Probable Sporadic Creutzfeld-Jakob Disease in a 59 year old male

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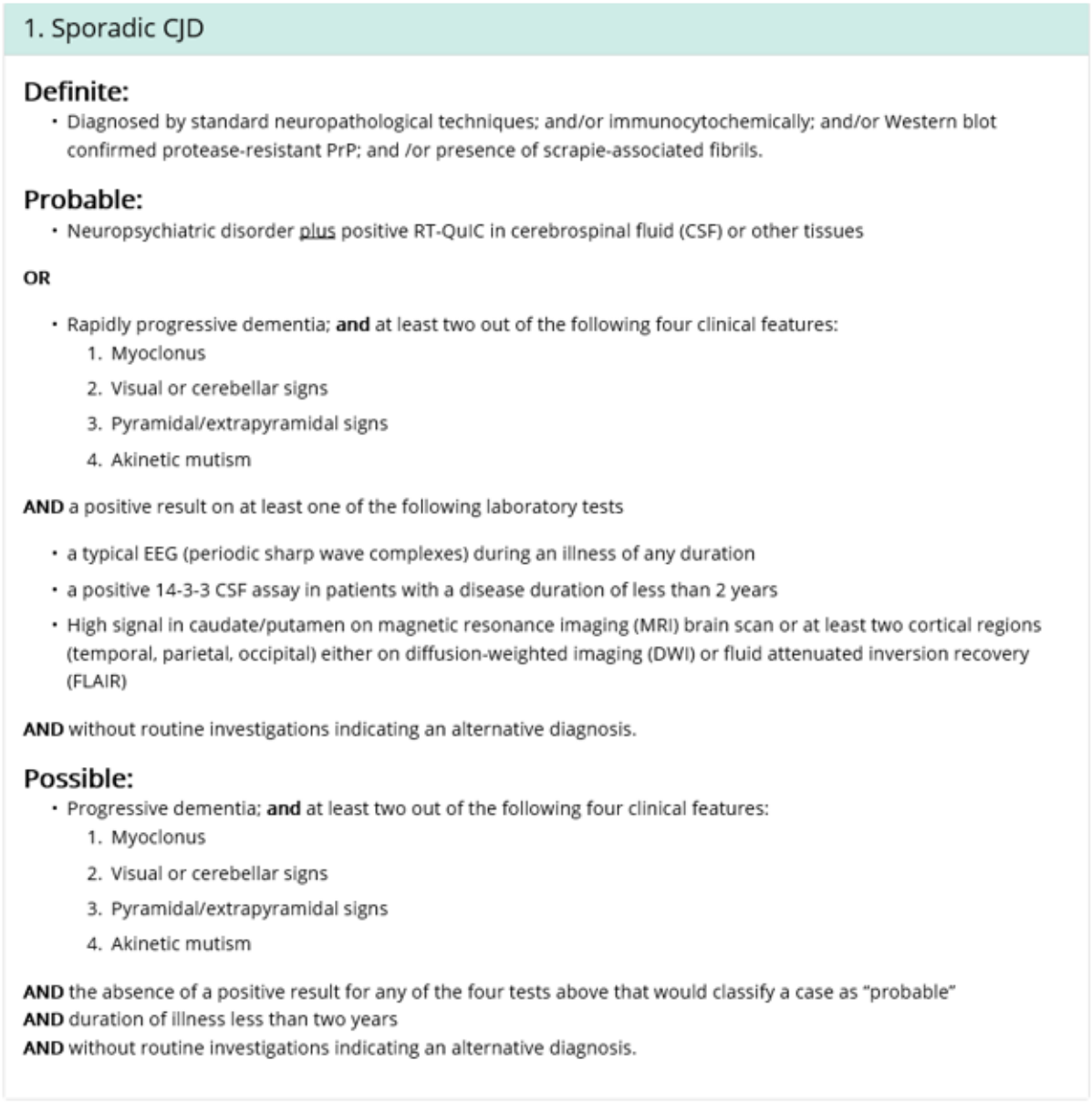
Abstract. Although rare, Creutzfeldt-Jakob disease (CJD) is the most common human prion disease. Creutzfeldt-Jakob disease (CJD) is characterized by rapid neurologic deterioration manifesting as spongiform changes in the brain, loss of neurons, and prion protein accumulation leading to mortality usually occurring within a year of disease onset. CJD is most often sporadic, but can exist in genetic, iatrogenic, and variant forms as well. Diagnosis requires histopathologic confirmation, however, that is not always readily available, or patients become lost to follow-up after discharge from the hospital. When histopathologic confirmation is not performed, a probable diagnosis of CJD can still be made.

