Creutzfeldt-Jakob Disease: A Geographic Case Series in the Northeastern United States

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Background

Human prion diseases are, in general, a rare occurrence in the United States, with greater than 90% being of the sporadic subtype (sCJD)[2]. The clinical course of CJD is often sinister with sudden and expeditious decline in neurocognitive status with death occurring within a year from the onset of symptoms.

Human prion diseases are categorized into 3 subtypes: sporadic (sCJD), genetic (gCJD), and acquired. Considering that sCJD is overwhelmingly the most common subtype of human prion disease, it is interesting to note of several reports detailing small clusters of sCJD cases[3] in which cases occur in higher frequency than expected. No causative agent is known, however, an external factor unknown to the literature is suspected to be at play, furthering the importance of case identification and description in the literature for future investigative efforts.

CJD can present with an assortment of neurological symptoms, making diagnosis based solely on clinical presentation difficult as it may mimic the presentation of more than several clinically distinct disorders. Initial manifestations of CJD are often confused for dementia, namely Alzheimer's and Lewy Body dementia. Psychiatric disorders must also be considered in the differential as auditory/visual hallucinations and behavioral disturbances can be seen in conjunction with cognitive decline. Other manifestations include cerebellar signs such as ataxia and extrapyramidal signs such as hypo/bradykinesia and rigidity/contracture.

Clinical Correlate

Case 1: 48-year-old Male - Rapid cognitive decline

Patient is a freight truck driver and got into an accident in the spring without significant injury. Over the next couple of months, he kept getting fired from multiple jobs as he was not able to complete tasks, which is unusual for the patient. In the Summer of the same year, he started experiencing visual hallucinations. By Autumn, he had more difficulty with IADLs and ADLs. The patient noticed that he was no longer able to handle finances and would get lost while driving. He found that he was no longer able to dress himself (putting clothes on backwards and placing socks on hands) and had much difficulty cooking (takes multiple slices of bread to make a sandwich, takes out multiple of the same utensil for himself, could not remember the function of knobs on the stove, etc.).

EEG Report – 2/27/20
This is an abnormal inpatient study due to the presence of generalized background slowing, which is a nonspecific finding which can be seen in toxic, metabolic, medication side effects or multifocal structural abnormalities.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: 993 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 2/26/20
- Results on 5/26/20

Case 2: 66-year-old Male – Visual symptoms and cognitive decline, now contracted

Presents with a several week history of blurry vision with intermittent double vision, occasionally worsening to the point of near blindness. The patient had no history of head trauma and, at neurologic baseline, was functionally independent with mild memory issues. Shortly after being admitted to the hospital, the patient had a precipitous decline over a course of several days. He quickly became unresponsive, even to simple commands, eventually becoming completely mute. He became contracted with bilateral upper extremity elbow flexion with his wrists assuming an ulnar deviation with fingers curled in. He was initially thought to have neurosyphilis given positive treponema pallidum antibodies. He underwent lumbar puncture but was negative CSF VDRL. He was initially treated with IV penicillin G and subsequently high-dose Solu-Medrol. The patient's mental status did not improve.

EEG Report – 6/11/20
This EEG was abnormal due to moderate generalized slowing and Triphasic waves. These findings indicate diffuse cerebral dysfunction as seen in toxic, metabolic, or diffuse or multifocal structural abnormalities.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: >20,000 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 6/12/20
- Results on 6/29/20

Case 3: 63-year-old Male - Rapid decline in mentation

Presents with concern for persistent encephalopathy. Recent history of rapid mental status decline associated with both visual and auditory hallucinations. Patient began exhibiting repetitive, uncontrollable right-sided movements. There is a suspicion for CJD encephalitis. Movements were noted to be choreiform in character but demonstrated no epileptiform correlates. Given continued decline in mental status and inability to protect his airway, the patient was intubated and transferred to the Neuro ICU.

EEG Report
None Performed.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: >20,000 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 8/16/20
- Results on 8/26/20

Case 4: 67-year-old Female – Psychosis & confusion

Initially presented to the ED with increasing confusion, word finding, and unsteady gait that has started in the Spring and worsened over the next several months. Patient had to stop working in the Summer due to her worsening symptoms. Patient has had several falls in the past week, with the last fall was yesterday landing on her buttocks. Her daughters are concern for patient's safety. She denies head strike, loss of consciousness, neck pain, or back pain.

