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Neurofibrillary Pathology in Progressive Supranuclear Palsy

N. R. Ghatak, D. Nochlin, and M. G. Hadfield

Department of Pathology (Neuropathology), Box 17, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, USA

Summary. We describe the fine structure of the subcortical neurofibrillary tangles (NFT) in 2 cases of progressive supranuclear palsy (PSP). In case 1 (69-year-old man) about one half of the NFT in the midbrain and pons examined were composed of 13–16 nm straight filaments and the others were made up of paired helical filaments (PHF) of Alzheimer type. The NFT in case 2 consisted of straight tubules with infrequent segments of unusual twisted fibril of unknown nature. The simultaneous occurrence of straight and PHF in one of these cases suggests that the NFT in PSP may be similar to those of Alzheimer type occurring in various conditions.

Key words: Progressive supranuclear palsy – Alzheimer's disease – Neurofbirillary tangles – Paired helical filaments – Twisted tubules

The occurrence of neurofibrillary tangles (NFT) composed of 15 nm straight tubules is regarded as the hallmark of progressive supranuclear palsy (PSP) also known as Steele-Richardson-Olszewski syndrome (Tellez-Nagel and Wisniewski 1973; Powell et al. 1979; Roy et al. 1974; Case Records of the Massachusetts General Hospital 1975; Bugiani et al. 1979; Jellinger et al. 1980). Recently, Tomonaga (1977) and Yagishita et al. (1979) reported two cases of PSP in which some of the NFT were composed of paired helical filaments (PHF) of Alzheimer type. We studied two cases of PSP and found typical PHF comprising some of the NFT in one case. In the other case we came across unusual twisted fibrillary structures mixed with 15 nm straight filaments. These findings indicate that the straight filaments of PSP and the PHF known to occur in Alzheimer's disease and several other conditions (Wisniewski et al. 1976, 1979) may be interrelated.

Offprint requests to: N. R. Ghatak, MD (address see above)

Material and Methods

The brains were obtained from two patients aged 69 years (Case 1) and 72 years (Case 2), respectively, who were clinically diagnosed as having PSP. Both patients died within 3 years after diagnosis.

The brains were examined in detail with the light microscope using various staining methods including Bodian and Holzer's stains. For electron microscopy, selected areas of the midbrain and pons were obtained from formalin-fixed brain tissue and paraffin blocks. These areas included the tegmentum, locus ceruleus, and substantia nigra.

Results

Gross Appearance and Light Microscopy

Both brains weighed about 1,250 g and displayed remarkable atrophy of the superior colliculi. The pathologic changes in these cases were basically the same as those described in PSP (Steele et al. 1964; Jellinger 1971). Briefly, there was a variable degree of neuronal loss with gliosis in various subcortical regions including the basal ganglia, thalamus, subthalamus and more conspicuously in different areas of the midbrain and pons. The remaining neurons in these areas often contained NFT (Fig. 1). The tangles in both cases had a similar appearance and consisted of flameshaped and globose types. Infrequently, the NFT occupied the central part of the neuronal perikaryon resembling a Pick body (Fig. 1a). An occasional NFT limited to the hippocampal cortex was seen in the first case. However, no senile plaques were present. There were no appreciable cortical changes in the second case.

Electron Microscopy

Case 1. About one half of the NFT examined were composed of interlacing bundles of straight filaments ranging from 13–16 nm in diameter (Fig. 2). The individual filaments often displayed irregular outline. Scattered among them was a variable amount of dense granules.

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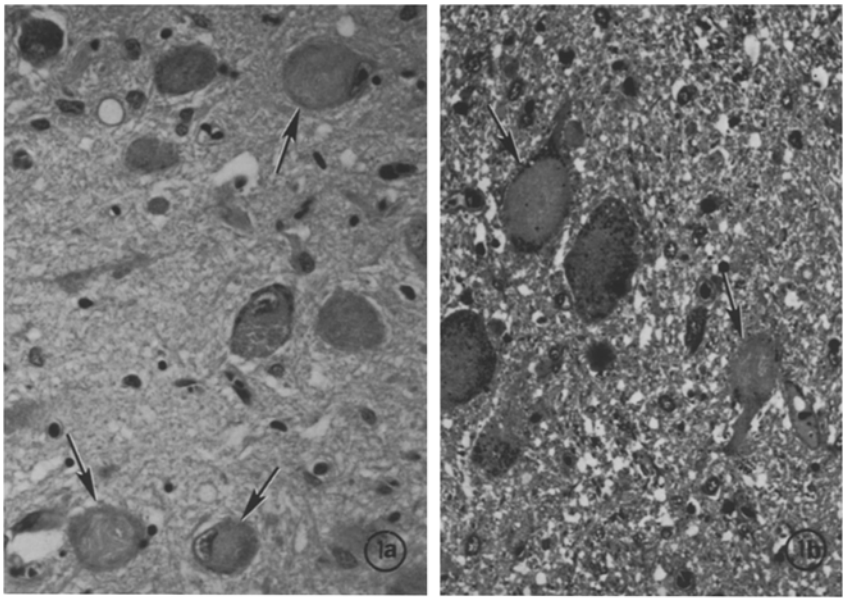

