DACKA, Michał, PORZAK, Mikołaj, BOCHYŃSKI, Karol, BIAŁOGŁOWSKI, Konrad, DĄBROWSKA, Paulina, ŻUBER, Michał, CIUBA, Katarzyna, MOLENDA, Katarzyna, BORODZIUK, Filip and BORODZIUK, Barbara. Frontotemporal Dementia: A Clinical Review. Journal of Education, Health and Sport. 2024;59:235-246. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.59.015
https://apcz.umk.pl/JEHS/article/view/48161
https://zenodo.org/records/10657197

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 17.01.2023. Revised: 08.02.2024. Accepted: 14.02.2024. Published: 14.02.2024.

Frontotemporal Dementia: A Clinical Review

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Abstract

Frontotemporal dementia is a disease in which atrophic changes occur in the frontal lobes and frontal temporal lobes of the brain. Frontotemporal dementias are a clinically, neuroanatomically and pathologically diverse group of diseases that collectively constitute an important cause of young-onset dementia. The most common form of frontotemporal dementia is the so-called behavioral variant of frontotemporal dementia. Underlying these pathological changes is the degeneration of nerve cells (i.e. neurons), which occurs through the accumulation of abnormal proteins inside them. Therefore, the review of current studies in the subject of Frontotemporal dementia was conducted in order to access possible risk factors and new ways of management and treatment of this complex disease.

Keywords: Frontotemporal dementia; Frontotemporal lobar degeneration; Primary progressive aphasia.

Introduction

The cause of dementia is an organic disease of the brain most often chronic and progressive. It is an acquired disorder and doesn't have to include intellectual disability. The essence of dementia is a disturbance of cognitive functions, behavioral and emotional disorders are also typical, expressed by changes in emotions. Dementia is a syndrome of symptoms, so the diagnosis of dementia cannot be made based on only one symptom, such as memory disorders. Frontotemporal dementia (FTD) Although substantially less common than Alzheimer's disease, the disorders that comprise the FTD spectrum have disproportionate clinical and neurobiological importance. [1] From a clinical perspective, FTD usually presents as a disturbance of complex behavior, affecting predominantly interpersonal conduct or language

(primary progressive aphasia, PPA), often in middle life. It is the major young-onset dementia besides Alzheimer's disease and takes a devastating toll on social and occupational functioning. Moreover, a substantial proportion of cases are genetically mediated, with implications for family counseling and presymptomatic diagnosis. From a neurobiological perspective, FTD illustrates the effects of pathogenic proteins in promoting selective disintegration of neural assemblies and has transformed our understanding of the molecular and network mechanisms of neurodegenerative disease.[2–4]

Epidemiology

Limited data suggest that the overall population prevalence of FTD is around 11/100,000 and incidence 1.6/100,000,19 but these values rise sharply between the fifth and seventh decades and are likely to be underestimates (chiefly on account of misdiagnosis), particularly in older age groups. The prevalence of dementia rises sharply with age. In the age group after 65 years of age, it is 5% Above 80 years of age it reaches as much as 20%. FTD accounts for around 40% of cases of young-onset dementia coming to postmortem.[1]

Pathomechanism

The fundamental pathological mechanism at the core of Frontotemporal Dementia (FTD) involves the intracellular deposition of abnormally aggregated proteins within neural tissue. Consequently, diseases within the FTD spectrum are classified as "proteinopathies," based on the major constituents of the cellular inclusions present. Approximately half of the cases examined postmortem exhibit abnormal deposition of transactive response DNA-binding protein 43 (TDP-43). This protein, ubiquitously expressed and broadly implicated in neuronal development and synaptic function, is variably associated with neuronal cytoplasmic and intranuclear inclusions, as well as dystrophic neurites. These cases can be further subclassified based on the morphology and laminar distribution of the cellular inclusions.[5–7]

In about 40% of postmortem cases, there is an abnormal accumulation of hyperphosphorylated microtubule-associated protein tau (MAPT). Tau is a microtubule-associated protein that has beenlinked to multiple molecular processes, including synaptic plasticity, cell signaling, and regulation of axonal stability. There are six isoforms of tau expressed in the brain from alternative mRNA splicing of a single gene, APT. [8] This

accumulation is likely to disrupt axonal transport and the maintenance of neuronal integrity. Immunohistochemical subclassification of these cases depends on whether the abnormally deposited tau contains predominantly three- or four-repeat microtubule binding domains.

A small minority of cases involve the deposition of a family of fusion oncogene proteins, which are implicated in DNA and RNA metabolism. Rarely, none of these proteins is present. The mechanisms through which these pathogenic proteins lead to neurodegeneration and cell death continue to be defined.[8,9]

Genetics

Frontotemporal lobar degeneration (FTLD) is the term used to refer to a group of progressive brain diseases that pre-dominantly affect the frontal and anterior temporal lobes.

