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Clinical spectrum of frontotemporal dementia: schizophrenia-like symptoms and amyotrophic lateral sclerosis (family case study)

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ABSTRACT

Frontotemporal dementia is a heterogeneous pathology with various clinical, histological, and genetic variants. The behavioral variant of frontotemporal dementia (bvFTD) in some cases presents differential diagnostic difficulties when distinguishing from primary mental disorders. The article provides an observation of patient K., who was observed at the initial stage of the disease with a diagnosis of schizophrenia. The comparison of psychopathological and behavioral symptoms with the presence of a family history of amyotrophic lateral sclerosis (ALS) served as a turning point to a different interpretation of the pathology and recognition and confirmation of the "definite diagnosis" — bvFTD.

Keywords: frontotemporal dementia; amyotrophic lateral sclerosis; schizophrenia; psychopathology.

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Клинический спектр фронтотемпоральной деменции: шизофреноподобные симптомы и боковой амиотрофический склероз (семейное наблюдение)

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АННОТАЦИЯ

Фронтотемпоральная деменция — гетерогенная патология с различными клиническими, гистологическими и генетическими вариантами. Поведенческий вариант фронтотемпоральной деменции в ряде случаев представляет дифференциально-диагностические трудности при разграничении с первичными психическими расстройствами. В статье приведён случай пациента К., на начальном этапе болезни находившегося под наблюдением с диагнозом «шизофрения». Сопоставление психопатологических и поведенческих симптомов с наличием семейного анамнеза бокового амиотрофического склероза послужило поворотной точкой к иной интерпретации патологии, распознаванию и подтверждению достоверного диагноза «поведенческий вариант фронтотемпоральной деменции».

Ключевые слова: фронтотемпоральная деменция; боковой амиотрофический склероз; шизофрения; психопатология.

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Фронтотемпораль деменциянең клиник спектры: шизофреник симптомнар һәм ян-як амиотрофик склероз (гаилә күзәтүе)

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Аннотация

Фронтотемпораль деменция — төрле клиник, гистологик һәм генетик вариантлары булган гетероген патология. Кайбер очракта фронтотемпораль деменциянең тәртип вариантын һәм беренчел психик тайпылышларны аерып карауда дифференциаль-диагностик кыенлыклар килеп чыга. Мәкаләдә авыруның башлангыч этабында «шизофрения»диагнозы белән күзәтү астында булган пациент К. очрагы китерелә. Психопатологик һәм тәртип симптомнарын ян-як амиотрофик склерозның гаилә анамнезы белән чагыштыру патологиянең башка интерпретациясенә, фронтотемпораль деменциянең тәртип вариантын тануга һәм ышанычлы диагнозын раслауга борылыш ноктасы булып хезмәт итә.

Төп сүзләр: фронтотемпораль деменция; ян-як амиотрофик склероз; шизофрения; психопатология.

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Frontotemporal dementia (FTD) is a common cause of early-onset dementia, with an average age of symptom onset of 45–60 years. The pathogenesis of FTD and its clinical spectrum have significantly evolved from Pick's disease to different variants of frontotemporal lobar degeneration, which includes more than 20 diseases.

The common characteristics of "frontotemporal lobar degeneration" include neuronal damage to the cortex and atrophy of predominantly the frontal and temporal regions of the brain. The distinctive features of these degenerations are determined by histopathological findings with the deposition of various variants of abnormal proteins, such as Tau, TDP-43, FET (FUS, EWS), etc., mainly in the anterior regions of the brain [1].

FTD has familial and sporadic forms, with 30%–50% of cases classified as familial [2] and 40%–70% as sporadic [3, 4]. Genetic abnormalities are confirmed in 30%–40% of patients with a family history of FTD and in 80% are explained by mutations in the major genes C9orf72, MAPT (tau), and progranulin (GRN) [5, 6].

To date, the prevalence of hereditary and sporadic forms remains unclear owing to a wide range of clinical manifestations of FTD, which can be interpreted as mental or neurological pathologies.

Genetic research is a modern field that has significantly expanded the understanding of the spectrum of PTD and determined the ambiguity of this problem. In recent years, researchers have discovered changes in other genes that lead to rare familial types of frontotemporal disorders, accounting for <5% overall. Most sporadic cases of FTD do not have known genetic variant.

The extent to which genetic abnormalities determine the clinical presentation of the disease remains to be described. Notably, several neurodegenerative diseases have similar clinical and molecular characteristics. On the one hand, overlapping genetic factors may predict the development of different types of dementia. On the other hand, the same genetic mutation can determine different clinical phenotypes [7].

