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Corticobasal degeneration: etiopathological significance of the cytoskeletal alterations

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Abstract We have studied brain tissues from three patients with corticobasal degeneration (CBD) histologically, ultrastructurally and immunohistochemically. Ballooned neurons in the cerebral cortex and severe degeneration of the substantia nigra were observed in them all and weakly basophilic neurofibrillary tangles (NFTs) were distributed widely in the basal ganglia and brain stem. Ultrastructural examination demonstrated that the NFTs comprised characteristic 15-nm-wide straight tubules, which showed positive immunohistochemical staining with an antibody against tau, but not ubiquitin. Tau-immunoreactive neuronal cell bodies without NFTs also were found in the cerebral cortex and subcortical nuclei, predominantly in the brain stem, and the greatest number of tau-positive glial inclusions occurred in the cerebral gray and white matter of the pre- and postcentral gyri. These inclusions comprised tubular structures with diameters of about 15 nm and were localized in the oligodendroglial cellular cytoplasm and processes. These findings indicate that there is a close cytoskeletal pathological relationship between CBD and progressive supranuclear palsy.

Key words Corticobasal degeneration
Ultrastructure · Tau · Glial inclusions
Progressive supranuclear palsy

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Introduction

Corticobasal degeneration (CBD) is a rare, sporadic, neurodegenerative disorder occurring in late life that is characterized clinically by apraxia, limb dystonia, akinesia, rigidity and action tremor and sufferers often exhibit impaired ocular movements and dementia [8, 10, 18, 26, 27]. The major neuropathological abnormalities include frontoparietal atrophy, the presence of ballooned neurons within the cerebral cortex and degeneration of the subcortical nuclei, particularly the substantia nigra [5, 8, 10, 18, 19, 21, 25–27]. In view of these features, CBD has been considered to be a discrete clinicopathological entity [10, 27]. However, with the exception of the consistent involvement of the substantia nigra, the extent and distribution of other subcortical lesions in the cases reported to date vary. Furthermore, neuronal inclusions similar to the neurofibrillary tangles (NFTs) of progressive supranuclear palsy (PSP) have been observed in the substantia nigra of some patients with CBD [10]. Recently, Paulus et al. [25] described a case of corticonigral degeneration with neuronal achromasia and basal NFTs, which presented clinically as PSP.

In this report, we describe the occurrence of NFTs comprising 15-nm-wide straight tubules in the brain stem neurons, which is considered to be one of the hallmarks of PSP, and the widespread distribution of tau-immunoreactive neuronal structures and glial inclusions in the brains of three patients with CBD and discuss the significance of these findings.

Case reports

Case 1

This 67-year-old right-handed man first presented in 1986 complaining of gradually worsening expressive language dysfunction. His speech became increasingly hesitant, he became dysarthric and was unable to speak spontaneously, but he watched television with interest and listened attentively to family conversations. At the age of 71, he consulted a physician, because of a common cold. At that time, he wrote down the address where he had lived 30 years ago. Furthermore, he would forget to pay his bill when he had lunch in a restaurant. At the age of 72, he became unable to dress himself and, 9 months prior to his death, his family discovered him falling forwards and putting the wrong leg into his trouser legs. He was admitted to Ojiya General Hospital on March 16, 1991. He remained alert, but could not speak. His ocular movements were not limited, but he had tetraplegia. A computerized tomography (CT) scan showed bilateral frontoparietal atrophy, sylvian fissure enlargement, which was more severe on the left side, and dilatation of the third ventricle. Progressive aphasia and traumatic cervical myelopathy was diagnosed. He did not recover from the tetraplegia, and gradually became unable to move his eyes in the direction he was told to. He died of bronchopneumonia at the age of 73 years.

Case 2

A 72-year-old housewife visited Sado General Hospital on March 24, 1986, because she had suffered from memory impairment and difficulty in carrying out housework over the previous 1 year. A neurological examination showed action tremor and mild akinesia and neuropsychological tests revealed mild cortical dementia. A CT scan showed mild brain atrophy. Electroencephalography (EEG) showed irregular theta burst while she was hyperventilating. At her initial hospitalization, she was diagnosed as having senile dementia with parkinsonism. During the next year, the akinesia worsened and rigidity of her extremities developed. A trial of L-DOPA was of no benefit. When she was 74 years old, she fell backwards frequently and showed vertical gaze palsy. Gradually, akinetic mutism developed until at the age of 75 when she was readmitted to the hospital. At this time, she was mute and showed a decorticate posture and apraxia of lid opening. A second CT scan revealed marked frontal and medial temporal atrophy. She died of bronchopneumonia at the age of 77 years. There was no family history of neurological disease.

