

## Corticobasal degeneration presenting with nonfluent primary progressive aphasia: a clinicopathological study

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### Abstract

A 62-year-old woman initially presented with slowly progressive nonfluent aphasia with minimal intellectual involvement. Echolalia and personality change were prominent whereas parkinsonian features and signs suggesting parietal lobe dysfunctions were not present. The patient's language deficit was consistent with transcortical motor aphasia. She did not manifest extrapyramidal signs. The patient was diagnosed as having Pick's disease or frontal lobe dementia. She died at age 65, 2 years and 9 months following disease onset. Neuropathological findings including cytoskeletal abnormalities, however, were clearly distinct from those of classical Pick's disease and were consistent with those reported in corticobasal degeneration (CBD). The distribution of her cortical lesions was accentuated in the frontal language-related area. The clinical manifestations in CBD are diverse, and primary progressive nonfluent aphasia should be considered as an initial symptom of CBD. Neuropathological examination of such patients should include cytoskeletal abnormality studies. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** Corticobasal degeneration; Primary progressive aphasia; Frontal lobe dementia; Pick's disease; Nonfluent aphasia; Cytoskeletal abnormality

### 1. Introduction

Corticobasal degeneration (CBD), originally reported by Rebeiz et al. [1], is a neurodegenerative disease primarily affecting the cerebral cortex and basal ganglia including the substantia nigra. Typical initial symptoms include akinesia, rigidity, involuntary movements, and apraxia. Concordantly, the pathological findings frequently demonstrate cortical degeneration in the frontoparietal region, especially around the central fissure. However, recent clinicopathological case reports of CBD have documented

considerably variable clinical manifestations and atypical distribution of cortical lesions [2,3]. Specifically, a small group of autopsy-confirmed patients with CBD have manifested primary progressive aphasia (PPA) as an initial clinical sign [4–10]. PPA is a clinical syndrome of a slowly progressive language disorder without generalized dementia, first described by Mesulam [11,12]. The pathological diagnoses of PPA are variable, and CBD is now well recognized as one of them [13,14].

In the present study, we report a patient with CBD who initially exhibited nonfluent PPA. Language examination demonstrated that her deficit was consistent with transcortical motor aphasia. Since the patient showed a significant personality change and behavioral abnormality, and, on the other hand, parkinsonian features were absent, the

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clinical diagnosis was consistent with Pick's disease or frontal lobe dementia [15]. Bifrontal atrophy on the neuroimaging studies supported this hypothesis. Although Pick's disease can be associated with PPA [16,17], post-mortem examination of our patient confirmed a diagnosis of CBD.

Disagreements exist on the clinical and pathological differences between Pick's disease and CBD. Recently, Kertesz et al. [18] emphasized the commonalities rather than differences between several entities including classi-

cal Pick's disease, CBD, PPA and frontal lobe dementia. They proposed the term Pick complex as a unifying concept of overlapping clinical syndromes and neuropathological findings, and they considered CBD as a variant within the spectrum of the Pick complex. Although this wider concept of Pick complex is useful for understanding the relationship between Pick's disease and CBD, we should also note the differences between these two entities. In this case report, we emphasize the clinical similarities and pathological differences between Pick's disease and CBD.

Table 1  
Longitudinal performance on neuropsychological examination at three time points

Date of examination	8/94	11/94	7/95
<i>Speech and Language</i>			
Oral agility			
pa+ta+ka *1	74	63	†
pataka *2	19	10	†
WAB AQ (/100)	77.5	77.8	49.7
spontaneous speech (/10)			
comprehension	8.8	8.4	3.7
repetition (/10)	9.2	9.2	10
naming (/10)	7.8	8.3	4.2
reading (/10)	4.4	4.5	1.8
writing (/10)	4.1	8.0	1.7
praxis right (/10)			
	9	8	3.5
left (/10)	9	8	3.3
construction (/10)	7.4	7.7	1.0
Token test (%)	74	74	37
Word fluency			
3 categories	10	7	1
3 initials	0	1	0
<i>Intelligence and Visuospatial</i>			
VIQ	55	60	51
PIQ	75	60	45
Raven's Colored Matrices (/36)	25	22	2
Rey-Osterrieth Complex Figure copy (/36)	29	29	3
<i>Memory</i>			
Paired Verbal Association (/10)	4-3-3	5-5-6	†
Benton Visual Retention, correct	3	3	0
Rey-Osterrieth Complex Figure delayed recall (/36)	5	5	0
<i>Attention and Executive Function</i>			
Digit span			
forward	5	5	4
backward	1	1	1
Number cancellation			
omission/114	8	5	†
commission/198	2	0	†
Letter cancellation			
omission/114	35	31	†
commission/198	0	0	†
Wisconsin Card Sorting Test			
categories achieved	2	1	0
perseverative errors	20	35	40

