Original Research Article

Neuropsychiatric Symptom Profile Differs Based on Pathology in Patients with Clinically Diagnosed Behavioral Variant Frontotemporal Dementia

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Key Words

Behavioral variant frontotemporal dementia · Neuropsychiatric Inventory Questionnaire · Neuropathology · National Alzheimer's Coordinating Center · Behavior-neuropathological correlation

Abstract

Background: Behavioral variant frontotemporal dementia (bvFTD) is pathologically heterogeneous. With emerging therapeutics, determining underlying pathology during life is increasingly important. Neuropsychiatric symptoms are prevalent and diagnostic in bvFTD. **Methods:** We assessed the neuropsychiatric profile of patients with clinically diagnosed bvFTD as a function of pathology at autopsy. Patients with a clinical diagnosis of bvFTD at the initial visit were selected from the National Alzheimer's Coordinating Center (NACC) database. Neuropsychiatric symptoms endorsed on the Neuropsychiatric Inventory Questionnaire (NPI-Q) were analyzed. **Results:** Of 149 patients with clinically diagnosed bvFTD, pathology was primarily Alzheimer's disease (AD) in 20.5%. These patients differed from those with underlying frontotemporal lobar degeneration: patients with AD pathology (plaques and tangles) were more likely to have hallucinations, delusions, or agitation. Patients were further differentiated into tau-positive (30% of cases, including Pick's disease, FTD and parkinsonism with tau-positive or argyrophilic inclusions, and other tauopathies) or tau-negative cases (70% of cases, including bvFTD tau-negative ubiquitin-positive inclusions). These patients also differed in some of the neuropsychiatric symptoms seen. Tau-negative cases were more likely to demonstrate depression, delusions, and changes in appetite and eating. **Conclusions:** These preliminary findings contribute to our increasing ability to predict, using simple clinical tools, the neuropathological underpinnings of bvFTD during life.

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Introduction

Frontotemporal dementia (FTD) – the preferred term now being promoted is frontotemporal degeneration (www.theaFTD.org) – is the clinical manifestation of a number of distinct neurodegenerative processes collectively labeled frontotemporal lobar degeneration (FTLD) [1]. With recent advancements in molecular staining, the different neuropathological underpinnings of these processes are being described [2]. Broadly, FTLD can be subdivided into pathology that is either tau positive (approx. 50%) or tau negative [3]. In addition to this pathological heterogeneity, FTLD can present as any of a number of distinct clinical profiles, including the behavioral variant FTD (bvFTD), the language variants (semantic and agrammatic) [4], and finally as parkinsonian or motor neuron disease syndromes [5].

As is the case in Alzheimer's disease (AD), there are currently no available therapeutics that target the underlying pathological mechanisms (amyloid plaques and tau-related tangles – henceforth referred to as pathological AD). Drugs targeting the pathological process are under development [6], but their efficacy (and our ability to demonstrate it) will depend on the selection of patients with a specific pathology, a process that remains challenging during life, even in the best academic centers. This diagnostic specificity will require two major distinctions: a correct diagnosis of bvFTD, and then the prediction of the underlying pathology. bvFTD is commonly misdiagnosed as AD, and, particularly in the absence of a genetic mutation, the prediction of its pathology is currently limited.

The diagnostic criteria for bvFTD require the presence of behavioral changes, including (1) disinhibition, (2) apathy, (3) loss of empathy, (4) new motor behaviors that are either compulsive, perseverative, or stereotyped, and (5) dietary changes including hyperorality [5, 7]. Many scales exist that attempt to capture and quantitate such changes [8–15], some of which have been specifically designed based on those changes most prevalent in FTD. The Neuropsychiatric Inventory (NPI) [8] is a scale that assesses behavioral and neuropsychiatric changes according to 12 subgroups. The NPI has been used to help differentiate bvFTD from other dementias, including AD [16–18]. A brief validated caregiver questionnaire version of this inventory has also been developed and validated: the NPI Questionnaire (NPI-Q) [19]. While the NPI is an interview-based scale, often requiring more than 15 min to complete (making it impractical in a general clinical practice setting), the NPI-Q is a series of specific validated questions derived from the NPI that can be answered in only a few minutes by a questionnaire administered to the caregiver. Conclusions drawn from the NPI-Q have been found to differ by no more than 5% from those of the NPI [19].