Case 3

A 64-year-old retired pharmacist noted hand tremor and akinesia in 1980, when he was diagnosed as having Parkinson's disease. Administration of L-DOPA and trihexyphenidyl hydrochloride (Artane) yielded some improvement in the tremor, but akinesia and rigidity gradually worsened over the next 4 years. In 1985, he noticed swallowing disturbance and fell down frequently. He was admitted to Shinrakuen Hospital on July 22, 1986. A neurological examination revealed marked akinesia, dysarthria, dysphagia, moderate rigidity and dysuria, but no pyramidal tract sign. He was alert and able to write down a short sentence and learnt how to use a word processor in the rehabilitation program. Ocular movements were normal. A CT scan showed frontal cortical atrophy. He was readmitted to the hospital on April 5, 1987 and died of bronchopneumonia at the age of 71 years. Clinically, striato-nigral degeneration was suspected.

Materials and methods

For routine histological examination, the nervous tissues were fixed with 4% paraformaldehyde in 0.1 M phosphate-buffered solution (PBS) and then embedded in paraffin. Sections were cut and stained with hematoxylin-eosin (H&E) and Klüver-Barrera (K-B) solution. Bodian, Bielshowski, Congo red, Holzer and Berlin blue staining procedures were carried out when necessary.

Paraffin-embedded, 4-μm sections were subjected to immunohistochemical investigations using the avidin-biotin-peroxidase complex (ABC) method [12] with a Vectastain ABC kit (Vector, Burlingame, Calif., USA). The following primary antibodies were used: rabbit anti-human tau (gift from Dr. Ihara [13, 23], 1:1,000); rabbit anti-cow ubiquitin (Dakopatts, Denmark, 1:150); monoclonal antibodies against two neurofilament proteins, phosphorylated (SMI31, 1:1,000) and non-phosphorylated determinants (SMI38, 1:600, both from Sternberger Monoclonals Inc., Baltimore, Md., USA) and a monoclonal antibody against glial fibrillary acidic protein (GFAP, clone ZCG29, Nichirei, Tokyo, Japan). Nonspecific binding of the biotin/avidin system reagents was blocked by pretreating the sections using a Blocking Kit (Vector), then incubating them with the required primary antibody overnight at 4°C, followed by the secondary reagent containing biotinylated anti-rabbit or anti-mouse IgG (diluted 1:200) for 30 min and finally with ABC for 30 min. The tissues were subjected to the peroxidase reaction using freshly prepared 0.02% 3,3'-diaminobenzidine-tetrachloride (DAB) and 0.005% H_2O_2 in 0.05 M TRIS-HCl buffer, pH 7.6, for 10 min at room temperature. Double immunostaining also was carried out, using the anti-tau and anti-GFAP antibodies, as described by Kageshita et al. [15].

Electron microscopic observations were carried out on several selected brain areas, including the superior frontal, anterior cingulate and precentral gyri, insular cortex, substantia nigra and locus ceruleus, of each patient. The tissues were fixed with 3% glutaraldehyde-1% paraformaldehyde in 0.1 M PBS, pH 7.4, post-fixed with 1% osmium tetroxide, dehydrated through a graded ethanol series and embedded in Epon 812. Toluidine blue-stained 1-μm-thick sections were examined using a light microscope and ultrathin sections were stained with lead citrate and uranyl acetate and examined using a Hitachi H-7100 electron microscope.

Results

Gross findings

The brain of case 1 weighed 1,050 g. There was marked atrophy of the frontal and parietal lobes. Examination of the sections revealed that the cortices of the superior frontal, precentral and parasylvian gyri were thin. The basal ganglia, thalamus, superior colliculus and tegmenta of the midbrain and upper pons were also atrophic. The substantia nigra and locus ceruleus were pale and the dentate nuclei showed a brownish discoloration.

The brain of case 2 weighed 1,120 g and there was marked frontal lobar atrophy which was more severe on the left than the right side. Examination of the sections showed that atrophy was most pronounced in the superior frontal gyrus and hippocampal formation. Both lateral ventricles were moderately enlarged. The globus pallidus showed a brownish discoloration and the thalamic medial nuclei were atrophic. The substantia nigra showed severe depigmentation and the midbrain and upper pontine tegmenta were atrophic.

The brain of case 3 weighed 1,200 g. The frontal lobes were slightly atrophic. The globus pallidus showed a brownish discoloration and the substantia nigra and locus ceruleus were extensively depigmented.

Light microscopy

Microscopic examination of the brain tissues demonstrated that all three patients had undergone essentially similar histological changes.

Cerebral cortex

The cerebral cortices of cases 1 and 2 showed diffuse neuronal loss with gliosis and scattered ballooned neurons, mainly in the third, fifth and sixth cortical layers, the cytoplasm of which was slightly eosinophilic, lacked Nissl substance, and was often associated with vacuolation (Fig. 1). Some proximal dendrites were swollen. The neuronal loss, gliosis and occurrence of ballooned neurons were most pronounced in the medial frontal, anterior cingulate and precentral gyri and insula and were much less marked in the parietal and occipital regions. In the precentral gyrus, there was severe neuronal loss in case 1 and mild to moderate loss in case 2, where the Betz cells had been mostly spared. Case 3 showed the same distribution of ballooned neurons as the others, but there were fewer of them, and the cortical neuronal density was slightly lower than those of cases 1 and 2.

