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Frontotemporal dementia; clinical-radiological study

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Summary

Frontotemporal dementia is the third most common degenerative condition (after Alzheimer Disease and Lewy Body Disease) of the brain. It occurs predominantly after the age of 40 and usually before the age of 65, with equal incidence in men and women. Unspecific behavioral symptoms often lead to misdiagnosis and FTD remains undetected. As in other degenerative dementias, there is no specific tissue marker; therefore, the diagnosis is established in vivo on the basis of clinical and radiological examinations. Structural and functional neuroimaging modalities are most useful in detection and differentiation of FTD as the findings are specific enough to be considered as criteria, based on which the diagnosis of this disorder can be established.

Key words: frontotemporal dementia • computed tomography • MR • Magnetic Resonance Spectroscopy

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Background

Frontotemporal dementia (FTD), in literature also referred to as frontotemporal lobar degeneration (FTLD), has similar occurrence to the Alzheimer's disease in the age group younger than 65 years old [1]. It represents clinically, pathologically and genetically diversified group of neurodegenerative states, in which the disease process affects with more or less asymmetry the frontal and/or temporal lobes.

Regarding the neuropathological lesions, FTD is divided to tauopathies and syndromes without tau protein aggregation in brain. As for genetics, FTD is also heterogeneous. In about 30-50% of cases FTD is familial and is usually inherited in an autosomal dominant way, including small number of cases of *fronto-temporal dementia with parkinsonism linked to chromosome* 17 (FTDP-17) caused by tau protein gene mutation. In several families there was also a link with chromosome 3 [2, 3]; however, in majority of non-tauopathy FTD cases the genetic background is unknown.

In clinical presentation, we mark out 3 main syndromes depending on topography:

- frontotemporal dementia with dominating behavioral disorders, also referred to as *frontal variant FTD* (fvFTD)
- frontotemporal dementia with dominating verbal disorders, also referred to as *temporal variant FTD* (tvFTD), in other words: semantic dementia (SD)
- *progressive non-fluent aphasia* (PNFA), which is least frequent

In FTD diagnosing, not only the presence of typical clinical symptoms is important, but also the result of structural and/or functional neuroimaging examinations. They are one of the most useful diagnostic methods for confirmation of the diagnosis based on clinical image, as well as for canceling out particular symptomatic causes of cognitive disorders, such as tumors, chronic posttraumatic hematomas or dilatation of ventricular system in course

of Hakim's syndrome. These examinations are also essential for differentiation from vascular dementia, particularly caused by multiple lacunar ischemic focuses and Alzheimer's disease. The knowledge about possible radiological lesions that occur depending on the clinical variant of FTD is also important.

Clinical picture

FTD is one of the presenile dementia. The disease usually starts between the age of 50 and 70. The occurrence is as equally often in women and in men.

Frontotemporal dementia – frontal variant (fvFTD)

The beginning is often delusive. Disease usually lasts for 10 years and proceeds slowly. Initial symptoms are often associated with changes in personality, mood, drive and behavioral disorders [4]. Most patients are brought to the doctor by an alarmed family as then patient himself is unaware of the disease. Affected orbital-basal part of cortex of the frontal lobe causes disinhibition, lack of insight, pathologic distraction and impulsiveness, whilst affected anterior part of cingulate gyrus and medial part of the cortex of frontal lobe causes lack of drive leading to akinetic mutism on an advanced stage [5]. Patients can either be motor and verbally overexcited, irritable, with uncontrolled attacks of anger or excessively sentimental, euphoric, also retreated, passive and apathetic. Both of the behavioral patterns can occur alternatingly.

The most typical behavioral disorders concern social behavior (including also crimes and inappropriate sexual behaviors) [6]. Stereotypic, persevering and compulsive behaviors are characteristic. Lack of empathy is one of the earliest symptoms. In some cases on a later stage we can observe elements of Klüver–Bucy`s syndrome which is caused by affected anterior parts of both temporal lobes (change in dietetic likings, usually to sweets, hyperorality, increase/decrease in sexual activity).

