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Prodromal and Early bvFTD: Evaluating Clinical Features and Current Biomarkers

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Despite the current diagnostic criteria, early diagnostics of behavioral variant of frontotemporal dementia (bvFTD) has remained challenging. Patients with bvFTD often present with misleading psychiatric phenotype, and, on the other hand, impairment in memory functions have increasingly been reported. However, impaired episodic memory is currently considered as an exclusion criterion for bvFTD. Single biofluid-based or imaging biomarkers do not currently provide sufficient sensitivity or specificity for early bvFTD diagnosis at single-subject level, although studies have suggested improved accuracy with different biomarker combinations. In this mini review, we evaluate the core clinical features of early bvFTD and summarize the most potential imaging and fluid biomarkers for bvFTD diagnostics.

Keywords: frontotemporal dementia, frontotemporal lobar degeneration, diagnostics, differential diagnostics, biomarker, neuroimaging, GRN, *C9orf72*

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INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is the second most common early onset memory disorder (Ratnavalli et al., 2002), accounting for approximately 10 % of all progressive neurodegenerative memory diseases. FTLD has a substantial hereditary nature, and the most common genetic causes are the hexanucleotide repeat expansion in *C9orf72* gene (later *C9orf72*-RE) and mutations in *MAPT* or *GRN* genes. The most common clinical subtype of FTLD is the behavioral variant frontotemporal dementia (bvFTD), covering over half of the FTLD cases (Johnson et al., 2005). The diagnostics of bvFTD is challenging. In bvFTD, deterioration of episodic memory functions are not typically observed similarly to other neurodegenerative memory disorders and the patients are mainly characterized by altered personality and behavior (Rascovsky et al., 2011). Thus, the correct diagnosis is often delayed and misdiagnoses as psychiatric disorders are frequent (Galimberti et al., 2015; Solje et al., 2015).

The main inadequacy of the current diagnostic criteria is the lack of specificity. The *possible bvFTD* criteria include only behavioral symptoms and thus bvFTD can be easily confused with psychiatric disorders. The *probable bvFTD* criteria include also atrophy or hypoperfusion in frontal and/or temporal lobes and significant functional decline in addition to behavioral symptoms. Visual assessment of brain MRI results requires an experienced neuroradiologist and is time consuming, yet it provides only moderate sensitivity and specificity (Harper et al., 2016). Furthermore, as brain

atrophy develops slowly, the observation of subtle brain changes in the early phase of the disease can be even more difficult.

Currently there are no routinely used and validated specific CSF or blood biomarkers for the diagnostics of bvFTD. However, there is an urgent need for such biomarkers for differential diagnostics, disease monitoring, and assessment of the effects of potential therapeutic treatments in FTLD patients. Biomarkers showing specific changes already at the presymptomatic or prodromal phase of the disease would be especially valuable for disease prediction and intervention when pharmacological, lifestyle, or psychosocial interventions become available. They would also be very useful for patient stratification in drug trials and would allow personalized medicine approaches for treatment and managing FTLD patients in the future.

In this minireview, we summarize core clinical features of early bvFTD and recent findings from studies examining novel brain imaging methods and biofluid biomarkers focusing on the early alterations in prodromal bvFTD. We attempt to provide some answers to the following questions. What are the most promising biomarkers for early bvFTD diagnostics? Is it possible to develop more sensitive multimodal diagnostic criteria or instruments to detect bvFTD during the early stages of the disease compared to the prevailing (Rascovsky et al., 2011) diagnostic criteria?

Early Clinical Features in bvFTD Patients

The characteristic behavioral features in bvFTD patients may be measured with scales such as frontal behavioral inventory (FBI), neuropsychiatric inventory (NPI), Cambridge behavioral inventory (CBI) or other similar ratings that are preferably based on overt behaviors rather than inferences about the patient's cognitive state (Rascovsky et al., 2011). Presymptomatic familial FTLD patients with known mutations have been reported to present cognitive changes in neuropsychological testing up to eight years before the estimated onset of symptoms (Geschwind et al., 2001; Janssen et al., 2005; Rohrer et al., 2008, 2015; Dopper et al., 2013; Jiskoot et al., 2016, 2018b). Changes in attention, executive function, and social cognition have been found particularly in presymptomatic *MAPT* and *GRN* mutation carriers (Geschwind et al., 2001; Dopper et al., 2013; Rohrer et al., 2015; Jiskoot et al., 2016, 2018b). Neuropsychological tools assessing ventromedial prefrontal cortex dysfunction, such as theory of mind (ToM) tasks (Poletti et al., 2012; Pardini et al., 2013; Dodich et al., 2016) and social cognition and emotional assessment (SEA), have been demonstrated to be able to detect and distinguish bvFTD at the very early stage from Alzheimer's disease (AD), and amnestic mild cognitive impairment (MCI) (Funkiewiez et al., 2012; Bertoux et al., 2013). Early decline in both affective and cognitive ToM component tasks has been noted in bvFTD patients, suggesting that impaired ventromedial prefrontal cortex function may explain the characteristic symptoms of bvFTD, such as early behavioral dysfunction, and loss of empathy (Gregory et al., 2002; Adenzato et al., 2010; Poletti et al., 2012).

