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FRONTOTEMPORAL DEMENTIA - COMPREHENSIVE INSIGHTS INTO PATHOGENESIS, DIAGNOSIS, AND INNOVATIVE TREATMENTS

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ABSTRACT

Frontotemporal dementia (FTD) is a clinically and genetically diverse group of neurodegenerative disorders predominantly affecting the frontal and anterior temporal lobes, leading to progressive changes in behavior, language, and executive function. FTD is the most common cause of young-onset dementia and third overall among degenerative dementias, with a prevalence of 15–22 per 100,000 and an incidence of 2.7–4.1 per 100,000. The core clinical syndromes include the behavioral variant (bvFTD), semantic and nonfluent primary progressive aphasias (svPPA, nfvPPA), and overlap with motor disorders such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). Genetic mutations, especially *C9orf72*, *GRN*, and *MAPT*, are responsible for most familial cases and involve proteinopathies with TDP-43, tau, and FUS proteins. Biomarkers (e.g., neurofilament light chain, progranulin) and neuroimaging are used to improve detection and differentiate subtypes, although reliable biomarkers are lacking. Management is largely supportive, with a combination of non-pharmacological therapies (e.g., exercise, speech and occupational strategies, behavioral tactics, caregiver education) and pharmacotherapy for neuropsychiatric symptoms. Clinical trials explore gene therapies and disease-modifying drugs, indicating a move towards personalized medicine. Despite major advances, obstacles persist for early detection and effective therapies, underlining the need for sustained multidisciplinary research in FTD.

KEYWORDS

Frontotemporal Dementia (FTD), Neurodegeneration, Primary Progressive Aphasia (PPA), Genetics, Biomarkers, Caregiver Support

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Introduction

A broad spectrum of neurodegenerative disorders known as frontotemporal dementia (FTD) primarily targets the frontal and anterior temporal lobes of the brain, resulting in progressive behavioral, linguistic, and executive deficits. FTD can occur at almost any age, ranging from 21 to 85 years, but is most commonly seen in adults in their 50s and 60s [1, 2]. FTD affects 15–22 per 100,000 individuals and the incidence is 2.7–4.1 per 100,000 [3]. FTD is the most prevalent cause of early-onset dementia and the third most common cause of neurodegenerative dementias, after Alzheimer's disease (AD) and Lewy body dementia (LBD) [4]. FTD exerts a huge burden not only on patients who present with neuropsychiatric symptoms and cognitive deterioration but also on their caregivers with an average life expectancy after the first clinical manifestation ranging from 6 to 9 years [5]. This review provides a complete overview of FTD, covering the clinical course, genetics, neuropathology and current therapeutic strategies, highlighting progress and challenges in the area.

Methodology

A narrative literature review was undertaken using the databases PubMed and Google Scholar. Publications were first screened for priority to those exclusively addressing FTD. The review covered the modern aspects of the disorder such as pathophysiology, diagnostic approaches and current therapeutic choices.