The hippocampal formation of case 2 showed moderate neuronal loss with gliosis and the amygdaloid nucleus contained a number of ballooned neurons with gliosis. Several neurons in the hippocampus and parahippocampal gyrus contained Alzheimer's NFTs, but neither Pick bodies nor senile plaques were found in any of the three patients.

Subcortical nuclei

The most marked changes were observed in the substantia nigra and globus pallidus of each case. In the substantia nigra, severe neuronal loss, intense gliosis and abundant free melanin were observed, and numerous spheroids and brown pigmented, iron-positive, granules were found in this region. The globus pallidus showed marked neuronal loss with fibrillary gliosis and spheroids in the internal and external segments, which was most severe in the rostral portion. Brown pig-

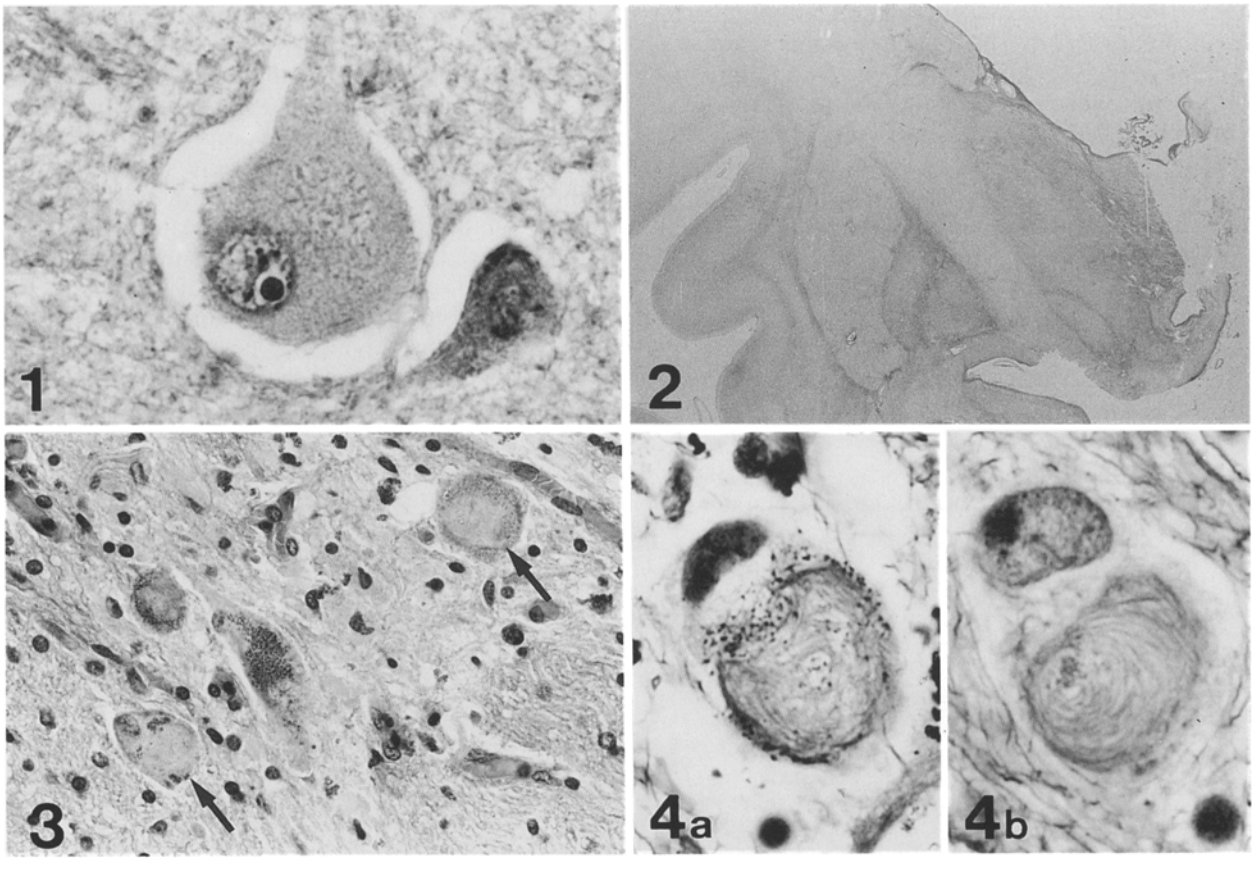


Fig. 1 A ballooned neuron in the motor cortex. Case 1; H&E, × 1,130

Fig. 2 Gliosis of the internal and external segments of the globus pallidus, subthalamic nucleus and thalamic medial nuclei. Case 2; Holzer

Fig. 3 Substantia nigra showing loss of pigmented neurons and weakly basophilic neurofibrillary tangles (*arrows*). Case 1; H&E, × 370