Early neuropsychiatric symptoms and early contacts to psychiatric services are characteristic features in especially the inherited bvFTD associated with the *C9orf72-RE* (Boeve et al., 2012; Mahoney et al., 2012; Snowden et al., 2012; Devenney et al., 2014; Solje et al., 2015). In particular, delusions and hallucinations are prevalent (Omar et al., 2009; Boeve et al., 2012; Kertesz et al., 2013), and predominantly the patients with a concomitant motoneuron disease (MND) may experience psychotic symptoms in the prodromal stages of the disease (Velakoulis et al., 2009; Lillo et al., 2010). In a Finnish study, up to 60% of bvFTD patients carrying the *C9orf72*-RE presented with psychiatric symptoms on average 4.6 years prior to diagnosis of bvFTD (Solje et al., 2015). Also, criminal behavior has been identified in about 30% bvFTD (Diehl-Schmid et al., 2013; Liljegren et al., 2015; Shinagawa et al., 2017). According to these studies, the most common criminal acts include theft, traffic violations, trespassing, willful damage to property, housebreaking, assault, sexual advances, and indecent behavior.

Impaired episodic memory has been considered as an exclusion criterion for bvFTD in the current diagnostic criteria (Rascovsky et al., 2011), but increasing evidence has suggested impairment of memory functions and subjective memory complaints in early stages of bvFTD (Hodges et al., 2004; Pijnenburg et al., 2004; Hornberger et al., 2010; Hornberger and Piguet, 2012). In approximately 60% of cases, bvFTD patients and their caregivers report episodic memory disturbances in the initial stages of the disease (Hodges et al., 2004). Recent studies have also demonstrated that episodic memory impairments in bvFTD patients in neuropsychological tests may even be as severe as in patients with AD (Irish et al., 2011, 2014; Pennington et al., 2011; Bertoux et al., 2013; Frisch et al., 2013; Fernández-Matarrubia et al., 2017; Jiskoot et al., 2019).

Early Imaging Findings in bvFTD Patients

The typical neuroimaging findings in bvFTD patients are atrophy and/or hypoperfusion of anterior temporal and frontal lobes, and these are included in the diagnostic criteria of probable bvFTD (Rascovsky et al., 2011). In the past 5–10 years, early structural and functional brain changes of bvFTD patients and presymptomatic carriers of the three main bvFTD-associated genetic mutations have been a target of intensive research. The focus of the studies has partially shifted from the conventional structural volumetric measures to measurements that are more novel, such as estimates of white matter tract integrity or functional network connectivity using diffusion weighted imaging and functional magnetic resonance imaging (MRI) methods and their quantification.

The earliest structural changes in presymptomatic mutation carriers can be detected in the insula and temporal and frontal areas as early as 10 years before the expected onset of the symptoms (Rohrer et al., 2015). Similar to symptomatic patients, the pattern of brain atrophy in the presymptomatic subjects varies depending on the mutation they carry (Lee et al., 2017; Bertrand et al., 2018; Cash et al., 2018; Olm et al., 2018; Wen et al., 2018). The characteristic brain changes according to predisposing genes are listed in **Table 1**. Presymptomatic *C9orf72*-RE carriers show earlier and more profound changes than *GRN* and *MAPT* carriers. However, similar findings are not evident in the offspring of MND patients carrying the *C9orf72*-RE (Walhout et al., 2015). In addition, a recent study with symptomatic bvFTD

patients reported that increased cortical mean diffusivity is detected earlier than decreased cortical thickness, suggesting that diffusion-weighted imaging could be a preferable imaging modality also for detecting presymptomatic bvFTD patients (Illán-Gala et al., 2019).

