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Familial parkinsonism and dementia with ballooned neurons, argyrophilic neuronal inclusions, atypical neurofibrillary tangles, tau-negative astrocytic fibrillary tangles, and Lewy bodies

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Abstract We report four patients with a new type of familial parkinsonism and dementia consisting of an autosomal dominant inheritance, dopa-responsive parkinsonism, severe dementia, variable myoclonus and autonomic disturbances. Autopsy of two patients revealed symmetrical cerebral atrophy with fronto-temporal dominant distribution, and marked depigmentation in the substantia nigra and locus ceruleus. Neuronal loss and gliosis were observed in the deep cerebral cortex and amygdala as well as in the areas vulnerable to Parkinson's disease. In the cerebral cortex, swollen neurons with frequent granulovacuolar changes were observed, consisting of ballooned neurons and those with argyrophilic intracytoplasmic inclusions, in addition to neuropil threads. Atypical neurofibrillary tangles, which barely stained with tau antibodies, were numerous in the upper cortical layers, consisting of 15-nm straight tubules. In addition, tau-negative astrocytic fibrillary tangles were also frequent. Electron microscopically, the ballooned neurons and argyrophilic neuronal inclusions contained filamentous structures coated with fuzzy electron-dense deposits. The inclusions showed immunohistochemical features different from those of cortical Lewy bodies and Pick bodies. Occasional Lewy bodies were present in the brain stem lesions of both patients. In two of our patients, the pathology in the brain stem was similar to that of Parkinson's disease, whereas their cerebral pathology was unusual and has not been reported previously.

Key words Familial Parkinson's disease · Dementia · Ballooned neurons · Neurofibrillary tangles · Astrocytic fibrillary tangles

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Introduction

Familial Parkinson's disease (PD) is an uncommon disorder, and only a few cases with histologically verified familial parkinsonism with Lewy body formation have been reported [11]. Such conditions include a familial extrapyramidal disorder involving corticostriatopallidonigral degeneration [34], familial fatal parkinsonism with alveolar hypoventilation and mental depression [45–47, 49], familial parkinsonism and depression [4], juvenile parkinsonism [58], familial parkinsonism-dementia syndrome [40], familial Alzheimer's disease presenting as levodopa-responsive parkinsonism [17], autosomal dominant PD [18, 19, 54], and familial diffuse Lewy body disease (DLBD) [36].

Neurological diseases with ballooned neurons (BNs) in the central nervous system are also uncommon disorders which can lead to parkinsonism, dementia or both [9]. They include corticodentatonigral degeneration with neuronal achromasia [48], which is also termed corticobasal degeneration (CBD) [16], Pick's disease [8], some cases

of Alzheimer's disease [9] and Creutzfeldt-Jakob disease [42], and pigment-spheroid degeneration [9].

Astrocytic fibrillary tangles are the abnormalities originally described in progressive supranuclear palsy (PSP) by Yamada et al. in 1992 [56]. The tangles are best visualized by the Gallyas silver impregnation staining method [7], and consist of tufted and thorn-shaped tangles [7], and astrocytic plaques [7, 13]. The tufted tangles are relatively specific for PSP, whereas the thorn-shaped ones are nonspecific and are found in various neurological diseases and aged controls [23]. Astrocytic plaques are observed in CBD [13] and some cases of PSP [7]. All of the astrocytic fibrillary tangles reported to date have shown tau immunoreactivity [7]; no tau-negative astrocytic fibrillary tangles have been reported. We encountered a familial disorder characterized by parkinsonism and dementia with BNs and Lewy bodies in two patients at autopsy [24, 38]. We studied the brains of these cases, and another clinical case, employing silver impregnation staining methods, immunohistochemical staining using various antibodies, and electron microscopy. We found an as yet unreported combination of histopathological abnormalities, which we had not detected in our previous studies [24, 38], such as argyrophilic neuronal inclusions, atypical neurofibrillary tangles, tau-negative astrocytic fibrillary tangles, and neuropil threads. We present the details of this unique familial parkinsonism.

Case report

Description of the family (Fig. 1)

The family originated from the suburbs of Tokyo, Japan. There were six affected individuals, two men and four women, embracing three generations. Symptoms first appeared at ages ranging from 24 to 59 years with the average of 39.4 ± 13.6 years, based on data from patients III-2, 4 and 5, IV-3, and IV-16. The duration of the disease was apparently 7 or more years, and the average duration was 8.8 ± 1.3 years, based on data obtained from patients III-2, 4 and 5, and IV-3. Two non-affected members of generation III reported that one of their sisters, patient III-2, and her mother, patient II-1, displayed neurological symptoms similar to those of patients III-4 and 5, and IV-3 and 16, and patient III-2 developed rapid neurological deterioration for her terminal 2 years. The non-affected members were also told by physicians that patient III-2 suffered from Creutzfeldt-Jakob disease. III-7 represents an instance of non-penetrance, as she is neurologically normal at the time of this study.

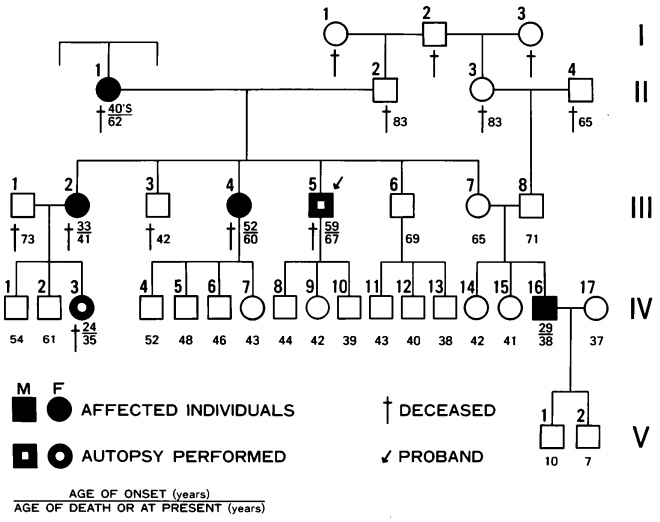


Fig. 1 Pedigree of our patients (see text)

Table 1 Clinical characteristics of our patients. The degree of neurological signs and symptoms, and effects of anti-parkinsonian drugs are given as: – absent, ± minimal, + mild, ++ moderate, +++ marked. The degree of constipation was difficult to evaluate because of insufficient data (see also Fig: 1) (*NA* not available)

Clinical features	Patients			
	III-5	III-4	IV-3	IV-16
Dementia	+++	+++	+++	+++
Parkinsonism	+++	+++	+++	+++
Effects of drugs	++	+	+++	+
Myoclonus	±	+++	+++	+
Convulsion	–	–	++	+
Gaze paralysis	–	–	+	–
Babinski's sign	– to +	+	+	+
Spasticity	–	–	++	+
Constipation	+	+	+	+
Urinary incontinence	++	++	++	+++
Orthostatic hypotension	+++	NA	–	–

Patient III-5 (Table 1)