We report the peculiar case of a 59 year old man who presented to the emergency department with a ground level fall and neurologic complaints. Following admission to the hospital, the patient received an extensive work-up to determine the cause of his inability to walk, dysarthria, and progressively worsening neurologic symptoms. Magnetic resonance imaging and cerebrospinal fluid analysis were obtained to aid in the diagnosis. Ultimately, the patient died following discharge from the hospital, but a probable diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) was made.

Introduction. A prion is a small, infectious, protein containing particle which can replicate over time and lead to neurotoxicity. This is achieved by converting the normal form of the prion protein into a misfolded protein via post-translational modification (1). The accumulation of these misfolded proteins leads to spongiform changes and neural degeneration (2). Prions have a long incubation period, but when symptoms do arise there is a rapid progression of neurologic disease that inevitably results in mortality. Approximately 90% of all cases are sporadic and there is typically one new case per million per year worldwide (3). The mean age of diagnosis is approximately 62 years and both genders are equally susceptible (4). It is rare for sCJD to afflict those under the age of 30 and those over the age of 80 (5). There does appear to be an increased incidence in North Africa, Italy, Israel, and Slovakia due to a higher incidence of the genetic type of CJD (6). Definitive diagnosis requires neuropathologic sampling for the typical findings of human prion diseases, however, a clinician can come to a probable or possible diagnosis when the patient's presentation fulfills certain criteria depending on lab and physical exam findings. Currently there is no cure for CJD, and most treatment modalities are aimed at reducing symptoms.

Often, there are delays that occur when the patient first presents with symptoms to the physician at the time a diagnosis of sCJD is made. Due to the delay sCJD can be misdiagnosed due to early symptoms and disease duration. (8) Clinical diagnostic criteria that was formed over 40 years ago for sCJD, which included using specific clinical features and EEG's. Over time, changes have been made progressing to the usage of biomarkers in the cerebrospinal fluid while updating clinical diagnostic criteria. (9) Definitive diagnosis requires neuropathologic sampling for the typical findings of human prion diseases, however, this is not always necessary as a clinician can come to a probable or possible diagnosis when the patient's presentation fulfills certain criteria depending on lab and physical exam findings. Multiple societies have developed and collaborated on diagnostic criteria for CJD, which can be seen in Figure 1 below. (10) We report the case of a man who developed respiratory and neurologic complaints requiring an extensive workup utilizing diagnostic criteria for CJD eventually leading to the diagnosis of probable sCJD.



1. Sporadic CJD

Definite:

- Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.

Probable:

- Neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid (CSF) or other tissues

OR

- Rapidly progressive dementia; **and** at least two out of the following four clinical features:
  1. Myoclonus
  2. Visual or cerebellar signs
  3. Pyramidal/extrapyramidal signs
  4. Akinetic mutism

AND a positive result on at least one of the following laboratory tests

- a typical EEG (periodic sharp wave complexes) during an illness of any duration
- a positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
- High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)

AND without routine investigations indicating an alternative diagnosis.

Possible:

- Progressive dementia; **and** at least two out of the following four clinical features:
  1. Myoclonus
  2. Visual or cerebellar signs
  3. Pyramidal/extrapyramidal signs
  4. Akinetic mutism

AND the absence of a positive result for any of the four tests above that would classify a case as "probable"
AND duration of illness less than two years
AND without routine investigations indicating an alternative diagnosis.

Figure 1 Diagnostic criteria for sCJD obtained from the Center for Disease Control and Prevention.

Case report. A 59-year-old man initially presented to our emergency department with symptoms of worsening shortness of breath, subjective fever and cough on January 15th, 2020. He had recently been seen in the ER multiple times before this for similar respiratory complaints as well as neurologic complaints and a ground level fall. Per the obtained history, the patient had been seeing an outpatient neurologist and as of August 2019, he had lost his ability to walk and was noted to be wheelchair bound. At that time, he was diagnosed with Parkinson's disease and was started on levodopa-carbidopa without any benefit. He was given propranolol which did help

with the tremor he had developed. Prior to this, he was known to be a physically active professional landscaper who had a medical history of essential hypertension, gout, major depression, an unprovoked DVT, which at the time of admission needed chronic anticoagulation and placement of an IVC filter.