According to the recent guidelines of European panel of experts (EANM-EAN), fluorodeoxyglucose positron emission tomography (FDG-PET) should be used in the early diagnosis of bvFTD, particularly because of its high negative predictive value (Grimmer et al., 2016; Arbizu et al., 2018; Caminiti et al., 2018). Characteristically bvFTD presents as uni- or bilateral hypometabolism in the prefrontal cortex, anterior temporal lobe, anterior cingulate, and basal ganglia (Morbelli et al., 2016; Krämer et al., 2018). However, the changes vary between individual patients, as some patients show a more prominent frontal hypometabolism, while the others present with a more prominent temporal lobe hypometabolism (Cerami et al., 2016). In patients with MCI, FDG-PET is useful in distinguishing patients with a progressive neurodegenerative disease from subjects with subjective symptoms or non-progressive conditions. However, at early stage, FDG-PET lacks specificity in differentiating between various neurodegenerative diseases (Arbizu et al., 2018).

The changes in spatially distinct, but functionally connected networks in cortical and subcortical areas in presymptomatic bvFTD patients have been evaluated using functional MRI (fMRI) methods. The main functional networks associated with bvFTD are the salience network (SN) and the default mode network (DMN) (Greicius et al., 2003; Menon and Uddin, 2010; Pievani et al., 2011; Farb et al., 2013; Lee et al., 2014). In symptomatic bvFTD patients, atrophy and hypoconnectivity in SN related areas is detected regardless of genetic etiology or neuropathologic presentation (Seeley et al., 2009; Zhou et al., 2010; Whitwell et al., 2011; Farb et al., 2013). Considering DMN, the studies show contradictory results, varying from hyper- to hypoconnectivity compared to healthy controls (Zhou et al., 2010; Whitwell et al., 2011; Farb et al., 2013; Rytty et al., 2013; Lee et al., 2014). In the presymptomatic *C9orf72*-RE carriers, there is hypoconnectivity in the SN compared to healthy controls, and this can be already distinguished in persons younger than 40 years of age (Lee et al., 2017).

Even though the results of recent neuroimaging studies appear promising in differentiating presymptomatic bvFTD from healthy controls, the imaging modalities and analysis methods need to be validated to obtain uniform protocols. In addition, also electro encephalogram and transcranial magnetic stimulation have been studied for diagnostic and even therapeutic purposes for bvFTD, but the results remain contradictory (Chan et al., 2004; Pijnenburg et al., 2008; Moretti et al., 2016; Carlino et al., 2014; Benussi et al., 2018). Moreover, large prospective studies are needed to validate the predictive value of different brain imaging techniques. Today, group level differences of presymptomatic bvFTD and healthy controls can be detected, but the predictive value of multimodal imaging at single-subject level can be considered suggestive at the most (Feis et al., 2018). Summary of the early imaging findings in bvFTD is provided in **Table 1**.

TABLE 1 | Summary of the early imaging findings of bvFTD according to different mutation carriers compared to non-carrying healthy controls.

Group	Early imaging findings	References
Presymptomatic C9ORF72-RE	Reduced volume in thalamus, cerebellum, parietal and frontal lobes. Reduced WM tracts connecting frontal lobes, thalamic radiation, corticospinal tracts.	Lee et al., 2017; Papma et al., 2017; Bertrand et al., 2018; Cash et al., 2018; Floeter et al., 2018; Jiskoot et al., 2018a; Popuri et al., 2018; Wen et al., 2018
Presymptomatic GRN	Reduced volume in insula, orbitofrontal, posterior frontal and anterior temporal lobes, and striatum. Reduced WM tracts in corpus callosum, superior longitudinal fasciculus and internal capsule.	Borroni et al., 2008; Pievani et al., 2014; Cash et al., 2018; Jiskoot et al., 2018a; Olm et al., 2018
Presymptomatic MAPT	Reduced volume in anterior and medial temporal lobes and the orbitofrontal lobe. Reduced WM tracts connecting frontal lobes.	Cash et al., 2018; Jiskoot et al., 2018a

