Fatal insomnia: the elusive prion disease

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SUMMARY
A previously well 54-year-old woman presented with a short history of diplopia, cognitive decline, hallucinations and hypersomnolence. The patient had progressive deterioration in short-term memory, ocular convergence spasm, tremor, myoclonus, gait apraxia, central fever, dream enactment and seizures. Results of investigations were normal including MRI brain, electroencephalogram, cerebrospinal fluid (CSF, including CSF prion protein markers) and brain biopsy. The patient died from pneumonia and pulmonary embolus. Brain postmortem analysis revealed neuropathological changes in keeping with Fatal familial insomnia (FFI); the diagnosis was confirmed on genetic testing. FI is caused by an autosomal dominant and highly penetrant pathogenic Prion Protein gene PRRP. Although usually familial, fatal insomnia (FI) also occurs in a rare sporadic form. FI is a rare human prion disease with prominent sleep disturbance, autonomic, motor, cognitive and behavioural involvement. Patient management is with best supportive care and early suspected diagnosis allows for timely palliation.

BACKGROUND
This report illustrates a difficult case of a patient with the presenting features and natural history of a prion disorder, in the face of negative familiar investigations and newer highly sensitive and specific cerebrospinal fluid (CSF) methods. We aim to highlight that difficult and rare neurological cases may present acutely to hospital, sometimes via other specialties. The case is likely to resonate with BMJ readers as our initial "gut" diagnosis proved correct despite off-putting investigation results. We discuss the epidemiology, clinical features, investigations, neuropathology, neurogenetics and supportive management of patients with fatal insomnia (FI).

CASE PRESENTATION
A previously well 54-year-old woman developed new onset diplopia followed by hearing impairment and ‘seashell’ tinnitus over several weeks. Four months following symptom onset, ophthalmic assessment found decompensated esophoria and ocular convergence spasm. Her family told the ophthalmologist that she had been struggling with ocular convergence spasm, tremor, myoclonus and severe gait apraxia. At times she appeared to have hypnogogic hallucinations. There were no pyramidal, extrapyramidal or cerebellar signs. Addenbrooke’s Cognitive Examination (ACE)-III revealed a score of 34/100, deficient in all domains, particularly memory and verbal fluency. Her clinical state deteriorated rapidly; she had multiple fevers of central origin and developed clinically apparent sleep apnea (although this could not be confirmed formally as she removed pulse oximetry leads). The patient had several probable seizures with eye rolling, unresponsiveness, posturing of the right arm and limb twitching. One month after admission to the hospital, her ACE score fell to 20/100.

The results of in-hospital radiographic and specialist investigations are summarised in table 2.

DIFFERENTIAL DIAGNOSIS
We initially considered differential diagnoses of Creutzfeld-Jakob disease (CJD), autoimmune encephalitis, intravascular lymphoma and Dementia with Lewy Bodies (DLB). Serological tests of nutritional status were not performed, but in retrospect measures of vitamin B12 for Wernicke’s encephalopathy and vitamin E for ataxia, would have been appropriate additions to our test battery, in view of the possibility of malnutrition linked to past bariatric surgery.

Given a positive Dopamine active Transporter (DAT) scan result (figure 1) in the face of otherwise negative investigation including brain biopsy, atypical DLB was our working diagnosis.

Subsequent postmortem brain examination showed marked gliosis of the thalamic and inferior olivary nuclei (figure 2A,B). However, immunohistochemistry showed no evidence of any spongiform change or convincing prion protein (PrP) accumulation in the brain (figure 2C). Subsequent paraffin-embedded tissue (PET) blot analysis undertaken by...
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Table 1 Summary of results of blood tests and CSF examination performed during hospital admission

| Serum results               | Normal   | Normal   |
|-----------------------------|----------|----------|
| WCC                         | 12.5     | HbA1C    |
| Platelets                   | 454      | Plasma viscosity |
| CRP                         | 11       | B12 and folate |
| Urea and electrolytes       | Normal   | TSH      |
| Liver function tests        | Normal   | T4       |
| Calcium and phosphate       | Normal   | Vasculitic screen |
| Magnesium                   |          | ANA speckled |

| Negative antibody screen    | Glycine receptor |
|-----------------------------|------------------|
| Voltage-gated potassium channel | NMDA receptor |
| NMDS receptor               | Glutamic acid decarboxylase |
| Antineuronal                | Acetylcholine receptor |
| IgLONS                      | TSH receptor |
| Antiganglioside (GQ1b)      | Thyroid peroxidase |

| Negative microbiology and virology tests |
|-----------------------------------------|
| HIV screen                              |
| VDRL test                               |
| Legionella                              |
| Pneumococcal disease                    |
| Mycoplasma                              |
| Cytoxella burnetti                      |
| Viral hepatitis screen                  |

