CLINICAL VIGNETTE

Creutzfeldt-Jakob Disease (CJD) in a 65-Year-Old Male

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Introduction

Creutzfeldt-Jakob Disease (CJD) is a rare, neurodegenerative form of prion disease that is life-ending and virtually untreatable. It affects approximately 1 in 1 million people annually worldwide, with about 350 cases in the United States.[1] Given clinical similarity with dementia, it is valuable to have CJD on the differential diagnosis as well as be able to distinguish treatable vs non-treatable forms of dementia.

Case Presentation

A 65-year-old male with a history of hypertension and prediabetes, initially presented to the ER with complaints of intermittent non-positional dizziness for 3 months. Neurological exam was non-focal. CT non-contrast of his head showed chronic small vessel ischemic changes and mild generalized volume loss. He was discharged with aspirin and meclizine as needed.

Seven days later he returned with new-onset ataxia, "seeing weird things in peripheral vision", and right hand discoordination not allowing him to play the flute, which was a passion of his. On exam he was alert and oriented with normal speech and thought content. Neuro exam was remarkable for horizontal and vertical nystagmus. CTA head and neck showed no significant stenosis or occlusion. Arterial carotid Doppler was normal. CT chest/abdomen/pelvis with IV contrast was unremarkable. MRI brain, non-contrast, showed moderate chronic microvascular ischemic changes. MRI C-spine was pertinent for severe right foraminal stenosis; suggesting possible radiculopathy of C4 and C6.

During the hospitalization he undergoes lumbar puncture. Results show 0 WBCs, 24,250 RBCs, and 121 mg/dl of protein. CSF studies were negative for HSV, VZV, and oligoclonal bands. CSF cultures were negative. Three days after admission he was discharged with methylprednisolone taper and valcyclovir for presumed viral labyrinthitis. CSF studies were felt to be from a traumatic tap, despite the elevated protein.

Two weeks after discharge, family brings the patient to the ER for hallucinations, confusion, personality changes, and labile emotions, as well as worsening ataxia. Admitting exam notes report laughing one moment then crying the next. Speech is very loud and animated; dictated by active hallucinations. He continues to have horizontal and vertical nystagmus.

Given that the infectious encephalitis workup previously was negative, but CSF studies showed elevated protein, neurology suggested treatment for presumed autoimmune encephalitis. He was started on high-dose IV methylprednisolone and quetiapine for behavioral disturbances without effect. Repeat lumbar puncture again showed elevated CSF protein (98 mg/dl); in addition to elevated IgG synthesis rate. EEG was consistent with a moderate degree of encephalopathy, but no underlying seizure activity. Repeat brain MRI stated "subtle signal hyperintensity on diffusion weighted sequences in the parietal cortex basal ganglia bilaterally; these can be seen in CJD". Plasmapheresis was then done for 5 days. This was followed by a trial of IVIG with IV steroids. All therapies were futile. About two weeks after the lumbar puncture was performed we received outside lab results confirming the 14-3-3 protein in CSF as well as elevated CSF tau level.

During this admission he progressively became less verbal and interactive, with lessened oral intake. Given the patients clinical presentation with this adjunctive laboratory data, we felt confident diagnosing this patient with CJD. Family eventually placed patient on hospice.

Discussion

CJD typically has an onset at the early to mid-60s. There are four recognized variations of CJD: sporadic, familial, variant, and iatrogenic. We will focus our discussion on the sporadic form as it is by far the most common; accounting for 85-95% of cases.[1]

CJD is a prion disease. Prions are abnormally folded proteins that act as pathogenic agents capable of inducing normal cellular proteins into pathological and "infectious" proteins. On histopathological examination the features of prion diseases include neuronal loss, glial cell proliferation, and vacuole formation that gives a spongiform appearance to brain tissue.[2] On gross visualization, the brain can appear atrophic.

The clinical presentation of a patient is variable. Myoclonus is notable in about 90% of patients at some point in the disease process.[3] Indications of extrapyramidal symptoms include hypokinesia, nystagmus, and ataxia. These can be the presenting symptoms in up to 40% of patients.[3] Cognitive changes can present in various ways as well. These include behavioral disturbances, concentration difficulty, lapses in memory, mood

changes, emotional lability, and sleep disturbances.[3] These features can make it difficult to differentiate dementia from CJD. However, the rapidity of progression of dementia-like symptoms increase likelihood of CJD.

In 1998, the World Health Organization (WHO) published diagnostic criteria for CJD. Since then, multiple organizations and publications have recommended revisions. The WHO criteria, include EEG abnormalities with, characteristic findings of periodic sharp wave complexes (PSWCs) which are not present until advanced stages of the disease. CSF biomarkers show the highest sensitivity. Multiple studies suggest that the presence of 14-3-3 protein in CSF is 92-96% sensitive for diagnosing sporadic CJD.[4] The 14-3-3 protein is a marker of neuronal destruction and therefore levels increase as the disease advances. In regards to imaging, brain MRI has highest yield. Suggestive findings include diffusion restriction in cortical regions or the caudate and putamen, with 92–96% sensitivity and 93–94% specificity for sporadic CJD.[5]

Despite the high sensitivities of the previous testing methods, there are confirmed CJD cases that demonstrate unremarkable EEG or MRI findings. A newer molecular technique, real-time quaking-induced conversion (RT-QuIC) has proven to be superior to the 14-3-3 protein detection due to its 100% specificity (80-90% sensitive).[6] CSF samples undergo RT-QuIC technique and detect the scrapie isoform of the prion protein (PrP^{Sc}) in a quantitative result. Given that RT-QuIC is a relatively non-invasive test, its use for the future seems to be very promising.

Unfortunately, currently there is no cure for CJD and death generally occurs within a year of symptoms. Treatment is supportive and directed at managing symptoms.

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