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Distribution of cortical neurofibrillary tangles in progressive supranuclear palsy: a quantitative analysis of six cases*

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Summary. Progressive supranuclear palsy is characterized neuropathologically by the presence of high densities of neurofibrillary tangles in several subcortical structures. In some cases, neurofibrillary tangles have also been described in the cerebral cortex. We performed a quantitative regional and laminar analysis of the distribution of these lesions in six cases of progressive supranuclear palsy. We observed that the neurofibrillary tangle distribution in the cerebral cortex was largely confined to the hippocampal formation. In particular, in all the cases neurofibrillary tangles were observed in the granule cell layer of the dentate gyrus. In the prefrontal and inferior temporal cortex, neurofibrillary tangles were predominantly distributed in layers II and III. In addition, there were moderate-to-high neurofibrillary tangle densities in the primary motor cortex. This localization pattern contrasts with the neurofibrillary tangle distribution observed in the cerebral cortex of Alzheimer's disease cases, where tangles are denser in layer V than in layer III, and where the primary motor cortex and the dentate gyrus are usually not involved. These results suggest that specific elements of the cortical circuitry might be differentially vulnerable in progressive supranuclear palsy as compared to Alzheimer's disease.

Key words: Alzheimer's disease – Cerebral cortex – Neurofibrillary tangles – Progressive supranuclear palsy – Tau protein

Neurofibrillary tangles (NFT) are a classical hallmark of Alzheimer's disease (AD). However, other neurodegenerative disorders are also characterized by the presence of large numbers of NFT in the cerebral cortex and subcortical structures. In particular, NFT are abundant in the cerebral cortex of cases with Down's syndrome, dementia pugilistica, and amyotrophic lateral sclerosis/parkinsonism-dementia of Guam. In the cerebral cortex of AD cases, lesions are preferentially located in the hippocampal formation and neocortical association areas, whereas primary motor and primary sensory areas are relatively spared [3, 12, 18, 22–26, 34, 38, 41]. The analysis of the regional and laminar distribution of NFT in the neocortex of AD cases revealed that a strong correlation exists between NFT localization and the distribution of the neurons of origin of the long corticocortical projections [3, 18, 22–26, 29, 34, 36–38]. The NFT density in neocortex has also been correlated with the loss of specific populations of pyramidal cells, suggesting that certain subgroups of neurons might be more prone to degeneration, whereas other neuronal populations might be relatively resistant to the degenerative process [23, 26, 36]. It has been proposed that a selective loss of specific elements of the cortical projections occurs in AD, leading to a neocortical isolation syndrome that results in dementia [18, 22–26, 28, 29, 34, 36–38, 41].

Progressive supranuclear palsy (PSP) was originally recognized as a clinical and neuropathological entity by Steele, Richardson and Olszewski [46] and is characterized clinically by a supranuclear ophthalmoplegia of the vertical gaze, pseudobulbar palsy, dysarthria, facial, nuchal and troncular muscular dystonia, and in most cases a certain degree of dementia [1, 2, 4, 7, 11, 33, 39, 45, 46]. Histopathologically, PSP is characterized by variable degree of NFT formation and neuronal loss in several subcortical structures such as globus pallidus, subthalamic nucleus, zona incerta, substantia nigra, nucleus basalis of Meynert, tegmentum, raphe, nuclei of the cranial nerves, and dentate nucleus of the cerebellum [1, 4, 7, 11, 16, 33, 35, 39, 40, 46, 47]. In particular, Westphal-Edinger nucleus, and the nuclei of the III, IV, dorsal X, and XII cranial nerves are affected, whereas the nuclei of the V, VI, and VII cranial nerves show fewer changes [4, 40, 44]. At the ultrastructural level,

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NFT in PSP cases are different from those observed in AD, and are composed of 13- to 16-nm straight tubules, although 22-nm twisted tubules have also been reported [6, 48, 49, 52]. Classically, few NFT have been described in the cerebral cortex of PSP cases, making PSP a prototype of the "subcortical dementias" [2, 8, 35]. However, several authors have stressed the cortical involvement in PSP [1, 20, 30, 31], and in particular have pointed to the differences in NFT distribution between PSP and AD [20, 30, 31]. In this article, we report a quantitative regional and laminar analysis of NFT distribution in the cerebral cortex of six patients presenting with PSP. Our results are compatible with previous studies on neocortical involvement in PSP [20, 30, 31], and suggest that the cerebral cortex might be more frequently involved in the degenerative process that takes place in PSP than usually thought. In addition, we observed in all our PSP cases the presence of NFT in the granule cell layer of the dentate gyrus where these lesions have not been previously reported.

Materials and methods

The brains of six patients presenting with PSP (two males, four females, 69.0 ± 5.0 year old) were obtained at autopsy (postmortem delay 8–24 h) and fixed in a 15% formalin solution. The clinical and neuropathological data were obtained from the clinical records of the Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland. The clinical presentation of all the cases was consistent with the diagnosis of PSP and included ophthalmoplegia, dysarthria, neck and trunk rigidity, bradykinesia and slowness of mental activity. One of our cases has been previously reported in detail (case 2) [7]. Routine neuropathological evaluation of the six cases revealed the usual features of PSP with widespread NFT, gliosis and neuronal loss in several subcortical areas, in particular in the inner segment of the globus pallidus, subthalamic nucleus, substantia nigra and tegmentum. A detailed study of the nucleus basalis of Meynert of cases 1 to 4 has been reported separately [47]. Cortical NFT were observed in these cases in the hippocampus and neocortex, however, they were fewer than generally observed in AD cases. Senile plaques were very rare in cortical and subcortical areas except in case 6.