In particular, the MAPT (TAU) gene is involved in the development of FTD and such types of neurodegenerative pathologies including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) [7, 8]. The GRN gene, in addition to FTD, plays a role in Alzheimer's disease, Parkinson's disease, parkinsonism, and ALS [9, 10]. Moreover, abnormalities of the C9orf72 gene are factors in the development of FTD, ALS, Alzheimer's disease, and parkinsonism [11]. Genetic pleiotropy in neurodegenerative diseases is confirmed by the fact that 50% of FTD patients have rare missense mutations of genes associated with Alzheimer's disease, Parkinson's disease, ALS, and dementia with Lewy bodies [5].

Thus, predicting the genetic basis of the disease based on clinical manifestations is challenging because of the high degree of overlap between neurological phenotypes [1]. A clinical genetic analysis of 509 patients with FTD did not reveal a significant correlation between clinical diagnoses and pathological genes, which confirmed the results of previous studies and summarized the rule "any gene — any clinical subgroup of FTD" [5]. Furthermore, an association between the FTD/ALS phenotype with C9orf72 genetic anomaly was noted.

FTD is a heterogeneous syndrome that combines three clinical forms, namely, the behavioral variant (behFTD), or "frontal" variant of FTD, and two forms of primary progressive aphasia, the "non-fluent speech" variant ("agrammatic") and semantic ("temporal") type [12]. Additionally, the clinical presentation of FTD may include motor disorders, such as parkinsonism syndrome (progressive supranuclear palsy, corticobasal degeneration), and motor neuron diseases including ALS [13].

BehFTD is the most common clinical subtype of FTD, accounting for approximately 50% of familial and 69% of sporadic cases [14]. A characteristic feature of behFTD is progressive personality and behavioral changes in the early stages of the disease. In this regard, the diagnosis of behFTD often becomes a subject of debate and can lead to diagnostic errors. Approximately 50% of behFTD patients are preliminarily diagnosed with a psychiatric disorder, and the correct diagnosis is established only 5–6 years after the onset of initial symptoms. The opposite, i.e., patients with primary mental disorders are mistakenly diagnosed with behFTD, is also common [15]. The wide range of mental manifestations of FTD and presence of overlapping symptoms with various primary types of mental pathology [16] cause false diagnosis of bipolar disorder, depression, schizophrenia, and other psychoses [17, 18].

The most common mental phenomena of behFTD are determined by damage to the frontotemporal region, which is manifested by clinical symptoms of disorders of attention, empathy, interpersonal relationships, social behavior, and apathy. These symptoms are not specific, and their clinical overlap with manifestations of schizophrenia is notable. Differentiation between schizophrenia and behFTD is critical in choosing a therapeutic strategy and determining the prognosis owing to the potential treatability of the primary mental disorder.

The presented clinical case describes a "traditional" diagnostic dilemma, which has received a modern genetic interpretation within the family history.

CLINICAL CASE

Patient K, 56 years old, is a professional pop musician who recently worked as a taxi driver. For 8–10 months before seeking medical help, he was jobless. The patient is divorced, has three children, and lives alone.

Anamnesis. A change in the patient's habitual behavior was first noticed by relatives in the Spring of 2021 after a severe form of COVID-19, which occurred with febrile fever

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and hallucinatory syndrome and was initially interpreted as a consequence of infection. However, the "strange behavior" gradually progressed. Therefore, in August 2022, the patient's father initiated a visit to a psychiatrist.

The following behavioral changes were noted. The patient became reserved, stopped leaving the house, began to avoid meeting with friends, minimized communication with relatives, spent all his time watching TV, cooked the same food for himself (pasta and sausages), and showed little initiative in searching for a lost job. His mood seemed low, and he looked depressed. He showed emotional withdrawal, indifference. Moreover, he had episodes of memory loss when he periodically "got confused" about the names of his children, "suddenly forgot that he had a daughter", and could not remember some geographical names. However, in general, according to relatives, memory and intellectual functions were not impaired. The patient continued to work as a taxi driver, knew the area well, and cared about himself.

In the Summer of 2022, the patient repeatedly demonstrated "ridiculous statements and actions". For example, one time he went on an allegedly appointed date with a girl at a restaurant; however, it turned out later that no date was planned. After waiting in vain for the "girl", he did not express any disappointment or bewilderment. Another time, he refused to move to a new place of residence closer to his father, justifying this with an expected visit from his beloved woman, who, according to the patient, is "the lead singer from the group ABBA" and with whom he "talks every day via messenger in Russian". Other absurd behaviors occurred from time to time, particularly episodes of communication with a photograph of a woman as if she was a real person.