Comparisons of neuropsychiatric symptoms in patients with clinical diagnoses of dementia have demonstrated distinctions between clinically (but not pathologically) diagnosed AD and bvFTD. Bathgate et al. [14] explored this distinction using their own caregiver questionnaire. They found that changes in emotions and insight, selfishness, disinhibition, personal neglect, gluttony and sweet food preference, wandering, stereotypies, loss of sensitivity to pain, echolalia, and mutism were more characteristics of bvFTD and differentiated the most bvFTD cases from AD cases. Bozeat et al. [13] also designed their own questionnaire, based largely on the NPI. They demonstrated that only the presence of either stereotypic and eating behaviors or loss of social awareness reliably differentiated patients with clinically diagnosed bvFTD from patients with AD. Kertesz et al. [10, 20] designed the Frontal Behavioral Inventory (FBI) to probe for the presence of particular behavioral elements that are known to predict FTLD. This scale is both sensitive and specific at differentiating FTD from AD and also appears sensitive to progression [21]. In a large, well-defined clinical cohort, it has also demonstrated a strong correlation with the changes captured by the NPI and was better able to differentiate AD from bvFTD [22].

Other studies with standard or specifically designed scales to assess behavioral changes or changes associated with frontal lobe pathology have been variably successful in differentiating AD from bvFTD [10, 11, 15, 16, 18, 23–25]. In particular, Levy et al. [16] used the NPI to show that, compared to patients with AD, patients with FTD were more likely to exhibit apathy, disinhibition, euphoria, and aberrant motor behaviors. Using a validated Japanese translation of the NPI, Hirono et al. [18] showed nearly identical distinctions demonstrating that patients with bvFTD had significantly more euphoria, aberrant motor activity, and disinhibition, but also significantly fewer delusions compared to patients with AD [18]. Nagahama et al. [25], using the Cambridge Behavioral Inventory (CBI) initially developed by Bozeat et al. [13], showed that disinhibition, stereotypic behavior, elation, anxiety, poor self-care, and changes in eating habits occurred more frequently in patients with bvFTD than in patients with AD. Mendez et al. [11] used the BEHAVE-AD scale to show that patients with bvFTD were more likely to have worse overall scores, with significantly higher incidences of verbal outbursts (inappropriate personal comments) and inappropriate activity (disinhibited acts or immodest behavior), than patients with AD.

While the majority of studies on neuropsychiatric symptoms involve clinically diagnosed patients, Liscic et al. [26] showed that behavioral abnormalities in general, including impulsivity, disinhibition, social withdrawal, hyperorality as well as aphasia, were more likely present in patients with pathologically confirmed FTLT than in patients with pathologically confirmed AD. Of note, nearly one quarter of the patients with FTLT were also found to have AD pathological changes.

While to date there is no published research using neuropsychiatric symptoms to separate tau-positive and tau-negative patients, other clinical changes have been investigated. In a large postmortem analysis of 114 cases from two major centers, Forman et al. [27] demonstrated an association of social and language difficulties and motor neuron disease with non-tau bvFTD pathologies, while bvFTD associated with tau was more likely to show parkinsonism. Detailed information on the neuropsychiatric changes was not available.

Specific neuropsychiatric symptoms have been previously associated with particular pathologies in dementias more generally. Perhaps most specific, hallucinations are considered to be related to underlying synucleinopathy in Lewy body disease [28], although more recently hallucinations have been described in progressive supranuclear palsy, a tauopathy [29]. In bvFTD patients with one particular genetic variant linked to chromosome 9 with tau-negative pathology (and representing 8% of bvFTD patients in this recent study), this variant has been associated with particular symptoms such as psychosis at a much higher rate than in patients with bvFTD who do not have this genetic mutation, and a much lower rate of sweet food preference [30]. Otherwise, to date, there has been no specific set of symptoms associated with tau-negative or tau-positive pathology in bvFTD.

