Neurofibrillary Tangle Predominant Dementia: Clinical and Pathological Description in a Case Series

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Abstract

Objective: The aim of this study is to contribute to an understanding of the clinical presentation and pathological features of neurofibrillary tangle predominant dementia (NFTPD) that will assist with the eventual development of methods for its ante-mortem identification.

Method: We contrast eight NFTPD cases identified in the Banner Sun Health Research Institute Brain and Body Donation Program (SHRI-BBDP) database to 114 Alzheimer's disease (AD) subjects, in terms of their demographics, clinical features, and pathological features.

Results: When NFTPD subjects were compared to AD subjects, they were found to have a later onset of symptoms, an older age at death, less impairment prior to death, and less frequent appearance of the Apolipoprotein E ε4 variant. None of the eight NFTPD subjects met the clinical criteria for probable AD. They possessed a diverse range of diagnoses including possible AD, mixed vascular dementia (VAD), dementia NOS, and dementia with Lewy bodies (DLB). AD-related pathology, for both amyloid plaques and neurofibrillary tangles, was less severe in NFTPD subjects than in AD subjects. All eight NFTPD subjects were classified as neurofibrillary tangle Braak stage IV and therefore had fewer tangles in the neocortex when compared to AD subjects with mean Braak stage V (range II–VI).

Conclusion: NFTPD subjects have dementia despite a lower pathological burden when compared to AD subjects. In this small sample, the ante-mortem presentation is such that NFTPD subjects are not diagnosed with probable AD. The cognitive and non-cognitive clinical features (delusions, depression, parkinsonism, and hallucinations) of NFTPD and AD are very similar and do not serve as indicators for a diagnosis, but older age (>80), lack of an ApoE ε4 allele and less severe cognitive impairment should further inform the differential diagnosis of NFTPD from AD.

Introduction

Neurofibrillary tangle predominant dementia (NFTPD) is a sporadic subtype of progressive dementia, affecting elderly patients, as defined by a clinical diagnosis of dementia, the presence of 3R and 4R neurofibrillary tangles (NFT) isoforms in limbic areas (usually Braak Stage IV), and the absence or relative scarcity of amyloid (Aβ) plaques in the brain [1-4]. In contrast, Alzheimer's Dementia (AD) is a progressive dementia characterized by the presence of 3R and 4R neurofibrillary tangles and abundant amyloid plaques [5]. In AD, neurofibrillary tangles are understood to be closely linked with the severity and duration of dementia [6-10]. Approximately 15-30% of those clinically diagnosed with mild to moderate probable AD lack sufficient plaques and/or neurofibrillary tangles to meet AD neuropathological criteria [11,12]. Some of these [12,13] are neuropathologically demonstrated NFTPD but are not clinically distinguishable from AD or other dementias ante-mortem. In a set of individuals clinically diagnosed with mild to moderate AD derived from US National Institute on Aging AD centers, Monsell et al. found that 45% had extensive neurofibrillary degeneration and minimal Aβ plaques [13]. In a group of Apolipoprotein E ε4 (APOE4) non-carriers with mild to moderate AD, 37% had low amyloid levels [13]. In contrast, only 13% of APOE4 carriers with the same diagnosis had low amyloid levels [13]. Identifying individuals who are diagnosed with AD, but have low amyloid levels will be critical as more amyloid-targeted treatments for AD are developed [14]. Clinical characterization of NFTPD has been limited by the dementia's relatively

low prevalence: only 0.7% to 5.8% of clinically diagnosed dementia cases are pathologically diagnosed as NFTPD [4].

Previous research on NFTPD has not established differences between the clinical presentation of NFTPD and AD. The aim of this study is to contribute to an understanding of the clinical and pathological presentation of NFTPD that might eventually enable ante-mortem diagnosis. We contrast eight NFTPD cases identified in the Brain and Body Donation Program (BBDP) database to 114 AD subjects [15,16].

Method

Human subjects

Complete clinical and neuropathological examinations were performed on deceased subjects who had enrolled in the Banner Sun

Health Research Institute Brain and Body Donation Program (BSHRI-BBDP) [15,16]. All enrolled subjects or their legal representatives signed an Institutional Review Board-approved informed consent form before the time of death. All subjects received annual standardized test batteries that include general neurological, cognitive, and movement disorder components.