Fig. 4 Neurofibrillary tangles in the substantia nigra (**a**) and periaqueductal gray matter (**b**). Case 1; Bodian, **a** × 1,140; **b** × 1,420

mented granules, identical to those seen in the substantia nigra, were scattered in the neuropil and around the blood vessels. There was mild neuronal loss with moderate gliosis in the medial third of the subthalamic nucleus (Fig. 2). There was mild to moderate loss of large neurons with mild gliosis in the caudate nucleus and putamen, moderate gliosis was observed in the anterior and medial thalamic nuclei and the hypothalamus showed atrophy and moderate gliosis, particularly in the posterior nuclei. In the midbrain, the periaqueductal gray matter showed mild neuronal loss with evident gliosis spreading to the superior colliculi. Neuronal loss was moderate in the pedunculopontine tegmental nucleus and mild to moderate in the locus ceruleus and nucleus basalis of Meynert. The cerebellar dentate nuclei showed Grumose degeneration.

In addition to the above findings, weakly basophilic, fibrillary inclusions, which were considered to be NFTs, were distributed widely in the subcortical nuclei of all the cases (Fig. 3). They were slightly argyrophilic in Bodian-stained preparations (Fig. 4), but were not stained by Congo red. Although NFTs were observed in a few remaining neurons, they were found in the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, hypothalamus, septal nucleus, nucleus basalis of Meynert, periaqueductal gray matter, superior colliculus, substantia nigra, pedunculopontine tegmental and pontine nuclei, brain stem reticular formation, inferior olivary nucleus and spinal gray matter.

A few Lewy bodies were observed in the reticular formation of the medulla oblongata of case 2 and in the locus ceruleus, dorsal vagal nucleus, brain stem reticular formation and intermediolateral nucleus of the spinal cord of case 3.

Fig. 5a–c Glial cytoplasmic inclusions in the subcortical white matter of the motor cortex. Case 1; **a** Bielshowski, × 1,420; **b** tau, × 580; **c** tau, × 1,140

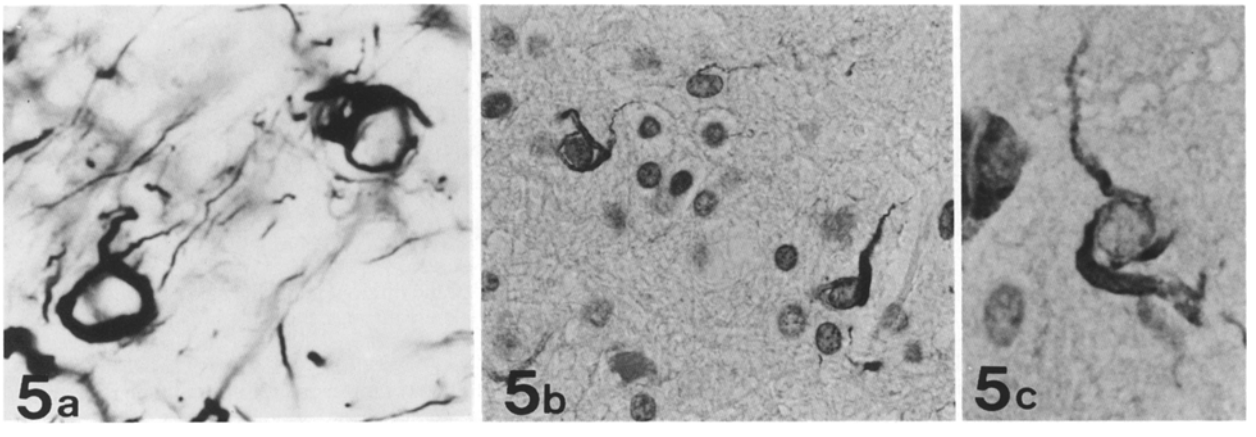
Glial inclusions

Bielshowski's silver staining revealed a number of glial inclusions in case 1 and fewer in cases 2 and 3. The intracytoplasmic fibrillary structures formed a characteristic flame-like shape (Fig. 5a) and occurred most frequently in the frontal, pre- and postcentral cortices and in the white matter underlying the degenerated cortex. Some scattered inclusions also were present in the deep white matter of the frontal and parietal lobes, corpus callosum, internal capsule, basal ganglia, thalamus, midbrain, pons, medulla oblongata and cerebellar white matter. They could not be identified using H&E, K-B, Holzer, Congo red or Bodian staining techniques.

Immunohistochemistry

Almost all the ballooned neurons in the cerebral cortex and amygdaloid nucleus were positive for the phosphorylated neurofilament (Fig. 6a), whereas very few or none were positive for the non-phosphorylated determinant. A few ballooned neurons were immunostained weakly with the antibody against ubiquitin (Fig. 6b). Tau-immunoreactivity was observed in a few ballooned neurons (Fig. 6c) and in several non-ballooned cortical neurons.