Because agents that target the underlying pathology are more likely to work when administered early in the course of the disease, securing an early accurate diagnosis is an important goal. Although certain clinical signs are more prevalent in association with a given underlying process – for instance, the presence of parkinsonism or motor neuron disease in a patient with clinically diagnosed bvFTD is suggestive of tau-positive or tau-negative pathology, respectively [31] –, such findings typically emerge later in the course of the illness. Advanced structural neuroimaging analysis can also increasingly predict the pathological status in groups of individuals [32], but this remains expensive, available only in select academic centers, and its reliability in individual patients is unproven. The identification of early clinical characteristics that betray the underlying pathological process would allow for a less expensive and more rapid orientation of patients with a particular pathology to appropriate clinical trials involving specific etiologic agents. Once agents have been isolated and proven effective, these early clinical characteristics would also help safely select future patients for a given agent.

The National Alzheimer's Coordinating Center (NACC) database represents a unique opportunity to investigate in vivo symptomatology while knowing ultimate pathology derived at autopsy in a large sample. The database includes clinical details of patients diagnosed and followed longitudinally at academic AD centers across the country. The data consist of early and behaviorally (including the NPI-Q) well-characterized patients who have been followed to autopsy. We analyzed data from the first NPI-Q administered to patients with both clinically diagnosed AD and bvFTD, and explored for the existence of patterns of endorsement that could be associated with specific pathologies, including FTLN subtypes. While the use of inventories more sensitive to FTLN (such as the FBI) may have represented better choices, this analysis was constrained by its retrospective nature from an available data set and the initial decision by the creators of the database to include the NPI-Q.

Methods

Participants

Data from the NACC neuropathology data set were used. The NACC database contains data from 34 past and present AD centers. In our sample, locked March 2012, we included all cases of clinically diagnosed (initial visit) and autopsy-proven AD and all cases of clinically diagnosed bvFTD (initial visit) irrespective of pathological diagnosis. Details of these two groups of patients are presented in table 1.

We then used frequency statistics to compare the prevalence of each of the 12 NPI-Q symptoms in the two groups. The bvFTD group was further broken down into the type of ultimate pathology detected. Thirty-one (20.5%) of the clinically diagnosed bvFTD cases had primary pathological diagnoses of AD. Eighty-two (54.3%) of the cases had primary bvFTD diagnoses. Given that there are various tauopathies found in bvFTD, we divided the patients into tau-positive (including Pick's disease, FTD and parkinsonism with tau-positive or argyrophilic inclusions, and other tauopathies) and tau-negative cases (FTD tau-negative ubiquitin-positive inclusions). In the NACC data set, 18 of the bvFTD patients were not given specific pathologies, but rather 'other' histology was checked. In these cases, a note was written to explain the primary pathology. In 10 of these cases, the cause was clearly definable as an FTLN tauopathy (these had noted 'Pick's disease', 'PSP', 'FTD-P', or 'CBD') and a further 5 had a nontauopathy FTLN ('FTLN-U TDP', 'MND', or 'DLN'). These cases were relabeled as FTLN tauopathy and FTLN nontauopathy, respectively. The demographic details of the bvFTD tauopathy and FTLN nontauopathy groups are shown in table 2. Details were not available on 39 cases.

Results

Comparison of Patients with a Clinical Diagnosis of bvFTD (Any Pathology) and Pathologically Confirmed Cases of Clinically Diagnosed AD

Patients with clinically diagnosed bvFTD more frequently presented with symptoms of anxiety ($\chi^2 = 5.97$, $p = 0.015$), elation ($\chi^2 = 21.97$, $p < 0.0005$), apathy ($\chi^2 = 19.21$, $p < 0.0005$), disinhibition ($\chi^2 = 64.67$, $p < 0.0005$), motor changes ($\chi^2 = 30.20$, $p < 0.0005$), and nighttime behavior ($\chi^2 = 41.86$, $p < 0.0005$) compared to patients with pathologically confirmed clinical diagnoses of AD. These findings are depicted in figure 1.

Comparison of Clinically Diagnosed bvFTD Patients with AD versus FTLN Pathology

Of the patients diagnosed in clinic with bvFTD, those with AD pathology were significantly more often ascribed delusions ($\chi^2 = 7.36$, $p = 0.007$), hallucinations ($\chi^2 = 4.32$, $p = 0.039$), and agitation ($\chi^2 = 3.87$, $p = 0.050$) compared to those with one of the FTLN pathologies. These results are depicted in figure 2.

