The Essentials in Behavioral Variant Frontotemporal Dementia

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Abstract

Behavioral variant frontotemporal dementia (bvFTD) is an important dementia syndrome in clinical practice. In this paper, we describe the clinical, anatomical, genetic, pathological and neuroradiological features of this entity. We discuss diagnostic strategies and how to approach the management of the different symptoms. bvFTD is a clinical syndrome, not a disease, and there are controversies regarding the definitive diagnosis. This syndrome must be distinguished from psychiatric diseases and other neurodegenerative syndromes that present a predominant behavioral component. Accurate knowledge of the underlying proteinopathy remains a challenge, however, the ability to differentiate bvFTD from atypical forms of Alzheimer's disease (AD) has improved. In the management of this condition, consideration should be given to: 1-preventing caregiver distress, 2-defining behavioral strategies, 3-symptom-based psychopharmacology, and 4-genetic counseling. Understanding the genetic basis of individuals with familial fronto-temporal dementia (fFTD) allows for an early and accurate diagnosis. Clinical trials designed to delay the onset of symptoms or slow their progression are currently underway, but several questions remain. No treatments have been found that significantly improve symptoms or modify the biological course of bvFTD. A better understanding of the pathophysiology will allow for the development of new and effective therapies. The clinical characteristics and the different pharmacological and non-pharmacological treatment options are discussed.

Keywords: Fronto-Temporal Dementia; Neurodegeneration; Diagnosis; Treatment

Introduction

The behavioral variant of frontotemporal dementia (bvFTD) accounts for approximately 50% of all frontotemporal dementias (FTD) and is characterised by a progressive alteration in personality and behaviour, accompanied by a gradual decline in social and emotional functioning, which often complicates its diagnosis. bvFTD, is associated with asymmetric involvement-predominantly affecting the non-dominant cerebral hemisphere-of the insular region, anterior cingulate cortex, prefrontal cortex, amygdala, striatum, and thalamus. In the past two decades, advances in molecular biology and genetics have contributed substantially to a deeper understanding of this condition,

which may represent the clinical manifestation of various neurodegenerative diseases typically emerging in mid to late adulthood. However, a definitive diagnosis can only be established through post-mortem neuropathological examination [1].

History

In 1882, Arnold Pick (Figure 1) described a patient who presented progressive aphasia and behavioural disturbances. Post-mortem findings revealed marked bilateral atrophy in the frontal convexity and anterior temporal regions. In 1911, Alois Alzheimer (Figure 2) studied similar cases and identified their histopathological features: (1) Pick bodies-spherical inclusions that stained positively with silver salts, and (2) Pick cells-swollen achromatic neurons. He referred to this condition as Pick's disease or Pick's dementia. Subsequently, clinical cases with similar presentations but lacking the specific histopathological findings of Pick's disease were described, prompting recognition of the condition based on neuropathological characteristics. This gave rise to the concept of frontotemporal dementia (FTD), encompassing clinical syndromes characterised by language and behavioural disturbances associated with frontotemporal atrophy. In 1982, Marcel Mesulam identified aphasic syndromes in patients with left cerebral hemisphere atrophy and introduced the term primary progressive aphasia (PPA), later subdivided into: (1) non-fluent/agrammatic variant PPA (nfvPPA), (2) semantic variant PPA (svPPA), and (3) logopenic variant PPA (lvPPA). The clinical form of FTD characterised primarily by alterations in personality and behaviour was termed behavioural variant frontotemporal dementia (bvFTD), typically associated with atrophy of the frontal and temporal cortices of the right (non-dominant) hemisphere in right-handed individuals. In 1998, Neary and colleagues established the first consensus criteria for frontotemporal lobar degeneration (FTLD), which encompassed the three major clinical presentations: (1) bvFTD, (2) nfvPPA, and (3) svPPA. These criteria were revised by Rascovsky and colleagues in 2011 through the International Behavioural bvFTD Criteria Consortium. In 2013, Harris evaluated the updated diagnostic criteria for bvFTD, reporting high sensitivity and specificity, establishing them as a key tool for both researchers and clinicians [2].

Figure 1: *Arnold Pick.*

Figure 2: Alois Alzheimer.

Epidemiology and demographics

Frontotemporal dementia (FTD) is considered a relatively uncommon clinical form of dementia with early onset. Peak prevalence is observed between the ages of 58 and 59. Recent epidemiological studies have revised earlier perspectives. The incidence rate ranges from 1 to 8 per 100,000 individuals per year, while the prevalence rate varies from 2 to 20 per 100,000 individuals [3-5]. Both incidence and prevalence tend to increase with age, subsequently plateauing or declining after the age of 70. A minority of patients with late-onset dementia present with underlying FTD and/or frontotemporal lobar degeneration (FTLD) pathology, or both [6]. No sex predilection has been identified. The vast majority of reported FTD cases involve Caucasian individuals, with cases being less frequently observed among Asian, Hispanic, or African populations. The reasons behind these differences in incidence across ethnic and racial groups remain poorly understood [7].

Impact of bvFTD on patients and their social and family environment

Behavioural variant frontotemporal dementia (bvFTD) exerts a significant impact on both affected individuals and their caregivers. The behavioural and cognitive changes experienced during both the pre-diagnostic and post-diagnostic stages of the disease affect various domains of life, including: (1) breakdown of family and social relationships, (2) marital separation or divorce, (3) poor work performance and job loss, (4) loss of income, health insurance, and pension benefits, (5) sexual disinhibition, (6) excessive spending or gambling, (7) financial ruin due to poor business decisions, and (8) tragic accidents. The progressive loss of empathy and emotional connectedness leads to increasing social isolation and deterioration of close personal relationships. The disease imposes a substantial burden on caregivers-most often family members-who frequently describe the experience as "exhausting". In a 2022 focus group study, one patient's partner expressed: "They just don't understand what we go through" [8], while another stated: "I feel like I've lost my partner and now I'm just a caregiver" [9]. From an economic perspective, surveys conducted among caregivers of individuals with bvFTD report a decline in household income, deterioration in caregivers' health, and an increase in healthcare-related costs-approximately double those observed in Alzheimer's disease (AD). This is primarily due to the specific care requirements and early onset of the disease, which contribute to both direct treatment costs and indirect costs, such as reduced working hours for both the patient and the caregiver [10]. Caregiver stress refers to the medium- and long-term effects of the disease on those providing care. Caregivers often experience symptoms of depression and prolonged feelings of loneliness [11]. A majority report a sense of relief once their caregiving responsibilities come to an end [12].

