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Chapter 4

SCHIZOPHRENIA AS A MIMIC OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

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ABSTRACT

Recently the diagnostic criteria for the behavioral variant of frontotemporal dementia were revised. Although these criteria offer a relatively high sensitivity, their specificity is yet unknown. We describe a 54-year-old woman fulfilling criteria for both late-onset schizophrenia and probable behavioral variant frontotemporal dementia. Following an initial presentation with psychosis, she developed progressive apathy, compulsiveness and executive dysfunction. Moreover, bilateral frontotemporal hypometabolism was seen on [^{18}F]FDG-positron emission tomography. A post-mortem diagnosis of schizophrenia was established, given the clinical picture combined with the pathological exclusion of a neurodegenerative cause. Our case suggests that patients with other brain disorders may meet the current diagnostic criteria for probable frontotemporal dementia. Further clinicopathological validation of these criteria is needed to determine their exact specificity.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative disorder primarily affecting the frontal and/or temporal lobes [1]. The bvFTD syndrome is characterized by deterioration of social-emotional function, followed by progressive changes in behavior and personality and disorders of executive functioning, memory and language [2].

The clinical diagnosis of bvFTD is based on consensus diagnostic criteria. The formerly used international diagnostic criteria by Neary et al have recently been revised by the International bvFTD Criteria Consortium (FTDC) [3;4]. One of the considerations inciting this revision was the difficulty in the application of 5 obligatory core behavioral criteria, which were subject to multiple interpretations. Moreover, a variety of psychiatric disorders could easily be misdiagnosed as bvFTD, based on the presence of overlapping symptoms [5].

The FTDC introduced a level of certainty and a more flexible clinical rating system within the new diagnostic criteria. According to these criteria, *probable* bvFTD requires at least three out of six symptom clusters in the presence of both functional decline and characteristic neuroimaging abnormalities. A specific pattern of mainly fronto-temporal atrophy can be found on structural magnetic resonance imaging (MRI) [2]. [18F]FDG-Positron Emission Tomography ([18F]FDG-PET) has an added value over MRI alone in identifying disease specific neuronal correlates in bvFTD [6]. Although it has been confirmed that the new criteria offer a reasonable sensitivity of 76% for probable bvFTD, their specificity is still unknown. The distinction of bvFTD from psychiatric disorders is essential, especially since bvFTD is progressive and will eventually lead to death whereas most psychiatric disorders are potentially treatable.

In this case report we describe the diagnostic dilemma that may occur when bvFTD symptom clusters occur in late-onset psychiatric disorder and are accompanied by functional decline and neuroimaging abnormalities.

CASE

A 54-year-old woman was admitted to a geriatric psychiatry hospital with newly developed psychotic symptoms, consisting of both delusions and auditory hallucinations. According to the patient, strangers entered her house to steal her letters and passing black cars were out to kidnap her. She also heard accusing male voices when she was alone in her house. Twenty years before she had successfully received behavioral therapy for an anxiety disorder. Nine years prior to admission, she had had complaints of tiredness and lack of energy that had been interpreted as work related stress. Although previously well-functioning in her job as an executive secretary, thereafter she never returned to her old level of functioning.

Her somatic history revealed hypertension and cardiac arrhythmia with an implantable cardioverter defibrillator. Her brother had been diagnosed with schizophrenia and committed suicide at the age of 45 years. The family history was negative for dementia. Although she had always preferred an isolated life style, she had two close friends. Her 15-year lasting relationship ended 5 years prior to presentation.

Apart from the psychotic features, psychiatric examination revealed a paucity of spontaneous speech without any apparent cognitive or motor symptoms.

She was diagnosed by the old-age psychiatrist with late-onset schizophrenia, meeting the DSM-IV criteria of (late-onset) schizophrenia [7]. The persecutory and reference delusions and hallucinations disappeared with 10 mg Olanzapine daily within three months. The remaining lack of initiative and paucity of speech were considered so called "negative" symptoms of schizophrenia. After discharge, however the clinical picture deteriorated rapidly. She did not cook for herself, forgot her appointments with her therapist and stayed in bed all day. Moreover, she developed strikingly compulsive behavior, consisting of a strong attachment to daily schedules and preoccupation with the same subjects. Additionally she was not able to organize complex tasks, such as finances and household tasks. Because of this unexpected behavioral and cognitive decline, within three months the patient was readmitted for further observation and neurological consultation.

Formal neurological examination revealed no abnormalities. On observation, she was rigid in her day program and fixated on her medication. She became very agitated when challenged to deviation. She had some awareness of her disease, but her disease-insight was reduced. Spatial orientation and memory were not disturbed. On the Frontal Assessment Battery she scored 15 out of 18. Her Mini-Mental State Examination was 29 out of 30. A neuropsychological examination confirmed the executive dysfunction (reduced planning and flexibility, impulsivity) and demonstrated minor memory impairments, with decreased learning and information retention abilities.