EEG Report – 11/1/19
This EEG was normal awake, drowsy, and asleep.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: 3253 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 11/4/19
- Results on 11/25/19

Case 5: 49-year-old Female – Sudden onset ataxia, unsteady gait, and altered speech

Presents with at least 2 months' history of a constellation of neurological symptoms including progressive weakness, confusion, slurring of speech, imbalance, issues with her gait, frequent reports of dropping objects, falls and cognitive and memory decline. She has been developing an apathetic affect. The patient's symptoms were waxing and waning with good and bad days. Previously, she was evaluated by outpatient neurology and had a normal EMG, which was done on May 29, 2019. She also had an EEG done on June 11, 2019. She also had a negative myasthenia workup

EEG Report – 6/11/19
Normal awake and drowsy outpatient EEG.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: >4000 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 7/1/19
- Results on 7/16/19

Case 6: 54-year-old Male – Rapid onset dementia

Patient was admitted to the hospital in the Summer and found to have a left hippocampal infarct. After several days, he was discharged to rehabilitation center. One month later, he had an abrupt change in his condition with decreased ability to do his activities of daily living and worsening of his dysarthric speech. On arrival to the emergency department, his speech was incomprehensible, but he appeared to comprehend what was being said to him. He was able to move all extremities and had decent strength.

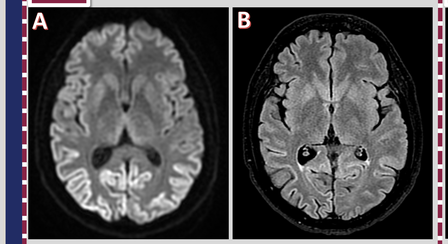
EEG Report – 7/20/16
Abnormal EEG:
1) left hemispheric slowing
2) moderate generalized slowing, and
3) triphasic waves.

Generalized slowing indicates diffuse cerebral dysfunction as seen in toxic, metabolic, or diffuse or multifocal structural abnormalities. The increased slowing over the left indicates more dysfunction in that hemisphere. Triphasic waves are usually consistent with a history of diffuse cerebral dysfunction. In this case with a question of CJD, this would also be consistent as this disease often has periodic triphasic sharp waves, occasionally with multiphasic or polyspike components, although that was not seen here, associated with disease activity.

RT QuIC (CSF): POSITIVE
- T tau protein (CSF)++: 10380 pg/mL
- 14-3-3 protein (CSF)++: POSITIVE
- Sample submitted 7/21/16
- Results on 8/23/16

Imaging Findings

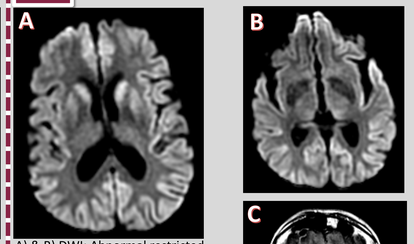
Case 1

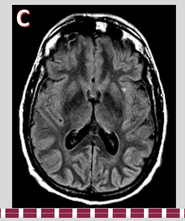


A)DWI: Symmetrical cortical restricted diffusion in the occipital lobes, parietal lobes and possibly in the frontal lobes.

B) FLAIR: No significant signal abnormality on FLAIR sequence

Case 2

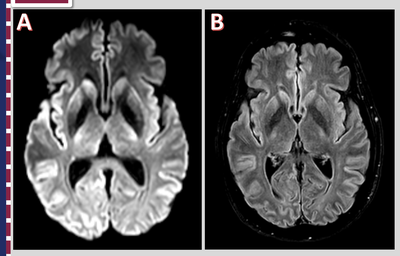




A) & B) DWI: Abnormal restricted diffusion of the caudate nuclei, putamen, and left greater than right medial thalami. Relatively diffuse abnormal diffusion hyperintensity of the cerebral cortices.

C) FLAIR: few scattered hyperintense foci within the periventricular and subcortical white matter.

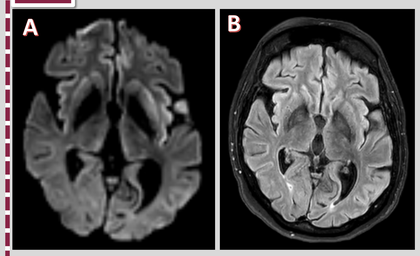
Case 3



A) DWI: Abnormal cortical reduced diffusivity seen predominantly along the right cerebral hemisphere. There is also abnormal reduced diffusivity involving bilateral caudate nuclei and putamen, more so than what is typically expected. No abnormal enhancement

B) FLAIR: Both caudate nuclei and putamen demonstrate slight increased FLAIR signal.