Table 2 Summary of radiographic and specialist investigations performed during hospital admission

| Imaging                          | Non-specific deep white matter vascular changes with a normal circle of Willis, no evidence of restricted diffusion |
|----------------------------------|-------------------------------------------------------------------------------------------------|
| MRI brain with contrast and MR angiogram |                                                                                      |
| Chest X-ray                      | Normal                                                                                       |
| CT thorax, abdomen and pelvis    | Oesophageal thickening, but no evidence of overt malignancy                                 |

| Specialist investigations        | Intermittent sharp waves in the left centroparietal region but no periodic sharp wave complexes seen |
|----------------------------------|-------------------------------------------------------------------------------------------------|
| Electroencephalography           |                                                                                                  |
| Repeat electroencephalography    | Excess bilateral slow waves but no abnormality correlating to myoclonus                        |
| Fluorescein retinal angiogram    | No evidence of retinal vasculitis                                                                |
| Frontal brain and meninges biopsy| Normal specimen, no evidence of prion protein, lymphoma or leptomeningeal vasculitis            |

| Oesophageal duodenoscopy         | Atypical oesophagitis, histology revealed a gastro-oesophageal ulcer                           |

Frontal cortex (FC) and cerebral cortex (CC) samples were selected for biochemical analysis. The tissue samples were homogenised and precipitated with sodium phosphotungstic acid (NaPTA) followed by proteolytic digestion with proteinase K.

Figure 1  DaT scan showing bilaterally reduced uptake of tracer in the basal ganglia.

Frontal cortex (FC) and cerebral cortex (CC) samples were selected for biochemical analysis. The tissue samples were homogenised and precipitated with sodium phosphotungstic acid (NaPTA) followed by proteolytic digestion with proteinase K.

Figure 2  Neuropathological analysis, undertaken at the National Creutzfeldt-Jakob Disease Research and Surveillance Unit. Routine histological assessment using a H&E stain showed striking thalamic gliosis (A; 10× magnification) confirmed by immunohistochemical assessment of glial fibrillary acidic protein expression (B; 10× magnification). Immunohistochemical assessment of abnormal prion protein expression was assessed using a number of antibodies but was mostly negative (C; 12F10, 10× magnification) and only focal weak expression. However, the paraffin-embedded tissue blot technique clearly demonstrated abnormal prion protein (D). Western blot analysis of PrPSc in FFI, codon 129 MM, type 2B (FFI), compared with sporadic CJD MM1 (sCJDMM1), type 1A; sporadic CJD MM2 (sCJDMM2), type 2A and variant CJD MM (vCJD), type 2B. For the FFI case, PrPSc analysis of FC and CC were considered (E). CC, cerebral cortex; CJD, Creutzfeldt-Jakob disease; FC, frontal cortex; FFI, fatal familial insomnia; M, molecular marker; PrPSc, misfolded form of the prion protein.
(PK) and high-sensitivity Western blotting. Western blot analysis showed detectable levels of partially protease-resistant fragments in brain samples (FC and CC) using the monoclonal antibody 3F4, typed as ‘type 2B’ (figure 2E). Genetic analysis revealed the D178N (aspartic acid to arginine) pathogenic variant in the PRNP gene (c.532G>A p.(Asp178Asn)), in combination with methionine homozygosity at codon 129 (MM) of the same gene in keeping with a diagnosis of Fatal familial insomnia (FFI).

TREATMENT
Treatment with rivastigmine for atypical DLB was unhelpful. No immunotherapy was tried on the basis that the aetiology was unknown but was presumed to be a neurodegenerative process.

Family members were subsequently offered counselling by our clinical genetics team.

OUTCOME AND FOLLOW-UP
The patient was discharged to a nursing home but readmitted 48 hours later with hospital-acquired pneumonia and pulmonary embolus. She died 2 days later, 6–7 months after first symptom onset.

DISCUSSION
FI is a rare human prion disease, which occurs in both sporadic (sFI) and familial forms (FFI). It typically presents with prominent sleep disturbance, and is usually inherited. As a group, the transmissible spongiform encephalopathies—prionopathies or prion diseases—occur in sporadic, inherited and acquired forms. All involve the accumulation of an aggregated and partially protease-resistant form (PrPSc) of the PrP with the capacity to drive the further conversion of normal PrP molecules (PrP) into the misfolded, protease-resistant and disease-associated isoform. Sporadic Creutzfeldt-Jakob disease (sCJD) is the most common human prion disease, with a worldwide incidence of around 1–2 cases per million population/year. FI is much rarer: only 70 known affected kindreds and 25 typical cases of sFI have been reported worldwide. Age of onset in FFI varies between 36 and 72 years affecting males and females equally. SFI has been reported in a handful of cases with similar clinical and neuropathological features to the familial phenotype. The clinical features of FI involve sleep, autonomic, motor, behavioural and cognitive disturbance. However, although titled FI, insomnia is not a defining feature of the disease. Involvement of the thalamus, hypothalamus and higher brainstem can affect sleep in a variety of ways. Insomnia is the most frequently observed sleep disturbance, but Rapid Eye Movement (REM) sleep behaviour disorder and dream enactment may also be seen. Early clinical manifestations include altered vigilance, fluctuating diplopia, disrupted circadian rhythm, apathy and executive dysfunction. Nocturnal sleep disturbance can lead to daytime somnolence. Autonomic features may then ensue with hypotension, central fever, perspiration, lacrimation, salivation and impotence. Gait apraxia, ataxia, myoclonus and other motor signs (table 3) may emerge as the disease progresses. Occasional convulsive seizures have been reported. Patients may die as a result of secondary pneumonia.

