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Review

Behavioral Variant Frontotemporal Dementia

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Abstract

Frontotemporal dementia (FTD) is a sporadic or genetic neurodegenerative disease in which frontotemporal involvement is typically encountered. According to clinical features, three groups are distinguished as behavioral (bvFTD) and progressive aphasia variants; semantic dementia and progressive non-fluent aphasia. The most common type is bvFTD mimicking as disinhibition, apathy, loss of empathy, perseverative / compulsive behaviors, hyperorality, executive dysfunction and diagnosed with imaging, pathogenic mutation and histopathological evidence as well as clinical diagnosis. Brain magnetic resonance imaging (MRI) studies show atrophy especially in ventromedial frontal cortex, posterior orbital frontal regions, insula, anterior cingulate cortex and subcortical structures; the degeneration of these structures, known as the salience network, is held responsible for deterioration of the executive functions. In the early period, the presence of frontotemporal hypometabolism in positron emission tomography is more sensitive than MRI, parietal hypometabolism and amyloid deposition are not seen. Tau levels in cerebrospinal fluid may be low or high in FTD, but the tau / amyloid-beta ratio is found to be highly specific. More than 40% of bvFTD cases have family history and most autosomal dominant inheritance patterns are present. In FTD, cholinergic system is protected, cell loss in serotoninergic receptor and raphe nucleus is evident. Dopaminergic and cholinergic therapy has not been found to be useful and even worsening of behavioral symptoms with cholinesterase inhibitors has been reported. Selective serotonin reuptake inhibitors and trazodone are effective on behavioral symptoms and sleep problems. Pharmacological and non-pharmacological interventions, training and counseling services are important for the relatives of patients.

Keywords: Frontotemporal dementia, genetics, pathology, clinical

Davranışsal Varyant Frontotemporal Demans

Özet

Frontotemporal demans frontotemporal tutulumun tipik olduğu sporadik veya genetik bir nörodejeneratif hastalıktır. Klinik özelliklerine göre davranışsal varyant (dvFTD) ile progresif afazi varyantları olan semantik demans ve progresif akıcı olmayan afazi olarak üç gruba ayrılır. En sık görülen tip dvFTD olup klinikte disinhibisyon, apati, empati kaybı, perseveratif/kompulsif davranışlar, hiperoralite, nöropsikolojik profilde yürütücü işlev bozukluğu belirgindir. Kesin dvFTD tanısı ise klinik tanı yanında görüntüleme, patojenik mutasyon ve histopatolojik kanıt ile konulur. Beyin manyetik rezonans (MR) incelemelerinde özellikle ventromedial frontal korteks, posterior orbital frontal bölgeler, insula, anterior

singulat korteks ve subkortikal yapılarda atrofi gözlenir; yürütücü işlevlerdeki bozulmadan salience şebekesi olarak bilinen bu yapılardaki dejenerasyon sorumlu tutulmaktadır. Erken dönemde Pozitron emisyon tomografide frontotemporal hipometabolizma olması MR'a göre daha duyarlıdır, parietal hipometabolizma ve amiloid birikimi görülmez. Beyin omurilik sıvısındaki tau düzeyleri FTD'de düşük ya da yüksek olabilir ancak tau/amiloid-beta oranı yüksek özgüllükte bulunmuştur. dvFTD vakalarının %40'ından fazlasında aile öyküsü vardır ve çoğu otozomal dominant kalıtım paterni gösterir. FTD'de kolinerjik sistem korunmuştur, seratoninerjik reseptör ve rafe nükleusta hücre kaybı belirgindir. Dopaminerjik ve kolinerjik tedavi yararlı bulunmamıştır, hatta kolinesteraz inhibitörleri ile davranış semptomlarında kötüleşmeler bildirilmiştir. Selektif serotonin gerialım inhibitörleri ve trazodon, davranış semptomları ile uyku problemleri üzerinde etkili bulunmuştur. Hasta yakınlarına yönelik farmakolojik ve nonfarmakolojik girişimler, eğitim ve danışmanlık hizmetleri önemlidir.

Anahtar Kelimeler: Frontotemporal demans, genetik, patoloji, klinik

INTRODUCTION

DEFINITION

Frontotemporal dementia (FTD) is a group of inherited or sporadic neurodegenerative disorders affecting frontotemporal regions and in which posterior cortical regions are relatively preserved. FTD accounts for 10% of all pathologically proven dementia cases and has the same prevalence as Alzheimer's Disease (AD) in dementia cases encountered before the age of 60.[92] In accordance with the predominant onset symptoms , three different clinical presentations which are language and behavior based are mentioned as behavioral variant frontotemporal dementia (bvFTD) and progressive aphasia variants semantic dementia (SD), and progressive non-fluent aphasia (PNFA). Among all these clinical conditions, bvFTD ,a FTD subtype, is the most commonly encountered one and this subtype presents numerous symptoms overlapping with primary psychiatric disorders such as schizophrenia, obsessive-compulsive disorder, borderline personality disorder and bipolar disorders.[83] Almost half of bvFTD cases receive psychiatric diagnosis before receiving this diagnosis.[122] Behavioral variant frontotemporal dementia has been shown to be encountered four times more frequently than progressive aphasia variants including SD and PNFA. Neuropathological identification is made based on the accumulated protein in brain. Among the most commonly encountered of these are tau, trans-activator regulatory deoxyribonucleic acid (Tr-DNA) binding protein 43 (TDP-43)[39] and fused in sarcoma (FUS) proteins.[59] Tau accumulation is observed in progressive supranuclear palsy (PSP); corticobasal degeneration (CTD) and as for TDP-43, it is encountered in ALS cases.[83] Pathogenic mutations causing this accumulation and located in different genes have been reported. Although specific pharmacological therapy is currently subject of the most basic research, there is no treatment currently known that could change the course of disease. Current attempts are focused on reaching to a correct diagnosis, relief of symptom, supporting and training of those caregivers.[113] Frontotemporal lobar degeneration (FTLD) is a pathological definition and comprises FTD-motor neuron disease (FTD-MND)[62], PSP[19] and corticobasal syndrome (CBS)[58,89] which overlap with Parkinsonism and motor neuron symptoms aside from the above mentioned three clinical presentations.[76]