Regarding the support available to families during and after the illness, the importance of structured support systems is emphasised in the guidelines issued by the National Consensus Project for Quality Palliative Care (United States). Key elements include peer support groups composed of fellow caregivers, professional psychological assessment and counselling, and broader individual social support networks. These resources assist caregivers in coping with emotional distress and in adapting to life following the loss of their loved one [13].

Sporadic and familial bvFTD

The majority of patients with bvFTD present with a sporadic form of the condition (s-bvFTD), without a family history of neurodegenerative disease and without identifiable mutations in genes associated with bvFTD. The underlying mechanisms of s-bvFTD remain unknown and are the subject of ongoing research. Between 20% and 40% of patients with bvFTD exhibit an autosomal dominant inheritance pattern, referred to as familial bvFTD (f-bvFTD) [14]. The mutations associated with f-bvFTD occur in the following genes: 1- microtubule-associated protein tau gene (MAPT) [15], 2- progranulin gene (GRN) [16], and 3- chromosome 9 open reading frame 72 gene (C9orf72) [17,18]. These genes represent the three major genetic contributors to bvFTD and account for at least 50% of f-bvFTD cases. Penetrance is greater than 95% for MAPT and ranges from 70% to 90% for GRN and C9orf72. Notable clinical, psychiatric, and neuroimaging similarities exist between familial and sporadic bvFTD. Mutations in over a dozen other genes have been reported in f-bvFTD, with new gene discoveries continuing to emerge each year [19]. In terms of clinical characteristics, patients with s-bvFTD tend to score higher on the Neuropsychiatric Inventory Questionnaire (NPI-Q) (p = 0.0183), indicating a higher frequency of psychiatric symptoms such as depression and irritability. Familial bvFTD generally presents at an earlier age than its sporadic counterpart, with mean onset at 59 years compared to 63 years, respectively. This earlier onset may reflect a more aggressive tau-mediated pathology in carriers of MAPT mutations. Longitudinal characterisation of both s-bvFTD and f-bvFTD is crucial to further our understanding of the condition [20].

Diagnostic criteria

Neary., *et al*. (1998) formulated the diagnostic criteria for behavioural variant frontotemporal dementia (bvFTD) [21]. These criteria were subsequently revised by Rascovsky., *et al*. (2011) and are now recognised as the "International Consensus Criteria for bvFTD". The updated criteria are widely employed in both clinical practice and research owing to their clarity and practical applicability. Their establishment provided a diagnostic framework with appropriate sensitivity and specificity for the identification of bvFTD [22] (Table 1).

I Neurodegenerative disease
To meet the criteria for bvFTD, the following symptoms must be present: A gradual cognitive decline and/or behavioural changes as observed or reported in the clinical history (as provided by an informant).
II Possible bvFTD
Three of the following behavioural/cognitive symptoms must be present persistently or recurrently, rather than as isolated or single events: A. Early behavioural disinhibition (one of the following symptoms [A1-A3] must be present): A1. Socially inappropriate behaviour A2. Loss of manners or decorum A3. Impulsive, hasty, or careless actions. B. Early apathy or inertia (one of the following symptoms [B1-B2] must be present): B1. Apathy B2. Inertia. C. Early loss of sympathy or empathy (one of the following symptoms [C1-C2] must be present): C1. Reduced response to the needs and feelings of others C2. Decreased social interest, interaction, or personal warmth. D. Early perseverative, stereotyped, or compulsive/ritualistic behaviour (one of the following symptoms [D1-D3] must be present): D1. Simple repetitive movements D2. Compulsive or ritualistic behaviour D3. Speech stereotypy. E. Hyperorality and dietary changes (one of the following symptoms [E1-E3] must be present): E1. Altered food preferences E2. Binge eating, increased consumption of alcohol or cigarettes E3. Oral exploration or consumption of non-edible objects. F. Neuropsychological profile: executive/generative deficits with relative preservation of memory and visuospatial functions (all of the following symptoms [F1-F3] must be present): F1. Deficits in executive tasks F2. Relative preservation of episodic memory F3. Relative preservation of visuospatial skills.

III Probable bvFTD
To meet the criteria, all of the following symptoms (A-C) must be present: A. Meets the criteria for possible bvFTD. B. Exhibits significant functional impairment (as reported by the caregiver or as evidenced by the Clinical Dementia Rating Scale or the Functional Activities Questionnaire scores). C. Neuroimaging studies consistent with bvFTD (one of the following [C1-C2] must be present): C1. Frontal and/or anterior temporal atrophy on MRI or CT. C2. Fronto/temporal and/or anterior hypoperfusion or hypometabolism on PET CT or SPECT.
IV bvFTD with defined pathology of frontotemporal lobar degeneration (FTLD)
Criteria A and either criterion B or C must be present to meet the criteria: A. Meets the criteria for possible or probable bvFTD. B. Histopathological evidence of FTLD on biopsy or post-mortem examination. C. Presence of a known pathogenic mutation.
V Exclusion criteria for bvFTD
The criteria A and B must be answered negatively for any diagnosis of bvFTD; Criterion C may be positive for possible bvFTD but must be negative for probable bvFTD. A. The pattern of deficits is better explained by other non-degenerative disorders of the nervous system. B. The behavioural disturbance is better explained by a psychiatric condition. C. Biomarkers strongly indicative of Alzheimer's disease or another neurodegenerative process.

Table 1: *International consensus criteria for bvFTD. Rascovsky K, Hodges JR, and Knopman D [22].*

CT scan: Computed Tomography; MRI: Magnetic Resonance Imaging; PET CT: Positron Emission Tomography-Computed Tomography; SPECT: Single-Photon Emission Computed Tomography; 'early' refers to symptoms occurring within the first 3 years of evolution.

