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ORIGINAL ARTICLE

Atypical Progressive Supranuclear Palsy With Corticospinal Tract Degeneration

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Abstract

Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), sporadic multisystem tauopathy, and some forms of frontotemporal dementia with Parkinsonism linked to chromosome 17 are characterized by neuronal and glial lesions accumulating tau protein containing 4 conserved repeats in microtubule-binding domain (4R tau). Corticospinal tract degeneration is not a common feature of 4R tauopathies. Our objective was to describe 12 cases with pathologic features similar to those of PSP but with prominent corticospinal tract degeneration. We reviewed the historical records and neuropathologic evaluation using standardized sampling, immunohistochemistry, semiquantitative analysis, image analysis, and electron microscopy. The mean age at onset and illness duration was 71 and 5.7 years, respectively. Eight cases were female. Eleven cases had clinical evidence of prominent upper motor neuron disease plus extrapyramidal features. There was focal parasagittal cortical atrophy involving motor cortex and degeneration of corticospinal tract with sparing of lower motor neurons like in primary lateral sclerosis. Prominent tau pathology was found in oligodendrocytes in motor cortex, subjacent white matter, and corticospinal tract characterized by globular cytoplasmic filamentous inclusions that were immunoreactive for 4R tau. The clinicopathologic features of these 12 cases expand the spectrum of 4R tauopathies.

Key Words: Corticospinal tract, Electron microscopy, Immunohistochemistry, Microglia, Oligodendroglia, Progressive supranuclear palsy, Tauopathy.

INTRODUCTION

Some mid to late life neurodegenerative disorders are characterized by fibrillary cytoplasmic inclusions within neurons and glia. Recent biochemical studies have identified abnormally phosphorylated tau as a major component of the inclusions in a subgroup of these disorders, leading to their classification as "tauopathies" (1). Tauopathies with lesions composed of tau protein with 4 30 to 32 amino acid-conserved repeats in the microtubule-binding domain (4R tau) are known as 4R tauopathies (2). Differentiation of 4R tauopathies into specific disease entities is based on the histopathologic characteristics of the inclusions, the distribution of the lesions, and associated distribution of neuronal loss, gliosis, and other pathologic features. Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), sporadic multisystem tauopathy, and some forms of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) are 4R tauopathies (3–6). Other tauopathies include Pick disease, a 3-repeat (3R) tauopathy (3), and Alzheimer disease (AD), in which an equal mixture 3R tau and 4R tau accumulates (7). In Pick disease and AD, most of the tau pathology is within neurons, whereas in the 4R tauopathies, the intracellular inclusions are found in both neurons and glia, including both astrocytic and oligodendroglial lesions (3–6, 8, 9).

In the present report, 12 cases of a 4R tauopathy with tau-immunoreactive globular lesions in oligodendroglia, but with corticospinal tract degeneration, are described. The clinical and pathologic features of these cases are summarized and compared with all other major 4R tauopathies.

MATERIALS AND METHODS

Case Material

From a series of 405 cases submitted to the Society for Progressive Supranuclear Palsy (SPSP) Brain Bank from 1998 to August 2004 (10), of which 289 have been pathologically diagnosed as having PSP, 9 cases were identified. The brains were either donated to the SPSP Brain Bank at the time of death (given an antemortem diagnosis of PSP) or were sent to the SPSP Brain Bank after pathologic examination elsewhere suggested a histologic diagnosis of PSP. One case came from the State of Florida Brain Bank, another from Mayo Clinic Jacksonville, and the twelfth case from the Mayo Alzheimer's Disease Research Center in Rochester, Minnesota.

Quantitative analyses of the corticospinal tract at the level of the medullary pyramid was performed on 10 of the

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12 cases and compared with 10 cases of pathologically typical PSP matched for age (cases: 78.6 ± 8.1 years; controls: 78.4 ± 9.3 years) and sex (3 men and 7 women).

Pathologic Methods

The left hemisphere of each brain was fixed (except case 4 slides only and case12 both hemispheres were fixed) in formalin and tissue blocks were taken from representative areas, including the neocortex (middle frontal, superior temporal, inferior parietal, pre- and postcentral gyri, superior frontal and cingulate, and visual), hippocampus (anterior and posterior levels), basal forebrain, basal ganglia, thalamus, midbrain, pons, medulla, and cerebellum (including dentate nucleus and vermis). Sections were embedded in paraffin, cut at a thickness of 5 μm, and stained with hematoxylin and eosin (H&E), thioflavin-S, Gallyas-Braak, and Luxol fast blue (LFB) methods for histologic examination. The degree of neuronal loss and corticospinal tract degeneration was semiquantitatively evaluated for select brain regions and graded as follows: 0 = absent, 1+ = mild, 2+ = moderate, and 3+ = severe.

