Frontal Lobe Dementia With Novel Tauopathy: Sporadic Multiple System Tauopathy With Dementia

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Abstract. We present a novel tauopathy in a patient with a 10-yr history of progressive frontal lobe dementia and a negative family history. Autopsy revealed mild atrophy of frontal and parietal lobes and severe atrophy of the temporal lobes. There were occasional filamentous tau-positive inclusions, but more interesting were numerous distinctive globular neuronal and glial tau-positive inclusions in both gray and white matter of the neocortex. Affected subcortical regions included substantia nigra, globus pallidus, subthalamic nucleus, and cerebellar dentate nucleus, in a distribution similar to progressive supranuclear palsy (PSP), but without significant accompanying neuronal loss or gliosis. Predominantly straight filaments were detected by electron microscopy (EM), while other inclusions were similar to fingerprint bodies. No twisted ribbons were detected. Immuno-EM studies revealed that only the filamentous inclusions were composed of tau. Immunoblotting of sarkosyl-insoluble tau revealed 2 major bands of 64 and 68 kDa. Blotting analysis after dephosphorylation revealed predominantly 4-repeat tau. Sequence analysis of tau revealed that there were no mutations in either exons 9–13 or the adjacent intronic sequences. The unique cortical tau pathology in this case of sporadic multiple system tauopathy with dementia adds a new pathologic profile to the spectrum of tauopathies.

Key Words: Corticobasal ganglionic degeneration; Dementia; Frontal lobe dementia; Frontotemporal degeneration; FTDP-17; Progressive supranuclear palsy; Tauopathy.

INTRODUCTION

Abnormalities in the microtubule-associated protein tau are associated with an array of neurodegenerative disorders, including Alzheimer disease (AD) (1–5), Pick disease (2, 3, 6–9), progressive supranuclear palsy (PSP) (6–17), corticobasal ganglionic degeneration (CBGD) (6–8, 12, 14, 15, 18), neurofibrillary tangle-predominant senile dementia (NFT-SD) (19), and the frontotemporal degenerations (FTD) (1–4, 20, 21) including frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) (21–51). Tau-positive inclusions are found in neurons, astrocytes, and oligodendrocytes in these disorders (1, 4, 5, 8, 9). In fact, tau-positive tufted astrocytes and glial plaques practically define the pathology of PSP and CBGD (2, 3, 10–17), while in the FTDP-17 families, tau-positive inclusions are more prominent in oligodendrocytes than in astrocytes (1, 4, 5, 9).

The frontotemporal degenerations, including the FTDP-17 tauopathies, have similar clinical profiles, with variable impairment of behavioral, cognitive, and motor function (2, 3, 24, 25, 30). They generally present with abnormalities in behavior and personality, develop dementia and language difficulty, and may develop parkinsonism and eye movement abnormalities (2, 3, 28, 29, 33, 34, 36, 46, 48, 49). Onset is usually younger than in AD, most often in the fifth decade, with familial cases having a younger age of onset than sporadic cases (23, 24, 28, 29, 33, 34, 36, 46, 48, 49).

We present a tauopathy with novel inclusions in a patient with a non-familial frontal lobe dementia without parkinsonism.

MATERIALS AND METHODS

Case History

A Caucasian woman began experiencing progressive memory decline at age 75, in 1987. Her speech became simplified and she had difficulty naming objects. She had significant personality and behavior changes with emotional outbursts, increasingly aggressive behavior, and decreased attention to personal hygiene. On the other hand, she had no visuospatial difficulties and was still driving when first evaluated in February of 1990 at age 78.