Proteinopathies and FTLD

Neuroimaging, histopathological, and genetic studies have allowed the underlying alterations in FTLD to be elucidated. The observed atrophy is due to a neurodegenerative process resulting from the abnormal accumulation of intracellular proteins (proteinopathies), with clinical manifestations depending on the predominant location of such deposits. A clinical picture initially characterised by behavioural changes (bvFTD) may, over the course of the disease, develop cognitive and/or language symptoms [23]. FTLD presents clinical and neuropathological overlap with other predominantly motor neurodegenerative disorders: 1) corticobasal degeneration (CBD), 2) progressive supranuclear palsy (PSP), and 3) amyotrophic lateral sclerosis (ALS). CBD is due to the abnormal accumulation of the 4-repeat tau protein and is clinically characterised by asymmetric parkinsonism, apraxia, myoclonus, dystonia, and alien limb syndrome. PSP is also caused by abnormal accumulation of the 4-repeat tau protein and is characterised by impairment of conjugate gaze, primarily in the vertical axis (Parinaud syndrome), axial dystonia, postural disorders, bradykinesia, rigidity, and frequent falls [24] and amyotrophy). In 20% of ALS patients, the diagnostic criteria for bvFTD are met (Figure 3).

Patients with bvFTD associated with ALS tend to exhibit more psychotic symptoms than those with bvFTD not associated with ALS. FTLD can be further subdivided based on the type of abnormally accumulated protein: 1) tau, 2) TDP-43, and 3) FUS. In 50% of FTLD patients, deposits consist of hyperphosphorylated tau protein (FTLD-tau). Two isoforms of hyperphosphorylated tau protein are known
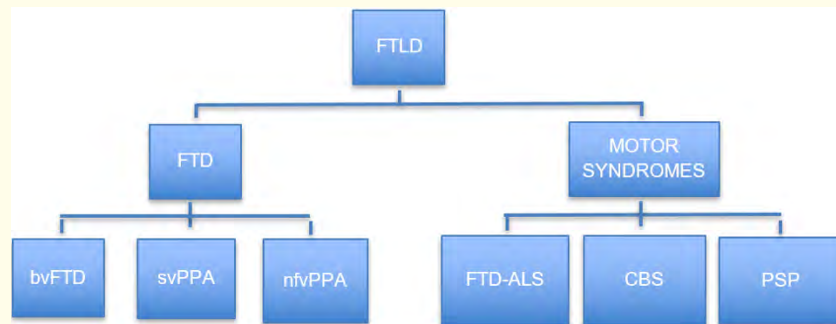
Figure 3: *FTLD classification scheme.*

(3R and 4R). FTLD-Tau is therefore further subdivided into 3R, 4R, and 3R/4R. In 40% of FTLD patients, deposits consist of TDP-43 protein and can be subdivided into 4 different types based on the presence of 1) neuronal cytoplasmic inclusions (NCI), 2) intranuclear neuronal inclusions, 3) dystrophic neurites, or 4) glial cytoplasmic inclusions. FUS (fused in sarcoma) is a multifunctional DNA and RNA binding protein that shares actions with TDP-43. The gene encoding FUS is located on chromosome 16 [25].

Methodology for the study of patients with bvFTD

Approximately 40% of patients with bvFTD required more than one year to establish a diagnosis, 60% of them were evaluated by three or more physicians, and 80% required three or more consultations prior to diagnosis [26]. In 20% of patients, at the onset of the clinical picture, the condition is often confused with depression or another psychiatric disorder, making the diagnosis of bvFTD a challenging task. Laboratory tests, neuropsychological assessments, and structural and/or functional neuroimaging studies are recommended when evaluating patients with gradual cognitive decline. Concepts related to the methodology for studying patients with bvFTD will be developed [27].

Clinical features

Any patient presenting with a progressive condition characterised by 1-behavioural disinhibition, 2-apathy or inertia, 3-loss of sympathy or empathy, 4-perseverative, stereotyped, or compulsive behaviour, or 5-hyperorality and/or dietary changes should raise suspicion of bvFTD [28]. Family members should be interviewed separately to evoke more detailed characteristics, which are often difficult to discuss in the presence of the patient. The insidious changes in personality, interpersonal behaviour, and emotional regulation characterise bvFTD and indicate the progressive disintegration of the neural circuits involved in social cognition, motivation, and decision-making. Apathy is commonly observed and manifests as inertia, lack of interest in previous hobbies, and progressive social isolation. Disinhibition often coexists with apathy, producing impulsive actions that lead to excessive spending, inappropriate comments or sexually inappropriate behaviour, and a variety of socially embarrassing actions. Gambling behaviour or hyperreligiosity may be early symptoms of the disease. Stereotypical behaviours and a tendency to repeat phrases, stories, or jokes (perseveration) are commonly observed. Patients often lack empathy and exhibit an inappropriately low reaction to grief. Mental rigidity and difficulty adapting to new routines are common. Affective blunting and emotional expression blocking are also frequently seen. Some patients exhibit elevated mood (hypomania) with agitation, disinhibition, and irritability, which are more common in the advanced stages of the disease [29]. Some patients with bvFTD develop a Klüver-Bucy syndrome, characterised by 1-emotional flattening, 2-hypersexuality, and 3-hyperorality, which are present throughout the course of the disease. Changes in eating, such as altered satiety, changes in preference for sweet foods, and dysregulation in food intake, are common and are thought to relate to hypothalamic alterations, which are crucial for coordinating metabolic and dietary needs. Psychotic

symptoms, such as paranoid ideations, hallucinations, and delusions, are rare in bvFTD, except in patients with motor neuron diseases (ALS) or those with juvenile-onset [30]. Apathy becomes more prominent in late-onset bvFTD. Many of the clinical features observed in bvFTD can also be seen in other dementias, making diagnosis challenging. Disability in daily life is pronounced, with early deterioration; however, many patients in formal neuropsychological tests may obtain results within normal limits. The presence of severe episodic memory deficits, characteristic of AD, serves as an exclusion criterion for the clinical diagnosis of bvFTD, with early memory deficits being more likely attributed to inattentive or disorganised learning rather than a defect in hippocampal-mediated memory consolidation. In patients who exhibit hallucinations and/or delusions, a rare genetic association of bvFTD with C9orf72 may be considered [31]. In the early stages, the patient's lack of awareness (anosognosia) of cognitive and/or behavioural symptoms may lead to a misdiagnosis of AD; however, a notable difference in patients with bvFTD is the absence of appropriate emotional engagement during the clinical evaluation and diagnostic procedure [32].