Immunohistochemistry and Antibodies

The paraffin-embedded sections were immunostained using the following primary antibodies: anti-tau (CP13, monoclonal, mouse, 1:100; donated by Dr. Peter Davies, Albert Einstein College of Medicine, Bronx, NY), anti-3-repeat tau (RD03 (11), monoclonal, mouse, 1:100 (donated by Dr. R de Silva, University College London, London, U.K.), anti-4-repeat tau (ET3 (5), monoclonal, mouse, 1:25 (donated by Dr. Peter Davies, Albert Einstein College of Medicine, Bronx, NY), anti-ubiquitin (Ubi1, monoclonal, mouse, 1:3000; EnCor Biotechnology, Alachua, FL), anti-α-synuclein (NACP (12), polyclonal rabbit, 1:1000); anti-PrP (3F4, monoclonal, mouse, 1: 200; DAKO, Carpinteria, CA); α-internexin (Mab 2E3, 1:2000; EnCor Biotechnology, Alachua, FL); αB-crystallin (polyclonal, rabbit, 1:500; Novocastra, Newcastle, U.K.); anti-HLA-DR (LN-3, monoclonal, mouse, 1:10; ICN Biomedicals, Costa Mesa, CA), and anti-CD68 (KP1, CD68, monoclonal, mouse, 1:250; DAKO, Burlingame, CA). Immunolabeling was detected using the avidin-biotinylated HRP complex (ABC) method (Elite Kit; Vector) and visualized with diaminobenzidine (DAB) and 0.03% H_2O_2. The sections were counterstained with hematoxylin. Sections routinely had pretreatment in a steam bath for 30 minutes. For some antibodies (RD03, ET3, NACP, and 3F4), sections were also pretreated with 95% formic acid for 30 minutes and microwaved for 10 minutes. The degree of CP13-positive structures was semiquantitatively evaluated for brain regions and graded as follows: 0 = absent, 1+ = mild, 2+ = moderate, and 3+ = severe.

Image Analysis

In 10 cases and 10 controls of PSP with typical clinical and pathologic features, the medulla was immunostained with KP1, a marker for activated macrophages, as a means to assess the severity of Wallerian degeneration. The total area of the medullary pyramid was assessed with stereology software package (Stereologer; Systems Planning and Analysis, Inc., Alexandria, VA) on a Leitz microscope equipped with a motorized stage driver. The area of the pyramid was expressed as the number of fields to cover the entire pyramid, which was defined by the user. The burden of KP1 immunoreactivity was assessed in the 3 randomly selected nonoverlapping fields and expressed as a ratio of immunoreactive pixels to total pixels in the 3 fields.

Immunoelectron Microscopy

Small pieces of tissues were removed from the gray and white matter junction of the motor cortex of one case (case 2) and dehydrated in 30%, 50%, 70%, and 90% EtOH for 10 minutes each infiltrated with 1:1 and 1:2 ratio of 90% EtOH: LR White for 20 and 40 minutes, respectively, followed by pure LR White for 1 hour and overnight at room temperature. The tissues were embedded in BEEM capsules, capped, and polymerized in a vacuum oven at 50°C for 2 days. Immunogold labeling was performed according to previous published methods (13).

Genetic Analysis

The gene for tau, *MAPT*, was screened for mutations in all 12 cases as previously described (14). Exons 1–5, 7, and 9–13 were amplified and directly sequenced. Primers from the intronic sequences surrounding the exons were used so that the entire exon sequence and the splice signals could be analyzed. Standard amplification reactions were done with 50 ng of genomic DNA, and the amplified products were then gel-purified. Asymmetric amplification using the DTCS Quick Start Kit (Beckman Coulter, Fullerton, CA) was performed. The amplified products were precipitated and resuspended in sample loading solution and loaded onto a CEQ 200XL DNA Analysis System (Beckman Coulter). The sequences were compared with those of normal controls and with the published MAPT sequence.

RESULTS

Clinical Features

The clinical features of all 12 cases are summarized in Table 1. The mean age of onset was 71 years (range, 58–85 years) with mean duration of illness 5.7 years (range, 3–12 years). Eight of the 12 cases were female.

In 6 cases, the presenting symptom was asymmetric in onset, mainly with difficulty with the use of a hand, often the right hand; in one case (case 12), onset began in the leg. In 3 cases, the initial presenting symptom was falls; in 2 cases, it was cognitive impairment; and one initially experienced photosensitivity. Prominent features noted in all cases (except case 9, which had limited data) were upper motor neuron signs, including spasticity, hyperreflexia, a Babinski sign, and upper motor neuron pattern of weakness. Other common features were Parkinsonism, with bradykinesia, rigidity, and postural instability. In only 2 cases was there upgaze and downgaze palsy. Limb apraxia occurred in 7 cases, being more severe in the limb with upper motor neuron findings. In 9 cases, the neurologic deficits were strikingly asymmetric with the most affected limb commonly described as "flexed