His physical exam did demonstrate significant neurologic findings, which included dysarthria, mild difficulty with upward gaze, normal cranial nerve testing, inconsistent findings to vibration sensation but his pin and position sense were intact, no obvious dysmetria, and had normal muscle strength throughout as well as absent deep tendon reflexes. Notably, the patient did have difficulty with gait which was described as not being broad based but being more of a gait apraxia. In order to successfully walk, the patient had to be held upright. It seemed as if the patient had no sense of where his legs were in space when attempting to walk. With these findings our inpatient neurologist recommended a workup which included MRI of the brain with and without contrast as well as MRI of the cervical spine. Lumbar puncture was performed for typical CSF studies along with VDRL, gram stain, cryptococcal antigen, fungal culture, smear, NMDA-R, Whipple PCR, 14-3-3 protein and Tau level. A paraneoplastic workup of the serum and CSF was also performed.

The results of the brain MRI shown in Figures 1 and 2, show subtle restricted diffusion in a pattern sometimes referred to as the “hockey stick sign” on diffusion-weighted imaging as well as a prominent “hummingbird sign” on the sagittal image. The “hockey stick sign” manifests as a restriction involving the pulvinar and dorsomedial thalamic nuclei bilaterally. The “hummingbird sign” indicates atrophy of the midbrain in which the body of the pons resembles the body of a bird and the midbrain represents the head and beak which extends toward the optic chiasm. Figure 3 shows hyperintensity of gyri forming a “Cortical Ribbon Sign” indicative of a potential prion disease such as sCJD. Not necessarily relevant to this case, there was a subdural hematoma which was the impetus to remove anticoagulation and place an IVC filter during this admission. The cervical and thoracic spine MRIs were essentially non-diagnostic due to motion artifact.

