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Recent biomarker approaches in the diagnosis of frontotemporal lobar degeneration

Neurochemische Ansätze in der Diagnose der Frontotemporalen Lobärdegeneration

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Abstract

Frontotemporal lobar degeneration (FTLD) is a heterogeneous group of syndromes with different symptoms. Frontotemporal lobar degeneration is mostly used as a clinical umbrella term for different diseases. In some clinical subtypes of the FTLD spectrum, a close correlation with underlying pathology can be found. Neuroimaging techniques, such as magnetic resonance imaging and position emission tomography help to detect neuroanatomical lesions and therefore obtain relevance for in vivo prediction of neurodegeneration. However, there is still a lack of neurochemical biomarkers helping to differentiate between underlying histopathologies. The following review gives an overview about present neurochemical biomarker studies and perspective approaches in the diagnosis of FTLD.

Keywords: cerebrospinal fluid (CSF); C9ORF72; frontotemporal lobar degeneration; neurochemistry; primary progressive aphasia; progranulin; TDP-43.

Zusammenfassung

Die frontotemporale Lobärdegeneration umfasst eine heterogene Gruppe von Syndromen, deren klinische Symptomatik sehr vielfältig ist. Die frontotemporale Lobärdegeneration ein Überbegriff für unterschiedliche Erkrankungen. Für einige dieser klinischen Untergruppen im FTLD-Spektrum kann ein enger Zusammenhang mit der zugrundeliegenden Neuropathologie gefunden werden. Mit Hilfe von Bildgebungstechniken, wie der Kernspintomographie (MRT) und der Positronen-Emissions-Tomographie (PET), können neuroanatomische Veränderungen festgestellt werden und sind damit von hoher Relevanz neurodegenerative Veränderungen zu Lebzeiten vorherzusagen. Jedoch gibt es immer noch keine neurochemischen Biomarker, mit deren Hilfe man einzelne histopathologische Subtypen unterscheiden kann. Die folgende Übersicht stellt die derzeitigen Biomarker-Studien und künftige Ansätze zur Diagnosestellung der frontotemporalen Lobärdegeneration dar.

Schlüsselwörter: C9ORF72; frontotemporale Lobärdegeneration; Liquor; Marker; Neurochemie; primär progrediente Aphasie; Progranulin; TDP-43.

Introduction

Frontotemporal dementia (FTD) comprises the second most common type of early onset dementia accounting for 5–10% of cases of dementia. FTD, however, as a diagnostic spectrum refers to subgroups of clinical syndromes with different symptoms. There is some consensus that FTD is used as a clinical umbrella term for clinical subtypes and frontotemporal lobar degeneration (FTLD) is used for the neuropathological description. Recently, the consensus criteria for a behavioral variant frontotemporal dementia (bvFTD) and for a language variant known as primary progressive aphasia (PPA) were revised [1, 2]. The spectrum of FTD also includes atypical parkinsonian syndromes: corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Additionally, amyotrophic lateral sclerosis (ALS) patients who develop a bvFTD in the course of the disease are included in this spectrum (ALS-FTD). Approximately 10% of patients with FTD develop ALS and patients with ALS show behavioral and language changes (FTLD-ALS) [3–6].

On the basis of neuropathological findings, FTD is associated with FTLD and abnormal protein aggregates in almost all cases. Historically, FTLD patients were subclassified as

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tau-positive cases (FTLD-tau) and those with tau-negative, ubiquitin-positive inclusions (FTLD-U). In most FTLD-U cases, the ubiquitinated protein is TAR DNA-binding protein-43 (TDP-43) [7] and the term FTLD-TDP was recently introduced for this subgroup [8], whereas in approximately 10% of FTLD-U cases FUS (fused in sarcoma) protein pathology could be found [9, 10], and the term FTLD-FUS was introduced for this FTLD subtype [11]. TDP-43 and FUS pathology are also found in patients with ALS. Recently, as a specific feature of FTLD-FUS, but not of ALS-FUS, the co-accumulation of all members of the FET protein family that also includes Ewing's sarcoma protein (EWS), TATA-binding protein-associated factor 15 (TAF15) and the *Drosophila* ortholog Cabeza, was recently described by Neumann et al. and proposed to be designated as FTLD-FET cases [12]. In a small subset of cases, inclusions are positive for proteins of the ubiquitin proteasome system, but negative for tau protein, TDP-43 and FUS (FTLD-UPS), suggesting that additional protein abnormalities will be found in FTLD [11]. The link between the protein tau and FTLD was further strengthened by the discovery that mutations in the microtubule-associated protein tau gene (*MAPT*) cause familial FTLD-tau [13]. Later, other mutations, e.g., in the progranulin gene (*GRN*) were discovered in the majority of familial FTLD-TDP cases [14]. Rare forms of FTLD-TDP are associated with mutations in the *TAR-DNA*-binding protein [15–17] or valosin-containing protein gene (*VCP*). Most recently a hexanucleotide repeat expansion in C9ORF72 was described to be one cause of chromosome 9p21-linked ALS-FTD [18, 19]. In addition, mutations in the charged multivesicular body protein 2B gene (*CHMP2B*) are associated with FTLD-UPS [20, 21].

