Reviewer's report

Title: Sporadic Fatal Insomnia in Texas: A pre-mortem diagnostic challenge: Case report

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Reviewer: Jed Barash

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Sporadic Fatal Insomnia in Texas: A pre-mortem diagnostic challenge: Case report

Summary:
Through a review of medical records, neuropathological examination, and a post mortem interview with family, this case report addresses a particularly unusual presentation of sporadic Creutzfeldt-Jakob disease, known as sporadic fatal insomnia (sFI). When considering prion disease in the differential diagnosis, the authors recommend that clinicians inquire about changes in sleep patterns and, under the appropriate clinical circumstances, consider the use of polysomnography (PSG), nuclear brain imaging, and genetic testing to identify possible cases of sFI.

Major Compulsory Revisions:

Background:
1. As an introduction for the reader, the background should contain a short clinical overview of the subtypes of prion diseases that the authors subsequently address, including sporadic, familial, iatrogenic, and variant CJD, as well as fatal familial insomnia. Since some may be unfamiliar, it should also briefly describe the molecular classification of CJD through characterization of PrP (the polymorphism at codon 129 and possible mutations at other locations, such as D178N) and the prion protein (including physiochemical properties, such as relative molecular mass and glycosylation patterns). A basic understanding of these subjects is essential in interpreting the clinical findings that come later.

Case Presentation:
1. Under “Clinical Findings,” the authors should clarify the history a bit. The cognitive examination is well-described, but other portions of the neurologic examination receive little comment. Anisocoria, “unfocused hand gestures,” and “constant movement” are mentioned in Table 1, but would be worth mentioning in the text. A clearer description of the movement abnormalities and gait difficulties would be helpful, if available. Most importantly, a major theme of the manuscript
is the “diagnostic challenge.” Other than CJD, what diseases were the clinicians (including neurologic and psychiatric consultants) considering in the differential? Were other subacute neurodegenerative disorders in a 33-year-old woman addressed (such as paraneoplastic encephalitis)?

Minor Essential Revisions:

Title:
1. The title of the manuscript (“Sporadic Fatal Insomnia in Texas: A pre-mortem diagnostic challenge: Case report”) should be streamlined and more clinically applicable. “Sporadic Fatal Insomnia in a Young Woman: A Diagnostic Challenge” is one possibility.

Abstract:
1. Under “Conclusions,” the authors should simplify. Consider: “In cases of suspected prion disease, a characteristic change in sleep patterns can be an important clinical clue for identifying sFI or FFI; polysomnography (PSG), nuclear imaging of the brain, and genetic analysis may aid in diagnosis.”

Background:
1. The last sentence of the background should succinctly capture for the reader why the case is being reported. There seem to be two reasons: 1) to make clinicians aware of an unusual presentation of spongiform encephalopathies and 2) to demonstrate the importance of pursuing a thorough sleep history when prion disease is being considered in the differential diagnosis.

Case Presentation:
1. The final two sentences of “Histological Examination” should be more clearly worded. Consider: “Except in the hippocampus, where only the molecular layer was even weakly stained, immunohistochemical evaluation for the prion protein (PrP) in the cerebral cortex demonstrated intense staining in a predominantly ‘synaptic’ pattern with occasional, small clusters of coarse granules. Meanwhile, the basal ganglia, thalamus, and cerebellum were just faintly stained.”
2. Under “Molecular Study,” it appears that the sentence beginning with “Minimal amounts of…” should refer to Figure 2A, not Figure 2B as is listed. The following sentence (beginning with: “Detectability of PrPres…” should explicitly refer to Figure 2B. The next sentence (“No PrPres was detected in the cerebellum…”) should therefore be moved between these two sentences above, as it refers to Figure 2A.

Discussion and Conclusions:
1. In the first sentence, the “aspects of the patient history” should be emphasized above ancillary testing on two grounds: 1) it is the history that guides a clinician’s differential diagnosis and therefore which confirmatory tests are ordered and 2) one of the major points in this manuscript is that a careful sleep history might have made the diagnosis of sFI antemortem. Additionally, the word “special” is used twice and should be omitted in both instances.
2. In the first paragraph, it should be mentioned that EEG, cerebrospinal 14-3-3 protein, and MRI are all typically unrevealing in cases of sFI.

3. The first sentence of the second paragraph should be amended for clarity and the authors should change it to: “…unusual for the most common subtype of prion disease—sporadic CJD (sCJD).” Following this sentence (and prior to the next one beginning: “Although this young patient showed…”), a transition to the rest of the paragraph should be inserted to explicitly state that other forms of CJD were effectively excluded.