Sections (30-μm-thick) were cut on a cryostat and stained with modified thioflavine S [19, 50], Gallyas [15], modified Globus [17], and hematoxylin-eosin techniques. From each block, additional sections were processed with a specific antibody to the microtubule-associated protein tau. Characterization of this antibody has been fully reported elsewhere [9, 10, 13]. Briefly, 30-μm-thick sections were incubated overnight with the anti-tau antibody at a dilution of 1:2000. Following incubation, sections were processed by the avidin-biotin method using a Vectastain ABC kit (Vector Laboratories), and diaminobenzidine. Some sections stained with the anti-tau antibody were counterstained with hematoxylin-eosin to clarify the cytoarchitecture. The following areas were analyzed (numeration according to Brodmann's nomenclature): 9 and 46 in the prefrontal cortex, 4 (primary motor cortex), 17 and 18 in the occipital cortex, 20 and 21 in the temporal cortex, perirhinal cortex, entorhinal cortex and hippocampus. All the sections were systematically surveyed and lesions werre counted using a computer-assisted image analysis system consisting of a Zeiss Axiophot photomicroscope equipped with a motorized stage, a high sensitivity SIT camera, a DEC 3100 workstation and Macintosh II microcomputer, and custom software. Quantitative analyses were performed on thioflavine S-stained sections. On each slide, NFT were counted under five to ten 1-mm-wide traverses in layers II–III and V–VI separately in the areas 4, 9 and 20, and in the pyramidal layer of the hippocampus proper. In the dentate gyrus, the total number of NFT per section was recorded (see Table 1). In neocortical areas, traverses were counted in regions where the tissue was cut perpendicular to the pial suface to avoid artifacts resulting from oblique sectioning of the cortical layers. Also, computer-generated maps of lesion distribution were created at a magnification of 200 × by collecting the x–y coordinates of all the lesions present under adjacent 250-μm-wide tissue traverses through the entire extent of the hippocampal formation, and the perirhinal and inferior temporal cortex. These tissue traverses were then automatically assembled to create the map (Fig. 1).

Results

Neurofibrillary tangles were present in relatively moderate amounts in the cerebral cortex in all the cases. Senile plaques with amyloid cores were rarely observed and occurred principally in the hippocampal formation and in the superficial layers of the neocortex. Lesion densities were highly variable between cases (Table 1) in all the cortical areas investigated. Staining with the anti-tau antibody revealed NFT densities comparable to thioflavine S-stained materials. Rare neuritic plaque-like structures and numerous neuropil threads were also decorated by the anti-tau antibody. Cases 1 (70 years old) and 6 (75 years old) displayed tau-positive neuritic plaques in the motor, inferior temporal, perirhinal, and entorhinal cortex, and CA1 field of the hippocampus. Case 6 in particular had high densities of neuritic plaques in the primary motor cortex. The other cases (60, 67, 74, and 68 years old, cases 2 to 5, respectively) were practically devoid neuritic plaques.

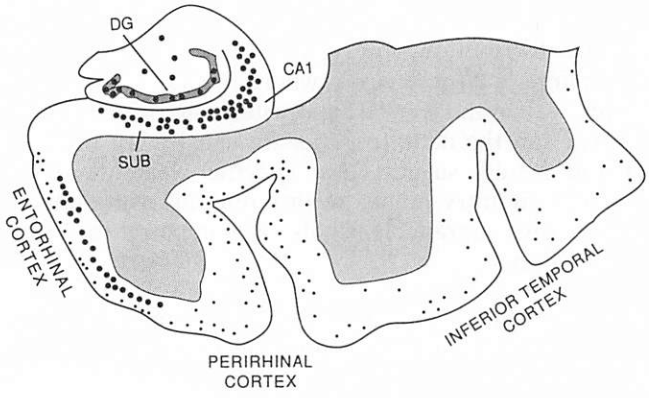

Fig. 1. Computer generated map of neurofibrillary tangle (NFT) distribution in the hippocampal formation and inferior temporal cortex of case 5. The map was created at a magnification of 200 × by collecting the x–y coordinates of all the thioflavine S-positive lesions present under adjacent 250-μm-wide tissue traverses through the entire extent of the section. The tissue traverses were then automatically assembled to create the map. NFT are labeled by *black dots*. Note the presence of NFT in the granule cell layer of the dentate gyrus (*shaded*), and the higher NFT densities in the superficial layers of neocortical areas. NFT located in the dentate gyrus, CA fields of the hippocampus, subiculum, and layer V of the entorhinal cortex have been emphasized and appear as *larger dots*. The white matter is *shaded*. *DG:* dentate gyrus; *CA1:* field CA1 of the Ammon's horn; *SUB:* subiculum