As shown in Figure 1 for some clinical subtypes of the FTLD spectrum, a close correlation with underlying pathology can be found. PSP with predominantly parkinsonian symptoms is positive for tau protein inclusions [22, 23], other FTLD variants, such as CBS and progressive nonfluent aphasia (PNFA) show tau protein and TDP-43 pathology [24]. The most common clinical type bvFTD can be associated with all three molecular subtypes [9, 25], whereas the motor neuron disease variant is mainly associated with TDP-43 positive inclusions. As TDP-43 is also found in familiar and sporadic ALS a pathophysiological continuum of both diseases is suggested [5].

Neurochemical markers are therefore needed for early and differential diagnosis and for clinical definition of molecular subtypes of FTLD to allow the perspective of subtype specific treatment.

Two research approaches can be considered for the laboratory diagnosis of FTLD: (i) the direct detection of pathological hallmark proteins and (ii) the detection of surrogate markers in biological materials that show an altered pattern of expression in early stages of the disease or are used in the differential diagnosis of other dementias and thus enable an exclusion diagnosis. Thus far, information on specific markers, such as tau protein, TDP-43 or FUS aggregates is limited or does not exist, which might also be due to the fact that these neuropathological hallmarks were only detected
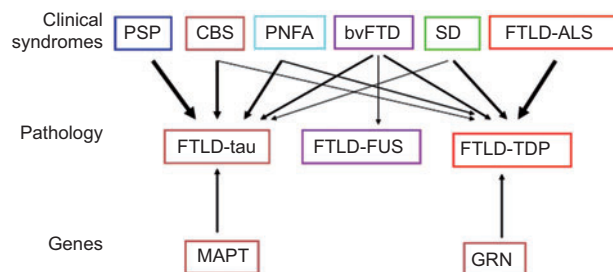

Figure 1 Clinical syndromes (top row), pathological subtypes (middle row), and common gene mutations (bottom row) in FTLD are shown.
Arrows represent links between clinical syndromes, genes, and underlying histopathology, with thicker arrows corresponding to stronger relationships. bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; FTLD-ALS, FTLD with amyotrophic lateral sclerosis; FTLD-TAU, FTLD with tau-positive inclusions; FTLD-FUS, FTLD with fused in sarcoma (FUS)-positive inclusions; FTLD-TDP, FTLD with TAR DNA-binding protein 43 (TDP-43)-positive inclusions; MAPT, microtubule-associated protein tau; PGRN, progranulin; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia [3]. Reproduced by kind permission from Rabinovici GD and Miller BL, CNS Drugs 2010. Clinical, pathological and genetic spectrum of frontotemporal lobar degeneration (FTLD).

recently. Thus, most of the studies have predominantly concentrated on evaluating biomarkers which are used for the differential diagnosis of FTLD vs. Alzheimer's disease (AD).

However, the combination of symptoms in FTLD can be highly variable and multifaceted, and for a biomarker study either a neuropathological verification or at least highly standardized protocols for the clinical examination are necessary. However, ascertainment of a pathological diagnosis is seldom done and in the absence of reliable and valid measuring methods usually non-standardized "tests" are used. This also holds true for magnetic resonance imaging and additional neuroimaging techniques. These are major drawbacks in determining the quality of a biomarker study for FTLD.

Among the studies investigating cerebrospinal fluid (CSF) as a diagnostic tool, only a few comprehensively deal with FTLD. In several studies, FTLD patients were analyzed in "control" groups, but because the clinical information was so limited these studies were not included here.

tau and amyloid-β in FTLD

For tau protein and amyloid-β mainly mild changes have been described (Table 1). Bian et al. [29] show that tau protein is a potentially valuable biomarker for differentiating FTLD from AD. Four histopathological tau-negative patients of the FTLD spectrum had significantly reduced CSF tau levels compared with AD, whereas three of the FTLD-tau cases showed elevated CSF tau levels. None of the FTLD cases presented elevated tau/amyloid-β_{1-42} levels. The ratio of tau protein and amyloid-β_{1-42} was significantly

Table 1 Studies for standard CSF biomarkers: protein tau and amyloid-β in 2002–2011.

