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REVIEW ARTICLE

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Frontotemporal dementia as underlying cause of newly altered mental status in a 59-year-old female: a case presentation and literature review

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ABSTRACT

59 y.o. female is evaluated for chronic behavioral abnormalities. We describe the diagnostic approach to cases of altered mental status.

Before considering the different possible etiologies including, for example, metabolic, infectious, toxic, hypoxemic, endocrine, or iatrogenic ones, we underline the importance of assessing patient's baseline functional status. Often, in particular in older patients' population, dementia is the underlying culprit of mentation abnormalities.

Through extensive history and with the help of neuroimaging studies, our patient was diagnosed with frontotemporal dementia.

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1. Case presentation

We present the case of a 59-year-old female former psychiatric social worker with past medical history of poorly controlled hypertension, who was brought to the emergency room by her family for acute on chronic behavioral abnormalities. Before coming to the emergency department, the patient had been driving in circles for 3 hours and was agitated. Her family reported that over the last year and a half, the patient's mental status had been deteriorating. She had progressive memory loss to the point where she no longer remembered details that were mentioned to her 5 minutes prior. She had also become more aggressive over the past few weeks and had been harassing her coworkers to the point where she was suspended from work. Most recently, she could only sleep 2 hours per night. She had no neurological deficits as far as her ability to speak, eat, or ambulate. According to her family, at home, her systolic blood pressure was often above 200 mmHg with diastolic blood pressure up to 130–140 mmHg. She had established care with a new primary care physician 3 weeks prior to presentation. At that time, the patient was started on metoprolol but was not compliant in taking her antihypertensive medication.

On admission to the emergency department, the patient was afebrile, blood pressure was 200/116 mmHg, with heart rate of 70 bpm, and O2 saturation of 97% on room air. On physical examination, the patient was anxious and fidgety but was otherwise alert and oriented. She had intact cranial nerves II–XII, preserved motor function and sensation bilaterally and no focal neurological deficits. Her head, neck, lung, heart, abdominal, extremities, and skin examinations were unremarkable. Workup in the emergency department included complete blood count, basic metabolic panel, urine toxicology screen, cardiac markers, EKG, and head CT. The complete blood count was normal and basic metabolic panel unremarkable. The urine toxicology was negative. The high sensitivity Troponin T value was less than 6 ng/mL and EKG showed normal sinus rhythm with no acute ST changes or other abnormalities. A head CT was performed and was significant for extensive age-related brain involutional changes with findings of chronic microvascular ischemic disease. In the ED, in order to control her blood pressure, the patient was treated with intravenous amlodipine and labetalol. Her agitation improved with the administration of lorazepam but did not completely resolve. The patient was admitted to the hospital to better assess the etiology of her agitation and personality changes.

Because of patient's strong family history of vascular dementia and her underlying history of uncontrolled hypertension, vascular dementia was initially considered a likely cause of her behavioral abnormalities. However, other potential causes of rapidly progressive dementia were taken into consideration as well including neurosyphilis, Wilson's disease, vitamin deficiencies, endocrinopathies, paraneoplastic syndromes, and CNS infections.

Thyroid function, anti-TPO and antithyroglobulin antibody were checked and revealed to be unremarkable (TSH value was 2.7 uIU/mL). ESR, CRP, RPR, paraneoplastic antibody panel, serum copper, and ceruloplasmin, vitamin B12, folate, and homocysteine

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levels were also checked and were within normal limits.

To assess for the presence of any structural abnormality or other intracranial pathologic processes that could contribute to her clinical presentation, the patient underwent an MRI of the brain. This did not show any evidence of acute infarct or intracranial hemorrhage but did show multiple punctate foci of remote microhemorrhage. These findings were interpreted as either the sequelae of microangiopathy or as part of another process such as amyloid angiopathy. In addition, marked parenchymal volume loss was noted. The ventricles and sulci were markedly prominent consistent with marked diffuse cerebral atrophy. Right temporal lobe encephalomalacia was noted. An EEG was also ordered to investigate for any epileptiform activity and did not reveal any abnormality. Despite treatment with quetiapine during her hospitalization, the patient remained confused and agitated. The inpatient team remained concerned about missing a possible reversible cause of her underlying rapidly progressive dementia. Given the lack of improvement in her symptoms and the unremarkable workup, the patient was transferred to the Neurology service of Massachusetts General Hospital for further assessment.