TABLE 1. Demographics and Clinical Features of the 12 Cases

Case	Sex	Age at Onset	Age at Death	DOI	Initial Symptoms	Prominent Parkinsonian Features	Pyramidal Tract Signs	Asymmetry	Other Pertinent Features	Clinical Diagnosis
1	F	65	69	4	Falls and difficulty using left hand	Axial and limb rigidity, hypophonia, bradykinesia, postural instability	Upper motor neuron pattern of weakness	+	Upgaze and downgaze palsy, cognitive impairment, dysphagia, limb apraxia, levodopa unresponsive	PSP
2	F	85	88	3	Slowness of movements	Hypomimia, limb rigidity, bradykinesia	Upper motor neuron pattern of weakness	−	Insomnia, mild neck flexor and mild bifacial weakness early falls, dysphagia, dysarthria	PSP versus PLS
3	F	80	85	5	Falls	Axial and limb rigidity, postural instability, bradykinesia	Upper motor neuron pattern of weakness, Babinski sign present (R)	+	Dysphagia, dysarthria, bradyphrenia, limb apraxia, personality change, levodopa unresponsive	PSP
4	F	63	69	6	Cognitive impairment (aphasia)	Limb rigidity, postural instability	Upper motor neuron pattern of weakness	+	Early falls, tongue thrusting movements, limb apraxia, mute, positive 14-3-3	CJD
5	F	69	75	6	Falls	Postural instability, hypomimia, limb rigidity	Upper motor neuron pattern of weakness, spasticity present	+	Executive dysfunction, hypomimia, urinary incontinence	PSP
6	F	74	80	6	Difficulty using the right hand (e.g. writing)	Hypomimia, postural instability, rigidity	Upper motor neuron pattern of weakness, spasticity present	+	Expressive aphasia, executive dysfunction, limb apraxia, dysarthria, levodopa unresponsive	CBS versus PLS
7	M	58	63	5	Light sensitivity	Axial limb rigidity, postural instability, bradykinesia	Upper motor neuron pattern of weakness, hyperactive tendon reflexes	−	Mild left ptosis dysarthria, diplopia, upgaze and downgaze palsy, cognitive impairment, retrocollis, levodopa unresponsive	PSP
8	M	64	76	12	Difficulty using the right hand (e.g. writing)	Postural instability bradykinesia	Upper motor neuron pattern of weakness	+	Falls, limb apraxia and dystonia, levodopa unresponsive, personality change	PSP
9	F	77	84	7	Cognitive impairment	NA	Upper motor neuron pattern of weakness	NA	Executive dysfunction, personality change	AD
10	F	79	83	4	Difficulty using the right hand (e.g. writing)	Hypomimia, limb rigidity, bradykinesia	None	+	Dysarthria, limb apraxia, dystonia, levodopa unresponsive	CBS
11	M	73	77	4	Difficulty using right hand with right hand weakness	Limb rigidity	Upper motor neuron pattern of weakness, spasticity present	+	Mild right facial weakness, dysphagia	PLS
12	M	69	75	6	Difficulty with left leg movements	Limb rigidity, postural instability, hypomimia, bradykinesia	Spasticity, hyperactive tendon reflexes, Babinski sign present (L)	+	Few falls, levodopa unresponsive	CBS

DOI, duration of illness; PSP, progressive supranuclear palsy; AD, Alzheimer disease; CBS, corticobasal syndrome; PLS, primary lateral sclerosis; asymmetry, cases in which parkinsonism and pyramidal tract signs were asymmetric; NA, data not available; (R), right; (L), left.

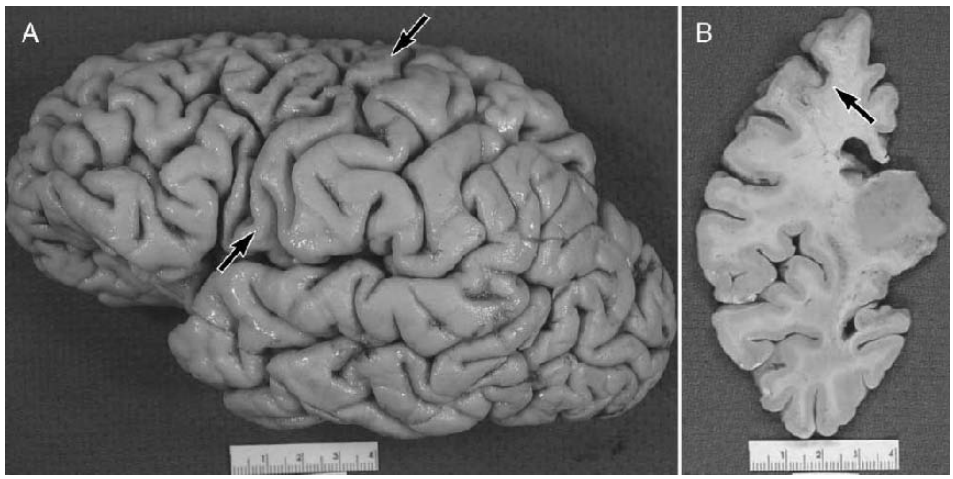

FIGURE 1. **(A)** External examination of the brain reveals cortical atrophy in the superior frontal, especially the premotor cortex, and in the pre- and postcentral gyri (precentral gyrus indicated by arrows). **(B)** The coronal section demonstrates thinning of the cortical ribbon (arrow) (case 5).

and useless," "flexed with dystonic posturing," or "fixed and stiff." No lower motor neuron features were described.

The most common clinical diagnoses were PSP, primary lateral sclerosis (PLS), and corticobasal syndrome. Treatment with levodopa/carbidopa was unsuccessful. In one case with a relatively rapid progressive course, Creutzfeldt-Jakob disease was diagnosed after 14–3–3 protein was positive in the cerebrospinal fluid (CSF). This patient had cognitive impairment for 4 years followed by a more rapid cognitive decline. When first evaluated elsewhere, 4 years after symptom onset, the combination of positive CSF 14–3–3 protein and the history of a more rapid cognitive decline resulted in the patient being diagnosed with CJD. Family histories were negative for parkinsonian, motor neuron disease, or dementing illnesses.

Laboratory Testing

Laboratory studies, including complete blood counts, electrolytes, liver, renal, and thyroid function tests, autoimmune markers, and paraneoplastic antibodies were either normal or negative. CSF studies were normal with the exception of the 14–3–3 protein, which was positive in case 4. Electroencephalograms revealed only background slowing without epileptiform activity or periodic discharges. Electromyogram was completed in 5 cases (cases 2, 6, 8, 11, and 12) and did not reveal any evidence of lower motor neuron disease.