Table 1. Neurofibrillary tangle (NFT) counts in the cerebral cortex of the six progressive supranuclear palsy (PSP) cases

Area	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Dentate gyrus	2.5 ± 1.0	13.0 ± 1.0	10.5 ± 0.5	1.0 ± 0.5	11.4 ± 2.1	4.0 ± 1.3
CA1	30.5 ± 5.6	10.7 ± 2.5	5.4 ± 1.3	2.1 ± 0.3	7.4 ± 2.2	35.6 ± 3.9
20 Layers II–III	26.7 ± 3.2	3.3 ± 1.0	6.5 ± 1.5	3.1 ± 0.4	4.5 ± 1.2	36.8 ± 4.5
Layers V–VI	12.6 ± 1.7	1.0 ± 1.0	2.5 ± 1.7	None	2.4 ± 1.5	28.3 ± 3.3
9 Layers II–III	8.9 ± 2.1	3.0 ± 1.2	5.8 ± 1.9	None	3.4 ± 1.4	3.5 ± 1.4
Layers V–VI	3.7 ± 1.9	0.5 ± 0.4	2.0 ± 1.2	None	1.5 ± 1.0	3.0 ± 1.0
4 Layers II–III	4.2 ± 1.9	3.7 ± 1.0	0.7 ± 0.6	–	1.0 ± 1.0	12.0 ± 1.2
Layers V–VI	5.5 ± 1.3	6.7 ± 1.8	2.0 ± 1.0	–	3.3 ± 1.4	25.0 ± 3.5

Results represent means ± SD and are expressed as NFT counts/mm cortical traverses, except in the dentate gyrus (granule cell layer) where the values show NFT counts/section. Primary motor cortex (area 4) from case 4 was not available. Neocortical areas are numbered according to Brodmann's nomenclature

A striking feature of these six PSP cases was the presence of numerous NFT within the granule cell layer of the dentate gyrus (Figs. 1, 2A,B). In some cases, as many as 15 NFT/section were counted in this region. To our knowledge this is the first report of the presence of NFT in the dentate gyrus in PSP cases. The pyramidal layer of the Ammon's horn was characterized by moderate-to-high NFT densities, with values ranging from 1 (case 4) to 44 (cases 6) NFT/mm of cortical traverse (Table 1, Figs. 1, 2C). Only the CA1 field contained NFT. The CA3 field was devoid of lesions and only rare NFT were observed in the CA4 region (Fig. 1). The subiculum contained NFT densities comparable to those observed in the Ammon's horn (Fig. 1). The entorhinal cortex displayed a laminar pattern of NFT distribution comparable to that observed in AD, with numerous NFT in layers II and V (Figs. 1, 2D). In the neocortex, temporal lobe areas generally contained slightly more NFT than prefrontal regions. Contrasting with the laminar NFT distribution observed in AD [18, 22–26, 29, 34, 38] in which NFT density is higher in layer V–VI as compared to layers II–III, PSP cases exhibited more lesions in the superficial layers. The highest NFT densities were found in the perirhinal cortex (Fig. 1). The inferior temporal cortex contained intermediate NFT densities, with values ranging from 2 to 44 NFT/mm of cortical traverse in layers II–III, and 2 to 33 NFT/mm of cortical traverse in layers V–VI (Table 1; Figs. 1, 2E,F). These values were lower in the prefrontal cortex, where they ranged from 1 to 8 in layers II–III, and 0 to 3 in layers V–VI (Table 1). Finally, we observed numerous NFT in the primary motor cortex in five of our six PSP cases. In addition, case 6 displayed a marked bilateral atrophy of the precentral gyrus (Fig. 3A). Densities ranged from 1 to 15 NFT/mm of cortical traverse in layers II–III and 2 to 30 NFT/mm of cortical traverse in layers V–VI. A similar finding has been reported by Hauw et al. [20]. We have reported that in primary motor cortex of AD cases NFT are preferentialy located in the superficial layers, in contrast to neocortical association areas [18]. It is interesting to note that in the primary motor cortex of the PSP cases, NFT were predominantly distributed in layer V (Table 1; Fig. 3B,C). Areas in the occipital cortex (primary and secondary visual cortex) were devoid of NFT.

Discussion

Although PSP cases contained generally moderate cortical NFT densities, a cortical involvement was observed in all six cases. In the neocortex, NFT were predominantly distributed within the superficial layers. The primary motor cortex was involved in five cases. In this area NFT were concentrated in layers V and VI. The hippocampal formation contained numerous NFT with a distribution pattern similar to that found in AD. However, NFT were systematically present in the granule cell layer of the dentate gyrus, a location where they are usually not observed in AD. In all the areas investigated, NFT were stained by an anti-tau antibody. The presence of tau-positive elements further confirms that abnormal deposition of this protein occurs in PSP [14, 40, 43, 44]. Abnormal tau protein species are accumulated in neurons prone to NFT formation in AD [9, 10, 13]. These abnormal proteins have been characterized as a triplet referred to as tau 55, tau 64 and tau 69 [9, 10, 13]. Recently, a similar deposition of abnormal tau species has been documented in PSP brains [14]. However, the tau produced in PSP differed from those observed in AD, since tau 55 was not detected and tau 64 and 69 were present but with a modified isoelectric point on two-dimensional electrophoreses [14]. Furthermore, these abnormal tau proteins were also observed in neocortical areas. These biochemical findings indicating pathological changes of the tau proteins in the cerebral cortex of PSP patients are in good agreement with the neuropathological observations reported in the present article and by other investigators [20, 30, 31].