Blood/urine

Patients with bvFTD do not exhibit alterations in blood or urine laboratory tests. Plasma biomarkers sensitive and specific for AD have been identified, which help differentiate AD from bvFTD [33,34], such as phosphorylated tau protein (p-tau181) and (p-tau217) [35]. The high cost of these studies limits their routine use. In the future, these biomarkers could be employed to confirm or rule out AD and FTLD, representing a significant advancement in diagnosis and reducing the need for costly diagnostic tests (such as amyloid and tau protein quantification in cerebrospinal fluid or FDG-PET CT). The neurofilament light chain (NFLC) serves as a sensitive marker of neurodegeneration and may be useful in differentiating a neurodegenerative disease from a psychiatric disorder in patients with a presentation similar to that of bvFTD [36,37].

CSF analysis

There are no identified cerebrospinal fluid (CSF) markers that are sensitive or specific for FTLD. The development of markers for FTLD-tau and the DNA/RNA-binding protein 43 (TDP-43), which is involved in FTLD transactive responses, is currently an area of active research. Phosphorylated tau protein levels in the CSF are useful for differentiating AD from FTLD as the cause of bvFTD. In the coming years, the role of CSF testing in patients with clinical presentations similar to bvFTD will be valuable for ruling out AD and investigating infectious, immune-mediated, inflammatory, and/or paraneoplastic processes associated with the condition [38].

Neuropsychological evaluation

Neuropsychological evaluation involves a battery of tests that assess multiple primary cognitive domains: 1-attention/concentration, 2-executive functions, 3-learning/memory, 4-language, and 5-visuospatial functions. In patients with bvFTD, the cognitive profile shows impairment in attention/concentration, executive functions, and language, with preservation of memory and visuospatial functions [39]. In bvFTD, there is also impairment of social cognition, with deficits in emotion recognition and empathy [40]. Questionnaires have been developed to objectively assess social cognition deterioration in patients with bvFTD; however, these questionnaires are rarely included in neuropsychological batteries used in clinical practice [41]. Standard neuropsychological evaluation may yield results within normal limits in patients in the early stages. While memory is typically preserved, there are cases of patients with sporadic or familial bvFTD who show memory function impairment. In patients with atypical forms of AD or Lewy Body disease (LBD), neuropsychological profiles similar to those of bvFTD may be observed, meaning that a "typical bvFTD deterioration profile" in neuropsychological tests does not exclude other etiologies [42].

Structural neuroimaging

The presence and topography of cortical atrophy on CT or MRI scans correlate with the degree of atrophy and provide diagnostic information. The degree of atrophy in the frontal and/or temporal lobes, which is typically focal and asymmetric, supports the clinical suspicion of bvFTD (Figure 4). In the early stages of the neurodegenerative process, the clinical presentation may coexist in the absence

of cortical atrophy. Certain atypical variants of Alzheimer's disease may manifest primarily as a dysexecutive syndrome, with associated frontal and/or temporal atrophy. Extensive tumoural lesions (gliomas) involving the frontobasal and/or temporopolar regions may mimic bvFTD [43].
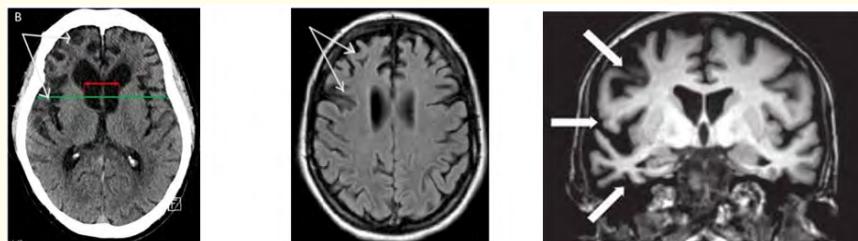

Figure 4: A: CT scan of the brain. B: Axial MRI T1. C: Coronal MRI T1.

In figure 4 (A, B, C), marked cortical atrophy (retraction) is observed in the bilateral frontal and temporal lobes, predominantly in the right hemisphere (white arrows), characteristic of bvFTD.

Functional neuroimaging

Positron emission tomography with fluorine-18-labelled deoxyglucose (FDG-PET/CT) can aid in differentiating Alzheimer's disease (AD) from behavioural variant frontotemporal dementia (bvFTD) by demonstrating differences in the distribution of hypometabolic regions [39-41]. In AD, these areas are typically located in the posterior temporoparietal association cortex and the posterior cingulate cortex; whereas in bvFTD, they are found in the anterior frontal lobes, the anterior temporal cortex, and the anterior cingulate cortex (Figure 5 and 6). Although the clinical and research utility of FDG-PET/CT in bvFTD has been established, the findings are not 100% sensitive or specific for a disorder within the FTLD spectrum [39-41]. FDG-PET/CT with amyloid-binding ligands identifies individuals with cerebral amyloid deposits and can assist in distinguishing underlying AD from other neurodegenerative disorders in patients with a bvFTD-like clinical presentation [42]. Despite initial enthusiasm, current evidence does not support the routine use of FDG-PET/CT with tau-binding ligands to differentiate tauopathies from non-tauopathies in patients with underlying bvFTD-spectrum disorders [43]. The 18F-MK-6240 tracer has demonstrated potential for tau binding in bvFTD, particularly among MAPT mutation carriers, who are expected to exhibit significant tau pathology [44]. Similarly, the 18F-PI-2620 tracer has been evaluated and shown heterogeneous, low-intensity binding in patients with suspected FTLD, suggesting that its utility outside the AD continuum remains to be clarified [45]. The F-PM-PBB3 tracer has demonstrated reactivity to tau deposits in FTLD in clinical studies, offering potential for identifying the neuropathological underpinnings of clinically diverse FTLD phenotypes [46]. Thus, although several tau PET tracers are under investigation in the context of bvFTD, their clinical applicability remains in development, and further studies are required to determine their diagnostic and prognostic value [47].
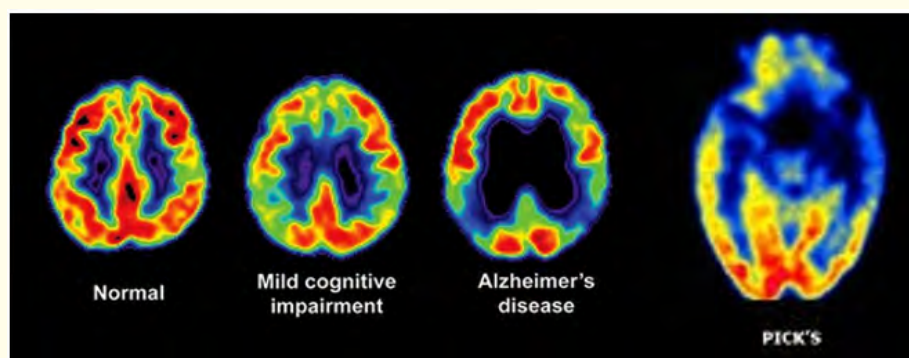