Early Biological Fluid Biomarkers of bvFTD

The most studied biomarkers in the cerebrospinal fluid (CSF) of bvFTD patients have been phospho-tau, total tau, amyloid-β_{1-42} (and their ratios), and, more recently, neuronal cytoskeletal protein neurofilament light chain (NfL). Tau, phospho-tau and amyloid-β_{1-42} are validated biomarkers primarily in the diagnostics of AD. A few studies have shown that high CSF ratio of tau/amyloid-β_{1-42} or phospho-tau/amyloid-β_{1-42} can discriminate patients with AD from those with bvFTD (or FTLD in general) (Rivero-Santana et al., 2017; Paterson et al., 2018). However, decreased amyloid-β_{1-42} levels have been found in 25% of definite FTLD cases without any signs of AD (Kämäläinen et al., 2015). Similarly to other neuronal cytoskeletal proteins like tau and phospho-tau, NfL release into the CSF is considered as a marker for neuronal injury and neurodegeneration. Altered levels of NfL can be detected in the CSF of patients with different brain diseases, suggesting that NfL may represent a general, rather unspecific marker for neurodegeneration. On the other hand, several studies have suggested that FTLD patients (including bvFTD) display higher levels of CSF NfL and/or lower ratio of phospho-tau/tau compared to healthy controls or patients with other neurodegenerative or psychiatric diseases, including e.g., AD (Skillbäck et al., 2014; Meeter et al., 2016; Vijverberg et al., 2017; Abu-Rumeileh et al., 2018; Goossens et al., 2018; Meeter L.H.H. et al., 2018; Niikado et al., 2018). Notably, combined assessment of NfL levels with the AD biomarkers in the CSF could provide additional value in the differentiation diagnostics of AD and bvFTD (de Jong et al., 2007). Additionally, concomitantly increased NfL levels and reduced phospho-tau/tau ratio in the CSF, and increased NfL levels in serum might show potential as biomarkers discriminating bvFTD from psychiatric disorders (Vijverberg et al., 2017; Al Shweiki et al., 2019).

It has been reported that elevated NfL levels and low phospho-tau/tau ratio in the CSF associate with poorer survival and

especially with manifestation as motoneuron disease (FTLD-MND), suggesting that these biomarkers may be useful in disease monitoring in FTLD patients (Meeter et al., 2016; Ljubenkov et al., 2018; Meeter L.H.H. et al., 2018). In the same study, longitudinal data on CSF NfL levels did not indicate differences between control subjects and presymptomatic carriers of *GRN* or *MAPT* mutations or *C9orf72*-RE. However, the NfL levels showed a substantial increase after disease onset in all these patients, with the *GRN* mutation carriers showing the highest levels (Meeter et al., 2016). These data suggest that at individual level, NfL-test, with particular cut-off based reference values, may not necessarily be suitable in the very early stages of the disease when the neuropathological changes have already started to take place, but when there is not yet detectable neurodegeneration in the CNS. On the other hand, repeated analysis of CSF NfL levels at different time points during the very early stages of the disease in a patient could provide information about whether the NfL levels remain stable over time or show a rapid increase, allowing prediction of a potentially progressive neurodegenerative disease.

Reliable discrimination between FTLD-tau and FTLD-TDP, the two most common neuropathological subtypes of bvFTD patients (Perry et al., 2017), has remained challenging. Tau or TDP-43 levels in the CSF of neuropathologically confirmed FTLD-TDP and FTLD-tau cases were reported to show a great overlap (Kuiperij et al., 2017). Another study with neuropathologically confirmed FTLD-TDP and FTLD-tau patients suggested some other analytes, such as IL-17, IL-23, eotaxin-3 (CCL26), and macrophage-derived chemokine (MDC), as potential diagnostic biomarkers distinguishing between FTLD-TDP and FTLD-tau cases (Hu et al., 2010), and possibly reflecting involvement of different immunological processes in these neuropathological FTLD subtypes.