Discussion

Clinical Manifestations

FTD comprises three major clinical syndromes: the behavioral variant of FTD (bvFTD), the semantic variant of primary progressive aphasia (svPPA), and the nonfluent variant of primary progressive aphasia (nfvPPA). A third form of PPA is the logopenic variant (lvPPA) – most usually connected with AD due to the observed short-term memory impairments and the rate of progression of cognitive abnormalities [6]. These syndromes typically have overlapping neuropathology and etiology with progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and FTD with motor neuron disease/amyotrophic lateral sclerosis (FTD-MND/ALS) [7]. BvFTD represents the most frequent clinical manifestation of the disease. It is characterized by significant behavioral changes. The major clinical aspects include disinhibition, apathy, loss of empathy, and modified eating behaviors that often contribute to the risk of obesity. Disinhibition is marked by inappropriate behavior, and apathy results in reduced interest and social retreat. Distractibility and poor decision-making are examples of executive dysfunction, and neurological examinations frequently reveal normal results despite motor neuron injury [6]. SvPPA is defined by severe impairment in semantic knowledge across modalities, which frequently affects the left anterior temporal lobe and leads to anomia and decreased single-word comprehension. Language remains fluent but content is sparse, with prominent semantic paraphasias and circumlocutions. Phonology, grammar, and syntax are relatively preserved. Memory and visuospatial abilities remain intact; nevertheless, there may be a decline in object pantomime and limb imitation. When the right anterior temporal lobe is implicated, behavioral and affective abnormalities such as irritability, loss of empathy and social cognitive deficiencies become more severe and typically resemble symptoms observed in bvFTD [8]. Some patients, particularly those with left-sided svPPA, may develop new artistic abilities early in the disease [9]. NfvPPA accounts for around a quarter of FTD cases. It is typified by agrammatic, effortful speech with apraxia, shorter utterance length, and largely intact comprehension, except for complex syntax. Mutism and mild executive dysfunction may develop over time [8]. LvPPA is characterized by reduced verbal output, episodic disruptions in fluency, and increased rates of phonological errors (mistakes in the sound structure of words during speaking, e.g., "flutterby" for "butterfly"), but with preserved grammar and motor aspects of language. Patients generally display poor single-word retrieval in both spontaneous speech and confrontational naming, as well as impaired repetition [10]. The recently reported right temporal variant of FTD (rtvFTD) is characterized by right anterior temporal atrophy, prosopagnosia (difficulty recognizing familiar faces), spatial disorientation, and severe personality changes [11]. Motor syndromes such as PSP and CBS further extend the spectrum. PSP is manifested by axial rigidity, bradykinesia, and gaze palsy, and CBS by asymmetric parkinsonism, apraxia, and alien limb syndrome, sometimes overlapping with AD [12]. Neuropsychiatric symptoms, especially apathy and disinhibition, are prevalent across the FTD spectrum and may have a major impact on quality of life [13].

Genetics

FTD is a set of neurodegenerative disorders, clinically and genetically heterogeneous. Around 40% of patients report a family history of dementia, mental illnesses or motor symptoms and 10–20% exhibit a clear autosomal dominant pattern of inheritance [14]. Genetic factors significantly influence cases of bvFTD and FTD-ALS, whereas PPA, particularly svPPA, is less commonly hereditary. The predominant heritability of FTD is attributed to autosomal dominant mutations in three genes: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) [15]. The hexanucleotide repeat expansion (GGGGCC) in the non-coding region of the *C9orf72* gene is the predominant genetic factor associated with FTD and ALS [9]. It is inherited with close to 100% penetrance by age 80 [16]. While healthy individuals generally possess 2–20 repeats, patients usually present 30–1000 repeats [15]. The underlying pathogenesis remains incompletely elucidated; however, suggested mechanisms encompass toxic gain of function, modification of RNA expression and haploinsufficiency [17]. The clinical spectrum includes bvFTD, ALS and frequent psychiatric features like psychosis, delusions, hallucinations and obsessive-compulsive behavior [9]. Progranulin, encoded by the *GRN* gene on chromosome 17q21, is a key multifunctional growth factor in the central nervous system (CNS), influencing cell growth, inflammation, autophagy, and lysosomal function [18]. Over 70 mutations, mainly heterozygous, cause progranulin haploinsufficiency and TDP-43 type A pathology, which account for around 8% of familial FTD cases [19]. Symptoms usually occur between 50 and 80 years of age, most often as bvFTD, nfvPPA or CBS [20, 21]. Progranulin deficiency leads to severe

lysosomal dysfunction and neuronal ceroid lipofuscinoses manifested by dementia, cerebellar ataxia, convulsions, and visual loss presenting in the third decade of life [22]. The microtubule-associated protein tau (*MAPT*) gene is located on chromosome 17q21.31, and encodes tau protein, which plays a major role in the stability of the neuronal cytoskeleton and axonal transport. Tau exists primarily in six isoforms, arising from alternative mRNA splicing, notably affecting the 3R and 4R repeat domains. More than 80 *MAPT* mutations are a major cause of familial FTD but rare in spontaneous cases. These mutations disrupt the balance of 3R and 4R tau isoforms, leading to neurotoxic hyperphosphorylated tau aggregates – a hallmark of tauopathies. Pathogenic variants cause neurotoxicity by loss of tau function (microtubule destabilization), toxic gain of tau function, and tau mislocalization [23]. Clinical manifestations vary widely, often presenting as bvFTD, PSP, CBS, svPPA, or nfvPPA, typically with onset before age 60 [5, 12]. The severity of the symptoms and the clinical presentation depend on the kind of MAPT mutation in addition to the common haplotypes H1 and H2 that increased the risk of sporadic tauopathies [24]. Other rare genetic contributors are mutations in *CHMP2B*, *VCP*, *CHCHD10*, *TBK1*, *TARDBP*, *FUS*, *UBQLN2* and *TUBA4A*, implicating common pathogenic pathways with ALS and highlighting the disease continuum between FTD and ALS [14].