The NFTs in the hippocampal formation were positive for tau and ubiquitin, but not for the phosphorylated or non-phosphorylated neurofilaments, whereas those in the subcortical nuclei were labeled with the antibody against tau (Fig. 6d–f), but not with those against ubiquitin or phosphorylated and non-phosphorylated neurofilaments. Tau immunoreactivity also was observed in the cytoplasm of some nerve cells without NFTs: many in the substantia nigra, midbrain and upper pontine tegmenta, posterior hypothalamus and reticular formation of the medulla oblongata, several in the neostriatum, globus pallidus, subthalamic nucleus, thalamus and pontine nucleus and a few in the inferior olivary and dentate nuclei and spinal gray matter. Tau-immunoreactive nerve cell processes also were found in these subcortical nuclei.



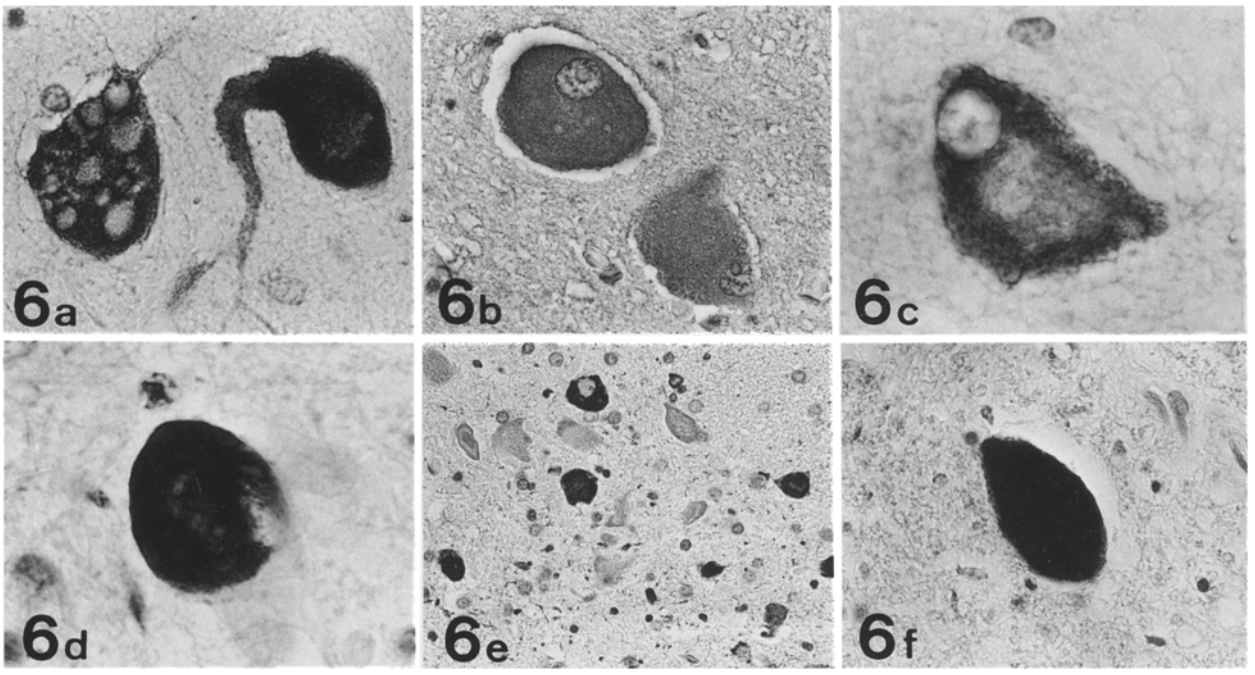


Fig. 6 **a** Phosphorylated neurofilament-reactive ballooned neurons in the cingulate cortex. Note the cytoplasmic vacuolations in the one on the *left side*. Case 2; × 710. **b** Ubiquitin-immunoreactive ballooned neurons in the amygdaloid nucleus. Case 2; × 510. **c** Tau-immunoreactive ballooned neuron in the cingulate cortex. Case 2; × 1,020. **d** A neurofibrillary tangle in the substantia nigra immunostained intensely with the antibody against tau. Case 1; × 1,140. **e** Tau-immunoreactive neurons in the pontine nuclei. Case 1; × 285. **f** Tau-immunoreactive anterior horn cell in the thoracic cord. Case 2; × 450

The glial inclusions were tau positive (Fig. 5b, c), but were not stained with antibodies against ubiquitin, phosphorylated and non-phosphorylated neurofilaments or GFAP. Double immunostaining using anti-tau and anti-GFAP antibodies demonstrated that these inclusions were not astrocytic in origin.

Electron microscopy

The cytoplasm of the ballooned neurons contained fibrillary structures, lipofuscin granules, mitochondria and vesicular and membranous structures. The fibrillary structures comprised neurofilaments with diameters of approximately 10 nm and scattered fibrils that were about 20 nm wide and coated with granular materials.

The NFTs of the substantia nigra and locus ceruleus comprised exclusively bundles of straight tubules, about 15 nm in diameter (Fig. 7). Very rarely, twisted tubules, about 20 nm in diameter with periodicity, were found intermingled with the neurons of the locus ceruleus of case 2.