Because of the striking apathy, compulsiveness and executive dysfunction in the presence of functional decline over a relatively short time, a diagnosis of bvFTD was now considered. MRI of the brain was within normal limits, particularly lacking frontotemporal atrophy (Figure 1a and 1b). Subsequently, [^{18}F]FDG-PET was performed and showed bilateral frontal and anterior temporal hypometabolism on visual rating. A voxel-by-voxel analysis using a validated discrimination tool comparing the regions to a mask based on age and gender matched controls showed hypometabolism in frontal, temporal and cingulate regions (figure 1c) [8].

Analysis of the cerebrospinal fluid showed slightly decreased amyloid-beta(1-42) levels (471 ng/L) in combination with a normal total tau level (59 ng/L) and a normal phosphorylated tau level (<16 ng/L). A decreased CSF amyloid-beta(1-42) level combined with increased total tau and phosphorylated tau levels fit an Alzheimer's disease (AD) profile. However, the

clinical relevance of an isolated decreased amyloid-beta(1-42) level is unclear, especially at an older age [9-11]. In order to obtain more certainty, a ^{11}C-Pittsburgh compound B-PET scan was performed, which did not show any amyloid deposition. So even though a frontal variant of AD should be considered in behavioral changes at an older age, this seemed not to be the case in this patient [12]. Based on these findings a diagnosis of probable bvFTD was deemed plausible, although some diagnostic doubt remained since she kept some awareness of her illness and was remarkably empathic towards personnel and other patients. Because of serious self neglect the patient was transferred to a long stay ward.
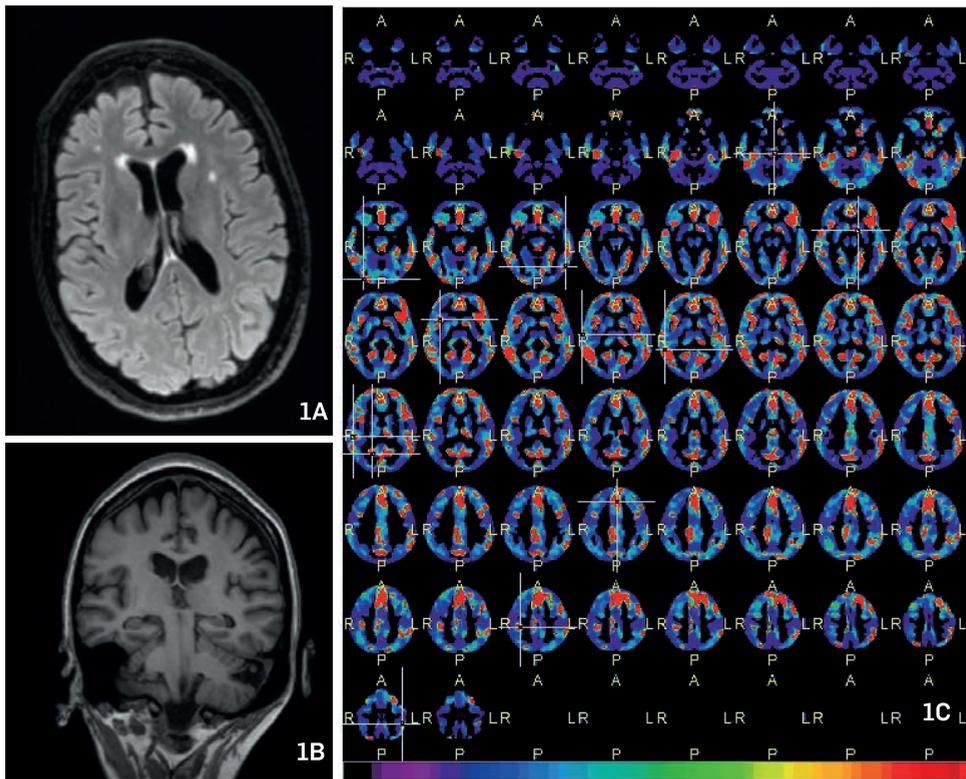
Figure 1: a. Structural axial MRI (fluid-attenuated inversion recovery (FLAIR)): atrophy is within the normal age range. Some white matter hyperintensities in the frontal periventricular regions. b. Structural coronal MRI (T1): atrophy is within the normal age range. c. Results of the [^{18}F]FDG-PET images: A substantial amount of voxels in the frontal, temporal and cingulate cortex were abnormal compared to a healthy reference group. Higher values (red areas) indicate more abnormal voxels and thus more profound metabolic impairment. A: anterior, P: posterior, L: left, R: right.