Fig. 1. a Pontine reticular formation in case 1 showing globose type NFT. Hematoxylin-eosin stain. × 290. **b** Locus ceruleus in case 2 showing NFT. Epon section stained with toludine blue. × 290

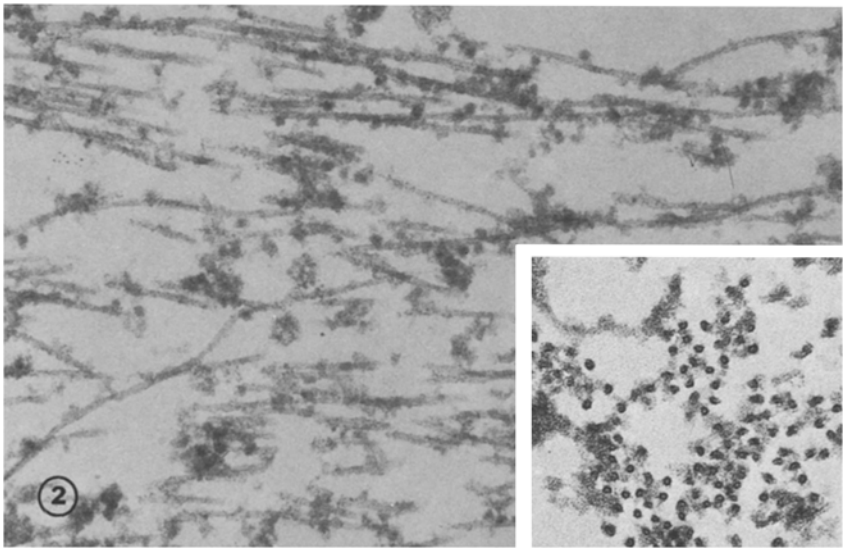

Fig. 2. Straight filaments comprising NFT in pontine reticular formation (case 1). Inset shows circular profiles on cross section. × 70, 000

The remaining tangles were made up to typical PHF measuring 20–22 nm in width with regular constriction at 70–90 nm intervals (Fig. 3).

Case 2. The filaments comprising the tangles were straight and appeared identical to those usually seen in PSP. Occasionally, twisted fibrils usually in short segments, were seen intermingled with the straight filaments (Fig. 4). They measured 25–30 nm in width with constrictions at 140–160 nm intervals and thus were much larger than the PHF described in the first case (Fig. 4). These atypical filaments occurred infrequently.

Discussion

The fine structural studies of the NFT in PSP reported thus far clearly indicate that in most instances the tangles were composed of straight filaments. In only