Figure 5: Normal FDG-PET CT, mild cognitive impairment, AD, and bvFTD.
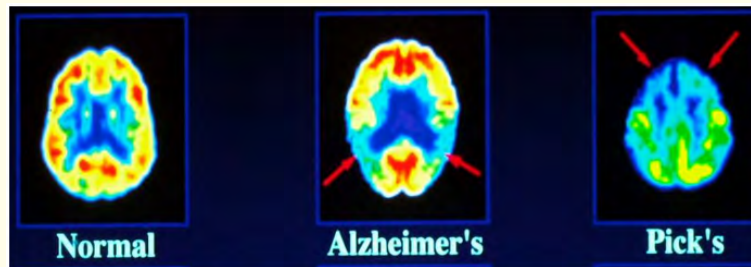
Figure 6: Normal FDG-PET CT, AD, and bvFTD.

Genetic testing for bvFTD

The request for genetic testing to detect known mutations associated with FTLD is considered appropriate in patients with bvFTD and a positive family history of dementia, parkinsonism, or motor neuron disease (MND), particularly in those with an autosomal dominant (AD) inheritance pattern. Initially, single-gene or limited multi-gene testing was the norm-albeit costly-especially when initial results were negative. Today, gene panels assessing several genes implicated in FTLD are available at an accessible cost. It is essential to provide adequate genetic counselling to both the patient and their family before and after the genetic study [48]. TDP-43 has been identified as the pathological protein in the majority of FTLD clinical and pathological subtypes, as well as in most cases associated with MND. Mutations in the progranulin gene (GRN) currently represent the most common cause of familial bvFTD, accounting for approximately 20-25% of cases. All pathogenic mutations in this gene result in null alleles that reduce functional progranulin, ultimately causing disease. The GRN gene is located on chromosome 17 and is responsible for the vast majority of chromosome 17-linked FTD cases. A particularly challenging scenario arises when a patient with bvFTD has no convincing family history suggestive of an AD inheritance pattern. In such presumed sporadic cases, it remains possible to identify a causative mutation. The decision to request genetic testing in patients with early-onset bvFTD should be made on a case-by-case basis, acknowledging that the likelihood of a positive result is low. Approximately 20% of FTD cases are due to a genetic mutation, and 40% have a family history of dementia, psychiatric illness, or motor symptoms, even in the absence of a clearly defined inheritance pattern. Most genetic causes of bvFTD follow an AD inheritance pattern, with variable penetrance and expressivity depending on the specific gene involved. Below, we briefly summarise the most relevant mutation:

1. MAPT: The gene that encodes for tau protein, which plays a crucial role in assembling tubulin monomers into microtubules. These microtubules are essential for maintaining cell shape, serving as tracks for axonal transport, and linking microtubules to other proteins. The reduced ability of tau to interact with microtubules is the most likely primary effect in FTD-17 mutations. This leads to tau accumulation in the cytoplasm of neurons and results in hyperphosphorylation. Eventually, hyperphosphorylated tau assembles into abnormal filaments. Although neuronal death doesn't seem to occur via an apoptosis mechanism, the transition from a soluble form of tau to an insoluble, filamentous form is central to the neurodegenerative process in FTD-17 MAPT.

2. Progranulin (GRN): A mutation in the GRN gene on chromosome 17 reduces circulating progranulin by 20%, which participates in tissue repair processes by binding to TNF receptors. This alteration results in lysosomal dysfunction and neuronal inflammation.

3. C9orf72: A hexanucleotide repeat expansion generates cytoplasmic inclusions of TDP-43, a nuclear protein involved in regulating DNA and RNA splicing. This mutation plays a role in the pathology of bvFTD and ALS.

4. FUS: A gene encoding a nuclear protein of the same name, which accumulates abnormally in the cytoplasm due to genetic mutations.

Clinical trials are currently underway aiming to modify the pathophysiology of several genes associated with familial FTLD. There are genetic panels approved by the Clinical Laboratory Improvement Amendments (CLIA) that include many of the genes linked to FTLD-such as the less common mutations in VCP, CHMP2B, TARDBP, SQSTM1, UBQLN2, TBK1, TREM2, and CHCHD10-at a reasonable cost. Ongoing clinical trials are also targeting the underlying disease mechanisms in some of these genes [49].

Neuropathology

The term frontotemporal lobar degeneration (FTLD) refers to the spectrum of histopathological entities that may manifest as behavioural variant frontotemporal dementia (bvFTD) and related syndromes. The clinical syndromes of FTD are associated with macroscopic changes characterised by atrophy of the frontal (prefrontal) and temporal (temporo-polar) lobes (Figure 7), and microscopic changes marked by gliosis, microvacuolation, synaptic loss, and neuronal loss (Figure 8). These macro and microscopic changes are not specific to the clinical variants of FTLD. Immunohistochemistry is helpful in identifying the specific molecular protein aggregates found in FTLD. Almost all cases of FTD show positive immunostaining for one of three major protein groups: Tau (40% - 45%), TAR DNA-binding protein 43 (TDP-43) (40% - 45%), and Fused in Sarcoma (FUS) (5%). A small minority of cases (5%) present with alternative pathologies. These protein aggregates have distinct morphologies and show predilection for specific anatomical regions, cortical layers, neuronal types, and glial cells. Atrophy in FTD follows a progressive pattern that correlates with the severity and duration of the disease, and can be described in stages as follows:

1. Initial involvement of the anterior frontal cortex and hippocampus;
2. Spread to the orbitofrontal gyrus, basal ganglia, and temporal lobe;
3. Progression of frontal and temporal atrophy with white matter involvement;
4. Severe atrophy in the frontotemporal regions, basal ganglia, and thalamus [50].

