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Frontotemporal dementia: clinical, neuroimaging, and molecular biological findings in 6 patients

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Abstract Establishing the diagnosis in patients with clinical signs and symptoms suggesting primary degenerative disease with marked frontal lobe involvement is difficult. Neuroimaging methods, in particular positron emission tomography (PET) with the tracer ^{18}fluoro-2-deoxyglucose (FDG) and cerebrospinal fluid (CSF) examination of β-amyloid and tau-protein levels may give additional information. We report five patients with clinical and radiological features of degenerative dementia with predominantly frontal involvement and one patient with primary progressive aphasia Diagnostic work-up included computed tomography (CT), magnetic resonance imaging (MRI), PET and tau-protein and β-amyloid level determination in CSF. While neuropsychological performance varied among patients, CT and MRI demonstrated persistently frontal lobe involvement. PET revealed corresponding changes with frontal hypometabolism, but in addition, four patients (among them two with no corresponding temporal changes in CT or MRI) showed a decreased glucose uptake in the temporal cortices. CSF samples from five patients revealed elevated β-amyloid 1–42 and tau levels in three and two patients, respectively. Reduced β-amyloid 1–40 was found in two patients. We conclude that occurrence of clinical symptoms of frontotemporal dementia is accompanied by frontal hypometabolism regardless of additional clinical findings. The value of determination of β-amyloid and tau protein levels remains to be determined.

Key words Frontotemporal dementia · Magnetic resonance imaging · PET · Tau protein · β-amyloid

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Introduction

Clinical signs of frontotemporal dementia (FTD) comprise disinhibition, loss of initiative, hyper-oral tendencies, utilization behavior, echolalia, perseveration and reduced speech output [2, 19, 20]. Assessment includes a thorough physical and neurological examination, neuropsychological testing and neuroimaging procedures such as computed tomography and magnetic resonance imaging especially to exclude other types of dementia such as vascular dementia or brain tumors.

Accurate clinical diagnosis is often difficult to establish. While definite diagnosis can be obtained only by analysis of neuropathological features, correct diagnosis is of increased importance with the advent of new drugs for the treatment of Alzheimer's disease.

Recent studies indicate that functional neuroimaging methods such as positron emission tomography (PET) with ^{18}fluoro-2-deoxyglucose (FDG) may facilitate the diagnosis of Alzheimer's disease [7], but only sporadic reports exist about the diagnostic value of PET for diagnosis of FTD [8, 34].

Cerebrospinal fluid (CSF) examinations are necessary to exclude other medical conditions in particular inflammatory diseases of the central nervous system. CSF examinations can be extended to β-amyloid 1–42, β-amyloid 1–40 [10, 29] and tau-protein [9], which are

discussed to be biochemical markers for Alzheimer's disease.

We report a series of 6 patients with clinical symptoms of FTD with special emphasis on clinical work up including PET and CSF levels of β-amyloid 1–42, β-amyloid 1–40, and tau-protein.

Patients and methods

Between 1992 and 1996, six patients admitted to the Section of Geriatric Psychiatry, University of Heidelberg were clinically diagnosed as FTD or primary progressive aphasia according to history, medical and psychopathological state and neuropsychological assessment after exclusion of a history of head trauma, birth injury, electroconvulsive therapy, or substance abuse. Symptoms of frontotemporal dementia were quantitatively assessed using the 9-point FTD scale [6]. According to latest consensus criteria [21] that have considered frontotemporal dementia and primary progressive aphasia as prototypic syndromes for frontotemporal lobar degeneration we have included both patients with clinical diagnosis of frontotemporal dementia and with primary progressive aphasia [16].

Clinical evaluation and assessment

All patients underwent thorough general and neurological examinations including computed tomography, MRI, and laboratory studies in order to exclude metabolic, toxic, and inflammatory causes of their dementia syndrome. None of the patients had evidence of cerebrovascular disease on CT and MRI scans.

Severity of cognitive impairment was assessed using the Mini Mental State Examination (MMSE) [3], the Global Deterioration Scale (GDS) [25], and the Brief Cognitive Rating Scale (BCRS) [24].

For further neuropsychological characterization, the following tests were applied: *cognitive flexibility* – Farbworttest (FWT) [22]; *verbal fluency* – controlled word association (FAS) [31]; *attentional performance* – Alterskonzentrationstest (AKT) [22]; *declarative memory performance* – Buschke selective reminding task (BSR) in the German version [12] and *praxia* – Apraxia test [12].

