The behavioral variant of frontotemporal dementia: a clinical case

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The paper is devoted to frontotemporal dementia (FTD), one of the most common forms of frontotemporal degeneration. The main symptoms of the disease include disinhibition, lack of empathy, obsessive-compulsive symptoms, apathy, cognitive impairment, appetite changes, and progressive changes in social behavior. In parallel, there are personality changes that are characterized by lower levels of self-awareness and by progressive psychological and social maladaptation of patients in society.
The paper describes a clinical case of FTD in a female patient with marked behavioral changes and personality disorder. A 52-year-old woman was admitted to the alcoholism treatment department for alcohol intoxication and symptoms of mental confusion. According to her relatives, drinking too much alcohol every day, she was found to become rude, indifferent to others and her own duties, sharply limited the range of her activities and communication, and showed a decline in memory for current events. Psychopathological examination determined a distinct motivational-volitional decrease, the patient's inability to mobilize mental activity, non-critical thinking, and indifference. X-ray diagnosis revealed the changes characteristic of frontotemporal neurodegeneration (atrophy of the frontal and temporal lobes prevails). The described case confirms that alcohol abuse can mask organic disorders that develop in systemic cerebral atrophy.

Keywords: *frontotemporal dementia; behavioral variant of frontotemporal dementia; cognitive impairment; dementia; degenerative brain diseases; functional magnetic resonance imaging; tractography.*
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Frontotemporal lobar degeneration is a group of heterogeneous disorders which differ in their clinical, neuropathological and genetic characteristics, but include different varieties of frontotemporal dementia, motor neuron disease, progressive supranuclear palsy and corticobasal degeneration.

This article is devoted to one of the most common forms of frontotemporal degeneration which is called frontotemporal dementia (FTD).

The first patient with FTD was described in 1892 by Arnold Peak, and this disease was considered in the diagnostic framework of Peak's disease for more than a century. At present, only a small subset of FTD with specific histopathological characteristics is related to this disease [1]. In 1998 FTD was divided into several clinical subtypes regardless of the recorded pathomorphological changes: the behavioral variant (BV FTD) and primary progressive aphasia (PPA FTD) [2; 3; 4; 5]. In 2004 a classification was proposed according to which PPA FTD was divided into the following subtypes, depending on the clinical features of speech defects: semantic aphasia without impairment of speech fluency, agramatic aphasia with impairment of speech fluency, and logopenic aphasia [6]. However, if at the onset of the disease these subtypes appear in isolation, as the disease progresses, they often represent a single aphatic complex [7].

The behavioral variant of FTD (BV FTD) is the most common subtype which is characterized by pronounced changes in behavior and personality disorder [2; 8; 9].

Despite the fact that BV FTD is considered a single syndrome, there is significant variability in its clinical picture [9], which is a clinically, pathologically and anatomically heterogeneous disorder and the second most common neurodegenerative disease after Alzheimer's disease (AD) with a cognitive defect and the debut before the age of 65. So, the average age of clinical manifestation of this disease is 58 years, and in general, not older than 65 years [8].

The development of the clinical syndrome may be preceded by a long phase of subclinical behavioral changes and social disorders [5]. Some researchers note that the initial symptoms can be barely distinguishable, «confusing» and can be taken by clinicians for depression or adaptation disorders [10]. Unlike AD, memory impairment during the development of BV FTD at the initial stages of the disease is less dramatic.

Cognitive deficit in the premorbid period is the cause of judgment impairment, inattention and increased distractibility, loss of planning ability and disorganization of activity. At the same time, patients become overly trusting and often fall under the influence of financial fraudsters, as they lose their ability to assess possible rewards or punishments [11]. In the prodromal phase, patients conflict with their family members, show alienation from the family and friends, and may find new hobbies [5].

The main symptoms of the disease include disinhibition, obsessive-compulsive symptoms in the absence of empathy and the presence of apathy, cognitive impairment, changes in appetite and progressive changes in social behavior [2; 1; 5]. In parallel with this, personality changes develop, which are characterized by a decrease in the level of self-awareness and increasing psychological and social maladaptation of the patients in society [10].

In 2011, the diagnosis recommendations for BV FTD were revised by the International Consortium [12; 5]. According to the criteria developed by the consortium, the following symptoms should be present in the clinical picture:

1. Disinhibition of behavior (loss of manners, negligent actions, inadequate or puerile behavior). In 76% of patients [12], depending on gender and personality characteristics, the style of interpersonal communication changes. They lose control over the privacy of the interlocutor, encroaching on the personal space of another person, and can make offensive jokes, comment aloud the words or actions of other individuals, and speak frivolously with strangers.

