Progressive Supranuclear Palsy with Dementia: Cortical Pathology

EILEEN H. BIGIO, MD, DANIEL F. BROWN, MD, and CHARLES L. WHITE III, MD

Abstract. Patients with progressive supranuclear palsy (PSP) often develop dementia, and cortical pathology has been documented in PSP. However, there are no reports correlating dementia in PSP with cortical pathology. We hypothesized that cases of PSP presenting with cognitive impairment would have more severe cortical tau pathology than those without. We compared 7 cases of PSP presenting with cognitive deficits (group 1) with 4 cases of PSP that did not (group 2). The subcortical tau pathology was almost identical in both groups. The cortical tau pathology was strikingly different in group 1, in which it was on average moderate, compared with group 2, in which it was minimal. The accumulation of cortical neurofibrillary pathology is central to the onset of dementia in PSP.

Key Words: Alzheimer disease; Cortical; Dementia; Pathology; Subcortical; Supranuclear palsy; Progressive; Tau.

INTRODUCTION

Eighty-two percent (114 of 139) of the brain autopsies of demented patients from the Alzheimer Disease Center (ADC) at UT Southwestern Medical Center at Dallas have had neuropathologically confirmed Alzheimer disease (AD), a percentage similar to that of other institutions (1, 2). The remaining 25 cases have a variety of diagnoses, including 4 (16% of the non-Alzheimer diagnoses) with neuropathologically proven progressive supranuclear palsy (PSP). We retrieved 7 other non-ADC cases of PSP from our files. Of our total of 11 cases of PSP, 7 had dementia.

The surprising number of PSP cases we encountered that presented with cognitive impairment gave us the opportunity to investigate whether there were any histopathologic differences between these 7 cases of PSP with dementia and the 4 without. The dementia in PSP is often ascribed to subcortical pathology (3–5). However, the severity of the subcortical pathology in the 7 demented patients was not significantly different from that of the 4 nondemented patients. Cortical tangles, and in particular, tau pathology, is considered by many to be intrinsic to the constellation of histologic abnormalities in the brains of those with PSP (6–18). We hypothesized that there might be a difference in the severity of cortical tau pathology between these groups of PSP cases, which might account for this difference in clinical presentation.

Table 1

We divided our cases of PSP into 2 groups. Group 1 consisted of 7 cases presenting with cognitive impairment. The ages of these patients at death ranged from 70–85, with an average age at death of 78, and average disease duration of 6.9 years. Ages at onset ranged from 62 to 79, with an average age of onset of 71. All 7 patients presented with some degree of cognitive deficit, and all 7 were ultimately frankly demented. Six of them (cases 1–6) presented with difficulty with attention or immediate memory and the other presented with linguistic deficits (case 7). Two of these cases were diagnosed with "dementia" at presentation (cases 2 and 6). The other 5 experienced progression of their cognitive deficits and were diagnosed as demented later in their course (cases 1, 3–5, and 7). In 2 of the 7 cases, there were motor, pseudobulbar, or extrapyramidal signs at presentation (cases 1 and 5) and the remaining 5 (cases 2–4, 6, and 7) developed them later in their course.

Initially, we included 2 additional cases in group 1. Although the subcortical pathology in these 2 cases fit the pathologic diagnosis of PSP, they had more extensive cortical tau pathology and occasional glial plaques and balloononed neurons. These features enabled us to reclassify the 2 cases as corticobasal ganglionic degeneration (CBGD) and omit them from the study.

Group 2 consisted of 4 patients with PSP who did not present with cognitive impairment. Their ages at death ranged from 61–76, with an average age at death of 67. Disease duration could not be determined from the clinical records of case 9. The average disease duration of cases 8, 10, and 11 was 4.3 years. Ages at onset of these 3 patients ranged from 59 to 70, with an average age of onset of 63. Case 9, in whom disease duration was not known, died at age 63. All 4 presented with motor, pseudobulbar, or extrapyramidal signs. One patient in group 2 (case 10) later developed memory problems and linguistic deficits, the other 3 remained cognitively intact at death. A confident antemortem clinical diagnosis of PSP was made in only 2 cases, 1 from group 1 (case 3), and 1 from group 2 (case 8). The most frequent clinical diagnosis in this study was AD + Parkinson disease (PD), made in 3 cases (cases 2, 4, and 6). The NINCDS clinical diagnoses of the other 6 cases by the time of death were: PSP vs possible AD (case 10), PD vs PSP (case 9),
TABLE 1
Cases: Order of Onset of Clinical Signs

