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An Ultrastructural Study of Pick Bodies

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Summary. We report the results of an ultrastructural study of Pick bodies (PB). A histogram constructed with the maximal width of each filamentous component in PB revealed a wide range of sizes among the filaments, in contrast to the unique composition of the paired helical filaments (PHF) seen in the neurofibrillary tangle of Alzheimer type (NFT-AT). Morphologically, three groups of filaments could be distinguished. The first group consisted of straight smooth-surfaced filaments of 10–14 nm diameter, which were presumably altered neurofilaments. The second one was of straight smooth-surfaced "tubules" of 15–22 nm diameter, smaller than normal microtubules. The third one was of PHF thought to be formed by a pair of filaments of the first group. The PHF found in PB differed from PHF of NFT-AT in the distance between crossovers, and rather resembled the loosely interwinding PHF reported in NFT of progressive supranuclear palsy.

Key words: Pick's disease – Neuronal inclusion – Paired helical filament (PHF)

Introduction

Most workers on the ultrastructural composition of the argentophilic neuronal inclusions in Pick's disease are of the opinion that Pick bodies (PB) are basically and predominantly composed of randomly oriented straight filaments of 10–12 nm diameter which seem to be derived from neurofilaments (Rewcastle and Ball 1968; Schochet 1972; Towfighi 1972; Wisniewski et al. 1972; Brion et al. 1973; Mikol et al. 1980), and some of them reported the coexistence of microtubules of 24 nm diameter (Wisniewski et al. 1972; Brion et al. 1973), or the characteristic parallel formation and the occasional geometric pattern resulting from crossing over of these parallel running filaments (Mikol et al. 1980; Oyanagi 1983). In addition, a few observations noted the accumulation of paired helical filaments (PHF) very similar to the PHF found in neurofibrillary tangles of Alzheimer type (NFT-AT) and to these occasionally found in NFT in progressive supranuclear palsy (PSP) (Schochet et al. 1968; Oyanagi 1974; Shibayama et al. 1983). Consequent to these findings, several attempts were made to immunocytochemically compare the components of PB with those of NFT-AT and NFT in PSP in search of a possible common structural link between these three degenerative conditions.

In the present study, we report ultrastructural observations of the fibrillary structures found in Pick bodies from a typical case of Pick's disease and morphological comparisons with those fibrillary structures found in NFT-AT and NFT in PSP.

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Materials and Methods

Specimens were taken from a 57-year-old man at the time of death following an 11-year history of clinically diagnosed Pick's disease. His history dated back to July 1968, when he was admitted to hospital with rapidly progressing dysphasic symptoms that were thought to be transcortical motor aphasia. Following deterioration in language function and memory, he began to show gradual diminution in initiative with stereotype behavior appearing in 1973. Two years later, he manifested global aphasia with apraxic symptoms. A pneumoencephalographic study showed remarkable enlargement of the ventricular system. At this time, bowel and bladder incontinence was noted together with the appearance of muscle rigidity, hyperreflexia, and primitive reflexes. He regressed to an apallic state by the middle of 1977 and expired in 1979 with general emaciation.

The brain was fixed in 10% neutral formalin and processed according to convention for neuropathologic examination. Tissue blocks were taken from superior temporal and inferior frontal gyri, washed with phosphate buffer, postfixed in 1% osmic acid, dehydrated through graded alcohol, and embedded in Epon 812 for electron-microscopic study. Ultrathin sections were made using a Porter-Blum MT-2 ultramicrotome with glass blades, stained with

uranyl acetate and lead acetate, and examined by a JEOL JEM 100-CX electron microscope.

A histogram was constructed distributing the measured maximal widths of the filaments examined in the inclusion bodies and photographed at a uniform magnification of 100,000. Structures identified as PHF were included in the histogram.

Results

Neuropathologic Findings

Grossly, the brain, weighing 970 g after fixation, showed severe, localized atrophy over the frontal lobe, temporal lobe, and insula (Fig. 1). Microscopically, marked neuronal loss and astrocytosis with profound fibrous gliosis predominated the atrophic area. Moderate fibrous gliosis appeared conspicuously in the crus cerebri, basis pontis, olivary, and dentate nuclei. The characteristic ballooned neurons containing argentophilic inclusion bodies found most abundantly in the frontal cortex also appeared in the temporal, insulate, and hippocampal cortices and in the striatum and pontine tegmentum. While a majority of the PB presented as well demarcated uniformly homogenous inclusions, some showed uneven inner structure with Bodian stain (Fig. 2).