Initial psychiatric evaluation revealed dysnomia, hypofluency, and diminished concentration. On neuropsychologic testing, she had a verbal IQ of 82, performance IQ of 103, and full-scale IQ of 91, with bilateral cerebral hemispheric deficits, left worse than the right. The Mini-Mental State Examination (52) score declined from 26/30 in February of 1990 to 24/30 in July 1991. Her score on the Blessed Dementia Rating Scale (53) deteriorated from 3 on initial evaluation to 4.5 in July of 1991. At her initial evaluation, she had a Clinical Dementia Rating (54) score of 0.5, a Global Deterioration Scale (55) rating of 3, and a modified Hachinski Ischemic Score (56) of 1. Her neurologic examination revealed no focal deficits. MRI of the brain

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The patient was eventually transferred to a long-term care facility where she died in May of 1997, at age 85, after a 10-yr course of illness. An autopsy was performed 16 h after death.

We evaluated the case using hematoxylin & eosin stain for routine examination of neocortex (frontal, temporal, and parietal lobes and cingulate gyrus), hippocampus (anterior and posterior levels) amygdala, basal ganglia, thalamus and subthalamic nucleus, cerebellum including dentate nucleus, and brainstem (3 levels: midbrain,pons, and medulla), and used fluorescent thioflavin-S preparations to evaluate presence of AD pathology. Tissue for electron microscopy was obtained from formalin-fixed tissue 2 yr after autopsy and post-fixed in glutaraldehyde.

**Pathologic Studies**

We evaluated the case using hematoxylin & eosin stain for routine examination of neocortex (frontal, temporal, and parietal lobes and cingulate gyrus), hippocampus (anterior and posterior levels) amygdala, basal ganglia, thalamus and subthalamic nucleus, cerebellum including dentate nucleus, and brainstem (3 levels: midbrain,pons, and medulla), and used fluorescent thioflavin-S preparations to evaluate presence of AD pathology. Tissue for electron microscopy was obtained from formalin-fixed tissue 2 yr after autopsy and post-fixed in glutaraldehyde.

**Immunohistochemistry:** All immunohistochemical studies were performed at room temperature on a BioTek Solutions TechMate™ 1,000 automated immunostainer (Ventana BioTek Systems, Tucson, AZ). Buffers, blocking solutions, secondary antibodies, avidin/biotin complex reagents, chromogen, and hematoxylin counterstain were used as supplied in the ChemMate™ secondary detection kit (Ventana BioTek Systems). Optimum primary antibody dilutions were predetermined using known positive control tissues. A known positive control section was included in each run to assure proper staining.

Primary antibodies and dilutions are as follows: alpha B crystallin (polyclonal, Novocastra Laboratories, 1:100), alpha-synuclein (monoclonal, Zymed Laboratories, 1:300), beta-amyloid (monoclonal, Athena Neurosciences, 1:1,000), glial fibrillary acidic protein (polyclonal, Dako, 1:2,800), neurofilament (monoclonal, Dako, 1:1,600, PHF-1 (gift of Dr. Peter Davies, monoclonal, 1:100), synaptophysin (polyclonal, Signet Laboratories, 1:100), ubiquitin (polyclonal, Dako, 1:200).

Paraffin sections were cut at 3 μm on a rotary microtome, mounted on positively charged glass slides (POP100 capillary gap slides, Ventana BioTek Systems), and air-dried overnight. Sections were deparaffinized in xylene and ethanol, and placed in 200 ml heat-induced epitope retrieval (HER) buffer (Ventana BioTek Systems), pH 6.8. The buffer was brought to a boil, after which 50 ml of deionized water was added. The buffer was again brought to a boil for 5 minutes (min), then the slides were allowed to cool in buffer for 20 min, following which they were rinsed thoroughly in deionized water and then buffer. Sections were then incubated in unlabeled blocking serum for 5–10 min to block nonspecific binding of the secondary antibody. Next, sections were incubated for 25 min with either primary or with buffer alone as a negative reagent control. Following washing in buffer, sections were incubated for 25 min with biotinylated polyvalent secondary antibody solution (containing goat antibodies to rabbit, mouse, and rat immunoglobulin). Following another buffer wash, sections were incubated with 3 changes (2.5 min each) of 3% hydrogen peroxide to inhibit endogenous tissue peroxidase activity and again washed

**TABLE 1**

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<tr>
<th>Region</th>
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<th>Aβ</th>
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<tr>
<td>L hippocampus</td>
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<td>1+ GM, 1+ WM</td>
<td>nd</td>
</tr>
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<td>L amygdala</td>
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<tr>
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<td>negative</td>
</tr>
<tr>
<td>L subthalamic nucleus</td>
<td>1+ subth., hypoth., periaq. gr; 3+ IC</td>
<td>nd</td>
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<tr>
<td>midbrain/pons</td>
<td>2+ substantia nigra, c.n. III, retic. formation</td>
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1+ = mild, 2+ = moderate, 3+ = severe.

