CLINICAL VIGNETTE

Creutzfeldt-Jakob Disease in an Emergency Department Patient

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Introduction

Altered mental status is unique in its diversity of etiologies, each with important considerations for diagnostic approaches and therapeutic interventions. Although altered mental status is a common presentation in the emergency department, Creutzfeldt-Jakob disease (CJD) is rare with fewer than 350 diagnosed cases in the United States annually, but with increasing incidence.[1] Low awareness of the disease coupled with CJD's often nonspecific presentation, particularly early in the disease, makes diagnosis challenging. CJD belongs to a family of diseases known as transmissible spongiform encephalopathies, or prion diseases, and carries a grim prognosis with a mean survival of 4-5 months from symptom onset.[2] We present a patient diagnosed with CJD after extensive work up and multiple prior emergency department visits.

Case Description

A 53-year-old Spanish-speaking man was brought into the emergency department (ED) by family for one week of acutely worsening mental status after recent extensive work up at an outside hospital for similar concerns. History was provided by a brother who reported first noticing abnormal behavior during a trip to El Salvador one month prior, as the patient uncharacteristically stopped communicating with family and his exact location was unknown for a full week. Once back in the US, the patient complained of a persistent mild headache. His family noticed that he appeared confused and was having trouble driving, with difficulty staying within his lane.

One day after returning from El Salvador the patient sought medical care at an outside facility for headaches and blurred vision. He was diagnosed with new hypertension and discharged home with an undetermined antihypertensive medication. Over the next few days the patient presented twice to an outside community hospital ED for "pounding in the front and back of head" and continued vision changes, and he was discharged with OTC pain medication for headaches. A couple of days after the second ED presentation the patient was found lying on the floor at a fast food restaurant speaking coherently, but in a very soft tone. EMS was dispatched and found the patient pale, eyes rolled back in his head, and unable to stand on his own. No tongue lacerations, incontinence, or disorientation to time was noted, but the patient did not know where he was. He was admitted to an outside hospital for neurological work up, had a reportedly negative MRI, and was discharged with meclizine with instructions to follow up with outpatient neurology.

A few days after discharge, family brought the patient again to a community ED with continued headaches, loss of balance, dizziness, and new sensation of "chest pain." Exam demonstrated truncal ataxia despite full strength, finger-nose-finger aberrations, and worsened balance when walking. He was transferred to a tertiary care center and hospitalized for two weeks where he received an extensive neurological and infectious disease workup. MRI and pan-CT were negative for any acute abnormalities. The patient was noted to have persistent ataxia, disequilibrium, and "waxing and waning mental status." EEG showed diffuse cortical slowing. The patient had two negative lumbar punctures, and negative serology for measles, mumps, herpes, varicella, RPR, and hepatitis. Baseline metabolic labs, B12, TSH, thiamine, and folic acid were unremarkable. A paraneoplastic panel returned unremarkable as well. He was started on a steroid taper which was discontinued after developing severe agitation concerning for steroid-induced psychosis. Ultimately, he was discharged neurologically compromised, unable to walk independently, with a new diagnosis of diabetes and suspected thiamine insufficiency, despite family insisting he had never been a "heavy drinker." He was sent home on metformin, famotidine, gabapentin, thiamine, and senna. He continued to worsen neurologically over the next several days, with development of incontinence, change in personality, and hallucinations, and was brought to our ED. Further historical investigation indicated no history or exposure to heavy metals, and no family history of early onset dementia or ataxia.

On presentation to our ED his vital signs were: BP = 133/99; HR = 114; RR=18; O2 Sat=99% on room air; T=97.4. On examination, the patient was mildly agitated with incoherent slurred speech, often pointing to hallucinations of people on the ceiling. He exhibited no obvious toxidrome, and no signs of trauma. He had a normal physical exam excluding neurologic abnormalities. He had no signs of meningismus nor stigmata of liver disease, and did not have a rash. On neurologic exam he was oriented to name only and was unable to attend or follow

commands, but did spontaneously move all four limbs. His reflexes were brisk with myoclonus bilaterally in the upper and lower extremities. A notable resting tremor was present with a kinetic component. He had severe ataxia on gait assessment, exhibiting lack of balance, irregular jerky movements, and staggering. Strength appeared 5/5 in both upper and lower extremities, and there were no overt sensory deficits.

