Neuropathologic Overlap of Progressive Supranuclear Palsy, Pick's Disease and Corticobasal Degeneration

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Abstract. Several neurodegenerative disorders contain tau-immunoreactive neuronal and glial inclusions throughout the cerebral cortex and brainstem. Although these diseases have been considered distinct clinicopathological entities, recent recognition of many neuropathological and clinical parallels has raised the question of overlap between the disorders. In addition, histopathological similarities sometimes complicate neuropathological diagnosis. To address these issues, we examined the morphology and differential distribution of pathologic lesions in three disorders: progressive supranuclear palsy, Pick's disease, and corticobasal degeneration. We found considerable similarity in the anatomical regions affected by the three entities; however, semiquantitative analysis revealed differential anatomical susceptibility. Similarly, although overlap existed in the morphology of tau-immunoreactive inclusions, characteristic differences remained and may be useful in differential diagnosis. In particular, glial inclusions varied dramatically between the disorders. Despite significant overlap among the three neurodegenerative diseases examined, the morphological and regional differences suggest that each is a distinct pathophysiological entity.

Key Words: Corticobasal degeneration; Neurofibrillary tangles; Pick's disease; Progressive supranuclear palsy; Tau protein.

INTRODUCTION

Degenerative neurologic disorders with neurofibrillary pathology pose significant challenges for neurologists and neuropathologists alike. Neurofibrillary tangles (NFT) are perhaps best known as characteristic neuronal inclusions concentrated in the cortex and limbic regions of Alzheimer's disease (AD) brains, but similar inclusions are also found with more widespread distributions in a limited number of additional neurodegenerative disorders. Those most commonly encountered in clinical and pathological practice include progressive supranuclear palsy (PSP), Pick's disease (PD) and corticobasal degeneration (CBD). Although distinct clinical syndromes have been attached to PSP (1), PD (2) and CBD (3–5), experience has shown that PSP and CBD may be diagnosed as Parkinson's disease, or confused with one another (6, 7). In addition, all three diseases can present with a dementia difficult to distinguish from AD (8, 9).

These clinical similarities are particularly intriguing given recent neuropathologic findings. Although the description of argyrophilic intraneuronal inclusions in PSP, PD and CBD dates almost to the original case reports, the discovery that neuronal inclusions in all three disorders are composed of the same protein as in AD NFT, namely the microtubule binding protein tau (10–12), has materially altered thinking regarding these structures. Some antigenic (13–16), biochemical (17, 18) and ultra-

structural (19–23) distinctions do exist among inclusions from the three diseases, but all contain abnormally aggregated, hyperphosphorylated tau protein, like NFT from AD.

The clarification of the composition of NFT has also led to sensitive methods of detecting cytoskeletal abnormalities. Widespread use of tau immunohistochemistry has considerably expanded recognition of the variety and distribution of lesions described in disorders with neurofibrillary degeneration. For example, PSP was thought to spare cortical regions (1, 24), but now substantial neocortical pathology is recognized (17, 25–27). In fact, immunohistochemical data has suggested that PSP, PD and CBD all contain numerous tau-containing inclusions in both cortical and brainstem regions, in apparently similar distributions (8, 23, 28, 29). The morphologies of the inclusions may also be similar. Descriptions of astrocytic and oligodendroglial inclusions in these disorders has further extended the analogies between them (22, 23, 30–36).

The striking clinical and pathological similarities among PSP, PD and CBD have led to significant questions regarding the relationship between these degenerative disorders, and we wondered what characteristics, if any, could be used to distinguish the diseases. In addition to furnishing valuable information for differential diagnosis, such an analysis may also help explain the significance of apparently similar lesions in ostensibly distinct clinicopathological entities. The results of our semiquantitative analysis show regional differences between the disorders. In addition, certain morphologic features help to define the diseases. In particular, glial inclusions vary substantially in CBD, PSP and PD. Despite the presence of intriguing similarities, our results suggest that CBD, PSP and PD are not simply anatomic variants of the same

disease process, but represent distinct pathophysiological entities.

MATERIALS AND METHODS

Material

Cases were selected based upon availability of fixed or paraffin-embedded tissue from the 19 cortical and subcortical regions examined (see below). The cases were evaluated as part of the brain bank at Albert Einstein College of Medicine and included cases autopsied at our institution and those referred to us. For cases autopsied by us, tissue was fixed in additional solutions (see below) that optimize antigen preservation; this tissue was used for vibratome sectioning and immunocytochemical analysis. Frozen tissue was also obtained on these cases for biochemical analyses not included in this report. All cases had a detailed neuropathological evaluation that included analysis of hematoxylin and eosin sections, fluorescent microscopy with thioflavin-S, silver staining (Bodian's stain) to document cytoskeletal inclusions and axonal pathology, and Luxol fast blue stains to demonstrate the extent and severity of white matter pathology.

Brains of seven cases of CBD were examined, including six women and one man, ranging in age from 71 to 80 years old with a mean age of 73 years. Postmortem intervals were from 4 to 18 hours. Most patients presented with behavioral changes and cognitive impairment. Ideomotor apraxias and aphasias were also present in six cases, but in only one case was aphasia documented in the absence of significant intellectual impairment. In addition, two patients exhibited prominent parkinsonism, and one presented with oculomotor abnormalities compatible with PSP. The CBD cases had a variable degree of cortical atrophy that in most cases was most marked in the frontal and parietal lobes. Asymmetry was not assessed due to the presence of only one hemisphere in almost all cases, the other hemisphere having been frozen for biochemical studies. The pathological diagnosis of CBD was based on neuropathological findings of neuronal loss and gliosis in cortex and subcortical regions, ballooned neurons and characteristic tau-positive neuronal and glial inclusions (18, 36–38). Ballooned neurons were widespread throughout the cortex, and all cases had ballooned neurons in the parietal lobe.