\*1: numbers correctly articulated during 20 s for each syllable. \*2: numbers correctly articulated during 20 s.

†: Impossible.

## 2. Case report

A 62-year-old right-handed, female high school graduate initially presented with slowly progressive nonfluent aphasia in August 1993. She had been working as a waitress in a restaurant for 20 years when she began to feel unable to express herself, causing her to retire from work in June 1994. A month later, she visited our neurobehavior clinic and was admitted to our hospital for language evaluation and treatment. There was no family history of neurological problems.

Neurological examination revealed that her face was symmetric and eye movements were normal. Muscle strength was full and deep tendon reflexes were normal. Muscle atrophy and fasciculation were not noted. Snout reflexes were positive, but grasp reflexes were unremarkable. No involuntary movements were noted. Extrapyrarnidal signs including muscle rigidity, finger tremor, bradykinesia and Myerson's sign were absent. On neuropsychological examination performed in August 1994, her speech demonstrated marked simplification and echolalia. The profile of her language impairment was most consistent with that of transcortical motor aphasia in that repetition was surprisingly preserved in contrast to a striking nonfluency of spontaneous speech. Euphoria, indifference and impassivity were noted as evidence of personality change. She occasionally burst into laughter when she made errors. Severe perseveration was noted. Memory, visuospatial capacities, and skills in daily activities were mildly to moderately impaired. The results of the patient's neuropsychological examinations are summarized in Table 1.

Brain MRI and CT scan demonstrated significant cortical and subcortical atrophy in both frontal lobes, more prominent on the left. Bifrontal hypoperfusion, more prominently on the left, was present on technetium-99m hexamethylpropylene (99mTc-HMPAO) single photon emission computed tomography (SPECT). The clinical diagnosis was Pick's disease or frontal lobe dementia.

Although the patient did not show any significant extrapyramidal symptoms, she was treated with two dopamine agonists (bromocriptine and pergolide) from August to October 1994 in an attempt to ameliorate nonfluent

aphasia [19]. However, her language impairment did not benefit from dopamine therapy. The neuropsychological examination in November 1994, 1 month following discontinuation of dopamine agonists, revealed no significant interval changes in her language and cognitive functions (Table 1). However, subsequently her disease course progressed rapidly. Her overall daily activities had become significantly limited by August 1995 when the neuropsychological reevaluation demonstrated a noticeable decline in the whole range of cognitive functions including visuospatial functions, attention and memory. She was transferred to another hospital where she died of pneumonia on May 19, 1996, at age 65. The total length of illness was 2 years and 9 months.

### 3. Results

#### 3.1. Neuropathological findings

The weight of the brain was 1200 g. Macroscopic examination revealed atrophy of the middle part of the left frontal lobe including the premotor area, supplementary motor area, and pars opercularis of the inferior frontal gyrus (Fig. 1). Cerebral atrophy was more accentuated on the left. Histological examination disclosed neuronal loss with astrocytosis, status spongiosus, and numerous ballooned neurons in the cerebral cortex of the left frontal lobe, prominently in the middle part of the frontal lobe (Figs. 2 and 3). Neuronal loss with astrocytosis was evident in the striatum, pallidum, thalamus, substantia nigra (Fig. 4), and dentate nucleus. The distribution pattern of the basal ganglia lesions, including the striatum and pallidum (Fig. 5), showed that the pallidum contained large lesions with severe neuronal loss and prominent fibrillary gliosis, and that the striatum had moderate lesions with obvious neuronal loss and slight fibrillary gliosis. Neither Pick bodies nor senile plaques were seen in the cerebral cortex or the hippocampus. A few neurofibrillary tangles (NFTs)