From 1218 cases autopsied between January 1997 and December 2014, 848 individuals received a clinical diagnosis of dementia during their lifetime. Of these individuals, those with a neuropathological diagnosis of AD (n=114) and NFTPD (n=8) were included in this study. We excluded AD subjects with secondary pathological diagnoses and AD subjects who never received a complete cognitive assessment at BSHRI (n=575). Any individual with a diagnosis other than AD or NFTPD (n=151) was excluded.

Pathology

For neuropathological examination, multiple brain regions were microscopically examined. The neuropathological examination slide set included staining of paraffin-embedded sections (6 μm) with hematoxylin and eosin (H&E). Amyloid plaques, neurofibrillary tangles, and glial tauopathies, and white matter rarefaction were identified on 80 μm-thick, large-format (3 x 5 cm) formalin-fixed sections using two enhanced silver stains, the Gallyas and Campbell-Switzer methods, for neurofibrillary tangles (NFT) and plaques, respectively. Thioflavin S fluorescent stain was used for amyloid and NFT and H&E were used for white matter rarefaction. Neuritic plaques and NFT were graded as recommended by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) with separate semi-quantitative density estimates of none, sparse, moderate, or frequent (converted to a 0–3 scale for statistical purposes) using standardized published templates [17-19]. Neurofibrillary degeneration was staged by the original method of Braak, in thick sections using the Gallyas method. Regions scored included cortical gray matter from frontal (F), temporal (T), parietal (P), hippocampal CA1 (H), and entorhinal (E) regions. The individual carrying out the scoring (TB) was blinded to demographics and clinical diagnosis. Neuropathological AD diagnoses were made according to the National Institute on Aging/Reagan Institute criteria [18-20].

In addition, paraffin-embedded sections from multiple brain regions including the olfactory bulb, amygdala, brainstem and cerebral cortex were used to document α-synucleinopathies using an immunohistochemical method for α-synuclein phosphorylated at serine 129 [16,21-24].Densities of Lewy-type α-synucleinopathy (LTS) were graded by reference to the DLB Consortium III template.

Statistical analysis

All eight NFTPD subjects found in the BBDP database met the criteria of NFT Braak stage IV and a clinicopathological diagnosis of NFTPD [15,16]. The AD group was compared to the NFTPD group based on the following criteria: age at death, gender, years of education, ApoE genotype, post-mortem interval (PMI), time since last clinical assessment, age at onset, Mini Mental State Exam (MMSE), Global Deterioration Scale (GDS), Functional Assessment Staging Test (FAST), Braak stage, NFT density, total plaque density, cerebral white matter rarefaction, clinical diagnosis, CERAD diagnosis, argyrophilic grains, cerebral amyloid angiopathy, hippocampal sclerosis, and Unified Lewy Body stage.

The Mann-Whitney test was used to contrast clinical and neuropathological variables between the AD group and the NFTPD group. Categorical frequency values were compared using a Fisher test. Analysis of FAST scores was performed by replacing letter scores with number values according to the following transformation: 6a=6.0, 6b=6.2, 6c=6.4, 6d=6.6, 6e=6.8, 7a=7.0, 7b=7.16, 7c=7.32, 7d=7.48, 7e=7.64, 7f=7.8.

Results

A summary of demographics and clinical characteristics of the NFTPD subjects and AD subjects is presented in Table 1. Compared to AD patients, the NFTPD subjects had a similarly equal gender distribution (NFTPD 50% female vs. AD 46% female) and none of the NFTPD subjects were APOE4 carriers (0% vs. 48%; P=0.016). The NFTPD group had a slightly higher age of symptom onset (69-89, mean 80.5 vs. 58-96, mean 77.6) and age at death (78-94, mean 87.00 vs. 61-103, mean 85.60) than the AD group; however, these differences were

Characteristics	NFTPD	AD	P Value
N	8	114	
Demographic Features			
Age at Death	87.00 ± 4.90	85.60 ± 6.61	ns
Females (% total)	4 (50%)	53 (46%)	ns
Education (Years)	14.8 ± 2.7	14.5 ± 2.5*	ns
APOE4 Carrier (% total)	0(0%)	55 (48%)	0.016
Exam Features			
PMI (Hours)	3.14 ± 0.65	3.88 ± 4.89	ns
Time since last clinical assessment (Months)	12.29 ± 7.18	15.69 ± 17.85	ns
Clinical Features			
Age at Onset	80.5 ± 6.6	77.6 ± 8.3	ns
MMSE	24.17 ± 3.06*	13.16 ± 8.97	<0.001
GDS	4.43 ± 1.62*	5.20 ± 1.38*	0.001
FAST	4.83 ± 1.73*	5.43 ± 1.61*	ns
Pathological Features			
Braak Stage	4.0 ± 0	4.9 ± 1.004	<0.001