Investigations in FTLD patients with different genetic backgrounds have revealed that detection of CSF levels of dipeptide repeat proteins (DPR), namely poly-GP, in the *C9orf72*-RE carriers and progranulin in the *GRN* mutation carriers enables rather reliable separation of these patients from patients who do not carry these mutations (Ghidoni et al., 2012; Meeter et al., 2016; Gendron et al., 2017; Lehmer et al., 2017). On the other hand, poly-GP and progranulin levels in the CSF were increased already in the presymptomatic phase and did not show further significant increases during the symptomatic phase, thus suggesting that they do not predict disease onset or progression, but might be suitable for evaluating therapeutic effects (Meeter et al., 2016; Gendron et al., 2017; Lehmer et al., 2017). Furthermore, the poly-GP DPRs could be detected in the peripheral blood mononuclear cells (PBMCs) of the *C9orf72*-RE carriers, indicating that detection of poly-GP proteins in blood or other patient-derived cells might also be utilized in the diagnosis or therapy trials (Gendron et al., 2017). Also nuclear RNA foci, another pathological hallmark directly and specifically generated from the *C9orf72*-RE, can be detected for example in lymphocytes from the *C9orf72*-RE-carrying patients, and thus could potentially be exploited as biomarkers in assessing the effects of potential therapeutic substances, e.g., antisense oligonucleotides or small molecules (Su et al., 2014). However, it is still unclear at which point during the disease course these pathological hallmarks become detectable in different types of cells, and thus further studies are needed to evaluate their potential as early or prognostic peripheral biomarkers in *C9orf72*-RE carriers. Recent investigations have also suggested that decreased levels of *GRN* mRNA and progranulin in the serum can be used to identify affected and at-risk presymptomatic *GRN* mutation carriers from controls, suggesting potential as peripherally measurable biomarkers for these patients (Guven et al., 2019). Future longitudinal data on serum *GRN* mRNA or progranulin levels at different time points during the disease course would provide insights into their potential use as prognostic biomarkers.

Increasing amount of recent reports indicate a potential association between FTLD and inflammation. Therefore, assessing different inflammatory biomarkers in FTLD could provide diagnostic and/or prognostic value. Autoantibodies against AMPA receptor and antinuclear autoantibodies (ANA) were detected significantly more often in the sera of sporadic FTLD patients compared to control subjects (Borroni et al., 2017; Cavazzana et al., 2018). Levels of glial cell-derived inflammatory mediator YKL-40 (Chitinase 3-like 1) have been shown to be elevated in the CSF of both FTLD and AD patients compared to controls (Janelidze et al., 2016; Alcolea et al., 2017). On the other hand, similarly to several other biomarkers, also YKL-40 levels provide poor specificity between different neurodegenerative diseases (Alcolea et al., 2014; Janelidze et al., 2016). However, YKL-40 was found useful in the differential diagnostics between FTLD and psychiatric diseases, as higher YKL-40 levels in combination with higher NfL levels and reduced p-tau/tau ratio in the CSF could be used to distinguish FTLD patients from those with a psychiatric disease (Vijverberg et al., 2017). A key question considering the early diagnostics of FTLD is at which point during the disease course the inflammation occurs and can be detected. One of the important proteins related to inflammation is the triggering receptor expressed in myeloid cells 2 (TREM2), expressed in microglia. So far, only *GRN* mutations have been associated with elevated CSF soluble TREM2 (sTREM2) levels in FTLD (Woollacott et al., 2018). These data altogether thus suggest that specific inflammatory markers or a specific combination of them could have potential as early biomarkers of neurodegeneration and perhaps specifically also FTLD. The current CSF- or blood-derived biomarkers and their feasibility in the diagnostics of bvFTD are summarized in **Table 2**.

DISCUSSION

Despite recent advances in the early characterization of bvFTD, early clinical diagnosis is still a challenge. The primary symptoms of bvFTD include apathy, changes in personality, executive function deficits, and abnormal social behavior. According to current criteria, memory performance is not impaired at the early stage of the bvFTD, whereas memory loss and visuospatial problems are often the early symptoms in patients with AD (Dubois et al., 2007; Rascovsky et al., 2011; Ranasinghe et al., 2016). In contrast, patients with bvFTD may present with early neuropsychiatric symptoms, such as depression and

TABLE 2 | Current CSF- or blood-derived biomarkers and their feasibility in the diagnostics of bvFTD.