Twenty percent of Frontotemporal Dementia (FTD) cases are attributed to genetic mutations, and in 40% of FTD cases, there is a family history of dementia, psychiatric disease, or motor symptoms without a clear pattern of inheritance. Genetic FTD may manifest as atypical mixed FTD spectrum syndromes. [10] Most genetic causes follow an autosomal dominant inheritance pattern with variable penetrance dependent on the specific gene. Recognized genetic mutations associated with FTD include microtubule-associated protein tau (MAPT), GRN, C9orf72, VCP, chromatin-modifying protein 2B (CHMP2B), TARDBP, FUS, SQSTM1, UBQLN2, tank-binding kinase (TBK1), triggering receptor expressed on myeloid cells (TREM2), and coiled-coil-helix-coiled-coil-helix domain-containing protein 10 (CHCHD10). Among FTD clinical syndromes, FTD-ALS is the most heritable, while semantic variant primary progressive aphasia (svPPA) is the least heritable.[7,11,12]

Diagnosis

The onset of the disease is usually hardly noticeable and slowly progressive. Unlike other dementias, memory is initially well preserved, and the predominant symptoms are behavioral and speech disorders. The patient may have difficulty finding the right word, or his speech becomes partially unintelligible to those around him.[13]

The ailments described above are joined over time by steadily worsening personality changes. Patients with frontotemporal dementia are often unable to control their emotions and function

increasingly poorly in society. [14] Patients may have an altered mood, behave inadequately to the situation, be agitated, without critical evaluation of their own behavior.[5,15]

A detailed neurological examination is required to identify associated extrapyramidal or motor neuron deficits that frequently develop during the disease. Neuroimaging, ideally with magnetic resonance imaging (MRI) and interpreted by an experienced observer, is essential to corroborate the bedside impression, and, where available, neuropsychological assessment is very valuable, to quantify key deficits and their evolution over time (which may be decisive in clinically ambiguous cases) and also to capture associated cognitive deficits that help to define the phenotype.[16–18]

Considering the major role played by pathogenic genetic mutations in FTD, a searching family history is mandatory. This is particularly pertinent in behavioral variant of FTD.

Structural and functional neuroimaging play a crucial role in identifying patterns of atrophy, functional connectivity, and hypometabolism that can aid in the diagnosis of Frontotemporal Dementia (FTD). While not flawless, these imaging techniques can also provide insights into the potential underlying pathology. Neuroimaging findings are particularly valuable for diagnosing behavioral variant FTD (bvFTD) and excluding other conditions like tumors or cerebrovascular disease.

BvFTD (Behavioral version of Frontotemporal Dementia (FTD) is characterized by atrophy in the prefrontal and temporal lobes, with a more pronounced effect observed in the right frontal lobe. This syndrome is marked by an early and progressive decline in interpersonal and executive skills, accompanied by a loss of social and emotional awareness. The current diagnostic criteria, place a significant focus on various domains of behavioral and personality change derived from the patient's history. [19,20] Notably, these changes include social disinhibition, apathy and abulia (loss of motivation and initiative), emotional blunting with a decrease in empathy, perseverative, stereotyped, or compulsive verbal and motor routines (often involving hoarding, counting, or tidying), hyperorality, and altered feeding behavior with a tendency towards gluttony and a preference for sweets.[21]

The criteria further underscore executive dysfunction while relatively sparing episodic memory and visuospatial functions during neuropsychological assessment. The diagnosis is

categorized as possible, probable, or definite, based on the availability of corroborative neuroimaging, genetic, or histopathological information.[7]

These criteria have played a pivotal role in enhancing the recognition of this syndrome and advancing research in Frontotemporal Dementia (FTD) on an international scale. Even though cortical atrophy is evident when patients seek specialized care, it's important to recognize that early in the disease course, cortical volume may be normal or only minimally decreased. Emphasizing the need to scrutinize brain images, especially for focal atrophy in areas commonly associated with FTD, such as the anterior insula, anterior cingulate, orbitofrontal, dorsolateral prefrontal, and anterior temporal lobe.[11,22]

While the predictive accuracy of underlying pathology based on clinical syndrome and imaging findings is estimated to be around 60% in bvFTD, patterns of cortical atrophy can significantly contribute to narrowing down the potential pathological differential diagnosis.