Among all these clinical conditions, the most commonly encountered FTD subtype is bvFTD. It presents numerous symptoms

overlapping with primary psychiatric disorders such as schizophrenia, obsessive-compulsive disorder, borderline personality disorder and bipolar disorder.[83] It may be interlocked with presentations like movement disorders and motor neuron disease.[83]

HISTORY, EPIDEMOLOGY, PROGNOSIS

"Focal" dementia is not a new concept and was for the first time defined by Arnold Pick in a case report presenting aphasia and psychiatric symptoms in 1892.[56] From 1890s to 1980s, similar case reports on this subject were released and Mesulam Marsel in the US in 1980[68] reported six case reports accompanying with progressive language disorder and not presenting generalized dementia in the first two years and defined this case as "primary progressive aphasia". It was reported that these cases developed generalized dementia[55] and that the cases progressing with right frontal or temporal atrophy were less known and that they developed frontal lobe behavioral syndromes. Symptoms such as increases in face blindness (prosopagnosia) in individuals" families or in individuals themselves, not remembering the ways they know best, pietism, obsessive-compulsive tendencies, disinhibited behavior, increases in eating disorders or artistic ability were also reported in some patients.[25,49] In the same time periods in England and Europe, "frontal lobe dementia" phenomenon began to be defined. Neary and Snowden[72], Neary et al[73] and Snowden et al[106] reported a series of cases progressing with behavioral changes resembling to those of psychiatric disorder. The frontal lobe behavioral disorders have been defined as signs which include other frontal lobe behaviors such as inhibition loss, impulse control disorder, initiation loss, abulia, failure to maintain a mission, a lack of social awareness, making comments publicly about people when they are not present, the reduction of personal care, mental rigidity of the function, stereotyped behavior, inappropriate sexual interest and imitation.[60] Though frontal lobe behaviors include language problems, it is reported that rather than being a real aphasia emphasis symptoms such as decreasing amount of speech, mutism, echolalia and perseveration accompany. FTD is a less frequent cause of dementia than AD; however, among early-age onset of dementia, its incidence is equal to that of AD compared to AD or even greater under age of 60.[47] Manchester research center in UK and Lund research center in Sweden reported that FTD constitutes 8-10% of all dementia cases.[2]

If age range was between 60-70 years, the prevalence was reported as 28 in 100,000; The US and European studies reported an overall prevalence of 4-15 in 100,000.[11] In the order of prevalence, FTD can be ranked as the 4th most frequently encountered dementia reason after vascular dementia, dementia with Lewy body and AD, however, it can be said that the prevalence is much higher in the early-age onset of dementia cases.[83] Average age of onset varies depending on the subtype, while bvFTD, the most frequently observed one, starts at the youngest age, semantic dementia (SD) and PNFA cases follow it respectively.[114] While the mean life expectancy from diagnosis to death is around 3 years in the cases with bvFTD and MND, the same expectancy may extend up to 12 years in SD. Although the average age of onset for bvFTD is around 58, there are also cases in literature in their 20s and while there are also those even presenting in their 80s.[114,116,120] In a review from Canada examining 26 epidemiology studies and containing data from over 15 countries, the onset age for FTD was reported to be 65. However, in the same study 65+ age FTD prevalence was reported as 2,7%, incidence as 2.0%, while under age of 65 prevalence rate was reported as 10,2%, incidence as 15,3% . No significant difference was found between the total number of women (n =

373) and men (n = 338) cases.[39] FTD dementia cases are mostly diagnosed at the age of 50-60 or the even in 40s. In an old study, 112 patients were examined and the mean age of onset was found as 59.[116] Since family history was positive in almost one-quarter of the cases, this points out a genetic disorder.[120] In another study from the Netherlands, the presence of language and behavioral symptoms in 38% of relatives in the first degree with FTD was reported.[54,107] In another review, autosomal dominant inheritance was detected in 27% of the cases.[1]

NEUROANATOMY

Behavioral variant frontotemporal dementia is accompanied by especially right hemispheric orbitofrontal, anterior cingulate, anterior insular and anterior temporal cortex atrophy.[101] In addition to atrophy, functional imaging indicates, neuronal network dysfunction. Some networks in the brain exhibit peculiar impairment in neurodegenerative diseases; i.e while AD causes default mode network impairment, bvFTD affects only salience networks,[125] PSP changes mesencephalon, primary progressive aphasia affects dominant language networks.[29,33,116] bvFTD causes salience network impairment consisting of orbital-frontal cortex, anterior cingulate cortex, anterior insula and presuplementary motor area. It is suggested that this network selects among several environmental stimulants and determines the priority. After this network starts, executive control network (dorsolateral frontal and parietal cortex) steps in to process, plan and implement the inputs,[102] According to Ibanez and Manes,[45] social context is identified by the networks of fronto-insular-temporal region and this network, 1) updates and predicts context, 2) coordinates internal and external environment, 3) has a role in the learning in line with the context. bvFTD impairs especially social cognition, therefore, abilities including facial recognition, empathy, decision making and mind reading impair.

