Clinical Case Report

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Fatal familial insomnia presenting with agrypnia excitata and very low atonia index level

A case report and literature review

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Abstract

Rationale: Fatal familial insomnia (FFI) is a human prion disease that is characterized by sleep-wake cycle deterioration, loss of slow-wave sleep, and motor overactivation over the daily 24-hour period.

Patient concerns: Here, we report the case of a 57-year-old man who had an irregular sleep-wake cycle and exhibited frequent movements and vocalizations during sleep.

Diagnoses: Video-polysomnography showed disrupted sleep structure, rapid alternation between sleep stages, and an absence of sleep spindles and slow-wave sleep. Moreover, body movements persisted throughout the entire sleep period, including rapid eye movement (REM) sleep. The atonia index was very low (<0.025) during REM sleep. Genetic testing revealed a prion protein gene mutation at codon 178, and the patient was diagnosed with FFI.

Interventions: We tried to treat with amantadine, doxycycline, and immunotherapies, but the disease progressed.

Outcomes: Sleep disturbance is the most frequent and essential symptom of FFI.

Lessons: FFI is difficult to diagnose due to the low sensitivity of diagnostic tools. Diagnoses can be further supported by better knowledge of typical polysomnographic findings.

Abbreviations: EMG = electromyography, FDG-PET = ^{18}F-fludeoxyglucose positron emission tomography, FFI = fatal familial insomnia, NREM = nonrapid eye movement, PRNP = prion protein gene, RBD = REM sleep behavioral disorder, REM = rapid eye movement, RWA = rapid eye movement sleep without atonia, VPSG = video-polysomnography.

Keywords: agrypnia excitata, atonia index, fatal familial insomnia

1. Introduction

Fatal familial insomnia (FFI) is an inherited human prion disease caused by a missense mutation at codon 178 of the prion protein gene (*PRNP*) located on chromosome 20.[1] In this disorder, selective degeneration of the anteroventral and mediodorsal thalamic nuclei leads to sleep disturbances and motor overactivation.[2] Video-polysomnography (VPSG) of patients with FFI has demonstrated an absence of sleep spindles, K complexes, and slow-wave sleep, with unforeseen body movements occurring throughout the entire sleep period. Prominent motor overactivation during rapid eye movement (REM) sleep sometimes leads to misinterpretation of FFI as an REM sleep behavioral disorder (RBD). Accordingly, diagnosis of FFI can be difficult in the absence of a family history of the disorder. Improved awareness and knowledge about sleep disturbances as essential symptoms of FFI would improve the accuracy of diagnosing FFI and the understanding of FFI pathophysiology. Herein, we report a patient presenting with severe loss of sleep associated with generalized motor hyperactivation, that is, agrypnia excitata, and very low level of atonia index who was diagnosed FFI by genetic testing.

2. Report of case

A 57-year-old man visited the neurology department of our hospital complaining of declining memory, which began about 5 months prior. Around the same time, he began to experience

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The Human Research Ethics Committee of Seoul National University Hospital provided a waiver considering that approval is not necessary for a single case report. The wife of the patient provided written informed consent for publication of clinical details and images.

All authors have reviewed and approved the final version of the manuscript.

