HOW TO DIFFERENTIATE FRONTOTEMPORAL FROM ALZHEIMER'S DEMENTIA? RECENT DEVELOPMENTS IN MOLECULAR GENETICS AND NEUROPATHOLOGY

KAKO LOČITI FRONTO-TEMPORALNO OD ALZHEIMERJEVE DEMENCE? NAJNOVEJŠA ODKRITJA MOLEKULARNE GENETIKE IN NEVROPATOLOGIJE

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Abstract *Frontotemporal dementia is a major cause of non-Alzheimer dementia (AD). Frontotemporal lobar degeneration (FTLD) is used here as an umbrella term for both clinical and neuropathological entities starting before age of 65 years. FTLD differs clinically from AD because memory loss is rarely an early symptom. Instead, the dementia of FTLD is usually denoted by behavioral and language difficulties, although clinical and cognitive features of FTLD may overlap with AD. Aphasia may be prominent, either fluent or nonfluent. Clinical FTLD is associated with a variety of different neuropathological entities, which share common feature of preferential degeneration of the frontal and temporal lobes. Whereas, in the past, most attention focused on FTLD pathology associated with tau-positive inclusions and microtubule associated protein tau gene (MAPT) mutations (tauopathies), there has recently been greater attention paid to non-tau, ubiquitin positive inclusions (FTLD-U) or non-tauopathies. It is now recognized that FTLD-U is the most common pathology associated with clinical FTLD. Clinically, cases with FTLD-U may additionally present with or without motor neuron disease and parkinsonism. Majority of familial cases of FTLD-U have mutations in the progranulin (PRGN) gene. Some families of FTLD-U with PGRN mutation (hereditary dysphasic disinhibition dementia 1 and 2) are characterized, besides behavior and language difficulties, by additional memory loss and AD-type pathology. Recently, the ubiquitinated pathological protein in FTLD-U has been identified as TAR DNA binding protein (TDP 43) and found in an increasing number of neurodegenerative diseases, including AD. The overlap between FTLD-U and AD is important since as many as 20 % of AD cases show some FTLD-U type TDP-43 pathology. Recent developments have helped to clarify the relationship between different types of FTLD and related conditions. Understanding and differentiating between FTLD and AD is very important for the diagnosis when new diagnostic test and therapeutics are becoming realized.*

Key words *Alzheimer's disease; frontotemporal lobar degeneration; clinical and psychometric distinction;TDP-43; PGRN mutation*

Izvleček *Fronto-temporalna demenca je najpogostejša ne-Alzheimerjeva demenca (AD). Frontotemporalne lobarne degeneracije (FTLD) je širše ime za klinične in nevropatološke bolezni z začetkom pred 65 letom starosti. FTLD se klinično razlikuje od Alzheimerjeve demence, saj je izguba spomina le redko prvi simptom bolezni. Za demence v sklopu FTLD so značilne motnje vedenja in jezika, čeprav se klinične in kognitivne značilnosti obeh lahko prekrivajo. Afazija je lahko izrazita, tako fluentna kot nefluentna. Klinična oblika FTLD je lahko povezana z različnimi nevropatološkimi izvidi, ki jim je skupna degeneracija pretežno frontalnih in temporalnih režnjev. Medtem, ko je bilo v preteklosti več pozornosti posvečene patologiji FTLD povezani s tau pozitivnimi vključki in mutacijami gena za mikrotubule povezane s tau genom (tauopatije), se v zadnjem času več pozornosti posveča*

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ne-tau, ubikvitin pozitivnim vključkom (FTLD-U) ali ne-tauopatijam. Znano je, da je FTLD-U najpogostejša patološka najdba povezana s klinično obliko FTLD. Klinično, se lahko primeri FTLD-U kažejo tudi z ali brez bolezni motoričnega nevrona ali parkinsonizma. Večina družin z FTLD-U ima mutacijo gena za progranulin (PRGN). Nekatere družine s FTLD-U in mutacijo PRGN (hereditarna disfazična dezinibitorna demenca 1 in 2) imajo klinično poleg motenj vedenja in jezika še motnje spomina in patologijo, značilno za AD. Nedavno je bil pri FTLD-U odkrit ubikvitiran patološki protein, TAR DNA protein 43 (TDP-43), ki ga najdemo pri velikem številu nevrodegenerativnih bolezni, vključno z AD. Prekrivanje FTLD-U in AD je pomembno, ker kar 20 % primerov z AD kaže nekaj TDP-43 patologije tipa FTLD-U. Zadnja odkritja so pripomogla k razjasnitvi odnosa med različnimi vrstami FTLD in sorodnimi stanji. Razumevanje in razlikovanje med FTLD in AD je zelo pomembno za postavitev diagnoze, še posebej, ko bodo za razpolago novi diagnostični testi in zdravljenja.