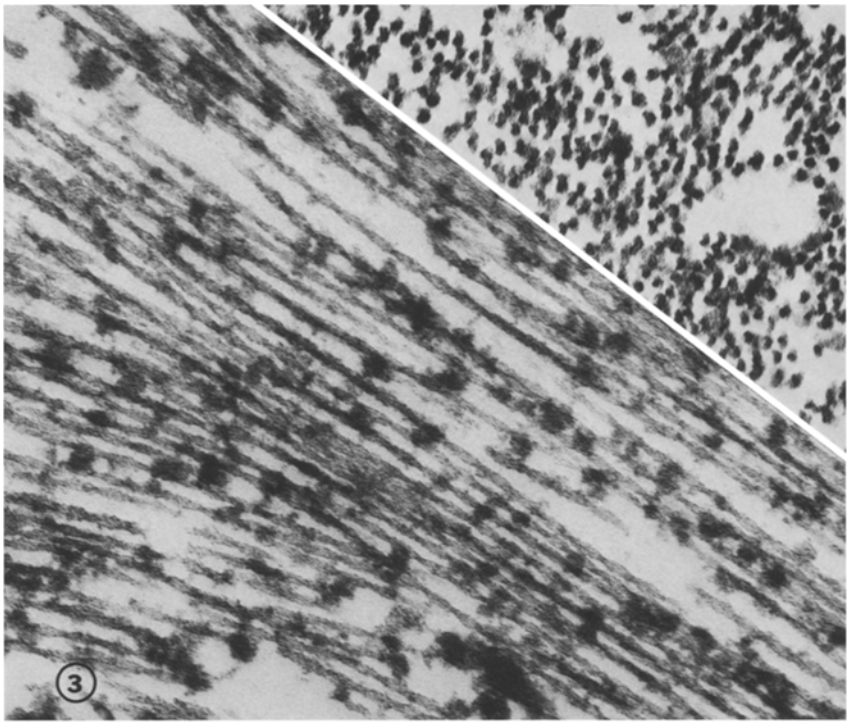

Fig. 3. Densely packed PHF of Alzheimer NFT in locus ceruleus (case 1). Inset shows acriform profiles on cross section. × 70,000

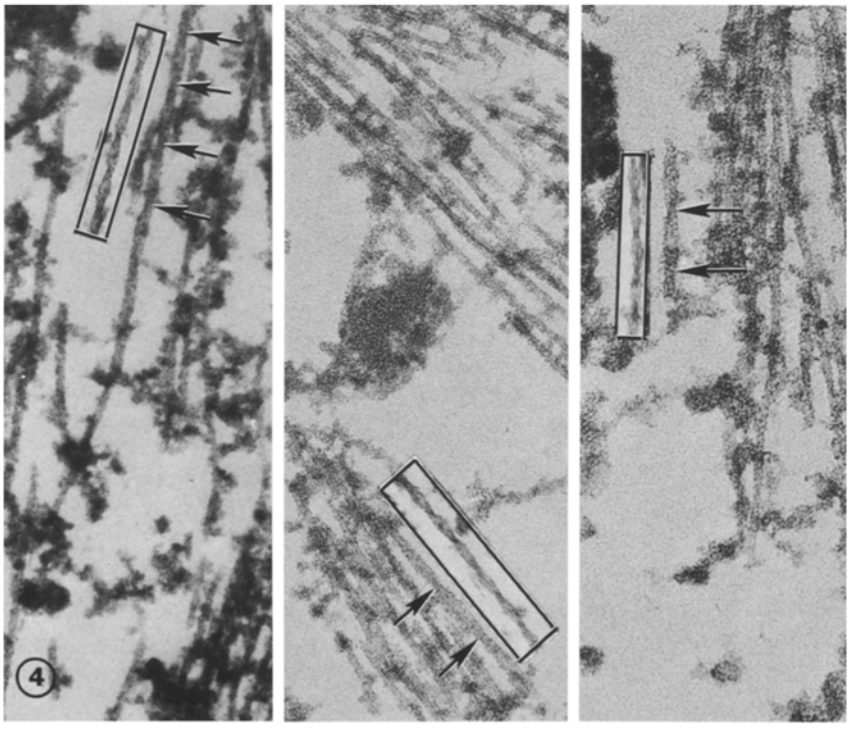

Fig. 4. NFT in substantia nigra of case 2 showing straight filaments and an isolated segment of twisted fibril intermingled with them. Arrows indicate constrictions in these fibrils. Insets next to them represent PHF of Alzheimer type from Fig. 3 with identical magnification for comparison. × 68,450

three cases including case 1 reported here, PHF of Alzheimer type comprised some of the NFT while the others were formed by straight filaments. Two possibilities might be considered to explain this phenomenon. The occurrence of Alzheimer type NFT in the brain stem next to those with straight filaments may suggest aging changes superimposed on PSP. Alternatively, these two morphologically dissimilar NFT may reflect different stages of a similar pathologic process involving the neurons.

In all three patients aged 64–69 years with both types of tangles in the brain stem, only occasional NFT were seen in the cerebral cortex. They were limited to the hippocampus and were not accompanied by senile plaque (Tomonaga 1977; Yagishita et al. 1979). The fine structure of the hippocampal NFT studied in one case revealed both straight filaments and PHF (Yagishita et al. 1979). If these cases indeed represented examples of coexistent PSP and aging phenomenon then one must assume that the latter predominently affected the subcortical neurons rather than the cortex. Interestingly, the occurence of fibrillary tangles in cortical neurons has been suggested as one of pathologic features of PSP (Ishino and Otsuki 1976).

The occurrence of 15 nm wide straight filaments is not limited to PSP alone. Hirano et al. (1968) demonstrated a mixture of straight and twisted tubules in Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. Similar findings have been reported in other conditions including Alzheimer's disease (Oyanagi 1974; Rewcastle 1976; Shibayama and Kitoh 1978). Thus, the simultaneous occurrence of straight filaments and PHF im PSP, albeit infrequent, is of considerable interest and might indicate a basic similarity in the neurofibrillary pathology in various conditions.