Abbreviations: GM = gray matter neuronal and glial inclusions (includes dense globular inclusions as well as filamentous NFT-like inclusions); WM = predominantly oligodendrogial inclusions–dense globular and filamentous; TA = tufted astrocyte-like inclusions; * = more inclusions where atrophy less severe; nbm = nucleus basalis of Meynert, gpi = globus pallidus interna; subth. = subthalamic nucleus; hypoth. = hypothalamus; periaq. gr. = periaqueductal gray; IC = internal capsule; c.n. III = cranial nerve III; retic. = reticular; nd = not done; DP = diffuse plaques; NP = neuritic plaques; AA = amyloid angiopathy.

in February of 1990 showed microvascular changes and generalized cerebral atrophy, more prominent in the temporal lobes. All laboratory values, including cerebrospinal fluid examination, were essentially normal. An EEG performed in February 1990 was normal. Although the clinical diagnosis was AD, the presentation was considered atypical, and the differential diagnosis included Pick disease, progressive dysphasic dementia, and vascular dementia.

The patient’s father had hypertension and died in his eighties with a clear sensorium. The patient’s mother had a stroke in her seventies and died in her eighties. Although a first cousin was described as a lifelong “recluse,” there was no known history of dementia in the family.

The patient developed hyperphagia, as well as increasing agitation, erratic behavior, and disinhibition. She never developed parkinsonism, motor signs, or eye movement abnormalities. The patient was eventually transferred to a long-term care facility where she died in May of 1997, at age 85, after a 10-yr course of illness. An autopsy was performed 16 h after death.

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**PHF-1 and Aβ Immunohistochemistry**

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in buffer. Sections were then incubated for 25 min with freshly prepared horseradish peroxidase-conjugated avidin-biotin complex or with alkaline phosphatase-conjugated avidin-biotin complex, followed by washing in buffer. They were then incubated either with 3 changes (5 min each) of a freshly prepared mixture of diaminobenzidine (DAB) and H_2O_2 in buffer, followed again by washing in buffer and then water, or with a solution of BT Red (a new fuchsin-type chromogen, Ventana BioTek Systems) in buffer containing levamisole (50 µl in 10 ml, to inhibit endogenous tissue alkaline phosphatase activity). Sections were then counterstained with hematoxylin, dehydrated in a graded series of ethanols and xylene, and coverslipped. Slides were reviewed by light microscopy. Positive reactions with DAB were identified as dark brown reaction product and those with BT Red as a bright red reaction product. Sections were photographed on a Nikon Optiphot microscope (Nikon Instruments, Melville, NY).

Fig. 2. Tufted astrocyte-like inclusion in temporal cortex with PHF-1 immunostain. Scale bar = 36 µm.

Fig. 3. Dense inclusions predominantly located in oligodendrocytes in white matter of temporal lobe. PHF-1 immunohistochemistry. Scale bar = 72 µm.