Brains of six PSP cases were analyzed, including two women and four men, ranging from 71 to 90 years with a mean age of 79 years. Postmortem intervals were less than 24 hours. One patient presented with classic clinical features of PSP and had been evaluated by several neurologists specializing in movement disorders. The other patients demonstrated parkinsonian features suggestive of PSP, including axial rigidity and unsteady gait accompanied by frequent backward falls. Eye movement abnormalities were not documented in some patients; however, several cases were nursing home patients who had no formal neurological evaluation. These cases were referred to our brain bank with a diagnosis of Alzheimer-type dementia. The pathology of the PSP cases that came to autopsy with a diagnosis of dementia did not differ substantially from the cases with classical clinical features. All cases met NINDS preliminary criteria for neuropathological diagnosis of PSP, which include numerous NFT and neuropil threads in multiple brainstem areas, the basal ganglia and subthalamic nucleus (39).

Brains of five cases of PD were analyzed, including two women and three men, ranging in age from 67 to 69 years with a mean age of 68 years. Postmortem intervals were from 2 to 8 hours. Three patients presented with prominent personality changes including inappropriate, bizarre behavior. One patient had predominant memory loss and was diagnosed with Alzheimer-type dementia. Neuropathologically, all cases had circumscribed atrophy affecting frontal and temporal lobes, with marked atrophy of the amygdala and hippocampus. All cases had characteristic histopathology with numerous argyrophilic, tau-positive Pick bodies (PB) in cortical areas and the hippocampus, including the dentate fascia.

Immunohistochemistry

Immunocytochemistry was performed on 10% formalin-fixed, paraffin-embedded 10 μm thick sections of all cases using standard methods and an avidin-biotin peroxidase detection kit (Vector Labs., Burlingame, CA). On a subset of cases from each diagnostic group, tissue was immersion-fixed at the time of autopsy for 12 to 16 hours in Bouin's fixative or 4% paraformaldehyde, stored in 30% sucrose and subsequently sectioned at a thickness of 40 μm on a vibratome. For immunostaining, sections were pre-incubated with 5% non-fat milk to block nonspecific antibody binding, then incubated with primary and secondary antibodies as described (40).

Monoclonal antibodies recognizing tau or paired helical filaments (PHF) were used to detect cytoskeletal pathology. All cases had immunostaining with Alz-50, which recognizes an amino-terminal epitope on tau; other anti-tau and anti-PHF antibodies were used on each case as well. The anti-PHF and anti-tau antibodies gave essentially similar results. Alz-50, PHF-1, AT8 and TG3 were particularly useful on paraffin sections. All antibodies gave optimal staining on vibratome sections of briefly fixed tissue. Rabbit polyclonal antibodies to glial fibrillary acidic protein (GFAP) were purchased from BioGenex, San Ramon, CA, and used at 1:400. Polyclonal antisera recognizing ubiquitin (41) was used at dilution of 1:400. The antibodies used for semiquantitative analyses are listed in Table 1.

Neuropathological Analysis

Tissue from the 19 cortical and subcortical areas was immunostained with antibodies recognizing phosphorylated neurofilament proteins and tau protein. Antibodies specific for ubiquitin were also employed. For semiquantitative analysis the following were assessed on immunostained sections: tau-positive neuronal cell body inclusions (NFT or PB), neuropil threads in gray and white matter, and glial (astrocytic and oligodendroglial) inclusions. Ballooned neurons were assessed separately on sections stained with antibodies to phosphorylated neurofilaments. Tau-immunoreactive inclusions and neurofilament-immunoreactive ballooned neurons were recorded on a four point scale (from 0 to 3: absent, low density, medium density, high density). In general, assessments were based on multiple slides of the same areas stained with several different antibodies. In the cases of nonuniform distribution of lesions, an average score was estimated based upon the entire region or nucleus in question.

For statistical analysis anatomical areas were grouped into three categories: (i) cortex: frontal, parietal, cingulate, insular

TABLE 1
Antibodies Used for Immunocytochemistry in Semiquantitative Analyses

Antibody	Epitope	Isotype	Dilution	Source
Alz-50	N-terminus of tau	IgM	1:5	Peter Davies, AECOM
PHF-1	Phosphorylated epitope in mid-region of tau	IgG1	1:100	Peter Davies, AECOM
Tau-46	C-terminus of tau	IgG1	1:500	Virginia Lee, Univ. Penn.
AT-8	Phosphorylated epitope in mid-region of tau	IgG1	1:1,000	Innogenetics, Ghent, Belgium
Ab39	Conformational epitope of PHF	IgG1	1:5	Shu-Hui Yen, AECOM
TG3	Phosphorylated epitope of PHF	IgM	1:5	Peter Davies, AECOM
NP18	Phosphorylated epitope of NF-H and NF-M	IgM	1:5	Peter Davies, AECOM
SMI-31	Phosphorylated epitope of NF-H and NF-M	IgG1	1:5,000	Sternberger Monoclonals, Gaithersberg, MD

and parahippocampal cortices; (ii) deep gray: putamen, globus pallidus, nucleus basalis, thalamus and subthalamic nucleus; and (iii) brainstem: substantia nigra, oculomotor nuclei, red nucleus, pons raphe, pons base, locus ceruleus, inferior olive and cerebellar dentate nucleus. The hippocampus, which was evaluated in all cases, was not included in quantitative analyses. Ballooned neurons were scored for cortical areas only. For estimates of oligodendroglial inclusion density all white matter areas were grouped. Statistically significant variations were determined using the nonparametric Kruskal-Wallis analysis of variance on ranks. All differences discussed in the text were significant with $p < 0.05$. Any comparisons that did not reach this level of significance are referred to as trends.