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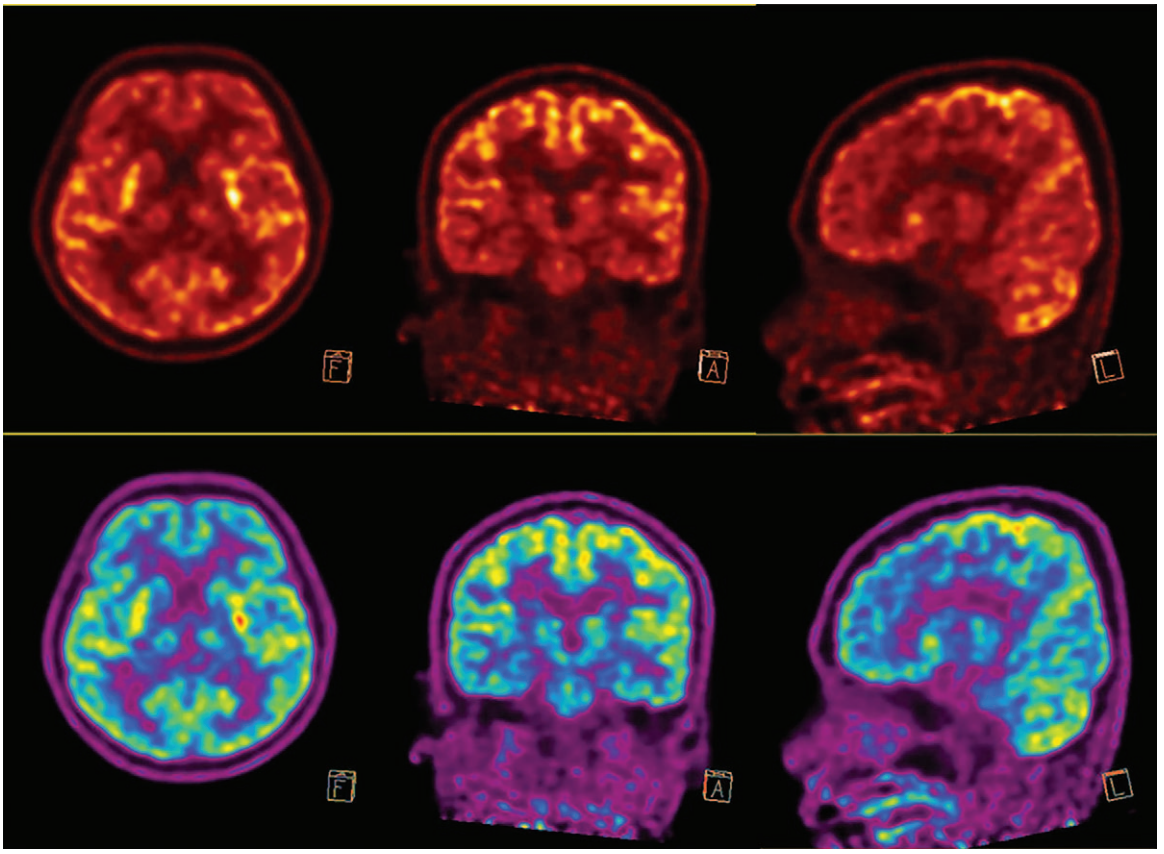

Figure 1. [^{18}F]-fludeoxyglucose positron emission tomography (FDG-PET) performed on admission. Axial (left), coronal (middle), and sagittal (right) views are presented. FDG uptake was slightly decreased in the bilateral thalamus (upper line). The color map of the bilateral thalamus shows a blue to sky blue color indicating a relative reduction in FDG uptake (lower line).

sleep disturbances, including difficulty falling asleep and maintaining sleep, and accordingly had problems staying awake during the day. He also presented with visual hallucinations, myoclonus, and ataxic gait. In addition, he lost 15 kg in weight over the 5-month period. At the time of visit, he was alert, but disoriented. Cranial nerve and motor power examination showed normal function. He, however, showed bilateral dysmetria on finger to nose test and ataxic gait. Neither of his parents had a history of any of these symptoms. His brothers and sisters could not confirm the occurrence of the symptoms because they had not been in contact with the patient for a long time.

Routine hematological, biochemical, and serological blood findings, including autoimmune indices, were unremarkable. Pleocytosis and 14-3-3 protein were not noted in a cerebrospinal fluid analysis. Electroencephalography presented diffuse slowing without periodic discharges. Brain magnetic resonance imaging demonstrated age-associated white matter lesions, whereas [^{18}F]-fludeoxyglucose positron emission tomography (FDG-PET) showed slight decreases in uptake in the bilateral thalamus (Fig. 1).

The patient's sleep disturbances deteriorated rapidly. He exhibited constant simple, stereotyped, and repetitive gestures with his eyes closed during sleep. He also smacked his lips and produced meaningless vocalizations during sleep. Accordingly, it was difficult to determine whether the patient was genuinely asleep. VPSG revealed severe sleep fragmentation as well as a lack of physiological cyclic sleep organization. Stage 1 nonrapid eye movement (NREM) sleep was observed for very short periods, and sleep spindles, K complexes, and delta activities were absent. REMs were observed in most of the VPSG. During wakefulness and sleep (including REM sleep), chin and leg electromyography (EMG) activities were increased (Fig. 2A). The patient frequently fiddled with his clothes, swung his hands, and kicked his legs (see Video, Supplemental Video, http://links.lww.com/MD/C232, which demonstrates the continuous body movements during entire sleep). This disrupted sleep was considered to represent agrypnia excitata. There was a large amount of REM sleep without atonia (RWA). The atonia index from the chin EMG signal was very low (<0.025) during REM sleep. When chin EMG amplitudes were divided into 10-s miniepochs and arranged chronologically, they revealed continuous increases in muscle activity regardless of the sleep stage (Fig. 2B). A genetic analysis revealed a *PRNP* mutation at codon 178 and a homozygous methionine polymorphism at codon 129. Follow-up all-day VPSG performed 3 months after admission revealed frequent REMs during sleep and, similar to the first VPSG, increased chin and leg EMG activities during REM sleep. We tried to treat with amantadine, doxycycline, and immunotherapies including high-dose steroid and immunoglobulin, but the symptoms of the patient were getting worse. Eventually, he died 8 months after admission.