2. Apathy or inertia; 85% of patients show a lack of spontaneity and a pronounced decrease in motivation for activity and typical targeted actions. Motor mutism develops with the disease progression or at its last stages [11].

3. Loss of empathy in the form of a pronounced decrease in motivation, social interest and need for communication [13], including the family circle. «Fading» of emotionality in the form of loss of warmth in relationship, reduced manifestations of attachment.

4. Perseverations (motor and speech), obsessive-compulsive symptoms. 71% of patients have complex movements and language rituals. They walk aimlessly, knock with their feet, play computer games for a long time, perform strange rituals [11].

5. Hyperorality and dietary changes in the form of overeating, alcoholization, smoking, possibility of consumption of inedible objects. Preference for sweet food develops, and sense of fullness may be absent. Patients empty fridges and kitchen cabinets, steal food in stores [11].

Positive symptoms (such as disinhibition and related behavioral deviations, obsessions, hyperorality) which appear at the onset of the disease, at the next stages of its clinical progression worsen, and at the later stages have a tendency to decrease. Speech is becoming stereotyped, echolalia is detected.

Negative symptoms (such as apathy, loss of empathy) intensify throughout the entire period of the disease [14]. The semantic deficiency is revealed during the disease progression [11].

Neuropsychological diagnosis reveals loss of sensory-motor and visual-spatial skills, and short-term memory impairment

Etiology

The molecular basis of BV FTD is heterogeneous, as with most other neurodegenerative disorders, and is characterized by the presence of protein deposits which form various organ inclusions in the central nervous system cells [7]. Specific protein deposits in the brain, such as microtubule-associated tau protein, DNA-binding protein with an active response with a molecular weight of 43 kDa (TDP-43), and multifunctional fused in sarcoma protein (FUS) play a specific role in the pathogenesis of degeneration. About 50% of cases of FTD are associated with the TDP-43 protein, including sporadic and familial forms, 45% are associated with tau protein. FUS protein deposition is much less common (5%) [5; 4].

Neuroimaging methods allow to estimate both structural and functional disorders. Atrophic changes mainly in the frontal lobes, as well as changes in the islets, temporal lobes and basal nuclei are detected during voxel MR-morphometry [15]. Structural MRI of the head is especially useful in differential diagnosis of FTD and AD, with sensitivity of 55–94% and specificity of 81–97% (by comparing atrophy patterns) [16]. In patients with frontotemporal degeneration, a significantly more pronounced atrophy of the frontal and temporal lobes with a relatively intact hippocampus is observed compared with AD patients.

Some researchers [9], based on a cluster analysis of the obtained neuroimaging data, distinguish four subtypes of the behavioral form of frontotemporal dementia (Table 1).

For assessment of functional impairment among patients with BV FTD, positron emission tomography (PET) with 18-fluorodeoxyglucose is used, which allows to identify areas of local glucose hypometabolism due to impaired neuron activity. The use of PET is justified, first of all, in connection with its negative prognostic value [17].

By the way of illustration, we present a clinical case of a patient with a history of long-time alcohol abuse, a detailed clinical, psychopathological and instrumental analysis of whom made it possible to diagnose a behavioral variant of frontotemporal-temporal degeneration.

Table 1. *BV FTD subtypes*

BV FTD subtypes	Atrophic process localization
Frontal-dominant	Predominant atrophy of the frontal lobes (50% of cases).
Frontotemporal	Atrophy of the temporal lobes predominates.
Temporal-dominant	It differs in atrophy of the temporal lobes (more on the right side), limited by the middle and lower temporal gyrus
Temporal-fronto-parietal	Atrophy of the parietal and temporal lobes (mainly on the right side) with the additional involvement of the medial sections of the frontal lobes predominates

Clinical case

***Patient S.**, 52 y.o., was admitted to the FSI «V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology», the department of alcoholism treatment with a diagnosis of amnestic syndrome due to alcohol consumption (ICD code: F10.6) in a state of intoxication and symptoms of mental confusion.*

According to the patient's relatives, over the past 5 years she has been systematically drinking alcohol in small doses, over the past 2–3 years she has been drinking alcohol daily. About two years ago, she was hospitalized with alcohol intoxication to a hospital of general somatic profile. Since then, a mild decrease in memory for current events has been noted. Before this hospitalization she was in a condition of heavy alcoholic intoxication in the toxicological department of I.I. Dzhanelidze Research Institute of Emergency Medicine. She was discharged and left the hospital independently, after that she was absent from home for three days. After she returned home, she could not say where she had been and what had happened to her.