Histologically, salience network ageants anterior insula and anterior cingulate involve von Economo neurons. These spindle-neurons are found in higher amounts especially in gorilla, elephant and whale, which are the animals socially developed. Therefore, von Economo neurons are thought to have an association with social behaviors.[100] In FTLD, these neurons are selectively lost.[15,66] In addition, it involves different macroscopic regions, but just like AD, neuron loss and gliosis are observed. Histological difference is the vacuolization of cortical neuropils.[72,106]

Neuropathology and genetic

Clinic presentation and molecular pathology are strongly associated. FTD and SD accompanied with MND have clear TDP pathology and tau protein pathology in CTD and PSP is quite clear. However, bvFTD is not directly associatied with any histopathology.[48] The common neuropathologies in FTD patients are spongiosis, gliosis and neuron loss in cortex superficial layer. Particularly, based on the classifications by the molecular features of familial FTD, there are several proteins in humans causing this disease by changing function in an unknown way. An advanced classification is made according to the different neuropathologies by these abnormal proteins. In general, 5 primary groups and some sub-types have been identified.[32]

FTD- tau (Tauopathies/Tau-positive FTD)

Tau protein is a low weighted protein having an important role in microtubule stabilization and axonal transport. Human tau gene is located in the long arm of 17th chromosome, and 6 different subtypes have been identified in human brain. Mutations in tau gene changemicrotubule structures in tau protein and impair

neuronal transport, thus causing neuron loss. In these patients, unstructured and hyperphosphorylated tau proteins accumulate in either intraneuronal neurofibrillary balls or Pick bodies.[32] Heutink et al[37], and then Hutton et al[44] and Poorkaj et al[82] identified tau (MAPT) gene mutation in chromosome 17 in FTD families. Afterwards, hereditary disphasic dementia, progressive supranuclear palsy, corticobasal degeneration and ALS-Parkinsonism dementia complex of Guam have been included in taupathy pathology subgroup.

FTD-U /FTD-TDP (Ubiqutinopathies/ Ubiqutin-positive, TDP-43-positive, tau and sinuclein negative inclusions)

Most of FTD cases do not exhibit tau pathology or mutation.[54] The subgroup cytoplasm, exhibiting ubiquitin inclusion in neuritis or nucleus previously named as "FTD-U", is much higher compared to the cases exhibiting tau pathology. The second gene found to be associated with FTD-U pathologic subgroup is progranulin gene and is located in chromosome 17.[6,20] While progranulin mutations cause haplo-insufficiency due to premature stop codon; tau mutations cause toxic effects. In progranulin mutations, TAR-DNA binding protein (TDP-43) is precipitated in neuron and glia, and forms ubiquitinated inclusions.[10] The clinical signs of this group may be FTD, PPA, CBD, MND.[16,74,98,111,124] Among other genes associated with TDP-43 accumulation are C9ORF72, located in chromosome 9, progressing with psychotic FTD, and ALS, and valosin-containing protein (VCP) mutations[27,42,63] progressing with Paget bone disease + inclusion body myositis. Wilke et al[119] showed that progranulin levels decreases in the cerebrospinal fluid in both groups with or without progranulin gene mutations. In the light of these findings, decreased levels of progranulin in central nervous system, independent from tau protein changes, are responsible for different pathological mechanisms underlying FTD neurodegeneration.

FTD-FUS (Ubiqutin-positive, TDP-43 negative, FUSpositive)

Frontotemporal dementia- Fused in Sarcoma is a very small group and though ubiqutin is positive in them , they are negative in terms of TDP-43. FUS protein consists of 526 amino acid nuclear protein and acts in DNA repair and RNA fusion. In FTD-FUS patients, there are younger onset bvFTD clinic, negative family history and atrophy of caudate in brain MRG.[59] FUS positive inclusions are identified in neuronal filament inclusion disease and bvFTD clinic without family history accompanied generally by pyramidal and extra pyramidal sympthoms is possible in these patients.[32]

FTD-UPS (Ubiqutin-positive, TDP-43 negative, FUS negative)

In this group known as FTD-UPS, ubiqutin is positive, TDP-43 is negative, while FUS antibody is negative. Most of these cases have CHMP2B (charged multi-vesicular body protein 2B) mutation. Dementia lacking distinctive histology is also listed in this group and though they have FTD-specific clinic and atrophy, there is no known abnormal protein accumulation and is associated with CHMP2B mutation.[32,40]

In a neuropathologic study with 95 FTD patients, Rohrer et al[95] reported that 51 % of the cases had TDP-43, 44 % had tau, while 5 % had FUS pathology.[114] In another study with pathologically confirmed 90 FTD patients, taupathy cases appeared in form of parkinsonism presentation; while the cases with ubiquitin body appeared as MND presentation.[32,36] The incidence of frontal, paralimbic and severe atrophy of caudate nucleus is more common in FUS pathology compared to FTLD-tau or FTLD-TDP pathology.[114]

Genetic evaluation

More than 40% of bvFTD cases have family history and 20-25% of them have

autosomal dominant hereditary pattern. To date, it was thought that most of the mutations causing FTD were MAPT and progranulin genes (GRN or PGRN) located on 17th chromosome. However, in the recent studies, C9ORF72 gene located in 9th chromosome has been shown to be responsible for more than half of the cases.[63] In a clinic study with 104 bvFTD patients, 27,6% patients had genetic mutation and more than 50% of these mutations were shown to be C90RF72 gene mutation.[87]

It was reported that different genetic types causes different types of atrophy. For example, while symmetric frontal, temporal and atrophy of inferior parietal lob were more apparent in the ones with GRN mutation; symmetric anteromedial temporal lobe and orbitofrontal atrophy were present in MAPT mutation, however, no significant correlation was found between genotype and phenotype.[114]