<table>
<thead>
<tr>
<th>Case</th>
<th>O.</th>
<th>D.</th>
<th>Dur</th>
<th>A/M</th>
<th>LD</th>
<th>Dem</th>
<th>Beh</th>
<th>Dep</th>
<th>Eye</th>
<th>Dys</th>
<th>B/T</th>
<th>Gait</th>
<th>Falls</th>
<th>Rig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>62</td>
<td>70</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>N + PR PaD</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>78</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
<td>3</td>
<td>AD + PaD</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>71</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>PSP</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>75</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>AD + PaD</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>81</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>Bins. D</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>79</td>
<td>84</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
<td>2</td>
<td>3</td>
<td>AD + PaD</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>85</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>C/AD/PSP</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>61</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>PSP</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>?</td>
<td>63</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>PaD/PSP</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>66</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>PSP/PO AD</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>76</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>PaD</td>
<td></td>
</tr>
</tbody>
</table>

Clinical diagnosis

Abbreviations: O. = onset, D. = death, Pseudobulb. = pseudobulbar signs, Dur = duration (years), A/M = deficits in attention or memory, LD = linguistic deficits, Dem = dementia, Beh = behavior problems, FS = frontal signs, Dep = depression, Eye = eye movement abnormalities, Dys = dysarthria/dysphagia, B/T = bradykinesia/tremor, Rig = rigidity, Clin Dx = clinical diagnosis, AD + PaD = Alzheimer disease + Parkinson disease, N + PR PaD = normal pressure hydrocephalus + Parkinson disease. Bins. D =Binswanger disease, C/AD/PSP = Corticobasal ganglionic degeneration vs AD vs PSP, PaD/PSP = Parkinson disease vs PSP, PSP/PO AD = PSP vs possible AD, PaD = Parkinson disease.

Note: Numbers refer to the order of onset of symptoms. e.g. a symptom given a “1” was noted at the time of clinical presentation, “2” developed later in the course, and so on.

corticobasal ganglionic degeneration vs AD vs PSP (case 7), PaD (case 11), normal pressure hydrocephalus + probable PaD (case 1), and Binswanger disease (case 5).

MATERIALS AND METHODS

We evaluated the 11 cases using hematoxylin & eosin stain for routine examination of neocortex (frontal, temporal, and parietal lobes), basal ganglia, thalamus and subthalamic nucleus, cerebellum, and brainstem (3 levels: midbrain, pons, and medulla, in most cases), and used fluorescent thioflavin-S preparations to evaluate the cases for AD pathology. Two neuropathologists independently evaluated and semiquantitated neuritic plaques and neurofibrillary tangles and classified them according to CERAD (Center to Establish a Registry for Alzheimer Disease) (19), Khachaturian (20), and Braak (21–25) criteria. The pathologic diagnosis of PSP was made in all cases by finding globular neurofibrillary tangles and neuritic threads in pertinent subcortical regions (substantia nigra, basal ganglia, subthalamic nucleus, pons) and cerebellum with either silver stains or immunostain for tau, and tufted astrocytes with tau staining, according to revised preliminary NINDS criteria (26).

In all cases, we used sections of frontal lobe to evaluate cortical tau pathology, because frontal lobe often contains at least moderate tau pathology in PSP (6, 7, 13, 27, 28). Two neuropathologists independently semiquantitated the cortical tau pathology, including neurofibrillary tangles, neuritic threads, tufted astrocytes, tau-positive plaques, and tightly wound oligodendrogial inclusions in each case. Each lesion was categorized as either absent (0), mild (1+), moderate (3+), or severe (5+). In general, the frequencies of tau-positive neurofibrillary tangles, neuritic threads, and tufted astrocytes in the substantia nigra, basal ganglia, subthalamic nucleus, and pons were similar within a given case, and therefore were tabulated together as subcortical pathology. The frequencies of tau-positive gray matter neurofibrillary tangles and neuritic threads were similar, and so were semiquantitated together as gray matter tau pathology. However, tau-positive tufted astrocytes in the gray matter were semiquantitated separately. In the white matter, tau-positive neuritic threads were as frequent as tightly wound oligodendrogial inclusions and so were semiquantitated together as "white matter tau pathology." We then compared the tau pathology in the 2 groups of patients.

All immunostaining was performed at room temperature on a BioTek Solutions TechMate™ 1000 automated immunostainer (Ventana Biotech 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 Biotech 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.