This 67-year-old proband has been briefly described previously [38]. At the age of 59 years, he developed tremor in his hands on the left side more than on the right while holding objects, followed by occasional episodes of delusions at the age of 60 years. The pertinent neurological findings on admission at the age of 62 were as follows: marked orthostatic hypotension of 160/90 mmHg with a pulse rate of 72 beats/min in a supine position and of 70/0 mmHg with 104 beats/min in a standing position, mild dementia with a Hasegawa's Japanese mini-mental state examination score of 13.5 points out of 32.5, a masked and oily face, a soft monotonous voice, marked bradykinesia, marked rigidity in the neck and four extremities, a small steppage gait with lack of postural reflexes as well as kinésie paradoxale, and mild postural tremor in the hands without resting tremors. The patient's parkinsonism showed marked improvement with anti-parkinsonian drugs. However, his orthostatic hypotension progressed, causing syncopes even in sitting positions, followed by progressive parkinsonism and dementia. The reactive tachycardia observed in the standing position remained throughout the patient's clinical course. Serial cranial computed tomographic (CT) scans demonstrated progressive, fairly symmetrical fronto-temporal cortical atrophy, most prominent around the Sylvian fissures, and dilatation of the lateral ventricles. An electroencephalogram (EEG) taken in the late stage of this illness revealed a basic activity consisting of 5–6 Hz activity mixed with frequent theta and occasional delta waves without asymmetry. The patient suffered and died of recurrent aspiration pneumonia at the age of 67. The clinical diagnosis was PD with dementia.

Patient III-4 (Table 1)

This 60-year-old woman entered a depressive state with emotional lability and change of character, and also began to make mistakes in the calculation of her money at the age of 52 years. Subse-

quently, she exhibited parkinsonian features, delusions and visual hallucinations. The pertinent neurological findings at the age of 53 included the following abnormalities: moderate dementia with incoherent speech, marked dyscalculia and loss of recent memory, dressing and construction apraxias but without aphasia and agnosia, a masked face, rigidity in the neck and four extremities, a mildly stooped posture with slight flexion posture of the four extremities, a small steppage gait, fine and irregular tremor at rest and on posture in the left arm more than in the right arm, occasional jerky involuntary movements in both arms, and mild dysarthria with a soft voice. Pneumoencephalography demonstrated marked cortical atrophy which was most prominent in the fronto-temporal cortex. The patient's gait and bradykinesia improved mildly with levodopa.

The parkinsonism and dementia in this patient progressed. Neurological examinations at the age of 56 revealed that she was mute and exhibited generalized myoclonus which worsened when her extremities were touched. EEG revealed a basic activity consisting of 5–7 Hz activity, mixed with a small amount of 3–4 Hz activity, and without asymmetrical and paroxysmal abnormalities. She developed progressive dysphagia and anasarca, and died at the age of 60. Her myoclonus diminished markedly as her death approached. The clinical diagnosis was Creutzfeldt-Jakob disease.

Patient IV-3 (Table 1)

This 35-year-old woman has been described previously [24]. Briefly, she developed tremor in her left leg at the age of 24 years. Neurological examinations at the age of 26 revealed a masked and oily face with prominent hypersalivation, resting tremor and rigidity in the four extremities, and a parkinsonian posture and gait with lack of postural reflexes. The patient's parkinsonism improved mildly to moderately with anti-parkinsonian drugs. Although the patient's parkinsonism improved on increasing the levodopa dose and a left subthalamotomy, her parkinsonism and dementia gradually progressed, followed by the development of myoclonus and the impairment of vertical gaze at the of 27. At the age of 29, she was in a state of quadriplegia-in-flexion with frequent myoclonic jerks, and occasional generalized convulsions. The patient died of uremia when aged 35. The clinical diagnosis was juvenile parkinsonism.

Patient IV-16 (Table 1)

This 38-year-old, currently alive man has been described previously [38]. Briefly, he developed tremor in his right hand and a tendency to write smaller letters at the age of 29 years, followed by gait disturbance with frozen phenomenon, urinary incontinence, and then intellectual dysfunction. Neurological examinations at the age of 31 revealed marked dementia and parkinsonism, and asymmetrical deep tendon reflexes with Babinski sign and spasticity on the right side. Serial cranial CT scans and magnetic resonance imaging showed progressive generalized symmetrical cortical atrophy, which was most prominent in the frontal lobe, and moderate ventricular dilatation. The patient's parkinsonism improved minimally to mildly with anti-parkinsonian drugs. At the age of 33, he suffered two episodes of generalized convulsions. His parkinsonism and dementia has been progressive, and he became mute and has received custodial care for the previous several years.

Materials and methods

The brain and spinal cord of patient III-5 were fixed in 10% phosphate-buffered formalin and those of patient IV-3 in 10% formalin. The materials were then embedded in paraffin. Multiple sections were taken from the brains and spinal cords, and stained by hematoxylin and eosin (H&E), Klüver-Barrera, Holzer, and silver impregnation methods. The silver staining included the Bodian, Bielschowsky-Hirano [21], and modified Gallyas-Braak [23] methods, in addition to methenamine Bodian and methenamine silver methods for representative sections. The sections were also stained by avidin-biotin complex (ABC) method (Vectastain, Vector, USA) using antibody to glial fibrillary acidic protein (GFAP) (Dako, USA). Gliosis was assessed by the H&E, Holzer and ABC methods. For electron microscopic examination, portions of the right anterior temporal cortex, locus ceruleus and dorsal vagal nucleus were taken from the formalin-fixed brain of patient III-5, and portions of the amygdala, hippocampus, oculomotor nucleus and locus ceruleus from the formalin-fixed brain of patient IV-3. The materials were fixed in 2.5% glutaraldehyde, post-fixed in 2% osmium tetroxide, dehydrated and then embedded in Epon. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined with a JEM 100CX.

We performed immunohistochemical staining on 4-μm sections of the anterior temporal cortex, cingulate gyrus, amygdala, hippocampus and parahippocampal gyrus of patients III-5 and IV-3, employing the ABC method, the peroxidase-antiperoxidase method, or both. We used the following antibodies (see also Table 3): those to ubiquitin, tau, phosphorylated and non-phosphorylated neurofilaments, paired helical filaments (PHF), neurofilaments of 200 kDa, 160 kDa and 68 kDa, β-protein, Alz-50, microtubule-associated proteins (MAPs), MAP-2, α-tubulin, b-tubulin, tubulin, actin, vimentin and myosin, as well as antibody to prion protein residues 220–231 [6] which was applied to the sections of patient III-5. Anti-β-protein antibodies were used after sections were pretreated with formic acid [28]. To make precise comparisons of the staining characteristics between BNs and neurons with argyrophilic neuronal inclusions, we obtained, using a mirror section technique, 4-μm mirror sections from the insula, cingulate gyrus, and amygdala of patient III-5, and stained one of paired mirror sections by the Bielschowsky-Hirano silver staining method and the other section by ABC method using antibodies to ubiquitin (Sigma), phosphorylated and non-phosphorylated neurofilaments (SMI-31, -33 and -34) or neurofilaments of 200-kDa (see Table 3). After that, we photographed stained sections and had the photographs printed in color. Then we correlated, both on the photographs and under a light microscope, Bielschowsky-Hirano stained sections with those stained with the antibodies. Further, we made immunohistochemical comparisons among BNs and argyrophilic neuronal inclusions observed in patients III-5 and IV-3, cortical Lewy bodies, and Pick bodies and BNs in Pick's disease. Sections (4 μm) of the cingulate gyrus and insula which contained cortical Lewy bodies were obtained from an 80-year-old patient with DLBD, and 64- and 76-year-old patients with PD, who have been reported previously as patients 3, 10 and 12, respectively [37]. Sections for Pick bodies and BNs were taken from the hippocampus and adjacent temporal lobe of three women with Pick's disease, who were 56, 64 and 67 years old, respectively. We also performed a double staining of astrocytic fibrillary tangles in the anterior temporal lobe section of patient III-5 by both the methenamine Bodian method and the ABC method using anti-GFAP antibody.