Fig. 1. Gray matter of temporal lobe, PHF-1 immunohistochemistry. A: Low power showing increased density of inclusions in deep cortex; scale bar = 360 µm. B: Higher power; scale bar = 70 µm. C: Higher power; scale bar = 36 µm.
**RESULTS**

**Neuropathology**

At autopsy the unfixed brain weighed 1,095 g. There was mild atrophy of frontal and parietal lobes and severe atrophy of the temporal lobes. There was no caudate or basal ganglia atrophy and no pallor of the substantia nigra or locus coeruleus. Microscopically, there was vacuolation in upper cortical layers in frontal and temporal lobes. There was mild gliosis in the frontal lobes and severe neuronal loss and gliosis in the temporal lobes. Outside of small cavitary infarcts in the basal ganglia, there was no appreciable neuronal loss or gliosis in this region. The substantia nigra was mildly depopulated and there was accompanying mild gliosis but no Lewy bodies. No NFTs (Braak stage 0) (57) were detected with thioflavine-S staining, and only rare cortical neuritic plaques (CERAD

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**Fig. 4.** Ballooned neurons in cortex immunolabeled with neurofilament immunohistochemistry. Scale bar = 72 µm.

**Electron Microscopy:** Transmission electron microscopy was performed on selected regions using a Japan Electron Optics Laboratory (JEOL) 100S electron microscope.

**Immunoblotting:** Immunoblotting studies were performed with the WKS44 antibody, an affinity-purified polyclonal anti-tau antibody that recognizes all forms of tau.

**Immunogold EM:** Immunogold EM was performed using the CP13 antibody, a monoclonal antibody to tau produced by immunizing mice with affinity purified paired helical filaments (PHF). The essential epitope for reactivity of this antibody appears to include phosphoserine 202, similar to the AT8 antibody.

**Fig. 5.** Neurons and NFT-like inclusions in substantia nigra neurons with PHF-1 immunostain. Scale bar = 145 µm.
A) (58) were confirmed by immunostaining with beta-amyloid (Table 1). No cortical Lewy bodies were detected by α-synuclein stains. PHF-1 immunostains for tau revealed widespread tau pathology in frontal and temporal lobes (Table 1). In the gray matter (Fig. 1A–C), dense globular neuronal and glial inclusions predominated, although occasional inclusions appeared densely filamentous. Inclusions were more numerous in the lower cortex and in the immediately subcortical white matter. There were no significant neuropil threads or grains, or swollen, tau-positive axons. Double-labeling with PHF-1 and anti-glial fibrillary acidic protein (GFAP) revealed no glial plaques of the type seen in CBGD. Rare tau-positive inclusions reminiscent of PSP-like tufted astrocytes were identified (Fig. 2). In the white matter (Fig. 3), many cells contained dense tau-positive inclusions that were not stained with antibodies to GFAP and had the morphology of oligodendrocytes. Anti-ubiquitin stained a portion of the inclusions in both gray and white matter, and ubiquitin, α-B-crystallin, and neurofilament antibodies highlighted rare ballooned neurons (BN) (Fig. 4). The inclusions were not stained with antibodies to alpha-synuclein, synaptophysin, or neurofilament. In subcortical regions, PHF-1 highlighted neurons and NFTs in substantia nigra (Fig. 5), globus pallidus (Fig. 6), subthalamic nucleus, and cerebellar dentate nucleus; a distribution similar to PSP but without significant accompanying neuronal loss.
or gliosis. There was abundant hemosiderin deposition in the basal ganglia and moderate hemosiderin in the substantia nigra.

**Biochemistry**

Immunoblotting of non-dephosphorylated sarkosyl-insoluble tau revealed 2 major bands of 64 and 68 kDa (Fig. 7). After dephosphorylation with hydrogen fluoride, these 2 bands co-migrated with all 3 bands of recombinant 4-repea (4R) tau expressing exon 10, including 4R, 4R + exon 2 (4R + E2), and 4R + exon 2 + exon 3 (4R + E2 + E3) (Fig. 7).

