Sudden-onset memory problems, visual hallucinations, and odd behaviors

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Ms. D, age 62, is disoriented, distractible, tearful, and tangential. She reports that 'aerialists' are climbing through her windows at night and stealing things. What could be causing her symptoms?

CASE A rapid decline

Ms. D, age 62, presents to a psychiatric emergency room (ER) after experiencing visual hallucinations, exhibiting odd behaviors, and having memory problems. On interview, she is disoriented, distractible, tearful, and tangential. She plays with her shirt and glasses, and occasionally shouts. She perseverates on "the aerialists," acrobatic children she has been seeing in her apartment. She becomes distressed and shouts, "I would love to just get them!"

Ms. D is unable to provide an account of her history. Collateral information is obtained from her daughter, who has brought Ms. D to the ER for evaluation. She reports that her mother has no relevant medical or psychiatric history, and does not take any medications, except a mixture of Chinese herbs that she brews into a tea.

Ms. D's daughter says that her mother began to deteriorate 5 months ago, after she traveled to California to care for her sister, who was seriously ill and passed away. After Ms. D returned, she would cry frequently. She also appeared "spaced out," complained of feeling dizzy, and frequently misplaced belongings. Three months before presenting to the ER, she began to experience weakness, fatigue, and difficulty walking. Her daughter became more worried 2 months ago, when Ms. D began sleeping with her purse and hiding her belongings around their house. When asked about these odd behaviors, Ms. D claimed that "the aerialists" were climbing through her windows at night and stealing her things.

A week before seeking treatment at the ER, Ms. D's daughter had taken her to a neurologist at another facility for clinical evaluation. An MRI of the brain showed minimal dilation in the subarachnoid space and a focal 1 cm lipoma in the anterior falx cerebri, but was otherwise unremarkable. However, Ms. D's symptoms continued to worsen, and began to interfere with her ability to care for herself.

The team in the psychiatric ER attributes Ms. D's symptoms to a severe, psychotic depressive episode. They admit her to the psychiatric inpatient unit for further evaluation.

Which features of Ms. D's presentation suggest an organic rather than a psychiatric etiology?

a) the onset of her symptoms relatively late in life
b) her rapid decline in function
c) her visual hallucinations
d) her complaint of feeling dizzy
e) all of the above

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The authors' observations

Ms. D was plagued by several mood and psychotic symptoms. Such symptoms can arise from many different psychiatric or organic etiologies. In Ms. D's case, several aspects of her presentation suggest that her illness was psychiatric. The severe illness of a beloved family member is a significant stressor that could cause a great deal of grief and devastation, possibly leading to depression. Indeed, Ms. D's daughter noticed that her mother was crying frequently, which is consistent with grief or depression.

Memory problems, which might manifest as misplacing belongings, can also indicate a depressive illness, especially in older patients. Moreover, impaired concentration, which can cause one to appear "spaced out" or distractible, is a core symptom of major depressive disorder. Sadness and grief also can be appropriate during bereavement and in response to significant losses. Therefore, in Ms. D's case, it is possible her frequent crying, "spaced out" appearance, and other mood symptoms she experienced immediately after caring for her sister were an appropriate response to her sister's illness and death.

However, other aspects of Ms. D's presentation suggested an organic etiology. Her rapid deterioration and symptom onset relatively late in life were consistent with dementia and malignancy. Her complaint of feeling dizzy suggested a neurologic process was affecting her vestibular system. Finally, while psychiatric disorders can certainly cause visual hallucinations, they occur in only a small percentage of cases.[1] Visual hallucinations are commonly associated with delirium, intoxication, and neurologic illness.

EVALUATION Severe impairment

On the psychiatric inpatient unit, Ms. D remains unable to give a coherent account of her illness or recent events. During interviews, she abruptly shifts from laughing to crying for no apparent reason. While answering questions, her responses trail off and she appears to forget what she had been saying. However, she continues to speak at length about "the aerialists," stating that she sees them living in her wardrobe and jumping from rooftop to rooftop in her neighborhood.