Results

Autopsy findings in patients III-5 and IV-3

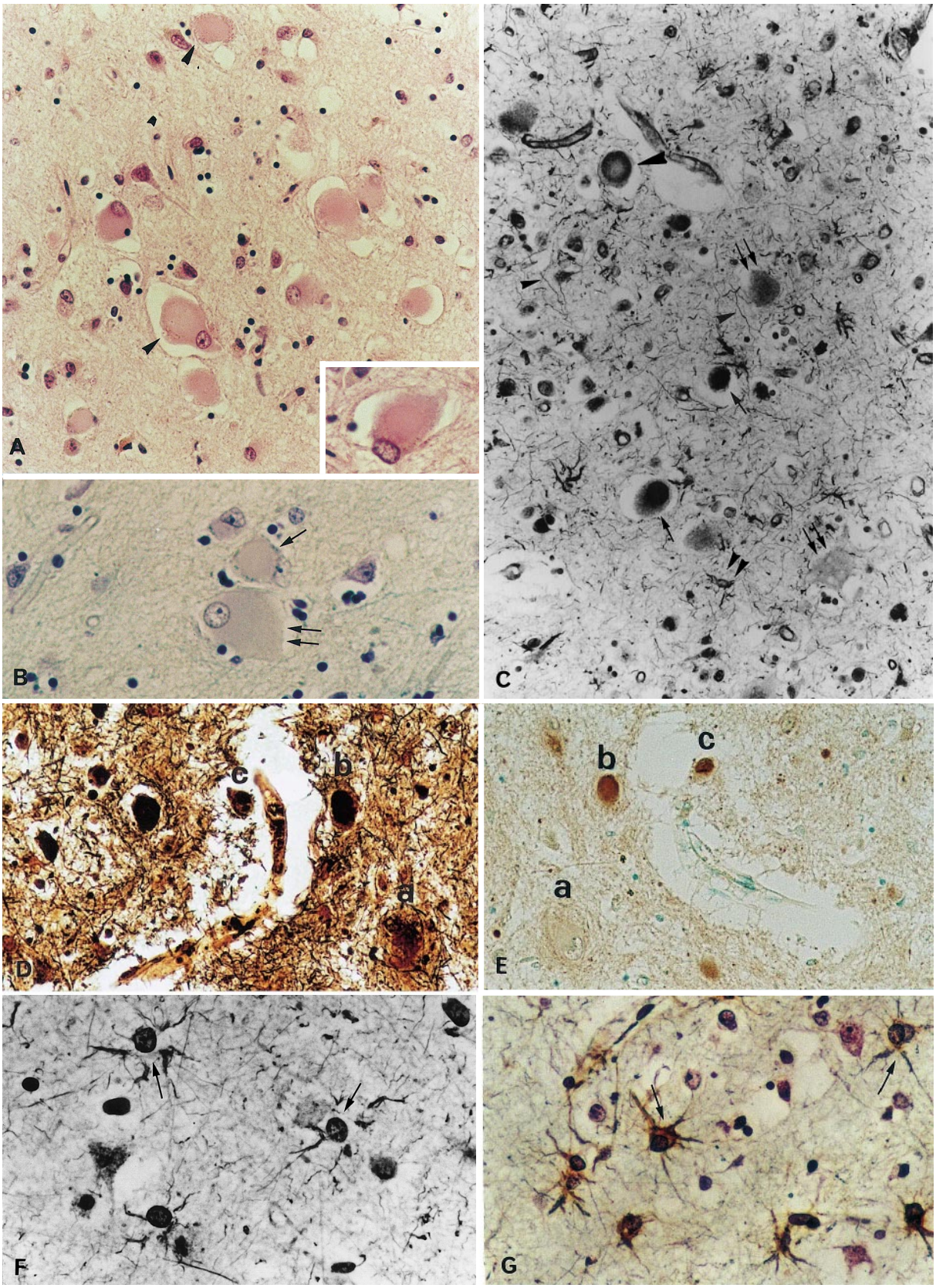
Histopathological findings of both patients have been described previously [24, 38], including the preliminary report of patient III-5 [38]. General autopsy of patient III-5 revealed bilateral moderate to marked bronchopneumonia with hemorrhagic pleurisy on both sides.

The brain of patient III-5 weighed 1210 g and the one of patient IV-3 990 g. Gross and light microscopic examinations revealed similar findings in the brains of both patients. The brains displayed symmetrical cortical atrophy in the frontotemporal lobes, particularly in the cortex

Table 2 Histopathological findings of patients III-5 and IV-3. The degree of neuronal loss and gliosis is given as: – absent, + mild, ++ moderate, +++ marked. The number of BNs, NFTs, AFTs, NPTs, and LBs are given as: – absent, ± rare, + occasional, ++ frequent, +++ numerous. Neurons with ANIs intermixed with BNs were primarily confined to the cerebrum and substantia nigra. BNs were rarely seen in the dorsal root ganglia of patient III-5, and were absent from the Auerbach plexus of the gastrointestinal tracts of both patients. (*BN* ballooned neuron, *NFT* neurofibrillary tangle, *AFT* astrocytic fibrillary tangle, *NPT* neuropil thread, *LB* Lewy bodies, *ANI* argyrophilic neuronal inclusions *Ant.* anterior, *Nb* nucleus basalis, *NA* not applicable; *NE* not examined)