were present in the amygdala by a modified Gallyas–Braak (G–B) method. A small number of NFTs were observed in the CA1 region of the hippocampus, with a small to moderate number of NFTs in the parahippocampal gyrus. The modified G–B method showed numerous abnormal structures, which consisted of massive argyrophilic threads, scattered coiled bodies, pretangles and astrocytic plaques (Fig. 6). This distributional pattern of argyrophilic threads and other abnormalities was almost equivalent with that of the degenerating area. Pretangles and astrocytic plaques were found mainly in the frontal cerebral cortex. All these G–B-positive structures were also positive for anti-tau antibody (pool 2, 1:50000, rabbit polyclonal, recognizes the amino acid sequence of 299–385 in the longest isoform of human tau, provided by Dr. H. Mori [20]). Ballooned neurons were only faintly positive for anti-tau antibody in their peripheral region. Origin of all these tau-positive structures was mentioned in the previous paper [21].

### 4. Discussion

The initial symptom of this patient was slowly progressive nonfluent aphasia. During the first year since the onset of illness in 1983, she was able to manage her household and her general intelligence was spared despite her significant language problems. Although the initial neuropsychological examination performed 12 months since onset already demonstrated mild attention and memory deficits as well as severe nonfluent aphasia, her prominent feature of language accentuated impairments was most consistent with PPA [11,12]. Her speech was severely nonfluent and echolalic whereas repetition was remarkably preserved, thus consistent with transcortical motor aphasia. Dopaminergic pharmacotherapy did not improve language functions. Among the pathologically confirmed CBD cases, both fluent [7–10] and nonfluent [4,5,13] types of PPA have been recognized. Although sparsely reported at

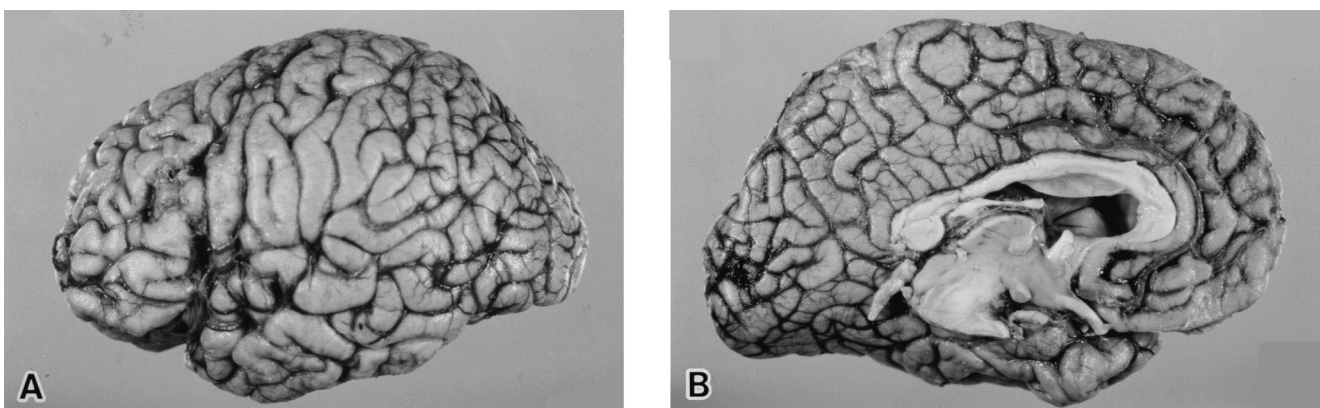


Fig. 1. (a) Lateral view of the left cerebrum showing atrophy of the middle part of the frontal lobe including the premotor area and pars opercularis of the inferior frontal gyrus. (b) Medial view of the left cerebrum showing atrophy of the middle part of the frontal lobe including the supplementary motor area.