For interindividual comparison, test results were converted into z-values on the basis of the norm values established for healthy controls [13, 22, 31]. Z-values of less than –1 represent a test performance below those of 66 % of an age-matched healthy control sample, while z-values of less then –2 refer to a performance worse than 98 % of an age-matched healthy control sample.

Apparative tests

CT was obtained using standard 8 mm slices parallel to orbito-meatal line, MRI was obtained with routine T1-weighted sagital and T2-weighted axial sequences. Both were rated qualitatively by the authors (J. P., M. E.) with respect to general and frontal atrophy on a 4-point scale (absent, mild, moderate, marked). Electroencephalography (EEG) was obtained using standard 16-channel recording using the 10–20 method for electrode placement, monopolar and bipolar leads were used. Methods for CSF analysis (β-amyloid and tau-protein) are described elsewhere [9, 10, 29].

PET scans were obtained after intravenous injection of 160–380 mBq ^{18}fluoro-2-deoxyglucose at the Max Planck Institute in Cologne. Patients were examined in a resting state on an ECAT EXACT scanner, and local cerebral metabolic rates of glucose (CMRGlc, in μmol/100 g/min) in the whole brain were determined in 47 slices comprising the whole brain using the Sokoloff model with adjustment of K1 to measured activity and a lumped constant of 0.42 [33]. Slices were oriented along the AC-PC line.

The study was approved by the local ethical committee.

Patient characteristics and apparative findings

The clinical, neuropsychological, neuroimaging, and PET findings of the patients are listed below and summarized in Table 1 (clinical rating scales), Table 2 (neuropsychological testing), and Table 3 (CSF findings).

Patient 1

A 51 year old male, (who ran a transportation business) was admitted with a 10 month history of progressive cognitive decline, memory deficits, and paranoid delusions.

Neurological findings were normal except for grasping and a positive palmo-mental reflex. During the clinical course he developed signs of severe behavioral dis-

Table 1 Clinical scales with the characteristics of the patients under investigation. BCRS axes are separated and mean values are given, where a maximum of 7 (severe impairment) and a minimum of 1 (unimpaired) can be obtained. The Hachinski ischemia score was evaluated according to [15]. BCRS 1–5 includes concentration, short-term memory, long-term memory, orientation and ability of patient to care for himself. BCRS 6–10 includes speech, psychomotor function, mood and behavior, constructive praxia and calculation

Characteristic	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6
MMSE	2	18	25	27	10	18
FTD scale	7	9	7	6	9	8
Hachinski ischemia score	2	1	3	2	1	2
Global deterioration scale	6	4	2	2	5	4
BCRS axes 1–5	3.4	3.6	2.2	1.8	5.3	4.2
BCRS axes 6–10	4.5	3	3	1.4	3.8	4.5

Table 2 Neuropsychological testing. Test scores are given in z values: z values of less than –1 represent a performance worse than 66 % of an age-matched group while a z value of less then –2 represent a performance worse than 98 % of an age-matched group (marked with bold letters in the table). *) not able to co-operate

Characteristic	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6
Cognitive flexibility (FWT)	*)	**–2.8**	**–2.5**	–1.1	**–2.3**	–0.8
Verbal fluency (FAS)	–1.9	–0.9	–0.8	**–2.9**	**–2.1**	–0.6
Attention performance (AKT)	–0.7	–0.8	–0.9	–0.6	–1.6	**–2.9**
Declarative memory performance (BSR)	–0.5	–0.4	–1.7	0.2	–1.9	–1.7
Praxia (Apraxia test)	–0.9	0.8	–1.3	0.8	–1.7	–0.6

Table 3 Laboratory characteristics. In healthy elderly controls (n=17) tau protein was 246.6 ± 111.4 pg/ml (mean and standard deviation) according to the laboratory reference. In healthy elderly controls β-amyloid 1–40 was 2311 ± 546 and β-amyloid 1–42 was 74 ± 30 pM [10]. *) marks a value beyond 2-fold standard deviation

Characteristic	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5
CSF protein [g/l]	0.40	0.11	0.31	0.55	0.36
CSF cells [per μl]	6	1	4	1	1
tau-protein [pg/ml]	164.0	174.4	138.0	323.30	315.40
β-amyloid 40 [pM]	920*	2056	767*	2363	1373
β-amyloid 42 [pM]	101	180*	201*	130	135*

inhibition such as hyperorality (eating candles and flowers). Neuropsychiatric testing revealed a lack of comprehension with a severely impaired attentional performance and verbal fluency. The patient was not able to co-operate in a test for cognitive flexibility (FWT).