Examined brain areas	Patient III-5/patient IV-3						
	Loss of neuron	Gliosis	BNs	NFTs	AFTs	NPTs	LBs
Orbital cortex	–/– to +	– to +/+ to ++	+/+ to ++	±/++	+/++	–/+++	–/–
Ant. temporal cortex	++/++	+++/+ to +++	+++/+ to ++	+++/+++	+++/++	++/++	–/–
Parietal cortex	–/+	–/+	±/+	–/++	+/±	–/–	–/–
Striate cortex	–/–	–/–	–/+	±/±	–/–	–/–	–/–
Cingulate gyrus	+/+	+/+	++/+	++/+++	+++/++	+/++	–/–
Insula	++/+	+++/++	+++/++	+++/+++	+++/+++	+ to ++/++	–/–
Amygdala	++/+++	+++/+++	+++/+++	+/++	–/–	+++/+++	–/–
Hippocampus	+ to +++/– to +++	– to +++/– to +++	+ to +++/± to +++	+/++[a]	+/±	+/+++	–/–
Parahippocampal gyrus	–/– to ++	–/– to +++	±/± to ++	+/+	+/±	+/+	–/–
Lateral occipitotemporal gyrus	++ to +++/+ to ++	+++/+++	+++/+++	+++/+++	+++/++	++/++	–/–
Nb of Meynert	++/++	+++/++	+++/++	–/–	–/–	+/+	–/–
Caudate nucleus	–/–	+/–	–/±	+/++	–/–	+/++	–/–
Putamen	–/–	+/+	–/+	–/++	–/–	±/+ to ++	–/–
Globus pallidus	–/–	+/–	–/–	–/++	–/–	–/±	–/–
Thalamus	–/–	+/–	±[b]/–	+/±	–/–	±[b]/+	–/–
Subthalamic nucleus	–/–[c]	–/–	–/–	–/–	–/–	–/–	–/–
Posterior hypothalamus	++/–	+++/–	+++/+	–/–	–/–	+/–	+/–
Substantia nigra	+++/+++	+++/+++	++/+	–/–	–/–	+/+	–/-
Superior colliculus	+/+	++/++	++/+	–/–	–/–	–/+	–/-
Periaqueductal gray matter	–/–	++/+	–/+	+/+	–/–	+/±	–/–
Dorsal raphe nucleus	–/–	++/–	+/±	++/±	–/–	++/+	+/–
Oculomotor nucleus	–/–	+/+	+/+	–/–	–/–	–/–	–/+[d]
Locus ceruleus	++/+++	++/++	+/+	–/–	–/–	–/+	+/±
Dorsal vagal nucleus	+++/++	++/++	+/+	–/–	–/–	–/+	–/+
Cerebellar cortex	–/–	–/–	–/–	–/–	–/–	–/–	–/–
Denate nucleus	–/–	+/+	–/–	–/–	–/–	–/–	–/–
Inferior olivary nucleus	–/–	++/++	–/–	–/–	–/–	–/–	–/-
intermediate lateral column	–/–	–/–	±/±	–/–	–/–	–/±	–/–
Sympathetic ganglia[e]	–/NE	NA/NA	± to +/NE	–/NE	NA/NE	NA/NE	–/NE

[a] Frequent NFTs were also present in the granular cell layer
[b] BNs neurons with ANIs, and NPTs were frequent and confined to the midline nucleus of the thalamus and its adjacent subependymal layer of the third ventricle
[c] Subthalamotomy caused cavitation in the subthalamic nucleus [24], but deep sectioning of the same block showed that the remaining part of the nucleus was preserved
[d] LBs were primarily present in the Edinger-Westphal nucleus
[e] Coeliac and thoracic ganglia were examined


A
B
C
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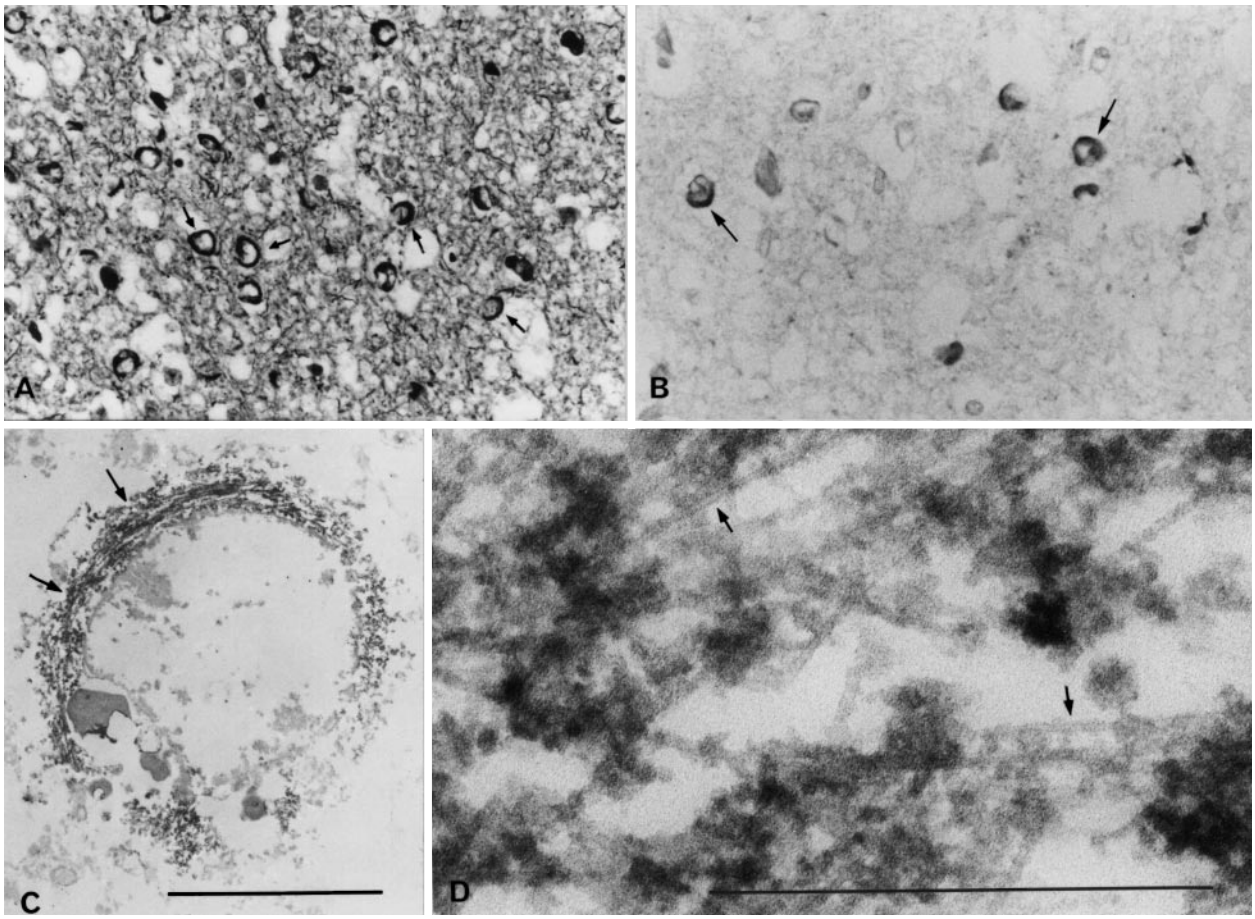
◀ **Fig. 2** The anterior temporal cortex (**A–C**, **F**, **G**) and amygdala (**D**, **E**) of patient III-5. **A–C** Hematoxylin and eosin (H&E) staining (**A**) showed that swollen neurons with frequent granulovacuolar changes were seen in small to large neurons, variably eosinophilic without a halo, and consisted of neurons with intracytoplasmic inclusion bodies (*inset* in **A**) and achromatic ballooned neurons (BNs; *double arrows* in **B**). The inclusion bodies showed distinct margins and staining characteristics almost identical to that of the surrounding cytoplasm (*inset* in **A**), being minimally basophilic by Klüver-Barrera staining (*single arrow* in **B**), and markedly argyrophilic by Gallyas-Braak method (*single arrows* in **C**), although a few were partially argyrophilic (*large single arrowhead* in **C**). The BNs were not stained or were minimally argyrophilic (*double arrows* in **C**). Small *single arrowheads* in **C** indicate neuropil threads, *double arrows* indicate astrocytic fibrillary tangle (see also text). **D**, **E** Minor sections showed that a BN in the Bielschowsky-Hirano-stained section (*a* in **D**) was not stained with ubiquitin (*a* in **E**), whereas argyrophilic neuronal inclusions (ANIs; *b* and *c* in **D**) were markedly stained (*b* and *c* in **E**). The neurons designated as *a*, *b*, and *c* in **D** and **E** correspond to one another. **F**, **G** The section showing astrocytic fibrillary tangles (*arrows* in **F** and **G**) by the methenamine Bodian method (**F**) was doubly stained by the avidin-biotin-peroxidase complex (ABC) method using anti-glial fibrillary acidic protein antibody (**G**) (see also text). **A**, **B** × 315; **C** × 260; **D**, **E** × 210; **F** × 576; **G** × 342