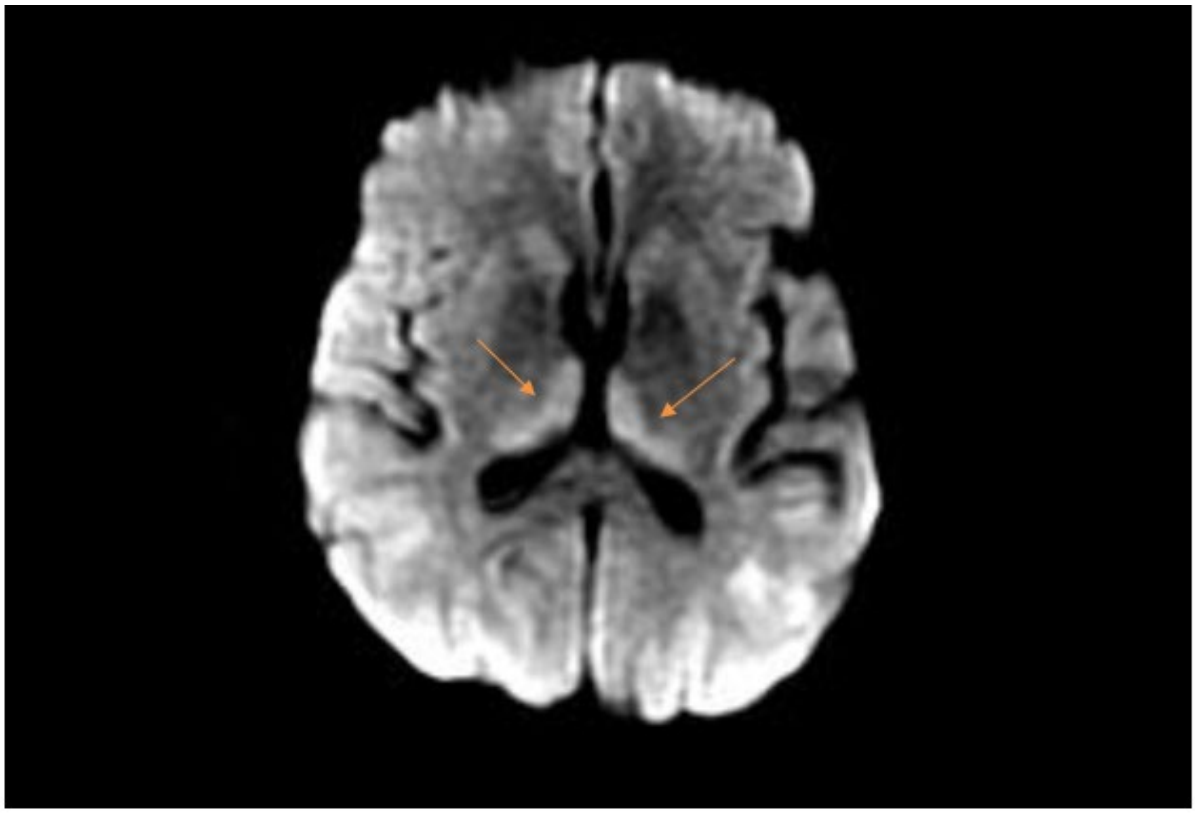


Figure 2: Diffusion weighted image showing hyperintensities forming a "hockey stick sign" at the pulvinar and dorsomedial thalamic nuclei bilaterally.