Other forms of human prion disease, atypical parkinsonism, DLB disease, autoimmune encephalitis and intravascular lymphoma should all be considered when investigating for FI.

As this case illustrates, standard investigations in life may be normal. The following investigations may assist in the suspected diagnosis of FI: MRI of the brain may show non-specific changes of cortical, cerebral and cerebellar atrophy. Cortical ribboning seen in sCJD and diffusion restriction changes on diffusion-weighted MRI brain, are not seen in FI. Periodic complexes on an EEG of the kind seen in CJD, are not typically present but may develop in patients with a long duration of illness. Abnormality of CSF 14-3-3 protein occurs in only 50% patients with FI. CSF Real-Time Quaking-induced Conversion is positive in 83% of FFI cases but only in 50% of patients with sFI. Positron emission tomography fluorodeoxyglucose scans have shown hypometabolism in the thalamus, basal ganglia and limbic system in some cases.

Polysomnography may show disruption of the sleep wake cycle, with sleep state dissociation (loss of the normal boundaries between non-REM sleep, REM sleep and wakefulness). Total duration of sleep is often reduced and slow wave sleep may be lost entirely. Hypercortisolaeemia and low melatonin levels have been reported.

FI is caused by the highly penetrant, autosomal dominant, pathogenic PrP gene (PRNP) variant c.532G>A p.(Asp178Asn) on chromosome 20, previously called the D178N mutation. The codon 129 variant on the same allele modifies the phenotype expressed at codon 178; with p.Met129 the phenotype is usually FI whereas with p.Val129 it is usually typical CJD.

Table 3 Phenotypic features of fatal insomnia

| Sleep and behavioural |
|-----------------------|
| Insomnia              |
| Sleep state dissociation with dream enactment |
| Altered vigilance     |
| Progressive dementia  |

| Motor                  |
|------------------------|
| Tremor                |
| Myoclonus             |
| Ataxia                |
| Dysarthria            |
| Dysesthesia           |
| Diplopia              |
| Pyramidal signs       |
| Positive Babinski reflex |
| Gait apraxia          |

| Dysautonomia           |
|------------------------|
| Hypertension           |
| Evening fever          |
| Perspiration           |
| Laceration             |

Learning points

- Fatal insomnia (FI) is a rare prion disease with prominent sleep disturbance, cognitive, autonomic, motor and behavioural involvement.
- Fatal familial insomnia is highly penetrant and arises from the prion protein gene (PRNP) variant c.532G>A p.(Asp178Asn) on chromosome 20, previously called the D178N mutation.
- Sporadic FI has similar clinical and neuropathological features to Fatal familial insomnia.
- Standard screening tests for investigating human prion disease such as MRI brain, electroencephalogram and cerebrospinal fluid can be normal. Polysomnography and fluorodeoxyglucose-positron emission tomography may support a diagnosis of FI but genetic and neuropathological assessment remains key to confirming the diagnosis.
- Management is best supportive care but early suspicion allows timely planning for the terminal phase of life. Family members should be supported and offered genetic counselling.
Neuropathological assessment at postmortem remains the definitive means of confirming a diagnosis of FI. Neuropathological changes in FI include prominent thalamic, and inferior olivary neuronal loss and astrogliosis. Cortical and subcortical gliosis may be seen to a milder degree as well as spongiform degeneration later in the course of disease, with more extensive changes observed as the disease progresses. PET blot analysis may be useful in the detection PrPSc when standard immunohistochemical methods fail to detect evidence of the PrP.

The management of FI is currently supportive, with genetic counselling for at risk family members.

CONCLUSION

We initially suspected a diagnosis of a prion disease in this case of rapidly progressive dementia with prominent somnolence, gait apraxia and myoclonus. We were discouraged from the diagnosis by negative investigations including CSF examination and brain biopsy. Formal polysomnography might have suggested the diagnosis, but was difficult to perform in this agitated patient. A neuropathological postmortem of the patient’s brain eventually provided the crucial clue to the correct diagnosis, of FFI, with confirmation by further specialised neuropathological and genetic assessment by the NCJDRSU. We have since offered genetic counselling to at risk family members. For those wishing to learn more of the human dimension of FFI, a moving documentary, Dying to Sleep, is available online (https://www.youtube.com/watch?v=AxjNay_TRRg).

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