Head Imaging

Magnetic resonance imaging of the brain was completed in all 12 cases and demonstrated mainly mild generalized cerebral atrophy. Left posterior frontal, parietal, and medial temporal lobe atrophy was observed in case 4. In all cases, there was a nonspecific increase T2 signal in the subcortical white matter. [18F] Fluorodeoxyglucose positron emission tomography scan completed in case 10 demonstrated hypometabolism in the left parietal lobe and bilateral basal ganglia. Technetium-99 m-ethylcysteinate dimer (Tc ECD) single photon emission computed tomography completed in cases 6 and 12 revealed reduced tracer uptake in the posterior frontal regions parasagittally, slightly more on the left (case 6), and mid and posterior frontal lobes, slightly more on the right (case 12).

Neuropathologic Findings

Macroscopic Findings

The calculated mean total brain weight (the average of the sum of the brain weights of each hemisphere multiplied by 2 for each of the 12 cases) was 1,142 g (range, 940–1600 g). The sulci and gyri revealed circumscribed cortical atrophy that was most marked in the superior frontal gyrus with mild atrophy in the superior parietal lobule, but also affecting the precentral and motor cortex (cases 1, 5, 6, 8, 10, and 11). In these cases, the cortical atrophy was more marked in the dorsal parasagittal regions than the ventral regions (Fig. 1). Cases 3 and 9 had mild diffuse cortical atrophy over the convexity. Sequential coronal sections through the supratentorial tissues revealed the ventricular system to be mildly dilated, especially the frontal horn of the lateral ventricles (cases 1, 2, 5, 6, 9, 11, and 12). Narrowing of the cerebral cortex and atrophy of the subcortical white matter were observed in the superior frontal, precentral (cases 1, 3, 5, 6, 8, 10, and 11) (Fig. 1) and superior parietal gyrus (case 5). The hippocampal formation and amygdala were free of atrophy, except for case 3.

The basal ganglia, thalamus, and subthalamic nucleus showed no significant gross pathology. Sequential sections of the midbrain, pons, and medulla at right angles to the neuraxis were unremarkable, although almost all cases had discoloration of the cerebral peduncle. Cases 3, 5, 7, 9, 10, and 12 had slightly decreased pigmentation in the substantia nigra and locus ceruleus and the subthalamic nucleus was deemed slightly small in cases 3 and 7. The superior cerebellar peduncles were moderately atrophic in case 7 and mildly atrophic in case 8.

Microscopic Findings)

The microscopic findings and semiquantitative results are summarized in Table 2 and compared with 10 controls of typical PSP and 10 CBD cases. The microscopic features of all 12 cases were similar and are summarized subsequently with exceptions reported (Figs. 2–5).

TABLE 2. Pathologic Features of the 12 Cases Compared to Typical PSP and CBD

Features	Cases	PSP	CBD
N	12	10	10
Most prominent cortical atrophy	Motor and premotor	Mild prefrontal	Superior frontal, pre- and postcentral, superior parietal
BN	1+	0	3+
Neuronal loss			
GP	0	1+–3+	1+–2+
STN	0	2+–3+	0–1+
SN	1+	3+	1+–3+
NFTs and pretangles			
Motor	1+–2+	1+–2+	1+–3+
GP	1+	1+–2+	1+
STN	1+–2+	2+–3+	1+–3+
SN	1+–2+	2+–3+	2+–3+
Pontine n.	1+	2+–3+	0–1+
Dentate n.	1+	2+–3+	0–1+
Astrocytic lesions (tau/GB staining pattern)	Tufted astrocytes (+/−)	Tufted astrocytes (+/+)	Astrocytic plaques (+/+)
Oligodendrocytic lesions	Coiled bodies and globular inclusions	Many coiled bodies	Few coiled bodies
SCP atrophy	0	2+–3+	0–1+
CST degeneration	3+	0–1+	0–2+
Other pathology	AGD (90%)	AGD (20%)	AGD (40%)

PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; BN, ballooned neurons; BS, Braak NFT stage; GP, globus pallidus; STN, subthalamic nucleus; SN, substantia nigra; NFT, neurofibrillary tangles; CSTD, corticospinal tract degeneration; SCP, superior cerebellar peduncle atrophy; GB, Gallyas-Braak; AGD, argyrophilic grain disease; AD, Alzheimer disease.

Cerebral Cortex

There was focal cortical atrophy with thinning of the cortical ribbon, spongiosis, and dense fibrillary gliosis in the motor cortex. Betz cells were markedly decreased (Fig. 2). Mild to severe neuronal loss and gliosis was observed in the premotor and motor cortices as well as the postcentral gyrus (cases 2, 3, and 5), superior frontal gyrus, and superior parietal lobule (case 5). The affected cortices also had a few ballooned neurons (except for cases 3, 7, 8, 10, and 12), many tau-positive threads, coiled bodies, and globular oligodendroglial inclusions. A few tau-positive pretangles and astrocytic inclusions were also observed in affected cortices. The white matter beneath the affected cortex had rarefaction and slight vacuolation with scattered myelin figures, lipid-laden macrophages (Fig. 2), and reactive astrocytes. The LFB stain showed marked myelin loss. The tau immunostain revealed many threads, coiled bodies, and globular oligodendroglial inclusions at the gray–white junction (Fig. 2).

Hippocampus

The hippocampus, entorhinal cortex, and amygdala had preservation of neuronal populations in almost all cases; however, cases 3, 4, 5, and 10 had variable, usually mild neuronal loss and gliosis in the hippocampus. The entorhinal cortex had mild neuronal loss in layer II in cases 3, 9, and 10, which had concurrent AD. A few ballooned neurons were observed in the amygdala and entorhinal cortex in almost all cases. Tau immunostaining demonstrated many pretangles, threads, and some grains in the CA1 and subiculum of hippocampus, amygdala, and entorhinal cortex. Varying numbers of neurofibrillary tangles (NFTs) and more numerous pretangles were observed in the entorhinal cortex and hippocampus.