Language disorders consist in vocabulary deficits leading to anomia, with preserved understanding of speech and repeating.

Frontotemporal dementia – temporal variant (tvFTD) – semantic dementia

The atrophy concerns mainly the anterior parts of temporal lobes and is more or less symmetrical; at first, it affects anterior part of the left temporal lobe.

What attracts most attention in clinical presentation is the deep semantic (acquired) memory disorders and loss of verbal memory. At the same time the episodic memory (concerning events in patient's own life) and day to day memory are usually preserved. When the right temple is involved prosopagnosia occurs- it can affect not only sight, but also other senses, e.g. associating voice with a person [7].

One of the typical features is fluent speech with tendency to loquacity, with simultaneous deficits in vocabulary of low informational value (so-called empty words). Difficulties with searching names dominate, but the grammatical structure remains relatively correct. Echolalia is a common concomitant symptom.

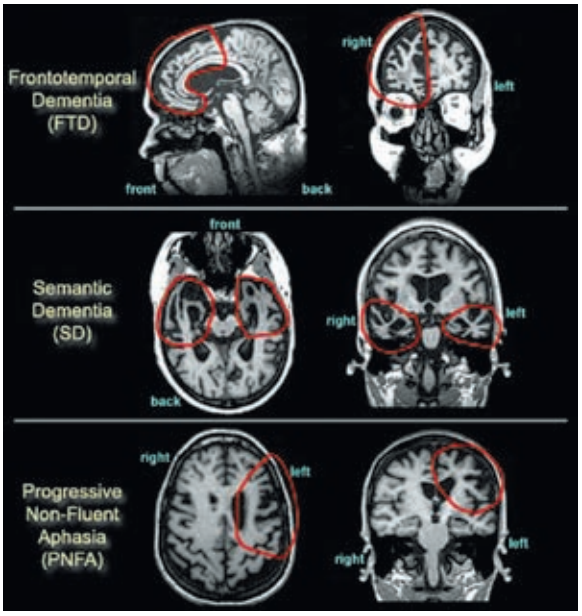
Behavioral disorders manifest early and are similar to those described in fvFTD. Lack of the ability to understand and express emotions is a typical symptom resulting from atrophy of the right amygdaloid body [8].

Progressive non-fluent aphasia (PNFA)

The syndrome is etiologically diversified; in about 50% of cases the diagnosis based on neuropathological examination is the Alzheimer's disease [9]. Brain atrophy is asymmetric and affects left temporal and frontal lobe. Patients with PNFA present lack of speech fluency with preserved understanding. Their utterances are grammatically incorrect, with dominating signs of omission and mistaken use of prepositions and paraphasia. They have difficulties in repeating, reading and writing. At first, the leading symptom is selective verbal unspontaneity. Speech apraxia is connected with involvement of insula [10].

Disordered speech is often a symptom isolated for a very long time.

Scheme 1.



Scheme 1. Examples of brain atrophy in particular types of FTD. The regions proper for FTD are outlined.

Neurological symptoms

Neurological symptoms include: at an early stage- often only deliberation symptoms, urinary incontinence is also possible; at a later stage – Parkinson symptoms, which can be asymmetrical in patients with PNFA syndrome.

Extrapyramidal syndrome of early occurrence suggests corticobasal degeneration (CBD), especially in patients with disordered speech [11].