A mental status examination finds evidence of severe cognitive impairment. Ms. D is unable to identify the correct date, time, or place, and appears surprised when told she is in a hospital. She can repeat the names of 3 objects but cannot recall them a few minutes later. Finally, she scores a 14 on the Mini-Mental State Examination (MMSE) and a 5 on the Montreal Cognitive Assessment (MoCA), indicating severe impairment.

On the unit, Ms. D cannot remember the location of her room or bathroom, and even when given directions, she needs to be escorted to her destination. Her gait is unsteady and wide-spaced, and she walks on her toes at times. When food is placed before her, she needs to be shown how to take the lids off containers, pick up utensils, and start eating.

All laboratory results are unremarkable, including a complete blood count, basic metabolic panel, liver function tests, gamma-glutamyl transpeptidase, magnesium, phosphate, thyroid-stimulating hormone, vitamin B12, methylmalonic acid, homocysteine, folate, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rapid plasma reagin, human immunodeficiency virus, and Lyme titers. The team also considers Ms. D's history of herbal medicine use, because herbal mixtures can contain heavy metals and other contaminants. However, all toxicology results are normal, including arsenic, mercury, lead, copper, and zinc.

To address her symptoms, Ms. D is given risperidone, 0.5 mg twice a day, and donepezil, 5 mg/d.

What should the psychiatry team do next?

a) repeat the MRI of the brain and consult the neurology team

b) consult the medical team and assess for an underlying malignancy

Clinical Point

Visual hallucinations are commonly associated with delirium, intoxication, and neurologic illness

Clinical Point

Sporadic CJD typically occurs in patients in their 60s and quickly leads to death

Table

Red flags for Creutzfeldt-Jakob disease in psychiatric patients

Dementia (sudden onset, rapidly progressive)
Myoclonus
Akinetic mutism
Visual symptoms (ie, cortical blindness)
Cerebellar symptoms
Extrapyramidal symptoms
Sleep disturbances
Chorea

c) diagnose the patient with a neurocognitive disorder and discharge her to a nursing home

The authors' observations

Despite her persistent psychiatric symptoms, Ms. D had several neurologic symptoms that warranted further investigation. Her abrupt shifts from laughter to tears for no apparent reason were consistent with pseudobulbar affect. Her inability to remember how to use utensils during meals was consistent with apraxia. Finally, her abnormal gait raised concern for a process affecting her motor system.

OUTCOME A rare disorder

Given the psychiatry team's suspicions for a neurologic etiology of Ms. D's symptoms, an MRI of her brain is repeated. The results are notable for abnormal restricted diffusion in the caudate and putamen bilaterally, which is consistent with Creutzfeldt-Jakob disease (CJD). EEG shows moderate diffuse cerebral dysfunction, frontal intermittent delta activity, and diffuse cortical hyperexcitability, consistent with early- to mid-onset prion disease. Upon evaluation by the neurology team, Ms. D appears fearful, suspicious, and disorganized, but her examination does not reveal additional significant sensorimotor findings.

Ms. D is transferred to the neurology service for further workup and management. A lumbar puncture is positive for real-time quaking-induced conversion (RT-QuIC) and 14-3-3 protein with elevated tau proteins; these findings also are consistent with CJD. She develops transaminitis, with an alanine transaminase (ALT) of 127 and aspartate transaminase (AST) of 355, and a malignancy is suspected. However, CT scans of the chest, abdomen, and pelvis show no evidence of malignancy, and an extensive gastrointestinal workup is unremarkable, including anti-smooth muscle antibodies, anti-liver-kidney microsomal antibody, anti-mitochondrial antibodies, gliadin antibody, alpha-1 antitrypsin, liver/kidney microsomal antibody, and hepatitis serologies. While on the neurology service, risperidone and donepezil are discontinued because the findings indicate she has CJD and there are concerns that risperidone may be contributing to her transaminitis.

After discontinuing these medications, she is evaluated by the psychiatry consult team for mood lability. The psychiatry consult team recommends quetiapine, which is later started at 25 mg nightly at bedtime.