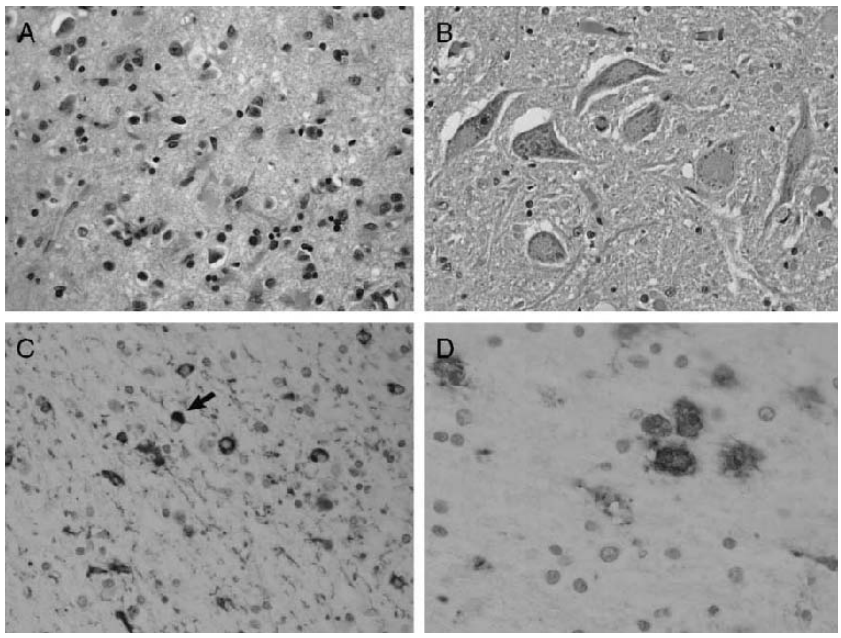

FIGURE 2. Motor neuron disease with brunt of the damage to upper motor neuron and sparing lower motor neuron. **(A)** Marked neuronal loss and gliosis in the motor cortex. **(B)** The hypoglossal nucleus is well populated and free of neuronal inclusions. **(C)** Many threads, coiled bodies, and globular oligodendroglial inclusions (arrow) are in the white matter beneath the motor cortex (phospho-tau immunostain). **(D)** Macrophages and activated microglia are present in the white matter beneath the motor cortex (HLA-DR immunostain).

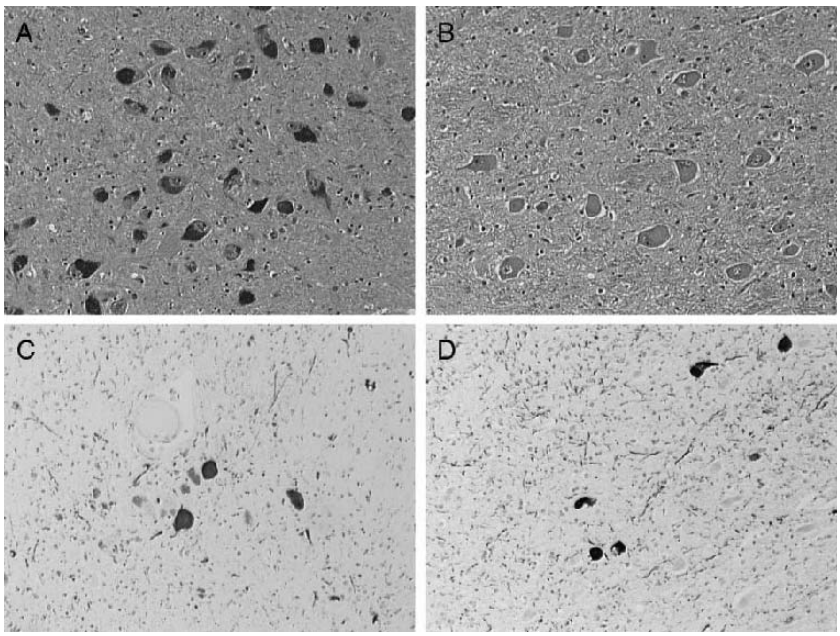

FIGURE 3. The cardinal nuclei affected in PSP are relatively spared. Minimal neuronal loss in the substantia nigra **(A)** and subthalamic nucleus **(B)**, whereas both nuclei show phospho-tau within mostly pretangles and threads (**[C]**, substantia nigra; **[D]**, subthalamic nucleus).

Subcortical Nuclei

The basal nucleus of Meynert had a normal neuronal population in most cases (except cases 3, 9, and 10) with only rare NFTs and more numerous tau-positive pretangles. The basal ganglia and thalamus had some tau-positive threads, coiled bodies, and globular oligodendroglial inclusions, as well as rare NFT and astrocytic inclusions. The subthalamic nucleus was free of neuronal loss and atrophy (Fig. 3), but had mild gliosis and a few NFTs, more numerous pretangles and threads (Fig. 3).

Internal Capsule

The genu of the internal capsule had fiber degeneration and many tau-positive threads, coiled bodies, and globular oligodendroglial inclusions. The LFB staining showed myelin loss in the corticospinal tract, and the macrophage stain showed many lipid-laden macrophages.