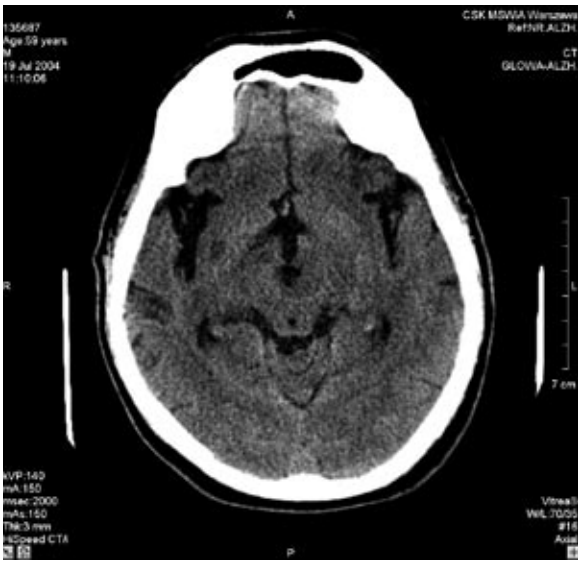


Figure 1. CT scan of the brain reveals widening of the lateral sulci as a reflection of cortical atrophy of temporal lobes. Hypodense lacunar lesion within deep structures of the right hemisphere. Male, aged 59. Secondary education, electrician, does not work (retired). 4 years ago diagnosed with frontotemporal dementia: • lost his interests, became jesting, stubborn, impulsive, excessively interested in sexuality, • started to neglect personal hygiene, • attacks of voracity. MMSE 26 points. Clock test 10 points. GDS 4. BCRS 5 points in the category „self-service". CDR 0,5/1. Neurological examination: deliberation symptoms on the right.

Neuropsychological examination

In clinical variants with dominating speech disorders the neuropsychological examination shows language disorders typical for them. Features characteristic for fvFTD include disorders of operational memory, speech fluency, abstractive thinking and executive functions. The deficit is usually more obvious in inertial patients than in those excessively active and disinhibited. On the other hand, memory, perception, visual-spatial analysis, praxia are normal or relatively well preserved.

Differentiation

Alzheimer's disease

Usually requires differentiation with FTD. Occurs in senior age, memory disorders are the first symptom and behavioral disorders manifest later. Also the ability to live on their own is lost gradually, with time, along with growing dementia, while FTD patients lose it early due to the type of cognitive and behavioral disorders. Stereotypies, perseverances, disinhibition, uncontrollable eating, low social consciousness, neglecting oneself, apathy and impulsiveness are often mentioned as most differentiating between FTD and AD [12].

Pattern of cognitive disorders, different for every patient, can also be helpful in differentiation. Neurological symptoms are not specific, although urine incontinence can happen earlier in FTD than in AD. The differences between neuroimaging examinations described below are also important.

Vascular dementia (VaD)

Patients with VaD caused by multiple lacunar ischemic focuses can manifest clinical symptoms similar to those typical for FTD. Another confusing factor is the slow course (instead of fast) of the disease and lack of stroke in clinical history. The result of CT or MR showing vascular lesions determines the diagnosis.

Treatment

No drugs are known to influence the development of FTD or modify its course. Cholinergic deficit, unlike in Alzheimer's disease, is hardly expressed. Cholinesterase inhibitors proved to be ineffective in treating the disordered cognitive functions and behavioral disorders are in some cases intensified by them.

Difficulties in neurotransmission in serotoninergic system observed in FTD are responsible for impulsiveness, irritability, changes in mood and diet routine. Hence there were attempts to apply selective inhibitors of serotonin uptake in FTD in order to control behavioral disorders. They were open examinations performed on small groups of patients. Fluoxetine, sertraline or paroxetine taken by 11 patients for 3 months gave improvement in disinhibition (6/9 patients), voracity (5/9), compulsion (4/7) and depression in 9 patients [13].

Trazodon has a serotoninergic effect- it is an antagonist of 5HTa/2c postsynaptic receptor and antagonist of 5HT1a receptor. Lebert and Pasquier (1999) observed the influence of trazodon on intensification of behavioral disorders measured with NPI in 14 patients with FTD. After 4 weeks of treatment with dose of 150 mg per day the patients showed lower intensity of illusions, aggression, fear and irritability. After another 2 weeks when patients took trazodon in dose of 300 mg per day additional improvement was observed considering depression, disinhibition and weird motor behaviors [14].

In clinical practice antiepileptic drugs (carbamazepine and valproic acid) and antipsychotic drugs are widely used to control the FTD agitation. Due to the safety profile, the drugs chosen from the latter group should be drugs of the new generation [15].