Treatment and Management

Currently, no treatments have demonstrated efficacy in altering the underlying disease process in any Frontotemporal Dementia (FTD) syndrome. As a result, the prognosis for FTD is characterized by a gradual increase in disability and continuous decline leading to dependency. However, life expectancy varies widely across the FTD spectrum, ranging from a few years in FTD–MND to over a decade in some patients with behavioral variant FTD (bvFTD) and semantic variant primary progressive aphasia (svPPA). As the disease progresses, syndromes often converge, and noncognitive neurological features may emerge. Unfortunately, reliable markers of disease severity, stage, and prognosis are currently lacking, making it challenging to provide precise counseling for individual patients and their families.[23,24]

Management of FTD commences with the provision of accurate information about the nature of the illness to the patient, family members, caregivers, and relevant health professionals. This diagnosis is truly life-changing; the erosion of the sufferer's personal identity (living with a stranger) can be profoundly distressing for those close to them. Understanding the impact on the patient's social milieu, day-to-day functioning, and care needs, along with appropriate safeguarding and anticipation of future loss of independence, is integral to successfully managing the illness. [23,25,26]

Nonpharmacological Strategies

In general, for symptom control, nonpharmacological strategies are favored over medications for individuals with Frontotemporal Dementia (FTD). Medications, due to their challenging rational use, limited efficacy, and potential for unwelcome side effects in people with FTD, are often less preferable. [4] The effective implementation of nonpharmacological strategies necessitates the involvement of local multidisciplinary support services, including speech and language therapy, occupational therapy, audiology, clinical psychology, and social work. Ideally, these services are coordinated by the general practitioner and/or the local community mental health team.[27]

Caregivers play a vital role and may require education and empowerment to actively manage the situation. Patients benefit from a stable and structured environment tailored to their specific capacities and interests. Safeguarding is essential and may include activities related to occupation, hobbies, responsibility for children or elderly dependents, financial decision-making, and driving. Addressing the last issue can be particularly challenging when manual competence is retained, but judgment and insight are compromised.[7]

Communication is a critical issue across syndromes and disease stages, especially in progressive aphasias. While the place of specific language retraining programs and electronic devices remains undefined, there is unquestionable value in simple communication aids such as cards, picture books, and medical alert bracelets.

As the disease progresses, the focus of management shifts from maintaining independence to controlling aggression and other challenging behaviors. Additionally, addressing neurological disability becomes crucial due to declining mobility, impaired swallowing and nutrition, and disturbed homeostatic and autonomic functions. It is important to ensure that general medical health needs are not overlooked in the face of anosognosia or altered awareness of pain and other bodily signals.[9,27]

Pharmacologically, deficits in presynaptic serotonin and dopamine, but not norepinephrine or acetylocholine, are observed in Frontotemporal Dementia (FTD), supporting the use of selective serotonin reuptake inhibitors in FTD spectrum disorders. Various clinical trials with

fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, and trazodone have demonstrated improvements in functional measures and better control of behavioral symptoms, including disinhibition, apathy, stereotypies, irritability, agitation, and dietary changes. [8,9] Generally, escitalopram and citalopram are preferable due to their better tolerability and minimal association with anticholinergic side effects. Dopamine augmentations with methylphenidate, dextroamphetamine, and bromocriptine have resulted in improved risk-taking behavior, apathy and disinhibition, and speech production, respectively.[8] Similar to patients with Lewy body dementia, some individuals with FTD may be sensitive to neuroleptics. Nonetheless, risperidone, aripiprazole, olanzapine, and quetiapine have shown improvements in cognitive and behavioral symptoms, including delusions, agitation, and caregiver burden. Tetrabenazine has demonstrated improvement in severe tics and stereotypies in FTD. [27] Quetiapine is preferable in patients with parkinsonism, given its low affinity for D2 blockage. Cholinergic medications such as donepezil have been associated with worsening symptoms. In fact, discontinuation of donepezil in patients with FTD initially diagnosed with Alzheimer's disease led to an improvement in behavioral symptoms and caregiver burden. Meanwhile, a noncompetitive inhibitor of the N-methyl-D-aspartate receptor showed no benefit in two well-designed trials, however, a more recent trial demonstrated improved behavioral symptoms in moderate-to-severe behavioral variant FTD.[8,27].

Current clinical trials and biomarkers

Promising clinical trials targeting tau and TDP-43 in FTD are a unique opportunity to find therapeutics in neurodegeneration.105 Tau-antibodies, tau phosphorylation and acetylation inhibitors, tau vaccines, and microtubule-stabilizing agents are currently underway in various phases of 8 Younes & Miller development. [7,28,29] Moreover, innovative gene-editing therapies using antisense oligonucleotides (synthetic nucleic acids that can inactive the mRNA of a target gene) to reduce C9orf72 expansion or increase PRGN expression in patients with genetic FTD are in active investigation and development.[27]

Molecule-based therapies are under consideration for the genetic forms of Frontotemporal Dementia (FTD) and for addressing the symptoms of the disease (refer to Table 2). Distinct approaches are required for each major genetic subtype, namely MAPT, GRN, and C9orf72. Notable advancements have paved the way for such endeavors. Firstly, the identification of robust biomarkers, such as the neurofilament light-chain protein (NfL), facilitates the tracking of progression in clinical trials. NfL begins to rise during the transition from asymptomatic to

mildly symptomatic FTD (130). Additionally, structural imaging can detect significant changes in atrophy over 6 months, suggesting that magnetic resonance imaging (MRI) could serve as a surrogate marker [11].