Neuropathology

From a neuropathological classification point of view, frontotemporal lobar degeneration (FTLD) can be subdivided into three categories based on the type of misfolded protein inclusions: FTLD-TDP (50%), FTLD-tau (40%), and FTLD-FET (the remaining 10%) [25]. The TAR DNA-binding protein 43 (TDP-43) is a nuclear protein that plays an important role in the metabolism of RNA, neurite outgrowth, and axonal repair [26]. In FTLD-TDP, TDP-43 is pathologically accumulated in the cytoplasm as ubiquitinated and phosphorylated inclusions, leading to neuronal cytoplasmic inclusions, dystrophic neurites, and glial cytoplasmic inclusions, which are further divided into four subtypes (A–D) according to their morphology and distribution [27]. Type A is often associated with *GRN* mutations and observed in bvFTD and nfvPPA. Type B is the most common in FTD-MND, as well as in ALS and is frequently linked to *C9orf72* mutations. Type C predominates in svPPA, present in about 83–90% of cases, while Type D is related to *VCP* gene mutations and some ALS cases [28]. Loss of TDP-43 from the nucleus leads to abnormal regulation of over 100 proteins including stathmin-2, which is currently being investigated as a potential therapy for FTLD-TDP [29]. Tau, a microtubule-associated protein, is produced by alternative splicing of the *MAPT* gene and exists as six isoforms that are classified as 3-repeat (3R) and 4-repeat (4R). In the mature brain, both isoforms are expressed at identical levels, although different patterns are observed in some tauopathies. 3R tau (Pick's bodies) is most prominent in bvFTD, while 4R tau is seen in CBS, PSP and globular glial tauopathy (GGT). Diseases such as AD and chronic traumatic encephalopathy exhibit mixed 3R-4R tau pathology. Phosphorylation modulates tau activity and pathophysiology by altering its ability to bind microtubules and promoting aggregation [30]. Paired helical tau filaments are generally observed in AD, while FTLD tau pathologies are characterized by isoform dominance as either 3R or 4R tauopathies and unique neuronal and glial inclusions such as neurofibrillary tangles (NFTs) or amorphous deposits [30, 31]. The fused-in-sarcoma (FUS) protein, a member of the FET family along with Ewing sarcoma RNA Binding Protein 1 (ESWR1) and TATA-box-binding protein-associated factor 15 (TAF15), is a crucial factor in binding DNA and RNA to modulate the expression of over 100 proteins and take part in alternative splicing, transcription, and RNA transport [32, 33]. FUS dysfunction has been associated with diseases, including FTLD and ALS, with particular effects on the expression of *MAPT* (tau) and the 4R/3R tau ratio [33]. FTLD-FUS is marked by neuronal cytoplasmic inclusions mostly involving the neocortex and dentate granule cells, detectable by immunohistochemistry [34]. FTLD-FUS usually occurs in early adulthood (20-40 years of age) with clinical symptoms like compulsive behavior, psychosis and hyperorality [28, 35]. FUS pathology relates to bvFTD, PPA, neuronal intermediate filament inclusion disease and ALS [32].

