnea, hypoxemia | Atrophy of the frontal, temporal and parietal lobes | D178N/129M haplotype of PRNP |

ECS = electrocardiograph, EEG = electroencephalogram, MRI = magnetic resonance imaging.
fluid (CSF) examination (intracranial pressure was 200 mmHg, cell number, glucose, chloride, protein, acetic acid, IgA, IgM, IgG, Oligoclonal bands, PCR for JC virus, EB virus, HSV-1 virus, Mycobacterium tuberculosis) appeared normal and 14–3–3 protein was negative. Autoimmune encephalopathy related antibodies (N-methyl-D-aspartic acid receptor, contactin-associated protein 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2 receptor, leucine-rich glioma inactivated protein 1, gamma-aminobutyric acid B), and paraneoplastic syndrome related antibodies (CV2/CRMP5, PNMA2, RI, Yo, Hu, Amphiphysin) in blood and CSF were all detected, but none of them indicates abnormality. Routine urinalysis and fecal analysis were normal. Hormone secretion detection demonstrated the abnormal secretory rhythmicity of prolactin and growth hormone.

Extensive θ activity and scattered slow waves are recorded in an electroencephalogram (EEG). Brain magnetic resonance imaging (MRI) revealed atrophy of the frontal and temporal. Polysomnogram (PSG) demonstrated the patient's obvious deprivation of total sleep time; neither spindle nor slow wave sleep was detected during his “fragmented sleep,” even when he showed snoring, mentalis relaxation, sleep apnea, and hypoxemia (Fig. 2).

The nucleotides from 12742 to 13318 (GenBank accession number U2918) of exon 1 in PRNP were amplified; then, polymerase chain reaction products were directly sequenced on an ABI 377 automatic sequencer. The results were analyzed using DNA Sequencing Analysis Software version 3.4.1 (Gene Codes Corp, Ann Arbor, Michigan). Genetic analysis found that the patient harbored a D178N/129M haplotype mutation in PRNP (a GAC → AAC homozygous mutation at codon 178 and a methionine polymorphism at codon 129).

The patient had been diagnosed with FFI and received treatment with drugs to improve brain metabolism, such as idebenone, ganglioside, and coenzyme Q10. During the follow-up by telephone, his wife told us that he got once improvement in his responsiveness soon after discharge; however, sudden death occurred 3 months later. The total disease course was 11 months.

The patient information involved in our manuscript has been obtained and informed consent was obtained from his legal representatives. All human studies have been approved by the appropriate ethics committee and have therefore been performed.
in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

3. Discussion

The latest incidence of human prion diseases is about 1.2 per 1 million. Approximately 10% to 15% of human prion disease cases are caused by mutations with PRNP, and appear as autosomal dominant inheritance, 80% to 95% of the patients are sporadic Jakob–Creutzfeldt disease (sCJD), and less than 1% of the patients are acquired in an infective way. Genetic prion disease has been divided into 3 forms based on clinicopathologic features: genetic Jakob–Creutzfeldt disease (gCJD), Gerstmann–Sträussler–Scheinker (GSS), and FFI. Its penetrance is geographical and race-associated variations; FFI is the most common genetic prion disease in China.[5] Several dozen of genotypes in PRNP have been found in gCJD or GSS, while only 1 haplotype D178N-129M can cause FFI.[6]

The age at onset of genetic prion diseases (30–55 years for gCJD, 40–60 years for GSS, and 20–72 years for FFI) is earlier than that of sCJD (55–75 years). gCJD, whose pathologic changes are diffusely distributed spongiform and neuronal destruction, it typically manifests with progressive confusion and memory impairment occur first, followed by ataxia and myoclonus.[7] GSS whose pathologic changes are abundant deposition of amyloid plaques stained by anti-prion antibodies, it typically begins with cerebellar dysfunction, as time progress, pyramidal sign and extrapyramidal syndrome such as bradykinesia and masked facies appeared, cognitive dysfunction and psychiatric symptoms arrived later and atypical.[8] FFI whose pathologic changes are neuronal loss and gliosis within thalamus and nucleus olivaris region, it typically presents with onset of insomnia and vivid nightmares, then a disturbance in autonomic function emerged, followed by brainstem symptoms and ataxia, cognitive capacity is relatively spared until late in the course.[9]