People taking care of FTD patients are subject to no less burden than those who look after AD patients, although some believe that the burden is even bigger for FTD. They require emotional support and detailed education concerning the course of disease, what helps to organize the care in a proper way.

Neuroimaging examinations

1. Structural CT, MR

Structural FTD examinations show typical topography of atrophy which includes a more or less symmetrical selective atrophy in anterior frontal and/or temporal lobes (fig. 1, 2/3). Classic FTD image is presented as a mixed atrophy of frontotemporal cortex with balloon-shaped dilatation

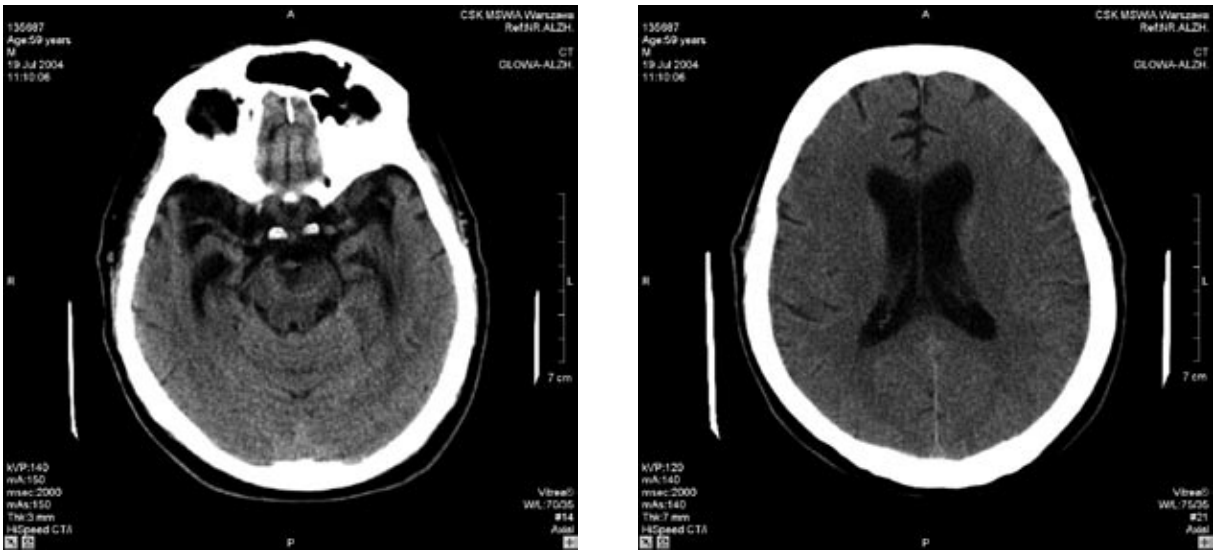


Figure 2/3. CT scan of the brain reveals symmetric atrophy of temporal lobes including their medial parts (MTL). Discrete frontal lobes atrophy. Continuation of examination of the patient from Fig. 1.

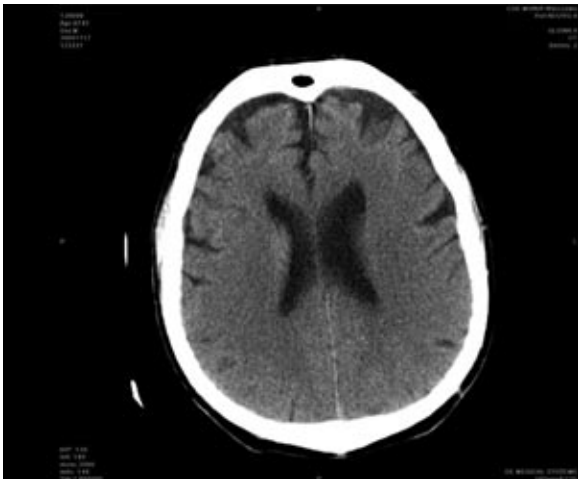


Figure 4. CT scan of the brain reveals cortical-subcortical atrophy of the frontal lobes. Male, aged 74. Secondary education, building technician, does not work (retired). 8 years ago diagnosed with frontotemporal dementia. MMSE 29 points.Test zegara 6 points. GDS 3. BCRS 5 points in category „self-service". CDR 0,5. Neurologically: bilateral grasp reflex, minor bradykinesia and mask-like face, gait without balancing of the upper limbs but with no tremor at rest.