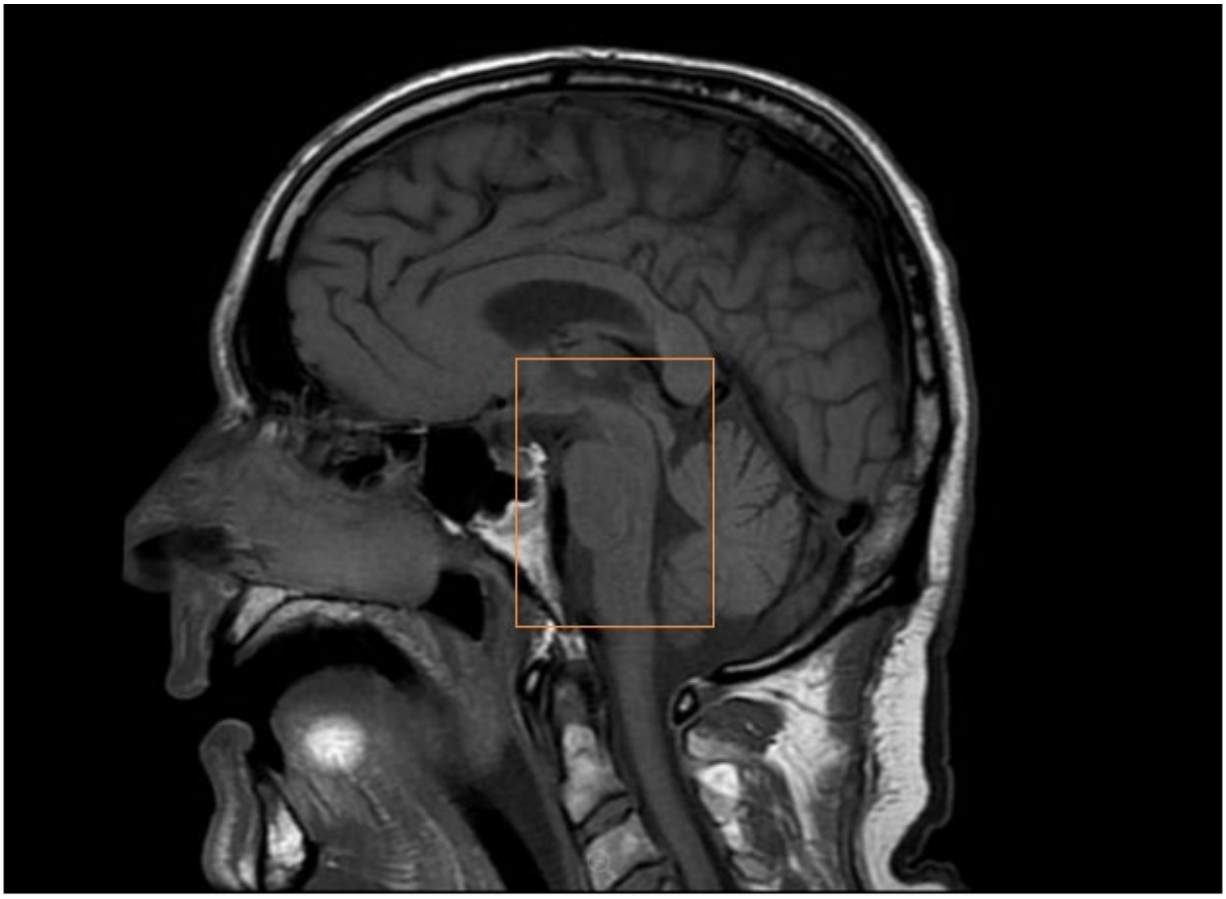


Figure 3: Sagittal Diffusion Weighted Image showing "Hummingbird Sign" indicating midbrain atrophy.

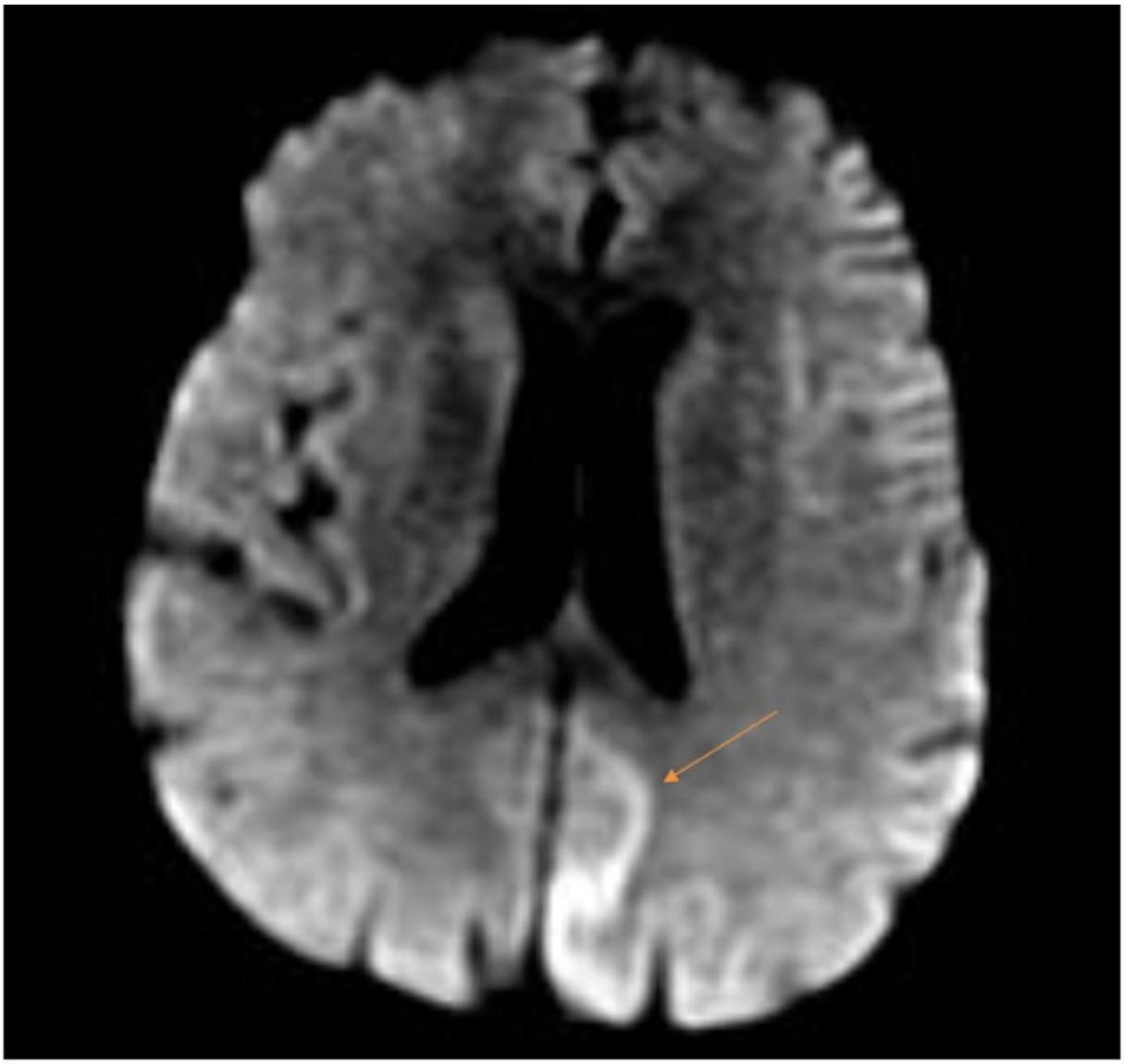


Figure 4: Diffusion weighted image shows hyperintensity of gyri forming a "Cortical Ribbon Sign"