The patient's family history is negative for mental diseases. She graduated from a university, worked as a teacher of a technical discipline at school. About 4 years ago she was transferred to the work of a teacher

of an extended-day group, and a year before this hospitalization she was dismissed. The reason for dismissal is unknown. She has not reached the retirement age. She is married, relationship with her husband is non-conflict. She has an adult son from her first marriage.

Somatic status. *The skin and visible mucous membranes are clean. Heart sounds are muffled, noises are not detected. Pulse is 88 beats/min, rhythmic, satisfactory characteristics. BP is 130/90 mm Hg. Harsh breath sounds are heard throughout all lung areas, no wheezing. Urination is painless, urine has a normal color. Intestinal dysfunction has not been identified.*

Neurological status: *There are no cerebral symptoms. Cranial nerves: the sense of smell is preserved on both sides. Eye fissures D=S, reaction to light direct, consensual, lively. Pupils D=S. There is no nystagmus. The face is somewhat asymmetrical, the tongue in the midline. Normal hearing acuity. No swallowing disorders, sonorous voice. The speech is distinct, but she answers with an obvious delay, using one-word replies. She executes simple commands. The pharyngeal reflex is invoked, taste is preserved. There is no paresis. Muscle tone in the extremities is normal, D=S. Muscle strength – 5 points. The patient performs coordination tests. Periosteal and tendon reflexes are lively on both sides. Neither pathological reflexes, nor gear wheel symptom have been found. Superficial and deep sensitivity is preserved. Symptoms of tension are absent. The function of the pelvic organs – urination is not completely under control, low sensitivity to the urge to urinate, she can urinate in bed, remove pampers. Unstable in the Romberg position.*

Mental status: *Consciousness is not clouded. The patient is sloppy. Contact is available, but only formally. Basically, she is oriented in the environment. She understands that she is in hospital, but does not comprehend the profile of the medical institution and the purpose of hospitalization. She can determine time using a watch, but there are signs of retrograde amnesia: she believes that she has been in the hospital for 2 days. She realizes her personality. The judgments are simple, primitive, limited to a narrow circle of domestic needs. Memory and intelligence are sharply reduced. No delirium or disturbances of perception. The patient is affectively smooth, indifferent to the environment. She smokes a lot, unceremoniously asks anyone for a cigarette, no other interests. Sleep and appetite are normal. After detoxification and alcohol withdrawal: the condition without significant dynamics.*

Report of a medical psychologist

Contact is possible, but unproductive. During a conversation, the patient is passive, inert, emotionally monotonous, indifferent to what is happening, stubborn. She is indifferent to her appearance, untidy, sloppy. Her speech is slow, with difficulties finding the right word, lexically impoverished. She understands addressed speech, answers in the context of the question asked, but briefly, formally, mostly with one-word replies (I don't know, I don't remember). She sets out biographical data only with reference to a question, evasively, and has difficulty recalling life events. She is uncritical of her condition and behavior; ignores comments, requests of medical personnel and other patients (for example, to put on outerwear when going outside to smoke; put on pampers; take a shower). She does not support contact with others, is uncommunicative. She realizes her personality, but is inaccurate in time (confuses the current date, though names the year and month correctly), partially in the setting (understands that she is in hospital, but cannot name the hospital type); she orients herself correctly in real space and is not lost when she goes outside. She doesn't have complaints and doesn't understand why she was hospitalized. She can't describe the history of her illness («I don't know ... I was at the cottage ... I fainted ... they brought me»). The use of alcohol is categorically denied.

Clinical and psychological examination

The instructions are generally understood and implemented correctly, sometimes additional explanations are required. The patient is not always immediately involved in the assignment, experiencing difficulty concentrating, maintaining concentration. Tasks are carried out formally, without making an effort. She needs motivation. The help of the experimenter is not always accepted. She does not show interest in the results. In 2/3 of the tasks «Find the odd one out» correctly sets out odd images but gives a random explanation. She doesn't understand figurative meaning of proverbs and metaphors (all answers are «I don't know»); comparison of pair concepts is difficult («I don't know»), a hint sometimes helps. Instability of the thinking process is obvious, judgments are often random, unmotivated, with casual associations, which is usually observed with fatigue and fragility of thinking processes. The level of generalization is reduced. One-word answers and extremely primitive verbalization are characteristic. The rate of sensory-motor reactions is moderately slowed down (the time for doing one Schulte table is 79 seconds, the norm is up to 50 seconds), with no signs of exhaustion. The «countdown» test (100–7) is verbally performed with numerous errors, reflecting both difficulty in intellectual activity and gross violations of voluntary attention (difficulty in maintaining and shifting attention, decreased concentration). The volume of short-term speech-auditory memory without repetition and working memory is not more than 4 units. Mnemogramma «10 words»: 4–5–4–5–5–4; delayed repetition is impossible; «extra» words appear during repetition. Wechsler's subtest «Repeating numbers»: direct count – 6 units, countdown – 4 units. She repeats complex sentences correctly, but cannot repeat them under conditions of interference, a hint does not help.