Paraffin sections were cut at 3µm 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 (HIER) buffer (Ventana Biotech 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, after which they were rinsed thoroughly in deionized water and then buffer. Sections were then incubated in unlabeled blocking serum for

J Neurosurg Exp Neural, Vol 58, April, 1999
CORTICAL PATHOLOGY IN PSP WITH DEMENTIA

Results: AD Classification/tau Pathology

<table>
<thead>
<tr>
<th>Case</th>
<th>AD path.</th>
<th>CERAD</th>
<th>Khachaturian</th>
<th>Braak stage</th>
<th>Subcortical path.</th>
<th>GM</th>
<th>TA</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3-5+</td>
<td>3+</td>
<td>5+</td>
<td>5+</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1-3+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>4</td>
<td>rare NP</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>1+</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1-3+</td>
<td>1+</td>
<td>3+</td>
<td>1+</td>
</tr>
<tr>
<td>6</td>
<td>mild NP</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1-3+</td>
<td>1+</td>
<td>3+</td>
<td>1+</td>
</tr>
<tr>
<td>7</td>
<td>mild NP</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3-5+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3-5+</td>
<td>rare</td>
<td>rare</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-3+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3-5+</td>
<td>1+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-3+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: subcortical path = substantia nigra, basal ganglia, subthalamic nucleus, and nuclei basis pontis pathology, GM = gray matter, TA = tufted astrocytes, WM = white matter, NP = neuritic plaques, 0 = absent, 1+ = mild or sparse, 3+ moderate, 5+ = severe or frequent.

CERAD criteria: C = definite AD, B = probable AD.
Khachaturian criteria: 0 indicates case does not fulfill Khachaturian criteria for diagnosis of AD.
Braak stage: 0 = no NFTs, 1-2 = transentorhinal stage, 3-4 = hippocampal stage, 5-6 = neocortical stage.

5-10 min to block nonspecific binding of the secondary antibody. Next, sections were incubated for 25 min with either primary antibody (tau-2, Sigma Chemical Company) at a 1:1000 dilution in buffer, 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 in buffer. Sections were then incubated for 25 min with freshly prepared horseradish peroxidase-conjugated avidin-biotin complex followed by washing in buffer. They were then incubated with 3 changes, 5 min each, of a freshly prepared mixture of diaminobenzidine (DAB) and H₂O₂ in buffer, followed again by washing in buffer and then water. Sections were then counterstained with hematoxylin, dehydrated in a graded series of ethanol and xylene, and coverslipped. Slides were reviewed by light microscopy. Positive reactions with DAB were identified as dark brown reaction product. Sections were photographed on a Nikon Optiphot microscope (Nikon Instruments, Melville, NY).

RESULTS

Table 2

Both Groups: All cases in the 2 groups had significant subcortical neurofibrillary pathology by tau immunostains (Fig. 1), with virtually all containing tau positive neurofibrillary tangles, neuroptil threads, and tufted astrocytes in the substantia nigra, globus pallidus, subthalamic nucleus, locus coeruleus, dentate nucleus of the cerebellum, and basis pontis. In many cases, the inferior medullary olives were involved. Among the cases there was variable involvement of the nucleus basalis, amygdala, periaqueductal gray matter, tectum, raphe nucleus, red nucleus, and superior colliculi.

Group 1: None of the 7 cases had appreciable cortical neuronal loss or gliosis. However, 3 cases had Alzheimer-type neuritic plaques, seen on thioflavin-S fluorescent stain. One case (case 4) had rare neuritic plaques and 2 cases (cases 6 and 7) had mild plaques. In none of these cases were plaques sufficiently numerous for the neuropathologic diagnosis of AD by either CERAD or Khachaturian criteria. The other 4 cases (cases 1-3 and 5) had no plaques. Tau pathology in all brain regions examined was prominent in this group. Gray matter tau pathology was moderate in 4 of the 7 cases (cases 1, 4, 6, and 7; Fig. 2), and mild in the other 3 (cases 2, 3, and 5). Tufted astrocytes were severe in 4 cases (cases 1, 5, 6, and 7; Fig. 3), moderate in 1 (case 4), and mild in 2 (cases 2 and 3). Interestingly, tau did not label any of the neuritic plaques seen in cases 4, 6, or 7. In the white matter, tau pathology was severe in 1 case (case 1; Fig. 4), moderate in 2 (cases 2 and 7), and mild in 4 (cases 3-6; Fig. 5).