FORMATION MECHANISM (Pathophysiology)

Neuroanatomical Regions and Related to Behavior Disorders in bvFTD

In a review by Perry et al,[77] it was reported that 78% of cases had an increased eating behavior and sweet tooth and 27% of them had early alcohol / drug addiction, while 17% were reported to present hypersexuality.[77] In a voxel-based morphometric study an association between reduction in right ventral putamen and pallidum volume and demonstrating reward-seeking behavior was detected. In these right hemispheric cycles, there are also putamen, globus pallidus, thalamus and insula. These findings give the impression that the reduction in subcortical structures might be responsible for the increased reward behavior and also this increased reward seeking behavior could be occurring as a result of increased thalamocortical feedback.[36,101] Although this statistical significance was not achieved for each individual, the group difference provided information about anatomical structures. For example, the processes related to eating behavior are organized through the above centers related to insula and reward behavior as internal centers. Previous imaging studies showed excessive eating behavior in FTD is associated with atrophies of right ventral insula and right striatal,[121] while sweet tooth is associated with right frontoinsular atrophy.[117] The behavioral disorders in bvFTD might not only occur as a result of impairment in reward systems but also be related to the deterioration in the reduction of body awareness or control. Nevertheless, when the relation of reward behavior with orbitofrontal cortex, ventral striatum, frontoinsular anterior cingulate and the dorsomedial thalamus is considered, it would not be wrong to assume that specific involvement of these areas in FTD could result in the related symptoms.[35,101] Although the responses of bvFTD cases to simple emotional stimuli such as acoustic startle are considered to be normal,[108] some studies have found that there are some disorders in the recognition of some negative emotions such as anger, fear and disgust.[51] These recognition disorders are associated mainly with lateral and inferior atrophy of right hemisphere orbitofrontal cortex, insula, the amygdala and the temporal lobe.[97,115] Some of the social disorders in this case are explained by the theory of mind. Theory of mind means the ability to evaluate other people's will, faith and intentions[90] and has been associated with rostral faces of medial prefrontal cortex.[3] Among the mentioned structures associated with the bvFTD, anterior insula in humans ranks first.[99] This region includes key points for speech-language and vissero-autonomic / social-emotional network. Frontoinsular degeneration in the early stages creates progressive "salience network disorder and brings the individual into a situation where he can not evaluate the consequences to arise as a result of his actions taken or left untaken. The von Economo neurons in these regions are found in mammals with

large brains and complex social life such as elephants and gorillas and exhibit selective degeneration in bvFTD.[18] The von Economo neurons are the neurons first described in 1925, and located on frontoinsular (FI) cortex and the anterior cingulate cortex layer V (Brodmann area BA 24) that are similar to the spindle and display projections.[102] In subsequent years, they were determined to be more predominant in subiculum and entorhinal cortex and in the right hemisphere in superior frontal cortex. While von Economo neurons show reduction by 69% in bvFTD in which feelings such as empathy, social awareness, self-control are seriously disrupted, this reduction would not be seen in the early stages of AD.[102]

In light of the new findings, the explaining the selective frontoinsular vulnerability observed in bvFTD on micro cycle or cellular level is among the important issues for FTD researches. Focal-onset degenerations that are increasingly generalized in time are a subject of the debate of Pick which returns to the issue of how progression in neurodegenerative diseases occurs. The transfer of pathology from neurons to neurons in AD, Parkinson"s disease (PD) and FTD in recent studies reminds us the similar transfer of abnormally folded amyloid beta synuclein or tau protein as in prion diseases such as Creutzfeldt-Jakob disease.[85]

NEUROLOGICAL EXAMINATION

One of the clinical presentations "focal syndromes of bvFTD" is a frontal lobe syndrome characterized with progressive behavior disorder. This presentation may be in the form of mimic stroke, brain tumor or traumatic brain injury. The patient"s insight is lost even in the early period; therefore, the patient's relatives may have to refer their patients to marital therapy, human resources department, dependency units of hospitals, psychiatrist or family practitioner for behavior problems, or to police stations and hospitals for judicial cases. bvFTD or in other words frontal variant (fv) FTD, is the personality changes causing social behavioral changes (Table 1).[54] The patients may become unconcerned and talk, gag and behave inconveniently (Witzelsucht sign). On the other hand, some of them become abulic or apathetic and they generally exhibit decrease in behaviors. They tend to just sit, speak less, and not communicate with others or environment. They do not care for themselves and are indifferent to the effects of their behaviors (phenomena of lost "mind theory"). Besides, hyperorality, abuse and imitation behavior, inappropriate sexual behaviors may also be observed. Spontaneous talk decreases, sometimes mutism is observed, or perseverative, stereotypic talk, parroting (echolalia) may also be observed.[72,106,114] 61% of bvFTD cases have only behavioral symptoms, while 39% have behavioral symptoms accompanying with impairment of language abilities.[39] Anamnesis should especially focus on the shame associated with their behaviors and speeches, loss of compassion to relatives or pets, the change of eating habits and food preferences, obsessive compulsive anxiety for "time loss", change of humor, new obsessive hobbies[69] or new (religious-spiritual) interests.[114]

The patients may exhibit antisocial/criminal behaviors and irritability. For example, one of our bvFTD patients, who was a former senior manager in a county had been kicked out from the house by his wife due to his inconvenient behaviors, then he had to live in a boat, but he was taken to police stations recurrently since verbally abusing women and inviting them to dinner, and he had been beaten by the relatives of the women. Just as in the example, the patient"s behaviors were thoughtless, not well planned and impulsive; for example, he might jaywalk or be punished for feckless speeches or talk to strangers warmheartedly and privately and act childishly. Excessive warmth and trust may cause personal/familial financial

loss. These cases should be distinguished especially from orbitofrontal cortex atrophy, subgenual cingulate, and medial prefrontal and anterior temporal cortex atrophy.[96]