RESULTS

Morphology

Immunostained sections from 19 cortical and subcortical areas in PSP, PD, and CBD with antibodies recognizing neurofilament and tau revealed ballooned neurons and a range of tau-positive lesions; the density of tau-positive inclusions and ballooned neurons was estimated in each area. Several different types of tau-positive structures were noted. All tau-positive inclusions in neuronal somata were scored in a single category and included classic flame-shaped NFT, globose NFT and PB, as well as a variety of other morphological lesions. Much variability occurred in neuronal cell body inclusions, both within and between disease entities (Figs. 1–3). In PSP approximately one-half of the NFT displayed an easily identified globose appearance, often with a multilamellar internal structure (Fig. 1a); however, a number of other types were present as well. Many had the classic flame-shaped morphology (Fig. 1b); the rest displayed a variety of morphologies (Fig. 1c–f). Some were smaller, often with a round or oval shape, and were occasionally indistinguishable from PB (Fig. 1c). The smallest neuronal inclusions sometimes resembled neuropil grains but were clearly contained within neuronal somata and were often present in diffuse collections throughout the cell soma (Fig. 1f). A variety

of irregular inclusions were present, varying from variants of globose or flame-shaped NFT to highly irregular structures (Fig. 1d, e).

Neuronal inclusions in PD displayed much less variability (Fig. 2). The PB had a highly distinctive round, regular shape, and the majority of the tau-positive neuronal inclusions in PD conformed to this description. They often had a dense, compact appearance, but occasionally had an irregular internal structure. Unlike NFT in PSP, PB varied primarily in size, and less in regularity of outline (Fig. 2a). The most common morphological variant was elongated and oval. Occasionally, more irregular forms were present (Fig. 2c); however, they were never as irregular as NFT. Pick bodies were occasionally multiple, particularly in the locus ceruleus (Fig. 2d). In some instances the PB appeared to coalesce into one large inclusion. These inclusions might be confused with globose NFT, but the characteristic laminations of NFT were generally absent. Instead, the large inclusions in PD often appeared to be composed of several small round structures.

Tau-positive neuronal inclusions in CBD differed from inclusions seen in both PSP and PD (Fig. 3). The CBD lesions varied more in size than inclusions in the other two diseases, were more regular in shape than NFT, but less regular than PB. Neurofibrillary lesions in the cortex in CBD were generally smaller than subcortical NFT and often had a "coiled" or "looped" appearance (Fig. 3a). We have confirmed the neuronal identity of the cells containing these smaller cortical NFT using double label immunohistochemistry with anti-neurofilament antibodies (36). The inclusions occurred in both pyramidal and in small, nonpyramidal neurons (36). Larger subcortical tau-positive neuronal inclusions displayed even more dramatic examples of the coiled-type filamentous appearance, often arising as a loose collection of tau-immunoreactive threads filling the cell body (Fig. 3e–g). These coiled tau-positive neuronal inclusions were quite characteristic of CBD; however, other neuronal inclusions
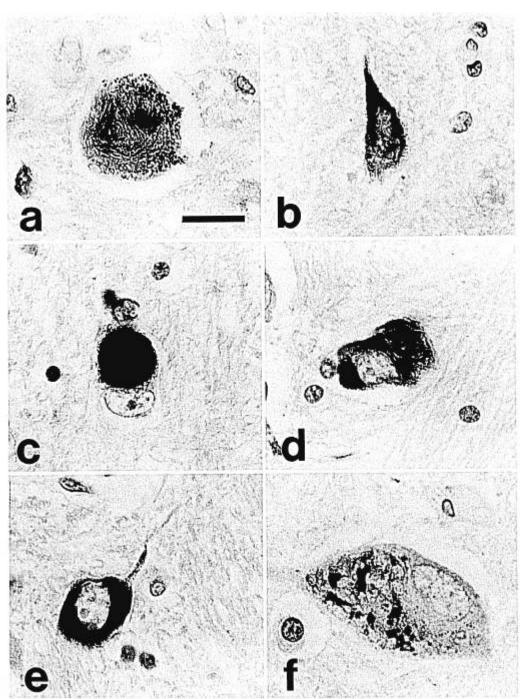
Fig. 1. Neurofibrillary tangles in PSP visualized with antibodies recognizing abnormal tau. (a) A typical globose-type NFT from the locus ceruleus, (b) a classic flamed-shaped NFT from the medullary reticular formation, (c) a PB-like inclusion from the cingulate cortex, and a variety of morphological types from the pons (d, e, f). Scale bar = 20 μm.

in CBD were very similar to globose NFT of PSP or even to classic PB (Fig. 3c). Morphology alone often provided an insufficient basis for distinguishing neuronal tau-positive inclusions from different diseases.

Each of the three disorders examined had a characteristic array of inclusion types, and little variability occurred within a single disease entity. The same range of morphologies appeared in all cases of each disorder. In PSP and PD inclusions did not vary dramatically from one anatomic region to the next, although minor differences appeared between cortical and subcortical lesions. In contrast, cortical tau-positive neuronal inclusions in CBD consisted almost exclusively of small coiled or looped structures (Fig. 3a, b), while a larger variety of
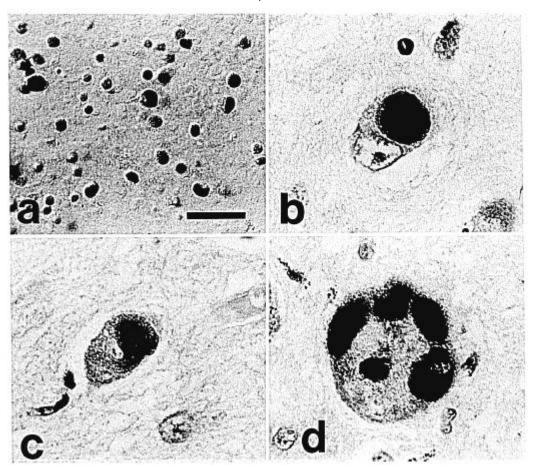
Fig. 2. Pick bodies in PD detected with antibodies recognizing abnormal tau. (a) Low power view of a vibratome section through the hippocampus demonstrating variability in the size of PB. Scale bar = 50 μm. Classic (b) and slightly irregular (c) PB from the amygdala. (d) Multiple PB in the locus ceruleus. Scale for b–d = 20 μm.

neurofibrillary lesions were present in the basal ganglia and brainstem (Fig. 3c–g).