All data are presented as mean ± standard deviation unless otherwise noted. Pairwise comparisons were performed using a student's t-test or Mann-Whitney rank sum test. Categorical frequency analysis was performed using the Fisher Test. *Indicates missing data points. The data points missing from the AD group are insignificant in light of the large n of the group. One NFTPD subject is missing an MMSE score due to being unresponsive at the time of examination. A different subject is missing GDS and FAST scores. In all cases of missing data points, the significance of the findings is not affected.

Table 1: Demographic and clinical characteristics of NFTPD and AD subjects.

not statistically significant. The NFTPD group was not significantly different from the AD group in terms of PMI (mean 3.14 vs. 3.88; P=0.67), time since last assessment (mean 12.29 vs. 15.69; P=0.62), and years of education (mean 14.8 vs. 14.5; P=0.78).

Before death, NFTPD patients had significantly higher MMSE scores than the AD group (20-28, mean 24.17 vs. 0-28, mean 13.16; P<0.001). GDS (2-7, mean 4.43 vs. 2-7, mean 5.20; P=0.001) and FAST (2-7, mean 4.83 vs. 1-7.48, mean 5.43; P=0.448) scores also indicated that the NFTPD group had significantly lower global impairment than the AD group. Table 2 summarizes the four major clinical findings in

the NFTPD group during the course of their dementia: depression (4/7), hallucinations (2/8), delusions (3/8), and parkinsonism (4/8). NFTPD cases were heterogeneous in their clinical diagnoses of dementia (Table 3). None were classified as probable AD [5]. Four cases were clinically diagnosed as possible AD [5] with the rest divided between mixed vascular dementia (n=2) [25,26], dementia NOS (n=1), and dementia with Lewy bodies (n=1) [27]. Post mortem examination revealed that none of the cases had enough infarcts or vascular pathology to qualify for a final diagnosis of VAD [25,26] or enough Lewy body pathology to be classified as DLB [27]. Further examination of the aggregate pathology is presented below.

NFTPD subjects had significantly lower Braak scores (all Braak stage IV) than the AD subjects (range II-VI, mean V; P=0.002). As expected by diagnostic definition, the NFTPD group had significantly lower densities of total plaques (0-1.5, mean 0.21 vs. 3-15, mean 13.27; P<0.0001) and neuritic plaques (0-1, mean 0.14 vs. 1-3, mean 2.83). Total cerebral white matter rarefaction was comparable in both groups overall (mean 4.00 vs. 4.77; P=0.74). Table 4 summarizes the pathology present in NFTPD and AD by region. NFTPD patients had similar tangle densities in the entorhinal cortex (mean 2.88 vs. 2.92; P=0.62) and hippocampus (mean 2.81 vs. 2.84; P=0.27), but had significantly lower tangle densities in the frontal (mean 0.38 vs. 1.83; P=0.0038), temporal (mean 1.38 vs. 2.42; P=0.002), and parietal lobes (mean 0.31 vs. 1.86; P=0.0027).

Group	Depression	Hallucinations	Parkinsonism	Delusions
Case 1	Yes	–	–	Yes
Case 2	Yes	Yes	Yes	Yes
Case 3	–	Yes	Yes	–
Case 4	–	–	–	–
Case 5	–	–	Yes	–
Case 6	Yes	–	–	–
Case 7	Yes	–	Yes	Yes
Case 8	N/A	–	–	–

A dash indicates that the clinical characteristic was absent. NFTPD patients presented with clinical characteristics including depression, hallucinations, parkinsonism, and delusions.

Table 2: Clinical characteristics of NFTPD subjects during dementia.