Figure 7: FTD. Macroscopy. External configuration. Prefrontal and temporo-polar cortical atrophy.
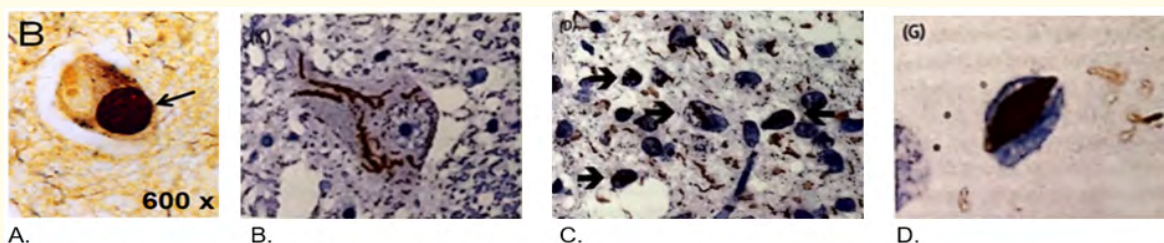

Figure 8: FTD. Histopathology. A: Pick bodies (black arrow) with silver staining. B: Cytoplasmic inclusions in spinal motor neurons. C: Dystrophic neurites and lentiform intranuclear inclusions. D: Intraneuronal inclusions in progranulin gene mutations.

Biomarkers in bvFTD

A biomarker is defined as any measurable evidence of a biological phenomenon. Several biomarkers have been identified in neurodegenerative processes and serve as objective measures of the underlying neurobiological process. In bvFTD, cortical thinning assessed via MRI constitutes a reliable biomarker, typically characterised by progressive, asymmetric, bilateral frontotemporal atrophy that is greater than expected for the patient's age and progressively worsens over time. Symptoms arise due to synaptic dysfunction in the affected neurons, which are not initially visible on brain MRI, making atrophy a useful but late-occurring biomarker. As such, a patient may present with bvFTD symptomatology in the absence of detectable atrophy on brain MRI. FDG-PET/CT scans may reveal hypometabolism in cortical areas without corresponding atrophy on MRI. This finding suggests the presence of abnormal protein deposition leading to synaptic dysfunction and consequent hypometabolism. However, MRI and PET brain findings are insufficient for a definitive diagnosis and cannot exclude a phenocopy-defined as other neurodegenerative conditions that mimic bvFTD, such as the frontal variant of Alzheimer's disease, which initially presents with behavioural symptoms (e.g. apathy), followed by memory impairment [51].

Neurotransmitters in bvFTD

A growing body of evidence points to the involvement of multiple neurotransmitter systems in the clinical presentation of bvFTD. This widespread neurochemical disruption helps explain the complex array of cognitive and behavioural symptoms typically observed in affected individuals. The dopaminergic system, particularly the mesocorticolimbic pathway, appears to be significantly compromised. Reduced dopamine levels in the prefrontal cortex and striatum have been linked to core features such as apathy, disinhibition, and impulsivity. Neuroimaging studies further support this, revealing diminished dopamine transporter binding in the striatum. The serotonergic system is also notably affected. Lower concentrations of serotonin in the prefrontal cortex and amygdala are thought to underlie emotional dysregulation, heightened aggression, and impulsive behaviour. A decrease in 5-HT2A receptor density in the frontal cortex has been reported, offering a neurochemical explanation for some of the prominent behavioural changes in bvFTD. Dysfunction of the glutamatergic system, particularly involving NMDA receptor alterations in the prefrontal cortex and hippocampus, may contribute to both the neurodegenerative process and associated cognitive deficits. Glutamate-mediated excitotoxicity is believed to play a role in neuronal loss in bvFTD. The GABAergic system also shows signs of impairment. A reduction in inhibitory GABAergic transmission has been associated with disinhibition and impulsivity, likely reflecting decreased GABAergic activity in key regions such as the orbitofrontal cortex and amygdala. The cholinergic system, which is profoundly affected in AD, appears to remain relatively intact in bvFTD. This distinction not only aids in differential diagnosis but also informs therapeutic decisions. Taken together, these findings suggest a rationale for various pharmacological strategies: 1-Selective serotonin reuptake inhibitors (SSRIs) may help manage disinhibition, aggression, and impulsivity, 2-GABAergic agents could prove beneficial for behavioural symptoms, while 3-Dopaminergic treatments might offer relief in cases of marked apathy [52,53].

Treatment

The treatment of bvFTD, remains a significant clinical challenge. Both pharmacological and non-pharmacological strategies must be considered, bearing in mind that the evidence supporting any of these approaches is still limited. At present, there is no specific treatment capable of slowing, halting, or reversing the course of the disease. Management is therefore symptom-oriented, with the aim of improving the patient's quality of life as much as possible. Care for individuals with bvFTD should be highly individualised, taking into account each patient's specific needs and circumstances. A multidisciplinary approach is essential, involving not only neurologists, but also psychiatrists, occupational therapists, and psychologists, working together to provide comprehensive support throughout the disease trajectory.

Non-pharmacological treatment

The initial manifestations of bvFTD typically include personality changes, altered social behaviour, and a gradual decline in cognitive function-symptoms that should serve as the primary focus of therapeutic management. The cognitive profile in bvFTD is commonly characterised by: 1-executive dysfunction, 2-impairments in selective attention and inhibitory control, 3-difficulties with task-switching and planning, 4-deficits in decision-making, and 5-general disorganisation [54]. Establishing a stable and supportive connection with the family environment has been shown to offer significant benefits to the patient. Non-pharmacological interventions primarily target environmental adaptations and therapeutic strategies that actively involve caregivers. These approaches promote the creation of basic daily routines, which contribute to behavioural regulation and reduce anxiety. Cognitive-behavioural therapy (CBT) can be employed to manage behavioural disturbances by encouraging cognitive restructuring and environmental adjustment. Limiting access to potentially problematic items such as credit cards, post, and car keys, and modifying public outings may help minimise inappropriate social interactions. Tailoring schedules and activities to the patient's preferences can also reduce conflict and promote cooperation. Cognitive stimulation plays a supportive role through the use of memory exercises, reminiscence-based activities, and cueing systems within the home, all of which help to reinforce orientation and maintain a degree of autonomy. Occupational therapy fosters engagement in meaningful and enjoyable tasks such as hobbies, crafts, games, and reading, while sensory stimulation, particularly through art and music therapy, has been shown to enhance mood and encourage emotional expression. With regard to physical activity, exercise programmes, including aquatic therapy, have demonstrated benefits in reducing behavioural symptoms and improving coordination, especially in those with concurrent motor impairments. Education and emotional support for both formal and informal caregivers are essential in enhancing their understanding of the disease and providing them with practical tools to cope with its demands [55].