Neuropil threads constitute the second major category of tau-immunoreactive lesion in these disorders. A variety of morphological types of threads occurred, but for the purpose of the semiquantitative analysis we designated all inclusions from long, wavy linear structures to dot- or grain-like particles as neuropil threads. Unlike neuronal cell body tau-positive inclusions, characteristic types of neuropil threads could not be distinguished among the three diseases (Fig. 4). All disorders contained neuropil threads, generally accompanying neuronal cell body inclusions. No clear differences between cortical and subcortical threads were obvious in any of the disorders.

Thread-like structures were not confined to the gray matter. The CBD cases in particular contained numerous threads in the white matter (Fig. 4c). We have demonstrated previously that some of these threads represent tau-immunoreactive inclusions in axons (36). CBD also contained numerous looped threads in the white matter

that represent oligodendroglial inclusions (Fig. 4e; 18, 22, 34, 36). White matter threads were also present in PSP and PD, although to a lesser degree.

Glia in the white matter of PD contained an unusual type of inclusion (Fig. 4d). Unlike the thread- and loop-like oligodendroglial inclusions, these tau-immunoreactive structures were small, round, compact juxtanuclear bodies. These inclusions were relatively numerous in PD but were not detected in the other disorders.

Astrocytic tau-immunoreactive inclusions comprised one of the most distinctive features of each disease. Tufted astrocytes have been documented in PSP (30–33), and we detected many such astrocytes in our PSP cases (Fig. 5a, b). We confirmed the astrocytic nature of the cells containing the tufted-type inclusions by double-labeling sections with antibodies to GFAP and abnormal tau (data not shown). Although tufted astrocytes were common in neocortical areas in PSP, they were seen throughout the neuraxis and varied little in morphology. Astrocytes in PD also contained abnormal tau immunoreactivity. In contrast to the tufted astrocytes of PSP, astrocytic
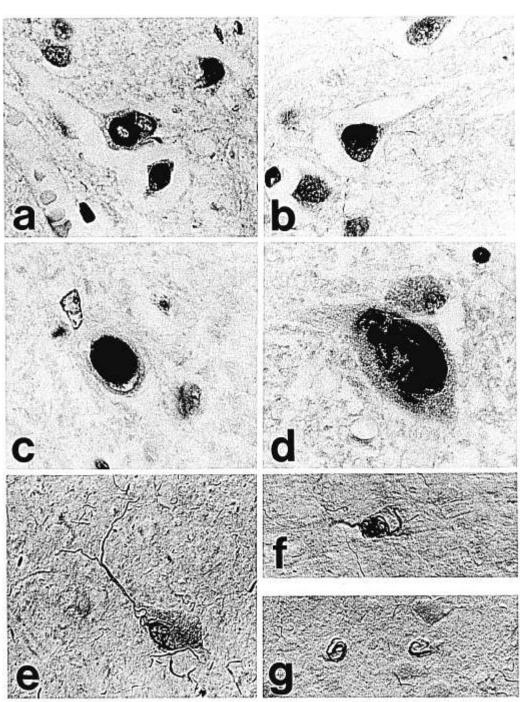
Fig. 3. Neurofibrillary tangles in CBD identified with anti-tau immunohistochemistry. (a, b) Small inclusions in parietal neurons. (c) A PB-like NFT. (d–g) Loose thread-like collections in pontine neurons. Scale for a–d = 20 μm. (e–g) Vibratome sections; scale for e–g = 50 μm.

inclusions in PD tended to occupy more of the cell body and to ramify into the astrocytic cell processes extending into distal domains of the glial cell process (Fig. 5c, d). Unlike abnormal tau in tufted astrocytes of PSP (Fig. 5a, b), astrocytic inclusions in PD were often localized to one side of the cell soma (Fig. 5c, d). Astrocytic inclusions in PD were not common in subcortical structures, but when present tended to have similar morphology to cortical astrocytic inclusions.

Astrocytic tau immunoreactivity in CBD differed dramatically from that seen in PSP and PD. We have demonstrated previously that CBD contains annular plaques formed by abnormal tau deposits in distal processes of individual astrocytes (36). Astrocytic plaques are quite
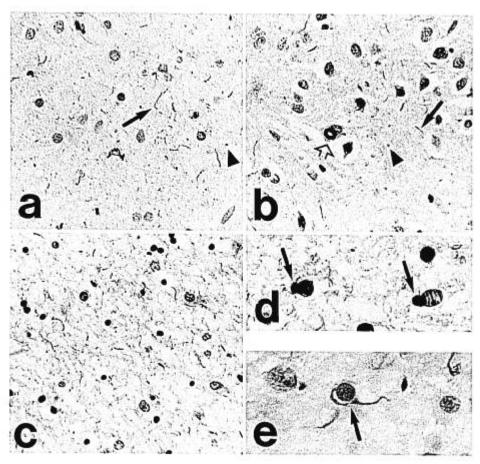
Fig. 4. Neuropil threads and glial tangles detected with antibodies recognizing abnormal tau. (a) Neuropil threads and grains in the subthalamic nucleus of a patient with PSP. Arrow indicates a thread, arrowhead points to a grain-like structure. Threads in the parietal cortex (b) and adjacent white matter (c) from CBD. Filled arrow in (b) indicates a thread, arrowhead points to a grain, and outline arrow demonstrates a typical ring-like CBD neuronal inclusion. Scale for a–c = 50 μm. (d) Arrows point to glial inclusions from parietal white matter in PD. (e) Arrow indicates an oligodendroglial inclusion from the parietal white matter in CBD. Scale for d, e = 20 μm.

