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A fatal familial insomnia patient initially misdiagnosed as Alzheimer's disease: a case report

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Abstract

Background Fatal familial insomnia (FFI) is a rare autosomal dominant inherited disease and a type of prion diseases. We report a case of fatal familial insomnia (FFI) in a 52-year-old man who was initially misdiagnosed as Alzheimer's disease.

Case presentation The patient presented with persistent insomnia as the initial symptom, accompanied by cognitive impairment, autonomic dysfunction, and disorders of voluntary movement. Cerebrospinal fluid analysis revealed a decrease in $A\beta_{1-40}$ levels and an increase in total tau protein. Cranial imaging demonstrated bilateral hippocampal atrophy, while long-term video electroencephalography indicated focal abnormalities. The patient's prion protein gene was D178N/129MM type, confirmed the diagnosis of FFI.

Conclusions The key characteristics of FFI include insomnia and rapidly progressive dementia, its differential diagnosis with AD has been extensively discussed in clinical practice. This is the first report of FFI concerning Aβ and tau protein, raises the awareness that the ratio of p-tau/t-tau in cerebrospinal fluid can provide valuable diagnostic clues for FFI.

Keywords Fatal familial insomnia, Alzheimer's disease, Prion disease, Amyloid-β, Case report

Introduction

Fatal familial insomnia (FFI) is a rare autosomal dominant inherited disease and a type of prion diseases [1]. Clinical manifestations include stubborn insomnia, autonomic nervous system function, and motor disturbances [2]. In 1986, Lugaresi et al. reported the first case of FFI [3]. The key characteristics of FFI encompass insomnia and rapidly progressive dementia. Notably, over 75% of patients with FFI experience drug-resistant insomnia, while approximately 24% of Alzheimer's disease (AD) patients also exhibit sleep disturbances; furthermore, 10%~30% demonstrate rapid cognitive decline [4, 5]. Consequently, AD has been recognized as one of the primary differential diagnoses for FFI and other CJD diseases by prion disease surveillance centers [6]. We report

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a rare case of FFI in a 52-year-old man who was initially misdiagnosed as Alzheimer's disease (AD). This is the first case report concerning Aβ and tau in FFI, offering new insights for differential diagnosis.

Case presentation

A 52-year-old man was admitted to his local hospital for difficulty falling asleep without any cause in autumn 2022. As a dentist, he exhibited mild pre-existing anxiety symptoms prior to the onset of the sleep disturbance but did not present any signs of delayed response, memory decline, or disorientation. Family members gradually observed a decline in the patient's short-term memory, accompanied by diminished interest and an apathetic demeanor as the condition progressed. He also experienced excessive sweating, dizziness, and constipation. In winter 2022, following infection with COVID-19, the patient developed involuntary movement that was more pronounced during sleep, along with high-pitched wheezing sounds from the throat. Dynamic electrocardiogram analysis indicated tachycardia and the heart rate variability (HRV) below the normal range. Despite symptomatic treatment at the local hospital, there was no significant alleviation of symptoms.

Three months later, he was admitted to the local tertiary hospital for treatment. The cranial MRI revealed punctate white matter demyelination in the left parietal lobe and mild brain atrophy. The electroencephalogram (EEG) was normal. Assessment of Anxiety and Depression Scale indicated mild anxiety state, severe depression state, and moderate somatization disorder. The patient was prescribed 10 mg of escitalopram, 1.25 mg of olanzapine, and 0.4 mg of alprazolam to improve sleep and migitate anxiety and depression; however, no significant improvement in symptoms was observed.

A month after being discharged from the local tertiary hospital, he was hospitalized in the geriatric department for further treatment. MRI-1.5T thin layer scan of the hippocampus revealed bilateral hippocampal atrophy and multiple ischemic changes in the brain (Fig. 1). His Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores were 19/30 and 16/30, respectively. Plasma biomarkers Aβ42 and p-tau181 showed elevated levels respectively. The patient underwent lumbar puncture. The cerebrospinal fluid (CSF) showed a nuclear cell count of 11×10^6/L with 14% mononuclear cells and 86% multinuclear cells. And no significant abnormalities were detected regarding CSF pressure or biochemical parameters including immunology or pathology assessments. AD biomarkers in CSF, including amyloid-β 1–42 ($A\beta_{1-42}$), $A\beta_{1-42}$/amyloid-β1–40 ($A\beta_{1-40}$), and phosphorylated tau protein181(p-tau181) were within normal range, while $A\beta_{1-40}$ decreased and total tau protein (t-tau) increased (Table 1). Considering the patient's progressive symptoms of memory loss alongside emotional state alterations such as apathy, combined with neuroimaging evidence indicating bilateral hippocampal atrophy, and elevated t-tau levels in cerebrospinal fluid led to an initial diagnosis of Alzheimer's disease. During hospitalization, memantine at a dosage of 10 mg was administered to improve cognition while antipsychotic medications were gradually tapered off until withdrawal. Nevertheless, there was no significant improvement observed in the patient's symptoms. Given the atypical changes in CSF biomarkers and the patient's young age for late-onset AD, the Geriatrics physician recommended