The laminar distribution of NFT in PSP cases displayed a reversed pattern as compared to the NFT distribution previously described in AD [18, 22–26, 29, 34, 38]. In PSP cases most of the NFT were located in layers II and III in neocortical association areas, whereas in AD they were preferentially located in layers V and VI [18, 22–26, 29, 34, 38]. In fact, the relatively high frequency and particular neocortical laminar distribution of NFT in PSP brains was first described by Ishino and Otsuki [30, 31], who demonstrated the constant involvement of the neocortex in PSP and pointed to the differences in NFT distribution as compared to AD. These authors concluded that there were very few

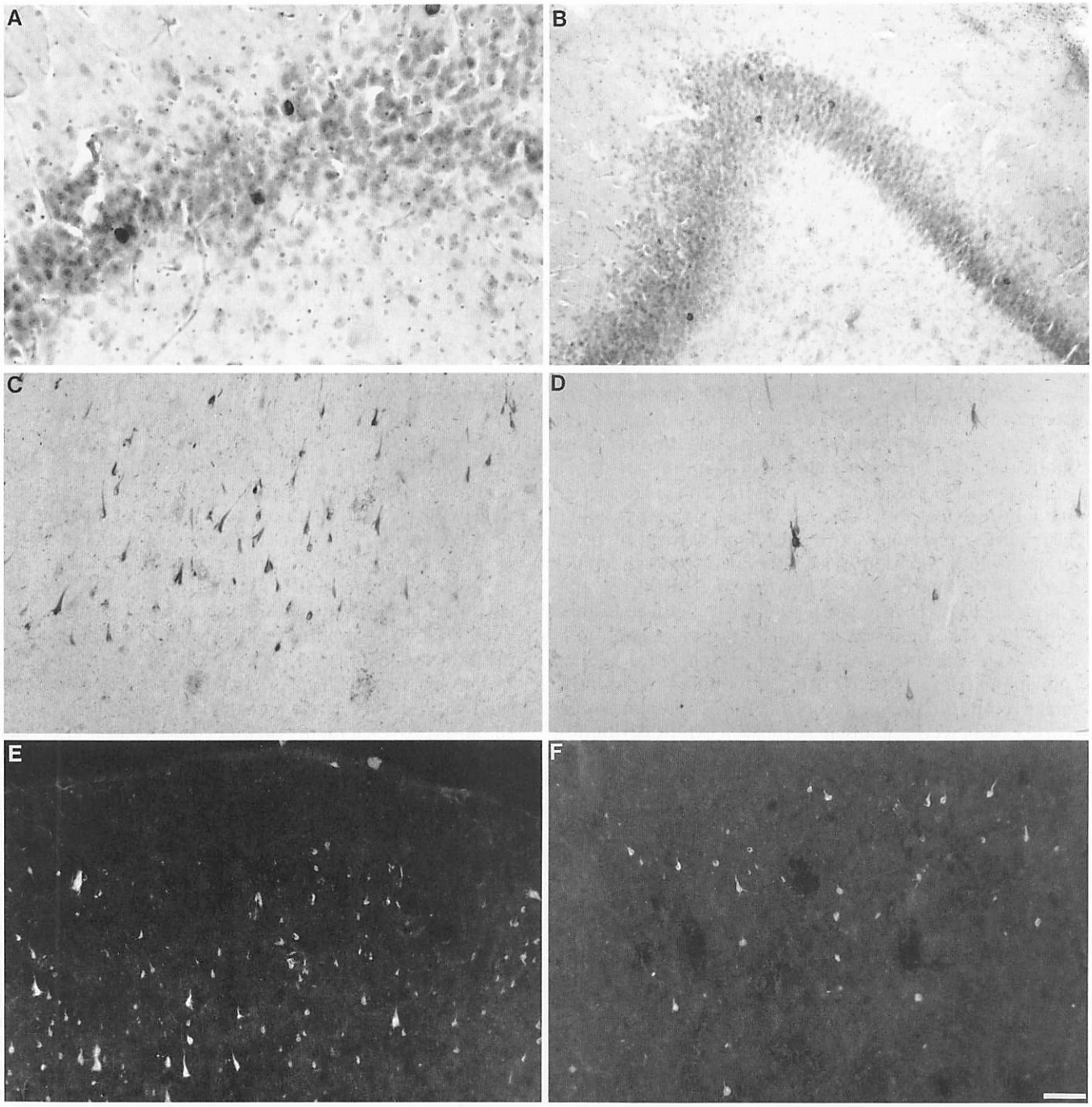

Fig. 2. Neurofibrillary tangles in the granule cell layer of the dentate gyrus of cases 3 (**A**) and 5 (**B**). Tissues were stained with the anti-tau antibody. **C** NFT in the CA1 field of the hippocampus in case 5; note the presence of tau-positive neuritic elements. **D** Layer IV of the entorhinal cortex of case 5; there are numerous large NFT. **E,F** NFT in layers III (**E**), and V (**F**) of the inferior temporal cortex (area 20) of case 1; note that NFT are more numerous in layer III. Tissues were stained with the anti-tau antibody (**A–D**) or thioflavine S (**E–F**). Scale bar (shown on **F**) = 50 μm (**B**), 100 μm (**A,C–F**)