Electron microscopic Findings

Identification of Pick bodies was not difficult because of their distinct morphology. In neurons containing a PB, the nucleus was dislocated to the periphery, and filamentous structures in random arrays dominated almost the entire cell body, with lipofuscin granules and other organellae scattered among the filaments. In contrast to the unfavorable preservation of intracytoplasmic organelles, the filaments were clearly and distinctly visualized (Fig. 3), even though amorphous electron-dense materials were scattered among the filaments.

Generally, the filaments in PB followed no definite pattern especially at the center, but toward the periphery they tended to course along the cytoplasmic rim. A few filaments in parallel array formed bundles toward the center (Fig. 4), but the definite geometric arrangement that results from crossing over of parallel filaments, as has been reported (Mikol et al. 1980; Oyanagi 1983), was not demonstrated in any sections examined.

At higher magnification, these fibrillar structures actually consisted of single, smooth surfaced, straight filaments with a range of 10–14 nm diameter, including bundle-forming filaments. In addition, occasionally, distinctly observable thicker filaments of 15–22 nm diameter with clear central lucency at transverse section (Fig. 5) indicating a tubular structure were seen. Further scrutiny of the longitudinal profile of these fibrillar structures, revealed a few filaments with perioic constrictions. These consisted of periodic higher density at narrowed portions and linear high density in the center along the course of filaments, clearly demonstrating the morphological profile of PHF (Fig. 6). The crossovers occurred every 130–160 nm with the maximal width of a pair of about 24 nm and the minimum of 12 nm. Sometimes two adjacent round profiles with slight central lucency were encountered, which may represent the transverse section of paired filament (Fig. 7).

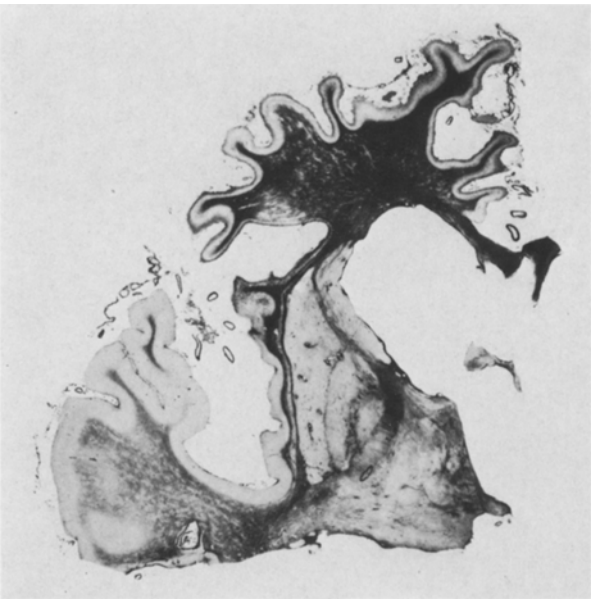

Fig. 1. Oblique section of the left hemisphere according to the CT plane, showing severe atrophy and localized fibrous gliosis in the frontal lobe. Holzer strain