At Massachusetts General Hospital, the patient had an extensive neurologic evaluation and work-up for cognitive and behavioral impairment. The earliest sign of personality change per family was about 4 years prior when the patient had a verbal altercation with one of the patients at her workplace on a psychiatric unit. Because of this episode, she was fired from her position. For the past year, the patient had exhibited memory deficits and would forget details of a recent conversation or event. She was also noted to be more irritable in her interactions. Several months prior to admission, the patient had another episode of verbal aggression towards her boss at her new job in a shelter for women and children which resulted in her suspension. She was also noted to have disinhibited behavior, such as expressing sexual comments in front of her young grandchildren or taking off her shirt in public. In addition, the patient was reported to have unstable mood. For instance, during the holidays the patient suddenly 'started to frantically cry' for no obvious reason. She was also reported to be irritable with family and at times yell at the grandchildren, a behavior that she had never exhibited in the past. The patient was also reported to eating more avidly than usual in the last period and asking repetitively for snacks. She had a weight gain of about 10 pounds over the previous few months. Although she had quit smoking in the past, she had started 'chain smoking' again. The patient was described by her family as capable of performing very basic activities of daily living such as bathing or dressing, but she had lost her ability to cook or drive.

During neurologic evaluation, the patient was found to be alert and cooperative but maintained a flat affect and had poor eye contact. She showed perseveration and lack of acknowledgement of her own clinical condition as she reported that her only complaint was with her memory. She also continued to think that she was working while she had been fired months prior. Her speech was fluent without paraphasic errors. She was able to follow multi-step commands. On recall testing, she recalled 0/3 words. No motor deficits were noted, including bradykinesia, fasciculations, myoclonus or tremor. Sensation was diffusely intact. Deep tendon reflexes were normal and symmetric bilaterally and tests for cerebellar function, e.g., finger-to-nose test, were within normal limits.

Given the patient's prominent personality changes and cognitive decline, further workup was ordered including lumbar puncture and brain PET scan. CSF analysis from lumbar puncture showed 1–8/uL red blood cells, 2–3/uL nucleated cells, 73–77% lymphocytes, 44 proteins and glucose level 79 mmol/L. Oligoclonal bands were absent. CSF autoimmune encephalopathy panel, ADMark biomarker panel, and 14-3-3 protein were also checked and results were negative. Isolated low amyloid was noted on CSF analysis; values of both P-Tau and T-tau were within normal limit.

PET scan of her brain revealed extensive areas of hypometabolism in dorsolateral, orbitofrontal, and temporal lobe bilaterally (right>left). At that point, the patient's clinical picture of personality changes and dementia in conjunction with her brain MRI and PET scan findings were considered highly suggestive of frontotemporal dementia.

2. Discussion

Dementia is a disorder characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) [1]. The deficits must represent a decline from previous level of function and be severe enough to interfere with daily function and independence. The differential diagnosis of dementia is broad and includes multiple diverse pathologies sometimes presenting with overlapping clinical features. Dementia is most often caused by a neurodegenerative disease, commonly Alzheimer disease, Parkinson disease dementia, Dementia with Lewy bodies, and Frontotemporal dementia (FTD). Less common neurodegenerative disorders such as progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, and Huntington disease can also be

associated with dementia. Dementia can also be non-degenerative in nature. The most common pathology under this umbrella of disorders is vascular dementia, characterized by a stepwise fashion cognitive decline secondary to repetitive vascular insults in the cerebral territory. Less common etiologies include alcohol-related dementia, chronic traumatic encephalopathy, normal pressure hydrocephalus, chronic subdural hematoma, and other central nervous system illnesses (e.g., prion diseases, HIV infection).

When evaluating a patient in the emergency setting presenting with acute on chronic behavioral abnormalities and possible dementia, as in the case of our patient, it is useful to consider other possible etiologies underlying the patient's altered mental status. These may be related to metabolic (vitamin deficiencies, e.g., cobalamin or thiamine deficiency, uremia) or electrolytic abnormalities (hyponatremia or hypernatremia; hypercalcemia), as well as infectious, toxic, hypoxemic, psychiatric, or iatrogenic causes. Vascular accidents including stroke, hypertensive encephalopathy, or hypercoagulability disorders (DIC) need to be considered, as well as endocrine abnormalities such as derangements in glycemia, cortisol or thyroid hormone levels. Acute events including seizures or trauma must be ruled out as well in the diagnostic workup of altered mental status.

Our patient presented to the emergency department with a history of personality changes and agitation in the setting of progressive cognitive decline. It appeared appropriate to first exclude obvious metabolic, hypoxic, and electrolytic derangements as well as thyroid function abnormalities. Acute infectious processes were also taken into consideration but considered unlikely given the patient's normal vital signs, leukocyte count, and inflammatory markers. Acute cardiovascular and cerebrovascular accidents were excluded with a normal EKG, cardiac markers, and neuroimaging. However, her head CT was significant for extensive age-related brain involutional changes with findings of chronic microvascular ischemic disease. Further neuroimaging studies showed atrophy and hypometabolism in the frontal and temporal lobe areas. When the patient was furthered assessed by neurological evaluation, it appeared that her personality and behavioral changes had started years prior to presentation and were accompanied by a progressive and not stepwise decline in her cognitive function. This pointed towards a degenerative type of dementia rather than non-degenerative. In addition, her behavioral pattern demonstrated the peculiar features of compulsive behavior and hyperoralia. All these clinical and radiologic findings were consistent with the diagnosis of FTD.