similarities between the two diseases [30, 31]. Moreover, in a recent quantitative neuropathological study Hauw et al. [20] further discussed the differences between AD and PSP. These authors found that NFT were predominantly located in the deep layers of the primary motor cortex in PSP, whereas in AD cases they are preferentially distributed in the superficial layers. Also, they found that the primary motor cortex was more severely affected than neocortical association areas in PSP as compared to AD [20]. In our cases, the primary motor cortex contained NFT densities comparable to those detected in association areas. Case 6 in particular displayed high NFT and neuritic plaque densities in both superficial and deep layers of the primary motor area.

It is interesting to note that the pattern of NFT distribution observed in PSP is similar to that existing in Guamanian amyotrophic lateral sclerosis/parkinsonism-dementia (ALS/PD) cases [27, 29]. In Guamanian

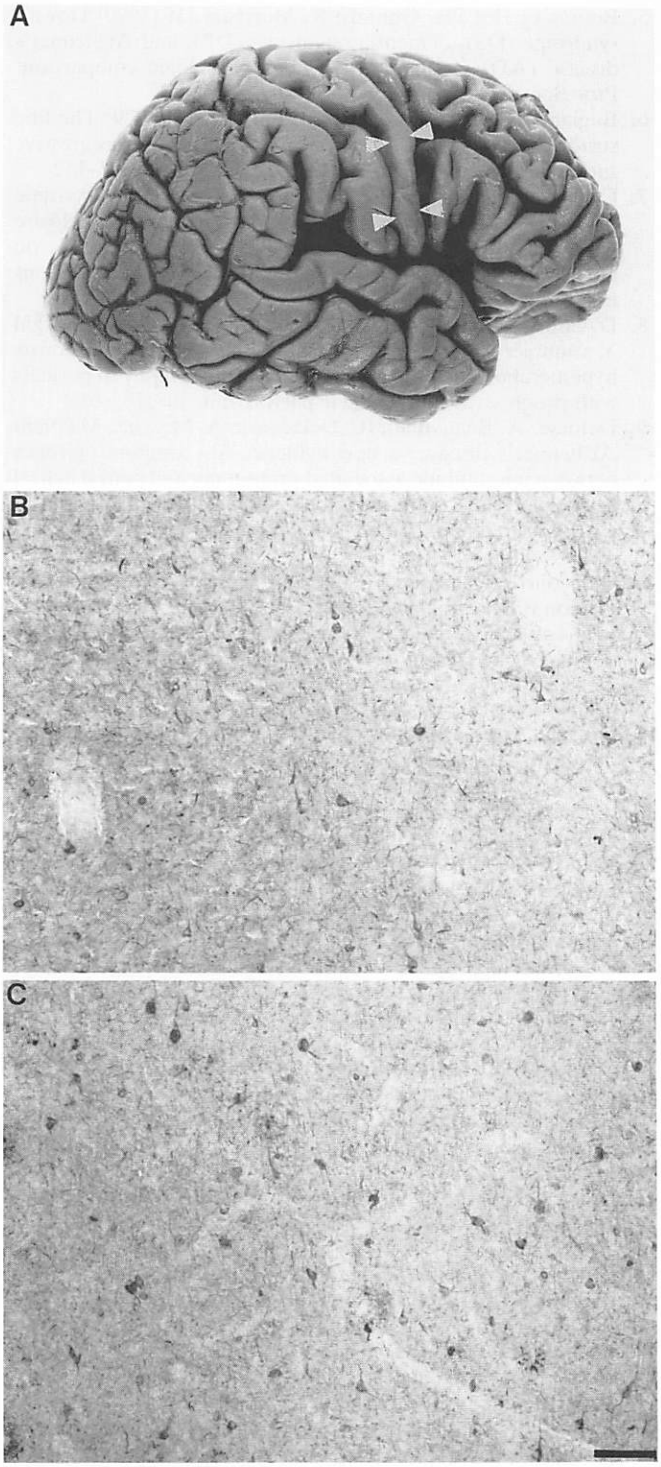

Fig. 3A–C. Primary motor cortex (area 4) involvement in case 6. **A** Lateral view of the right hemisphere of case 6 showing the atrophy of the precentral gyrus (*arrows*). **B,C** NFT in layers III (**B**) and V (**C**) of area 4; note the higher NFT density in layer V, and the numerous tau-positive neuritic elements in this case. Tissues were stained with the anti-tau antibody (**B,C**). Scale bar = 100 μm (**B,C**)

ALS/PD cases we found that layers II and III of neocortical areas were dramatically affected, while layers V–VI contained fewer NFT [27, 29]. As in PSP cases, the distribution of NFT in the hippocampal formation in ALS/PD cases was qualitatively comparable to that of AD cases. At variance with PSP, we did not observe NFT in the granule cell layer of the dentate gyrus of Guam ALS/PD cases, although Ito et al. reported such a localization in a recent study (see Fig. 3B in [32]). It should be noted that cortical NFT densities in our series of Guam ALS/PD cases were generally higher than in our PSP cases [29]. A preferential distribution of NFT in layers II and III has also been reported in cases of dementia pugilistica [5], and in the case of an autistic patient presenting with severe self-injury behavior [28].