along the Sylvian fissures, as well as symmetrical dilatation of the lateral and third ventricles. The degree of both cortical atrophy and ventricular dilatation was mild to moderate in patient III-5 and marked in patient IV-3. The substantia nigra and locus ceruleus were markedly depigmented. The cerebellum and spinal cord did not exhibit any significant abnormalities.

The distribution, nature and degree of histopathological abnormalities in the two patients are summarized in Table 2. Microscopically, neuronal loss and gliosis were observed to various degrees in the cerebral cortex, being most prominent in its deep layers, as well as in the amygdala and areas vulnerable to PD. In the cerebral cortex and amygdala, swollen neurons (Fig. 2 A) were frequently seen, consisting of BNs and neurons with argyrophilic neuronal inclusions (inset of Fig. 2 A, and Fig. 2 B, C), in addition to neuropil threads (Fig. 2 C). The argyrophilic inclusions were barely stained by the Bodian method, but stained markedly argyrophilic by the Gallyas-Braak (Fig. 2 C) and Bielschowsky-Hirano (Fig. 2 D) methods, although a few were not stained or were partially argyrophilic (Fig. 2 C). There appeared a transition between the BNs and the neurons with the argyrophilic inclusions in terms of argy-

Fig. 3 A–D The second layer of the anterior temporal cortex of patient III-5. **A–C** Numerous neurofibrillary tangles (*arrows*) demonstrated by the Bielschowsky-Hirano method (**A**) showed immunoreactivity to ubiquitin by the ABC method (**B**) and by immunoelectron microscopy (**C**). Electron microscopically, the tangles consisted of crisscrossing straight tubules of approximately 15 mm in diameter (*arrows*) in the sections without ubiquitin immunostaining (**D**). *Bars* in **C** = 5 μm, **D** = 0.5 μm. **A** × 360, **B** × 394, **C** × 5600, **D** × 134 000



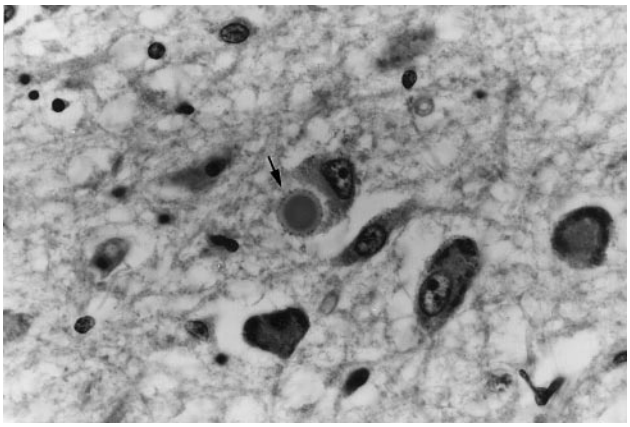


Fig. 4 A Lewy body (*arrow*) in the hypothalamus of patient III-5. H & E, × 380

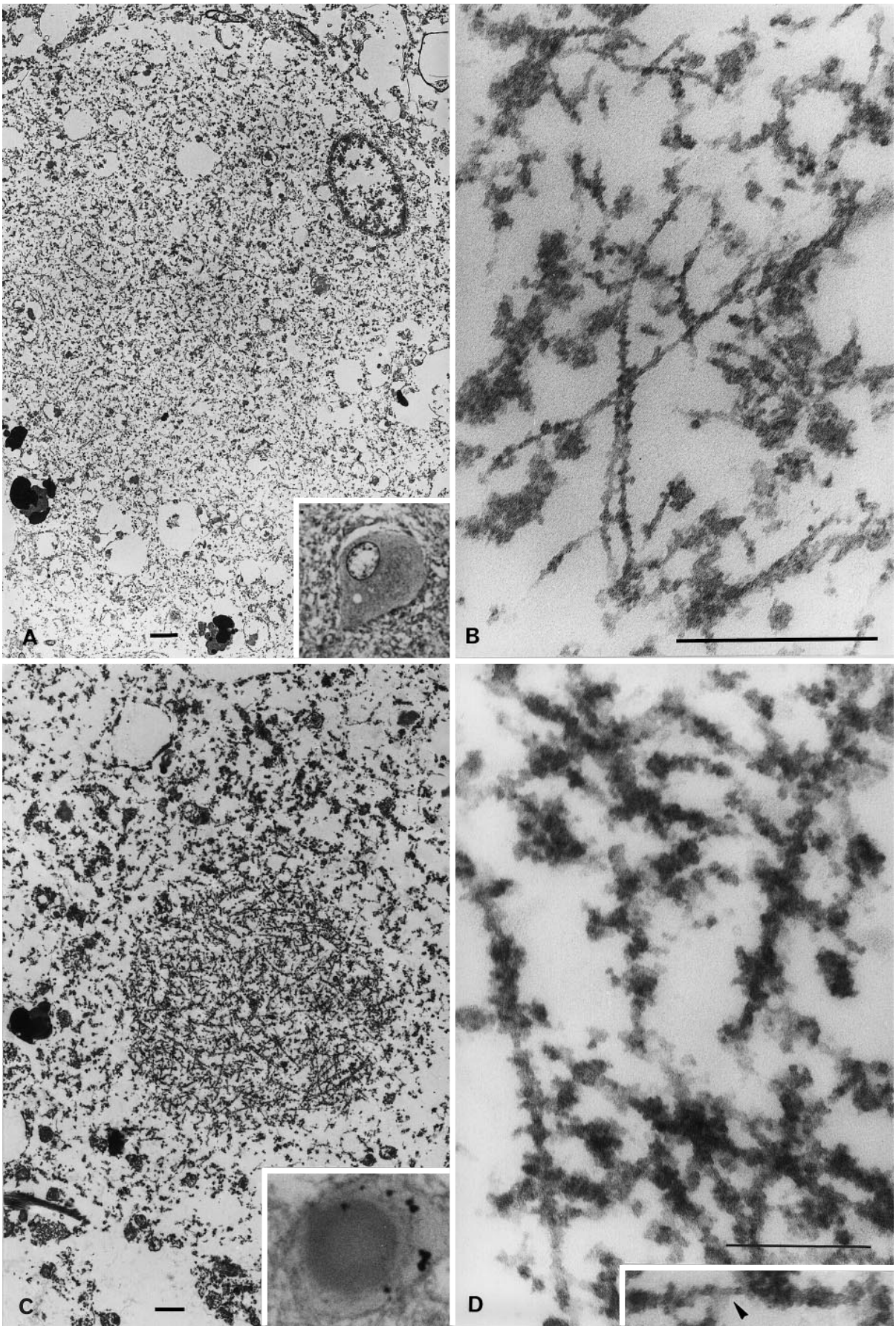
rophilia (Fig. 2 C). In addition, diffuse comma-shaped neurofibrillary tangles (Fig. 3, Table 2), detected by the Bielschowsky-Hirano and Gallyas-Braak methods, not by the Bodian method, were observed, most prominent in the second layer of the cerebral cortex of the patient III-5 and in the second to third layers of patient IV-3 (Table 2). The tangles were stained with anti-ubiquitin antibodies (Fig. 3 B, C), but seldom stained with antibodies to tau and PHF, thereby indicating that they were atypical tangles, although rare flame-shaped neurofibrillary tangles observed in the subiculum, parahippocampal gyrus and amygdala on the same examined sections were stained with the two kinds of antibodies. Further, astrocytes with argyrophilic slender radiating fibers (Fig. 2 C, F, G), consistent with tufted astrocytic fibrillary tangles [7], were frequently present, mostly in the middle and deep layers of the cerebral cortex. The astrocytic tangles were difficult to detect by the Bodian and Bielschowsky-Hirano methods, but were readily stained with the methenamine Bodian, methenamine silver and Gallyas-Braak methods. The astrocytic tangles were not stained with any of the antibodies used which included anti-tau antibodies listed in Table 3. Occasional oligodendroglial inclusion bodies consistent with coiled bodies [7] were scattered in the cerebral white matter of patient IV-3, but not found in the patient III-5. Astrocytic plaques [13] were not found. The degree and distribution of the astrocytic fibrillary tangles roughly correlated with those of the atypical neurofibrillary tangles (Table 2), although the preferential layers of the cortex were different between the two types of tangles. Senile plaques were not present in the cerebrum when sections were stained with various silver staining methods as mentioned above and ABC method using anti-β-protein antibody. In patient III-5, the hypothalamus showed marked degeneration of the posterior region, whereas other regions were minimally affected. Rare to occasional Lewy bodies (Fig. 4) were found in some of the areas vulnerable to PD (Table 2), although they were not found in the substantia nigra and nucleus basalis of Meynert.