Clinical diagnosis was frontotemporal dementia since clinical presentation revealed impairment of both frontal and temporal lobe functions.

EEG showed a mild general slowing with no focal abnormalities and no signs for Jacob-Creutzfeld disease (e. g. triphasic waves). CSF findings, except reduced β-amyloid 40, were within normal limits.

CT and MRI showed a marked internal and moderate general and a marked frontal atrophy.

In PET, CMRGlc was severely reduced bilaterally in inferior, middle and superior frontal gyrus (in all structures CMRGlc 24 µmol/100 g/min or less, normal ranges 26 to 49). Images also showed moderate reduction of CMRGlc in the inferior and middle temporal gyri and the parietal lobule on both sides. In contrast, CMRGlc was well preserved in the central gyrus, and even increased in the cuneus (CMRGlc 47, normal range 28 to 45), probably due to failure to comply with eye closure and associated visual activation.

The patient died 3 years after first admission in marantic state due to pneumonia. Neuropathology revealed frontal convex lobular atrophy with neuronal loss, cortical and subcortical astrocytosis and status spongiosus. There was no evidence for "Pick balls" or "Pick cells".

Neuropathological diagnosis was frontal lobe degeneration of non-Alzheimer type.

Patient 2

A 51 year old female (bookstore clerk) was admitted with an 18 month history of progressive memory disturbances, loss of initiative and inadequate affect with indifference and increased, inadequate speech production. Family history was positive with the father and a grandfather who suffered from a dementia of unknown type. Neuropsychological testing revealed severe deficits most prominent in cognitive flexibility while memory and attention were only moderately impaired. At follow-up two years later, the patient had developed a severe dementia (MMSE = 6) with severe deficits in the areas of orientation, memory, and praxia, while verbal fluency was still relatively preserved.

Due to the combination of frontal lobe symptoms and language impairment the clinical diagnosis was frontotemporal dementia.

EEG showed continuous alpha rhythm with no focal slowing. β-amyloid 42 in CSF was elevated, the other CSF findings were unremarkable.

Both, CT and MRI demonstrated a mild frontal atrophy with marked insular atrophy, with absent general atrophy.

In PET, the left side of the forebrain was much more affected than the right side. On the left side, CMRGlc was severely reduced in superior and middle frontal gyrus, orbitofrontal gyri, supramarginal gyri, and mesial temporal cortex (CMRGlc 24 or less). On the right side, CMRGlc was moderately impaired at the frontal pole and in hippocampal structures. Metabolism was higher than normal in thalamus, caudate nucleus, superior temporal and central cortex bilaterally.

Patient 3

A 51 year old male (business clerk) developed a 12 month history of cognitive decline with a severely impaired professional performance. Previous history was unremarkable except for lack of sexual contact during his entire life and a short psychiatric admission at the age of 17 due to a "neurasthenic syndrome". Family history was positive with a sister from his mother and a cousin suffering from dementia unknown type. Clinically he showed inadequate euphoric affect and loss of critical judgement. Neuropsychological testing demonstrated the most severe deficits in cognitive flexibility and slight deficits in memory performance and praxia. Verbal fluency was relatively unimpaired.

Due to predominating personality changes and relatively preserved language functions and other higher cognitive domains, the clinical diagnosis was Pick's disease.

EEG showed irregular alpha rhythm with moderate slowing and intermittent theta rhythm. Lumbar tap showed elevated β-amyloid 42 and reduced β-amyloid 40.

CT and MRI showed a mild general atrophy, and moderate frontal atrophy.

In PET, frontal brain metabolism was impaired bilaterally. Reduction of CMRGlc was not as severe as in patients 1 and 2. Frontal pole and superior frontal gyri were the most affected (CMRGlc 24 to 27, normal range 24 to 48).

Patient 4

A 54 year old male (high school teacher) presented with a two year history of a progressive loss of initiative, apathy, progressive weakness, reduced social activities and a mild depressive syndrome. First diagnosed as depressive pseudodementia, a progressive dysphasic speech disorder became apparent one year later. Neuropsychologic deficits were almost restricted to verbal fluency and cognitive flexibility tasks, while performance in the other fields was relatively intact. Symptoms remained relatively stable during the clinical course in the following 24 months.