Ključne besede *Alzheimerjeva bolezen; fronto-temporalna degeneracija; klinična prepoznava; psihometrična prepoznava; TDP-43; PGRN mutacije*

Introduction

Frontotemporal lobar degeneration (FTLD) is used here as an umbrella term to include both a clinical syndrome and one of the neuropathological entites. FTLD is a focal, non-Alzheimer form of dementia, clinically characterized as behavioral or aphasic variants, and later in the course of the disease dementia and parkinsonism.[1, 2] Most commonly, the behavioral or frontal variant is characterized by behavioral dysfunction and change in personal and social conduct. The aphasic variant is further divided into the non-fluent form (primary progressive aphasia) and the fluent form (semantic dementia). Typically, the patient with FTLD does not have amnestic syndrome, at least in the early stage of the disease, which distinguishes FTLD clinically from Alzheimer's disease (AD),[3] but there are exceptions.[4] Focal dementias account for up to 20 % of presenile dementia cases,[5] and FTLD is the second most common form of dementia in people under the age of 65 years after AD.[6] FTLD, however, may be mistaken for AD in the early clinical stages.[7] Accurate clinical diagnosis of the disease is critical for proper management and assessment of prognosis, especially as new treatments are being developed.

Neuropathology of FTLD

Clinical FTLD may be associated with a variety of different neuropathological entities, which share common features: frontal and/or temporal lobar degeneration, neuronal loss, superficial vacuolization and gliosis.[1, 8, 9] FTLD pathologies, based on the biochemical composition of cellular inclusions in the brain, are subdivided into tau-positive and –negative disorders according to wheater there are tau-immunoreactive neuronal and/or glial inclusions and ubiquitin-immunoreactive (ub-ir), tau-negative inclusions (FTLD-U). Whereas, in the past, most attention focused on FTLD associated with tau-based pathology and microtubule associated protein tau gene (*MAPT)* mutations *(tauopathies),* there has recently been greater attention paid to non-tau or tau-negative FTLD *(non-tauopathies).*[8]

Clinical phenotype of FTLD in comparison with AD

We have recently had the opportunity to examine retrospectively 48 cases of FTLD that met pathological criteria for FTLD[8, 9] out of a total of 935 cases (5.1 %).[3] Dementia was evaluated according to the Clinical Dementia Rating Scale (CDR)[10] with CDR 0.5 presenting a very mild dementia and CDR 1 mild dementia. The Mini-Mental State Examination (MMSE)[11] was not applied in this study due to lack of sensitivity to mild degrees of cognitive impairment.[12] Cases in which the clinical features were consistent with 1998 Neary et al. criteria[5] were included. Our sample was categorized into two groups according to neuropathological findings for FTLD and additional AD-type pathology, Table 1. Additionally, 27 age-, sex-, education-, and dementia severity at entry-matched neuropathologically confirmed AD cases were randomly obtained from the ADRC registry for comparison with the two FTLD groups. For psychometric assessment, a battery of standard psychometric tests[13] was applied. FTLD cases were diagnosed according to established and other neuropathological criteria.[8, 9] The neuropathological assessment of AD was based on the criteria of Khachaturian,[14] the CERAD,[15] or the National Institutes of Aging-Reagan Institute criteria.[16] Alzheimer's disease-type changes were rated according to neurofibrillary tangle stage IV or greater and β-amyloid stage B or C,[17] even in the presence of other pathology.

Clinically, behavioral and language features, including impulsivity, disinhibition, and social withdrawal significantly differed FTLD from AD, as reported previously.[18,19] Amnesia as an initial symptom, despite being characteristic of individuals with AD, was present in high percentage in both FTLD groups, as described previously.[18] Episodic memory loss in FTLD may derive from alterations in attention and working memory. The most distinctive feature of FTLD, on psychometric tests, was significant impairment of frontal lobe functioning, as reported by Rascovsky.[20] However, given the better performance by the FTLD on the nonverbal episodic memory test it is possible that

Table 1. *Demographic characteristics of the two FTLD groups.*[3]

Measure	FTLD (n = 37)	FTLD+AD (n = 11)	t (46)	p value
Estimated age at onset, y Mean (SD)	58.9 (9.9)	63.5 (5.8)	1.07	.15
Range	33–77	55–74		
F/M	14/23	5/6		.73
Positive family history (%)	54	73		.32
Age at death, y M (SD)	69.4 (11.6)	74.7 (6.6)	1.46	.15
Range	35–99	66–84		
Duration of illness, y M (SD)	9.6 (3.9)	11.2 (5.4)	1.09	.28
Range	2–19	6–72		