Brainstem and Cerebellum

The substantia nigra had only mild focal neuronal loss with extraneuronal pigment (Fig. 3), and a few NFT and pretangles (Fig. 3). When present, neuronal loss and gliosis tended to be more marked in the ventral and lateral tier of neurons. The cerebral peduncle had atrophy and tract degeneration in the middle third, with many tau-positive threads, coiled bodies, and globular oligodendroglial inclusions. LFB stains showed myelin pallor and myelin loss in the middle third of the cerebral peduncle (Fig. 4), and the macrophage stain showed lipid-laden macrophages and activated microglia. The midbrain tegmentum and tectum were unremarkable on H&E, but had tau-positive pretangles, threads and coiled bodies, and globular oligodendroglial inclusions. The oculomotor complex was evaluated in 10 of the 12 cases. With the exception of case7, tau pathology was mild. In case 7, tau deposition in the form of pretangles and NFT was marked, including many threads. The locus ceruleus was well populated. The raphe nucleus, locus ceruleus, and pontine and medullary reticular formation had some tau-positive pretangles and a few NFTs. The lower brainstem was remarkable for some tau-positive pretangles and a few NFTs in the pontine base and in the inferior olive.

The corticospinal tract in the pons and the medullary pyramids had moderate to marked fiber loss with myelin degeneration and lipid-laden macrophages on the HLA-DR and CD68 immunostains. The hypoglossal nucleus was well populated and free of neuronal inclusions (Fig. 2), except for isolated incidental colloid bodies. The cerebellar dentate nucleus was usually well populated but had a few threads and pretangles. There was grumose degeneration, mild to moderate loss of myelin fibers and dense fibrous gliosis of the superior cerebellar peduncle in only cases 7, 8, and 9.

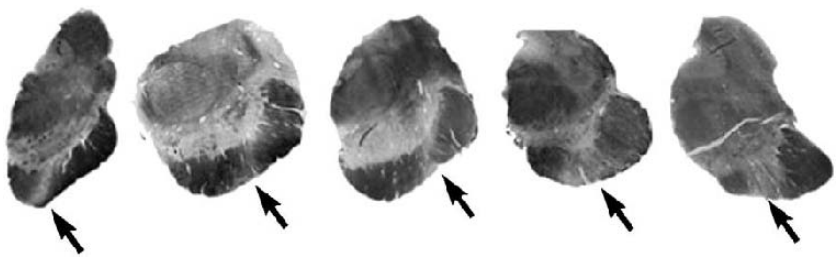

FIGURE 4. Myelin pallor (arrows) is seen in the middle third of cerebral peduncle corresponding to the distribution of the corticospinal tract. In a few cases (case 1), the myelin pallor was more marked in the medial third of the cerebral peduncle, corresponding to frontopontine fiber tract. Midbrain of cases 1 to 5 (left to right). Luxol fast blue stain (×2).

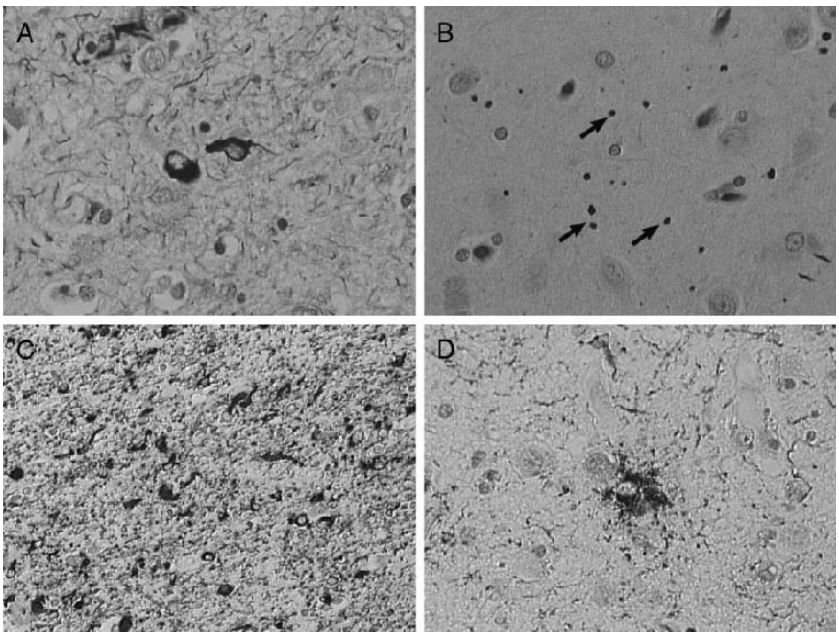

FIGURE 5. The cases displayed a range of tau pathology, including **(A)** oligodendroglial coiled bodies and globular inclusions (Gallyas stain), **(B)** argyrophilic grains (arrows) in the medial temporal lobe (Gallyas), **(C)** threads and glial lesions (phospho-tau), and **(D)** tufted astrocyte (phospho-tau).

Other Findings

Thioflavin-S fluorescent microscopy revealed varying degrees of Alzheimer-type pathology with mostly senile plaques and a few NFTs. Only 3 cases had a Braak neurofibrillary tangle stage of IV or more and were diagnosed as having concurrent Alzheimer disease based on NIA-Reagan criteria (15).

The cases displayed a range of tau pathologies (Fig. 5). There were tau-positive threads, coiled bodies, globular oligodendroglial inclusions, grains, and NFTs that were argyrophilic on the Gallyas-Braak stain, but both pretangles and astroglial inclusions were mostly negative with silver stains. A monoclonal antibody specific to 4R tau, ET3, immunostained the range of lesions detected with the phospho-tau antibody, except for some NFTs, especially in cases with concurrent Alzheimer-type pathology. A monoclonal antibody specific to 3R tau, RD03, immunostained only a few NFTs in the limbic area of the cases with concurrent Alzheimer-type pathology. A polyclonal antibody to ubiquitin stained a few limbic NFTs but failed to detect most of the neuronal and glial lesions.

