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CLINICAL VIGNETTE

A Case Report of Hereditary Pick's Disease

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A 73-year-old female presents for Geriatric consultation with her husband and daughter. The patient has no complaints; however, her family reports social inappropriateness and behavioral changes for the last 2 years. Approximately one year ago, she was diagnosed with Mild Cognitive Impairment amnestic (and likely to progress to Alzheimer's in a few years) by her Neurologist. She was started on donepezil and eventually memantine without significant improvement. Her husband reported her memory began to decline and she became more confused with the initiation of memantine. He discontinued both medications two weeks prior to the consultation. Since then, he believes the patient's mental status has improved although not to baseline.

The family describes the onset of cognitive impairment as the uncharacteristic lack of awareness and concern about her behavior in public. She has demonstrated impulsivity and intrusive behaviors by falling into the arms of complete strangers and later using inappropriate jocularity to describe the event.

Six months ago, she developed hyperphagia that resulted in weight gain of more than 25 pounds. On one occasion, she drank all of the blue cheese sauce out of the gravy boat, and on another occasion, she drank all of the syrup out of the bottle instead of putting it on her pancakes. At restaurants, she will drink all of the glasses of water (or any liquid) on the table very rapidly and without thought. Her family stopped eating out as a result. Most recently, she developed hyperorality in which she has started putting small objects into her mouth as if to eat them.

Approximately 2 months ago, the patient became profoundly disinhibited, described as undressing in public, including in a supermarket and a movie theater. She has walked outside her home completely naked. When questioned, she was aware of being naked but did not realize it to be inappropriate.

Recently, she developed agnosia and anomic aphasia, losing the ability to recognize common and basic objects, familiar faces, voices, events, and places. Her family describes her as uncharacteristically more selfish and self-absorbed. She has perseverative behaviors and repetitive storytelling to anyone that will listen. She also confabulates and has been repeating the same stories to family members and neighbors. The patient takes a walk daily with her husband. She uses Lumosity computer brain exercise program daily and has been scoring 93-97%. Her past medical history includes hypertension, hypertriglyceridemia, hypothyroidism, history of Legionnaires disease, and closed traumatic brain injury at age 8. Medications include daily amlodipine, fenofibrate, thyroxine, valsartan/hydrochlorothiazide, MVI, Aspirin, and Krill oil.

Her mother died of a massive MCA stroke at age 74 with Parkinson's disease and Pick's/FTD dementia. She is originally from Germany and is a holocaust survivor. Her traumatic brain injury at age 8 occurred after a forceful explosion caused her head to strike against a rock. She is fluent in English and German languages. She has 16 years of education. She is a non-smoker and drinks alcohol, approximately twice per week.

She is independent in 6/6 ADLs and 4/8 IADLs. She is able to use the telephone, take medications, and do the laundry and housecleaning. Eight months ago, she could not start the car and stopped driving. In the last 6 months, she has stopped cooking.

The patient's physical exam and laboratory studies were unremarkable. She received a total score of 25/30 on Mini Mental Status Examination (MMSE), missing points in orientation, delayed recall, and language tests.

She received a total score of 18/30 on Montreal Cognitive Assessment (MOCA), missing points in visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation.

An EEG was negative, and a brain MRI showed moderate diffuse cerebral atrophy predominately on the left frontal and temporal lobes, unchanged from prior studies.

PET/CT scan of the brain showed abnormal asymmetric metabolic activity in a diffuse pattern involving the entire left side of the brain, particularly the left frontal and temporal lobes. There was mild abnormal metabolic activity involving the right frontal lobe and left parietal lobe. The asymmetric metabolic pattern was more likely due to a frontotemporal disease and less likely a vascular etiology from small vessel microangiopathic disease. The associated CT scan and previous MR scan showed consistent asymmetric atrophy. While a neurodegenerative disorder such as Alzheimer disease

can be asymmetric, the asymmetric pattern in this case was more likely Frontotemporal Dementia.

Discussion

Pathophysiology

Dementia is defined as a clinical state characterized by the loss of function in multiple cognitive domains. "Pick's disease" was first described by Arnold Pick in 1892 when he reported a patient with dysfunction of the frontal and temporal lobes associated with variable degrees of cerebral atrophy in these regions. The preferred terminology of the clinical syndrome is Frontotemporal Dementia (FTD). Unfortunately, there is considerable confusion regarding FTD because authors have used nomenclature to describe similar clinical entities because symptoms of FTD are related to the anatomical areas affected rather than to precise neuropathological etiologies.[1]

The diagnosis of frontotemporal lobar degeneration (FTLD) encompasses three main clinical subtypes:

1. Frontotemporal Dementia of frontal-variant or behavioral variant (fvFTD or also just called FTD) is characterized by progressive behavioral disturbances including personality changes and uninhibited, self-centered and/or stereotypic behaviors;
2. Progressive Nonfluent Aphasia (PA) involves progressive, worsening of spontaneous speech; and
3. Semantic Dementia (SD) has decreased fluent speech output and loss of concept knowledge, resulting in loss of understanding of nominal terms, impairment of recognition of faces and common objects, and impairment of auditory comprehension.[2]

Overall, FTD accounts for approximately 20% of all neurodegenerative dementias and is considered to be the third most common clinical diagnosis after Alzheimer's Dementia (AD) and Dementia of Lewy Body (LBD). The age of onset is usually between ages 40-75 years old with a median age of 58 years. However, most cases occur at or around age 65. There is a mild male predominance, and a positive family history in about 20- 40 % of cases.[2]

The median duration of survival is 5-7 years from symptom onset. The reason for the short survival is partly due to the delay in diagnosis as studies have indicated that there is approximately a 3 year lapse between symptom onset and diagnosis.[3] In addition, studies conducted by Robertson et al[4] found that FTD progresses much more rapidly than Alzheimer's Dementia as estimated by 5.7 years vs 11.7 years.