3. Discussion

Patients with FFI can present with various symptoms due to selective neuronal degeneration of the thalamic nuclei.[1]

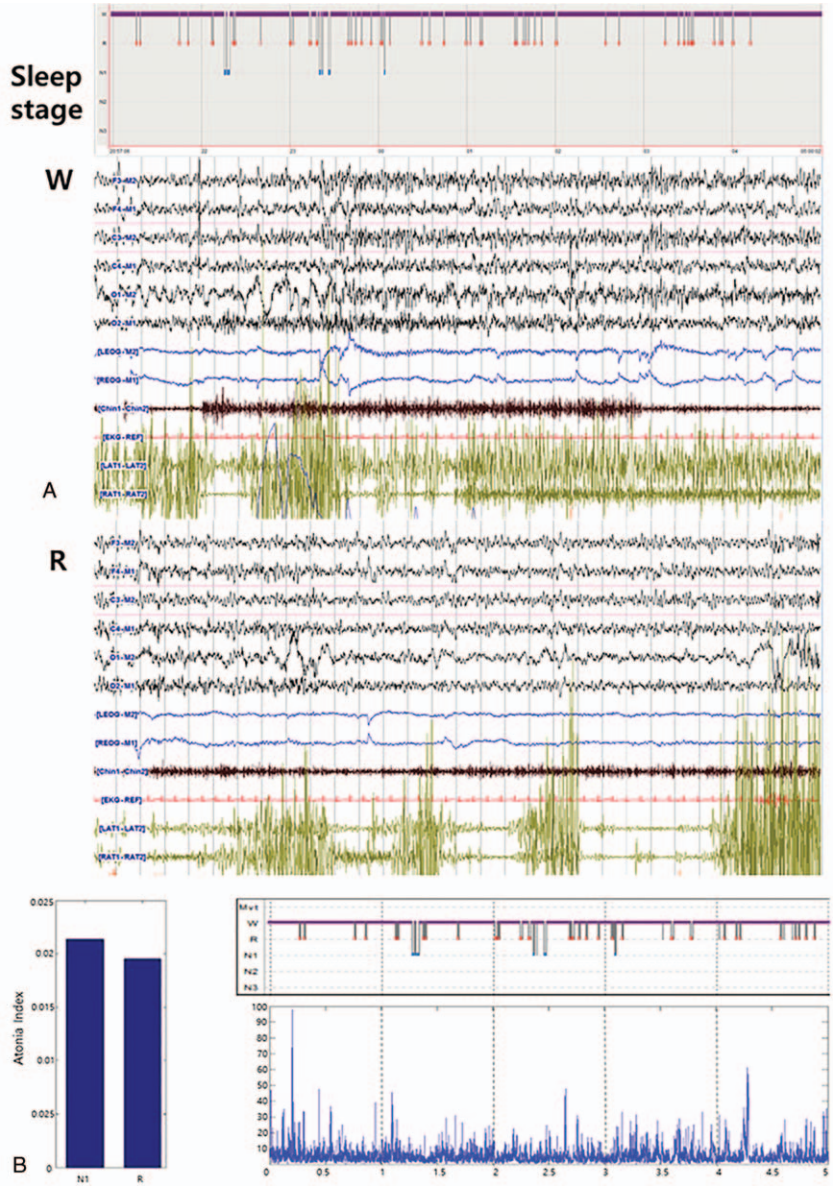

Figure 2. Video-polysomnography (VPSG) performed 1 month and 3 months after admission. Over an 8-hour period, small segments of sleep patterns were recognizable on the VPSG (A). Sleep alternated rapidly between wakefulness and rapid eye movement (REM) sleep. Sleep spindles, K complexes, and slow-wave sleep were absent, with REMs persisting through most the sleep period. Continuous body movements were observed throughout the recording period. During REM sleep, the atonia index was less than 0.02 (B-left). Nocturnal chin electromyography (EMG) amplitudes arranged in time order and matched with hypnography showed continuous increases in muscle activities regardless of sleep stage (B-right). Abbreviations (from top to bottom of the VPSG): W, wakefulness; R, REM sleep; N1, stage 1 nonrapid eye movement (NREM) sleep; N2, stage 2 NREM sleep; N3, stage 3 NREM sleep; F3–M2, F4–M1, C3–M2, C4–M1, O1–M2, O2–M1, electroencephalogram channels; LEOG–M2, left electrooculogram; REOG–M1, right electrooculogram; chin1–chin2, chin electromyogram; EKG, electrocardiogram; LAT, left anterior tibial muscle; RAT, right anterior tibial muscle.

Moreover, atypical clinical features and low diagnostic sensitivity combined with rapid disease progression make it difficult to diagnose FFI. A previous study described a diagnostic algorithm for FFI using symptoms and signs by categorizing disease features into 3 groups: organic sleep disturbances, Creutzfeldt-Jakob disease–like symptoms, and relatively disease-specific symptoms stratified by frequency and time of occurrence. According to this diagnostic pathway, organic sleep disturbance is the most frequent and essential symptom of FFI.[3] Consistent with this description, sleep disturbances, including insomnia, disrupted organic sleep structure, and a very low atonia index level, were the most remarkable findings in our case.

The VPSG revealed a lack of NREM sleep with an absence of sleep spindles, K complexes, and delta activities, as well as short, isolated, recurrent episodes of REM sleep and continuous body movements, regardless of sleep stage. These findings are consistent with agrypnia excitata, indicating a loss of slow-wave sleep with motor overactivation. The observed changes were likely due to the fact that different thalamic locations generate slow-wave sleep versus REM sleep; slow-wave sleep is generated in the limbic portion of the thalamus, whereas REM sleep is generated in the mesopontine region.[4] The bilateral thalamus is usually affected in FFI, primarily influencing slow-wave sleep. Morvan syndrome and delirium tremens can also