A polyclonal antibody to alpha-synuclein immunostained a few Lewy bodies in the amygdala and dorsal motor nucleus of the vagus in one case (case 3). No pathologic prion protein-immunoreactive structures were observed. The polyclonal antibody to αB-crystallin immunostained not only sparse ballooned neurons in the limbic lobe and cortex of some cases reported here, but also a few astrocytes in affected regions. The α-internexin immunostain did not reveal any neuronal inclusions. There were no astrocytic plaques and none of the cases had inclusions or an immunohistochemical profile similar to those described in neuronal intermediate filament inclusion disease (16). Image analysis demonstrated that the medullary pyramids were 22% smaller with more than twice the microglial density than in typical PSP cases matched for age and sex (Table 3).

At the electron microscopic level, the oligodendroglial lesions were cytoplasmic aggregates of filaments and granular material that displaced cytoplasmic organelles (Fig. 6). They were present in cells that had nuclear features consistent with oligodendroglia. The filaments were immunolabeled with phospho-tau and 4R tau antibodies and varied in thickness but were approximately 15 to 18 nm in diameter and straight (Fig. 6). Screening for mutations in the tau gene within exons 1–5, 7, and 9–13 as well as the intronic sequences surrounding the exons was negative in all 12 cases.

DISCUSSION

The pathologic features of these 12 cases do not exactly fit into any current pathologic criteria or recognized form of 4R tauopathy (17). The globular oligodendroglial inclusions are similar only to those reported in the few cases of sporadic multisystem tauopathy (4, 18, 19); however, corticospinal tract degeneration has not been described in multisystem tauopathy.

There are clinical features of our cases that overlap with clinical features of PLS, PSP, and CBD. PSP is a relatively symmetric disease characterized by early falls, vertical (upgaze and downgaze) supranuclear gaze palsy, axial more than appendicular rigidity, bradykinesia, and a

TABLE 3. Image Analysis of Macrophages in Medullary Pyramid

	Cases (n = 10)	Progressive Supranuclear Palsy Controls (n = 10)
Area of medullary pyramid	26.3 ± 2.4	33.6 ± 1.9*
Macrophage burden (x100)	4.1 ± 0.4	1.8 ± 0.2†

*, $p < 0.05$.
†, $p < 0.001$.

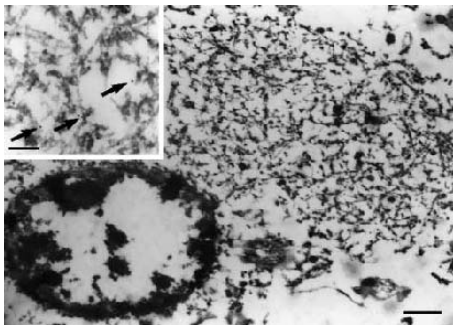

FIGURE 6. Electron micrograph of an oligodendrocyte showing an eccentric nucleus (N) with characteristic dense chromatin on the inner nuclear membrane. The cytoplasm is filled with filaments and granular material. Scale bar = 1 μm. Inset, immunogold labeling using tau antibody CP13. Gold

lack of significant clinical response to levodopa treatment (20, 21). Similarities to PSP included Parkinsonism, absent response to levodopa therapy, early unexplained falls in a few cases, and photosensitivity in one case (20–22). None of our 12 cases, with the exception of possibly case 7, would have satisfied the criteria for possible or probable PSP using either the NINDS clinical research criteria (21) or any of the other widely used criteria for PSP (22–25). One of the cardinal features of PSP is vertical, particularly downgaze, palsy (22, 26). In only 2 of our patients (cases 1 and 7) was there a report of downgaze palsy. Upgaze palsy, on the other hand, is much less specific and occurs quite commonly in this age range of patients. The biggest clinical difference between our cases and PSP was the prominence of asymmetric upper motor neuron features. Apraxia was present in 7 of the 12 cases. Apraxia and asymmetric rigidity are typical features of CBD (27), and many of our cases seem superficially to fit the loose criteria for corticobasal syndrome (28). Again, the most remarkable finding in most of our cases was upper motor neuron pattern weakness, less so Babinski sign and spasticity; characteristics of PLS (29, 30) and not corticobasal syndrome. Furthermore, corticobasal syndrome is characterized by prominent cortical abnormalities, including agraphesthesia, astereognosis, and alien limb phenomena, features not reported in any of our 12 cases.

Although upper motor neuron findings without lower motor neuron disease is characteristic of PLS (30), asymmetric PLS is much less common, and predominant and early upper motor neuron findings affecting just one limb as a feature of PLS is very rare. In addition, the prominent and early parkinsonian features that accompanied the upper motor neuron signs and symptoms of our cases are not in keeping with a diagnosis of PLS (30).

Finally, in the few reported cases of sporadic multisystem tauopathy (4, 18, 19), the clinical presenting syndrome and clinical course was in keeping with frontotemporal lobar degeneration (31) and is very different from the clinical features of these 12 cases.