The glial inclusions comprised straight tubules with diameters of approximately 15 nm (Fig. 8). They were observed in the cytoplasm and processes of cells with round or oval nuclei and moderately dense cytoplasm, which often contained 25-nm-wide microtubules, but no glial filaments. These cells were considered to be of an oligodendroglial nature.

Discussion

In 1968, Rebeiz et al. [26] described the clinical and pathological findings in 3 patients with a disorder they called "corticodentatonigral degeneration with neuronal achromasia". Since then, the findings in 13 additional autopsied patients with CBD have been reported in detail [5, 8, 10, 18, 19, 21, 25, 27]. The neuropathological characteristics of CBD are neuronal loss with gliosis and numerous ballooned neurons in the cerebral cortex, especially in the frontoparietal region, and degeneration of the substantia nigra. The cortical pathologies of our three cases were compatible with a diagnosis of CBD, except for the hippocampal formation involvement in case 2. The substantia nigra was the most severely affected of the subcortical nuclei in all three cases. On the basis of their clinicopathology, we diagnosed that our three patients had CBD.

Recently, Paulus et al. [25] reported a case of CBD with basal NFTs, which presented clinically as PSP. Gibb et al. [10] described the occurrence of slightly basophilic nigral inclusions, which resembled the globose-type NFTs of PSP, in 3 patients with CBD. Interestingly, the latter authors pointed out that similar inclusions were present in the substantia nigra of the original cases described by Rebeiz et al. [26] and concluded that the nigral inclusions were unique to CBD. In each of our 3 patients, the substantia nigra, globus pallidus, superior colliculus and midbrain tegmentum showed marked degeneration and mild to moderate

