Diagnostic Accuracy of CSF 14-3-3 Protein in Sporadic Creutzfeldt-Jakob Disease

Case Presentation

The Neurology service is consulted to assess a 55-year-old male with a history of depression who presents with rapidly progressing cognitive problems. The patient is seen on the medical wards with his wife, who provides most of the history. He used to work as an accountant and has a history of being very organized. About 6 months previously, the patient started to have problems at work. He started to show up late for meetings and miss deadlines. Initially, this was attributed to his depressed mood, as he was doing fewer and fewer of the things he usually did for fun. Despite seeing a psychiatrist and being started on citalopram for depression, his cognitive problems continued to progress. Over the months, he would repeatedly ask questions that he had recently been given the answer to and was very forgetful. He started having problems with multistep tasks and would often become distracted before finishing. On one occasion, he got lost driving home. Another time, he left the stove on and almost started a fire. During this period, he became more easily agitated and would yell at his children for the simplest mistakes. His wife states that, over the course of the last month, he has been moving more slowly and has started to experience falls. He has also been forced to leave work. Such problems continued to progress until the day of admission, when his wife started to notice brief jerks of his arms. There is no associated alteration in awareness with these jerks. These movements can be brought on when someone surprises the patient or when the patient hears loud noises.

His past medical history is significant for depression. There is no history of blood transfusions or nervous system surgeries.

His medications include citalopram.

He has no known drug allergies.

He does not smoke, abuse alcohol, or use illicit substances. The patient is married, with two teenaged children. He works as an accountant.

He has no family history of dementia or other neurologic problems.

In addition to what is noted above, a complete 14-topic review of systems is obtained and is unremarkable.
On physical examination, he is a well-developed and well-nourished male in no acute distress. His clothing is slightly disheveled. He is afebrile. His blood pressure is 110/70, pulse is 75, and respiratory rate is 12.

No bruits are heard over his neck. There are no murmurs or abnormal heart sounds.

He is alert but easily distracted. He is oriented to person, hospital, city, state, and country but he cannot tell you the floor of the building he is on. He knows the month but not the year or day. Registration is 2/3, and 5-minute recall is 0/3. He tries to spell the word *world* backwards. He is able to say “DL,” but after that he becomes distracted. He can name a pen and button. He repeats without difficulty. He has problems with multistep commands. His speech is fluent. The patient is slow in his responses.

Cranial nerve testing reveals pupils that are equal and reactive to light; optic discs are sharp, and visual fields are full on blink to threat. Extraocular muscles are intact. Facial sensation and strength are normal. Hearing is intact bilaterally to finger rub. Palate, tongue, and uvula are midline.

Motor strength is MRC grade 5/5 throughout. His tone is increased. The patient will have brief jerks of the arms that can be triggered by loud clapping of hands in front of him. He is bradykinetic.

He has normal pinprick, vibratory, and joint position sense in the extremities.

Reflexes are +3 throughout. Plantar responses are extensor bilaterally.

Coordination is abnormal with mild dysmetria on both finger-nose-finger and heel-knee-shin testing bilaterally.

He has a broad-based and unsteady gait.

You counsel the patient and his family that his presentation is quite concerning for a progressive neurologic process. Therefore, he will need an expedited workup, including laboratory screen, brain MRI, EEG, and lumbar puncture.

Over the next couple days, his results become available. He has unremarkable lab work for cell count, electrolytes, liver function testing, sedimentation rate, vitamin B12, HIV, heavy metals, thyroid studies, and rapid plasma reagin. His brain MRI shows cortical changes in the diffusion-weighted sequences. There is mild generalized cerebral atrophy. His EEG shows periodic synchronous triphasic sharp-wave complexes. His lumbar puncture shows normal cell count, glucose, protein, and VDRL (venereal disease research laboratory).

On the basis of the patient clinical presentation, examination, and diagnostic testing, you have a high suspicion for presence of sporadic Creutzfeldt-Jacob disease (sCJD). As guided by the recently published AAN evidence-based guideline “Diagnostic accuracy of
CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease, you send a CSF sample for 14-3-3 protein testing. You receive positive results for this testing a few weeks later. This result when viewed in the context of his presentation suggests that the patient has probable sCJD. Unfortunately, despite supportive care, he expires 5 months later (approximately 11 months after symptom onset). The family declines an autopsy.

Questions

1. With regard to the above case and the diagnosis of sCJD, which statement from the following list is correct?
   A. The positive result for protein 14-3-3 in the CSF confirms the diagnosis of sCJD.
   B. Only a pathological study of involved brain tissue can confirm the diagnosis.
   C. If the test result were negative, it would strongly suggest a different etiology.
   D. The MRI and EEG were unnecessary given the positive test result for 14-3-3 protein in the CSF.
   E. None of the above.

   **The correct answer is B.** Testing for presence of the 14-3-3 protein in the CSF lacks the diagnostic accuracy either to make a diagnosis of sCJD or to rule out the disease with absolute certainty; pathological examination is the gold standard for diagnosis.

2. In the above case scenario, testing for the presence of CSF 14-3-3 protein:
   A. Was very helpful to the clinician in order to diagnose sCJD.
   B. May have caused further confusion because it could have yielded a false-positive result.
   C. The diagnosis of sCJD could have been made with a similar level of confidence without testing for presence of the 14-3-3 protein.
   D. Was the most important part of the patient’s assessment.
   E. None of the above.