The patterns of NFT and senile plaques distribution in AD cases can be interpreted as the reflection of a widespread breakdown of corticocortical projections [18, 22–26, 29, 34, 36, 36–38, 41]. The distribution of NFT in AD is such that both forward corticocortical connections emanating from layer III and feedback projections from layer V are likely to be affected [22–26, 29, 34, 36, 38]. There are organizational schemes for corticocortical connections involving projections ascending a functional hierarchy (i.e., forward projections), and projections from high level association cortical areas back to primary and secondary sensory regions (i.e., feedback projections) that occupy a lower hierarchical level in cortical information processing (for review see [51]). Thus, neocortical association areas linked to numerous cortical target regions display a high representation of corticocortically projecting neurons in both layers III and V. It is worth noting that this pattern of connectivity is reflected by the distribution of NFT in AD brains [22, 23, 26, 29, 34, 36, 38]. Interestingly, in PSP cases (as well as in Guam ALS/PD cases [27, 29]), the NFT distribution also matches corticocortical connectivity, however, it is likely that forward projections are more susceptible to degeneration than feedback projections in these cases, since NFT exhibit a strong preference for layers II and III. Similarly, the dramatic pathological changes that occur in layer V of neocortical association areas in AD cases suggest that additional corticocortical circuits are compromised in AD as compared to PSP. In addition, the presence of numerous NFT in the granule cell layer of the dentate gyrus suggest that certain intrinsic elements of the hippocampal circuits are affected in PSP. Thus, it is possible, as proposed by Hauw et al. [20], that certain neuronal populations are selectively affected in the neocortex of PSP cases. It is, however, not clear how the distribution of NFT is related to the clinical presentation of the disease. In this context, the severe subcortical pathology characteristic of PSP is likely to play a major role in the progression of the disease [2, 4, 7, 8, 11, 33, 39, 45, 46], while dementia in AD could be more related to the massive cortical involvement. Finally, AD cases display numerous cortical senile plaques, whereas PSP cases had only rare plaques. A similar observation has been made by Hauw et al. [20], who found rare senile plaques and amyloid deposits in their PSP series. Recently, however, a case of PSP with widespread amyloid deposition has been reported [42]. The lesion distribution in this case were reminiscent of the diffuse amyloid deposits

observed in the early stage of AD, suggesting a possible co-occurrence of the two diseases [42]. Previous observations on the distribution of pathological lesions in AD have led to the hypothesis that senile plaques could represent the degeneration of axon terminals originating from the same corticocortical projections that are devastated by NFT formation [23, 26, 34, 36, 38, 41]. The nearly complete absence of senile plaques in PSP cases could be related to the possible sparing of certain of these projections as compared to AD.

The participation of the primary motor cortex to the motor symptomatology observed in PSP patient is not known. However, the fact that NFT occurred principally in layers V and VI in PSP cases as opposed to layer III (which contains the majority of NFT in the primary motor cortex in AD [18]), suggests that there is a selective damage to the output layers of the primary motor cortex in PSP. In this respect, it is relevant to note that we reported recently the case of an AD patient with severe motor impairment and who had a dramatic increase in NFT counts in the deep layers of the primary motor cortex as compared to other AD cases [18]. High neuritic plaque counts were found in the primary motor cortex of our case 6. However, the restricted localization of these lesions in this case suggests that coexisting AD is unlikely. Also, we have shown that in Guam ALS/PD the primary motor cortex is severely affected [27]. PSP has been documented clinically and neuropathologically in several Guamanian cases in the recent years [21]. Thus, PSP and Guam ALS/PD may share several pathological features, such as pathological changes in the motor cortex, preferential distribution of NFT in the superficial layers of the neocortex, and specific subcortical involvement. Thus, the similarities between PSP and Guam ALS/PD, the differential distribution of NFT in neocortical areas, the scarcity of senile plaques, and the differences in tau expression in PSP as compared to AD, may reflect the fact that the cognitive decline and dementia that are observed in patients with PSP evolve along different pathogenetic mechanisms than in AD.