Clinical diagnosis was slowly progressive aphasia with relative preservation of other cognitive domains but with lack of initiative as clinical indication of additional frontal lobe involvement.

EEG revealed a physiological alpha rhythm with no focal slowing. Lumbar tap was unremarkable.

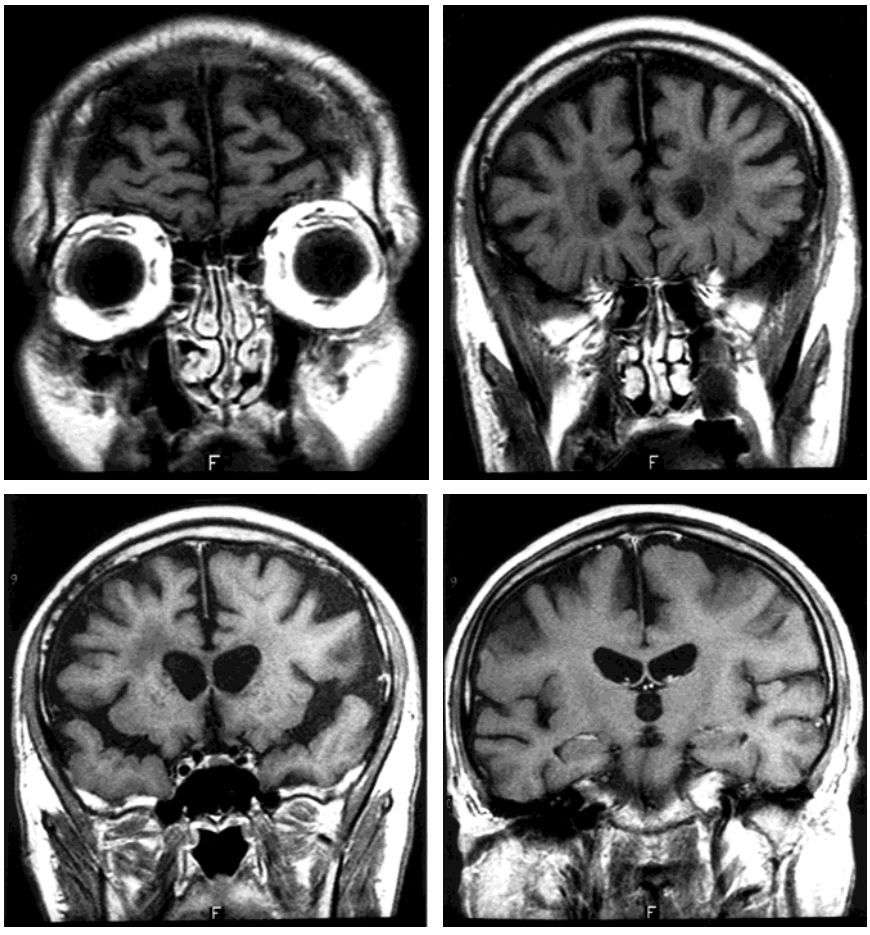

Fig. 1 MRI at admission of patient 3: four coronal slices of T1 weighted MRI with 8 mm thickness from occipital to frontal are displayed. Note that only every second acquired slice is displayed.