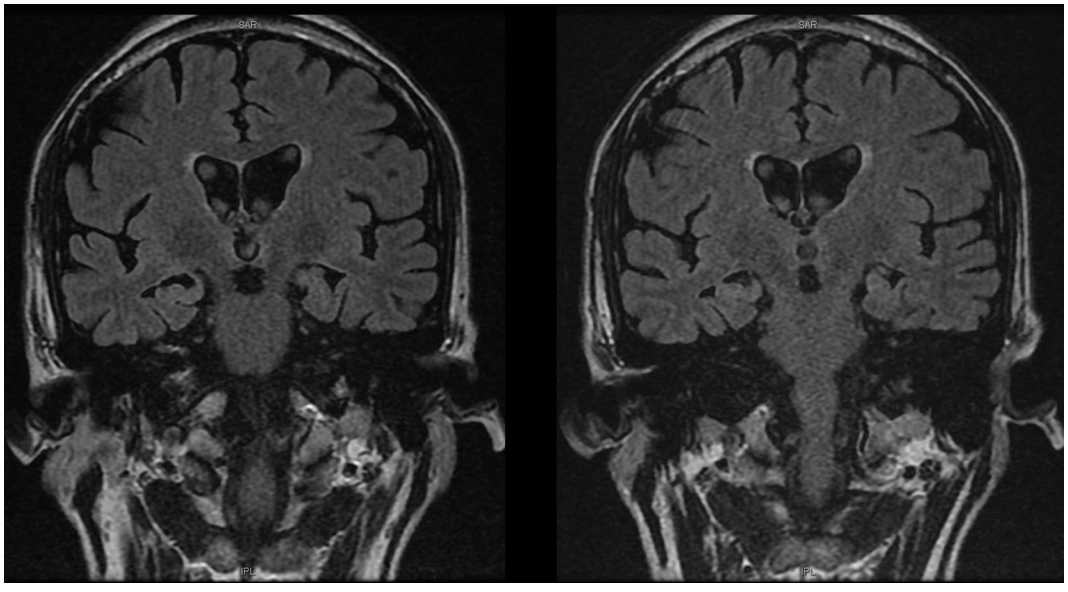

Fig. 1 MRI-1.5T thin layer plain scan of the hippocampus

Table 1 Results of AD biomarkers in CSF

Test method	Results		Reference interval	
ELISA	Aβ1–42 (pg/mL)	1027.06	< 550	Aggregated Aβ
			551–650	Suspicious
			≥ 651	Normal
ELISA	Aβ1–40 (pg/mL)	6974.66↓	≥ 7,000	Normal
			< 7,000	Aggregated Aβ
ELISA	Aβ1–42/ Aβ1–40	0.147	≤ 0.05	Positive
			> 0.05	Negative
ELISA	t-tau (pg/mL)	956.81↑	≤ 399	Normal
			> 399	Neuronal injury
ELISA	p-tau (pg/mL)	27.12	≤ 50	Normal
			> 50	Neurofibrillary tangles

undergoing genetic testing for both AD and CJD diseases, as well as consulting the neurology department for further diagnosis and management.

The patient then was admitted to the neruologic clinic of our hospital and was provisionally diagnosed with cognitive impairment. Throughout the course of his illness, the patient exhibited symptoms including mental fatigue, increased appetite, disrupted sleep patterns, constipation, frequent urination, and weight loss exceeding thirty pounds. He experienced progressive memory loss and impaired response latency for over six months. His mother was in good health and his father passed away due to stomach cancer; the family denied any history of similar diseases. Although the patient remained lucid, he demonstrated cognitive decline and speech articulation disorders. He had difficulties with calculations alongside memory impairment. Muscle strength was normal, with increased muscle tone and tendon reflexs in both upper limbs and normal in both lower limbs. The bilateral ataxia was positive and the patient's spatial and temporal orientation was impaired, while orientation to persons remained intact. No Kayser-Fleischer (KF) ring was detected in the patient.