Electron microscopic study of BNs, argyrophilic neuronal inclusions, atypical neurofibrillary tangles and Lewy bodies

Electron microscopically, the BNs in patient III-5 (Fig. 5 A, B) showed abundant cytoplasm with a relative paucity of organelles and the displacement of lipofuscin granules toward the periphery, and contained sparse filamentous structures which were interspersed among vesicular structures, granular materials, and mitochondria. The granulovacuolar changes in the BNs consisted of vacuoles and electron-dense granules inside (not illustrated here), similar to that reported in the hippocampus [43]. The argyrophilic neuronal inclusions (Fig. 5 C, D) consisted of clusters of filamentous structures similar, but not identical to those of the BNs. The atypical neurofibrillary tangles consisted of straight tubules of about 15 nm in diameter (Fig. 3 D). Lewy bodies found in the locus ceruleus and oculomotor nucleus of patient IV-3 had typical electron microscopic features [24]. The Lewy bodies in the dorsal vagal nucleus of the medulla of patient III-5 (not illustrated here) comprised a slightly electron-dense portion which consisted of criss-crossing filaments of 10–20 nm in diameter with or without some electron-dense deposits, surrounded by an electron-lucent halo, consistent with Lewy bodies [50].

Immunohistochemical study of BNs, argyrophilic neuronal inclusions, cortical Lewy bodies, Pick bodies and astrocytic fibrillary tangles

The staining characteristics of the BNs and argyrophilic neuronal inclusions in patient III-5, cortical Lewy bodies, and Pick bodies and BNs in Pick's disease are summarized in Table 3, and are illustrated in Figs. 2 E and 6. As regards the immunostaining with anti-ubiquitin antibodies, mirror sections (Fig. 2 D, E) revealed that the BNs (Fig. 2 E) were variably stained, from no staining to mild staining, whereas the argyrophilic inclusions (Fig. 2 E) were markedly stained. The BNs and argyrophilic inclusions were not stained with antibodies to 160- and 68-kDa neurofilaments, β-protein, prion protein, MAPs, MAP-2, α- and β-tubulins, tubulin, actin, vimentin, and myosin. Ubiquitin- and tau-positive granules were occasional to frequent in the hippocampus and deep cerebral cortex, but ubiquitin-immunoreactive neurites as seen in DLBD [10, 27] were virtually absent in the CA2-3 region of the hippocampus in both patients. The BNs and argyrophilic inclusions of our patients showed different staining characteristics to those of cortical Lewy bodies, although the argyrophilic inclusions shared some staining features (Table 3). The BNs resembled those of Pick's disease except for the positive staining of antibodies to some phosphorylated neurofilaments (SMI-34) and non-phosphorylated neurofilaments (SMI-33) (see Table 3). The argyrophilic inclusions of our patient were different from Pick bodies in terms of the staining features to tau, SMI 31, PHF and α B crystallin. The astrocytic fibrillary tangles observed


A
B
C
D

◀ **Fig. 5** Electron microscopic appearance of a BN (**A**, **B**) and an ANI (**C**, **D**) in the anterior temporal cortex of patient III-5. **A**, **B** *Inset* showed a BN stained with toluidine blue. The BN contained sparse filamentous structures (**A**) of about 15 nm in diameter, which were coated with fuzzy electron-dense deposits (**B**) (see also text). **C**, **D** Inset in **C** showed an ANI stained with toluidine blue. The ANI comprised clusters of crisscrossing filamentous structures of about 20 nm in diameter (**C**) with some tubular profiles (*inset* in **D**), coated with fuzzy electron-dense deposits of various shapes and densities (**D**), which were similar to those of the filamentous structures of B, but more prominent. *Bars* **A**, **C** = 1 μm, **B**, **D** = 0.5 μm. **A** × 4200, *inset* × 565; **B** × 71700; **C** × 5360, *inset* × 590; **D** and *inset* × 52000

here (Fig. 2C, F), whose astrocytic nature was confirmed by double staining using antibodies to GFAP (Fig. 2G), were not stained with any of the antibodies listed above, including those to tau.