The obsessive compulsive behaviors of bvFTD comprise wide range of behaviors including foot tapping, repetitive simple movements such as continuous walk, mixed rituals or mixed computer/card games. Collecting, saving and scavenging trash are frequent.[17] Some patients are very resistant to any change, and may never change their routines or plans.[78]

Eating behaviors of bvFTD vary in range. Some of them like and excessively consume sweet far beyond the limit.[121] The family of one case had to lock kitchen shelves and be on guard to prevent any food stealing act in the market. One of our cases with ALS and bvFTD always stole ice cream from the children in the street; therefore he was not allowed to go out in summers. In next periods, the patient can eat objects that could not be eaten. Our other case was eating soaps feeling like fruits in the early periods; and in the delayed periods, he tried to eat an ampule in a house without any objects around except from a carpet. On the contrary, some of the patients are very immobile, nonreactive, and present abulia and apathy. In the cases with eating disorders, right anterior cingulate and caudate atrophy should be investigated.[26]

In the neuropsychological tests, bvFTD is frequently characterized with executive dysfunction, and is frequently associated with dorsolateral prefrontal cortex atrophy. Memory functions are better than AD, yet, in the early periods, episodic memory disorders may be more frequent in early period bvFTD and this sign may be confused with AD.[41] On the other hand, figure copy and visual-spatial functions are greatly preserved and this preservation is a more distinctive sign compared to memory.[38,93] Although more than one executive dysfunction are similar features both in bvFTD and AD, after one year follow-up period, single disinhibition was found to be the most sensitive feature to differentiate two disorders. Moderate difference was found between two disorders in the tests on executive functions and memory functions. AD admitting with impaired executive functions and bvFTD admitting with severe amnesia may have similar features.[86]

According to physical examination, specific signs for bvFTD sometimes include FTD accompanied by PSP and CTD-specific Parkinson"s-resembling signs, visual disorders and apraxia. In classical PSP, axial weighted Parkinsonism, postural instability, dysphagia and dysphonia, vertical visual paresis are observed and response to levodopa is not increased compared to idiopathic Parkinson"s disease. REM sleep behavior disorder is not observed in PSP since this presentation does not belong to the sinucleopathy group disease.[104] On the other hand, slow onset asymmetric Parkinsonism, alien hand syndrome, hemineglect, myoclonus and asymmetric dystonia, frontal executive dysfunction and visual-spatial disorders, apraxia may indicate CTD.[5] Almost all of both cases are associated with tau pathology. Amyotrophic lateral sclerosis is found approximately in 15% of FTD cases; lower and upper motor neuron symptoms are also observed.[15,34]

Parkinsonism in FTD was first reported in microtubul-associated-tau (MAPT) and progranulin (PRGN) gen defects, then was reported in genes including chromosome 9 open reading frame 72 (C9ORF72), chromatin changing protein 2B (CHMP2B), valosin-containing protein (VCP), fused in sarcoma (FUS) and transactive DNA-binding protein (TARDBP). Clinical presentation may be very variational in these families, generally acinetic-rigid syndrome parkinsonism is accompanied by bvFTD, however clinical

presentation may appear idiopathic PH, PSP and CBD in some cases. Even it is rare, parkinsonism FTD cases may be accompanied by motor neuron disease.[103]

Diagnostic criteria

Since 1994, four diagnosis criteria have been published.[1,66,73,91] The last criteria, unlike the previous definition by Neary et al[73] defines three grade accuracy and indicates six behavioral and cognitive symptom group (Table-1).[91] So, inhibition loss, apathy, sympathy loss, perseverative and stereotypic behaviors and hyperorality-induced regression of social behavior and personal behaviors may be observed in early periods in patients in terms of bvFTD diagnosis. This criteria has 85% sensitivity and 95% specificity for histological FTLD in bvFTD, whereas previous criteria had 53% sensitivity[91] In another study, FTLD criteria had 93% sensitivity for possible bvFTD and 80% sensitivity for probable bvFTD, AD was the most common in this series for false positive diagnosis.[7]

For possible bvFTD criteria diagnosed through totally clinical features; 1) disinhibition, 2) apathy/excessive inactivity (inertia), 3) emphatic loss, 4) perseverative/compulsive behaviors, 5) hyperoralite, 6) executive dysfunction in neuropsychological profile, of these, three of six behavioral/cognitive features are adequate for diagnosis. This flexible classification allows diagnosis in the earliest period. Probable bvFTD diagnosis indicates underlying FTLD pathology. Here, clinical diagnosis as well as frontotemporal imaging (MRI, SPECT, PET) signs are required. Typically for bvFTD, frontoinsular structuralatrophy and other "salience network" atrophy are important. (Figure-1). For accurate bvFTD diagnosis, clinical diagnosis as well as pathogenic mutation and histopathological evidences are required (Figure-2).

Table 1. Behavioral variant FTD Consensus diagnosis criteria [91]

I. Neurodegenerative diseases
The symptoms below should be present to meet bvFTD diagnosis criteria
A. In follow up or history, behavioral and /or cognitive progressive impairment
II. To meet possible bvFTD criteria, following 3 behavioral/cognitive symptoms should be present (A-F). Study requirement: rather than single or rare, symptoms should be very continuous or recurrent.
A.* early behavioral disinhibition (at least one of the symptom (A.1-A.3).
A.1. Inconvenient social behavior
A.2. Improper attitudes in terms of social good forms
A.3. impulsive, immoderate, shameful behaviors
B. Early apathy and immobility (at least one of the symptoms (B.1-B.2).
B.1. Apathy
B.2. Immobility

C.Early sympathy and empathy loss (at least one of the symptoms (C.1-C.2).