produce agrypnia excitata. These disorders have a similar pathogenic mechanism, involving dysfunction of thalamolimbic circuits.[5,6]

The atonia index during REM sleep is usually above 0.9 in healthy individuals,[7] but was very low (<0.025) in the present case. Combined with the observation of increased chin and leg EMG activities during REM sleep and continuous movement regardless of sleep stage, the symptoms of FFI can initially be misleading and be interpreted as an RBD. However, RWA in RBD is clearly different from FFI in several respects. RBD preserves NREM sleep integrity and has normal sleep-wake cycles. RBD events most often occur 3 to 4 times a night usually in the latter part of sleep, whereas these movements persist nearly continuously in FFI. In addition, behaviors in RBD are purposeful and sometimes violent (reminiscent of punching and kicking someone), whereas nonpurposeful stereotyped and repetitive gestures are observed in FFI.[8]

RWA is related to dysfunction of the pontine tegmentum in the brainstem.[9] Although histopathological examination was not performed in our patient, FDG-PET revealed normal uptake in the brainstem, with slightly decreased uptake in the bilateral thalamus. A previous report described a case of FFI in which the brainstem was preserved in histopathology.[2] The atonia index, an objective measure of motor overactivation during sleep, was at a very low level, regardless of the sleep stages. This suggests that functional dysregulation is present beyond the REM sleep-related structures. Accordingly, RWA in FFI is probably caused by functional dysregulation of REM sleep-related structures associated with thalamic damage, such as the pedunculopontine nucleus and laterodorsal tegmental nucleus in the brainstem.[10]

FFI is difficult to diagnose due to the low sensitivity of diagnostic tools, and many patients might die without diagnosis. In the absence of a clear family history, typical VPSG findings, including agrypnia excitata, and low level of atonia index provide the crucial information necessary for diagnosis before genetic testing. Our case adds to the current knowledge about typical findings that will help to diagnose FFI.

Author contributions

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Validation: Byeongsu Park, Keun Tae Kim, Jin-Sun Jun.
Visualization: Byeongsu Park, Ki-Young Jung.
Writing – original draft: Tae-Won Yang.
Writing – review and editing: Ki-Young Jung.

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