Table 1. Demographic details of tau-negative and tau-positive patients with clinically diagnosed bvFTD who had FTLD pathology

	FTD tau negative (n = 77)	FTD tau positive (n = 33)
Age at death, years	65.95 (9.28)	66.58 (8.22)
Education, years	15.64 (3.26)	14.91 (2.35)
Male gender, %	68.8	63.6
White race, %	93.5	97.0
Values represent means (SD), unless otherwise indicated. There were no differences in these factors between the two groups.		

Table 2. Demographic details of the two clinical diagnostic groups

	FTD (n = 149)	AD (n = 578)
Age at death, years	67.15 (9.30)	79.98 (10.84)*
Education, years	15.23 (3.13)	15.76 (9.08)
Male gender, %	66.90*	56.8
White race, %	95.40	94.4
Values represent means (SD), unless otherwise indicated. bvFTD patients were significantly younger than AD patients, and there were more men in the bvFTD group. * p < 0.05.		

Comparison of Clinically Diagnosed bvFTD Patients with Tau-Negative versus Tau-Positive FTLD Pathology

Patients with bvFTD who had FTLD pathology were divided into tau-negative and tau-positive cases. The patients with tau-negative pathology were more likely to show delusions ($\chi^2 = 6.41$, $p = 0.012$), depression ($\chi^2 = 7.46$, $p = 0.007$), and changes in appetite and eating ($\chi^2 = 5.27$, $p = 0.022$). These results are depicted in figure 3.

Discussion

There is great interest in being able to define phenotypic signatures of the neuropathology underpinning clinical bvFTD during life, especially early in the course. Additionally, tools that predict pathology will be great aids in clinical diagnosis.

We examined the pattern of endorsement of items on the NPI-Q to identify possible links to the underlying pathology. We found that in patients with a clinical diagnosis of bvFTD but in whom the underlying pathology was actually AD, the presence of delusions, hallucinations, and agitation was much more frequent. Endorsement patterns also differed in patients with pathological diagnoses of FTLD depending on the pathological subtype, with caregivers of patients with tau-negative pathology being more likely to endorse delusions, depression, and appetitive changes. To our knowledge, this is the first study that explores and isolates patterns of presenting neuropsychiatric changes as they relate to tau-negative or tau-positive pathological diagnosis in bvFTD.

Similar to previous studies [13, 14, 16, 18] that used patients without pathological verification of their clinical diagnosis, we found that patients with clinically diagnosed bvFTD had more apathy, elation, disinhibition, aberrant motor behaviors, nighttime behaviors, and changes in appetite and eating compared with pathologically confirmed patients with clinical

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Fig. 1. % frequency symptom endorsement: bvFTD (clinical diagnosis, any pathological diagnosis) vs. AD (clinical diagnosis and pathological diagnosis). Significant difference: * $p < 0.05$ (see text for details).

Fig. 2. % frequency symptom endorsement for bvFTD patients: FTD pathological diagnosis vs. AD pathological diagnosis. Significant difference: * $p < 0.05$ (see text for details).

Fig. 3. % frequency symptom endorsement for bvFTD patients: tau-negative vs. tau-positive pathology. Significant difference: * $p < 0.05$ (see text for details).

cally diagnosed AD. This is not surprising given that criteria defining bvFTD require inclusion of a certain number of these neuropsychiatric symptoms for diagnosis. We further found that delusions, hallucinations, and agitation were more common in patients misdiagnosed clinically with bvFTD who had underlying AD pathology, compared to those with true FTLT pathology. This suggests that, for the most part, patients with psychoses go misdiagnosed. However, psychotic symptoms can occur in the minority of true FTLT cases [30, 33]. While we do not know what symptom profile led physicians in the NACC sites to define each of the patients, it could be that the clinically diagnosed bvFTD patients with AD pathology had the frontal variant of AD. This group has been defined before, and their neuropsychiatric profile has been described as well, but not in a pathologically confirmed sample [34]. Future research with the NACC data set or in prospectively studied groups might distinguish different neuropsychiatric profiles in more typical AD and pathologically defined groups of frontal variant AD and bvFTD patients.