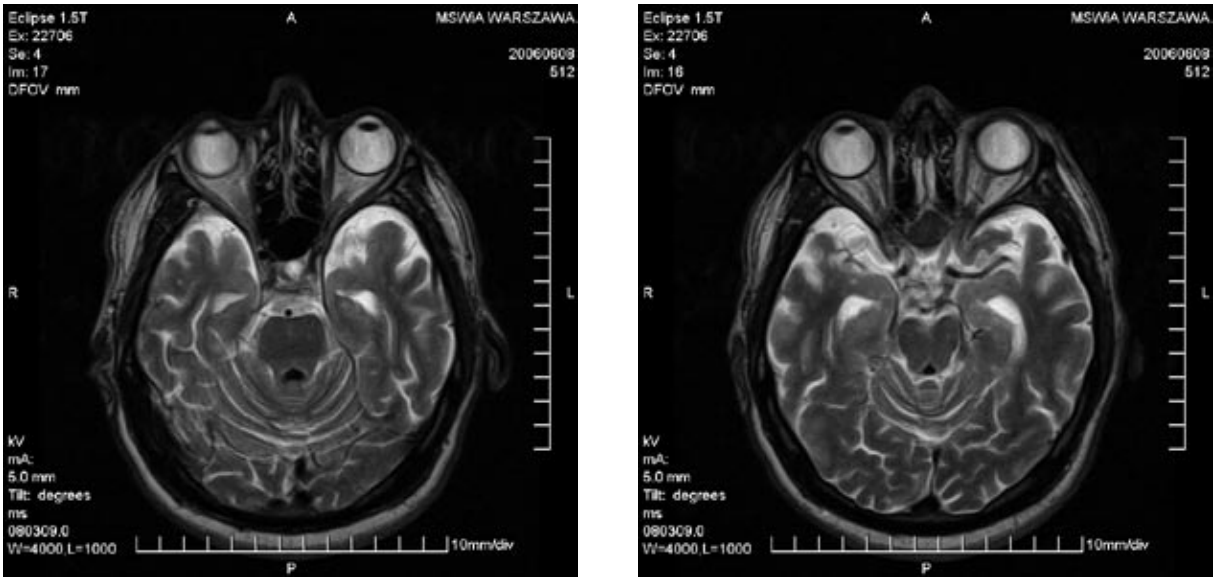
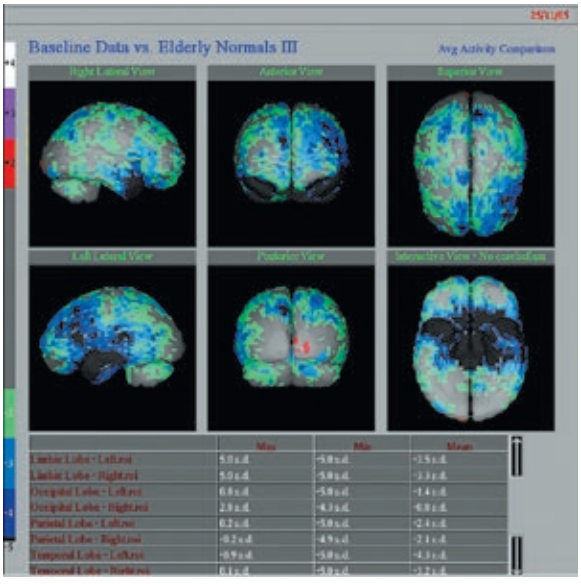


Figure 5. T2 FSE axial scan reveals general cortical-subcortical atrophy, particularly in frontal and temporal lobes. Patient aged 46 with generalized cognitive and behavioral disorders. Major difficulties in initiating and taking simple and complex actions. Multiple verbal and visual-spatial perseverance. Unspontaneous speech, patient with articulation problems, replacing speech with adequate and understandable gestures.