Frontotemporal dementias (FTDs) are a group of clinically and neuropathologically heterogeneous neurodegenerative disorders characterized by prominent changes in social behavior and personality or aphasia accompanied by degeneration of the frontal and/or temporal lobes. Some patients with FTD also develop a concomitant motor syndrome such as parkinsonism or motor neuron disease. FTD is one of the more common causes of early-onset dementia, with an average age of symptom onset in the sixth decade. Three different clinical presentations of FTD have been identified: behavioral variant FTD (bvFTD) and two forms of primary progressive aphasia, the nonfluent and semantic variants.

Early behavioral changes of bvFTD include disinhibition, apathy, compulsive behavior, and hyperorality. Patients are often found to have socially inappropriate behavior including touching or kissing strangers, urinating in public, or invading others' personal space. They often lose interest or motivation for activities and social relationships that were previously significant to them and are less engaged in conversation and interaction with others. At the same time, patients often show loss of empathy and sympathy and are reported to be emotionally cold by their families. Impairments in recognition of affect, emotions, and sarcasm [2] as well as difficulty understanding another person's perspective [3] are frequently reported. It is not uncommon that patient's apathy is misunderstood as depression, and patients are often referred for psychiatric treatment early in the disease course.

Compulsive behavior is also common in individuals affected by FTD. Perseverance and stereotyped or compulsive ritualistic behaviors can manifest in the form of simple repetitive movements or more complex rituals such as hoarding, checking, or cleaning. A tendency to adopt compulsive behaviors may also take the form of gambling or substance use. Increased consumption of alcohol or tobacco may occur.

Another feature of the personality changes observed in FTD is hyperorality. This can manifest as carbohydrate cravings, particularly for sweet foods, and binge eating, often to the extreme point in which patients completely fill their mouth with food and are not able to chew completely. Because of the possibly increased food intake, FTD can be associated with weight gain. Patients sometimes show rigid food preferences. A similar inflexibility is manifest in their rigid personality and inability to accept changes in their daily routine. Most patients lack insight into their behavioral changes and the distress experienced by family members [4] or are inappropriately unworried.

Personality changes and cognitive impairment follow the course of the disease and are usually apparent in different stages of bvFTD. In early bvFTD, damage to medial frontal and orbitofrontal regions results mainly in apathy and disinhibition. As disease severity

progresses to involve dorsolateral prefrontal regions, executive functions and verbal fluency decline. Memory and visuospatial functions are usually spared in FTD, although frontal lobe dysfunction can make it appear to families that patients have memory problems. Memory impairment, when present, has been associated with an increased rate of progression in several studies [5,6].

Our patient's earliest behavioral/personality change is reported 4 years prior to presentation. The altercation that she had with one of her patients in the psychiatric unit where she used to work represents indeed a sentinel event of her underlying personality change. It was considered unusual for her personal character to be engaged in such an explosive argument and it was extreme to the point that she was fired because of it. She also started showing an irritable mood and episodic agitation. For instance, before her presentation to the emergency department, the patient was reported to having been driving erratically for 3 hours in agitated state. Mood instability was manifest on multiple occasions when she displayed outbursts of crying or was found yelling at her grandchildren without obvious reason. Disinhibition was also apparent early on in her disease history. She expressed sexual comments in an inappropriate context and began undressing in public places. Hyperorality was also demonstrated by her avidity in eating and craving for snacks and resulted in significant weight gain. At the same time, compulsive behaviors also involving substance use were present, as our patient was engaged in chain smoking, a habit that she had lost years prior. Cognitive decline was apparent later as the disease progressed and resulted in our patient's loss of capability to cook or drive. Interestingly, our patient's cognitive deficits were mostly evident in the domain of memory, a function that is usually spared in FTD, at least in the first stages. She was reported to forget details of a recent conversation or event and failed 3-word recall on neurologic examination. In addition, upon testing, she displayed prominent deficits in delayed recall, a significant finding which is not usual in FTD patients. Verbal fluency remained instead intact and our patient did not show any difficulty in object-naming, word-finding and word usage, word comprehension, or sentence construction. She did not have articulatory difficulty, as her speech remained fluent and effortless without errors, distortions, or agrammatism in language production throughout the course of the disease.

Patients with bvFTD generally lack cranial nerve, sensory, cerebellar, pyramidal, and extrapyramidal motor findings, at least initially. On physical examination, our patient did not have any motor or sensory deficits and cerebellar function was intact. Reflexes, muscle tone, and gait were within normal limits.