C.1. Decreased sensitivity for other's feelings and needs

C.2. Decreased social interest

D. Early perseverative, stereotypical or compulsive/ritualistic behaviors (at least one of the symptom (D.1-D.3).

D.1. Simple repetitive movements

D.2. Complex compulsive or ritualistic behaviors

D.3. Stereotypical speech

E. Hyperorality and change of eating habits (at least one of the symptom (E.1-E.3).

E.1. Change of food preferences,

E.2. Overeating, increased alcohol and cigarette consumption

E.3. Trying to eat non-eatable a inappropriate objects

F. Neuropsychological Profile: Partly preservation of memory and visual-spatial functions with executive dysfunction (all symptoms should be present (F.1-F.3).

F.1. Loss of executive functions

F.2. Partly preservation of episodic memory

F.3. Partly preservation of visiospatial abilities

III. Probable bvFTD

All symptoms should be present (A-C).

A. Possible bvFTD criteria should be met.

B. Functional regression should be significant by Clinical Dementia Rating Scale or Functional Activity Scores or information from patient's relatives.

C. Imaging results should be compatible with bvFTD at least one of the symptom (C.1–C.2).

C.1. in MRI or CT, frontal and/or anterior temporal atrophy

C.2. In PET or SPECT, frontal and/or anterior temporal hypoperfusion or hypometabolism

IV. Accurate bvFTD with FTLD pathology

The criteria A should be present with B or C criteria.

A. Possible or probable bvFTD criteria should be met

B. Biopsy or post mortem histopathological evidence for FTLD

C. Known pathological mutation

V. bvFTD exclusion criteria

For any bvFTD diagnosis A and B criteria should be negative; for possible bvFTD diagnosis C criteria may be positive.

A. non-degenerative other nervous system diseases and other medical diseases should be excluded and the reason should be reported.

B. Behavioral disorders should be excluded from psychiatric diagnosis and the reason should be reported.

C. Biomarkers, should be strong indicators for AD or other neurodegenerative process

*Early means the symptoms beginning in the first three years

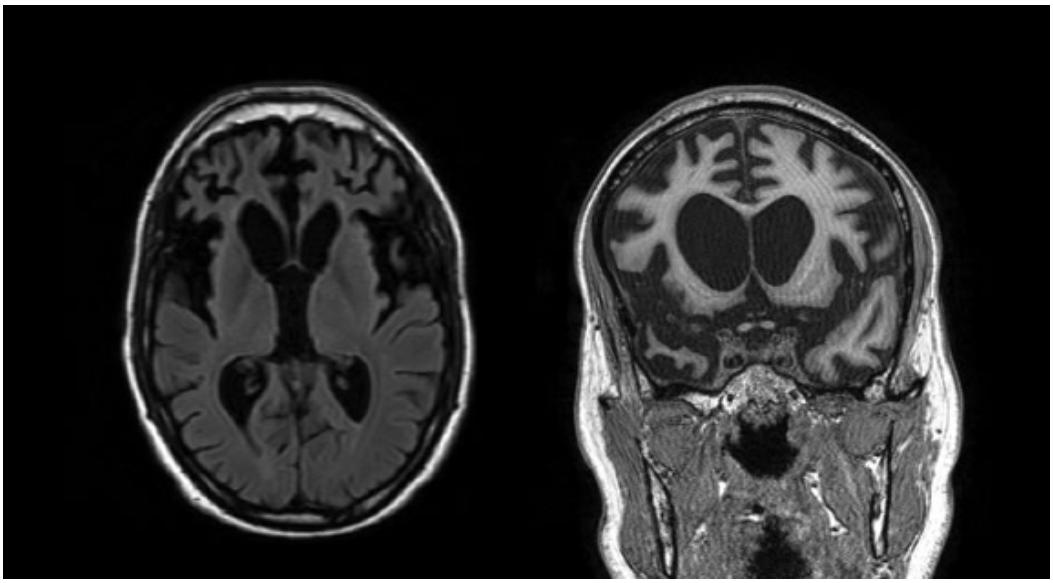

Figure 1: *According to cranial MRI of 38 years old male bvFTD patient, advanced grade atrophy is noted in anterior fronto insular, temporal cortex and subcortical caudate nucleus.*[32]

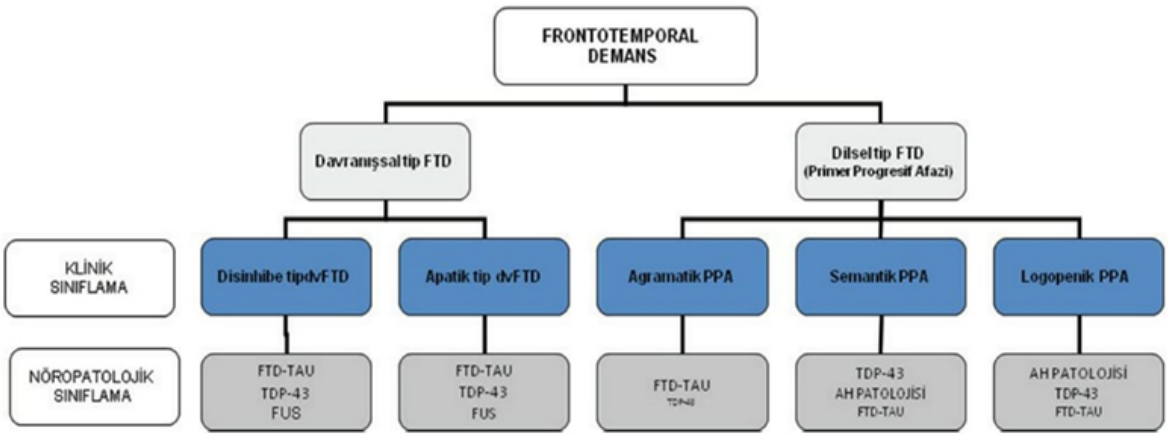

Figure 2: *Clinical and neuropathological classification of frontotemporal dementia.*[32]