Pharmacological treatment

When non-pharmacological treatment strategies fail to alleviate the disruptive symptoms of bvFTD, and when these symptoms pose a risk to the patient's life or to those in their immediate environment, pharmacological intervention becomes necessary. At present, there are no FDA approved drugs specifically indicated for the treatment of bvFTD. As such, management remains symptomatic, and the expected benefits and potential adverse effects of each medication must be carefully weighed in every case.

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) have proven useful in managing a range of behavioural symptoms, including disinhibition, compulsivity, and depression. However, the evidence supporting their use is largely derived from observational reports rather than controlled clinical trials. Citalopram has been reported as beneficial at a daily dose of 40 mg [56]. Similar outcomes have been observed with sertraline, typically administered in doses ranging from 50 to 100 mg per day [57]. Paroxetine at 20 mg per day has shown clinical efficacy, although higher doses (e.g. 40 mg per day) are generally discouraged due to their anticholinergic effects [58,59]. Trazodone, at a dose of 300 mg daily, has demonstrated effectiveness in controlling eating disturbances, agitation, irritability, and depressive symptoms. At lower doses (50 - 100 mg/day), it has also been found to be helpful in managing insomnia [60]. It is important to distinguish between depression and apathy, as the latter poses particular therapeutic challenges. Apathy may respond to treatment with sertraline (50 - 100 mg/day) and/or bupropion at doses ranging from 150 to 300 mg/day.

Antipsychotics: The prescription of antipsychotic drugs in patients with dementia carries a significant risk of increased mortality. This risk appears to be highest with haloperidol, risperidone, and olanzapine, and comparatively lower with quetiapine [61]. Despite these concerns, antipsychotics may be employed to manage psychotic symptoms and severe agitation. In outpatient settings, close monitoring is essential to detect the emergence of extrapyramidal side effects and to manage them appropriately. In 2023, the FDA approved brexpiprazole, an atypical antipsychotic with a multifunctional dopaminergic profile, for the treatment of agitation and aggression in Alzheimer's disease. Brexpiprazole acts as a partial agonist at dopamine D2 and D3 receptors, serotonin 5HT1A receptors, and as an antagonist at 5HT2A and alpha-1 adrenergic receptors. It has shown potential advantages over other atypical antipsychotics, including a

relatively low risk of inducing falls, sedation, or extrapyramidal symptoms [62]. Pimavanserin represents a novel atypical antipsychotic with a distinct pharmacodynamic profile. It functions as an antagonist at serotonin 5HT2A and 5HT2C receptors and lacks binding affinity for D2 receptors. It has been approved for the management of psychotic symptoms-namely hallucinations and delusions-in Parkinson's disease dementia. However, current evidence regarding its efficacy in treating psychosis associated with other forms of dementia remains insufficient [63].

Anticonvulsants: Certain antiepileptic drugs have demonstrated mood-stabilising and behavioural-modulating effects. Agents such as valproic acid, carbamazepine, lamotrigine, and topiramate have been used in the management of behavioural symptoms associated with bvFTD, particularly agitation, although their efficacy remains limited. Clinical reports have described potential benefits in specific presentations, including the use of valproic acid for agitation, topiramate for hyperorality, and carbamazepine for hypersexuality. Valproate may exert additional neurobiological effects by reducing tau phosphorylation through the inhibition of cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase-3 (GSK-3) signalling pathways.

Acetylcholinesterase inhibitors and memantine: These agents have not demonstrated clinical efficacy in the symptomatic management of bvFTD. In fact, memantine has been associated with worsening cognitive decline in some cases [64].

Final considerations on pharmacological treatment

Pharmacological management of bvFTD remains challenging due to the lack of disease-modifying therapies and the limited evidence supporting symptomatic treatments. Current approaches rely on the cautious use of antidepressants, antipsychotics, anticonvulsants, and other agents to address specific behavioural disturbances. However, efficacy is often modest, and treatment decisions must balance potential benefits against adverse effects-particularly in a population vulnerable to sedation, falls, and cognitive worsening. Given the heterogeneity of clinical presentations, a personalised and multidisciplinary approach remains essential. Continued research into the neurochemical mechanisms underlying bvFTD is crucial for the development of targeted therapies capable of modifying disease progression and improving patient outcomes.

Emerging therapies

Clinical trials are currently underway to evaluate novel pharmacological agents targeting specific molecular pathways implicated in the pathogenesis of frontotemporal lobar degeneration (FTLD). Although these treatments are not yet available in clinical practice, they represent a promising horizon for the future. The aim of these studies is to develop disease-modifying therapies that act on pathological proteins such as tau and TDP-43, or target specific genetic mutations, including C9orf72, GRN, and MAPT [65]. Ongoing clinical trials include approaches such as tau phosphorylation inhibitors, tau aggregation inhibitors, active and passive immunotherapies against tau, and antisense oligonucleotides (ASOs) directed at MAPT. In parallel, pharmacological strategies are being explored to counteract the effects of GRN and C9orf72 mutations [66]. These trials are currently in early stages (phase I/II), but are expected to provide valuable insights into future treatment possibilities [67]. Designing clinical trials for bvFTD presents significant challenges due to the disease's clinical and molecular heterogeneity. The implementation of specific biomarkers may improve patient selection and increase the likelihood of achieving meaningful outcomes in clinical trials [68]. Among the most promising research tools are antisense oligonucleotide (ASO) therapy and CRISPR-Cas9 gene-editing technology. Although both techniques aim to modify gene expression-either by silencing specific genes or altering genetic sequences, they differ in their mechanisms of action and applications. These technologies offer powerful avenues for genetic intervention and correction [69].