He was consulted twice by a psychiatrist in the Summer and Autumn of 2022; based on the consultation results, schizophrenia with predominantly negative symptoms was diagnosed, and antipsychotic drugs were prescribed, which the patient did not take. In the Autumn of 2022, the patient was examined by a neurologist, and no pathology was detected, no additional examinations were prescribed, and continued treatment with a psychiatrist was recommended.

In January 2023, the patient's ex-wife and children noted a behavior that was previously atypical for the patient when driving a car—he behaved impulsively and swore nastily. When meeting with children after a long separation, he showed aloofness, communicated with them formally and very briefly, and ate quickly and went into another room without explanation. According to the patient's ex-wife, he had previously been "not very sociable and talkative"; thus, she did not attach any importance to this.

Despite some aloofness from external events, the patient was able to travel independently by plane to his family, orientated himself well in the other city, and traveled by various types of transport. Subsequently, it turned out that approximately 2 years before the "first" symptoms of the disease, the patient began to "sell/mortgage" gradually his property, take out large amounts of bank loans, and "contacted" "fraudsters and a publicly traded company on the Internet". The patient himself was uncritical of this, believing that the money would definitely be returned to him, and became irritated in response to the admonitions of his relatives.

Family history. Coincidentally, the patient's mother underwent examination in 1986–1987 in the same clinic where the patient was examined and was diagnosed with a cervicothoracic form of ALS with the development of severe bulbar–pseudobulbar syndrome. Two years after, she died at the age of 47. At the advanced stage of ALS, there may have been cognitive decline and "inappropriately excited mood", which was difficult to qualify accurately because of the gross manifestations of bulbar–pseudobulbar syndrome and speech difficulties. According to anamnestic information, the patient's maternal aunt and grandfather had a disease with a clinical presentation similar to ALS.

Physical examination data. The patient did not actively express any complaints, except for "a possible slight decrease in memory". He was dressed neatly and appropriately for the situation. He did not participate actively in the conversation, and his speech was monotonous and unemotional. He answered the questions essentially, but briefly. His speech was grammatically correctly. He did not fully understand the belonging of words to a certain semantic category, could not determine the cardinal signs of similarity and difference between concepts (e.g., between "bird and plane"). He showed a slight decrease in the tempo and speed of speech and was apathetic, passive.

No cranial nerve pathology nor symptoms of oral automatism were observed. Strength in the limbs was preserved. No changes in muscle tone and reflexes were detected. Additionally, no muscle atrophies or fasciculations and hypo/bradykinesia were detected. Coordination tests showed no pathology. Frequent stereotypical rubbing of palms was noted, and secondary skin damage (redness, dryness, cracks) were observed. A brief neuropsychological study revealed decreased scores in the Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery scales, a set of tests for assessing frontal dysfunction, with 19 and 9 points, respectively.

Magnetic resonance imaging (MRI) of the brain (Fig. 1) showed signs of severe brain atrophy, mainly in the frontal and temporal regions. Electroneuromyography of the muscles of the upper extremities revealed that the conductive function of the motor and sensory fibers of the nerves of the arms was not impaired. The results of needle myography showed no signs of current denervation lesions in the arms and legs. When testing muscle strength, no signs of muscle weakness were noted. Tests for hidden weakness were negative. It was then concluded that no evidence for the presence of motor neuron disease was found.

Genetic study. As a result of analysis of deoxyribonucleic acid, an increased number of copies of the GGGGCC