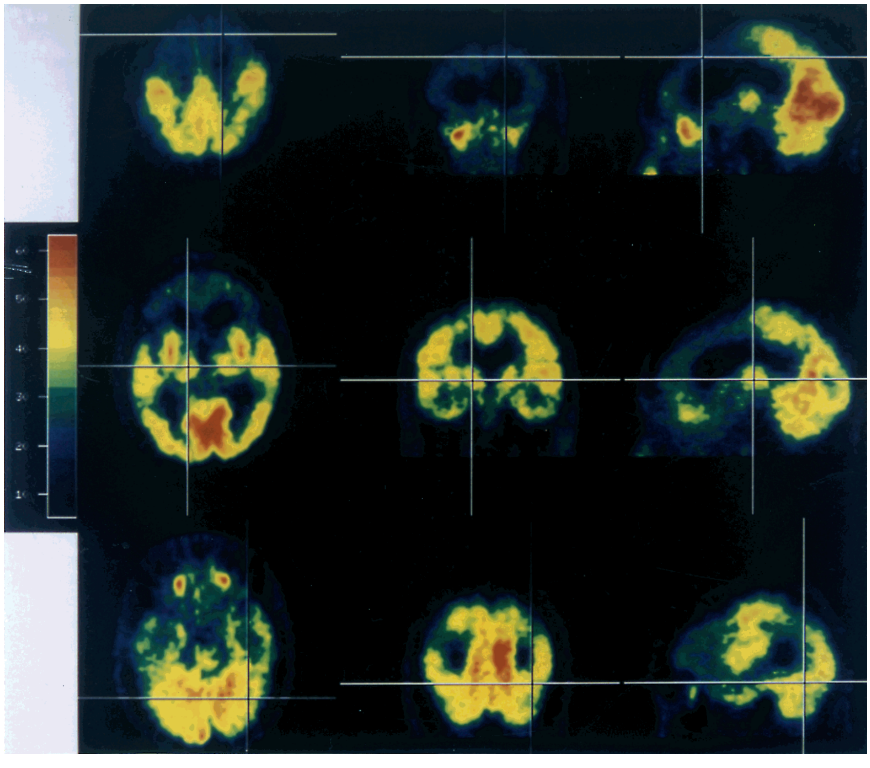

Fig. 2 FDG-PET image of patient 1: Representative transaxial (left column), coronal (middle column), and sagittal slices (right column). Right brain side is on the left and vice versa.

CT and MRI showed a mild frontal atrophy and marked left temporal lobe atrophy while general atrophy was absent. Similar findings were obtained at follow-up two years later.

PET showed metabolic impairment of the left temporal lobe (CMRGlc 23 to 28). Impairment was most severe in inferior temporal gyrus, temporal pole and mesial temporal structures (CMRGlc 24 or less). Frontal CMRGlc was slightly lower on the left side. On the right side metabolism was reduced at the temporal pole only. A moderate asymmetry with a lower left than right glucose uptake was found in the frontal lobe.

Patient 5

A 69 year old male (retired nurse) was admitted with a 3 year history of memory loss with aggressive behavior and delusion of jealousy, loss of impulse control, sexual disinhibition and violent outburst, increased appetite and first occurrence of increased alcohol abuse. Six months before admission, he developed disorientation and loss of interpersonal distance. Family history was unremarkable.

Neuropsychological testing revealed a generalized impairment with most severe deficits in verbal fluency and cognitive flexibility tasks.

FTD was diagnosed due to the relatively preserved memory and due to predominance of frontal symptoms.

The EEG showed mild, generalized slowing with focal slowing in the left frontal and right frontotemporal leads. CSF findings were in the normal range except reduced β-amyloid 42. CT displayed moderate general and frontal atrophy.

PET and MRI were not performed due to a metal foreign body in the left maxillary bone.

Patient 6

A 55 year old female (9 years of school, no further education, housekeeping duties) presented with a history of chronic paranoid symptoms for the last 4 years. Due to decreasing performance in daily living activities, she had to be admitted in a nursing home.

Clinical diagnosis was organic delusional disorder with the differential diagnosis of frontotemporal dementia with delusional symptoms.

Neuropsychological testing revealed severe deficits in attention and declarative memory performance.

EEG showed an alpha-rhythm with inconstant left occipital slowing.

CT scan revealed a mild general atrophy and moderate frontal atrophy with only mild progression compared to a previous CT 4 years ago. MRI was not tolerated due to claustrophobia. PET demonstrated frontotemporal hypometabolism.

Discussion

On clinical examination, the patients reported here presented a variety of psychopathological and neuropsychological symptoms including depressive and paranoid changes, mnestic deficits, behavioral changes and speech abnormalities.

Assessed by *neuropsychological testing* a moderate to high score (greater 6) on the FTD scale with severely impaired cognitive flexibility was characteristic for FTD and present in all but one patient. While verbal fluency was impaired in patients 1, 2, 4, and 5 only in patient 4 deficits were limited to verbal fluency corresponding to a circumscribed atrophy in the left temporal lobe. Extremely low values in MMSE in one patient (pat. 1) were due to limited capabilities in verbal comprehension affecting MMSE performance.