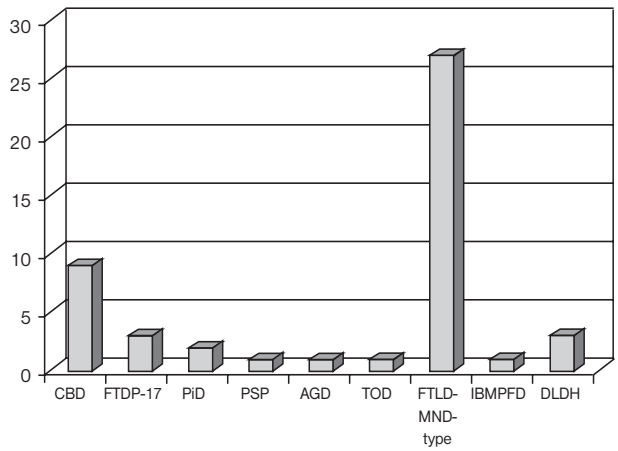

Figure 1. *Spectrum of FTLD*[8, 9] *in a cohort of 48 cases published elsewhere.*[3]
The FTLD-U is the most common pathology associated with clinical FTLD.[8, 9] *Concomitant AD-type pathology was present in 23 % of FTLD cases.*[31]

the mild memory loss in FTLD may represent primarily a language deficit, which would influence performance on verbal memory tests, rather than an episodic memory deficit as in AD. Varma and colleagues[21] however, failed to differentiate FTLD and AD using the National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)[22] clinical criteria, showing a lack of specificity in commonly used criteria for both diseases. For AD, NINCDS-ADRDA criteria achieved a good sensitivity (average 81 % across studies), but a low specificity (average 70 % across studies) for probable AD, based on studies with post-mortem confirmation.[23]

Chromosome 17-linked tau-negative FTLD is caused by mutations in PGRN

Various pathogenic mutations in the progranulin *(PGRN)* gene were recently reported in individuals with FTLD-U linked to chromosome 17q21.[24, 25] It is now recognized that FTLD-U is the most common pathology associated with clinical FTLD.[26, 27] The ubiquitinated pathological protein in FTLD-U has been identified as TAR DNA-binding protein 43 (TDP-43).[28–30] As more entities are investigated, the pathological TDP-43 protein is found to be a component of the inclusions of an increasing number of neurodegenerative diseases, including AD. The overlap between FTLD-U and AD is important since as many as 20 % of AD cases may show at least some FTLD-U-type TDP-43 pathology.[31] Several FTLD-U with *GRN* mutation families have been described, so far. The hereditary dysphasic disinhibition dementia 1 (HDDD1) family[32] and another kindred (HDDD2) with a similar clinical phenotype.[33–35] A complicating feature in both HDDD families is the presence of AD-type early memory loss which correlated with co-existing AD pathology in almost half of the cases, which distinguishes them from other reported families with no or little coexisting neurodegenerative disease.[32, 35] However, AD changes were not seen in the frontal lobes, where extensive deposition of progranulin was detected,[35] the two pathologies being most likely independent. Interestingly, another family with the same GRN A9D mutation has been reported in an individual with corticobasal syndrome,[36] indicating, again, clinical heterogeneity associated with the same mutation. Patients with *GRN* mutation have a variable age at onset, and the dementia is characterized by prominent behavioral and language dysfunction, usually a progressive non-fluent aphasia.[37, 38] Mild parkinsonism is common, but motor neuron disease is usually absent.[38] Magnetic resonance imaging and 18-fluoro-deoxyglucose positron emission tomography helps discriminate AD from FTLD.[39] Patients with *GRN* mutations had predominant frontal, temporal and, to lesser extent, parietal atrophy and hypometabolism with a right-sided predominance and this probably relates to the predominance of behavioral symptoms.[40] However, language dysfunction in patients with FTLD with *GRN* mutation,[37, 41] showed a left-sided predominance of atrophy on imaging.[41]

Summary

In summary, for the practicing clinicians, the knowledge that changes in behavior and language difficulties distinguish those with FTLD from AD is important, although clinical and cognitive features may overlap between the two. Typically, patients with FTLD do not have an amnestic syndrome, at least in the early stage of the disease which distinguishes them from AD. However, a memory loss we found in those with FTLD may in part reflect word-finding difficulties stemming from language dysfunction. FTLD with tau-negative, ubiquitinated inclusions (FTLD-U) is now recognized as the most common pathology associated with clinical FTLD. Patients with *GRN* mutation and FTLD-U pathology have a variable age at onset, and the dementia is characterized by prominent behavioral and language dysfunction, usually a progressive non-fluent aphasia. Understanding and differentiating between FTLD and AD is very impor-

tant for the diagnosis when new diagnostic tests and therapeutics are becoming realized.

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