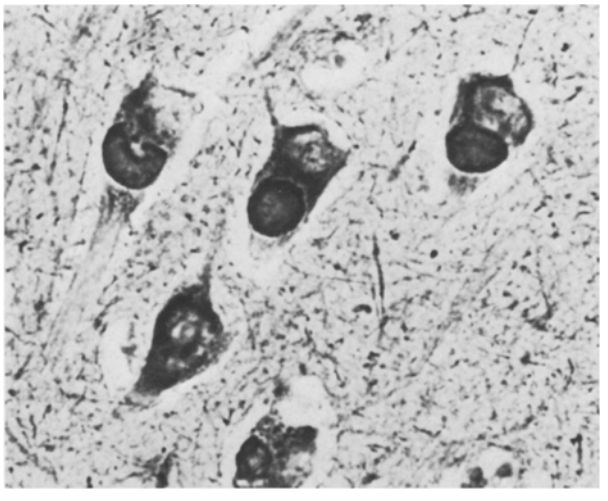

Fig. 2. Neurons containing Pick bodies in the frontal lobe. Bodian stain, × 590

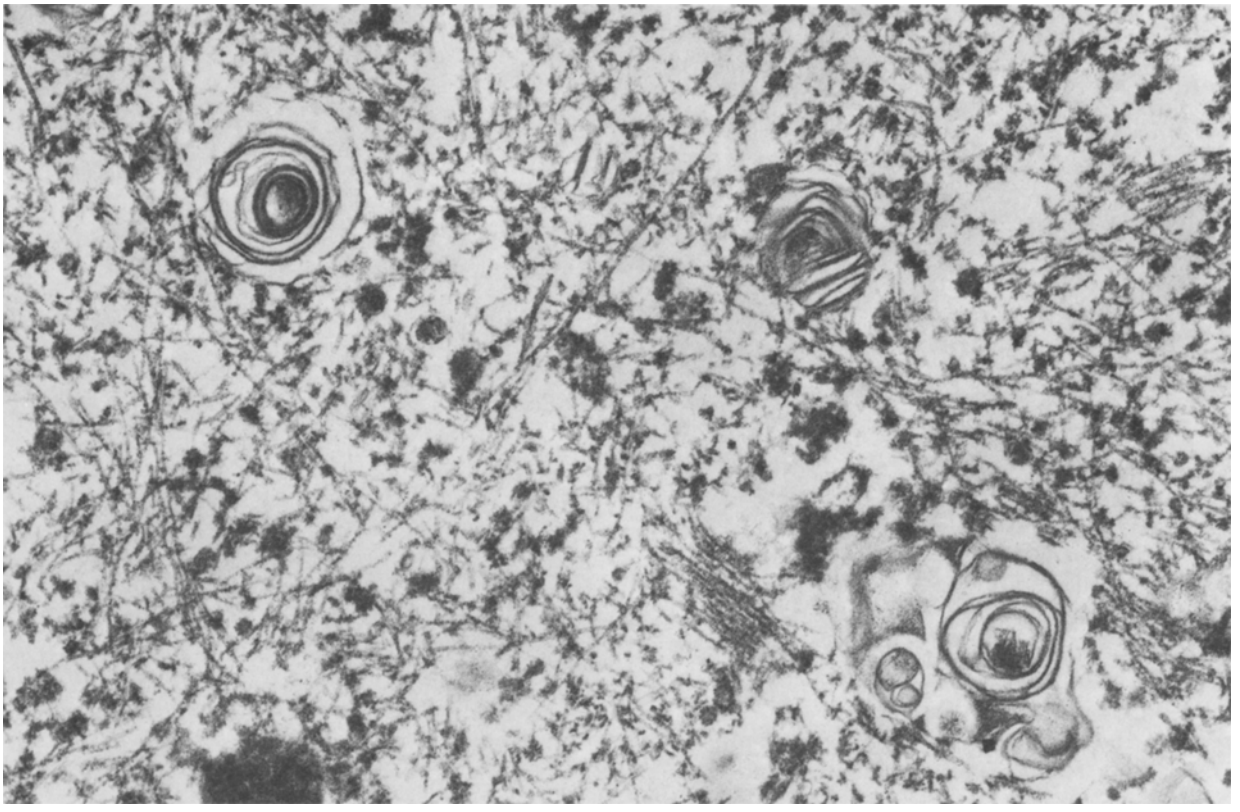

Fig. 3. Electron micrograph of a Pick body. Fibrillary structures are randomly oriented except for a small bundle in the lower middle of the figure. ×31,500