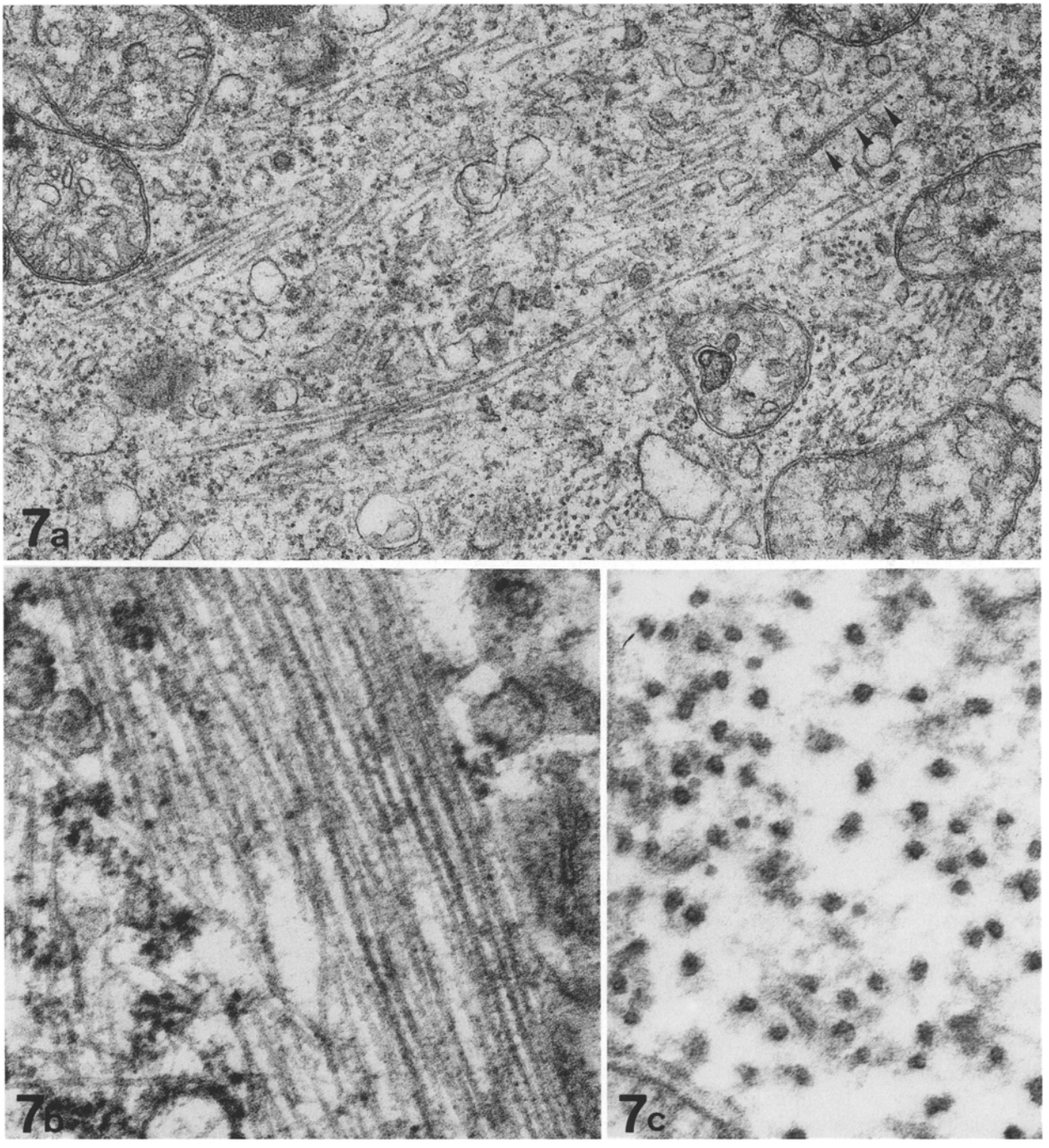


Fig. 7 Electron micrograph (**a**) illustrating a pigmented neuron containing bundles of abnormal filaments in the substantia nigra of case 1. *Arrowheads* indicate a 25-nm-wide microtubule. Higher-magnification views of another area in the same neuron showing longitudinal (**b**) and cross-sectional (**c**) profiles of the 15-nm-wide straight tubules. **a** × 28,000; **b** × 84,000; **c** × 168,000

neuronal loss was observed in the neostriatum, subthalamic and pedunculopontine tegmental nuclei and locus ceruleus. Moreover, NFTs were found in various subcortical nuclei, including those of the above regions. Such subcortical pathology has been suggested to resemble that of PSP [14, 22, 30, 31, 40]. However, to our knowledge, the ultrastructures of neither the NFTs nor the nigral inclusions in patients with CBD have been reported hitherto.

We have demonstrated that the NFTs observed in the substantia nigra and locus ceruleus of patients with CBD comprised 15-nm-wide straight tubules. Their ultrastructure closely resembled that of the NFTs observed in PSP patients [9, 23, 32, 34, 35]. A mixture of straight and twisted tubules has been reported in patients with normal cerebral aging, Alzheimer's disease [24], the Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam [11]. However, we observed 15-nm-wide straight tubules, but no