Study	Test persons, n						Total, n	Genetics	Autopsy	Mean value in FTLD vs. ND
Study groups	AD	FTLD	ND	ALS	ALS+DI	ALS+FTD				
[26]	74	34 – 24 FTD – 7 PPA – 3 SD	40				148	ApoE-ε4		tau ↑ Aβ-42 ↓
[27]	30	30	30				90			tau ↑ Aβ-42 ↓ Aβ-38 ↓ Aβ-40 ↑
[28]	39	21	30				90	1 FH		Aβ-42 ↓ Aβ-40 ↓
[29]	19	30	30				79	11 FTLD – 2 G272V – 6 P301L – 3 GRN	19 FTLD – 13 tau-positive – 17 tau-negative	tau ↑ Aβ-42 ↑
[30]		12 – 1 PPA	13	12	3	6	46	4 FH		Aβ-42 ↓
[31]	60	55 – 36 FTD – 14 SD – 12 PPA	40				155			Aβ-42 ↓ tau ↑
[32]	25	37 – 25 FTD – 12 PPA	20				82			Aβ-42 ↓ tau →

AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; ND, non-demented controls; ALS, amyotrophic lateral sclerosis; ALS+DI, amyotrophic lateral sclerosis with frontal disinhibition; ALS+FTD, amyotrophic lateral sclerosis with frontotemporal dementia; FTD, frontotemporal dementia; PPA, primary progressive aphasia; SD, semantic dementia; FH, family history.

lower in FTLD than in AD and discriminated FTLD from AD with a sensitivity of 79% and specificity of 97%. However, there was no discrimination between FTLD and non-demented control groups.

In summary, the mean concentration for total tau protein and amyloid-β_{1-42} is between the mean values of the AD group on the one hand and the control group (non-demented) on the other hand. The average value of amyloid-β_{1-42} is higher in FTLD than in the respective AD group and lower than the non-demented group. However, in another study with autopsy and genetically proven FTLD the mean value of amyloid-β_{1-42} was with 531 pg/mL higher compared with the lower mean value of 429 pg/mL in non-demented controls. The average value of tau protein in the respective groups is lower in FTLD compared with AD and higher compared with the control group. Within the amyloid-β peptides, the mean value of amyloid-β_{1-38} in the FTLD group is 160 pg/mL, which is lower than in the respective AD group (217 pg/mL) and the control group (226 pg/mL) [27]. Whereas one study shows that amyloid-β_{1-40} is increased in the FTLD group and the ratio of amyloid-β_{1-38} and amyloid-β_{1-40} seems to achieve the best discrimination with a sensitivity of 87% and a specificity of 90% [27], another study shows decreased amyloid-β_{1-40} levels with an increased ratio of amyloid-β_{1-42} to amyloid-β_{1-40} in comparison to the AD and non-demented control groups [28].

Other neurochemical markers for the diagnosis of FTLD

Apart from tau protein and amyloid-β_{1-42} several other markers were investigated (Table 2). Galimberti et al. [41] attracts attention with study groups with more than 100 patients investigated. Unfortunately, the biomarker result for MCP-1 in the CSF could only be evaluated in a subset of 23 FTLD patients. Others concentrated on the genetic contribution to the etiology of FTLD. As mutations in the *GRN* gene were identified as a causal mechanism underlying FTLD [14], some studies refer to FTLD cases with a positive proven *GRN* mutation (FTLD+GRN). It was shown that progranulin levels in plasma and CSF are lower in FTLD+GRN than in FTLD without *GRN* mutation. This was also evident when FTLD+GRN patients were compared with controls. Unfortunately, progranulin levels were only tested on eight FTLD (+) cases. Ghidoni et al. [38] established that in CSF a cut-off level of 518 pg/mL reaches a specificity and sensitivity of 100% and therefore seems to be a promising method of screening such cases. For plasma, the progranulin protein cut-off level was 74.4 ng/mL with a specificity and sensitivity of 100% for mutation carriers among unaffected subjects. In FTLD values ≤110.9 ng/mL give a specificity of 92.8% and a sensitivity of 100% for PGRN mutations. Finch et al. distinguished *GRN* mutation carriers from non-*GRN* carriers at a progranulin plasma cut-off level of 112 ng/mL [42].