Additional examinations conducted upon admission, including plasma ammonia levels, erythrocyte sedimentation rate, plasma biochemical indices and vitamin analysis, homocysteine, ceruloplasmin, and antibody testing for paraneoplastic neurological syndrome and autoimmune encephalitis, revealed no significant abnormalities. Immunoglobulin E was increased, while transferrin and complement C1q was decreased. Long-term video EEG monitoring depicted mild focal abnormalities (wakefullness period: slightly more 5–7 Hz medium-amplitude slow waves in the right frontal pole) (Fig. 2). Cranial MRI at 3.0T revealed mild cerebral atrophy and focal ischemic lesions in left parietal lobe (Fig. 3). The genetic test results for Alzheimer's disease indicate the presence of

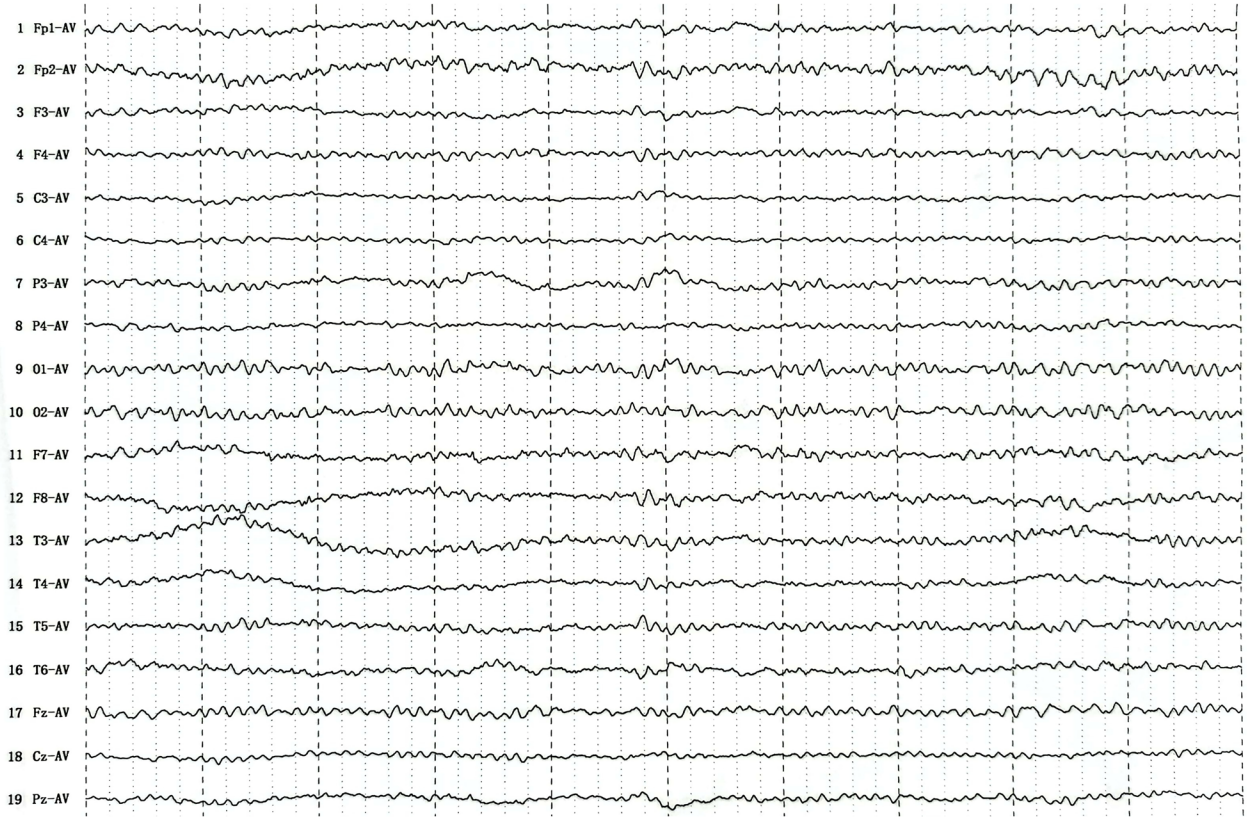

Fig. 2 Long-term video EEG monitoring report

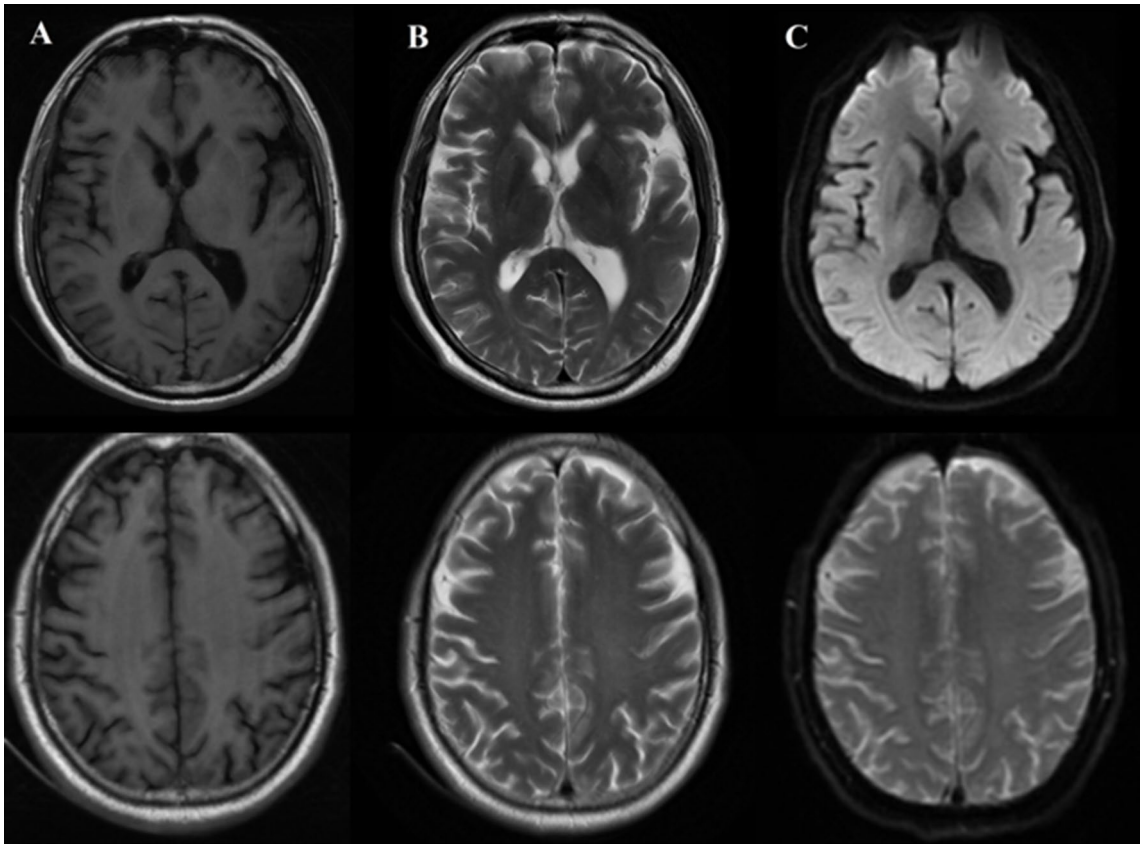

Fig. 3 Cranial MRI-3.0T (A. T1WI B. T2WI C. DWI)

APOE*ε2/ε3 alleles. Prion Protein (PRNP) gene sequence analysis showed the D178N mutation and the 129-position amino acid polymorphism was M/M type, confirming the diagnosis of FFI (Fig. 4). The same site was analyzed in family members, and similar mutations were found in his two daughters, son, and grandson (Fig. 5). Following symptomatic treatment with oryzanol, pramipexole, and clonazepam, involuntary movements and sweating were reduced; however, other symptoms did not exhibit significant improvement.

Discussion

Currently known human prion diseases include Creutzfeldt-Jakob disease, Gerstmann syndrome, Kuru disease, and FFI [7]. FFI is an autosomal dominant genetic disorder characterized by the replacement of aspartic acid (Asp) in the 178 codon of the PRNP gene with asparagine (Asn), alongside the presence of methionine at the 129 polymorphism site on the mutant allele [8]. This disease typically starts in middle age and progresses rapidly, with a median survival duration of approximately 18 months. The prognosis is poor, and there are currently no effective treatments available. Pathological involvement primarily affects the anterior ventral and dorsomedial nuclei of the thalamus, as well as the inferior olivary nucleus. Notable pathological changes include neuronal degeneration and glial cell proliferation [9]. Testing for mutations in the PRNP gene is crucial for diagnosing FFI.