**Electron Microscopy**

EM of fixed tissue revealed dense aggregates and sheaves of straight filaments with a diameter of 9–10 nm (Fig. 8A, B), as well as fingerprint-like bodies (Fig. 9). There were rare straight as well as PHF-like filaments with a diameter of 20–30 nm, many of which appeared to be located in oligodendrocytes (Fig. 10A, B). Although the PHF-like filaments appeared to contain foci of narrowing suggestive of paired helical filaments, the poor quality of the preparation—for technical reasons including the long postmortem interval and the fact that tissue for ultrastructural examination was obtained from formalin-fixed tissue more than 2 yr after autopsy—precluded determination of periodicity. There were no definitive twisted ribbons. EM of immunogold-labeled tissue sections showed labeling of straight filaments with a diameter of 10 nm but no labeling of fingerprint-like bodies (Fig. 11). While not every straight filament was labeled, which can also be ascribed to technical problems, only these structures were labeled. The dense sheaves of filaments seen in Figure 8 were not present in immunogold-labeled tissue. No other structures were labeled.

**Tau Sequencing and Extended Tau Haplotype**

No mutations were identified in exons 9–13 or in the 30–100 base-pair intronic regions surrounding each of these exons. Analysis of tau polymorphisms within these

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**Fig. 8.** Electron microscopy. A: Electron microscopy of fixed tissue from white matter of temporal lobes shows dense sheaves of straight filaments (boxed area enlarged in 8B. Scale bar = 1.3 μm). B: Higher power image of boxed area in (A) highlights the filamentous nature of the inclusions, which have a diameter of 9–10 nm. Scale bar = 210 nm.
regions revealed that the tau haplotype of this case was H1H2.

DISCUSSION

The ever-increasing spectrum of tauopathies (1) includes both frontotemporal dementias like Pick disease (6–9) and a number of FTDP-17 disorders (21–40, 43–51), which include FMSTD (48–50), familial PSG (43), N279K tauopathy (37, 59), FTD-Kumamoto (51), Duke family 1,684 (40), and Dutch family 1 (22, 31, 47), as well as the primarily parkinsonian disorders PPND (38, 39), PSP (6–18), and CBGD (6–18). Clinically, these disorders present with frontal lobe dementia, parkinsonism, or both (22–24, 28, 29, 33, 34, 36, 37, 46, 48–50). At least half of the frontotemporal dementias related to tau are familial, generally having an earlier age of onset than the non-familial dementias (22–24, 28, 29, 33, 34, 36, 48, 49). Our patient's relatively late age of onset (75 yr) is consistent with the non-familial nature of her disease. She had frontal lobe symptoms (including abnormalities in behavior, personality, and executive functions), but never developed parkinsonian symptoms, eye movement abnormalities, or other disturbances of motor function. Familial MSTD patients generally manifest parkinsonism and eye movement abnormalities along with dementia (48–50), but extrapyramidal signs are not consistently present.

Microscopically, the gross cortical atrophy and microscopic neuronal loss and gliosis with upper cortical vacuolation in the frontal and temporal lobes are similar to that of most FTDs. Immunohistochemically, the tau deposits in both neurons and glia (including astrocytes and oligodendroglial cells), the increased density of inclusions in deep gray and subcortical white matter, and the distribution of the pathology in the subcortical gray matter are similar to the N279K mutation tauopathy (37, 59), familial PSG (43), PPND (38, 39), PSP (6–18), and CBGD (6–18). Clinically, these disorders present with frontal lobe dementia, parkinsonism, or both (22–24, 28, 29, 33, 34, 36, 37, 46, 48–50). At least half of the frontotemporal dementias related to tau are familial, generally having an earlier age of onset than the non-familial dementias (22–24, 28, 29, 33, 34, 36, 48, 49). Our patient's relatively late age of onset (75 yr) is consistent with the non-familial nature of her disease. She had frontal lobe symptoms (including abnormalities in behavior, personality, and executive functions), but never developed parkinsonian symptoms, eye movement abnormalities, or other disturbances of motor function. Familial MSTD patients generally manifest parkinsonism and eye movement abnormalities along with dementia (48–50), but extrapyramidal signs are not consistently present.