Case	Gender	Age at Onset	Age at Death	Consensus Diagnosis	CERAD Diagnosis	Argyrophilic Grains	Cerebral Amyloid Angiopathy	Hippocampal Sclerosis	Cerebral White Matter Rarefaction	Unified Lewy Body Stage	Cerebral Infarct Volume (cm³)
1	F	81	83	Possible AD	Criteria Not Met	–	–	–	Yes	–	0
2	F	84	88	DLB	Criteria Not Met	Yes	–	–	Yes	Olfactory Bulb Only	0.2
3	M	77	87	VAD	Criteria Not Met	–	–	–	Yes	–	0.2
4	M	89	>90	Dementia NOS	Criteria Not Met	Yes	–	–	Yes	–	0
5	F	82	86	VAD	Criteria Not Met	–	–	–	–	Brainstem Predominant	0.1
6	M	87	>90	Possible AD	Possible AD	–	–	–	Yes	–	0.2
7	M	69	78	Possible AD	Criteria Not Met	–	–	–	Yes	–	0
8	F	75	89	Possible AD	Criteria Not Met	–	–	–	Yes	–	0

A dash indicates that the pathology was absent. NFTPD patients received four pre-mortem clinical diagnoses: possible AD (n=4), vascular dementia (n=2), dementia with Lewy bodies (n=1), and dementia NOS (n=1). All patients but one did not meet the CERAD criteria for AD. Agyrophilic grains were present in two subjects. Cerebral amyloid angiopathy and hippocampal sclerosis were absent in all cases. Cerebral white matter rarefaction was present in all but one case. Two subjects had Lewy bodies present, but the pathology did not qualify them for a diagnosis of DLB. The four subjects with infarcts did not meet the criteria for a diagnosis of VAD.

Table 3: Comparison of pre-mortem clinical consensus diagnosis with Post-Mortem CERAD pathological diagnosis in NFTPD cases.

	Frontal	Temporal	Parietal	Entorhinal	Hippocampus	Total
			Neurofibrillary Tangles			
NFTPD	0.38 ± 0.23	1.38 ± 0.64	0.31 ± 0.37	2.88 ± 0.35	2.81 ± 0.37	7.75 ± 1.04
AD	1.83 ± 1.18	2.42 ± 0.94	1.86 ± 1.20	2.92 ± 0.31	2.84 ± 0.51	11.85 ± 3.56
P Value	0.0038	0.002	0.0027	ns	ns	0.0028
Total Plaques						
NFTPD	0 ± 0	0.071 ± 0.19	0.21 ± 0.40	0 ± 0	0 ± 0	0.21 ± 0.57
AD	2.86 ± 0.48	2.86 ± 0.38	2.87 ± 0.43	2.6 ± 0.58	2.09 ± 0.84	13.27 ± 2.24
P Value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

All values are presented as mean ± standard deviation. Pairwise comparisons were performed using the Mann-Whitney rank sum test. Pathology density was graded on a semi-quantitative scale of none, sparse, moderate, or frequent. These estimates were converted to a 0-3 scale for statistical purposes. As expected based on the diagnostic criteria for NFTPD, NFTPD subjects have significantly lower densities of total plaques compared to AD subjects. Additionally, NFTPD subjects have a significantly lower, but still present density of neurofibrillary tangles compared to AD subjects.

Table 4: Pathology Density by Region in AD (Braak II–VI) and NFTPD (Braak IV).

Discussion

This paper compares the clinical and pathological presentation of autopsy-confirmed NFTPD to AD. We found that NFTPD cases had a later onset of symptoms, an older age at death, less impairment before death, and less frequent appearance of APOE4. We found that none of the NFTPD subjects met the clinical criteria for probable or definite AD. The overall AD-related pathology was less severe in NFTPD cases than AD cases. NFTPD subjects had lower neuritic plaque densities as well as total tangle density. All the NFTPD subjects were classified as NFT Braak stage IV and therefore had fewer tangles in the neocortex when compared to most AD subjects.

We found different rates of hallucinations, parkinsonism, and depression in our eight NFTPD cases than have been previously identified for NFTPD; however, our conclusions may be limited by our small sample size. We found that 37.5% of NFTPD cases presented with delusions during the course of the dementia. A study that found delusions in an NFTPD group attributed the symptom to the presence of argyrophilic grains in the nucleus accumbens [28]. However, only one case of delusions in our NFTPD group had argyrophilic grain pathology. We identified three clinical symptoms for which our prevalence was more frequent than what was reported by Jellinger and Attems: hallucinations (25% vs. 1.96%), parkinsonism (50% vs. 1.96%), and depression (50% vs. 17.5%) [4]. These differences suggest that hallucinations, parkinsonism, and depression may be present in NFTPD at a higher rate than has been previously identified.