The medical consultation experience of this patient is rather complex (Fig. 6). Consistent with the majority of reported cases of FFI, this patient presented with refractory insomnia as the initial symptom, characterized by difficulty in initiating sleep and accompanied by autonomic dysfunction such as sweating, constipation, reduced heart rate variability and high blood pressure. As the disease progressed, neurological and psychiatric symptoms emerged gradually, including cognitive impairment and an apathetic demeanor, along with involuntary movements, dysarthria, and disturbances in voluntary movement. The clinical manifestations observed in this patient are highly typical. Notably, during the onset of this condition, certain features distinguish it from other disorders. The symptoms of the patient began with sleep disorders and dysarthria, which should be differentiated from autoimmune encephalitis (such as anti IgLON5 antibody encephalitis). Anti IgLON5 antibody encephalitis is a progressive disease that encompasses both autoimmune mechanism and neurodegeneration; its core clinical features include severe sleep disturbances alongside significant cognitive impairment [10].

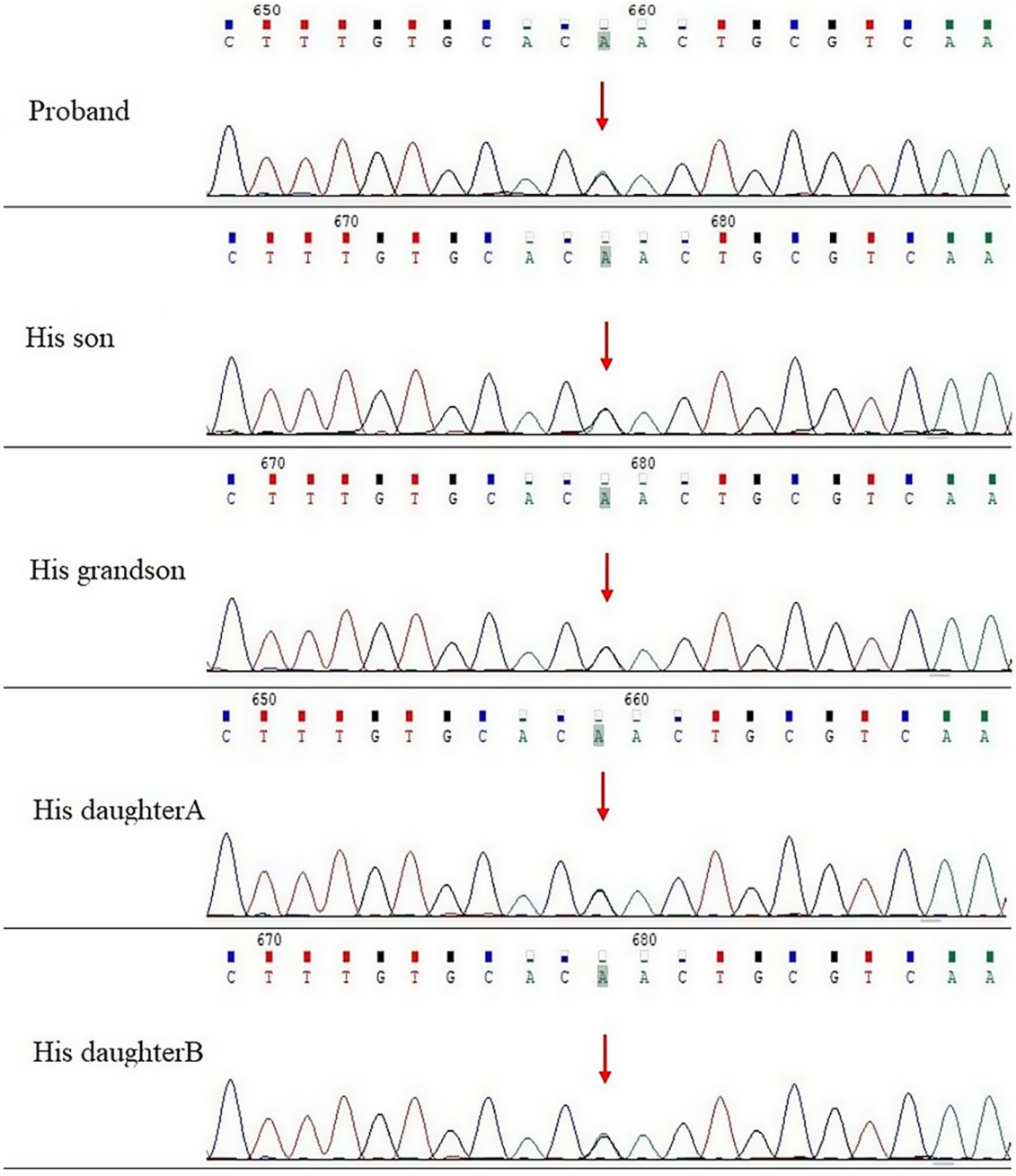

Fig. 4 Analysis of the PRNP gene sequence within the family

However, negative autoimmune encephalitis-related antibody in this case doesn't support the diagnosis of anti IgLON5 antibody encephalitis. In the early stages, the patient exhibited psychiatric symptoms such as anhedonia and down in spirits, which led to a misdiagnosis of severe depressive disorder. Due to the presence of involuntary movement, it is also necessary to differentiate it from hepatolenticular degeneration. However, the normal serum ceruloplasmin level and absence of Kayser-Fleischer ring do not support the diagnosis of hepatolenticular degeneration.

To date, there have been rare reports linking FFI with Alzheimer's disease biomarkers, either domestically or internationally. Aβ accumulates and precipitates in the cell matrix, which potentially causing neuronal cytotoxicity and degeneration of neuronal fibers. It has been reported that Aβ levels in CSF show circadian oscillations related to sleep-wake cycles and may be influenced by changes in neuronal activity or clearance mechanisms through the lymphatic pathways [11, 12]. Tau is a microtubule associated protein expressed in neurons and glial cells [13]. In addition to AD, inflammatory and neoplastic