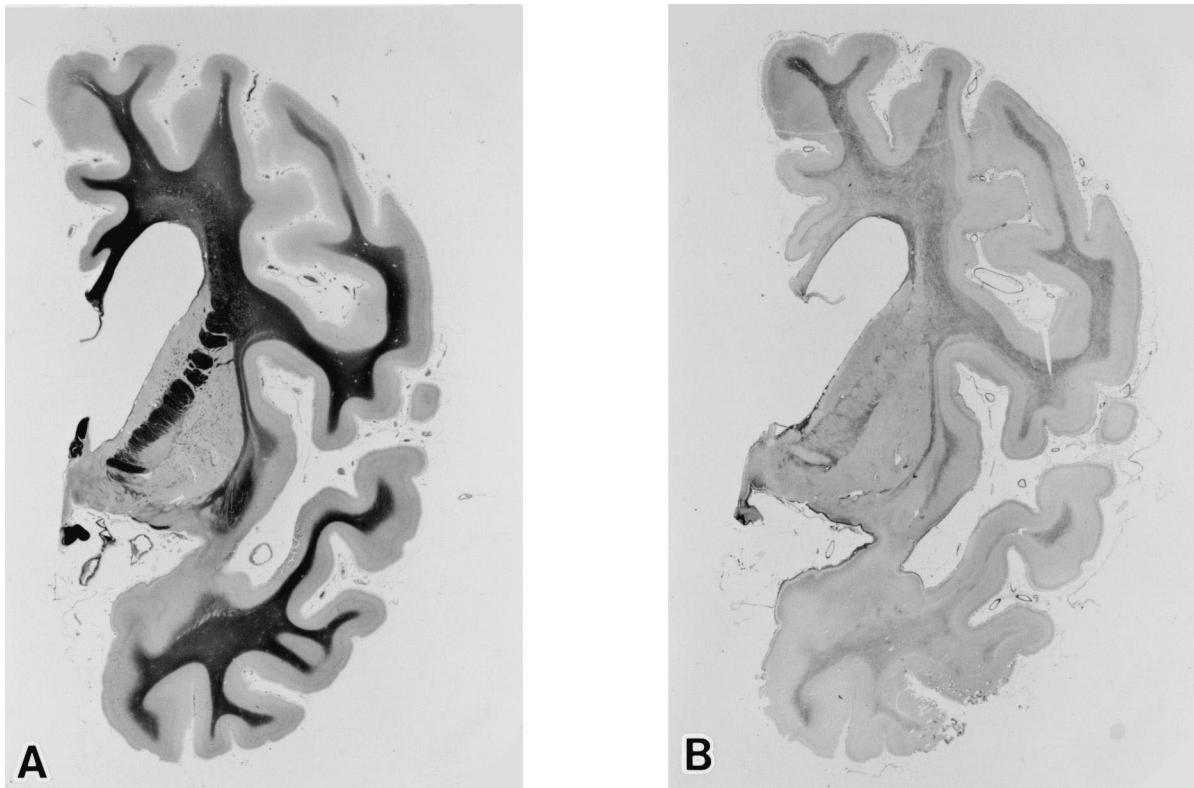


Fig. 2. Coronal section through the anterior part of the left temporal lobe showing atrophy of the caudate nucleus and gliosis of the cerebral white matter, prominently in the frontal lobe. (a) Kluver-Barrera stain  $\times 1.2$ , (b) Holzer stain  $\times 1.2$ .

present, nonfluent PPA in CBD may not be uncommon as was pointed out by Kertesz et al. [14]. Our patient was unique in that she presented with typical transcortical motor aphasia as an initial symptom caused by CBD. Detailed language evaluation and follow-up studies of aphasia symptoms are warranted in clinical examination of possible CBD patients.

An unusual aspect of our patient was that she also showed severe frontal lobe dysfunction, including personality change, perseveration and abnormal behaviors, whereas she lacked common features of CBD, including extrapyramidal signs. These findings lead to the clinical diagnosis of frontal lobe dementia or Pick's disease. Such discrepancy between the clinical diagnosis (Pick's disease) and the pathological diagnosis (CBD) has been reported [4,22–26]. These reports at least suggest that there exist atypical CBD cases which mimic Pick's disease, and hence CBD bears more wide-ranging clinical spectrum than originally had been thought.