Table 2   Studies for different biomarkers in CSF and plasma 2007–2010.

Study	Test persons, n								Total, n	Genetics	Autopsy	Biomarker
Study groups	AD	MCI	FTLD	ND	DLB	ALS	ALS+DI	ALS+FTD				
[33]	70		28	26	18				142			Neurofilaments/CSF
[34]	85		20	32					222			Cystatin C/CSF
[35]	102		35	85					132			TDP-43/plasma
[36]	24		28						52	6 FTLD+ GRN	14 FTLD-TDP 14 FTLD tau 16 AD+TDP	TDP-43/plasma
[37]			12	13		15	3	9	52			TDP-43/CSF
[38]			71	148					219	71 FTLD – 8 GRN+ 73 ND – 22 GRN+		GRN/CSF, plasma
[39]			16	12					28			Granins/CSF
[40]	4	9	2						15			ERK1/2/CSF
[41]			212	203					415		23 FTLD – 14 TDP-43 – 9 tau-positive	MCP-1A -2518G/CSF
[42]	72		219	70					361	28 GRN+ – 19 ND – 9 FTLD		GRN/plasma
[43]	66		23	33	2				124			AgRP/CSF

AD, Alzheimer's disease; MCI, mild cognitive impairment; FTLD, frontotemporal lobar degeneration; ND, non-demented controls; DLB, dementia with Lewy bodies; ALS, amyotrophic lateral sclerosis; ALS+DI, amyotrophic lateral sclerosis with frontal disinhibition; ALS+FTD, amyotrophic lateral sclerosis with frontotemporal dementia; GRN+, mutation in the progranulin gene.

Another study focuses on further classification of patients with neurodegenerative diseases with a negative biomarker profile for current AD markers using multi-analyte profiling (MAP). MAP biomarkers combined with current AD biomarkers achieved a sensitivity and specificity of 92% and 97% for diagnosing AD. In a subanalysis of this study, Hu et al. [43] analyzed 23 autopsy proven FTLD subtypes, including 14 TDP-43 positive and 9 tau protein positive FTLD cases. In the study, amyloid-β_{1-42}, p-tau 181 and agouti-related peptide (AgRP) were seen as useful classifying analytes: with AgRP levels elevated in a higher proportion of FTLD-TDP cases, compared with a small proportion of FTLD-tau cases. This study can be seen as a first approach for the differentiation between the subgroups of FTLD as autopsy proven diagnoses are applied. As TDP-43 inclusions are found in a major subgroup of FTLD, it is therefore becoming an important biomarker to clarify pathophysiologically regulated pathways and to create an opportunity to develop disease-modifying therapies. Increased amounts of TDP-43 and phosphorylated TDP-43 plasma levels have been found in patients with FTLD and AD compared with controls and thereby index TDP-43 pathology within the brain [35, 36]. Our studies focus on TDP-43 as a biological marker in CSF. As TDP-43 is mainly found in sporadic ALS cases and significantly higher levels of TDP-43 are found in their CSF when compared with age-matched controls [44], we decided to investigate these patients in a proof-of-principle type of manner, as here the neuropathology can be easier predicted compared with the other diagnosis of the FTLD spectrum, especially the bvFTD cases [37]. This included FTLD, FTLD+ALS and ALS cases.

Here, no evidence of pathologically altered TDP-43 proteins in CSF could be seen. Methodological difficulties, such as the heterogeneity of commercially available antibodies, antibody cross-reaction with IgG, and the possible dysfunction of the CSF-blood barrier with high TDP-43 immunoblot bands in plasma may account for variation in results. However, TDP-43 levels might aid in characterizing subgroups of patients across the ALS and FTLD disease spectrum.

In summary, sustainable success of biomarker projects will mainly depend on comparable protocols in either the preanalytical or clinical phases. This makes it necessary to specify and agree upon diagnostic criteria for the inclusion of test individuals into studies. Current contradicting results are most likely due to these methodical drawbacks.

In conclusion, the main explorative studies show that a relation between biomarkers and diagnostic groups cannot be excluded. As a minimum requirement, future studies with biomarkers should be based on an appropriate number of test individuals and clear predefined diagnostic criteria. Therefore, genetically or neuropathologically defined cohorts are mandatory. Newly set-up consortia between institutions specializing in the diagnostic spectrum of FTLD (www.ftld.de) are very promising to build-up a crucial number of patients allowing in-depth research in this area.

Conflict of interest statement

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