Discussion

The most critical question about the disease affecting this family was whether the disease represented one of familial PD or other kind of familial parkinsonism with partial resemblance to PD. The clinical and histopathological features of the disease observed in our patients included both typical and atypical elements of PD. The typical clinical features consisted of dopa-responsive parkinsonism, and autonomic disturbances [3]. The progressive dementia in our autopsied patients, which was explained by the lesions in the cerebral cortex and nucleus basalis of Meynert, has also been observed in some patients with PD [25, 37] and also represents one of the main features of DLBD [5, 29, 59]. The atypical features included the genetic transmission as an apparently autosomal dominant trait, myoclonus, convulsions and pyramidal tract signs. Myoclonus and pyramidal tract signs, however, have been reported in patients with DLBD [5], and pyramidal tract signs also in those with juvenile parkinsonism [57].

The most characteristic histopathological abnormalities observed in our two patients were: (1) degeneration involving the cerebral cortex, amygdala, and areas vulnerable to PD which included autonomic ganglia; (2) the histopathological findings in the brain stem which were similar to those of Lewy body PD, although the distribution of Lewy bodies was atypical because of their absence in the substantia nigra and nucleus basalis of Meynert [15, 25]; and (3) the pathology in the cerebrum, particularly its cerebral cortex, which was different from PD and DLBD, including BNs, argyrophilic neuronal inclusions, prominent atypical neurofibrillary tangles, and tau-negative astrocytic fibrillary tangles, but not senile plaques. Regarding the BNs and neurons with argyrophilic inclusions, there appeared an apparent transitional variability of argyrophilia (Fig. 2C) and immunostaining (Table 3) between the two. In addition, they contained filamentous structures

Table 3 Comparison of the epitopes of BNs and ANIs in patient III-5, cortical Lewy bodies, and BNs and Pick bodies in patients with Pick's disease. The degree of staining is given as: – negative, ± minimally or occasionally positive, + positive, ++ strongly positive. All of the stainings in this table were performed by the avidin-biotin complex method. The majority of the immunostaining results were based on the data obtained by the mirror section technique using both Bielschowsky-Hirano silver staining and ABC method (see text). Patient IV-3 showed diffuse pallor in repetitive immunohistochemical staining to most of the antibodies used, possibly due to loss of antigenicity caused by fixation, although some ANIs showed positive staining to ubiquitin and SMI-31 [*p* (+) phosphorylated, *p* (–) non-phosphorylated, *nfs* neurofilaments, *SM* Sternberger-Meyer USA, *ICN* Chemical Credential USA]

Specificity	Dilution	Reactivity					Commercial source or reference
		Patient III-5		Cortical LBs	Pick's disease		
		BNs	ANIs		BNs	Pick bodies	
Ubiquitin	1:50	– to +	+ to ++	++	±	±	Sigma no. U-5379
Ubiquitin	1:100	– to +	+ to ++	++	±	+ to ++	[39]
Tau	1:100	– to ±	–	–	–[a]	++	Sigma no. T-6402
Tau	1:2,000	– to ±	–	–	–[a]	++	[22]
Human tau	1:5,000	–	–	–	–[a]	++	[12]
Tau2	2,000	±	±	–	–[a]	++	Sigma no. T-5530
p (+) nfs							
(SMI-31)	1:50,000	– to ++	– to ++	–	– to ++	–	SM
(SMI-34)	1:2,500	– to ++	– to ++	–	±[a]	–	SM
p (–) nfs							
(SMI-33)	1:5000	+ to ++	+ to ++	–	–	–	SM
PHF	1:200	–	–	–	–[a]	++	ICN No. 64-742
α B crystallin	1:500	+ to ++	+ to ++	++	++	–	[52]
200-kDa nfs	1:500	+	++	±	++	– to ±	Sigma No. n-5389
Alz-50	1:50	±	±	ND	–[a]	++	[55]

[a] Ring-like staining was seen in the periphery of some BNs

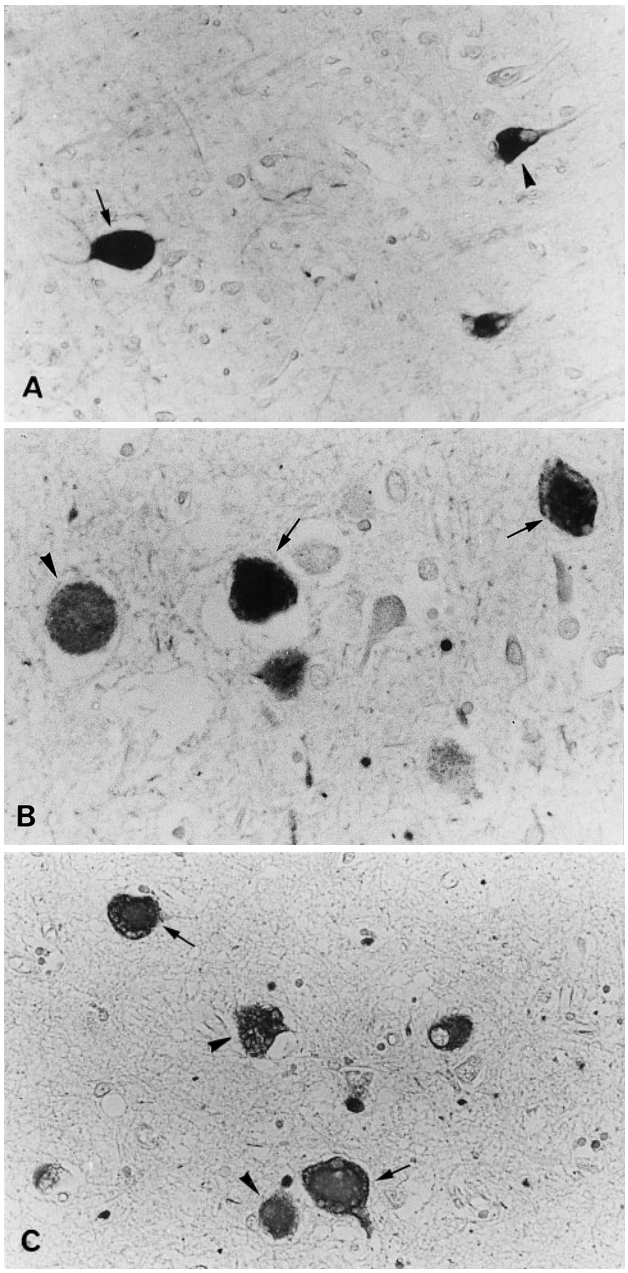


Fig. 6 A–C Immunohistochemical reactivity of BNs and ANIs in the anterior temporal cortex of patient III-5. The majority of the BNs (*arrowheads*) and ANIs (*arrows*) showed marked immunoreactivity to the phosphorylated neurofilaments (SM-31) (**A**), 200-kDa neurofilaments (**B**) and α B crystallin (**C**). Frequent vacuoles observed in some of the neurons in **B** and **C** were granulovacuolar changes (see also Table 3 and text). ABC method. **A** × 238, **B** × 440, **C** × 280

as revealed by electron microscopy. However, it is not clear whether there was a transition between the two, since the diameter of the filaments in the argyrophilic inclusions was slightly larger than that of the filaments in BNs (Fig. 5). Among the histopathological findings, the argyrophilic inclusions, atypical neurofibrillary tangles and tau-negative astrocytic fibrillary tangles were not described in the original histopathological studies of patients III-5 and IV-3 [24, 38], since the Bodian method used in those studies could not detect these abnormalities, and immunohistochemical staining methods using various antibodies except for the one to ubiquitin were not employed there.