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Approximately 20 tau mutations have been identified in the familial tauopathies to date. Some are missense mutations and some are intronic; some are in or near exon 10 and others are in exons 9, 12, and 13 (22, 25–27, 30–32, 36–40, 43–51). Most of these mutations alter the ability of tau to interact with microtubules (59–71). Tau is a microtubule-associated protein that promotes polymerization of tubulin into microtubules and acts to stabilize these structures (1, 4, 5, 21). Normally 6 isoforms of tau protein are produced by alternative splicing of the gene (1, 4, 5, 21). Recently, several authors have found that mutations in exon 10 and adjacent regions reduce the ability of tau to interact with microtubules, probably by influencing the splicing of exon 10 (22, 25, 27, 30–32, 36–40, 43–51). This results in neuronal and glial inclusions (8, 27) that are composed predominantly of 4R isoforms, and alters the ratio of 3R to 4R tau isoforms, which may be crucial to the proper functioning of tau (21, 22). Proof for this idea lies in the fact that some tauopathies, such as Pick disease (4, 5, 7, 9, 20), have an increased ratio of 3R to 4R isoforms, while others, like FMSTD (5, 50), familial PSG (43), PPND (38, 39), FTD-Kumamoto (51), and others measured 20–30 nm. Most of the filaments seen in 4R FTDs have a similar diameter. The filaments have irregular twists in some cases while in others, as in this case, they are straight (1, 4, 5, 8, 9, 21, 37, 48–50, 60) (Table 2). The dense sheaves of straight filaments seen ultrastructurally also appear unique and may correspond to the dense globular inclusions seen at the light microscopic level. Because only filamentous aggregates and not globular inclusions were present in immunogold EM preparations, the globular inclusions may in fact be composed ultrastructurally of filaments. An alternative possibility is that only filamentous aggregates and not globular inclusions were present in immunogold EM preparations.

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and N279K tauopathy (37, 59), have an increased ratio of 4R to 3R isoforms. Still others, like AD, Niemann-Pick type C, and the disorder in Seattle family A appear to have a mixture of 3R and 4R forms (4, 5, 20, 41, 42). Similar pathology, however, is found in PSP (5, 7, 9, 11, 12, 20) and CBGD (5, 7, 9, 12, 20), which are usually sporadic, although familial forms have recently been described (16, 18, 72, 73). The biochemistry of the sarkosyl-insoluble tau in this case, like in PSP, CBGD, the N279K mutation tauopathy, and familial MSTD, consists of 2 major bands of 64 and 68 kDa containing all three 4R isoforms. The tau pathology in this case, therefore, can be classified as type 3 described by Goedert (1) and by Spillantini et al (48). The type 3 tauopathies include PSP, CBGD, FMSTD, PPND, familial PSG, Duke family 1684 and Dutch family 1, disorders in which immunoblotting reveals 64 and 68 kDa bands consisting predominantly of 4R tau (1, 48) (Table 2). In the present case, no tau mutation was identified in exons 9–13 or in the intronic regions adjacent to these exons, and there was no family history of a similar disorder. Clinically, this case differed from FMSTD because the patient presented at a late age with no family history, and she had no parkinsonism or other movement abnormalities. Given the neuropathologic similarities to FMSTD, as well as the biochemical similarities to PSP, CBGD, and FMSTD, we have designated this case “sporadic multiple system tauopathy with dementia.” Because only regions with previously identified tau mutations were sequenced, there remains the theoretical possibility, although certainly small, that an undiscovered tau mutation is responsible for this disorder.

Recent publications have shown that PSP and CBGD more commonly have the H1/H1 extended tau haplotype, while H1/H2 is more common in the general population (10, 13, 17). This patient had the H1/H2 haplotype. While this does not rule out the possibility that the present case represents a variant of PSP, the pathologic features favor an alternative diagnosis.

This case is unique because of the distinctive globular tau-positive neuronal and glial inclusions in gray and white matter, the absence of tau-positive grains or threads, and the distribution of the pathology. While particularly similar to familial MSTD and PSP, precise classification into any previously described disorder is difficult. The constellation of clinicopathologic findings suggests designation of this neurodegenerative disorder as sporadic multiple system tauopathy with dementia, adding a new profile to the spectrum of tauopathies.
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