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References

1. Akashi T, Arima K, Maruyama N, Ando S, Inose T (1989) Severe cerebral atrophy in progressive supranuclear palsy: a case report. Clin Neuropathol 8:195–199
2. Albert ML, Feldman RG, Willis AL (1974) The 'subcortical dementia' of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 37:121–130
3. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW (1991) The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cerebral Cortex 1:103–116
4. Behrman S, Carroll JD, Jonata I, Matthews WB (1969) Progressive supranuclear palsy – Clinico-pathological study of four cases. Brain 92:663–678
5. Bouras C, Hof PR, Guntern R, Morrison JH (1990) Down's syndrome (DS), dementia pugilistica (DP), and Alzheimer's disease (AD): a quantitative neuropathologic comparison. Proc Soc Neurosci 16:1264
6. Bugiani O, Mancardi GL, Brusa A, Ederli A (1979) The fine structure of subcortical neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 45:147–152
7. Constantinidis J, Tissot R, De Ajuriaguerra J (1970) Dystonie oculo-cervico-faciale ou paralysie progressive supranucléaire de Steele-Richardson-Olszewski – Pseudo-paralysie du regard, troubles visuo-spatiaux, pseudo-démence, altérations neuronales. Rev Neurol (Paris) 122:249–262
8. D'Antona R, Baron JC, Samson Y, Serdaru M, Viader F, Agid Y, Cambier J (1985) Subcortical dementia – Frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. Brain 108:785–799
9. Défossez A, Beauvillain JC, Delacourte A, Mazzuca M (1988) Alzheimer's disease: a new evidence for common epitopes between microtubule associated protein tau and paired helical filaments (PHF): demonstration at the electron microscope by a double immunogold labelling. Virchows Arch [A] 413:141–145
10. Delacourte A, Flament S, Dibe EM, Hublau P, Sablonnière B, Hémon B, Scherrer V, Défossez A (1990) Pathological proteins tau 64 and 69 are specifically expressed in the somatodendritic domain of the degenerating cortical neurons during Alzheimer's disease: demonstration with a panel of antibodies against tau proteins. Acta Neuropathol 80:111–117
11. Dix MR, Harrison MJG, Lewis PD (1971) Progressive supranuclear palsy (the Steele-Richardson-Olszewski syndrome) – A report of 9 cases with particular reference to the mechanism of the oculomotor disorder. J Neurol Sci 13:237–256
12. Duyckaerts C, Hauw JJ, Bastenaire F, Piette F. Poulain C, Rainsard V, Javoy-Agid F, Berthaux P (1986) Laminar distribution of cortical senile plaques in senile dementia of the Alzheimer type. Acta Neuropathol (Berl) 70:249–256
13. Flament S, Delacourte A, Delaère P, Duyckaerts C, Hauw JJ (1990) Correlation between microscopical changes and tau 64 and 69 biochemical detection in senile dementia of the Alzheimer type. Tau 64 and 69 are reliable markers of the neurofibrillary degeneration. Acta Neuropathol 80:212–215
14. Flament S, Delacourte A, Verny M, Hauw JJ, Javoy-Agid F (1991) Abnormal tau proteins in progressive supranuclear palsy – Similarities and differences with the neurofibrillary degeneration of the Alzheimer type. Acta Neuropathol 81:591–596
15. Gallyas F (1971) Silver staining of Alzheimer's neurofibrillary changes by mean of physical development. Acta Morphol Acad Sci Hung 19:1–8
16. Ghatak NR, Nochlin D, Hadfield MG (1980) Neurofibrillary pathology in progressive supranuclear palsy. Acta Neuropathol (Berl) 52:73–76
17. Globus JH (1927) The Cajal and Hortega glia staining methods. A new step in the preparation of formaldehyde-fixed material. Arch Neurol Psychiatry 18:263–271
18. Golaz J, Bouras C, Hof PR (1991) Motor cortex involvement in presenile dementia: report of a case. J Geriatr Psychiatr Neurol 5:85–92
19. Guntern R, Bouras C, Hof PR, Vallet PG (1992) An improved thioflavine S method for neurofibrillary tangles and senile plaques in Alzheimer's disease. Experientia 48:8–10
20. Hauw JJ, Verny M, Delaère P, Cervera P, He Y, Duyckaerts C (1990) Constant neurofibrillary changes in the neocortex in progressive supranuclear palsy. Basic differences with Alzheimer's disease and aging. Neurosci Lett 119:182–186
21. Hirano A (1990) Amyotrophic lateral sclerosis on Guam. In pursuit of pathology over 30 years. In: Rose FC, Norris FH (eds) ALS. New advances in toxicology and epidemiology. Smith-Gordon, London, pp 103–111
22. Hof PR, Bouras C (1991) Object recognition deficit in Alzheimer's disease: possible disconnection of the occipito-