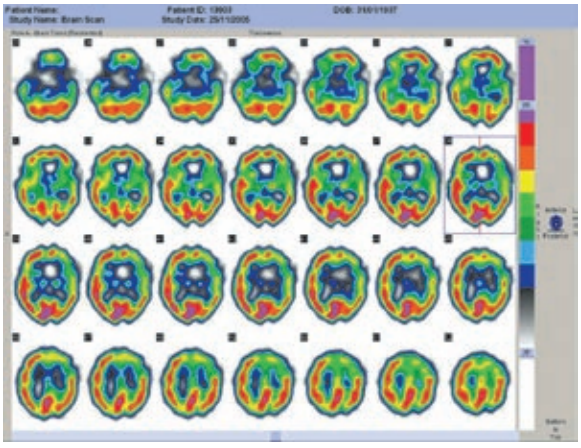


Figure 6. SPECT scans indicate bilateral profound decrease of perfusion/metabolism in both temporal lobes, more significant on the left side. Moderate decrease of perfusion/metabolism in frontal lobes bilateral, more significant on the left side also.

of frontal and temporal horns of lateral ventricles with accompanying variable level of gliosis focuses in the affected lobes, what is clearly visible in FLAIR images.

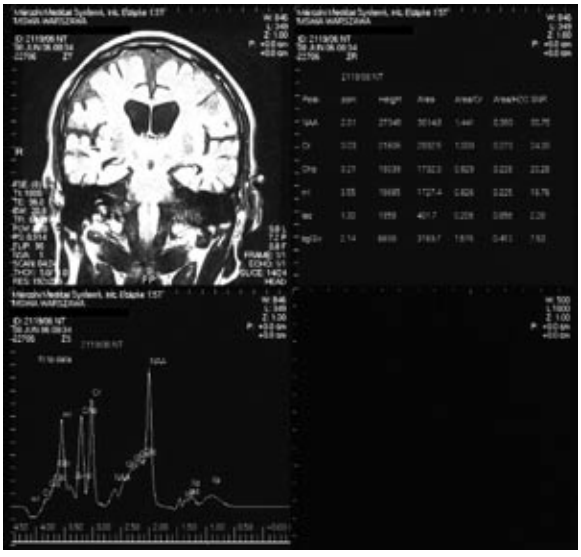
Such presentation in neuroimaging examinations is so typical that it is one of the elements that confirm the diagnosis in clinical criteria of the disease [16]. On the other hand, it needs to be emphasized that lack of atrophy in clinical suspicion of FTD does not cancel out such diagnosis.

In frontal variant of FTD the atrophy is usually bilateral (fig. 4); in PNFA the atrophy is left-sided and asymmetrical, initially limited to the anterior temporal lobe and then involving the left (dominating) hemisphere, while in SD-asymmetric atrophy of anterior parts of both temporal lobes [17]. More detailed volumetric examinations in magnetic resonance (voxel-based morphometry) [18, 19, 20] in fvFTD showed atrophy of orbital, dorsolateral frontal lobe, cingulate gyrus, insula and dorsolateral frontal lobe, usually visible better on the right side. In PNFA the result was visualized better on the left and involved orbital gyrus of frontal lobe, cingulate gyrus, insula and dorsolateral frontal lobe, while in tvFTD the atrophy affected orbital gyruses, anterior temporal lobe, amygdala and anterior part of insula.

In the semantic type of dementia (fig. 5) the atrophy is often larger than in patients with Alzheimer's disease and can involve medial structures of temporal lobe, but usually it is more symmetrical and is accompanied by elevated atrophy within the amygdala, pole of the temporal lobe, piriform gyrus and inferior-lateral temporal gyrus [21].