Both types of neurons in the cerebral cortex of our patients were different from cortical Lewy bodies for the following reasons. H&E staining revealed that the swollen neurons observed in our patients were of a homogeneously eosinophilic nature or contained intracytoplasmic inclusions with distinct margins, in addition to frequent granulovacuolar changes. Many BNs did not show positive staining to Bielschowsky-Hirano staining and ubiquitin, both of which are the best staining methods for cortical Lewy bodies [30, 32]. The two types of neurons also showed positive staining for antibodies to phosphorylated and non-phosphorylated neurofilaments, whereas cortical Lewy bodies were unstained, although the immunostaining of the cortical Lewy bodies to phosphorylated neurofilaments tends to be variable [2]. In addition, electron microscopically, the density and arrangement of filamentous structures in the two types of neurons were different from those of cortical Lewy bodies, although the filamentous structures with fuzzy electron-dense deposits resembled those of the Lewy bodies [53]. These differences in both light and electron microscopic findings led us to infer that the two types of neurons observed in patient III-5 were different from cortical Lewy bodies, although it was difficult to rule out the possibilities that a small number of cortical Lewy bodies were mixed, and that the two types of neurons were atypical cortical Lewy bodies which were modified by some gene abnormalities of our patients. Furthermore, our two patients did not reveal ubiquitin-immunoreactive neurites in the CA2-3 region of the hippocampus, which have been claimed to coexist frequently with cortical Lewy bodies [10, 27]. The two types of neurons resembled Pick bodies and BNs observed in Pick disease [8, 41]. The argyrophilic neuronal inclusions were different from Pick bodies because of the almost negative or negative staining to both the Bodian method and antibodies to tau and PHF [41], in addition to the positive immunostaining to antibodies to SMI 31, SMI 34, 200-kDa and αB crystallin [33]. The electron microscopic picture of the argyrophilic inclusions was also different because of the presence of fuzzy electron-dense deposits on the filamentous structures, whereas Pick bodies consisted of smooth straight filaments and paired twisted profiles without such deposits [41, 53]. The BNs observed here partially resembled those of Pick's disease in terms of immunohistochemical staining features, but differed electron microscopically since our BNs contained filamentous structures similar to those of the argyrophilic inclusions [41].

Comma-shaped atypical neurofibrillary tangles observed in the cerebral cortex of our patients were different from typical Alzheimer's neurofibrillary tangles because our tangles, difficult to detect by the Bodian method, showed the paucity of tau and PHF immunoreactivity, and consisted of straight filaments of about 15 nm in diameter.

Our tangles were also different from those of PSP because of the paucity of tau immunoreactivity [20]. Arima et al. [1] recently described similar neurofibrillary tangle-like inclusions in one patient with corticobasal degeneration. Although they consisted of identical 15-nm-thick straight tubules, in addition to tubules with constrictions at 120–150-nm intervals, they were different from ours because of positive immunoreactivity to anti-tau antibody and a weak reaction to anti-ubiquitin antibody. Regarding astrocytic fibrillary tangles, those observed in our patients were different from the ones reported to date [7, 13, 23, 56] in the absence of tau immunoreactivity. Although such tau-negative astrocytic fibrillary tangles have not been reported previously, the significance of the tangles awaits a further study. Electron microscopic study of the tangles is under investigation.

The familial parkinsonism with Lewy body formation reported to date includes patients described by Maeda et al. [34], Perry et al. [45, 46], Purdy et al. [47], Roy et al. [49], Bhatia et al. [4], Yokochi et al. [58], Muenter et al. [40], Giménez-Roldán et al. [17], Golbe et al. [18, 19], Waters et al. [54], and Mark et al. [36]. None of them revealed various cortical abnormalities as observed in our patients, except for those of Maeda et al., who described cortico-striato-pallido-nigral degeneration in three patients from the same family [34], in addition to one sporadic patient [35]. The clinicopathological features of these four patients resembled ours in terms of dopa-responsive parkinsonism, Parkinson pathology, and BNs and prominent neurofibrillary tangles in the cerebral cortex. However, these patients were different in regard to the absence of argyrophilic neuronal inclusions, and the presence of the neurofibrillary tangles in the brain stem areas vulnerable to PD, basal ganglia and subthalamic nuclei, although one of our patients (patient IV-3) showed neurofibrillary tangles in the basal ganglia. Tiller-Borcich and Forno [53] reported one additional patient who also closely resembled ours both clinically and histopathologically, having both BNs and Lewy bodies. However, this patient was different in terms of a negative family history and of marked argyrophilia in the BNs. Thus, some of the clinicopathological features of our patients were unlike those of hitherto described PD or its related diseases.

In view of the clinical and histopathological features in our patients, differential diagnosis other than DLBD and Pick's disease, should include CBD [13, 14, 16, 31, 44, 48, 51], PSP [20], Alzheimer's disease [9, 17], Creutzfeldt-Jakob disease [42] and cases of unclassified dementia [9]. Creutzfeldt-Jakob disease is considered less likely because of our patients' clinical features and the distribution of histopathological lesions which resembled that of PD, as well as the absence of status spongiosus in both patients, and negative immunostaining to prion protein in patient III-5. The illness of our patients was in part similar to CBD and PSP in its parkinsonism and dementia. The presence of myoclonus and BNs in the cerebral cortex resembled CBD more than PSP. However, the pathology in the our patients' cerebrum was different from that of CBD and PSP, consisting of argyrophilic neuronal inclusions, atypical tau-negative neurofibrillary tangles, tau-negative astrocytic fibrillary tangles, and frequent granulovacuolar changes in the BNs, although small vacuoles may be observed in the BNs of patients with CBD [9, 44, 51]. Further, other features of our patients were also different, including the familial occurrence, dopa-responsive parkinsonism, and distribution of histopathological lesions with occasional Lewy bodies, although one familial instance [48] and two patients with dopa-responsive parkinsonism [44] have been reported in CBD. Jendroska et al. [26] reported a woman with CBD and Pick bodies. However, the distribution of her BNs and Pick bodies was different, since they were not intermixed as in our patients. Tufted astrocytic fibrillary tangles are relatively specific for PSP [7], but the sparing of the subthalamic, pontine, inferior olivary, and dentate nuclei in our patients makes the possibility of PSP unlikely [20]. Alzheimer's disease with concomitant PD was also unlikely because senile plaques were not present in our patients, and their neurofibrillary tangles were different from Alzheimer's neurofibrillary tangles as discussed above.

In summary, the disease described here displayed clinicopathological features which did not coincide exactly with any of the diseases outlined above. The ubiquitous presence of BNs in the involved areas of our two autopsied patients may imply that this is a BN-type parkinsonism with partial resemblance to PD. However, the presence of Lewy bodies in both patients, a hallmark of PD [15], indicates that this disease is a new variant of familial PD with atypical pathology which is prominent in the cerebral cortex and amygdala. We speculate that some gene abnormalities in this family may have caused such an unusual combination of various abnormalities in the cerebrum.

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