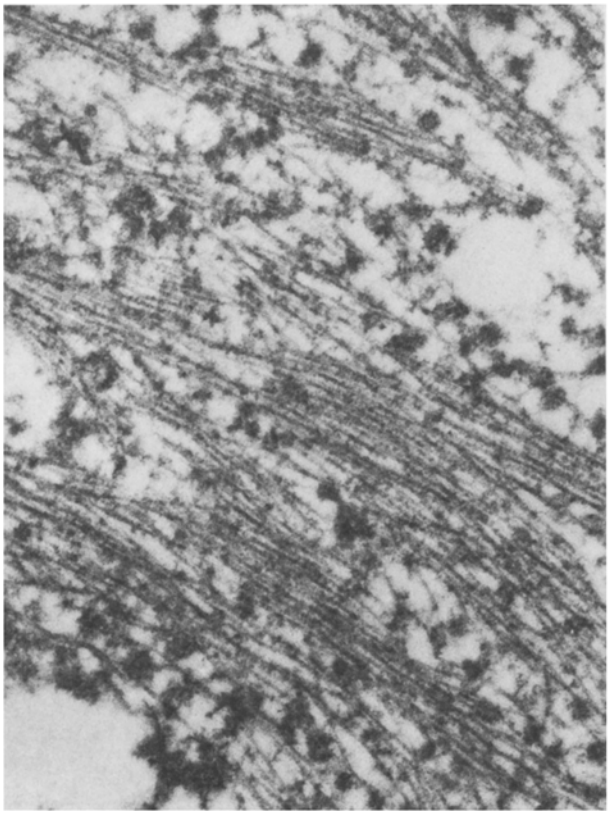

Fig. 4. Parallel arrangement of filaments rarely seen in Pick bodies. ×38,800

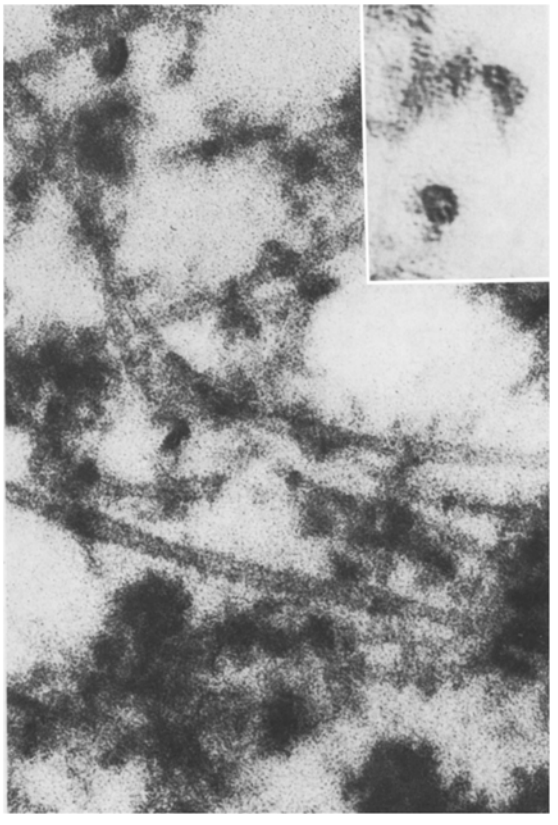

Fig. 5. Straight tubule at high magnification. The *inset* shows two round profiles of different size. ×197,000; *inset*: ×274,000

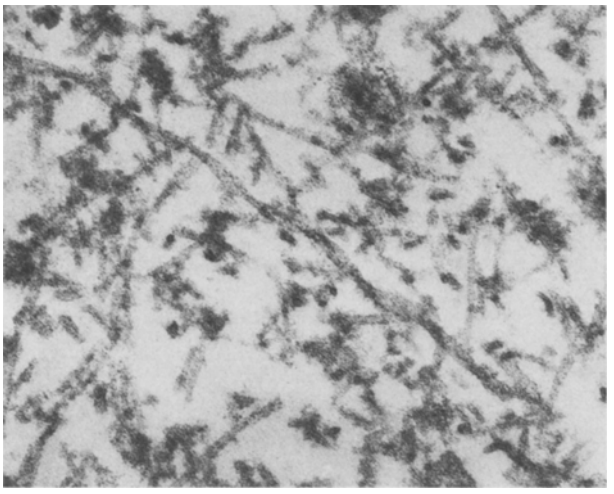

Fig. 6. A PHF seen among the other fibrillary structures. ×76,000

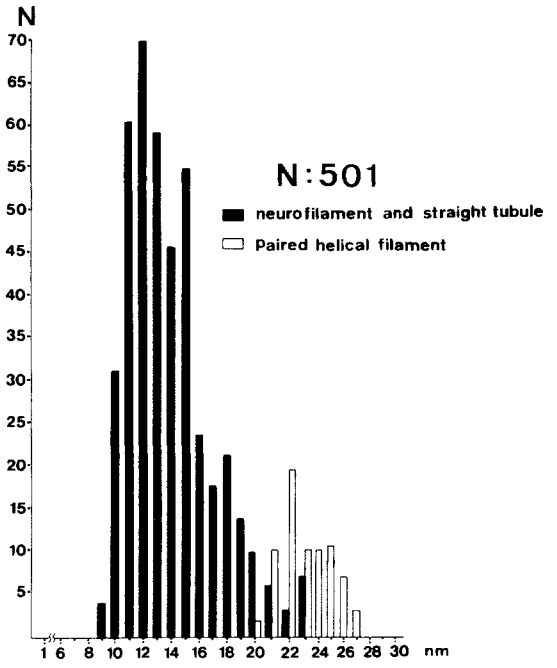

Fig. 8. Histogram distributing the measured maximal width of the filaments in PB

The histogram revealed a wide range of measured widths with two prominent peaks (Fig. 8): in the single straight filaments at 12 nm, and at around 18 nm for straight tubules. Those filaments identified as PHF had a single concentration at 21–26 nm. The number of PHF in all fields represented approximately 14% of the total measured filaments.