characteristic of CBD (Fig. 5e) and they were abundant in the cerebral cortex of all CBD cases in this study. In a small number of astrocytic inclusions tau immunoreactivity extended into the proximal processes and cell body of the astrocyte (36). Typical annular astrocytic plaques were present in subcortical regions in CBD, but they tended to be smaller than cortical plaques.

Tau-positive inclusions in PSP, PD and CBD tended to have variable immunoreactivity with anti-ubiquitin antibodies. Cortical neuronal cell body inclusions were weakly to moderately immunoreactive in PSP, PD and CBD. Cortical astrocytic inclusions in PD and CBD, but not in PSP, reacted with ubiquitin antibodies. Inclusions in subcortical areas occasionally demonstrated weak immunoreactivity, but were generally negative.

Distribution

Semiquantitative analysis of ballooned neurons and tau-immunoreactive lesions demonstrated that PSP, PD and CBD all had substantial numbers of lesions in cor-

tical and subcortical structures; however, the distribution of lesions was characteristic for each disorder.

Cortical regions in PD and CBD contained many ballooned neurons (Fig. 6a). There was a trend toward more ballooned cells in PD than in CBD, and the distribution of these abnormal neurons was similar in the two disorders. Ballooned neurons were present in subcortical areas in CBD, particularly in the basal ganglia, and most notably the claustrum, where they were often numerous. Using anti-neurofilament immunohistochemistry, rare ballooned neurons were seen in the midbrain of two cases, inferior olivary nucleus of one case and cerebellar dentate nucleus of two cases.

Only rare ballooned neurons were detected in PSP (Fig. 6a) using immunostaining with antibodies that recognize phosphorylated neurofilament subunits. These ballooned neurons were confined to subcortical and limbic regions. Ballooned neurons have been reported previously in pontine tegmental neurons in PSP (42). Only one ballooned neuron in each of two PSP cases was detected
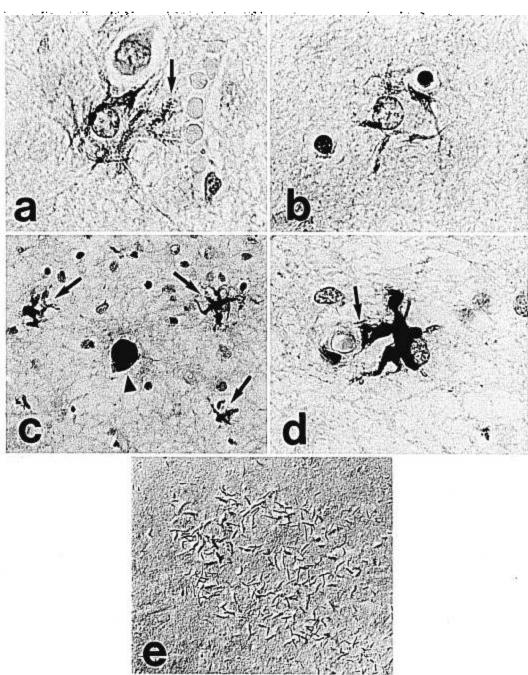
Fig. 5. Anti-tau immunoreactivity in glial cells from the putamen in PSP (a, b), and in neurons and glia of the parietal cortex in PD (c, d) and glia in CBD (e). Arrows in (a, d) show astrocyte foot processes contacting a vessel. Arrows in (c) point to astrocytes, arrowhead indicates a PB. Scale for a, b, d = 20 μm. Scale for c, e = 50 μm. (a–d) Paraffin sections. (e) Vibratome section.

in this location in the present study. In one PSP case, several neurons that reacted weakly with anti-neurofilament antibodies were detected in the parietal cortex. No ballooned cells could be identified on hematoxylin and eosin-stained sections of the same region.

Both PD and CBD had more neuronal inclusions in cortical regions than in subcortical areas and significantly more tau-positive cortical pathology than PSP (Fig. 6b). In contrast, no significant (p < 0.05, Kruskal-Wallis analysis of variance on ranks) difference was found in the density of NFT in cortex, deep gray matter or brainstem in PSP, although there was a trend for greater neurofibrillary pathology in deep gray matter and brainstem areas than cerebral cortex (Fig. 6b).

Ballooned Neurons

Neuronal Tau⁺ Inclusions (NFT or PB)

Fig. 6. Distribution of neuronal cell body inclusions. (a) The average score for ballooned neurons in all cortical areas is plotted with error bars, as indicated. No statistical differences were present between CBD and PD, but both were significantly greater than PSP. (b) Tau-positive neuronal inclusions. Only cortical areas of CBD and PD showed statistically significant differences from subcortical areas and from PSP. Error bars represent one standard error of mean.

Within each disorder the density of threads and neurofibrillary lesions roughly correlated; however, semi-quantitative analysis revealed more robust differences than for neuronal cell body inclusions (compare Figs. 6b and 7a). In particular, CBD had significantly more gray matter neuropil threads in the cortex and deep gray matter compared to PSP and more gray matter threads in deep gray and brainstem than PD (Fig. 7a). Both CBD and PSP had more gray matter threads in brainstem than PD (Fig. 7a). No significant difference was detected between the density of threads in the cortex of PSP and PD.