Biomarkers & Neuroimaging

Biomarkers for diagnosis and prognosis for FTLD are rapidly evolving, with major advances in blood, cerebrospinal fluid (CSF), genetic, and neuroimaging markers. Neurofilament light chain (NfL) has emerged as a sensitive marker of neurodegeneration, with increased plasma and CSF levels associated with disease severity, progression, and distinguishing FTLD from primary psychiatric disorders [36]. However, in mild symptoms there is overlap with healthy controls and NfL is not fully selective for FTLD compared to other neurodegenerative illnesses [37]. Phosphorylated tau in plasma and CSF facilitates the differential diagnosis from AD, while new methods for TDP-43 and tau (e.g., real-time quaking-induced conversion (RT-QuIC))

show potential for the direct detection of FTD and ALS [38, 39]. Biomarkers in CSF and blood such as progranulin and dipeptide repeats greatly enhance diagnosis and prognosis, particularly in hereditary forms. While technical challenges have been faced, identification of biomarkers in blood and CSF has progressed through specific immuno- and mass-spectrometry-based assays [40]. Genetic testing for mutations in *C9orf72*, *MAPT*, and *GRN* is recommended in patients with a family history of dementia, parkinsonism, or ALS [5]. Structural brain magnetic resonance imaging (MRI) is still the mainstay for FTLD assessment and commonly shows atrophy of the frontal or temporal lobe [6]. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in equivocal cases of MRI, demonstrating hypometabolism in typical brain areas [41]. Molecular PET imaging, especially amyloid PET, helps exclude AD, although first-generation tau ligands lack specificity for FTLD and novel tracers for tau and TDP-43 are under development [42, 43]. Multimodal imaging, including resting-state fMRI, aids in the diagnosis of early or pre-symptomatic disease, notably in the hereditary form of FTD, where atrophy and network dysfunction may precede symptoms by years [15]. Neuroimaging atrophy patterns correlate with clinical categories. BvFTD often presents with the atrophy of the bilateral medial prefrontal, right orbitofrontal, anterior insular and anterior cingulate cortex. SvPPA has asymmetric, mostly left-sided anterior temporal atrophy, whereas nfvPPA affects the anterior perisylvian cortex of the dominant hemisphere, specifically the left frontal operculum and Broca's areas [44]. RtvFTD is defined by right temporal lobe atrophy, with progression including medial temporal and insular regions [45]. Atrophic and hypometabolic patterns also help differentiate between hereditary subtypes and other dementias [15]. Biomarkers such as NfL, TDP-43, progranulin, β-amyloid, tau, glial fibrillary acidic protein (GFAP), protein triggering receptor expressed on myeloid cells 2 (TREM2), and dipeptide repeats are useful for diagnosis, prognosis, and research but none are completely specific or definitive on their own [40]. Combining clinical, genetic, imaging, and biomarker data improves diagnostic precision and may lead future disease-modifying therapies as research proceeds.

Treatment

Currently there are no FDA-approved disease-modifying therapies for FTD. Treatment is limited to pharmacological and non-pharmacological measures to relieve symptoms rather than to cure or reverse the disease. Interventions are primarily supportive including behavioral modifications, environmental approaches and education for caregivers, and pharmacological therapies for cognitive and behavioral symptoms. While progress has been made in understanding the molecular basis of FTD and clinical trials are underway, there are no preventive or curative interventions. Future therapies are likely to require early administration, perhaps at the preclinical stage, but the lack of reliable biomarkers predictive of pathology is a major hurdle.

Non-Pharmacological Interventions

Non-pharmacological therapies play a key part of holistic management of FTD, which has to accommodate the changing and heterogeneous requirements of patients and caregivers. Lifestyle adjustments, such as regular physical exercise and engagement in cognitive activities, are linked to slower disease progression and less severe symptoms, especially in familial FTD [46]. Physical activity enhances cardiovascular health, strength and balance, therefore decreasing the likelihood of falls [47]. A balanced diet and moderate alcohol intake are also recommended; however symptoms such as changes in appetite and low motivation may complicate consistent application of this in FTD populations. Speech therapy plays a crucial role for those with PPA and other speech and language problems in the FTLD spectrum. Individualized interventions include script training, compensatory communication strategies, and augmentative and alternative communication (AAC) devices, and are provided by speech-language pathologists skilled in neurodegenerative disorders. Research supports the effectiveness of video-based script training in improving intelligibility and maintaining language abilities even as disease progresses [48]. Speech therapy can be performed in person or by telehealth and swallowing examinations are advised for patients with dysphagia [49]. For individuals with motor symptoms, physical and occupational therapy is essential and aims at improving strength, gait, range of motion, and balance [50]. Occupational therapists evaluate the person's cognitive and physical condition and give supportive gadgets and techniques such as visual aids and step-by-step templates to optimise independence in everyday living. Additionally, they perform home safety assessments and suggest changes to prevent falls and injuries [47]. Behavioral therapies are adapted to the specific problems of FTD. Positive behavior support, therapeutic routines (replacing inappropriate behaviors with organized routines), and substitution methods (e.g., use of a squeeze ball or lollipop to redirect compulsive acts) have been shown to be useful in managing problematic behaviors [51, 52]. The ABC paradigm