Pathologically, all cases had cortical atrophy of the precentral gyrus and the corticospinal tract, as well as neuronal loss with gliosis in the motor cortex. There was also degeneration in the corticospinal pathway from the motor cortex to internal capsule and cerebral peduncle to the level of the medullary pyramids. In these areas, myelin and axonal loss were accompanied by positive lipid-laden macrophages consistent with Wallerian degeneration. Image analysis demonstrated pyramidal atrophy and increased macrophages in the pyramid compared with typical PSP cases. The lower motor neurons in the brainstem were preserved. The pathologic findings in upper motor neurons and corticospinal tract are similar to those in PLS (30), and they correlate with clinical evidence of limb weakness and pyramidal signs. On the other hand, there have been no reports in the medical literature of PLS with tau pathology, like in the present cases.

Immunohistochemically, the cases were studied with 3R and 4R anti-tau antibodies and found to have tau-immunoreactive neuronal, astrocytic, and oligodendroglial lesions that were positive for 4R, but not 3R tau. These findings are characteristic of the 4R tauopathies, including PSP, CBD, AGD, and multisystem tauopathy (2–6). Table 2 provides a pathologic comparison of the 12 cases with controls of typical PSP and CBD. Similarities to typical PSP were the findings of tau-positive neuronal inclusions in the globus pallidus, subthalamic nucleus, substantia nigra, and pontine nuclei, and the tau-positive astrocytes found in the affected brain regions superficially resembling the tufted astrocytes of PSP. On the other hand, the pathologic findings were somewhat inconsistent with a diagnosis of PSP (32). In particular, there was minimal neuronal loss and gliosis in the cardinal nuclei–globus pallidus, subthalamic nucleus, and substantia nigra. Moreover, atrophy of the superior cerebellar peduncle and grumose degeneration in the dentate nucleus of cerebellum, frequently observed features in PSP (33, 34), were absent in almost all 12 cases. The biggest difference from typical PSP, however, was the fact that typical cases of PSP do not have overt degeneration of the corticospinal tract, although they often have subtle evidence of motor system degeneration, especially evident with microglial/macrophage stains (35).

A separate category designed for cases that do not meet criteria for PSP is that of "atypical PSP" (32). This designation is meant to apply to cases that histologically resemble PSP, but in which the distribution or density of lesions is atypical. The features of these 12 cases do not exactly fit these criteria, because globular oligodendroglial inclusions and corticospinal tract degeneration are not features of atypical PSP. Nevertheless, this category best encapsulates the pathologic features of these 12 cases, and therefore we chose to consider them as atypical PSP. In our experience, which includes detailed histologic analysis of almost 300 cases of pathologically confirmed PSP received through the SPSP Brain Bank, at Mayo Clinic Jacksonville, cases with PSP pathology such as this are rare (<4%).

The presence of tau-positive pretangles, threads, and a few ballooned neurons in the affected cortex and subcortical white matter is reminiscent of CBD (36, 37); however, the

density and distribution of thread-like pathology was far less than in CBD. Furthermore, astrocytic plaques were not present and oligodendroglial coiled bodies were far more numerous than in CBD. Globular oligodendroglial inclusions are not typical of CBD (36). Increasingly, ballooned neurons are considered to lack diagnostic specificity, especially when limited to the limbic lobe (5, 36, 37).

The thread-like pathology and gliosis was particularly dense at the gray–white junction of affected cortices, reminiscent of changes described in progressive subcortical gliosis (38). Although familial cases of progressive subcortical gliosis have been shown to be the result of mutations in the gene for tau (39), none of the present cases had a MAPT mutation. Linkage to a novel mutation in the tau gene has been described in a large family with parkinsonism–ALS and dementia. In that family, however, the affected members had lower motor neuron disease with fasciculations and muscle atrophy (40). Features of PLS were not described in that family and none of our cases had lower motor neuron disease.

One of the most distinctive pathologic features in the present cases was tau-positive globular oligodendroglial inclusions. Globular oligodendroglial inclusions were composed of 4R tau and at the electron microscopic level contained granule-coated filaments approximately 15-nm in diameter, similar to filaments in other 4R tauopathies (41, 42). Inclusions of this type have not been emphasized in PSP, CBD, PLS, or AGD, but they have been described in reports of sporadic multisystem tauopathy (4, 18, 19). As noted previously, however, corticospinal tract degeneration has not been described in sporadic multisystem tauopathy, and all reported cases of multisystem tauopathy have had severe frontotemporal atrophy consistent with frontotemporal lobar degeneration.

In addition to the prominent tau pathology in the corticospinal tract, almost all cases had medial temporal tauopathy consistent with AGD and varying degree of Alzheimer-type pathology. This is not surprising because AGD and Alzheimer-type pathology are commonly found in aged individuals, and AGD is more frequently associated with other 4R tauopathies (6) than other neurodegenerative disorders (43). Only one of the 12 cases had Lewy bodies, which was found in one of the 3 cases with concurrent AD. This case did not have any features of dementia with Lewy bodies, including hallucinations, fluctuating mental status, or rapid eye movement sleep behavior disorder. However, the frequency of Lewy bodies in normal people over the age of 60 years (incidental Lewy body disease) is 8% to 12% (44) and the frequency of Lewy bodies in cases of typical PSP is approximately 12% (45). Because of the lack of clinical correlates, and a similar frequency to incidental Lewy body disease, we speculate that the findings in case 3 represent incidental Lewy body disease.

In summary, these 12 cases expand the spectrum of 4R tauopathies. They are characterized by globular oligodendroglial inclusions, corticospinal tract degeneration, and some overlapping clinical and histologic features of PSP, CBD, multisystem tauopathy, and PLS. Although they do not fit into any currently defined pathological or genetic diagnostic category, most of the pathologic features seem to overlap with PSP. We have therefore chosen to categorize these cases as atypical PSP. Future molecular studies may provide the means to further subclassify the 4R tauopathies.

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