Discussion

Available reports on the ultrastructure of PB agree with the characteristic proliferation of filaments with 10–12 nm diameter running in all directions, often avoiding bundle and parallel formations differentiating them somehow from NFT-AT. The present case is in agreement with this observation, but the finding of PHF in our case lends some support to other views that the neurofibrillary changes in both diseases may be somewhat related or similar. However, the prominent compact arrangement of PHF with a consistent and regular twist every 80 nm in NFT-AT suggests otherwise. In the present case, we observed rather a few pairs, and the periodicity of crossovers occurred at longer intervals of about 150 nm, a finding that obviously deviates from the constant compact appearance of the PHF in NFT-AT. Rather, these pairs in the present case resembled more those pairs that are sometimes found in the NFT in PSP (Ghatak et al. 1980; Takauchi et al. 1983). But again, the observed presence of thicker, tubular structures within the range of 15–22 nm diameter with clear central lucency, different in size from normal microtubules, is contrary to the straight tubules of 15 nm diameter

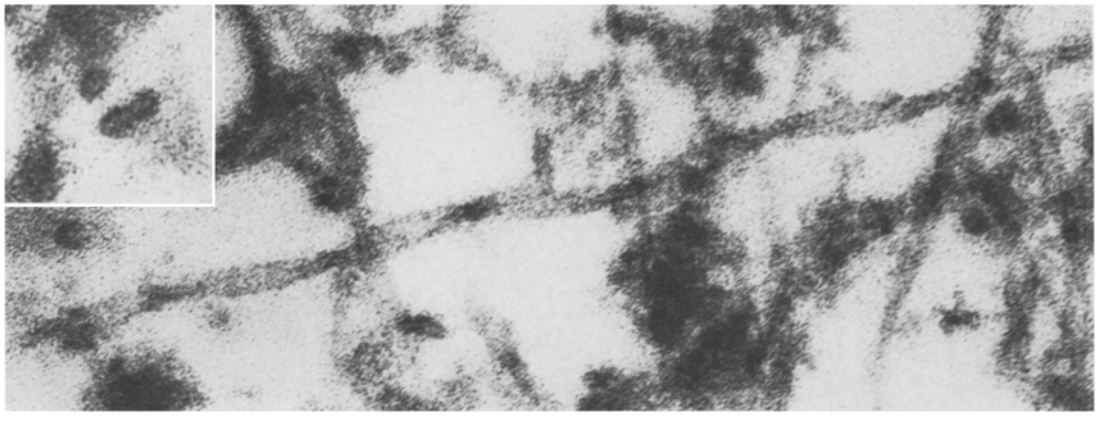

Fig. 7. PHF at higher magnification. Note the longer periodicity of crossovers than PHF in NFT-AT. The *inset* shows the transverse section of a PHF and a single filament. ×154,000; *inset*: ×314,000

characteristically dominant in PSP. Further, this observation is particularly absent in NFT-AT. Barring such negative aspects, we still feel that the ultrastructure of the present case may be closely related, if not very similar, to that occurring in PSP rather than in NFT-AT, although there are some suggestions from immunocytochemical studies that the neurofibrillary changes in these diseases, i.e., Alzheimer's disease, PSP, and Pick's disease, may share a common origin (Gambetti et al. 1983; Probst et al. 1983).

From the histogram with three distinct peaks including PHF, it is very tempting to assume that the unusual pairing may come from filaments with a diameter of 10–14 nm transformed in the diseased state, a statement which supports another report (De Boni and Crapper 1978). At this point, it is difficult to presume the origin of the thick, smooth tubular structures that constitute the second peak in the histogram. It may be possible, however, that these structures derive from deformation of neurofilaments (Schlaepfer 1978) rather than the microtubules.

The present case characteristically presents some bundle formation, a feature very seldom seen in other case of Pick's disease. Moreover, the geometric pattern reported in the past was not found at all in our case. We would like to stress however, that the presence or absence of such findings is not indispensable to the diagnosis of Pick's disease.

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