Retelling a short text after the first presentation is only partially possible; she does not understand the meaning of the stories. Long-term memory (stock of knowledge) is reduced (Wechsler's subtest «General awareness» is performed below standard values). When doing Benton visual retention test she does only 4 of 10 tasks with bad mistakes (perseveration, rotation). She can draw a required picture. The «Clock» test is satisfactory with difficulties in arranging numbers (at the beginning the numbers are in the reverse order, but when shown the error, she corrects it), the set time is indicated correctly. She has difficulty nominating images in pictures, naming surrounding objects; assistance helps to remember. Writing with errors – replacement of letters (literal paragraphy). Reading skills are preserved. In general, a marked decrease in cognitive processes is revealed: the ability to learn new information is reduced, short-term and speech-hearing memory is decreased. The phenomena of partial disorientation in space and time, a decrease in the level of generalization without distinct signs of exhaustion of mental processes are noted.

It should be noted that the quantitative indicators obtained in the study should be considered as indicative, since the results are largely due to a distinct motivational-volitional decline, the patient's inability to mobilize mental activity, and uncriticality.

Minnesota Multiphasic Personality Inventory (MMPI) profile is unreliable (F = 80), code F"L¯K÷ 50"689'274/1÷3≠.

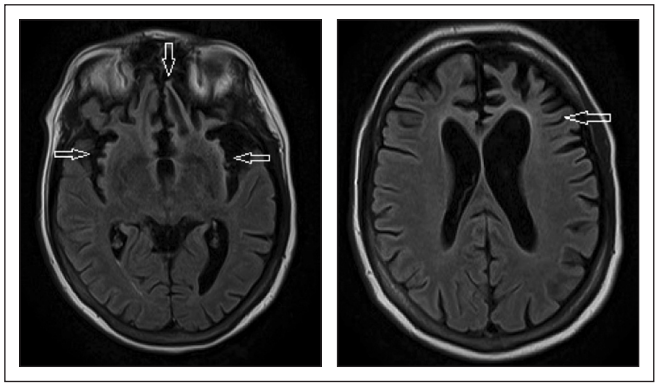

Fig. 1. *Brain magnetic resonance images of Patient S., IP FLAIR. Atrophic changes in the islets and frontal lobes, with a cortical signal increase on MR imaging. There is a compensatory expansion of the lateral fissures and frontal horns of the lateral ventricles. Changes are more pronounced on the left (the authors' own observation)*

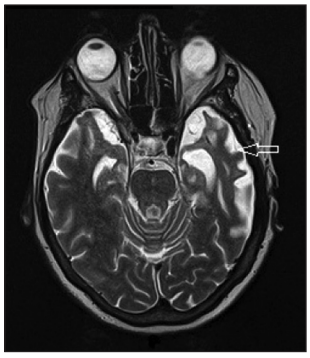

Fig. 2. *Brain magnetic resonance images of Patient S., T2-WI. Atrophic changes in the temporal lobes, mainly in the anterior parts, with compensatory expansion of the temporal horns of the lateral ventricles. Changes are more pronounced on the left (the authors' own observation)*

The leading psychopathological symptom is the psycho-organic symptom complex (amnestic version) with a pronounced decrease in attentive-mnestic processes, a decrease in the level of generalization, criticism, violation of motivational-volitional characteristics, with phenomena of partial amnestic disorientation.

Routine clinical and laboratory examination

Clinical blood analysis: hemoglobin 129 g/L; red blood cells 4.65; platelets 73; white blood cells 4.86; hematocrit 0.42; ESR 8 mm/hour; band neutrophil – 1; segmented neutrophils 60; eosinophils 3; lymphocytes 32, monocytes 4. Biochemical blood analysis: urea 3.18, glucose 6.2, total bilirubin 5.8, ALT 24, AST 39, GGT 24.