   **The correct answer is C.** The patient presented with rapidly progressing dementia and neurologic deficits involving the pyramidal and extrapyramidal systems. The physician already had evidence of a normal CSF and a suggestive MRI and EEG. The prediagnostic probability of sCJD was very high before the 14-3-3 protein test was ordered, and therefore the positive test result increased the suspicion only minimally (see figure 2 in the published guideline).

3. In a scenario where a 69-year-old male is suffering from cognitive decline spanning 20 months, along with normal routine laboratory workup of cognitive impairment, imaging, and EEG, testing the CSF for 14-3-3 protein:
   A. Would significantly influence the opinion of the clinician regarding sCJD if the test result is positive.
   B. Would rule out sCJD if the test result is negative.
   C. Should be repeated if the test result is negative.
   D. Is unnecessary in this scenario.
   E. A, B, and C are correct.
The correct answer is D. In this scenario, the pretest probability for sCJD is low. This is a situation where neither a positive nor negative test result would be helpful. It would be more important to continue assessing for a reversible cause or a degenerative disorder, or both.

Diagnosis Coding$^{2,3}$

ICD-9-CM codes are used for diagnosis coding in the United States until October 1, 2014. At that time ICD-10-CM becomes the official classification system for diagnosis coding.

This is a case study and not chart documentation. There is no diagnostic statement; only the information given to the family. We do not know if the patient was in the hospital when the initial study results were available. We do not know when the patient was discharged and whether he or she was at home or in an extended-care facility at the time of death. All that information is very important for correct diagnosis coding in this particular case.

ICD-9-CM and ICD-10-CM treat the modifiers “probable,” “possible,” “suspected,” and “rule out” differently in the inpatient (includes extended-care facility) and outpatient settings. In the inpatient setting, any diagnosis preceded by these modifiers is coded as if that diagnosis were confirmed at discharge. In the outpatient setting the diagnosis following these modifiers may not be used, and symptoms must be coded instead. This distinction does not usually cause problems, but in the case of sCJD, the CDC criteria assigns “probable” to sCJD in a patient such as this with dementia, ataxia, myoclonus, and typical EEG changes (in this case also positive 14-3-3 protein). Had this diagnosis been obtained in the outpatient setting, according to the ICD-9-CM Official Guidelines for Coding and Reporting and ICD-10-CM Official Guidelines for Coding and Reporting, the codes reported would be those for the symptoms of dementia, ataxia, and myoclonus. Fortunately, on the death certificate, the diagnosis Probable sCJD may be used and would be picked up by CDC for surveillance data.

Remember: In the outpatient setting, avoid using the terms “probable,” “possible,” “suspected,” and “rule out.” If these terms are an official diagnosis based on accepted criteria, then only the symptoms (which must also be documented) may be used for diagnosis coding. In the inpatient setting, anytime these modifiers are used, the discharge code will assume this diagnosis has been confirmed. So if you do use these terms in the hospital, be aware that your patient then receives that diagnosis on all billing documents and for morbidity reporting as if it had been confirmed.
At the time of the consultation, the only statement in the case study is “concern for a progressive neurologic process.” There is no diagnosis code for “progressive neurologic process.” The diagnostic statement should include the symptoms of dementia, ataxia, and myoclonus. If that documentation did exist, then the codes for that consultation would be:

ICD-9-CM:
   290.10 Presenile dementia, uncomplicated
   781.3 Lack of coordination
   333.2 Myoclonus

ICD-10-CM
   F03.90 Unspecified dementia without behavioral disturbance
   R27.0 Ataxia, unspecified
   G25.3 Myoclonus

When the decision is made to send off the CSF sample for 14-3-3-protein, it is not clear if there is a patient encounter on that same day. If there was an encounter, diagnosis coding depends on what was written in the chart and the location of the patient. If the physician states that this patient has Probable sCJD (as by CDC and other criteria mentioned in the guideline), then outpatient coding would remain unchanged from that listed above. If the encounter was during an inpatient visit or at an extended-care facility, the coding would become:

ICD-9-CM:
   046.19 Other and unspecified Creutzfeldt-Jacob disease

ICD-10-CM
   A81.09 Other Creutzfeldt-Jacob disease

Though this appears difficult, and the site where the patient is evaluated changes morbidity reporting, coding rules in the United States determine that only symptoms would be coded in the outpatient setting if “sCJD” is preceded by “probable.”

If the patient expired at home, there would be no encounter to code, but every outpatient encounter prior to death would use only symptoms for coding the probable sCJD. If the patient expired in a hospital or extended-care facility, the discharge coding would be the same as on the death certificate. Regardless of the place of death, the death certificate would reflect the final diagnosis:

ICD-9-CM:
   046.19 Other and unspecified Creutzfeldt-Jacob disease

ICD-10-CM
   A81.09 Other Creutzfeldt-Jacob disease
Evaluation and Management Coding
It is assumed the patient is not a Medicare recipient and has insurance with a private insurance company. The patient is a consult in the hospital, and one could bill for code 99255 (level 5 consult), as the history and physical examination are comprehensive and the medical decision making is of high complexity (new patient to the neurologist and a high risk of the morbidity, mortality, and complications). If the patient receives Medicare, the billing code would be 99223.4

It is not possible to determine billing for subsequent hospital care, as there is no information provided about changes in the patient, repeat examination, and lab testing on separate days. It also is not apparent how much time is spent with the patient on subsequent hospital days so one could bill for counseling and coordination of care.

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