

Insomnia as a benign presentation of fatal familial insomnia (FFI). A case report from Malaysia



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ABSTRACT

Fatal familial insomnia (FFI) is an extremely rare autosomal dominant prion disease. The chief clinical features include an organic sleep disorder associated with sympathetic overdrive, motor and bulbar compromise as well as progressive cognitive decline. Death ensues in 100% of cases with a mean survival duration of 18 months from time of symptom onset. Treatment strategies in the management of FFI remains largely symptomatic with greater emphasis placed on palliative care services. We report a case of a 31-year old gentleman (Mr G) who presented with insomnia, sleep behavior disturbances, diplopia, myoclonus and transient global amnesia. A family history of a paternal aunt with similar presentation who passed away raised the suspicion of probable FFI, which was subsequently confirmed by genetic testing. Mr G is the first reported definitive FFI case of Malaysian Chinese descent. Standard MRI imaging and CSF analyses are insufficient in the workup of an individual with probable FFI. PET scan, polysomnogram and genetic studies are required for cases with high index of suspicion. In view of the rapid progression of the disease with significant cognitive impairment within months of symptom onset, we advocate for early diagnosis and a biopsychosocial patient-centered treatment approach.

Key words: Fatal familial insomnia (FFI); Insomnia

INTRODUCTION

FFI is an extremely rare autosomal dominant prion disease resulting from missense mutation in the prion protein gene (PRNP).¹ The exact prevalence of the disease remains unknown with only a few dozen case reports published globally. Up until the time of writing, there is no published case of definitive FFI in Malaysia. The pathogenesis of FFI is postulated to result from triggered transformation of normal prion protein (PrP) into a misfolded form (PrPres) in genetically susceptible individuals. Although the exact pathways by which PrPres causes cellular death remain unclear, there is distinctly greater neural dysfunction with disease progression as suggested by more widespread areas of hypometabolism seen on PET scan in advanced disease.² The sequence of pathological progression parallels the clinical deterioration

of the individual and death ensues when sufficient vital systems are compromised.

FFI is characterized by an insidious onset of progressive and ferocious insomniaⁱⁱⁱ followed by abnormal sleep movement disorder and sympathetic overdrive characteristic of agrypnia excitata. The disease progression heralds rapid deterioration in motor and bulbar function with worsening confusion, ultimately culminating in death. The typical survival duration of FFI is between 7 and 36 months, with a mean duration of 18 months.³

Therapeutic options for FFI remain lackluster. Treatment strategies are largely symptomatic and to a greater extent palliative. Recent works to manufacture a curative drug have yielded disappointing results. To date, the only large-scale clinical trial in the field of FFI is the use of doxycycline

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(with anti-prion properties) to prevent or delay disease onset in genetically positive asymptomatic carriers.⁴

CASE PRESENTATION

Mr G is a 31-year-old gentleman of Malaysian Chinese descent. He held a corporate level job and is the father to two healthy young children. He was previously well with no significant medical illness. Mr G was brought to the hospital following an acute episode of transient global amnesia (TGA). A missing person alert was lodged by his family members after Mr G failed to return home from work one day. The police officer reported finding Mr G in a “confused and disoriented state.”

Mr G had been under the care of a family physician for treatment-resistant insomnia for five months prior to hospital admission. His self-reported total sleep duration has more than halved over the course of his illness. At the time of his admission, Mr G estimates that he averages approximately two hours of interrupted sleep per night. He also complained of occasional “hand tremor” and bilateral lateral gaze “double vision” which started three months after onset of insomnia. Mrs G started to notice that Mr G had abnormal purposeful movements during sleep with “dream re-enactment” and confusion upon awakening- “often mistaking dreams from reality” one month prior to admission. Routine blood investigations done at the family physician clinic were unremarkable. A brain MRI performed one month prior to TGA was normal. A significant family history of Mr G’s paternal aunt who passed away five years ago after battling a similar disease was noted during history taking. She was diagnosed with a rapidly progressive dementia of unknown cause at the time of her demise. Mr G’s father passed away at age 33 due to brain cancer and little is known regarding Mr G’s paternal grandparents.