The nature and their significance, if any, of the apparently twisted fibrillary structures in Case 2 remain obscure. They seemed to differ from the PHF of Alzheimer's type in two ways. First, they were larger in diameter with constrictions at longer intervals (Fig. 4). Second, they were seen only on rare occasions in an isolated manner. They were not observed in Case 1 in association either with the straight filaments or with PHF. It should be noted that occasional constrictions have been noted in 15 mm straight filaments of PSP (Bugiani et al. 1979; Jellinger et al. 1980). However, the filaments with constrictions in our case appeared wider than the adjacent straight filaments. It is conceivable that these unusual twisted fibrillary structures might represent pairs of helically arranged straight filaments.

Little is known about the pathogenesis of NFT whether composed of straight or twisted tubules. Recent biochemical and immunlogic studies indicate that the twisted tubules of Alzheimer's NFT are probably derived from the pre-existing fibrous protein in the neurons (Iqbal et al. 1976; Grundke-Iqbal et al. 1979; Ishii et al. 1979). Interestingly, Schlaepfer (1978) has induced in vitro transformation of rat neurofilaments into 15–20 nm wide straight tubules similar to those seen in PSP and also into twisted tubules resembling those of Alzheimer's NFT. Thus, perhaps different fibrillary structures forming NFT in various unrelated conditions have a common origin and reflect a nonspecific neuronal change.

References

Bugiani O, Mancardi GL, Brusa A, Ederli A (1979) The fine structure of subcortial neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 45:147–152

Case Records of the Massachusetts General Hospital. Weekly clinicopathological exercises: Case 32–1975 (1975) N Engl J Med 293:346–352

Grundke-Iqbal I, Johnson AB, Terry RD, Wisniewski HM, Iqbal K (1979) Alzheimer neurofibrillary tangles. Antiserum and immunhistological staining. Ann Neurol 6:532–537

Hirano A, Dembitzer HM, Kurland LT, Zimmerman HM (1968) The fine structure of some intraganglionic alternations. J Neuropath Exp Neurol 27:167–182

Ishii T, Haga S, Tokutake S (1979) Presence of neurofilament protein in Alzheimer's neurofibrillary tangles (ANT). An immunofluorescent study. Acta Neuropathol (Berl) 48:105–112

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

Iqbal K, Grundke-Iqbal I, Wisniewski H, Korthals JK, Terry RD (1976) Chemistry of the neurofibrous proteins in aging. In: Terry RD, Gershon S (eds) Neurobiology of aging. Raven Press, New York, pp 315–360

Jellinger K (1971) Progressive supranuclear palsy (subcortical argyrophilic dystrophy). Acta Neuropathol (Berl) 19:347–352

Jellinger K, Riederer R, Tomonaga M (1980) Progressive supranuclear palsy. Clinico pathological and biochemical studies. J Neurol Trans [Suppl] 16:111–128

Oyanagi S (1974) On the ultrastructure of the aging structure of the brain. Brain Nerve (Tokyo) 26:637–653

Powell HC, London GW, Lampert PW (1974) Neurofibrillary tangles in progressive supranuclear palsy. Electron-microscopic observations. J Neuropathol Exp Neurol 33:98–106

Rewcastle NB (1976) The 15 nm filament neurofibrillary tangle. Neuropathol Appl Neurobiol 2:490

Roy S, Datta CK, Hirano A, Ghatak NR, Zimmerman HM (1974) Electron-microscopic study of neurofibrillary tangles in Steele-Richardson-Olszewski syndrome. Acta Neuropathol (Berl) 29:175–179

Schlaepfer WW (1978) Deformation of isolated neurofilaments and the pathogenesis of neurofibrillary pathology. J Neuropathol Exp Neurol 38:244–254

Shibayama H, Kitoh J (1978) Electron-microscopic structure of the Alzheimer's neurofibrillary changes in a case of atypical senile dementia. Acta Neuropathol (Berl) 41:229–234

Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy. Arch Neurol 10:333–359

Tellez-Nagel I, Wisniewski HM (1973) Ultrastructure of neurofibrillary tangles in Steele-Richardson-Olszewski syndrome. Arch Neurol 29:324–327

Tomonaga M (1977) Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 37:177–181

Wisniewski HM, Narang HK, Terry RD (1976) Neurofibrillary tangles of paired helical filaments. J Neurol Sci 27:173–181

Wisniewski K, Jervis GA, Moretz RC, Wisniewski HM (1979) Alzheimer neurofibrillary tangles in diseases other than senile and presenile dimentia. Ann Neurol 5:288–294

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

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