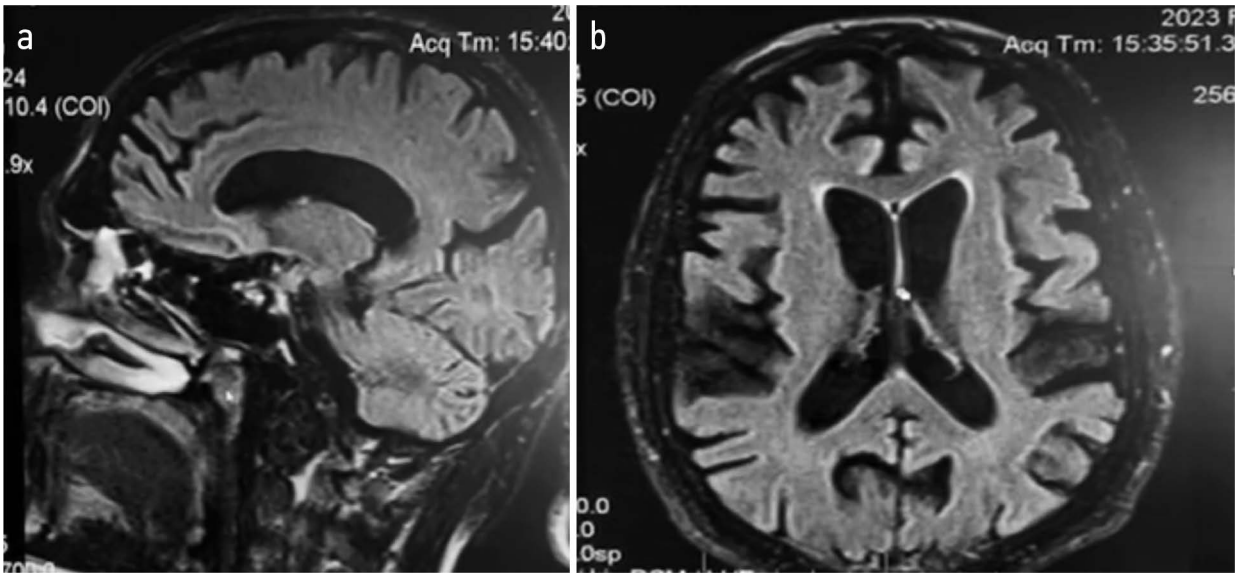

Fig. 1. Magnetic resonance imaging of the brain in the sagittal plane (*a*) and axial plane (*b*): signs of marked atrophy (predominantly frontal and temporal).
Рис. 1. Магнитно-резонансная томография головного мозга в сагиттальной плоскости (*a*) и аксиальной плоскости (*b*): признаки выраженной атрофии (преимущественно-лобной и височной).

repeat, localized in the C9orf72 gene, responsible for the development of ALS and/or FTD, were identified in one of the chromosomes.

Diagnosis. Significant frontotemporal degeneration associated with a mutation in the C9orf72 gene (mainly behavioral variant; progressive aphasia to a lesser extent) was diagnosed.

DISCUSSION

In most cases, the predominance of mental and behavioral disorders in the clinical presentation of the disease in the absence of obvious neurological changes favors the diagnosis of primary psychiatric pathology, as demonstrated in the case of patient K. For a long time, the patient was considered to have schizophrenia, and treatment was aimed at relief of negative psychopathological symptoms. This diagnosis was justified by absurd behavior, personality changes, apathy, and "emotional hardening". The question of the need to revise the diagnosis, interpret psychopathology differently, and order additional studies arose later and was due to the discovery of a family history of ALS. This was the turning point in the diagnostic process.

Clinical data analysis showed that the disease symptoms appeared in the patient more than 3–4 years before contacting doctors. The first signs of behavioral disorders manifested in the fact that patient K began to behave extremely frivolously and made risky financial transactions for a large amount. Moreover, he was uncritical of this and subsequently did not admit his own mistake. A significant exacerbation of clinical manifestations occurred against COVID-19, when obvious signs characteristic of the current dementing process appeared. The clinical onset of the disease was characterized by distinct psychopathological manifestations with predominantly negative symptoms (social and emotional isolation, apathy, abulia) and delusional and hallucinatory episodes.

Negative psychopathological symptoms that prevailed in the patient's disease presentation often become diagnostically ambiguous and lead to the need to differentiate schizophrenia from behFTD. In a subset of FTD patients, psychotic/behavioral symptoms appear before the onset of cognitive decline. This often leads to a delay in accurate diagnostics and inadequate prescription of antipsychotic drugs. Among predictors of psychotic symptoms, several studies have reported the role of greater involvement of certain anatomical regions, such as the right frontotemporal lobe [18].

The spectrum of clinical symptoms in behFTD, in addition to negative ones, includes aggressive behavior, irritability, and disinhibition and, less commonly, loss of interpersonal communication skills and socially unacceptable actions. Delusions, hallucinatory behavior, and suspiciousness are considered much rarer variants and are present in only a fifth of patients [19, 20]. Evidence of the dynamics of mental symptoms is noted as the disease progresses and when manifestations of disinhibition and compulsive behavior are reduced and apathy increases, which is associated with continued medial frontal cortex degeneration [21].

The difficulties of distinguishing between behFTD and schizophrenia, especially when the neurodegenerative process develops at an early age, are aggravated by the fact that no cognitive test clearly distinguishes behFTD from primary mental disorders [22]. A comparison of the diagnostic criteria for these diseases shows that 41% of patients with schizophrenia met the classifier criteria for behFTD [23].

