A rare case of rapidly progressive dementia with elevated RT-QuIC and negative 14-3-3 and tau proteins

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\textbf{ABSTRACT.} Creutzfeldt-Jakob disease (CJD) is characterized by rapidly progressing dementia with death usually occurring within 6 months. There is no verified disease-specific pre-mortem diagnostic test besides brain biopsy. We describe a 66 y old previously high functioning male who presented with a 5 month history of rapidly progressive dementia. Neurological examination revealed a score of 19/30 on MOCA testing. An extensive workup into various causes of dementia including electroencephalography and imaging studies was unremarkable. The cerebrospinal fluid was sent to National Prion Disease Center and it revealed elevated RT-QuIC levels with negative 14-3-3 and T tau proteins. Based on literature review, our case is one of few living subjects with elevated RT-QuIC levels and negative 14-3-3 and tau proteins.

\textbf{KEYWORDS.} Creutzfeldt-Jakob disease, dementia, prions, RT-QuIC, tau protein

\textbf{INTRODUCTION}

Prion diseases, also known as transmissible spongiform encephalopathies are a class of fatal neurodegenerative diseases that typically have long incubation periods and progress inexorably once clinical symptoms appear. In humans, 6 prion diseases are currently recognized: kuru, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), iatrogenic, and fatal familial insomnia (FFI). CJD accounts for approximately 90 percent of sporadic prion disease. It frequently presents with a rapidly
progressing dementia, ataxia and myoclonus, and death typically occurs within 6 months. There is no disease-specific pre-mortem diagnostic test for sCJD. Brain biopsy is close with 100% specificity and high sensitivity. Current clinical diagnostic criteria rely on clinical features and the results of investigations such as EEG, brain MRI and the presence of 14-3-3 or tau in the cerebrospinal fluid (CSF). Recent studies demonstrate that real-time quaking induced conversion (RT-QuIC) analysis of CSF, a prion protein conversion assay, from patients with suspected sCJD has the potential to be a more accurate pre-mortem diagnostic test for sCJD than either CSF 14-3-3 or tau proteins.

CASE

We describe a 66 y old male who presented with a 5 month history of rapidly progressive dementia. Prior to this, patient was a relatively high functioning individual, and explained being able to do calculus with relative ease. His dementia had worsened to a point where he was having difficulty performing activities of daily living such as buttoning his shirt or putting on a pair of pants. On one occasion, patient was found at a gas station unaware of how or when he got there. There was no history of drug abuse, alcohol abuse, stroke, seizures, signs of infection, trauma, blood transfusion, surgeries or psychiatric disorders in the past. Neurological examination was unremarkable except for a score of 19/30 on MOCA testing (Montreal Cognitive Assessment). Although memory and orientation were intact, most points were lost on visuospatial/executive functioning and attention. Patient underwent an extensive workup for reversible causes of dementia including infectious, autoimmune, malignant, and metabolic causes which were largely unremarkable. Electroencephalography (EEG) and magnetic resonance imaging (MRI) studies of the central nervous system were found to be inconclusive. A lumbar puncture was performed and the cerebrospinal fluid (CSF) was sent to National Prion Disease Pathology Surveillance Center in Cleveland, Ohio, USA for further evaluation. Given family history of early-onset Alzheimer's in his mother, he was discharged home on Donepezil with a Neurology follow-up in 6 weeks while awaiting CSF results. At the time of follow-up, he scored 18/30 on MOCA testing once again losing most points of visuospatial/executive functions and attention. Memory, recall and orientation remained intact. His CSF was negative for 14-3-3 protein and T tau protein was found to be 471 pg/ml (normal <1150pg/ml). Interestingly, the RT-QuIC was positive.

DISCUSSION

Clinically, in addition to rapidly progressive dementia, sCJD is associated with behavioral abnormalities, mood disturbance, sleep disorders, startle myoclonus, extra-pyramidal signs and cerebellar abnormalities. EEG frequently reveals periodic synchronous bi- or triphasic sharp wave complexes (PSWC) and MRI brain is associated hyper-intensity of the caudate or putamen. For the longest time, detection of 14-3-3 protein in the CSF was regarded as a highly specific test for diagnosing sCJD. However, false positive elevations in CSF 14-3-3 have recently been reported in herpes simplex encephalitis, hypoxic encephalopathy, cerebral metastases, paraneoplastic disease, and metabolic encephalopathies. A variety of other CSF diagnostic tests have been reported in small series, including the S100 protein, neuron specific enolase, thymosin β4, and tau protein. In one large case series, tau had superior accuracy and specificity when compared to 14-3-3 protein as a diagnostic test for CJD, although both tests produced a significant number of false negative and false positive results.

Definite diagnosis of sCJD requires neuropathological or immunohistochemical detection of the prion protein (PrP-CJD) in brain tissue. PrP-CJD arises through the post-translational conformational conversion of the normal endogenous PrP (PrPC or PrPSen) and accumulates preferentially in nervous tissue. PrP-CJD is also the main component of the infectious CJD agent and propagates itself by seeding or templating the assembly of PrPC into misfolded multimers that can take the form of amyloid fibrils.

Although PrP-CJD was identified as the marker for CJD, it was difficult to identify a PrP-CJD assay and a non-invasive method of obtaining a tissue from living subjects that was adequately
sensitive. CSF testing with a new in vitro PrP-CJD amplification technology, a designated real-time quaking-induced conversion (RT-QuIC) has recently been identified as a highly specific diagnostic test for sCJD. In the RT-QuIC assay, recombinant prion protein (rPrPSEN) is mixed, or seeded, with a small amount of PrP-CJD, resulting in the formation of amyloid fibrils that are detected by thioflavin T (ThT) fluorescence. RT-QUIC analysis of CSF of post-mortem subjects with sCJD had a sensitivity of 80 to 90% and specificity of 99 to 100%. These results suggest that RT-QuIC can provide promising diagnostic information than tests for surrogate markers of sCJD in the CSF. The National Prion Disease Pathology Surveillance Center now includes RT-QuIC in addition to tau and 14-3-3 levels in their analysis of CSF.

CONCLUSION

Although our patient did not have EEG, MRI and CSF findings of sCJD, RT-QuIC analysis of CSF confirmed the presence of CJD. Based on the review of literature, our case is one of few living subject with elevated RT-QuIC levels and negative 14-3-3 and tau proteins in the CSF. It is hard to conclude that the patient has CJD pre-mortem without the brain biopsy. Although 14-3-3 in CSF is not always associated with sCJD, elevations in RT-QuIC has usually been associated with high tau proteins in the CSF. Our case is unusual in that the only bio-marker performed that is elevated is the RT-QuIC together with inconclusive EEG and MRI findings of sCJD.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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