Our patient had three neuropathological features consistent with CBD and distinct from Pick's disease. Firstly, our patient did not have Pick bodies in the hippocampus and cerebral cortex, which excluded the diagnosis of Pick's disease with Pick bodies. Secondly, the distribution of the basal ganglia lesions in our patient showed that the pallidum contained severe lesions, but that the striatum had moderate lesions. This distribution pattern of basal ganglia

lesions was consistent with that seen in CBD [3]. Third, the modified G–B method revealed massive argyrophilic threads in the central nervous system and many astrocytic plaques in the cerebral cortex of our patient, which are the most prominent cytoskeletal abnormalities in CBD [10]. Numerous astrocytic plaques found in our patient were characteristic for CBD and different from astrocytic inclusions of progressive supranuclear palsy and Pick's disease. Also, the tau-immunohistochemistry demonstrated hallmark findings of cytoskeletal abnormalities, which coincide with those reported in CBD [27,28]. All these neuropathological findings argue against this patient being included in the category of Pick's disease with or without Pick bodies.

Recently, Kertesz et al. [14,18] proposed the concept of Pick complex which entails both classical Pick's disease and CBD as variants. It is clear that our patient falls somewhere within the spectrum of this Pick complex. However, it is not clear how to treat such borderline cases, whose pathology lacks Pick bodies and has neuronal swelling (i.e., group B patients in Tissot et al. [29] classification). It appears that some researchers consider such intermediate cases within the category of Pick's disease while others consider such cases variants of CBD. We may consider our patient as having Group B Pick's disease, but recent immunohistochemical studies strongly suggest this patient to be CBD. We speculate that at least

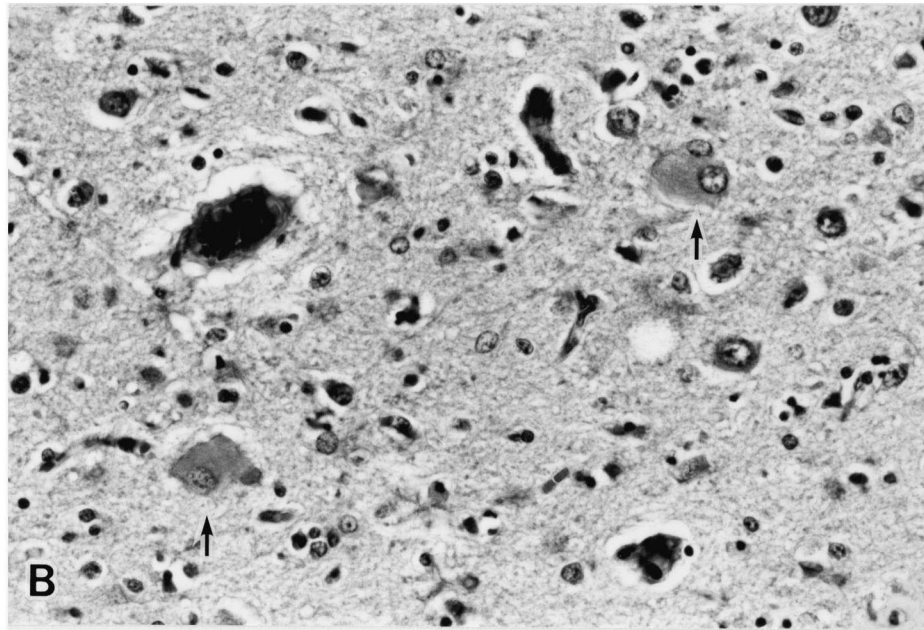
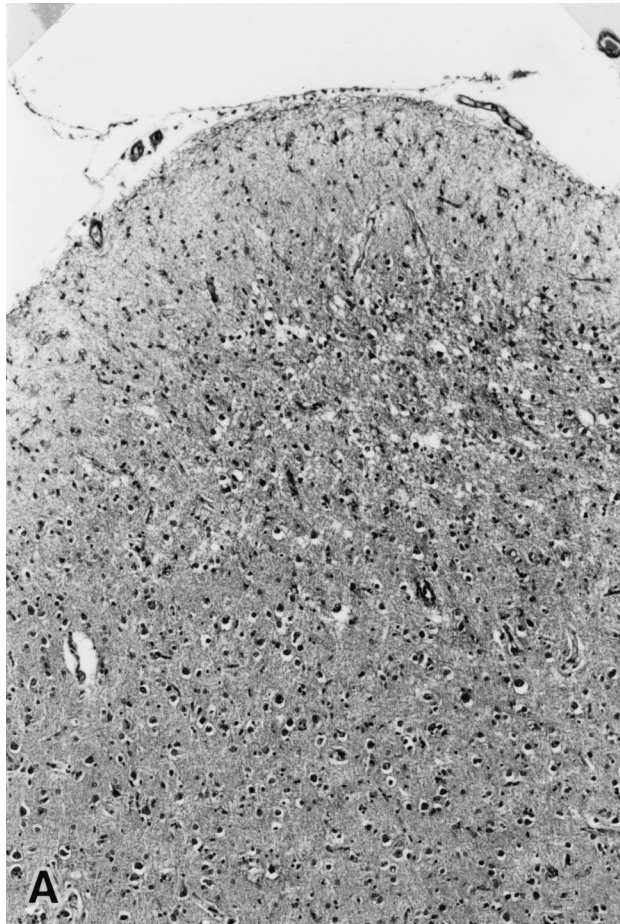