Therefore, the International Neuropsychiatric Consortium has established consensus recommendations for the

assessment of adults with new-onset behavioral changes in middle and old age that may indicate behFTD. A checklist for the diagnosis of behFTD versus a primary mental disorder and recommendations for medical history taking, clinical tests, neuropsychological and physical examinations, social cognition tests, neuroimaging, blood and cerebrospinal fluid tests, and genetic testing have been developed [24].

The crucial points of differentiation are the aspects characteristic of behFTD, namely, progression over 1–2 years, pathology according to MRI and/or positron emission tomography of the brain, decreased social intelligence (recognition of emotions, "theory of mind"/"understanding of other person's mind", moral reasoning, and empathy), presence of a genetic mutation (C9orf72 gene), and presence of new biomarkers, namely, the light chain of neurofilaments in the blood serum or cerebrospinal fluid [24].

Current international criteria for behFTD indicates a diagnosis of possible, probable, and definite behFTD [25]. A diagnosis of possible behFTD requires the presence of three of six criteria (i.e., disinhibition, apathy or passivity, loss of sympathy or empathy, perseveration/stereotypy/compulsiveness, hyperorality, and dietary changes) and executive deficits with relative preservation of memory and visuospatial functions.

Our patient showed four of the symptoms, namely, apathy, loss of empathy, compulsions in the form of hand rubbing, and executive dysfunction. The diagnosis of probable behFTD was complemented by symptoms of progressive behavioral/cognitive deterioration and MRI signs of frontotemporal cortical atrophy [25]. Thus, there are different ideas about the sensitivity and specificity of clinical criteria for diagnosing probable behFTD. Some authors revealed high specificity (99%) [26] and sensitivity (85%) [27]. Others defined the criteria as having "acceptable sensitivity" (76%) and unclear specificity. In later stages of behFTD, there may be a reduction in symptoms of disinhibition and compulsive behavior, but an increase in apathy, which indicates further cortical degeneration [21]. The preservation of memory and visual–spatial functions is characteristic. The false impression of memory impairment in some cases may be due to dysfunction of the frontal lobes, associated perseverations, and impaired attention [21].

Furthermore, the early stages of behFTD are characterized by relative preservation of executive functions, which become disrupted as dorsolateral prefrontal cortex degeneration progresses [28, 29]. The dissociation of behavioral and cognitive symptoms in the early stages of behFTD results in significant difficulties in distinguishing from primary mental illnesses. Traditional screening diagnostics using the MoCA and Mini-Mental State Examination (a brief scale for assessing mental status) in cases of suspected behFTD is found to be low-informative, and the presence of apathy can introduce significant errors in the test results. Existing clinical criteria for behFTD in most cases allow a high probability of distinguishing this variant of dementia from Alzheimer's disease. Moreover, ensuring reliable differentiation with their help from primary mental pathology is questionable [30]. However, in the early stages of the disease, there may be no signs of atrophy of the brain substance according to MRI [31].

Reliable behFTD was diagnosed in the patient based on combined clinical and neuroimaging criteria and identification of a known genetic abnormality, C9orf72. The C9orf72 repeat expansion explains almost 50% of familial and 30% of all frontotemporal lobar degenerations. A recent large genetic study of confirmed behFTD demonstrated a male predominance in this group (61%) [5].

Additionally, an abnormality of the C9orf72 gene determines the development of ALS, which is detected in approximately 15% of patients with behFTD [32], or a combination of behFTD and ALS. Patients with behFTD combined with ALS most probably have an inherited disorder. In the present case, the clinical distribution was different in the family history; hence, no signs of ALS were revealed in patient K with behFTD, but his mother was diagnosed with ALS without signs of behFTD, at least in the early stages of the disease, and it is also possible that the patient's aunt and maternal grandfather had ALS.

Thus, the presented clinical case is an example of a diagnostic error caused by the use of psychopathological and behavioral symptoms as diagnostic reference points. Worrying "signs" in patients with mental pathology regarding the presence of behFTD may include late (relative to primary psychopathology) age of disease manifestation, relatively higher rate of progression of symptoms, and positive family history of dementia or ALS. These points become decisive for genetic testing for C9orf72. Identification of key mutations is required for the diagnosis of reliable behFTD and determines the need to use the genotyping method in widespread clinical practice to avoid diagnostic errors.

ADDITIONAL INFORMATION

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