Perhaps most interestingly, we found differences between tau-positive and tau-negative bvFTD groups. Tau-negative patients were, as a group, more likely to have delusions, depression, and changes in appetite and eating. There is little literature for comparison, although patients bearing the newly characterized C9ORF72 mutation tend to have more psychotic behavior and possibly less appetitive changes [30]. Future research with scales probing the full range of neuropsychiatric symptoms in bvFTD such as the FBI may be more informative in determining the predictive relationship between neuropsychiatric symptoms and pathology. However, the information from this study may be pertinent to clinical diagnosis and will be informative to these future studies.

A limitation of this study includes the fact that the NACC database does not supply neuroanatomical details about the distribution of pathological findings. This will be important since it is likely that the specific networks disrupted, rather than the particular cellular changes, lead to particular behaviors. The relationship of particular neuropsychiatric changes and specific neuroanatomically localized pathologic burden has been shown in AD, where post-mortem neurofibrillary tangle counts in the left and right orbitofrontal and in the left anterior cingulate were found to be correlated with agitation, while load in the left anterior cingulate alone correlated with chronic apathy [35]. Furthermore, specific networks or cell types may have particular vulnerability to certain pathologies [36]. As more advanced neuroimaging techniques are being applied to the problem of predicting pathology and the neuroanatomical signature of the various pathologies is becoming more precise [37], these applications may further reveal the underlying networks involved in the various neuropsychiatric symptoms.

Another limitation, related to the retrospective nature of the database, involves the nonavailability of newer staining techniques for the analysis of the neuropathological changes. This is particularly true for the different forms of tau-negative inclusions (that currently number at least 7: 4 TDP-43 and 3 FUS varieties), which have been much better characterized over the last 5 years and which show fairly specific association with genetic variants and certain phenotypic presentations [2].

While this study concentrated on neuropsychiatric symptoms in relative isolation, phenotypes of FTLT pathology are more likely to be defined by combinations of neuropsychiatric, cognitive, and motor symptoms. In a pathologically confirmed series, Hodges et al. [38] found that behavioral symptoms were associated with a range of pathologies, while other clinical phenotypes had relatively uniform underlying pathologies: motor neuron disease predicted tau-negative inclusions, parkinsonism and apraxia predicted corticobasal (tau-positive) pathology, and nonfluent aphasia predicted tau-positive Pick bodies. Since motor and behavioral symptoms usually co-occur in the same patients, clustering of signs and behavioral changes should be explored further. The current study concentrated on bvFTD; however, neuropsychiatric symptoms occur in the language variant [39] and this is also pertinent to explore.

Shortly after the submission of this paper, a similar study of the NACC data was published by Mendez et al. [40]. Their study was based on a similar data subset. The data lock used in their study ended in July 2011, 8 months before the data lock in our study (March 2012), reducing the total number of subjects available in their study. The statistical analyses were equivalent. As found in this study, slightly more than 20% of patients with clinically diagnosed bvFTD were found to have AD pathology. The authors were able to show that patients with bvFTD-AD (i.e. with AD pathology) in comparison to patients with bvFTD-FTLD (i.e. with FTLD pathology) were more likely to have memory loss and less likely to show judgment/problem solving deficits or personality change as first symptoms. Personality change remained the only significant ‘current’ symptom difference (i.e. from the most recent visit as opposed to the initial visit). Also similar to our findings, bvFTD-AD patients were more likely to show hallucinations, delusions, or agitation on the NPI-Q. When comparing the tau-negative and tau-positive pathologies, they found that only personality change was significantly more frequent in tau-positive patients; additionally, they found no statistical differences in NPI-Q question endorsement. In contrast, we found that tau-negative patients were more likely to demonstrate depression, delusions, and changes in appetite and eating. This discrepancy is most likely explained by the inclusion of a larger number of subjects in our study.

Future studies may use prospective techniques to predict pathology based on symptoms, including neuropsychiatric manifestations. Novel PET ligands and genetics will soon make ‘pathological diagnosis’ possible during life, allowing for the in vivo correlation of clinical phenotypes with underlying pathology. To that end, the findings of this study represent a first small step in this direction.

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