When the cognitive assessment and detailed clinical presentation of our eight NFTPD cases is compared to the documented clinical presentation of AD cases, there is no distinguishable difference in the rates of delusions (NFTPD 37.5% vs. AD 30-55% [29-31]), hallucinations (25% vs. 3-53% [29-33]), and depression (57% vs. 20-52% [29,34-37]). Further studies are needed in order to explore if the presentation of delusions underlies the pathological damage of the limbic area in both diseases.

There may be a slightly higher rate of parkinsonism in NFTPD than AD (50% vs. 9-36% [32,38]). The four non-cognitive clinical features (delusions, hallucinations, depression, and parkinsonism) examined here do not clinically distinguish NFTPD patients from AD patients, suggesting that, as documented by autopsy studies, the dominant underlying cause of dementia in both diseases, accumulation of neurofibrillary tangles, results in a very similar clinical profile.

Our group of NFTPD patients received a mixed set of clinical diagnoses: possible AD (50%), VAD (25%), dementia NOS (12.5%) and DLB (12.5%). Post-mortem, none of the cases had enough pathology to meet criteria for clinical-pathological diagnosis of AD, VAD, or DLB. These clinical diagnoses differ in frequency from those reported by Jellinger and Attems. The three most frequent diagnoses in Jellinger and Attems' results were probable AD (47%), possible AD (17.6%), and nonspecific dementia (17.6%) [4]. Differences in the rate of cases that meet a clinical diagnosis of probable AD might reflect how rigorously the clinical criteria for diagnosing AD were used in each study. In this study we analyzed a small group comprised of eight subjects while Jellinger and Attems presented data for fifty-one subjects [4]. The wide variety of clinical diagnoses received by NFTPD patients might indicate that clinicians often recognize that these subjects have something other than the common presentation of AD.

Recently, the diagnosis, primarily age-related tauopathy (PART), has been introduced as a contrasting diagnosis to NFTPD [2]. The PART diagnosis is based on the presence of neurofibrillary tangles and the absence of amyloid plaques in the brain of an individual with or without dementia [2]. PART is distinct from NFTPD because it is a purely pathological diagnosis that does not consider the clinical presentation of the individual [2]. While PART may be advantageous in a pathology setting by increasing the diversity of vocabulary available to pathologists to accurately describe patients, it does not contribute to this study's consideration of NFTPD. The PART diagnosis has also been challenged in its distinction from AD. An examination of the pathology present in age groups ranging from 0 to 100 years old indicates that tauopathies may be part of the pathological process that produces AD [39]. The aim of this study is to identify clinical features that may distinguish NFTPD patients from AD patients. The usage of the PART diagnosis would include individuals who do not have dementia and who are not at risk for an AD misdiagnosis.

The APOE4 allele is known to be associated with an increased risk of developing AD and can contribute to an earlier onset [40-46]. Along with other researchers, we found that, compared to AD, NFTPD subjects have a lower carriage rate of the ε4 allele [4,47-51], a later onset of disease and death [4,48,50] and a lesser degree of cognitive impairment [4,48,50,52]. Both plaques and tangles are correlated with the degree of cognitive impairment, but this correlation is stronger for tangles [53]. This may explain why cognitive impairment is less severe in NFTPD with few or no plaques and a more restricted distribution of tangles. Overall NFTPD clinical syndrome is very similar to AD probably due to the dominance of tangles causing cognitive impairment.

In over 15 years of data collection including 1,218 cases, the BBDP diagnosed only eight cases of NFTPD, which represents only one percent of dementia cases. This may be partially reflective of a decreased tendency to diagnose NFTPD in earlier years, prior to its widespread recognition as a diagnostic entity. The BBDP performs detailed brain examinations on every subject who comes to autopsy and several staining's are performed to unmask a myriad of possible pathologies [15,16]. The strength of our eight cases lies in the detailed clinical data collected and the thorough pathological analysis.

Conclusion

The findings of our study and others on the clinical diagnoses of NFTPD patients indicate that this dementia is often recognized by clinicians as something different from classical AD, but there is no clear set of differentiating features. The cognitive and non-cognitive clinical features of NFTPD and AD are very similar and do not serve as indicators for a diagnosis, but older age (>80), lack of an ApoE ε4 allele and less severe cognitive impairment should bring NFTPD into the differential diagnosis. The details that will clinically distinguish NFTPD from AD most likely lie in the nuances of neuropsychological testing. An in-depth review of testing results for large cohorts of NFTPD and AD has the potential to reveal the distinguishing factors that will allow for the pre-mortem diagnosis of NFTPD.

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