Similarly, CBD had more tau-immunoreactive threads in cortical white matter than PSP or PD (Fig. 7b). In white matter tracts in subcortical regions, such as the pencil fibers in the basal ganglia or the thalamic fasciculus, both CBD and PSP contained more white matter threads than PD. White matter threads were more numerous in cortical than subcortical regions in both PD and CBD compared to PSP, while the areas were not significantly different in PSP (Fig. 7b).

Although the relative numbers of tau-positive neuronal cell body inclusions and neuropil threads varied among the diseases, the two types of lesions shared similar overall distributions. In contrast, tau-positive astrocytes were more numerous in cortical regions in all disorders (Fig. 8a). In the cortical areas both CBD and PD had more tau-positive astrocytic inclusions than PSP. In PD many brainstem areas were devoid of astrocytic inclusions, while the cortices were often affected. Astrocytic inclusions were also significantly more common in cortex than

in deep gray matter or brainstem in CBD. In PSP astrocytic inclusions were widespread in both cortex and deep gray matter regions, but again more numerous in cortex compared to brainstem.

DISCUSSION

Morphology

Recent studies have suggested that PSP, PD and CBD have substantial neuropathologic overlap. Reports discussing single disease entities have identified characteristic neuronal inclusions and suggested overlap in their morphology. To define the relationships among these diseases, we compared the morphology and distribution of pathologic lesions throughout the neuraxis in multiple cases of the three disorders. Our direct comparison both confirms and further delimits these observations. No one type of neuronal cell body inclusion was pathognomonic of a particular disorder; however, important differences did exist in the appearance of neuronal inclusions in the three disorders. In PD, tau-positive neuronal inclusions, PB, had a highly characteristic appearance, and in sufficient quantities and the appropriate distribution, they confirm the diagnosis of PD. The presence of characteristic inclusions can be crucial for sound differential diagnosis. In a recent study testing the accuracy of neuropathologic diagnosis of degenerative diseases containing tau-immunoreactive inclusions, all neuropathologists surveyed easily identified cases of PD, citing the presence of highly characteristic PB (Litvan et al, unpublished data).
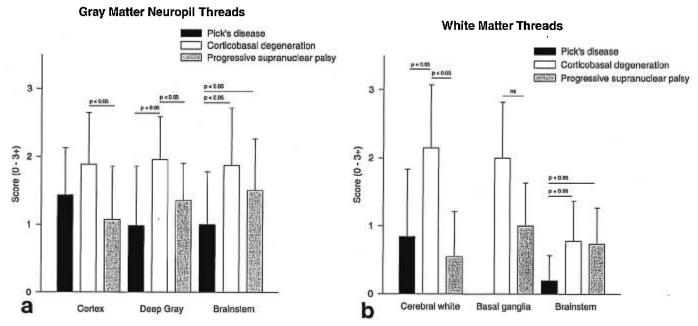
Gray Matter Neuropil Threads

White Matter Threads

Fig. 7. Distribution of gray and white matter neuropil threads. (a) Neuropil threads in gray matter of CBD are significantly greater than PSP in cortex and deep gray matter and greater than PD in deep gray matter and brainstem. Both CBD and PSP have more gray matter threads in brainstem than PD. (b) Neuropil threads in cerebral white matter are markedly increased in CBD compared to PSP and PD. Both CBD and PSP have more white matter threads in brainstem compared to PD.
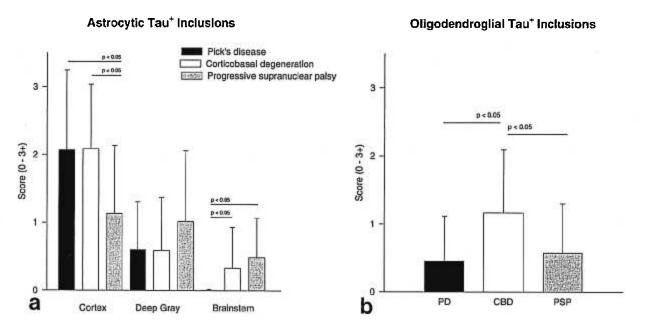
Astrocytic Tau⁺ Inclusions

Oligodendroglial Tau⁺ Inclusions

Fig. 8. Distribution of tau-positive glial inclusions. (a) Astrocytic inclusions are more numerous in cortical gray matter than in either deep gray matter or brainstem. Both PD and CBD have significantly more astrocytic inclusions in the cortex than PSP. In the brainstem both CBD and PSP have more astrocytic inclusions than PD. (b) The score for oligodendroglial inclusions as pooled for all white matter areas demonstrates significantly more oligodendroglial inclusions in CBD than both PD and PSP.

Although PB would seem to define PD, the light microscopic appearance of an individual inclusion is nonspecific. Both PSP and CBD contained tau-immunoreactive structures that appeared similar to PB. Indeed, even some neurofibrillary lesions in AD may resemble PB

(43). The presence of PB-like structures in PSP and CBD should not raise serious diagnostic difficulties because they constitute only a minority of the inclusions. The globose-type NFT was common in PSP. Globose NFT have been considered relatively characteristic of PSP, but

our analysis suggests that they are less specific than PB. Subcortical inclusions in CBD, so-called corticobasal bodies, were indistinguishable from globose NFT. On the other hand, globose-type NFT predominated in PSP, but not in the other two disorders. In CBD neuronal cell body inclusions were more delicate, fibrillary and pleomorphic than in the other two disorders. A wide range of neuronal structures showed tau immunoreactivity in CBD.