(Antecedent-Behavior-Consequence) assists caregivers to identify triggers and effects of behaviors [53]. The DICE model (Describe-Investigate-Create-Evaluate) has been a systematic method for planning and evaluating interventions [54]. Evidence has shown that individualized techniques are more effective than cognitive training for FTD specific behavioral symptoms [55]. Environmental improvements are meant to provide supportive and safe areas for patients. Strategies include, but are not limited to, setting up consistent routines and furniture arrangements, reducing noise and clutter, posting warnings, and limiting access to dangerous objects such as credit cards or guns [53, 55]. Caregivers should also allow safe routines and choose familiar environments to reduce anxiety and confusion. For those with driving difficulties, regular assessments are recommended, and legal considerations might require reporting dementia diagnosis in some regions [55]. Caregiver education and assistance is critical as care partners of FTD patients report high levels of burden, stress and sadness [56]. Educational tools, support groups, and organized programs such as The Savvy Caregiver minimize caregiver stress, enhance coping skills, and promote confidence in behavior management [57]. Respite care, day programs and reputable organizations such as the Association for Frontotemporal Degeneration can help lighten the load for caregivers. Neurophysiological techniques such as transcranial magnetic stimulation (TMS) are being investigated for their ability to monitor and differentiate neurodegenerative disorders and may contribute to the development of future therapies. [58] The management of FTD is holistic and multidisciplinary and includes lifestyle, rehabilitative, behavioral, environmental, and caregiver-support strategies to stabilize symptoms and improve the quality of life of the patient and family.

Pharmacotherapy

There are no FDA-approved disease-modifying treatments for FTD, and pharmacologic treatments are aimed only at symptom relief. The approach focuses on off-label use of medications tailored to specific behavioral and motor symptoms, and decisions about pharmacotherapy always demand a careful risk-benefit analysis. Before initiating any medication, clinicians must rule out alternative causes of behavioral disturbances, such as infection, metabolic imbalances, drug intoxication, or structural brain lesions, as treating these could alleviate symptoms without the need for ongoing pharmacotherapy. Medications commonly effective in AD such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine, have not shown benefit in FTD. In fact, they may worsen behavioral or cognitive symptoms and are not recommended [59, 60]. The mainstay of pharmacologic management in FTD is the use of selective serotonin reuptake inhibitors (SSRIs), including citalopram, sertraline, fluoxetine, and paroxetine. These agents target serotonergic deficits in FTD and have the best evidence for efficacy in reducing problematic behaviors such as disinhibition, irritability, agitation, compulsive behaviors, and abnormal eating [28]. Escitalopram and citalopram are generally preferred drugs for neuropsychiatric symptoms in FTD, given their excellent tolerability and minimal anticholinergic side effects [61, 62]. Trazodone, another serotonergic agent, has also been shown to reduce agitation, aggressiveness and depressive symptoms and may be helpful as a sleep aid [59]. Atypical antipsychotics such as quetiapine, olanzapine, aripiprazole, and sometimes risperidone can be used for severe agitation, psychosis, or aggression that is unresponsive to other therapies. However, these medications carry significant risks of extrapyramidal symptoms and increased mortality in older dementia patients, and as such carry an FDA black box warning [63]. If antipsychotics are prescribed, preference is given to medicines with less dopamine receptor blockage (e.g., quetiapine, aripiprazole). Patients should be started on the lowest possible dose and monitored regularly [64]. Anticonvulsants such as carbamazepine, valproic acid, and topiramate have been used as mood stabilizers or to treat symptoms like hyperorality, agitation, and hypersexuality, but the data is mainly anecdotal and restricted to case reports [65-67]. Stimulants like methylphenidate and bupropion that increase dopaminergic transmission, may be considered for severe apathy or behavioral disinhibition. However, the use of these agents is experimental, and caution should be exercised because of possible adverse effects [68]. Oxytocin is also under investigation for potential benefits in treating behavioral symptoms, with preliminary studies showing promise [69]. For patients with parkinsonism due to PSP or CBS, dopamine replacement therapy may offer mild, transient benefit but is typically less effective than in Parkinson's disease, and may sometimes worsen behavioral symptoms [12, 63, 70]. Pharmacologic treatments for FTD should follow non-pharmacological interventions or be used for severe symptoms. Medications should begin at the lowest effective dose with regular monitoring for side effects. The goal is to reduce distressing symptoms to enhance patient quality of life and ease caregiver burden.