Clinical Scales

A new scale named FTD-CD has been added to Clinical Dementia Rating Scale (Clinical Dementia Rating), commonly used for AD, by adding two special terms (language and behavior / attitude / personality) to FTD.[37]

Similarly, Clinician's Global Impression, CIBIC +, Addenbrooke Cognitive Assessment-R (ACE-R) scales have also been found responsive in some clinical trials to track changes in FTD.[70]

Among scales commonly used in FTD concerning behaviors, there is Neuropsychiatric Inventory which has, at the same time, been validated in Turkish.[21] Also, Cambridge Behavior Inventory[14] and Frontal Behavior Inventory (FBI)[52] were used for this purpose. The questionnaires given also to care givers were found useful in evaluations.[71]

Also, among objective testing methods; "Social Observer Social Behavior Checklist" developed by Rankin et al[88] measures the spontaneous social behaviors of an individual during routine cognitive examination.

Measurements include inertia, perseveration, failure to comply with social norms, etc. Also, there are other tests that are apathy / inertia-driven[65] and focused on using behavior.[30] In a near future, new developments are expected through such tests about the strength of orbital and ventromedial frontal regions that are especially related to the processes of emotion, social cognition and decision-making.

METHODS OF DIAGNOSIS

Neuro-imaging

Quantitative mapping of local cortical atrophy can be provided by MRI using Voxel-based morphometric techniques. FTD subtypes present focal atrophy in different areas. In one of them known as bvFTD, severe atrophy is encountered in bilateral frontal cortex for one or more times. Particularly, ventromedial frontal cortex, posterior orbital frontal regions, the insula and anterior cingulate cortex and subcortical structures are monitored in bvFTD. However, these changes may not be very apparent in the early stages. While amygdala atrophy is useful for bvFTD and AD distinction, hippocampus atrophy is not that guiding.[22,95,110]

Rohrer et al[95] reported with regard to atrophy on MRI that progranulin mutations tend to produce more asymmetric atrophy, while MAPT mutations produce more symmetrical ones. But it should be kept in mind that the number of exceptional cases is not so small; for example, non-fluent aphasia cases are listed among asymmetric tau pathologies.[95]

In a retrospective observational study which investigated brain MRI, genetic analysis and analysis of clinical features of 104 patients diagnosed with bvFTD, a relationship was established between atrophy areas on MRI and specific functional network damage.

Four bvFTD subgroups have been identified as predominant frontal, frontotemporal predominant under the group of salience network; temporal predominant under the group of semantic evaluation network and as subcortical predominant independent from these networks. It is claimed that the affected areas on MRI play an important role in identifying bvFTD subgroups and predicting genetic and clinical characteristics.[87] Focal hypermetabolism areas are observed in functional neuro-imaging, for example, in PET. The frontal and / or temporal hypometabolism pattern on PET has more sensitivity than MRI for FTD in the early stages.[83] It is much different from the hypometabolism monitored in parietal cortex in early AD. While Pittsburgh component B which

allows amyloid imaging and PET which uses florbetapir F18 show accumulation of amyloid in the brain in individuals with AD, this accumulation cannot be observed in FTD.

Amyloid deposition can be seen in more different areas than hypometabolism encountered in the same area as focal atrophy and reflecting neurodegeneration monitored through glucose PET.[23] Also, PET using tau ligands have the potential to be used more widely in future researches.[64]

Cerebrospinal Fluid (CSF)

High tau and low beta-amyloid levels in Cerebrospinal Fluid (CSF) obtained by lumbar puncture indicate AD.[54] However, tau levels in CSF could be high or low in FTD, so CSF biomarkers cannot make the distinction between FTD and AD with high accuracy.[32] Shortly, there is no CSF biomarker to identify FTD positively.[93] Nevertheless, the cut-off value for tau / amyloid-beta ratio is 1.06 and with 79% sensitivity and 97% specificity FTD syndrome can be distinguished from AD.[8] When biomarkers for FTD are looked, studies show conflicting results.[32] Tau value was reported to be normal or increased,[94] and the amyloid-beta value was in somewhere between healthy control group and AD.[28] According to recent studies, the ratio between Abeta 1-42 / Abeta 1-38/ p-tau is a powerful biomarker with high diagnostic value in distinguishing AD from other dementia.[24] In some studies, when CSF Abeta 1-38 Abeta 1-40 Abeta 1-42, total tau and phosphorylated tau (p-tau) values were compared with bvFTD, PPA, AD and healthy controls, it was seen that p-tau value was high, while Abeta 1-42 / Abeta 1-40 and Abeta 1-42 / Abeta 1-38 rates were low. Compared to other groups, Abeta 1-38 value was found to have decreased and tau and P-tau levels were found to be higher in PPA patients from FTD group.[9] In another ongoing study, CSF p-tau and Abeta 42 levels of FTD patients and healthy control group were compared and it was found that p-tau levels increased in FTD, Abeta levels decreased, p-tau / Abeta ratio increased. Abeta values in FTLD were determined to be between AD and healthy controls.[24]

DIFFERENTIAL DIAGNOSIS

Conditions that creates similar manifestations to FTD such as neurological infection, metabolic disorders, vascular diseases and paraneoplastic condition can be excluded easily with a history taken carefully.