Bioethical considerations of the end of life

An equilibrium between fundamental bioethical principles, quality of life, and patient autonomy is required. These aspects include:

1. Autonomy and advance decision making: In the early stages of the disease, it is essential to discuss with the patient and their family advance directives, treatment options, and palliative care. bv-FTD impairs judgment and decision-making capacity, raising dilemmas about to what extent the patient's prior decisions should be respected when they can no longer reaffirm them.

2. Therapeutic limits: As it is an incurable neurodegenerative disease, the scope of medical interventions (hospitalizations, artificial nutritional support, antibiotics for infections) must be evaluated, limiting disproportionate artificial measures in end-of-life management.

3. Beneficence and non-maleficence: The patient's well-being must be prioritized by avoiding unnecessary suffering. Neuropsychiatric symptoms (agitation, aggression, disinhibition, and apathy) require specialized palliative care.

4. Role of family in decision making: The emotional burden on caregivers is significant. Ethical and psychological support helps prevent decision-making based on exhaustion or desperation. If family conflict arises regarding the patient's management, bioethical mediation is advisable.

5. Possibility and equity in access to palliative care: Access to palliative care remains limited in many healthcare systems. It is crucial to ensure an interdisciplinary and equitable approach for these patients [70].

Discussion

bvFTD presents as a distinct clinical syndrome characterised by progressive changes in personality, social behaviour, and executive function. Its diagnosis remains challenging due to symptom overlap with psychiatric disorders and other neurodegenerative conditions, particularly in early stages. Despite advances in neuroimaging and the development of revised diagnostic criteria, delayed recognition continues to hinder timely intervention and appropriate support for patients and caregivers. Unlike AD, bvFTD is primarily a disorder of behaviour rather than of cognition (particularly memory) in its initial phases. The underlying neuropathology is heterogeneous, involving various proteinopathies, chiefly tau and TDP-43, as well as genetic mutations in genes such as C9orf72, GRN, and MAPT. This biological diversity not only complicates diagnosis but also poses significant challenges for the development of effective therapies. At present, treatment remains symptomatic and largely empirical. Pharmacological interventions, including SSRIs, atypical antipsychotics, and mood stabilisers, may alleviate certain behavioural symptoms, though evidence for their efficacy is limited and often based on observational studies rather than randomised controlled trials. Moreover, these treatments carry the risk of adverse effects, particularly in older adults with neurodegeneration. Non-pharmacological strategies, focused on environmental adaptation, routine structuring, and caregiver engagement, play a critical role in maintaining functional independence and improving quality of life. Multidisciplinary care, with input from neurologists, psychiatrists, occupational therapists, and psychologists, is essential to address the complex and evolving needs of patients. Ongoing research is paving the way for disease-modifying therapies. Trials targeting molecular mechanisms, such as tau and TDP-43 pathology, and genetic interventions using antisense oligonucleotides or CRISPR technology, offer a glimpse of potential breakthroughs. Nevertheless, the success of these approaches will depend on improved biomarkers for early diagnosis, better stratification of patients, and the refinement of clinical trial design. bvFTD remains a profoundly disruptive condition, not only for those diagnosed, but also for their families and support networks. Future research must continue to integrate clinical, genetic, and molecular insights to move beyond symptomatic relief and towards therapies capable of altering the course of the disease [70].

Conclusion

The behavioural and cognitive disturbances that occur during the pre- and post-diagnostic phases of behavioural variant frontotemporal dementia (bvFTD) have a profound impact on patients and their social and familial networks. At least 20% of individuals with bvFTD present with a condition following an autosomal dominant inheritance pattern, with the most common mutations involving genes encoding the microtubule-associated protein tau (MAPT), progranulin (GRN), and the chromosome 9 open reading frame 72 (C9orf72).

The consensus diagnostic criteria for bvFTD are of practical value in clinical settings. The diagnostic journey experienced by patients and their families is frequently complex and challenging. Any patient exhibiting one or more of the following clinical features should be considered a potential bvFTD case: (1) disinhibited behaviours; (2) apathy or inertia; (3) loss of sympathy or empathy; (4) perseverative, stereotyped or compulsive/ritualistic behaviours; or (5) changes in dietary habits and/or hyperorality. When bvFTD is suspected, family members should be interviewed individually, and a thorough exploration of relevant clinical features should be undertaken. Although, at present, there are no specific findings on routine laboratory tests (blood, urine, or CSF) that are characteristic of frontotemporal lobar degeneration (FTLD), plasma and CSF biomarkers sensitive and specific to Alzheimer's disease (AD) can aid in differentiating it from bvFTD. Neuropsychological test results in patients with suspected bvFTD typically support the initial clinical impression. A normal or atypical cognitive profile on neuropsychological assessment should not dissuade the clinician from considering a diagnosis of bvFTD, if the clinical history is compelling. Focal or asymmetric atrophy in the frontal and/or temporal lobes observed on CT or MRI lends support to the diagnosis of bvFTD in the appropriate clinical context. In early clinical stages, the absence of obvious frontal and/or temporal lobe atrophy on brain imaging does not exclude the diagnosis. Various patterns of atrophy in the frontal and/or temporal lobes on neuroimaging may also be seen in other neurodegenerative conditions, including atypical forms of AD. A fluorodeoxyglucose (FDG) PET-CT scan should be considered in patients with clinical suspicion of bvFTD when MRI findings are normal or only mildly suggestive of the condition. The clinical utility of molecular PET-CT imaging with amyloid and tau ligands remains incompletely defined. However, PET imaging with amyloid-binding ligands may help distinguish AD from other non-AD neurodegenerative disorders in patients presenting with a bvFTD-like clinical picture. Genetic counselling and testing for known FTLD-associated mutations are useful in bvFTD patients with a positive family history of dementia, parkinsonism, or motor neuron disease (MND), particularly in those with a pattern suggestive of autosomal dominant inheritance. In clinical practice, accurately predicting the underlying proteinopathy in suspected bvFTD cases is currently not feasible. The management of bvFTD remains challenging, requiring consideration of both pharmacological and non-pharmacological therapeutic strategies. Although several clinical trials are currently underway, no conclusive evidence has yet demonstrated their effectiveness in slowing, halting, or reversing the clinical progression of the disease. In advanced stages of bvFTD, aggressive life-sustaining interventions should be avoided [71].

Acknowledgements

Clarification

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