Current Clinical Trials

Recent advances in FTD research have resulted in several new targeted treatments. Potential gene therapies for *GRN* mutation carriers include PBFT02, PR006/LY3884963 and AVB-101 (ongoing trials include NCT04747431, NCT04408625, NCT06064890). PBFT02 is a viral vector (AAV1 serotype) which directly delivers a functional copy of the *GRN* gene into the brain to restore progranulin levels and neurological function. Early clinical trial data has demonstrated that PBFT02 can significantly increase CSF progranulin which is promising for disease modification [71]. PR006/LY3884963 also utilizes an AAV9 vector to deliver the *GRN* gene requiring a single injection to the cisterna magna and is in trials currently to assess safety and efficacy [72]. AVB-101 is a single dose gene replacement therapy given to the thalamus by minimally invasive neurosurgery to restore progranulin levels by targeted brain delivery. The ASPIRE-FTD study is currently evaluating its safety and efficacy, supported by preclinical data showing widespread progranulin expression and good tolerability [73]. Anti-diabetic medication metformin is under investigation for potentially neuroprotective benefits in *C9orf72* carriers. Preclinical results suggest that metformin may diminish the generation of the detrimental dipeptide repeat proteins produced by *C9orf72* repeat expansion and clinical trials are underway to evaluate the efficacy in FTD and ALS (NCT04220021) [74]. Treatments that target tau include bepranemab (UCB0107), a monoclonal antibody that binds to the core area of the tau protein, to help remove the protein and avoid toxic aggregation. It is currently being evaluated in clinical studies for PSP (NCT04658199) [75]. Another strategy under research for slowing disease development in tau-related FTD subtypes is using the Rho-associated protein kinase inhibitor Fasudil to enhance tau autophagy and reduction of tau mRNA (NCT04734379) [76]. Additionally, AADvac1, an active vaccine targeting pathological tau, aims to stimulate an immune response that curbs the spread of tauopathies [77]. Initial trials have demonstrated safety and tolerability and further studies will explore its use as a disease-modifying medication (NCT03174886). Together these therapies represent a move towards precision medicine in FTD through targeting the genetic and molecular basis of disease to improve patient outcomes.

Conclusions

Frontotemporal dementia (FTD) is a broad group of neurodegenerative diseases with significant clinical, genetic and pathological heterogeneity. Diagnosis and management are hampered by early start, rapid progression and substantial effects on behavior, language and executive function. Recent advances in molecular genetics, discovery of biomarkers and neuroimaging approaches have enhanced diagnostic accuracy and ongoing research into the underlying mechanisms continues to provide insight into the complicated relationship between FTD and related conditions such as ALS. Current treatment is symptomatic and there is increased promise for disease modification as the pipeline of targeted gene and protein based therapies continues to expand. Ultimately, enhancing outcomes and quality of life for patients and families affected by FTD will require a multidisciplinary approach including clinical care, caregiver support, rehabilitative therapies, and ongoing research.

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