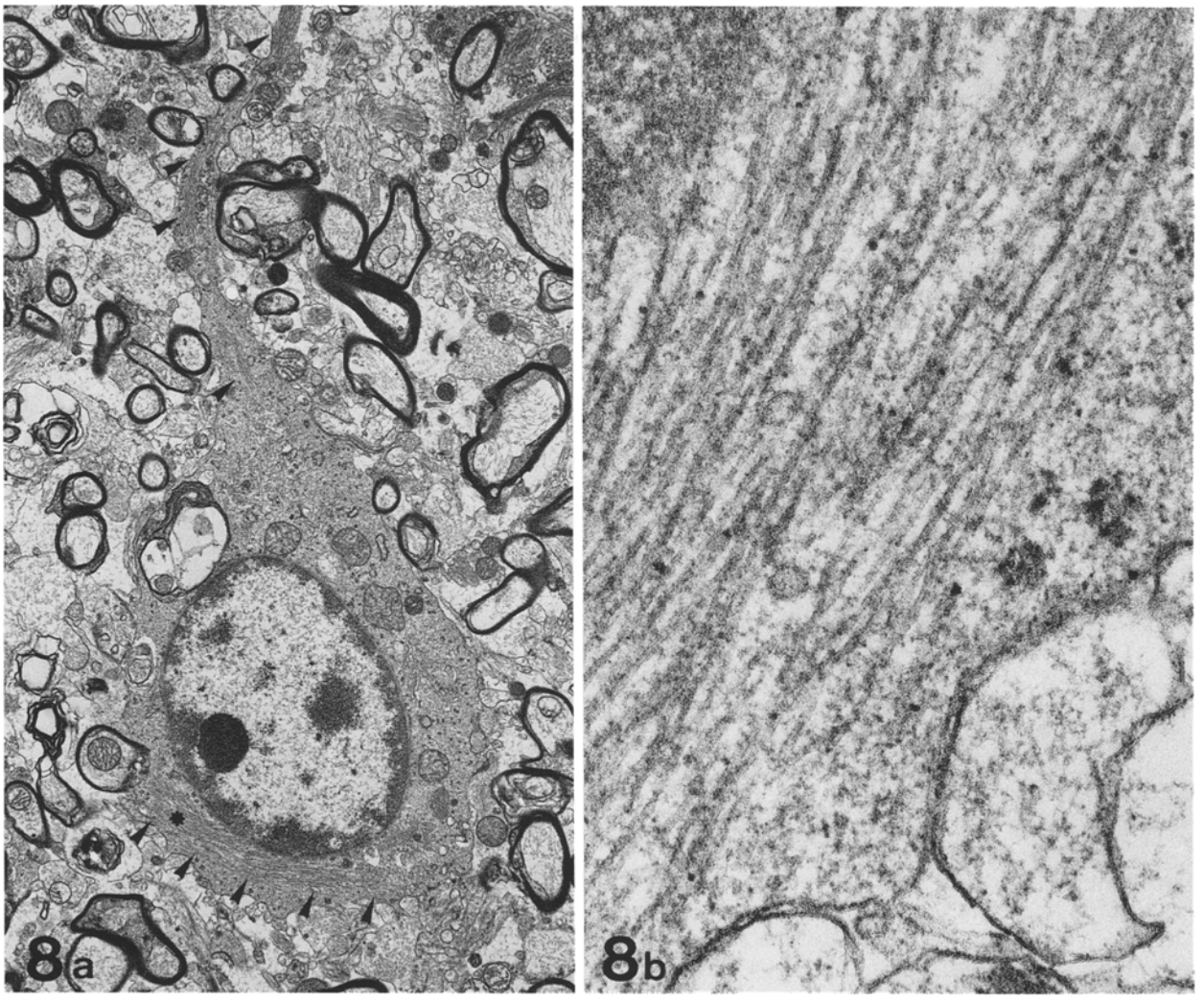


Fig. 8 Electron micrograph (**a**) illustrating an oligodendroglial cell in the subcortical white matter of the motor cortex of case 1; note the bundles of abnormal filaments in the cytoplasm and processes (*arrowheads*). A higher-magnification view (**b**) of the area indicated by the *asterisk* in (**a**) shows tubular structures with diameters of about 15 nm. **a** × 7,000; **b** × 84,000

twisted tubules, in the NFTs found in the substantia nigra. Furthermore, our immunohistochemical study demonstrated that the NFTs in the subcortical nuclei immunostained positively for tau, but not for ubiquitin. Similar immunohistochemical findings in a patient with CBD [25] and in others with PSP have been reported [3, 6]. Therefore, in view of the above findings, we consider that similar, or identical, cytoskeletal abnormalities are present in the subcortical regions of patients with CBD and PSP.

In patients with PSP, 15-nm-wide straight tubules were found in the neocortical neurons by Takahashi et al. [33], which suggests that the cerebral neocortex also is affected by the disease process. However, severe cerebral atrophy has been reported in only a few PSP cases [1, 28] and even in these, no ballooned neurons were present in the cerebral cortex. Arima et al. [2] observed 15-nm-wide straight tubules in the brain stem neurons of a 59-year-old male with presenile dementia in whom scattered ballooned neurons were present in the cerebral cortex. They considered that this patient's condition could be distinguished from CBD, in view of his pronounced temporal lobe atrophy and the presence of Pick bodies. Yamamoto et al. [39] found PSP tangles in the pontine tegmentum and dentate nucleus in a 64-year-old male with pallido-nigro-luysian atrophy, PSP and adult-onset Hallervorden-Spatz disease, who had no cerebral cortical involvement, but his subcortical pathology resembled that of our cases. These findings suggest that there is a considerable overlap between the neuropathologies of CBD, PSP and the disorders discussed above.

Previous immunohistochemical studies demonstrated that ballooned neurons in the cerebral cortices of patients with CBD are positive for phosphorylated neurofilament [7, 18, 21, 25, 29] as are those in patients with other neurological disorders [7, 16, 17]. Paulus et al. [25] observed tau immunoreactivity in a few ballooned neurons and tau-positive small globular inclusions in numerous small neurons of the second and third cortical layers of a patient with CBD. Recently, Nukina

et al. [21] demonstrated tau immunoreactivity in many cortical neurons with and without ballooning in a CBD case. Although only a few NFTs were found in the substantia nigra and midbrain tegmentum of the latter case, abnormally phosphorylated tau was observed in the cerebral cortical and subcortical neuronal elements. In our three cases, tau-immunoreactive neuronal cell bodies and processes were distributed widely in the brain and spinal cord, predominantly in the brain stem. These findings suggest that a tau abnormality is a feature of CBD.

Recent histological and immunohistochemical studies have demonstrated argyrophilic, tau-positive, glial cytoplasmic inclusions in the brains of patients with various neurodegenerative disorders: coiled bodies in argyrophilic grain dementia [4]; oligodendroglial microtubular masses in Alzheimer's and Pick diseases; argyrophilic grain dementia [36] and PSP [38]; and glial fibrillary tangles [20] and paired, nucleated, tau-positive astrocytes in PSP [37, 38]. In our study, tau-positive glial inclusions were found to be distributed widely in the cerebral gray and white matter, brain stem and cerebellar white matter. The distribution and immunohistochemical properties of these inclusions resembled those of the oligodendroglial microtubular masses observed in the brains of PSP sufferers [38]. Similar inclusions were also observed in a case of CBD [21]. Our electron microscopic examination showed that these inclusions occurred in the oligodendroglial cellular cytoplasm and processes and comprised tubular structures with diameters of about 15 nm, which were indistinguishable from the straight tubules in the NFTs of PSP patients. More recently, Nishimura et al. [20] reported the presence of 15-nm-wide straight tubules in the astrocytes of brains of PSP patients. Taken together, these findings indicate that both astrocytes and oligodendroglial cells can produce abnormal fibrillary structures, which have similar antigenic and ultrastructural features to those of the NFTs observed in PSP patients.

In conclusion, we believe that CBD is a distinct disease entity from a neuropathological viewpoint, and that there is a close cytoskeletal pathological and etiopathogenetic relationship between CBD and PSP.

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