Clinical Manifestations

There are no specific risk factors identified for FTD, but some positive correlations in patients who have had a confirmed diagnosis. Those correlations include a positive family history, a personal history of head trauma, and a diagnosis of thyroid disease. Thyroid disease was associated with 2.5 times increased risk of FTD.[1,2] Ironically, our patient had all three of these correlations. She has a positive family history with her mother's diagnosis of Pick's Disease, her personal history of head trauma at the age of 8, and diagnosis of hypothyroidism.

The presence of Pick bodies is the principal pathological hallmark of Pick's disease and now only cases with Pick bodies on autopsy are diagnosed as Pick's disease. Pick bodies are round or oval argyroghilic intraneuronal cytoplasmic inclusions. The inclusions are observed in the hippocampal dentate gyrus, CA1, subiculum, entorhinal cortex and frontal, temporal, cingulate, and insular cortices. In the cerebral cortex, Pick bodies are often found in the superficial and deep layers.[1,5] The most frequent early symptoms in Pick's disease/FTD are disinhibited behavior and impairment of speech output, followed by apathy, stereotypic behaviors, and impairment of auditory comprehension

The clinical presentation of FTD results in behavior, cognitive, and neurological changes — and generally occur in this sequence. Initially, patients lose appropriate basic and social emotions. They may present with disinhibition and overactivity, while others present with apathy and a blunted affect. Patients with FTD may suffer from moral agnosia (i.e., inability to differentiate between right and wrong, or lose the capacity to reason). As with our patient's performance in the MMSE and MOCA, patients with FTD have marked deficiencies in executive functioning and working memory. They manifest deficiencies in abstraction and attention and have difficulty shifting mental set and perseveration. However, spatial skills may remain unaffected as in our patient. Some patients with FTD may develop neurologic signs including parkinsonism, repetitive motor behaviors and muscular rigidity. This is usually associated with a more rapid disease progression.[1,2,6]

Diagnostic Workup

Clinical diagnosis of FTD can be difficult and is most often mistaken for Alzheimer's Dementia. FTD is a heterogeneous group of disorders that share several clinical features with AD, such as progressive cognitive deterioration and alterations in demeanor and behavior. Many FTD patients are also aphasic and manifest preserved motor integrity. The language disturbance of these disorders initially includes anomia with a more stereotyped and perseverative verbal output than that found in AD. In the early stages of FTD, unlike AD, memory, calculation, and visuospatial function are relatively well preserved.[3,4]

The most striking feature of this disorder is an extravagant change in the patient's demeanor, including disinhibition, impulsivity, inappropriate jocularity, and intrusiveness. In some patients, the behavioral changes consist of especially prominent passivity or atypical depressive symptoms. Also there may be elements of the Kluver-Bucy syndrome such as hyperorality, dietary changes, compulsive exploratory behaviors, hypersexuality, agnosia, and placidity.

Generally, the evaluation includes a complete history and physical, dementia labs (primarily TSH and Vitamin B12 level), neuropsychological testing, and neuroimaging. The Mini Mental Status Examination is unreliable for the diagnosis

and maintenance monitoring of FTD as these patients frequently perform normally even when they require full-time assistance. The Montreal Cognitive Assessment may be more sensitive for maintenance monitoring.

Imaging usually begins with a non-contrast Brain CT or MRI, which generally shows diffuse atrophy or frontal and temporal atrophy with frequent focus of the atrophy is in the left temporal lobe. Functional neuroimaging including single-photon emission computed tomography (SPECT) or positron emission tomography with computed tomography scan (PET/CT) may provide additional information such as relative reduction of blood flow to anterior temporal and frontal regions (SPECT) or reduced glucose metabolism (PET) scans in the same anatomic distribution. Foster et al found that diagnostic accuracy of PET/CT for FTD was approximately 90% specific.[7]

Treatment

The treatment of FTD includes both non-pharmacological management and pharmacological options. FTD is thought to have a deficiency in serotonin, which may indicate serotonergic dysfunction. Therefore, the first line therapy includes SSRIs (Selective Serotonin Reuptake Inhibitors), which have shown a beneficial effect on behavior but not on cognition. Trazodone is an atypical serotonergic agent and second line therapy with dose-dependent improvement in behavioral symptoms but less impact on cognition. Dopamine and antipsychotics remain a controversial treatment in the demented elderly. Cognitive enhancers such as Donepezil and Rivastigmine have shown general amelioration of behavioral changes and may reduce caregiver burden.[8]

Unfortunately, none of the pharmacotherapeutic options are excellent options. Therefore, a non-pharmacological approach should also be attempted. Patient centered care is generally the approach that provides the patient with the proper support. In addition, providing psychoeducation to change caregivers' behavior could have a positive effect on the patient's behavioral symptoms.

SUMMARY

Pick's disease is currently referred to as Frontotemporal Dementia, which is divided into three subtypes including frontal variant, progressive non-fluent aphasia and semantic dementia. FTD initially manifests with behavioral changes, then cognitive decline and may or may not develop neurological changes. Diagnosis includes a history and physical, labs, neuropsychological testing, and neuroimaging. Treatment has been difficult in FTD and is predominantly targeted at behavioral management with a non-pharmacological approach.

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