Structural and functional neuroimaging plays an important role in the diagnostic flow of FTD, even though it provides supportive rather than diagnostic evidence for bvFTD [7–9]. Structural and functional imaging in patients with FTD may demonstrate atrophy, hypometabolism, and/or hypoperfusion in the frontal and/or temporal lobes, in a pattern specific to the clinical variant. Even though neuroimaging may appear normal early in the disease course [10,11], in 50% to 65% of patients focal frontal or temporal atrophy manifests as the disease progresses [12–14]. The pathologic process may also involve the anterior insula, anterior cingulate cortex, and amygdala [15–18]. The earliest regions of damage in bvFTD include the anterior insula in the right hemisphere, pregenual anterior cingulate, and orbitofrontal cortex. Findings on neuroimaging can be asymmetric at the early stages of the disease, for example there can be more prominent atrophy in one cerebral hemisphere with respect to the other. However, as disease progresses, the pathological changes tend to involve both hemispheres in a more symmetrical fashion.

The brain MRI that our patient underwent was remarkable for extensive areas of atrophy in the frontal, temporal, and hippocampal regions bilaterally. Her PET scan showed extensive areas of hypometabolism in dorsolateral, orbitofrontal, and temporal lobe bilaterally. These changes were asymmetric, as they were more pronounced on the right cerebral hemisphere when compared to the left. The areas involved by either atrophy or hypometabolism in our patient's case seem to correlate with her changes in behavior and personality as well as her cognitive decline. Neuroanatomic-behavior correlation studies reveal indeed that medial frontal and anterior cingulate damage correlates with apathy, while right anterior temporal and right medial frontal atrophy correlates with loss of empathy [19,20]. Damage to orbitofrontal, right insula, and striatum correlates with changes in eating behavior [21–23]. Simple motor stereotypies correlate with striatal atrophy, while complex ritualistic compulsions are related to atrophy in orbitofrontal, caudate, and temporal lobe atrophy [24,25]. Our patient's atrophy in the orbitofrontal lobe as evidenced by neuroimaging appears to be associated with her compulsive behavioral pattern of eating and hyperorality. In addition, both damage at the level of the orbitofrontal and temporal lobe are possibly correlated with the onset of compulsive behaviors as demonstrated by her substance abuse (chain smoking). Interestingly, our patient did not show prominent apathy or loss of empathy, as instead it would have been expected,

given the involvement of the temporal and frontal lobe.

According to the International Behavioral Variant FTD Criteria Consortium (FTDC) [7], the diagnosis of bvFTD is based on clinical features, neuroimaging, neuropathology, and genetic testing [7,8]. A diagnosis of possible bvFTD is based solely on the clinical syndrome and requires a combination of three of six clinical features: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychologic profile. Probable FTD requires the same clinical criteria, plus demonstrable functional decline and imaging findings that reflect the principal anatomic location of neurodegeneration in bvFTD (i.e., frontal and/or temporal lobe atrophy, hypometabolism, or hypoperfusion). Both possible and probable bvFTD require the exclusion of other neurologic, medical, and psychiatric disorders that would better account for the pattern of deficits and behavioral disturbance. A third diagnostic category, bvFTD with definite FTLD pathology, is satisfied when cases of possible or probable bvFTD are accompanied by either biopsy or postmortem histopathologic evidence of FTLD or evidence of a known pathogenic mutation. Taking into consideration the presence of multiple and diverse clinical features (her disinhibition, compulsive behaviors, hyperorality and dysexecutive neuropsychological profile), and her neuroimaging findings demonstrating frontal and temporal atrophy and hypometabolism, our patient's diagnosis was consistent with probable bvFTD.

It appears reasonable to speculate that in our patient a vascular disease component was present in addition to the neurodegenerative pathological process. She had family history of vascular dementia in two family members, her hypertension was not controlled due to patient's noncompliance to treatment, and neuroimaging studies identified multiple punctate foci of remote microhemorrhage and other findings of chronic microvascular disease. It seems reasonable to hypothesize that this represented a potentially contributing factor to her cognitive decline and behavioral changes. It remains unclear if vascular changes preceded the onset of the primary neurodegenerative process. Alternatively, her cognitive dysfunction in the form of dementia may have come first and played a major role in determining patient's nonadherence to the hypertensive treatment. Nevertheless, the peculiar personality changes and atrophic and hypometabolic findings on neuroradiological studies strongly favor neurodegeneration in the form of bvFTD as the primary pathologic process in our patient's case.

Disclosure statement

Dr. Coraini and Dr. Basciotta report no disclosures relevant to the manuscript.

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Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from the individual participant included in the study. The patient described in our paper has given written consent to the inclusion of material pertaining to herself. Our patent acknowledges that she cannot be identified via the paper; we have fully anonymized our participant.

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