The morphology of the second major type of tau-immunoreactive inclusion, the neuropil thread or grain, did not vary greatly among PSP, PD and CBD. Consistent with the high sensitivity of immunohistochemical techniques, we found numerous neuropil threads throughout cortical and subcortical regions in all our cases. Although neuropil threads and grains have been described previously in PSP (44, 45) and CBD (18, 22, 23, 34, 36), tau-immunoreactive neuropil threads have not generally been associated with PD (46, 47). One study using the fluorescent stain Di-I found collections of enlarged, dystrophic cellular processes in PD that were presumed to be neuritic, but no abnormal tau was detected in these processes (48). In contrast, we document substantial numbers of neuropil threads and grains in PD. Although less dense than in PSP and CBD, neuropil pathology was conspicuous in PD, and along with astrocytic tau-positive lesions (see below) expands the range of lesions identified in PD.

Astrocytes contained tau-immunoreactive inclusions with distinctive morphologies in the three disorders. Only recently described, astrocytic inclusions seem to be present in many diseases with neurofibrillary degeneration (23, 30–36). Direct comparisons of astrocytic inclusions in representative series of different diseases, however, have not been reported. We show that the inclusions in PSP, PD and CBD are qualitatively different. In each disease abnormal tau accumulates preferentially in specific domains of the astrocyte. The most striking subcellular compartmentalization occurred in CBD, where modified tau accumulated almost exclusively in distal astrocytic processes, producing the characteristic astrocytic plaque of CBD. In contrast, astrocyte tau immunoreactivity in PSP collected preferentially at the periphery of the cell soma and extended only into the proximal processes, producing a tufted appearance. Finally, in PD, modified tau was found more generally throughout the astrocytic cell body and processes. The mechanisms underlying differential susceptibility of distinct subcellular domains of astrocytes and neurons for accumulation of filamentous aggregates remain enigmatic, but should be included in theories regarding pathogenesis.

Distribution

Significant overlap occurred in the anatomic areas affected by PSP, PD and CBD. Both cortical and subcortical regions were involved in all three disorders; however, semiquantitative analysis of multiple cases revealed distinctive differences. Overall, PD demonstrated a cortical preponderance, PSP a subcortical predilection, and CBD contained abundant pathology in both areas. The disorders were distinguished by both the anatomic regions affected and by the relative abundance of specific lesions. In particular, CBD had numerous neuropil threads in gray and white matter and more oligodendroglial inclusions than PSP or PD (Fig. 8b). White matter pathology especially distinguished CBD. Thinning and discoloration of cortical white matter may be noted on gross examination of CBD brains and correlates with abundant tau-immunoreactive threads and oligodendroglial inclusions (22, 23, 34, 36). White matter pathology has also been noted in PD in areas with lobar atrophy, but axonal and myelin loss has not previously been associated with abnormal structural lesions. White matter threads and oligodendroglial inclusions were detected in PD as well as in PSP, but were less frequent than in CBD.

Although the relative proportion of neuronal inclusions to neuropil threads in gray and white matter varied from one disease to another, neuronal cell body and neuropil threads generally affected each anatomic area to a similar extent. In contrast, astrocytic inclusions demonstrated a marked cortical, particularly neocortical, predilection in all disorders. Abnormal cortical astrocytes are particularly noteworthy in PSP because of the tendency for NFT and neuropil threads to affect subcortical structures preferentially in this disorder, with relative sparing of the cortex.

The relationship, if any, between cortical astrocytic pathology and cognitive dysfunction is unclear, but recent evidence suggests that astrocytes may play an important role in signaling events (49). PSP patients present with a characteristic frontal lobe behavior pattern, and functional neuroimaging studies have documented relative frontal hypometabolism (50). Because early studies emphasized the lack of pathology in the cerebral cortex (1, 24), frontal lobe dysfunction had been attributed to "frontal deafferentation" through loss of subcortical inputs (51); however, documentation of significant astrocytic abnormalities and other reports of cortical pathology in PSP (25–27, 30–33) indicate that the cortex itself is altered. How tau-immunoreactive astrocytic inclusions might impair performance remains unclear. Abnormal astrocytes could contribute directly or be indicative of more widespread cellular dysfunction.

Astrocytic inclusions have been noted previously in the disorders we examined, but the extensive nature of the pathology has not been documented. In selected cases of PD, neocortical tau-immunoreactive astrocytes appeared to equal or even outnumber PB. Like neuropil threads and grains, astrocytic inclusions should be recognized as an important pathological feature of PD. The description of numerous astrocytic inclusions in PSP, PD, and CBD not only expands the range of lesions expected in the

disorders, but also carries important pathophysiological implications. Widespread astrocytic involvement, combined with documented oligodendroglial inclusions (36), suggests that a generalized disruption of cytoskeletal organization occurs irrespective of cell type in these disorders.

We analyzed many anatomical areas, but compared groups of regions to facilitate statistical comparisons among the disorders; however, specific areas have distinctive pathology. Flame-shaped NFT characteristic of AD were not infrequent in the hippocampus and parahippocampal gyrus. In PSP, the relative sparing of other cortical regions highlighted hippocampal pathology. Although some authors have suggested that AD is a frequent concomitant of PSP (9) and PD (26), our cases had few senile plaques and those that were present were mostly diffuse amyloid deposits not unlike those detected in elderly normal brains. In contrast neuritic plaques and NFT in neocortical association areas, features critical for the diagnosis of AD (52, 53), were absent. Rather than AD, hippocampal and parahippocampal NFT in these cases may represent nonspecific vulnerability of these neurons to neurofibrillary degeneration in older people. Relatively large numbers of hippocampal NFT can be found in non-demented individuals with little or no additional AD pathology (54–57).