Group 2: None of the 4 cases in group 2 had appreciable neuronal loss or gliosis, or neuritic or diffuse plaques. There was virtually no white matter tau pathology in the group. Interestingly, however, the 1 case in
In recent years, cortical tau pathology has been recognized as part of the spectrum of the neuropathology of PSP, thought by some to be a virtually constant feature, most prominent in motor cortex and moderately prominent in frontal cortex (6, 7, 9, 13, 16, 17, 26, 27, 30, 31). In particular, tau-positive tufted astrocytes are found almost exclusively in PSP (9, 10, 13, 17, 18, 32). Additionally, molecular tau abnormalities have been identified in PSP (33–35), some of which distinguish PSP tau from AD tau (12, 21, 36, 37). Bergeron, et al, in a recent paper (17), discussed the tau pathology of CBGD and PSP presenting with cognitive decline. There was, however, no comparison of cortical tau pathology between PSP cases with and without dementia.

In AD, neocortical neurofibrillary tangles have been found to correlate with cognitive decline (22, 24, 38, 39). A logical question to ask, then, is whether cortical tau pathology correlates with cognitive status in PSP? Our results show a distinct difference in the amount of cortical tau pathology between PSP cases having virtually no AD-type pathology and presenting with cognitive impairment (group 1), in which cortical tau pathology was prominent, and PSP cases without dementia (group 2), in which there was little or no cortical tau pathology. Interestingly, case 10, the only case in group 2 with mild cortical tau positive neurofibrillary tangles, was the only case that developed cognitive deficits later in the clinical course.

The average age of onset of disease of group 2 was 63, and the average duration of disease in this group was 4.3 years, while the average age of onset of group 1 was 71, and the average duration of disease 6.9 years. Group 2 had the earlier average age of onset and a shorter duration of disease than group 1. This suggests that either the age of onset or the duration of disease may play a role in determining the clinicopathologic phenotype of PSP, or at least whether the patient will or will not have dementia and cortical tau pathology. Certain additional factors, such as the ability of aged cells to neutralize free radical damage, may also contribute to this difference. However, the small sizes of the groups preclude more definitive conclusions on this issue of age.

If dementia in PSP were due to subcortical pathology, one would expect significant differences in subcortical quantities or distribution in these cases. However, subcortical tau pathology was virtually identical in all 11 cases.

The results of our study demonstrate a distinct difference in the amount of cortical tau pathology between cases of PSP with and without dementia. We believe that our study lends credence both to the theory that the accumulation of abnormally phosphorylated tau in neurons contributes to cognitive decline, and to the possibility that neurofibrillary pathology is central to the pathophysiology of many neurodegenerative diseases.

Fig. 1. Subthalamic nucleus tau pathology in groups 1 and 2, ×300. (a) 3 + tau pathology, case 7, group 1. (b) 3 + tau pathology, case 11, group 2.

which the patient developed cognitive impairment later in the clinical course (case 10) had several tangles and threads in the gray matter, but no tufted astrocytes. Another case (case 8; Fig. 6) had rare cortical tau pathology (2 tufted astrocytes and 4 tangles in the entire slide).

DISCUSSION

Steele, Richardson, and Olszewski first described the pathology of the degenerative disease commonly known as progressive supranuclear palsy (PSP) in 1964 (29). Of their 9 cases, 5 presented with either intellectual impairment or dementia, which in all cases was mild and non-progressive. Two later developed mild dementia and the other 2 did not become demented. They found only rare cortical pathology in their cases, using Bielschowsky silver-stained sections.
Fig. 2. 3 + cortical tau pathology, case 6, group 1, ×150.
Fig. 3. Tau-positive tufted astrocyte in cortex, case 5, group 1, ×300.
Fig. 4. S + white matter tau pathology including numerous tightly wound oligodendroglial inclusions, case 1, group 1, ×300.
Fig. 5. I + white matter tau pathology, case 3, group 1, ×300.
Fig. 6. 1 + cortical tau pathology, case 8, group 2, ×150.
ACKNOWLEDGMENTS

We greatly appreciate the generous assistance of Dr. Dennis Dickson in reviewing and reclassifying our cases. In addition, we would like to thank Lauren Lee and Christa Hladik for their histochemical and immunohistochemical expertise.

REFERENCES


Received August 17, 1998
Revision received November 4, 1998 and January 7, 1999
Accepted January 7, 1999