For carriers of the MAPT gene, clinical trials will primarily focus on lowering tau levels, either by reducing its production or enhancing its clearance. Extensive evidence indicates that lowering tau can alleviate symptoms in animal models of Alzheimer's disease (AD) and FTD (132, 133). Moreover, in humans, antibodies against tau have been shown to reach the brain and transport tau into the plasma [2,30]. However, clinical trials utilizing antibodies for both AD and FTD have faced disappointments, likely due to relatively low levels of antibody penetration across the blood-brain barrier. CRISPR technology holds the potential to significantly lower tau levels in a highly effective manner. If individuals carrying the MAPT gene, when treated with effective tau-lowering therapies, demonstrate a slowdown, halt, or even regression of the disease, these approaches may be extended to treat other tau-related forms of Frontotemporal Dementia (FTD). Alternative efforts are directed towards enhancing the degradation of tau in the lysosome or the proteasome.[31,32]

For individuals with GRN mutations, distinct mechanisms and approaches are being explored. Those with GRN mutations exhibit markedly reduced brain and blood levels of progranulin, indicating a haploinsufficiency mechanism where the deficiency of progranulin production on one chromosome is sufficient to cause FTD. Numerous strategies are under consideration to increase brain progranulin, with a focus on improved methods for delivering progranulin into the brain. Studies by Arrant and colleagues utilizing an AAV vector (AAV-Grn) to deliver progranulin in GRN2/2 mice demonstrated amelioration of lysosomal dysfunction and microglial pathology. In the upcoming year, AAV transplantation studies are likely to commence with GRN gene carriers, and various delivery systems are also under consideration.[1–3]

Lastly, C9orf72 mutations result in a long hexanucleotide repeat that is already a target for gene carriers with ALS, and therapies for FTD are being explored. As with all gene-related therapies, numerous questions must be addressed, including drug delivery to the brain, the timing of therapy (presymptomatic versus symptomatic), the reliability of biomarkers, and, most crucially, efficacy. A new era in therapy for FTD and related conditions is commencing. Once the genetic forms of the disease are effectively treated, novel approaches to the sporadic form of the disease are likely to emerge.

Conclusions

Frontotemporal Dementia (FTD) is frequently misdiagnosed, often occurring late in the disease course or being overlooked. The challenge lies in recognizing that behavioral changes signify a neurodegenerative condition, leading clinicians to sometimes misdiagnose it as a primary psychiatric disorder. [9] Additionally, access to diagnostic tools such as blood biomarkers or neuroimaging can be challenging, particularly in low- and middle-income communities.

FTD treatment has historically focused on managing neuropsychiatric symptoms, which are prominent features of the disease. Therapeutic approaches include nonpharmacological interventions such as behavioral and environmental manipulation, caregiver interventions, and speech therapy for language variants of FTD. Pharmacological treatments have also been employed with variable but occasionally positive results[27].

With advancing knowledge of FTD's pathophysiology, pharmacological interventions like selective serotonin reuptake inhibitors (SSRIs), trazodone, and second-generation antipsychotics now have a solid scientific basis for treating FTD.

Over the past decade, advancements in neuroimaging, genetics, and biomarker analysis have revealed much about the underlying phenomena in frontotemporal lobar degeneration.[6] These discoveries have paved the way for the development of new molecule-based therapies, still in early research stages but showing promising results. Active clinical trials targeting specific genetic subtypes, such as MAPT, GRN, and C9orf72, demonstrate the growing optimism for more effective treatments in the future.

Author contributions

Conceptualization: Michał Dacka, Konrad Białogłowski, Katarzyna Ciuba; methodology: Michał Dacka, Michał Żuber, Mikołaj Porzak, Katarzyna Molenda; writing - review and editing: Michał Dacka, Michał Żuber, Karol Bochyński, Paulina Dąbrowska, Filip Borodziuk, Katarzyna Molenda; resources: Michał Dacka, Katarzyna Ciuba, Mikołaj Porzak; supervision: Michał Dacka, Konrad Białogłowski, Paulina Dąbrowska.

All authors have read and agreed with the published version of the manuscript.

Funding statement: The article did not receive funding.

Statement of institutional review board: Not applicable.

Statement of informed consent: Not applicable.

Statement of data availability: Not applicable.

Conflict of interest statement: The authors declare no conflict of interest.

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