Clinical Reasoning: A 59-year-old man who became lost in his own home

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SECTION 1

A 59-year-old right-handed man was referred to the Memory Center of an academic hospital for progressive cognitive decline. His past medical history included hypertension, diabetes mellitus, and prostate cancer. There was no family history of any psychiatric or neurologic disorders.

The patient's symptoms began 3 years prior to presentation with memory loss and word-finding difficulties. Six months later, his wife observed a progressive loss of interest in his previous hobbies and increasing apathy. Twelve months after symptom onset, the patient began having trouble finding his way home when driving. At the same time, his wife observed a personality change, describing her husband as "childlike," and said he began to follow her wherever she went. A year later, the patient developed difficulties with reading and spelling and became unable to plan ahead. His memory for events deteriorated and he had difficulty recognizing familiar faces. He became preoccupied over an old conflict with his son. He was unable to perform everyday activities autonomously. His difficulties in spatial orientation progressed until he ultimately got lost in the home he had lived in for 10 years. Prior to presentation, he began making sexually inappropriate comments that contrasted with his concurrent loss of libido.

The neuropsychological evaluation upon admission revealed a severe amnestic syndrome, difficulties in naming and verbal comprehension, visuospatial impairment, a cognitive and behavioral prefrontal syndrome, and multimodal visual agnosia including prosopagnosia. The rest of the neurologic examination was normal.

Questions for consideration:

1. What is early-onset dementia?
2. What are the etiologies of early-onset dementia?
3. What is the diagnostic strategy?

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SECTION 2

The International Classification of Diseases–10 criteria[1] for dementia include "impairment of memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment." Early-onset dementia (EOD) is defined as dementia occurring before the age of 65,[2] a cutoff determined by prevalence rates in epidemiologic studies.

The clinical characteristics of EOD are different from those of late-onset dementia. EOD affects males more often than females, the duration from disease onset to the first consultation is longer, the progression of the dementia is slower, finding a nondegenerative etiology (e.g., traumatic brain injury, toxin) is more likely, and the prevalence of frontotemporal lobe degeneration is higher than in late-onset dementia.[3]

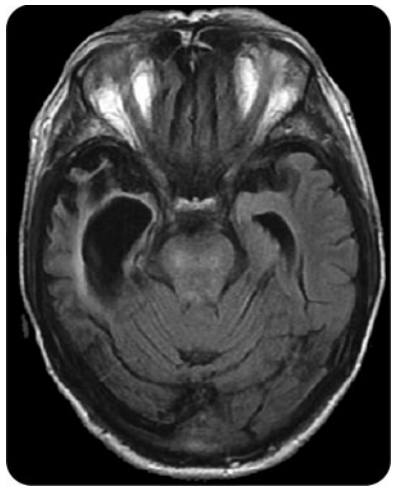
In this case, progressive worsening over a 3-year period is a strong argument in favor of a neurodegenerative process. Nevertheless, as mentioned above, the high prevalence of nondegenerative causes of dementia, the heterogeneity of etiologies, and potentially curable diseases in EOD[4] all require a systematic approach.

First, potentially curable causes of dementia should be excluded. MRI can evaluate for neoplastic, vascular, traumatic (traumatic brain injury, dementia pugilistica), or inflammatory (multiple sclerosis) lesions. Laboratory tests assess the most frequent endocrine and metabolic disorders (thyroid, parathyroid, B12, thiamine, folate and niacin deficiencies, hypoglycemia, hepatic encephalopathy, renal failure). Viral and bacterial serologies can rule out HIV and syphilis. An EEG looks for epileptic disorders and encephalopathies. Lumbar puncture for CSF can detect infectious causes of dementia such as chronic infectious meningitis, Creutzfeldt-Jakob disease, and other prions.

Depending on the results of the abovementioned studies and the clinical context, the evaluation could also include testing for Lyme disease, Whipple disease, subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, sarcoidosis, Hashimoto encephalopathy, paraneoplastic encephalopathy, and heavy metal poisoning. Laboratory tests of the adrenal and pituitary functions could be performed. Metabolic studies can assess for leukodystrophies, encephalopathies, and porphyria. If sleep apnea is suspected, polysomnography can be undertaken. If imaging suggests normal pressure hydrocephalus, a CSF depletion test could be done.