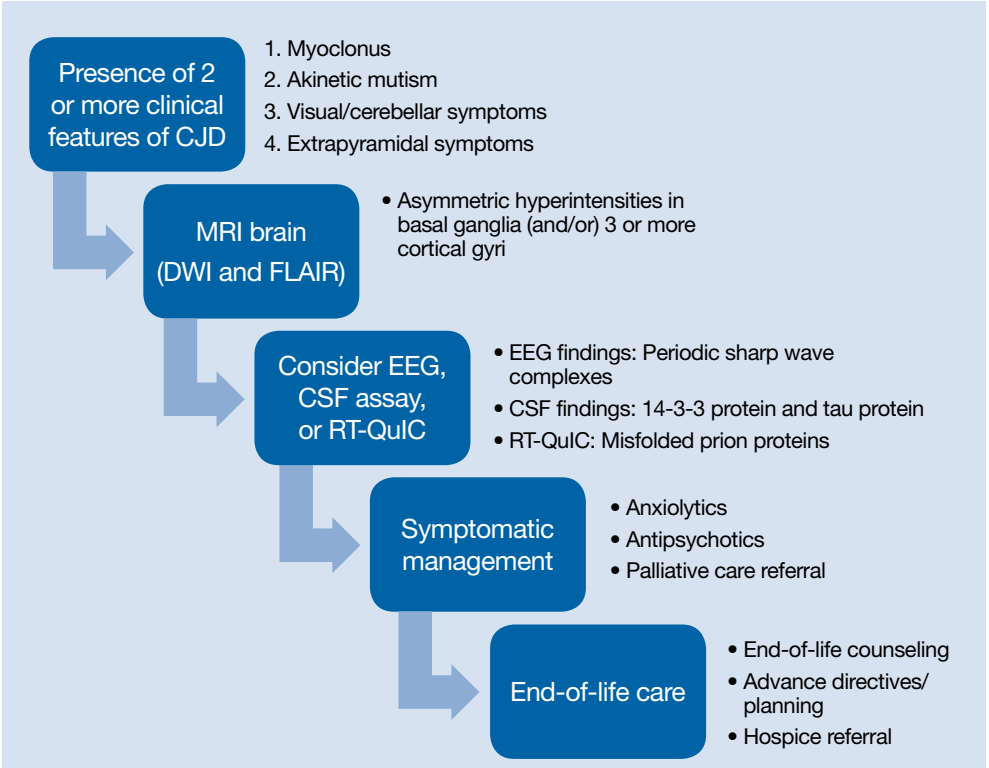
Clinically, Ms. D's mental status continues to deteriorate. She becomes nonverbal and minimally able to follow commands. She is ultimately discharged to an inpatient hospice for end-of-life care and the team recommends that she continue with quetiapine once there.

The authors' observations

CJD is a rare, rapidly progressive, fatal form of dementia. In the United States, the incidence is approximately 1 to 1.5 cases per 1 million people each year.[2] There are various forms of the disease. Sporadic CJD is the most common, representing 85% of cases.[3] Sporadic CJD typically occurs in patients in their 60s and quickly leads to death—50% of patients die within 5 months, and 90% of patients die

Figure

Proposed algorithm for diagnosis and management of Creutzfeldt-Jakob disease



CJD: Creutzfeldt-Jakob disease; DWI: diffusion weighted imaging; FLAIR: fluid-attenuated inversion recovery; RT-QuIC: real-time quaking-induced conversion

within 1 year.[2,3] The illness is hypothesized to arise from the production of misfolded prion proteins, ultimately leading to vacuolation, neuronal loss, and the spongiform appearance characteristic of CJD.[3,4]

Psychiatric symptoms have long been acknowledged as a feature of CJD. Recent data indicates that psychiatric symptoms occur in 90% to 92% of cases.[5,6] Sleep disturbances and depressive symptoms, including vegetative symptoms, anhedonia, and tearfulness, appear to be most common.[5] Psychotic symptoms occur in approximately 42% of cases and may include persecutory and paranoid delusions, as well as an array of vivid auditory, visual, and tactile hallucinations.[5,7]

There is also evidence that psychiatric symptoms may be an early marker of CJD.[5,8] A Mayo Clinic study found that psychiatric symptoms occurred within the prodromal phase of CJD in 26% of cases, and psychiatric symptoms occurred within the first 100 days of illness in 86% of cases.[5]