An attempt lowering the Olanzapine dose did not yield any changes in negative symptoms, but led to increased compulsive behavior. This treatment was therefore maintained. Nearly

15 months later, the patient insisted on discharge to her home, which was permitted with intensive psychiatric and domestic support. There were no signs of psychosis. However, her compulsiveness and apathy remained. A few months later she was found home in a confused state and examined at the emergency ward on the suspicion of dehydration and pneumonia. Shortly after admission on the internal medicine department she suddenly died. Autopsy revealed a fatal thrombus in the pulmonary artery.

Autopsy of the brain was performed and the obtained material was examined independently by AR and WWS. Her brain weighed 1283 grams, without macroscopic atrophy. There was mild arteriolosclerosis without micro-infarction. Nonspecific neurodegenerative changes, such as superficial spongiosis, gliosis, and neuronal loss, were absent. There was a mild amount of diffuse amyloid plaque in the neocortex, extending lightly into entorhinal cortex and CA1/subiculum. Tau-immunoreactive neurofibrillary pathology was mild and limited to locus ceruleus, entorhinal cortex, subiculum, cornu ammonis1, and amygdala, consistent with Braak Stage 2. Immunostains for transactive response DNA Binding Protein-43, alpha-synuclein, and p62 were negative in cortex, basal ganglia, amygdala, substantia nigra, brainstem, pons, locus coeruleus and cerebellum. A post-mortem diagnosis of frontotemporal lobar degeneration or another neurodegenerative disease was excluded. A diagnosis of schizophrenia was established, given the clinical picture combined with the pathological findings.

DISCUSSION

We describe a case with autopsy verified schizophrenia that fulfilled diagnostic criteria for both late-onset schizophrenia and probable bvFTD. We demonstrate that not only symptom overlap with psychiatric disorders may be a pitfall in bvFTD diagnosis, but also that functional decline and abnormal functional neuroimaging findings may occur in psychiatric disorders, therefore questioning the specificity of the bvFTD diagnostic criteria. In this case, psychotic symptoms prevailed initially, leading to a diagnosis of schizophrenia. The patient met the DSM-IV criteria for schizophrenia with delusions, hallucinations and negative symptoms for a period longer than six months. Because compulsive behavior, apathy, and prominent executive dysfunction developed in addition to functional decline, and frontotemporal abnormalities were shown on [18F]FDG-PET, her diagnosis changed to bvFTD according to the FTDC criteria. Because of a decreased CSF amyloid-beta(1-42) level a diagnosis of atypical AD was considered, but regarded unlikely and rejected based on normal CSF tau and phosphorylated tau levels combined with a negative 11C-Pittsburgh compound B-PET scan. Neuropathological examination showed no clinically relevant stage of AD related pathology.

The differentiation between schizophrenia and bvFTD remains a main diagnostic dilemma: for both diagnoses functional decline is required. Although not necessary for diagnosing late-onset schizophrenia, executive abnormalities are often seen upon neuropsychological examination [13]. Furthermore, frontotemporal abnormalities on both structural and functional neuroimaging are common in schizophrenia [14;15]. The overall prevalence of psychosis in bvFTD is about 10%, with relatively higher frequencies in subjects carrying a C9orf72 repeat expansion or progranulin mutation [16]. In this case bvFTD could only be excluded by autopsy.

In the described case, some symptoms cast doubt on the diagnosis of schizophrenia during the course. In contrast to early-onset schizophrenia, the development of negative symptoms and functional decline are uncommon in late-onset schizophrenia, i.e. after the age of 45 years [17]. Moreover, severe compulsiveness is uncommon in schizophrenia [18]. On the other hand, although the absence of empathy is not obligatory for a diagnosis of bvFTD, the relative preservation of empathy in this case is remarkable.

BvFTD symptoms such as apathy, disinhibition and compulsive behavior are seen in other psychiatric disorders such as depression, mania or obsessive-compulsive disorder, but usually do not occur simultaneously in contrast to bvFTD. Apparently due to this symptom overlap, about 50% of bvFTD patients receive a psychiatric diagnosis initially [19]. On the other hand it is currently unknown which proportion of patients with an initial diagnosis of bvFTD turns out to have a psychiatric disorder.

In the FTDC consensus criteria it is stated that the behavioral syndrome should not be better accounted for by a psychiatric condition [4]. This issue is difficult to resolve when the specificity of structural and/or functional neuroimaging appears to be insufficient. Prospective studies addressing this issue among subjects presenting with a late-onset frontal lobe syndrome will hopefully bring answers to this question [20].

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