If the evaluation remains inconclusive, degenerative etiologies should be considered. When pyramidal, peripheral, or bulbar signs are present, electroneuromyogram should be performed to document dementia associated with a motor neuron or muscle disorder. When pyramidal, cerebellar, or choreiform movements are observed, a genetic study for Huntington disease or spinocerebellar ataxia should be performed. Motor impairment or a concurrent movement disorder suggests subcortical causes of dementia such as Parkinson disease dementia, progressive supranuclear palsy, and corticobasal degeneration. Finally, global (Alzheimer disease) or lobar predominant (frontotemporal lobe degeneration) cortical dementias need to be considered.

Figure Fluid-attenuated inversion recovery MRI



Axial section through the temporal lobes showing significant right temporal lobe atrophy.

If the pattern of atrophy is not suggestive of a specific type of degenerative disease, metabolic imaging can be performed (brain perfusion imaging) to further differentiate between the cortical dementias. Positive Tau, phosphotau, and beta-amyloid titers in CSF can help diagnose AD.[5]

In this patient, the routine laboratory tests, vitamin levels (B12, folate), CSF analysis (presence of cells, protein and glucose levels, A-beta42, and tau protein levels), and serologies (HIV, syphilis) were all normal. The EEG showed a preserved alpha rhythm with a widespread increase in theta activity, predominately in the temporal regions. The MRI showed bilateral temporal lobe atrophy, markedly more severe on the right side (figure), while the other cortical regions, including the frontal lobes, were normal. There were no white matter abnormalities.

Question for consideration:

1. What is the most probable diagnosis?

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SECTION 3

The most likely diagnosis is a right temporal variant of frontotemporal lobe degeneration (RV-FTLD).

The clinical syndrome of FTLD is characterized by the insidious onset of behavioral disturbances, personality changes, and aphasia.[6] Despite a wide overlap between the FTLD subtypes, 3 different syndrome variants are recognized depending on the preeminent symptoms and the pattern of brain atrophy.[7] The behavioral variant of FTLD is characterized by personality changes and behavioral disturbances associated with a severe dysexecutive syndrome. In this subtype, atrophy occurs predominately in the right frontal regions. The progressive nonfluent aphasia variant of FTLD is characterized by a progressive loss of vocabulary, nonfluent speech output, and agrammatism. Atrophy predominates in the left frontal regions. The semantic dementia variant of FTLD is a verbal-associative agnosia characterized by a progressive loss of word sense and object knowledge with personality changes appearing later. This subtype is characterized by left temporal atrophy.

From a neuropathologic point of view, more than 15 different pathologies can underlie FTLD syndromes, which can be divided into 3 groups: 1) tauopathies with an accumulation of microtubule-associated protein tau (MAPT); 2) accumulation of ubiquitinated neocortical lesions called TAR DNA binding protein 43 (TDP-43); and 3) atrophy and gliosis without specific abnormalities, called "dementia lacking distinctive histopathology."[7]

The right temporal variant is a fourth and rare subtype of frontotemporal lobe degeneration. For a long time, prosopagnosia was considered the main and earliest clinical feature of the syndrome. Affected patients exhibit progressive difficulties in recognizing and identifying the faces of familiar persons due to the multimodal loss of person-based knowledge.[8] Thus, the right temporal variant of frontotemporal lobar degeneration can be considered to be the right hemispheric variant of semantic dementia.

Recently, investigators delineated the cognitive profile of RV-FTLD.[9] They observed that the most frequent symptom is impaired episodic memory (90% of patients) which can appear prior to prosopagnosia, which is less frequent, affecting 60%. Another common symptom is topographic disorientation (getting lost) in familiar places (65%). Some additional symptoms are less frequently observed but are suggestive in this context: hyper-religiosity (15%), complex visual hallucinations (10%), and difficulties in performing calculations (5%). Finally, more typical symptoms of FTLD are also seen, such as apathy, disinhibited social conduct, alteration in eating habits, changes in food preferences, and mood disturbances. There is significant overlap in symptomatology between the different subtypes of FTLD, but the core symptoms of RV-FTLD are getting lost, prosopagnosia, and behavioral disorders.[9]

RV-FTLD is an unusual subtype of FTLD. Neurologists need to be aware of the clinical characteristics of this entity, which have recently been described, in order to avoid misdiagnosis and potentially deleterious interventions.

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