Fig. 3. Frontal cortex showing neuronal loss with status spongiosus (a) and numerous ballooned neurons (arrow) (b). Haematoxylin and eosin stain, (a)  $\times 85$ , (b)  $\times 340$ .

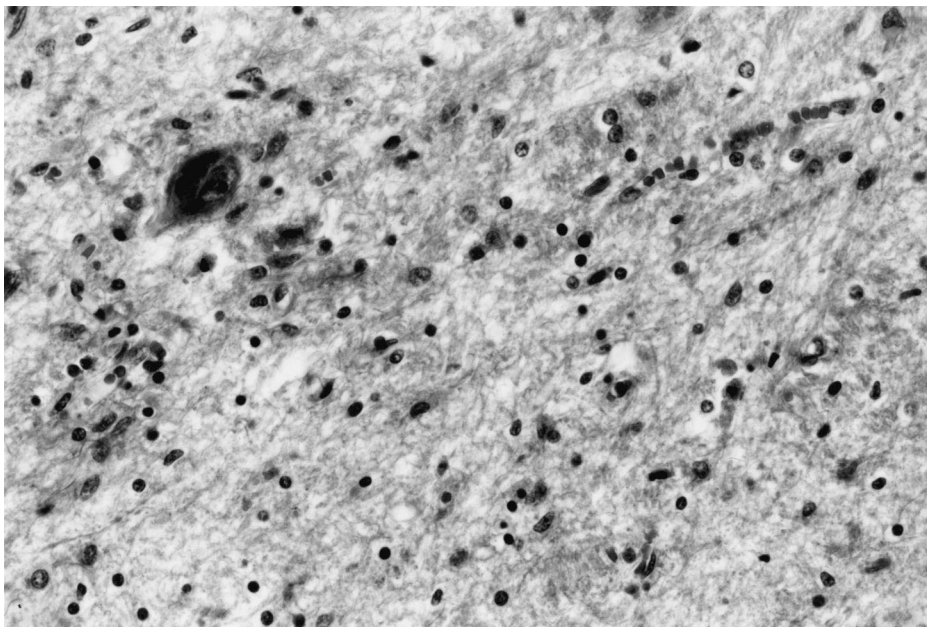


Fig. 4. Substantia nigra showing prominent neuronal loss and astrocytosis. Haematoxylin and eosin stain,  $\times 340$ .

some of Tissot et al. [29] group B patients may well have had CBD under the current neuropathological standpoint. Improved detection of cytoskeletal abnormalities including numerous argyrophilic threads by G–B and anti-tau methods should enable the differentiation of CBD from Pick's disease more clearly in the future [10,30]. We should note that focal cerebral atrophy of CBD is more multicentric than were initially thought and that the cortical "atrophic center" of CBD may resemble that of Pick's disease.

Neuropathological examination in Pick's disease and

CBD is also useful in reconsidering patients with PPA. Postmortem examination of patients with PPA reported by Wechsler et al. [16] and by Graff-Radford et al. [17] demonstrated Pick bodies and typical pathological findings consistent with Pick's disease. However, the patients with PPA who were reported by Holland et al. [31] and in Case Records of the Massachusetts General Hospital [32] as having Pick's disease showed atypical pathological features in both the distribution of basal ganglia lesions and in microscopic findings. Accordingly, CBD cannot be ruled