Case reports have described patients with CJD who initially presented with depression, psychosis, and other psychiatric symptoms.[9-11] Interestingly, there have been cases with only psychiatric symptoms, and no neurologic symptoms until relatively late in the illness.[10,11] Several patients with CJD have been evaluated in psychiatric ERs, admitted to psychiatric hospitals, and treated with psychiatric medications and ECT.[5,9] In one study, 44% of CJD cases were

Clinical Point

Evidence suggests that psychiatric symptoms may be an early marker of CJD

misdiagnosed as "psychiatric patients" due to the prominence of their psychiatric symptomatology.[8]

Making the diagnosis in psychiatric settings. Often, the most difficult aspect of CJD is making the diagnosis.[3,12] Sporadic CJD in particular can vary widely in its clinical presentation.[3] The core clinical feature of CJD is rapidly progressive dementia, so suspect CJD in these patients. However, CJD can be difficult to distinguish from other rapidly progressive dementias, such as autoimmune and paraneoplastic encephalopathies.[2,3] The presence of neurologic features, specifically myoclonus, akinetic mutism, and visual, cerebellar, and extrapyramidal symptoms, should also be considered a red flag for the disorder[3] (***Table, page 50***).

Finally, positive findings on MRI, EEG, or CSF assay can indicate a probable diagnosis of CJD.[13] MRI, particularly diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR), is recognized as the most studied, sensitive, and overall useful neuroimaging modality for detecting CJD.[2,3,12] Although the appearance of CJD on MRI can vary widely, asymmetric hyperintensities in ≥3 cortical gyri, particularly in the frontal and parietal lobes, provide strong evidence of CJD and are observed in 80% to 81% of cases.[4,12] Asymmetric hyperintensities in the basal ganglia, particularly the caudate and rostral putamen, are observed in 69% to 70% of cases.[4,12,13]

EEG and CSF assay also can be useful for making the diagnosis. While diffuse slowing and frontal rhythmic delta activity appear early in the course of CJD, periodic sharp wave complexes emerge later in the illness.[4] However, EEG findings are not diagnostic, because periodic sharp wave complexes are seen in only two-thirds of CJD cases and also occur in other neurologic illnesses.[3,4] In recent years, lumbar puncture with subsequent CSF testing has become increasingly useful in detecting the illness. The presence of the 14-3-3 protein and tau protein is highly sensitive, although not specific, for CJD.[3] A definite diagnosis of CJD requires discovery of the misfolded prion proteins, such as by RT-QuIC or brain biopsy.[2,3,13]

Management of CJD in psychiatric patients. CJD is an invariably fatal disease for which there is no effective cure or disease modifying treatment.[2] Therefore, supportive therapies are the mainstay of care. Psychotropic medications can be used to provide symptom relief. While the sleep disturbances, anxiety, and agitation/hallucinations associated with CJD appear to respond well to hypnotic, anxiolytic, and antipsychotic medications, respectively, antidepressants and mood-stabilizing medications

Related Resources

- National Institute of Neurological Disorders and Stroke. Creutzfeldt-Jakob disease fact sheet. http://www.ninds.nih.gov/disorders/cjd/detail_cjd.htm.
- Centers for Disease Control and Prevention. Creutzfeldt-Jakob disease, classic (CJD). http://www.cdc.gov/prions/cjd.

Drug Brand Names

Donepezil • Aricept
Quetiapine • Seroquel
Risperidone • Risperdal

Clinical Point

The core clinical feature of CJD is rapidly progressive dementia

Bottom Line

Patients with Creutzfeldt-Jakob disease (CJD) may present to psychiatric settings, particularly to a psychiatric emergency room. Consider CJD as a possible etiology in patients with rapidly progressive dementia, depression, and psychosis. CJD is invariably fatal and there is no effective disease-modifying treatment. Supportive therapies are the mainstay of care.

appear to have little benefit for patients with CJD.[5] During the final stages of the disease, patients may suffer from akinetic mutism and inability to swallow, which often leads to aspiration pneumonia.[14] Patients should also be offered end-of-life counseling, planning, and care, and provided with other comfort measures wherever possible (***Figure, page 51***).

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Clinical Point

Supportive therapies are the mainstay of care for CJD