Labs initially included: Point-of-care glucose, CBC, chemistry panel, LFTs, UA, CXR, urine toxicology, ammonia level, acetaminophen levels, as well as blood and urine cultures. All returned normal with only a slight elevation of white blood cell count to 13.4K. Additional pertinent labs that returned after admission were negative RPR, HIV, and normal TSH and B12. MRI brain demonstrated mild cortical hyperintensity in the frontal and parietal lobes consistent with nonspecific encephalitis, toxic/metabolic encephalopathy, or prion disease. EEG was notable for generalized slowing and characteristic sharp 1Hz sharp wave complexes consistent with diffuse cerebral dysfunction and prion disease respectively. Admission to the neurology service and further testing confirmed probable sporadic Creutzfeldt-Jakob disease (CJD) given: rapidly progressive dementia; and at least two clinical features including: myoclonus, visual or cerebellar signs, pyramidal/ extrapyramidal signs as well as exhibited akinetic mutism. Diagnosis was further supported with MRI notable for signal irregularities. Repeated lumbar puncture was negative for 14-3-3 CSF assays.

Discussion

We describe a challenging case of CJD in a Spanish speaking male presenting with rapidly progressive decline in cognitive and motor function. The approach to altered mental status in the ED must initially consider immediate life threats and reversible etiologies, and once initial stabilization of the patient has been attained a more thorough investigation is warranted. It is often worthwhile to build our differential based on a systems approach and the information gathered from history and physical exam. A useful mnemonic for a more systematic approach is AEIOU-TIPS.[3]

Initial approach for these patients should include a primary survey and consider common etiologies including but not limited to: assessment of the ABC's, cardiac monitoring and pulse oximetry, point-of-care glucose testing, intravenous access, evaluation for signs of trauma (consider c-spine stabilization), and consider naloxone administration if narcotic overdose is suspected. Once the patient is stable, we consider and address other potentially reversible causes of altered mental status. Using the AEIOU-TIPS framework here we considered the following: (A)Alcohol toxicity/withdrawal, (E) Epilepsy, Electrolytes, and Encephalopathy, (I) Insulin, (O) Opiates and Oxygen, (U) Uremia, (T) Trauma and Temperature, (I) Infection, (P) Poisons and Psychogenic, (S) Shock, Stroke, Subarachnoid Hemorrhage, and Space-Occupying Lesions.[3] Based on this framework some of the etiologies we considered in the context of the patient's PMH as well as recent evaluations were encephalopathy due to his recent hypertension diagnosis or infectious or autoimmune etiology (eg NMDA receptor encephalitis), electrolyte and metabolic sources, medication reaction or other poisoning (eg heavy metal), and endocrine disorders.[4] Primary central nervous system abnormalities such as subclinical status epilepticus or recurrent seizures are important to consider. The majority of patients with significant altered mental status will ultimately require admission unless a reversible cause is identified and able to be corrected in the ED. The hallmark of our patient's presentation, which made us suspect CJD in the ED, was the rapidly progressive dementia, especially in conjunction with ataxia and myoclonus, and his otherwise negative work up.[5] Patients such as the one described here presenting with rapidly progressive dementia warrant extended diagnostic workup besides standard methods and should include search for neoplasia as well as atypical encephalitis.[6]

We identified an important issue in our case. The family reported that in prior ED visits and medical evaluations appropriate translation services were not provided. Thus, the clinicians may not have obtained a complete or accurate history, and the family's understanding of the patient's condition was compromised. Language justice is an important social issue; failure to communicate with patients leads to inappropriate and incomplete work up, more revisits, and violates their civil rights.[7-9]

Initial presentation of sporadic CJD frequently occurs in the fifth decade of life with patients exhibiting an array of symptoms including rapidly progressing dementia, ataxia, and myoclonus. Confirmation of sporadic CJD diagnosis relies on updated 2018 CDC guidelines that stratifies patients into three categories, "definite," "probable," or "possible".[10,11] Positive immunohistochemistry defines "definite" and includes, post mortem pathology or western blot CSF analysis for hallmark protease resistant PrP, which was negative in our patient.[12] "Probable" is defined as presence of neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid or rapidly progressing dementia with at least 2/4 of the following cardinal features: myoclonus, visual or cerebellar signs, pyramidal/ extrapyramidal signs, akinetic mutism. This must be coupled with at least one positive result on EEG, 14-3-3 protein on CSF assay, or high signal in caudate/putamen on MRI. "Possible" CJD is defined as progressive dementia with 2/4 of the above cardinal features and negative for other routine investigations indicating an alternate diagnosis. At time of admission from the ED, our patient qualified as "probable" given his rapidly progressive dementia with the presence of at least 2/4 cardinal symptoms, and MRI results suggestive of the disease, and with an initially negative work up for other more common reversible etiologies.

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