The patient was discharged to the care of his wife on January 20th, 2020 with follow up with neurology and primary care whilst many of his CSF studies were pending. As the results were completed, he was found to have an elevated striated muscle antibody at 1:40, a normal CSF flow cytometry, a slightly below normal serum IgG of 672mg/dL, a CSF IgG index of 0.9, a CSF IgG synthesis rate of 4.8, a non-reactive VDRL, a negative NMDA receptor IgG, a negative Cryptococcus antigen, a positive RT-QuIC, an elevated T-Tau at 1958 pg/mL, and a positive 14-3-3 protein in the CSF. The CSF was sent to the National Prion Disease Surveillance Center Case Western Reserve in Cleveland, Ohio and analyzed. From medical and public records, the

patient expired in March of 2020 while on hospice, secondary to his progressive neurologic deterioration and pneumonia and an autopsy with brain biopsy was not performed.

Test Name	Result	Reference Range for Non-Prion Disease
T-tau protein (CSF) ++	1958 pg/ml	0-1149 pg/ml
14-3-3 protein (CSF) ++	Positive	Negative
Albumin	4,100 mg/dL	3, 484-4,756 mg/dL
IgG	672 (L) mg/DL	701-1,469 mg/dL
IgG, CSF	2.4	0.5-6.0 mg/dL
Serum IgG/Alb Ratio	0.16	
IgG Index	0.9 (H)	0.0-0.7
IgG Synthesis	4.8 (H)	0.0-3.0
CSF Albumin	16.7	13.4-23.7 mg/dL
CSF Elect	Oligoclonal banding is not demonstrated	
Pathology Interpretation	CSF immunochemical studies show normal IgG/albumin ratio: 0.14, elected IgG index: 0.9 and elevated calculated CSF IgG synthesis: 4.8 mg/day.	

Table 1: Contains information from labs collected indicating the diagnosis of probable sporadic Creutzfeldt-Jakob Disease.

Discussion. Making a diagnosis of CJD is difficult, due to some overlap in symptoms with other more common neurologic disorders such as Parkinson's disease. However, utilizing specific diagnostic criteria we were able to form this conclusion as a probable diagnosis of sCJD. For example, a patient whom has a positive RT-QuIC either in the CSF or other tissues and the presence of a neuropsychiatric disorder can be diagnosed with probable sCJD. Another criterion for making the diagnosis of probable sCJD includes a rapidly progressive dementia with at least two of the following four clinical features which includes myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, and akinetic mutism. Not only must they fulfill two out of the four aforementioned clinical signs, they must also have at least one of the following positive results which include a typical EEG with periodic sharp wave complexes during an illness of any duration, a positive 14-3-3 CSF assay with a disease duration of less than two years, a high signal in the caudate and putamen, or two cortical regions on DWI or FLAIR. If these findings are satisfied alternative diagnoses must be ruled out.

It is important to note that there is a distinction between probable and possible sCJD. Some patients could be considered to have possible sCJD if they exhibit at least two of the previous clinical features and the absence of any of the previously mentioned test results. Additionally, a possible case of sCJD would need to have a duration of illness less than two years and alternative diagnoses ruled out. Our patient would fit the criteria of a probable diagnosis rather than a possible diagnosis given that he had a positive RT-QuIC in his CSF along with recent onset neuropsychiatric disorder. He also had other lab tests which were suggestive of sCJD as there was a positive 14-3-3 CSF assay and concerning physical exam findings which had progressively worsened. Although CJD requires an autopsy for confirmation, the patient had laboratory and physical exam evidence which are congruent with a probable diagnosis of sporadic Creutzfeldt-Jakob Disease. With there being no cure for sCJD, utilizing the diagnostic criteria for the diagnosis of probable and possible sCJD can help physicians better diagnosis this disease and help scientists conduct biochemical analyses in order to determine the transmissible agents of cause and to reduce the burden of this neurological disease.

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