At the time of admission, Mr G had low grade temperature, mildly raised blood pressure and tachycardia with bilateral upper limb myoclonus. Montreal Cognitive Assessment (MoCA) testing revealed mild difficulties in high level attention, immediate recall and organizational skills. Other neurological examination was unremarkable. Bedside electroencephalogram did not show any epileptiform activity. A complete blood count, metabolic panel, thyroid function test, hepatitis panel and HIV testing were all normal. A plain CT brain showed no abnormal pathology. CSF biochemistry analysis was normal and test for infectious disease was negative. CSF analyses with antibody panel (for autoimmune encephalitis) and 14-3-3 protein (for Creutzfeldt-Jacob disease) were negative. Serum anti-TPO

antibody (for Hashimoto’s encephalopathy) was negative. MRI brain done during admission was normal.

A brain PET scan showed significant reduction in metabolic activity in bilateral thalami, posterior cingulate gyrus, right cerebellar hemisphere and right cerebral cortex. Video-polysomnogram demonstrated very poor sleep efficiency with abnormal sleep architecture featuring isolated epochs of N1 and a brief period of REM (after accounting for first night effect). Isolated microsleeps shorter than 10 seconds duration were also observed. Atypical chin EMG as well as bilateral upper and lower limbs movements were observed during REM period. Finger waving and grabbing hand movements were captured on video. Several hypopnea events were noted associated with cortical arousal and 3-5% oxygen desaturation. However, the apnea-hypopnea index was inconclusive in view of poor sleep efficiency. Genetic testing confirmed pathogenic heterozygous variant in the PRNP gene with Met-Met homozygosity at codon 129, thus establishing diagnosis of definitive FFI.²

Mr G was fast-tracked into an integrated care pathway involving a team consisting of neurologists, psychiatrists, palliative care physicians, speech and language pathologists, occupational and physical therapists as well as the medical social worker. He was allowed home leave and prescribed tab clonazepam 2mg once nightly, crushed melatonin 8mg once nightly, tab metoprolol 12.5mg twice daily and tab pregabalin 25mg once nightly for symptomatic relief.

In the subsequent four months, Mr G’s condition deteriorated quickly with new onset of dysarthria, ataxia with frequent falls, dysphagia and rapidly progressive dementia. He had several episodes of aspiration pneumonia. He finally succumbed to his illness ten months from the time of insomnia onset.

DISCUSSION

FFI is rare neurodegenerative disease. To the best of our knowledge, we report the first case of FFI in a patient of Malaysian Chinese descent. The clinical syndrome of an organic sleep disorder associated with autonomic hyperactivity and progressive neurological deficit should prompt physicians to consider the possibility of FFI. MRI and CSF analyses are often normal and unhelpful. Video-polysomnography and PET scan are important adjunct investigation modalities but genetic study is necessary for diagnosis of definitive FFI.

There is currently no effective treatment for FFI and thus, we advocate for an early patient-centered multi-disciplinary

care model with emphasis on palliative care and early advanced care planning. Ongoing research focuses on the use of doxycycline for prevention of disease onset in asymptomatic carriers. We anticipate that with the rapid advancements in the field of molecular biology, future gene therapy options may offer potential cure to this devastating multi-generational disease.

REFERENCES

1. Baldelli L and Provini F. Fatal familial insomnia and Agrypnia Excitata; Autonomic dysfunctions and pathophysiological implications. *Autonomic Neuroscience*. 2019; 218: 68-86. <https://doi.org/10.1016/j.autneu.2019.02.007>
2. Wu LY, Zhan SQ, Huang ZY, Bin Z, Tao W, Liu CF, et al. Expert Consensus on Clinical Diagnostic Criteria for Fatal Familial Insomnia. *Chin Med J*. 2018; 131:1613-1617. <https://doi.org/10.4103/0366-6999.235115>
3. Schenkein J and Montagna P. Self management of fatal familial insomnia. Part 1: what is FFI? *Med Gen Med*. 2006; 8(3): 65.
4. Forloni G, Tettamanti M, Lucca U, Albanese Y, Quaglio E, Chiesa R, et al. Preventive study in subjects at risk of fatal familial insomnia: Innovative approach to rare diseases. *Prion*. 2015; 9(2): 75-79. <https://doi.org/10.1080/19336896.2015.1027857>

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