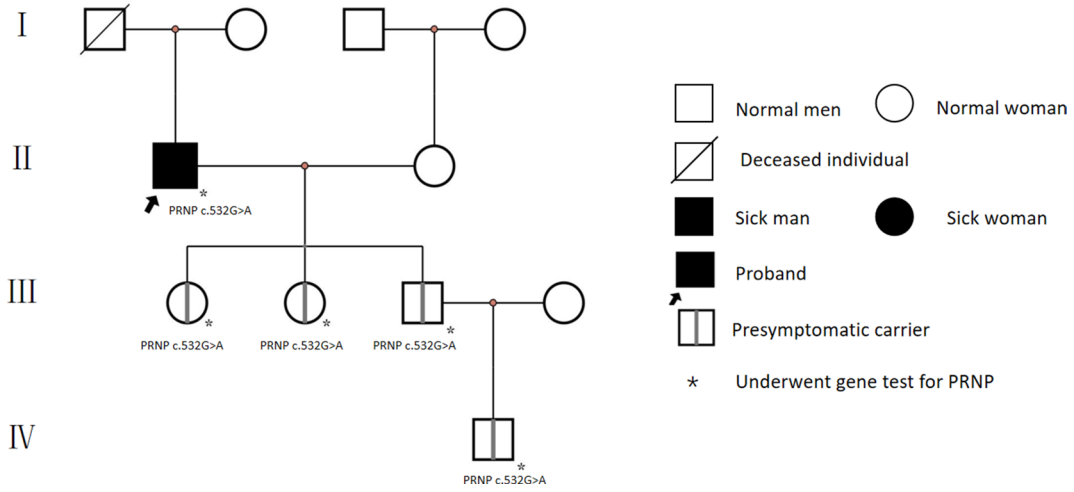

Fig. 5 The genetic pedigree of the patient's family

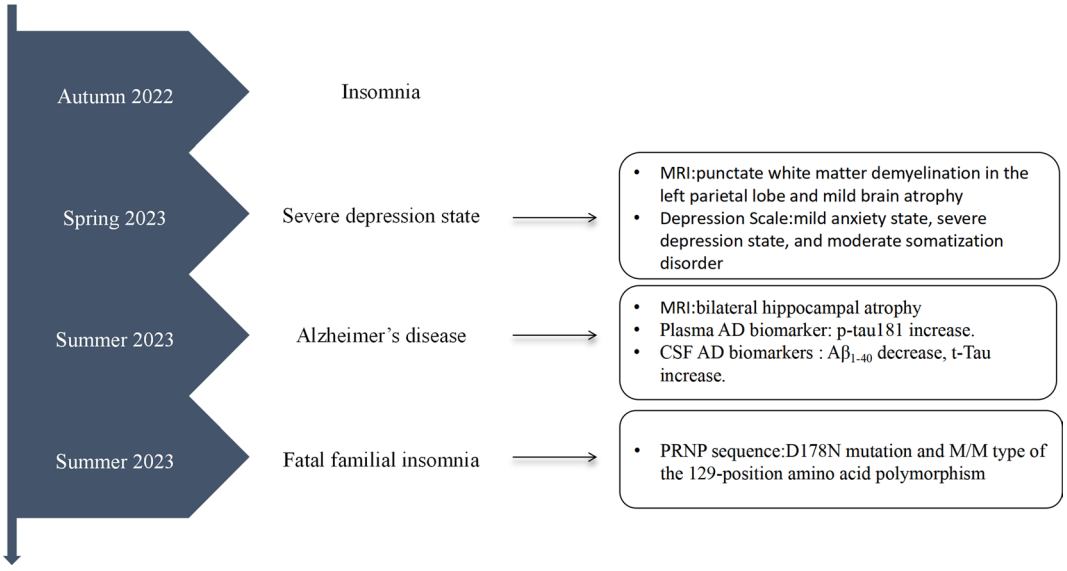

Fig. 6 The timeline of the patient's diagnostic process

central nervous system diseases are important differential diagnoses for elevated t-Tau levels [14].

Given that both rapidly progressive AD and CJD manifest as fast-progressive dementia, their differential diagnosis has been extensively addressed in clinical practice. In terms of CSF biomarkers, typical AD is characterized by a decrease in Aβ and an increase in p-tau and t-tau, whereas CJD presents a significantly elevated t-tau without a corresponding increase in p-tau. The ratio of p-tau to t-tau can be utilized in the differential diagnosis. Several studies examining the ratio of p-tau/t-tau have suggested that p-tau/t-tau holds promising diagnostic potential for distinguishing CJD. Although FFI shows a relatively lower elevation in t-tau compared to other forms of CJD, the t-tau remains significantly higher than AD. The decreased $A\beta_{1-40}$ and increased t-Tau in this case did not align with the typical changes of AD biomarkers; while the p-tau181/t-tau ratio of 0.02834 (<0.075) suggests the possibility of CJD [15]. This report further substantiates the diagnostic ablility of p-tau/t-tau, thereby highlighting its potential clinical utility for the future diagnosis of CJD-related diseases.

Conclusion

In summary, the primary characteristics of FFI include insomnia and rapidly progressive dementia, rendering it a critical condition to consider when differentiating from AD. Gene sequencing is the most reliable method for diagnosing the disease, and targeted screening for D178N mutations of PRNP can facilitate early diagnosis. This case underscores that the p-tau/t-tau ratio in cerebrospinal fluid may also provide valuable diagnostic insights

for FFI. Furthermore, these insights can aid clinicians in making informed decisions regarding genetic testing.

Abbreviations

AD	Alzheimer's disease
Aβ	amyloid-β
CSF	Cerebrospinal fluid
EEG	electroencephalogram
FFI	Fatal familia insomnia
PRNP	Prion Protein
MRI	Magnetic resonance imaging

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Author contributions
MQ, HW, LC and QY contributed to obtain the clinical information. QY, XQ and XY prepared Figs. 1, 2, 3 and 4. MQ, HW and LC prepared the main manuscript and prepared Figs. 5 and 6. XL and MT performed final manuscript review and editing. All authors contributed to the article and approved the submitted.

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Data availability
The data of PRNP mutation during the current study are available in the Single Nucleotide Polymorphism Database, access number rs74315403.

Declarations

Ethics approval and consent to participate
This report has been approved by the Research Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University reference No. 2024-KY120–01(F). Our study is in accordance with the Declaration of Helsinki and CARE guidelines. Written informed consent was obtained from the patient and his family for genetic analysis and publication of this case report.

Consent for publication
Written informed consent was obtained from the individual and his family, who signed the the power of attorney, for the publication of any potentially identifiable images or data included in this article.

Competing interests
The authors declare no competing interests.

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