Structural imaging (CT, MRI) revealed frontal (pat. 1 and 3), frontotemporal (pat. 2, 4, and 6), and basal ganglia atrophy (pat. 5). In patient 4, structural imaging demonstrated pronounced atrophic changes of the left temporal lobe while the frontal lobes were only mildly impaired. Since re-examination two years later revealed similar findings with pronounced speech abnormalities but only discrete frontal signs on clinical examination, a slowly progressive aphasia [17] was diagnosed in this patient. Frontal atrophy in FTD was described by previous studies in 15 FTD patients [18] and 18 FTD patients, respectively [13]. In accordance with the present findings, these studies demonstrate that atrophic changes are not always restricted to the frontal lobe but may also extend to the temporal lobe in a number of patients.

Recent studies identified hippocampal atrophy to be typical for AD [23]. However Laakso who compared hippocampal atrophy between patients with AD and FTD found diffuse hippocampal atrophy in AD, while atrophic changes were predominantly observed in the anterior hippocampus in the FTD patients [14].

Electroencephalographic examinations were normal or showed mild generalized slowing. This confirms previous studies [5, 11] which found abnormalities such as generalized severe slowing in AD but not FTD patients. However, two patients (patient 5 and patient 6) showed focal involvement indicating circumscribed changes.

PET with FDG as a tracer revealed a markedly reduced glucose uptake in the frontal lobes in all but one patient. While functional changes were restricted to the frontal lobes in a single patient only, three patients (1, 2, and 6) also showed an impaired temporal glucose uptake reflecting an extension of degenerative processes beyond the frontal lobes. On neuropsychological testing these patients showed a severely impaired cognitive flexibility. The lack of temporal involvement in patient 3 was further substantiated by an only moderately impaired verbal fluency.

A similar pattern of abnormalities was communicated by Miller and Gearhart and Garraux who investi-

gated 15 FTD patients in a SPECT study [18] and 6 FTD patients in a PET study, respectively [4]. Moreover, Miller and Gearhart described a close association between morphological and functional changes using SPECT: while frontal atrophy on MRI was present in all but one patient a reduced frontotemporal regional cerebral blood flow in SPECT was demonstrated in the entire FTD group.

Patient 4 showed a severely impaired verbal fluency with PET changes being almost restricted to the left temporal lobe. These findings reassemble results from a previous PET study [32] which found no involvement beyond the temporal regions in six patients with primary progressive aphasia.

A reduced glucose uptake in the temporo-parietal association cortex and in the medial temporal lobe is commonly found in AD [27, 28]. However, Ishii et al. who investigated regional glucose metabolism in 21 FTD and 21 AD patients using PET found significantly lower hippocampal values in the FTD patients [8]. When compared with both normal controls and AD patients, the FTD patients were characterized by a reduced glucose uptake in five of six frontal regions including also patient 5 who clinically presented only with temporal lobe symptoms.

Although PET may be helpful to understand patterns of metabolic impairment in neurodegenerative disease it is expensive and therefore only rarely used for clinical diagnosis. The fact that diagnosis often relies on clinical criteria and morphological imaging procedures is considered in the consensus criteria on frontotemporal lobar degeneration [21].

Recent studies of *protein markers in CSF* described increased β-amyloid 1–42 and tau levels in AD [10, 26]. While β-amyloid 1–42 levels decrease with further clinical progression of AD [10, 29], increased tau levels are found in the majority of AD patients, irrespective of their clinical stage. Among the FTD patients reported here, 3 patients showed increased β-amyloid 1–42. The inconstant elevated β-amyloid 1–42 values in our group of FTD may reflect the limitation of neurodegenerative process in contrast to AD patients where in later stages the degenerative process is extended almost to the entire cortex. Only a small amount of information on CSF tau-levels in FTD patients exists. None of our patients demonstrated markedly elevated tau levels (more than a twofold standard deviation above our laboratory reference values) in accordance with previous studies describing less marked tau level elevation in FTD patients than in AD patients [1] or even normal tau levels [30].

The group of patients combined under the clinical diagnosis of FTD is heterogeneous. However, we conclude that occurrence of clinical symptoms of frontotemporal dementia is accompanied by frontal hypometabolism regardless of additional clinical findings. Larger studies are required in order to better establish the use of CSF markers in the diagnostic process. Despite different clinical presentation, variations in neuropsychological profile and diverse results in ancillary testing, PET demonstrated frontal or temporal hypometabolism in all cases and contributed therefore significantly to the diagnostic process.

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