A number of neurodegenerative changes were revealed according to the data of the planned magnetic resonance imaging (MRI) of the brain. MRI findings: expansion of the perivascular spaces of Virchow–Robin at the level of the basal nuclei and semi-oval centers along the penetrating vessels. The lateral ventricles are significantly expanded, asymmetric (D <S), mainly in the frontal and temporal horns, the third ventricle is expanded to 14 mm, the fourth ventricle and the aqueduct are not changed. The fissures of the subarachnoid space are significantly and unevenly widened along the convexity surface of the frontal and parietal lobes of the cerebral hemispheres, at the level of the lateral cisterns (S>D), poles of the frontal and temporal lobes against the background of an asymmetric decrease in the volume of the frontal and temporal lobes, predominantly in the anterior sections (S>D), and insular lobes (S>D). Thinning and reduction in the volume of the corpus callosum with signs of its underdevelopment (atrophy against the background of agenesia) is detected. The chiasmal-sellar region and structures of the brain stem without signs of pathological changes (Fig. 1, 2).

The results of MRI diagnostics correspond to neurodegenerative brain lesion characteristic of the frontotemporal type of dementia (atrophy of the temporal lobes predominates).

Discussion. The patient with a rare debut in the form of chronic alcoholization within the framework of the behavioral variant of FTD. The clinically developed stage is characterized by the following: positive symptom complexes, which are expressed moderately and gradually increase; negative symptom complexes, which are moderate and maintained at the plateau level.

Currently, BV FTD remains a poorly curable disease; severe disability develops already 8 to 11 years after the onset of the first symptoms. Understanding the progression of behavioral symptoms is particularly important for caregivers [14].

Thus, in clinical practice, in order to avoid a diagnostic «scotoma», a multidisciplinary diagnostic approach is recommended. A typical picture of BV FTD is characterized by hypometabolism in the frontal, temporal lobes, basal nuclei. Some researchers note unilateral or bilateral hypometabolism in the prefrontal cortex, anterior temporal lobe, anterior cingulate gyrus, and basal ganglia [18; 19; 20]. According to some researchers [21], with the help of PET-FDG, two variants of brain hypometabolism were identified depending on the predominant location – «frontal» and «temporal limbic», which correlate with various cognitive impairments.

The analysis of clinical and morphological changes in the brain has allowed many authors to identify areas of the brain that are responsible for particular symptoms (Table 2).

Therefore, at the stage of the clinical and instrumental diagnostics, it is necessary to take into account not only the presence of local atrophy detected by routine methods, but also evaluate the functional connectivity of the pathways of the brain.

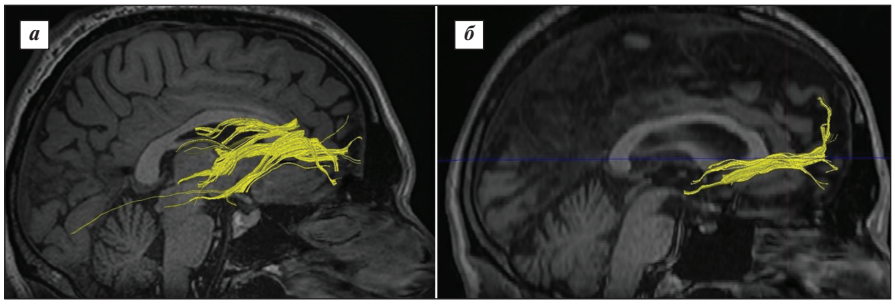

Fig. 3. *Images obtained using voxel-based MR morphometry: a – a norm; b – atrophy of the orbitofrontal cortex and secondary selective degeneration of the corticostriatal fibers (the authors' own observation)*

Table 2. *Clinico-morphological correlations in BV FTD*

Symptoms	Morphological changes
	Positive symptoms
Disinhibition of behavior	Convexity surface of the orbitofrontal cortex [11]
Perseveration (motor and speech)	Atrophy of the orbitofrontal cortex and secondary selective degeneration of corticostrial fibers with the formation of atrophy of the striatum [3; 22] (Fig. 3).
Eating disorder	Direct curvature of the frontal lobe and convexital parts of the frontal lobes [23] and atrophy of the lateral orbitofrontal cortex with secondary degeneration and atrophy of the posterior parts of the hypothalamus without reducing the level of neuropeptides (typical for TDP-43-pathia) [24]
	Negative symptoms
Apathy or inertia	The symptom is associated with dysfunction of the neural networks of the prefrontal cortex with the anterior part of the cingulate gyrus and the right head of the caudate nucleus, including the ventral striatum [11; 10]
Loss of empathy	Degeneration of several «key points»: the anterior divisions of the right temporal lobe (non-dominant hemisphere), the fronto-insular cortex on the right, the right anterior cingulate cortex and the ventral striatum [25]
Cognitive deficiency	Atrophic process of the dorsolateral cortex, anterior cingulate gyrus and dysfunction of the frontostriatal loop [25]

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Conflict of Interest Statement

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