4. The last sentence of the third paragraph mentions a duration exceeding 14 months, though the reason for this particular threshold is unclear. Hamaguchi (reference 7) includes a case of 13 months’ duration. Why wouldn’t the threshold be more than 12 months?

5. The fourth paragraph is lengthy and the authors should consider more pithy discussion here. At the very least, the sentence beginning “Landolt et al reported the presence of sleep-wake symptoms…” should be a new paragraph with a new topic sentence. Maybe the final sentence (“Combined, the studies of…”) could be adjusted and moved up to serve as the lead for the new paragraph.

6. In the final paragraph, the authors write: “If confirmed, this case indicates that, as in sCJD, occasional and unexplained phenotypic variations have to be expected in sFI.” Rather than occasional “exceptions to the rule,” might the possibility of a spectrum of prion disease more parsimoniously explain such variations? Also, the use of the phrase “as in sCJD” seems to imply that sCJD and sFI are different entities, when in fact sFI is most commonly classified as a particular subtype of sCJD.

Table 1:

1. Under January 2007, “places arms and legs in sustained postures” is not a description of akathisia, which is instead a sense of inner restlessness sometimes manifesting with an inability to remain motionless. Are these sustained postures dystonic? If both akathisia and sustained postures were observed, these should be mentioned on separate lines.

2. Under June 2007, it might be best to include a summary description of the neuropathology on the last line (MM2 sCJD, thalamic type consistent with “sFI”).

3. Consider also mentioning MRI results in this table.

Discretionary Revisions:

Abstract:

1. Under “Results,” it seems important to describe the interview with the “a close family member” as “post mortem.” This addition underscores the point that clinicians may miss questions about sleep patterns, which can yield an important diagnostic clue if prion disease is suspected.

Case Presentation:

1. Under “Clinical Findings,” it may be best to place “(Table 1)” at the end of the
first sentence so that the reader is aware of the table as he or she proceeds through the case history.

2. A history of two spinal surgeries is outlined in the third paragraph of “Clinical Findings.” Although reassurances regarding the low likelihood iatrogenic transmission come later (in the second paragraph of the “Discussion and Conclusions”), it might help a reader who is curious about an iatrogenic etiology to at least mention here that the donor of the bone transplant was pre-screened, thereby minimizing this possibility (after the sentence mentioning “cadaver-donated bone”).

3. In the second sentence of “Histological Examination,” the authors should consider changing “…especially the temporal cortex” to “including the parietal and temporal cortex” since the fine spongiform degeneration described in Figure 1F is in the parietal (not temporal) cortex. Additionally, changing the structure of the following sentence might make for easier reading. One possibility: “The hippocampal formation, basal ganglia and cerebellum were much less affected except for the presence of “torpedoes” (fusiform swellings of the Purkinje cell axons in the granule cell layer of the cerebellum) and SD in the molecular layer of the hippocampus.”

4. A figure of FFI pathology (Figure S1) is displayed separately from all other neuropathologic images (Figure 1). Might it make more sense to incorporate the FFI slide in Figure 1 for comparison, perhaps between panels A and B?

Figure 1 Legend:
1. Rather than “prion-unaffected, age-matched subject” in B, it might be more appropriate to use “age-matched subject without prion disease.” Similarly, rather than “prion-unaffected control subject of the same age” in C, it might be more appropriate to use “control subject of the same age without prion disease.”

Figure 2 Legend:
1. After mentioning PrPres type 1, would consider including “21 kDa” in parentheses.

Minor Issues Not for Publication:

Abstract:

Background:
1. In the final paragraph, “EEG” should be spelled out as “electroencephalogram” with the accompanying abbreviation when it is used for the first time. The phrase “recording during sleep” following “EEG” should be deleted.

Case Presentation:
1. “Bed bound” in the third-to-last sentence of the first paragraph under “Clinical Findings” (and in Table 1) should be a single word (“bedbound”) or hyphenated (“bed-bound”).
2. Please indent the first sentence of the final paragraph of “Clinical Findings.” ("Following preliminary autopsy results...")

3. The final sentence of “Molecular Study” is a bit awkward and should be re-written. It might be necessary to put parentheses around “i.e. diglycosylated, monoglycosylated, and unglycosylated.”

Table 1:
1. Under August 2005, would change to “Onset: age 31.”
3. Under June 2007, would consolidate “deceased” and “Age: 33” to “Death: Age 33” on the first line. “Duration of illness: 22 months” would then be moved up to the second line.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.