Despite overall differences in the density of lesions in cortex compared to subcortical areas, individual regions often displayed similar susceptibilities. Anatomic areas that commonly had substantial pathology in PSP, PD, and CBD included the subthalamic nucleus, substantia nigra, and locus ceruleus. In contrast, specific regional variation occurred with respect to both number and type of lesions. For example, the globus pallidus was a preferential target of both threads and NFT in CBD and PSP, but not PD. The inner putamen, on the other hand, was vulnerable to PB. In the neurons of the basis pontis, NFT were often detected in PSP, and PB sometimes in PD, but this region predominantly had neuropil threads in CBD.

The similarity of the anatomic distribution of lesions among the three disorders emphasizes their similarity, as does the immunoreactivity with antibodies that recognize abnormal tau. A number of studies have examined additional antigenic properties of inclusions in these diseases. Although differences in defined tau (16) and phosphorylated neurofilament (14) epitopes have been demonstrated, most studies have focused on ubiquitin immunoreactivity.

Unlike NFT in AD, subcortical NFT in PSP do not react with anti-ubiquitin antibodies (13, 15), although cortical NFT may be positive (15). Cortical and subcortical inclusions in CBD have generally been reported as negative (22, 23); although, as for PSP, hippocampal inclusions may display immunoreactivity (23). Differences in the anatomic regions examined and intercurrent AD

pathology complicate the interpretation of these studies. Our analysis of the same regions in PSP, PD, and CBD, along with the numerous tau-immunoreactive lesions detected allowed us to address these difficulties. We found that subcortical inclusions were generally negative in all three disorders, while cortical inclusions were typically weakly to moderately immunoreactive. The one exception was the lack of immunoreactivity of cortical astrocytic inclusions in PSP. Cortical versus subcortical location appears to be a strong determinant of ubiquitin immunoreactivity but does not account for all differences among the diseases, given the lack of immunoreactivity in PSP cortical astrocytes.

Ballooned neurons comprise an additional similarity among the disorders. These swollen, achromatic neurons are well known in PD and CBD (3–5, 58, 59). We observed abundant ballooned cells in all cases of both disorders. A trend existed toward a greater number of ballooned cells in PD than in CBD. Several reports have suggested the presence of ballooned cells in PSP (9, 42, 60). We observed infrequent ballooned cells in the limbic areas in a few PSP cases, but ballooned neurons were much less frequent in PSP than in PD or CBD. Control AD cases and other age-associated disorders occasionally have comparable numbers of ballooned neurons in paralimbic areas (59). A report of ballooned neurons in the pontine tegmentum in PSP (42) has been widely cited as evidence of ballooned neurons in PSP (28). Using a sensitive anti-phosphorylated neurofilament immunohistochemical technique, we identified only one ballooned neuron in the pontine tegmentum in each of two PSP cases. Our data suggest that although occasional ballooned neurons may occur in limbic cortex or subcortical regions in PSP, ballooned neurons are neither a frequent nor characteristic feature of PSP. The presence of ballooned neurons in neocortical association areas in a case with neuronal loss and NFT in the basal ganglia and substantia nigra should prompt a re-evaluation of the diagnosis of PSP, and consideration of CBD.

Many reports have documented case-to-case variation in degenerative diseases associated with cytoskeletal pathology, including AD, but particularly in PSP and CBD (7, 28, 34, 61). We were able to detect differences between PSP and CBD with between-group comparisons, but individual cases of CBD and PSP sometimes presented diagnostic difficulties. The presence of numerous ballooned neurons in the neocortex often remained the best means of differentiating PSP from CBD by neuropathological criteria.

Individual cases of each of the disease entities studied in this report had variability in the severity of pathology in the 19 anatomic areas. The degree of severity, however, is not likely to explain all the variance in the analysis between the groups. Most cases of PD had relatively more cortical pathology and less involvement of subcor-

tical structures, while most cases of PSP showed the opposite pattern and CBD was intermediate in showing both cortical and subcortical pathology. Pathology in regions like the globus pallidus, oculomotor nuclei and inferior olivary nuclei varied substantially, even among cases with the same diagnosis, most notably PSP.

Although most cases of PD, PSP and CBD can be classified as distinct clinicopathological entities, the results of the present study emphasize that overlapping pathology clearly exists. One case of apparent combined PSP and PD has been reported (62). In addition, varying combinations of PSP with AD (9) and with Lewy bodies (63, 64) have been documented. PD can apparently coexist with AD (65), with a multisystem atrophy (66), and with Creutzfeldt-Jakob disease (67).

Cases in which characteristic types of cytoskeletal pathology coexist emphasize one of the major results of this study: substantial overlap exists among morphology, distribution, and antigenic characteristics of tau-immunoreactive lesions. What is the significance of such similar pathology in apparently different diseases? Although we cannot provide a complete answer, our data does suggest certain constraints on possible models. For instance, by demonstrating characteristic morphological types of both neuronal and glial inclusions, and by showing robust differences in relative abundance of particular types of lesions in the same anatomic areas, we provide strong evidence that the three disorders do not simply represent anatomic variants of one another, or of AD. The pathology produced, although demonstrating obvious similarities, is likely, therefore, to be inextricably linked to distinct etiological insults.

Independent of pathophysiological speculations, our data have important implications for differential diagnosis. We suggest that both the anatomic distribution of lesions and their morphology are important criteria in the differential diagnosis of a disorder with tau-immunoreactive inclusions involving cortical and subcortical areas. Recently described astrocytic inclusions may be quite informative and should not be overlooked. Finally, given the variation documented in this study and reports in the literature, problematic cases will doubtless arise that may require "combined" or "atypical" diagnoses. The accuracy of diagnosis can be improved by using all available clinical information and employing sensitive silver staining methods and immunocytochemistry for tau and neurofilament to reveal recently recognized cytoarchitectural hallmarks of these diseases.

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