Sometimes bvFTD cases can be confused with obsessive-compulsive disorder, bipolar disorder, schizophrenia or depression.. Though low or normal pressure hydrocephalus is sometimes preliminarily diagnosed as FTD, it can easily be distinguished from FTD via screening.[118]

Defined by Hodges and Kipps, "slowly progressive FTD" is a diagnostically challenging clinical presentation.[53] Although these patients meet bvFTD criteria, they may seem to be advancing very slowly or even not and atrophy is not so noticeable on MRG. These cases might be the individuals with a FTD clinic or very slow-progressing gene carriers.

Although psychiatric cases can be diagnosed as FTD, FTD cases mostly have non-degenerative psychiatric diagnosis.[123] The fact that apathy, interest reduction, social withdrawal seen in major depression could also be seen in bvFTD may lead to the confusion of these two conditions. The fact that sadness, personal doubts, suicidal thoughts seen in depressed individuals are encountered in bvFTD is of importance for differential diagnosis.[93] The likelihood of FTD in individuals under 65 years of age with dementia is statistically equal to the likelihood of AD.[92] Since the first symptoms are not memory impairments in early-age onset AD, but executive function or language disorders, these two tables can be easily confused with each other.[67] The

reverse memory impairment may sometimes be one of the early symptoms of FTD. Deterioration in interpersonal relationships the may be a very useful indicator in distinguishing AD from bvFTD.[83] However, detection of known genetic mutations has become more important than histological diagnosis for precise diagnosis today.[54]

PROGNOSIS

The studies indicate that bvFTD cases present more functional disorders, while AD and FTD subtypes are in the same cognitive level as bvFTD.[61] There are not enough publications on FTD prognosis. In a retrospective longitudinal study examining 177 FTD and 395 AD cases, mean life expectancy was found to be 8.7 years (+/- 1.2) and 11.8 years (+/- 0.6) respectively. Among FTD subtypes, while the mean life expectancy of the subtypes accompanying with language involvement was similar to that of AD, bvFTD exhibits the shortest survival. As for the FTD cases accompanying with MND with bulbar involvement, this life expectancy is around 2 years.[17]

TREATMENT AND REHABILITATION

Since there is no available treatment in FTD to change the course of the disease, the approach must be personal-based.[79] Because behavioral problems create a huge burden on caregivers in bvFTD, pharmacologic and non-pharmacologic interventions for patient"s proxies, education and counseling about the nature of the disease for caregivers are very important. Some websites (www.alzheimer.org.tr; www.theaftd.org; www.ftd-picks.org; www.nia.nih.gov; www.ninds.nih.gov; www.alz.org; www.caregiver.org) are useful resources for such briefings. Non-pharmacological interventions are particularly important for FTD. Monetary issues of the relatively young patients should be discussed in advance with other individuals in the family. Providing a safe environment for the patients with impulse control disorders and judgement issues is crucial. Taking the individual under custody for taking big financial decisions, preventing him/her from driving and weapon use, and planning an early retirement may be appropriate steps to be taken.[80,109]

Compared with AD, cholinergic system is preserved in FTD.[84] Meanwhile, cell loss in serotoninergic HT1A and 5-HT2A receptors as well as raphe nucleus is noticeable.[105] Also, it was found that putamen and caudate dopamine metabolite levels and presynaptic dopamine receptors decreased. However, dopaminergic and cholinergic therapy was not found to be beneficial for FTD. Cholinesterase inhibitors such as donepezil, rivastigmine, galantamine could be useful for memory in some patients with FTD, behavior symptoms may be worsened in others.[43] While memantine, the NMDA glutamate receptor antagonist, was reported to be anecdotally useful in FTD, recent clinical trials have reported the otherwise.[13,112] Selective serotonin reuptake inhibitors (paroxetine, sertraline, citalopram),[54] in pharmacological treatment are often useful.[93] British Association of Psychopharmacology with a class B rating proposed selective serotonin reuptake inhibitors for behavior problems in FTLD.[75] Trazodone can be helpful for both frontal and sleep behavior disorders.[57] In one study, the positive effects of oxytocin were reported.[46] Atypical antipsychotics should not be used unnecessarily considering the side effects.[50] Antipsychotics are added to the treatment in all dementia patients for disinhibition and agitation generally without considering etiology. However, there is no controlled study on antipsychotics for FTD in literature.

Although the positive effects of risperidone, olanzapine and aripiprazole have been reported[79], extrapyramidal side effects increasing mortality[31] and this group of patients who are particularly

vulnerable to Parkinsonism[81]) need to theoretically refrain from antipsychotic treatment. The biomarkers to be used in differentiating pathological subtypes in FTDL may contribute to the personalization of treatment.

Pathological biomarkers to be used to differentiate among FTDL subtypes may give rise to specialized treatment. Tau and TDP-43 pathologies are particularly the focus of these researches. The results of the study on tau aggregation inhibitors in bvFTD "methylene blue" which protects against the toxicity of TDP-43 are yet to be reported (ClinicalTrials.gov ID: NCT01626378).

The agents that can change the course of the disease; glycogen synthase inhibitor lithium, sodium channel blocker riluzole, mitochondrial function enhancing coenzyme Q10, monoamine oxidase inhibitor rasagiline, microtubule stabilizer davunetide and tideglusib have been tested in some clinical trials but have not proved positive. After the detection of low levels of GRN progranulin in individuals with gene mutations, preclinical studies have begun to reduce the clearance or to increase GRN production.[12] Prospectively, antibodies against tau, antisense oligonucleotides and drugs raising progranulin level are among the promising therapies.

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