The pathologic and clinical features of sCJD are the same as in gCJD; however, the duration of disease is much shorter (usually 6–12 months for sCJD, several months to 5 years for gCJD or GSS, and 12–16 months for FFI). A periodic sharp wave complexes in EEG and signal hyperintensity within the cortical ribbon and/or basal ganglia in diffusion-weighted MRI (DWI) are common characteristics of sCJD, but they were observed in a few patients with genetic prion disease. CJD-like clinical phenotype and spongiform degeneration pathology appear to be more likely to display the characteristic signs in EEG and MRI. Detection of the 14–3–3 protein in CSF is not specific for genetic prion disease; sensitivity averages only 50%, far below than that in sCJD (sensitivity averages 92%).[10,11]

Two men (II-7 and III-23, father and son) and 2 women (III-13 and III-9, cousins) in the large family (Fig. 1, Pedigree chart) had manifested identical symptoms and died within a year after onset. The patient involved in our manuscript showed sleep disorder, autonomic nervous system dysfunction, cognitive deficit, brainstem symptoms, myoclonus, and ataxia in order, and nonspecific changes were detected from the EEG and MRI. The symptoms in this ancestry appeared as an autosomal dominant genetic disease. He was clinically diagnosed with FFI according to the proposal of new diagnostic pathway for FFI[12]; then, genetic testing confirmed it. The disease phenotype for FFI varies considerably, even among individuals with the same D178N/129M haplotype; the particular insomnia pattern like the patient (involuntary movements during sleep time and snoring) is easy to go unnoticed, and PSG is necessary for recognizing the sleep loss. PSG typically shows the large loss of total sleep time, deep-sleep stages, and slow-wave EEG activity; sleep spindles and K complexes are not induced by barbiturates or benzodiazepines. The disruption of the cyclical organization of sleep translated into generalized overactivity; patient may show moving, talking, and producing noises such as stridor, nocturnal groaning, and snoring; periodic limb movements are also to be noted. Severe insomnia accompanied by mental oneirism, motor, and autonomic sympathetic activation has been proposed as agrypnia excitata, which was recognized as a syndrome of thalamolimbic dysfunction.

Various agents displayed no significantly affect to the progression of disease. New research found that mitochondrial...
and protein synthesis machinery decline in the mediodorsal thalamus\textsuperscript{[13]}; these data provide the basis to devise novel therapeutic strategies for FFI. Our patient responded well to drugs that strengthen the function of mitochondria such as idebenone and coenzyme Q. The patient’s sudden death may be attributed to autonomic cardiovascular disturbances caused by obstructive apnea and hyoxemia. Another patient who developed hypercapnic respiratory failure attributed to Biot breathing during the early course of FFI has been reported.\textsuperscript{[14]} Respiratory disturbances and sleep disordered breathing may be a consequence of olivary regions neuronal loss. Whether positive pressure ventilation can improve the life quality and prognosis is also worthy of further study.

On the basis of the clinical case analysis and literatures review, we concluded that genetic and clinical heterogeneity exists in human prion disease, and sleep disorder should be worthy of attention when a patient showed rapidly progressive dementia, ataxia, and myoclonus. There were several limitations of the study: Further pedigreed analysis cannot be performed because of incomplete data (II-2 and III-14 were lost due to war or family disputes). Detailed clinical data about 3 other patients (II-7, III-13, and III-9) were not accessed. Several insiders in the large family do not want others to know the deadly diseases runs in family, so individual genotypes of the family members with \textit{PRNP} and follow-up study would be difficult to obtain.

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