temporal component of the visual system. Neursci Lett 122:53–56
23. Hof PR, Morrison JH (1990) Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. J Comp Neurol 301:55–64
24. Hof PR, Bouras C, Constantinidis J, Morrison JH (1989) Balint's syndrome in Alzheimer's disease: specific disruption of the occipito-parietal visual pathway. Brain Res 493:368–375
25. Hof PR, Bouras C, Constantinidis J, Morrison JH (1990) Selective disconnection of specific visual association pathways in cases of Alzheimer's disease presenting with Balint's syndrome. J Neuropathol Exp Neurol 49:168–184
26. Hof PR, Cox K, Morrison JH (1990) Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: I. Superior frontal and inferior temporal cortex. J Comp Neurol 301:44–54
27. Hof PR, Perl DP, Steele JC, Janssen W, Morrison JH (1990) Quantitative neuropathologic analysis of ALS-PD cases from Guam. Proc Soc Neurosci 16:1264
28. Hof PR, Knabe R, Bovier P, Bouras C (1991) Neuropathological observations in a case of autism presenting with self injury behavior. Acta Neuropathol 82:321–326
29. Hof PR, Perl DP, Loerzel AJ, Morrison JH (1991) Neurofibrillary tangle distribution in the cerebral cortex of parkinsonism-dementia cases from Guam: differences with Alzheimer's disease. Brain Res 564:306–313
30. Ishino H (1976) Frequency of Alzheimer's neurofibrillary tangles in the cerebral cortex in progressive supranuclear palsy. Folia Psychiatr Neurol Jpn 78:463–470
31. Ishino H, Otsuki S (1976) Frequency of Alzheimer's neurofibrillary tangles in the cerebral cortex in progressive supranuclear palsy (subcortical argyrophilic dystrophy). J Neurol Sci 28:309–316
32. Ito H, Goto S, Hirano A, Yen SHC (1991) Immunohistochemical study of the hippocampus in parkinsonism-dementia complex on Guam. J Geriatr Psychiatr Neurol 4:134–142
33. Jellinger K (1971) Progressive supranuclear palsy (subcortical argyrophilic dystrophy). Acta Neuropathol (Berl) 19:347–352
34. Lewis DA, Campbell MJ, Terry RD, Morrison JH (1987) Laminar and regional distribution of neurofibrillary tangles and neuritic plaques in Alzheimer's disease: a quantitative study of visual and auditory cortices. J Neurosci 7:1799–1808
35. Mitsuyama Y, Seyama S (1981) Frequency of Alzheimer's neurofibrillary tangle in the brains of progressive supranuclear palsy, postencephalitic parkonsonism, Alzheimer's disease, senile dementia and non-demented elderly people. Folia Psychiat Neurol Jpn 35:189–204
36. Morrison JH, Hof PR, Campbell MJ, De Lima AD, Voigt T, Bouras C, Cox K, Young WG (1990) Cellular pathology in Alzheimer's disease: implications of corticocortical disconnection and differential vulnerability. In: Rapoport SR, Petit H, Leys D, Christen Y (eds) Imaging, cerebral topography and Alzheimer's disease. Springer, Berlin Heidelberg New York Tokyo, pp 19–40
37. Mutrux S (1947) Diagnostic différentiel histologique de la maladie d'Alzheimer et de la démence sénile – Pathophobie de la zone de projection corticale. Monatsschr Psychiatr Neurol 113:100–117
38. Pearson RCA, Esiri MM, Hiorns RW, Wilcock GK, Powell TPS (1985) Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. Proc Natl Acad Sci USA 82:4531–4534
39. Probst A, Dufresne JJ (1975) Paralysie supranucléaire progressive (ou dystonie oculo-facio-cervicale). Schweiz Arch Neurol Neurochir Psychiatr 116:107–134
40. Probst A, Langui D, Lautenschlager C, Ulrich J, Brion JP, Anderton BH (1988) Progressive supranuclear palsy: extensive neuropil threads in addition to neurofibrillary tangles – Very similar antigeneicity of subcortical neuronal pathology in progressive supranuclear palsy and Alzheimer's disease. Acta Neuropathol 77:61–68
41. Rogers J, Morrison JH (1985) Quantitative morphology and regional and laminar distribution of senile plaques in Alzheimer's disease. J Neurosci 5:2801–2808
42. Sasaki S, Maruyama S, Toyoda C (1991) A case of progressive supranuclear palsy with widespread senile plaques. J Neurol 238:345–348
43. Schmidt ML, Lee VMY, Hurtig H, Trojanowski JQ (1988) Properties of antigenic determinants that distinguish neurofibrillary tangles in progressive supranuclear palsy and Alzheimer's disease. Lab Invest 59:460–466
44. Shin RW, Kitamoto T, Tateishi J (1991) Modified tau is present in younger nondemented persons: a study of subcortical nuclei in Alzheimer's disease and progressive supranuclear palsy. Acta Neuropathol 81:517–523
45. Steele JC (1972) Progressive supranuclear palsy. Brain 95:693–704
46. Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy – A heterogeneous degeneration involving brain stem, basal ganglia and cerebellum, with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol 10:333–359
47. Tagliavini F, Pilleri G, Bouras C, Constantinidis J (1984) The basal nucleus of Meynert in patients with progressive supranuclear palsy. Neurosci Lett 44:37–42
48. Tellez-Nagel I, Wisniewski HM (1973) Ultrastructure of neurofibrillary tangles in Steele-Richardson-Olszewski syndrome. Arch Neurol 29:324–327
49. Tomonaga M (1977) Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 37:177–181
50. Vallet PG, Guntern R, Hof PR, Golaz J, Delacourte A, Robakis NK, Bouras C (1992) A comparative study of histological and immunohistochemical methods for neurofibrillary tangles and senile plaques in Alzheimer's disease. Acta Neuropathol 83:170–178
51. Van Essen DC (1985) Functional organization of the primate visual cortex. In: Peters A, Jones EG (eds) Cerebral cortex, vol 3. Plenum, New York, pp 259–329
52. Yagishita S, Itoh Y, Amano N, Nakano T, Saitoh A (1979) Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 48:27–30