Biomarker	In clinical use (currently; yes/no)	Potential utility value	References
CSF amyloid-β1–42	Yes; AD diagnostics	Useful in differentiating AD vs. bvFTD (decreased in AD).	Rivero-Santana et al., 2017; Paterson et al., 2018
CSF tau	Yes; AD diagnostics	Combined with decreased amyloid-β1–42 (tau/amyloid-β1–42 ratio), high levels indicate AD over other neurodegenerative diseases, including bvFTD.	Rivero-Santana et al., 2017; Paterson et al., 2018
CSF phospho-tau	Yes; AD diagnostics	Combined with decreased amyloid-β1–42, high levels indicate AD over other neurodegenerative diseases.	Rivero-Santana et al., 2017
CSF phospho-tau/tau ratio	No; Not routinely used	Especially low values observed in Creutzfeldt-Jakob disease. In general, lower values indicate more severe neurodegeneration (for example ALS or rapidly progressive FTLD), and indicate FTLD over psychiatric disorders or AD.	Riemenschneider et al., 2003; Pijnenburg et al., 2015; Vijverberg et al., 2017
CSF and blood NfL	No	Disease severity assessment and diagnostics between bvFTD and non-neurodegenerative diseases (psychiatric). Higher levels in bvFTD compared to AD have been observed. Similar results found in both blood and CSF.	Vijverberg et al., 2017; Steinacker et al., 2018; Abu-Rumeileh et al., 2018; Al Shweiki et al., 2019
Specific markers for genetic forms of FTLD - CSF/blood poly-GP - Nuclear RNA foci from C9orf72-RE - CSF/blood progranulin	No	Detectable in presymptomatic phase. Potentially useful in the future when evaluating the effects of therapeutic interventions in genetic bvFTD.	Ghidoni et al., 2012; Su et al., 2014; Gendron et al., 2017
Inflammatory markers - anti-AMPA GluA3 - ANA - YKL-40 - sTREM2	Yes; ANA detection is used in diagnostics of several systemic and especially rheumatic autoimmune conditions	Diagnostics between FTLD and non-neurodegenerative diseases. Might indicate inflammation as a potential target for therapeutic approach.	Vijverberg et al., 2017; Borroni et al., 2017; Cavazzana et al., 2018; Woollacott et al., 2018

psychosis, that are compatible with a range of neurologic and psychiatric disorders. Those patients, who lack the key symptoms for the clinical diagnosis of bvFTD and do not meet full diagnostic criteria, are initially often misdiagnosed as psychiatric disorders, and other neurological diseases, most often AD. Therefore, misrecognition of symptoms in the early stages of bvFTD frequently delays a correct diagnosis (Mendez and Perryman, 2002; Rosness et al., 2008; Landqvist Waldö et al., 2015; Bertoux et al., 2016). Despite the significant clinical overlap between bvFTD, other neurodegenerative diseases and psychiatric disorders, the clinical phenotype has a great emphasis in the current diagnostic criteria as the clinical phenotype solely forms the first level (possible bvFTD) of the diagnosis. Additionally, the further criteria require positive imaging findings (for probable bvFTD) and genetic confirmation (for definite bvFTD), although the imaging findings may be absent especially in the early stages of bvFTD. Moreover, most of the cases are sporadic without a known genetic alteration underlying the disease. Thus, diagnosing bvFTD solely based on the "possible bvFTD" criteria lacks specificity, but on the other hand it is often not possible to increase the diagnostic certainty to the "probable" or "definite" levels.

Due to the limitations in the current criteria, more sensitive and specific neuroimaging and biomarker assessments are needed for early and more accurate diagnosis. On the other hand, the current criteria should remain as the clinical gold standard at least until bvFTD-specific biological markers become available. Future biomarkers should ideally be able to differentiate FTLD patients with different underlying pathological processes or genetic backgrounds, as potential treatment strategies will likely be targeted for specific patients or group of patients in a more personalized manner. Additionally, identifying individuals at increased risk for FTLD before disease onset and at still early stages of neurodegeneration could enable earlier diagnostics and increase potential for interventions.

To date, individual imaging or biomarker analysis tools do not yet provide sufficient sensitivity and/or specificity. On the other hand, combining different diagnostic instruments (neuroimaging, serum NfL measurement, immunological/metabolic biomarkers, and neuropathological biomarkers) could result in greater applicability to clinical diagnostics, compared to the prevailing diagnostic criteria. For instance, combination of serum NfL and diffusion weighted MRI scans could provide greater sensitivity and specificity in differentiating bvFTD from other neurodegenerative and psychiatric disorders and could possibly be included in the diagnostic criteria in the future. However, the biomarkers considered in this review still require extensive research as the current literature for them in FTLD or bvFTD rests on only a few suggestive findings. As bvFTD can be considered a clinically, genetically and pathologically heterogenous disease, the composition of large and well-defined cohorts is necessary. This emphasizes the need of multicenter, international collaboration,

as larger study populations are needed to validate and screen the existing and upcoming diagnostic tools for clinical use.

AUTHOR CONTRIBUTIONS

ES, AR, and AH contributed to the conception and design of the study. All authors wrote the sections, edited, read, and approved the final version of the manuscript for submission.

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