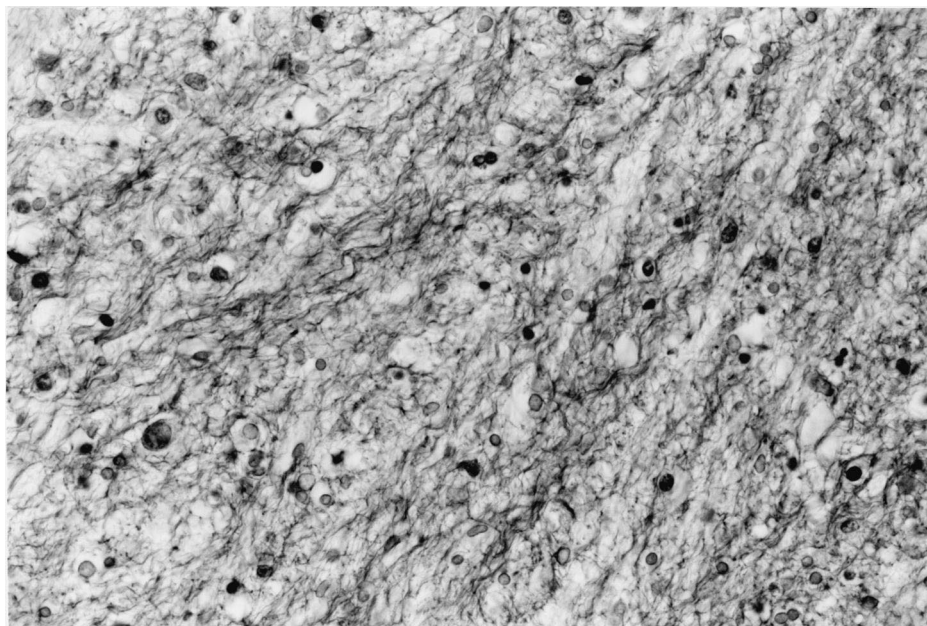


Fig. 5. Inner segment of the pallidum showing prominent fibrillary gliosis. Holzer stain,  $\times 340$ .

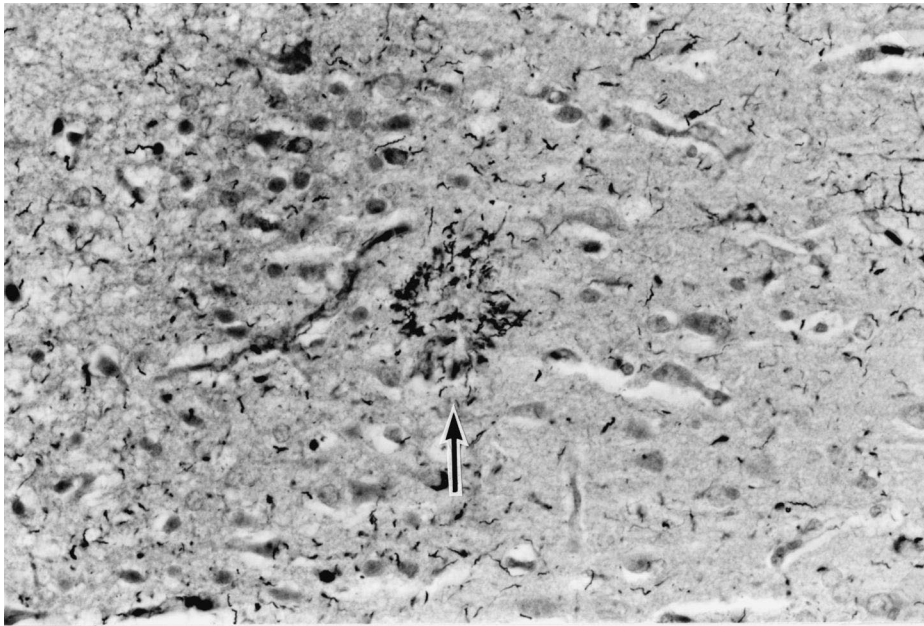


Fig. 6. Cerebral cortex of the frontal lobe showing widespread appearance of argyrophilic threads and astrocytic plaque (arrow). Modified Gallyas–Braak method,  $\times 340$ .

out in such patients, and further specific neuropathological and cytoskeletal examinations are warranted for similar patients. It is possible that CBD covers a wider range of the spectrum in the PPA complex than is usually believed.

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