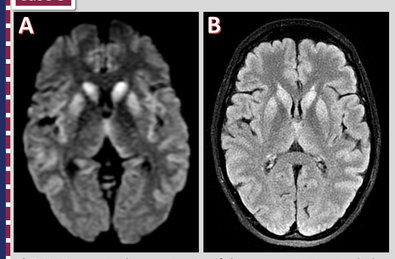
Case 4



A) DWI: Relatively symmetric cortical reduced diffusivity along the medial frontal & parietal lobes and insular cortices, left greater than right. Reduced diffusivity of the caudate nuclei, putamen, and medial thalami.

B) FLAIR: Mild scattered FLAIR hyperintense foci of the periventricular subcortical white matter.

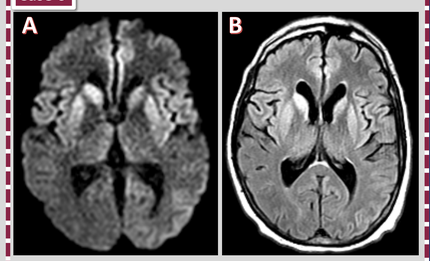
Case 5



A) DWI: Symmetric hyperintensity of the corpus striatum including the caudate/lentiform nucleus and globus pallidus. Gyriform hyperintensity at the left temporoparietal lobe ("cortical ribbon" sign)

B) FLAIR: Corresponding hyperintensity at the corpus striatum and the left cerebral cortex. Also of note is hyperintensity involving the left greater than right posterior medial thalami demonstrating a "hockey-stick" appearance and the pulvinar (posterior) nuclei of the thalami "pulvinar" sign.

Case 6



A) DWI: Reduced diffusivity within the following locations: Ventromedial thalami, both caudate nuclei, the putamen bilaterally, the cortex of the paramedian frontal lobe bilaterally, and the insular cortex bilaterally.

B) FLAIR: T2 prolongation throughout the deep gray nuclei as well as the paramedian frontal lobe and insular cortex bilaterally.

Discussion

Initial radiological evaluation for investigating the underlying causes of dementia typically begin with CT or MRI. The varied constellation of neuropsychiatric findings should strike suspicion for CJD and clinical diagnostic testing should proceed unimpeded, allowing for the possibility of diagnosis. Of all imaging modalities, evaluation for human prion diseases is best performed with MRI[4] with FLAIR and diffusion weighted imaging (DWI) sequences providing the most value.

There are classic signs on FLAIR MRI that are suggestive of CJD, particularly for sCJD and vCJD. The, "pulvinar sign" is composed of bilateral increased signal involving the posterior nuclei of the thalamus, which can be appreciated in cases 2 & 5. The "hockey stick" sign is composed of increased signal involving the pulvinar and dorsomedial thalamic nuclei, seen in case 5.

Findings on diffusion-weighted imaging is typically present as regions of increased gyriform intensity of the cerebral cortex, otherwise known as the "cortical ribbon" sign. Regional localization of gyriform hyperintensity may be useful in correlating with findings on electroencephalogram (EEG). Having said that, a common pattern seen on EEG of sCJD patients (and sometimes with gCJD) are periodic high-voltage synchronous bi or triphasic periodic sharp wave complexes (PSWC). Of note, these findings are not entirely specific to CJD patients and can also be seen in patients Alzheimer's dementia. In addition, as the disease progresses and neurologic activity decreases, EEG findings may disappear entirely[5], and so their absence do not definitely exclude the diagnosis.

Lastly, markers on cerebrospinal fluid (CSF) analysis can be used to confirm the diagnosis through real-time quaking-induced conversion (RT-QuIC). The basic principle of this analysis is the measurement of indirect amyloid formation in which the prion at fault (PrP^{Sc}) is converted to a recombinant prion protein that causes the creation of amyloid (samples are either positive or negative). Detection of proteins can also add validity to a positive RT-QuIC, with detection of Tau and 14-3-3 proteins. Although false positives can occur with either protein, false positives with 14-3-3 can be seen in the setting of encephalopathy of other etiologies (viral, metabolic) although these are not very common and a positive result actually increases the likelihood of CJD in the setting of other present pertinent positives.

CJD is a diagnosis of devastating consequence to the patient and their loved ones given its rarity and often-times confusing clinical presentation. Prognosis for CJD is grim, with death typically occurring within 12 months of diagnosis, often times sooner. At the time of writing, there is no treatment that provides any compelling long or even short-term mortality benefit. Treatment is mainly supportive, with a large focus on alleviating the severity of neuropsychiatric symptoms. It is for this reason that, identifying characteristic imaging findings with MRI can mean prompt diagnosis and greater quality of end-of-life care while avoiding unnecessary therapeutic and diagnostic procedures.

References

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