2. Functional examinations: Single photon emission computed tomography (SPECT), positron emission tomography (PET)

Functional examinations visualize early the FTD disorders and are particularly useful in differentiation with the



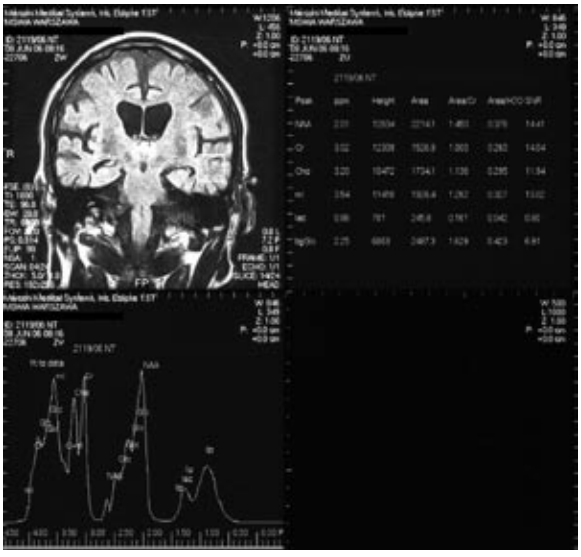


Figure 7/8. Single-voxel H^1MRS reveals abnormally low NAA as well as Cho and ml expression in circumferential parts of left temporal lobe. H^1MRS spectrum profile from the right temporal lobe reveals fewer abnormalities than the one proceeding from the contralateral lobe.

Alzheimer's disease. Although Knopman et al. (2001) did not recommend using SPECT and PET in routine diagnostics of dementia, Centers for Medicare Services (CMS) have agreed on using the FDG-PET for differentiation between FTD and Alzheimer's disease in doubtful cases [22].

SPECT examinations show typical selective hypoperfusion of varied intensity in frontal lobes and anterior temporal lobes (fig.6). The lesions can affect all the mentioned structures, concern only the frontal and/or temporal lobes, or can be marked better on left or right side [23]. According to some authors, the differences in SPECT (lower perfusion in frontal lobes and /or anterior temporal lobes in FTD, and parietal lobes and posterior part of temporal lobes in AD) allow an almost 100% sure diagnosis [24].

Examinations using FDG-PET show decrease in glucose metabolism in frontal and/or temporal lobes [25, 26]. It also presents differences according to clinical variant of FTD. Diehl et al. (2004) found in frontal FTD symmetrical hypometabolism of glucose in frontal lobes with spared motor cortex, while in semantic variant the hypometabolism of glucose was observed only in the whole left temporal lobe and pole of the right temporal lobe [27].

3. Metabolitic examinations- H1 MRS spectroscopy, single-voxel method

Magnetic Resonance Spectroscopy is an exponent of metabolic processes in cerebral tissue by showing abnormal spectrum from frontal and temporal parts, with NAA lowering (neuron indicator) and mI concentration (gliosis indicators) (fig. 7/8). The spectra are similar in Alzheimer's disease but their typical location is different. In some cases, mainly with coexistence of ischemic lesions, higher lactate peaks can also be shown. Ernst et al. studied spectra from the white matter of frontal and temporo-parietal part and found that in FTD, apart from lower NAA and higher mI in some patients, there was also decrease in glutamates (Glx) and increase in lactate peak within the frontal lobes; in Alzheimer's disease similar spectra are present around temporo-parietal areas [28]. Kantarci et al. having examined AD, FTD, DLB and VaD patients using the MR spectroscopy prove that NAA/Cr is most lowered in patients with AD, FTD and VaD. The mI/Cr level is significantly higher in dementia characterised by gliosis, such as AD, FTD, while Cho/Cr is higher in cases of cholinergic defect, in other words: in AD and DLB [29].

In spite of many diagnostic methods, the FTD diagnosis presents various difficulties.

Only complex imaging diagnostics and cooperation of neurologist, neuropsychologist and radiologist allows reaching the final diagnosis.

Moreover, today we rest great hopes in molecular imaging, which is likely to enable faster and more precise diagnosing.

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