MAYO CLINIC

58-Year-Old Woman With Diarrhea, Weakness, and Memory Loss

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A 58-year-old woman with a medical history of osteoporosis and Crohn disease presents with her husband for evaluation of chronic diarrhea. Her medications included mesalamine and alendronate, as well as an over-the-counter multivitamin. Recently, Crohn colitis had been diagnosed when colon biopsies revealed scattered colonic inflammation and ulcerations. In addition to unrelenting diarrhea during the months before her presentation, she had experienced a severe functional decline. Six months before her visit, the patient could care for herself and walk several miles at a time without trouble. More recently, the patient was completely reliant on her husband for her daily activities.

Her husband described progressively worsening fatigue, weakness, confusion, and memory loss, in addition to an unintended weight loss of 11.25 kg over the previous year. She reported no fevers, chills, night sweats, headaches, vision changes, or incontinence of urine or stool. She did not drink alcohol or use illicit drugs. On physical examination, her vital signs were within normal limits. She was cachectic and ill-appearing. She had substantial ideomotor and gait apraxia, was unable to ambulate without assistance, and had slowing of bilateral rapid alternating movements. Her Kokmen Short Test of Mental Status score was 20 (maximum score, 38), with the greatest deficiencies occurring in calculation, construction, and recall. The rest of her examination results were unremarkable.

1. **In addition to routine blood count, chemistries, and thyroid function tests, which *one* of the following would be *most helpful* in the initial evaluation of this patient?**
   a. Electroencephalography
   b. Fecal calprotectin test
   c. *APOE* ε4 genetic assay
   d. Human immunodeficiency virus (HIV) antibody/antigen test
   e. Stereotactic brain biopsy

This patient presented with substantial cognitive decline that met criteria for a neurocognitive disorder. Both gastrointestinal tract and central nervous system disorders have many possible causes, but attention should be focused on those that are reversible. Electroencephalography detects abnormal electrical activity in the brain. Its main use is for diagnosis of seizure. This patient's symptoms were not episodic and were associated with a progressive functional decline, making a diagnosis of epilepsy less likely. Fecal calprotectin is a biomarker associated with inflammatory bowel disease, a diagnosis this patient has already; although it may explain her gastrointestinal tract symptoms, it does not account for the neurologic decline.[1] The ε4 variant of the *APOE* gene is a known risk factor for sporadic late-onset Alzheimer disease. Its utility as a diagnostic tool has not been established and certainly should not be part of an initial evaluation. Dementia associated with HIV may lead to severe neurocognitive deficits and substantial functional impairment. The fact that the patient did not disclose risk factors for HIV infection in her history does not mean that she should not be tested for this infection. She also noted unintentional weight loss and chronic diarrhea, which also could be related to HIV/AIDS infection. Other opportunistic infections associated with HIV also could lead to her neurocognitive changes and functional decline. Testing for HIV is the highest-yield test in this case. A brain biopsy is not indicated as part of the initial evaluation. Knowing what to biopsy without any previous imaging would be difficult, and it is inappropriate without exhausting noninvasive diagnostics.

See end of article for correct answers to questions.

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The patient was referred to the neurology service for further evaluation of the progressive functional decline. Magnetic resonance imaging (MRI) of the brain revealed moderate generalized brain atrophy disproportionate to patient age. Positron emission tomography (PET) of the head revealed decreased fluorodeoxyglucose uptake throughout the brain parenchyma. An HIV antibody/antigen screening was obtained as part of the neurologic evaluation. The test was positive, and the patient was referred to the infectious diseases clinic for further evaluation. The patient reported a monogamous relationship with her husband and no extramarital sexual encounters. She had no history of other sexually transmitted infections, and she did not have a history of blood transfusion. Previously, she had never been screened for HIV.

Additional testing revealed an HIV-1 viral load of 900,000 copies/mL and a CD4 count of 25 cells/μL (365-1437 cells/μL). Urine nucleic acid amplification screening was negative for chlamydia and gonorrhea. A syphilis test result was also negative. Results of viral hepatitis serologies and testing for *Toxoplasma* IgG antibodies were negative, but serologic testing for *Cytomegalovirus* (CMV) IgG antibodies yielded positive results. An interferon-γ-release assay was negative for latent tuberculosis.

2. Which *one* of the following is the *most appropriate* next step in evaluation of this patient's neurocognitive decline?

a. Computed tomography of the chest, abdomen, and pelvis
b. PET of the body
c. Lumbar puncture (LP)
d. Ophthalmologic evaluation
e. Initiation of antiretroviral therapy (ART) while awaiting the HIV genotype result

The diagnosis of HIV in this patient helps to narrow the most likely differential diagnosis for her neurocognitive decline and therefore guides the next diagnostic steps. Computed tomography of her chest, abdomen, and pelvis and PET body imaging are not the most valuable or cost-effective tests to perform at this step of the evaluation, as her weight loss most likely can be attributed to advanced HIV infection rather than occult malignancy. An LP is the most appropriate next step to evaluate for opportunistic infection such as central nervous system CMV or progressive multifocal leukoencephalopathy (PML). Cerebral toxoplasmosis is a possibility but is highly unlikely without characteristic imaging findings. Although no focal findings were noted on brain MRI, ruling out infection is important. Further, to make the diagnosis of HIV-associated neurocognitive disorder, concomitant infection must be excluded. Ophthalmologic evaluation is indicated in this patient to evaluate for CMV retinitis given her low CD4 count, but LP is a better option for the evaluation of the neurocognitive decline. Genotypic resistance testing is necessary for determination of the initial antiretroviral regimen, as up to 17% of new infections in high-income countries have antiretroviral resistance.[2]

The patient underwent LP for evaluation of opportunistic infections that might have led to her neurologic symptoms. A cerebrospinal fluid (CSF) specimen contained 7 nucleated cells per high-power field (0-5 cells per high-power field), no red blood cells, normal glucose level, and a protein level of 74 mg/dL (0-35 mg/dL). The opening pressure was normal. Tests of CSF for syphilis (Venereal Disease Research Laboratory test), cryptococcal antigen, and polymerase chain reaction (PCR) for CMV, Epstein-Barr virus, herpes simplex virus, and John Cunningham virus yielded negative results.

3. Which *one* of the following is the *most likely* cause of this patient's neurocognitive decline?

a. Alzheimer disease
b. HIV-associated dementia
c. PML
d. Neurosyphilis
e. Normal pressure hydrocephalus

The results of the patient's neuroimaging and CSF studies are very helpful in determining the most likely cause of her neurocognitive decline. Alzheimer disease would not have progressed as rapidly as did this patient's clinical course. Dementia associated with HIV is the most likely cause of her neurologic decline. The patient's brain MRI did not reveal multifocal subcortical white matter demyelination, nor was the PCR positive for John

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