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Distribution of cerebral cortical lesions in Pick's disease with Pick bodies: a clinicopathological study of six autopsy cases showing unusual clinical presentations

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Abstract We investigated six Japanese autopsy cases of Pick's disease with Pick bodies (PDPB) both clinically and pathologically, and examined the distribution of their cerebral cortical lesions using hemisphere and/or bisphere specimens. The lesions were classified into three categories (slight, moderate, and severe). Two patients with a clinical diagnosis of primary progressive apraxia and of slowly progressive aphasia had speech apraxia as their initial signs, and the other two patients were suspected as having Alzheimer's disease, with the clinical diagnosis of the remainder two patients being presenile dementia and depression, respectively. Extrapyramidal signs, believed to be rare in PDPB, were present in four patients. Severe

lesions were multicentrically present in the cerebral cortices of all six cases. In two patients with speech apraxia, severe lesions were seen in the primary motor area, which generally has not been regarded as an "atrophic center" in Pick's disease. Furthermore, in a patient with depression, severe lesions were more widespread in the convexity than in the orbital region of the frontal lobe. The parietal lobes, including the postcentral gyrus usually believed to be spared in Pick's disease, were severely involved in three patients. We postulate that the clinical features of PDPB have a much wider spectrum than previously believed. In addition, we believe that the distribution of the cerebral cortical lesions in PDPB is more widespread than previously assumed, and that clinical manifestations of PDPB depend to some extent on the topographic distribution of the cerebral cortical lesions.

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Introduction

Pick's disease, first described by Arnold Pick, is a rare degenerative disorder accounting for 0.4–2% of all dementia cases [30, 31, 49, 53, 56]. It has been believed that the disease is characterized clinically by a peculiar process of dementia, including the appearance of character changes, language disturbance, and elements of Klüver-Bucy syndrome in the early phase of the disease, relative preservation of memory and visuospatial abilities in the early or middle phase of the disease, inconsistent with Alzheimer's disease, and pathologically by localized atrophy of the frontal and/or temporal lobes with dense gliosis in the subjacent white matter [3, 12, 16, 37, 38, 48, 58].

There has been a lack of consensus regarding the neuropathological diagnostic criteria for Pick's disease [24, 51, 67]. Some neuropathologists require the presence of circumscribed lobar atrophy, Pick bodies, ballooned neurons, neuronal loss, and gliosis for a diagnosis of Pick's disease. Others use the presence of circumscribed atrophy,

neuronal loss and gliosis without Pick bodies or ballooned neurons [23, 41, 73]. At present, cases of circumscribed frontal and temporal atrophy with Pick bodies can be clearly neuropathologically diagnosed as Pick's disease [7, 13, 15, 20, 26, 27, 29, 40, 43, 46, 70].

Recently, it is thought that clinical manifestations of Pick's disease with Pick bodies (PDPB) have a wider spectrum than previously believed. In some patients with autopsy-proven PDPB, language disorders are an early, prominent and progressive feature, as was the case with Pick's original case [22, 32, 34, 74]. This is usually associated with perisylvian degeneration, especially affecting the dominant (usually left) hemisphere. Although Pick's disease rarely selectively affects the parietal lobe, cases of parietal PDPB presenting with progressive apraxia suggestive of corticobasal degeneration (CBD) have also been reported [8, 17, 18, 42, 57]. Furthermore, the concept of an overarching "Pick complex" has recently been championed by Kertesz and Munoz [33], given the overlap in clinical and pathological features of degenerative diseases producing focal cortical atrophy and the lack of specific markers for Pick's disease. It is well known not only that clinical syndromes reflect more the distribution of pathology than the nature of the underlying pathological changes, but also that there is heterogeneity in the distribution of pathology in various disorders that commonly produce focal cortical syndrome, including CBD and amyotrophic lateral sclerosis with dementia [69, 71].

The purpose of this study is to describe clinical and pathological findings on six Japanese patients with autopsy-proven PDPB, and to delineate the multiplicity of clinical features of this disorder. We also provide a detailed distribution of the PDPB cerebral cortical lesions based on histological examination, and verify that the precentral and postcentral gyri, traditionally believed to be spared in Pick's disease, are severely involved in PDPB showing atypical clinical presentation. In addition, we also address the clinicopathological correlation between atypical clinical presentations, including speech apraxia, depression, and clinical features mimicking Alzheimer's disease, and the topographical distribution of severe lesions in the cerebral cortex.

Materials and methods

The present investigation was carried out on six autopsy cases from three Japanese institutions. The clinical records and tissue specimens in cases 2, 3, 5, and 6 were from the Department of Neuropathology, Tokyo Institute of Psychiatry, and those in cases 1 and 4, from the Department of Clinical Neuropathology, Tokyo Metropolitan Institute for Neuroscience, and from the Department of Pathology, Kanagawa Rehabilitation Center, respectively.

After fixation in formalin, the brains of all six patients were sectioned coronally. Cerebral hemisphere and/or bisphere blocks, including the frontal lobe, temporal lobe, parietal lobe, occipital lobe, striatum, pallidum, subthalamic nucleus, thalamus, amygdala, and hippocampus, were taken in both the hemispheres and bispheres. For case 1, eight left hemispheric blocks were taken; for case 2, six; for case 3, six; for case 4, six; for case 5, eight; and for case 6, five. Additional tissue blocks were taken from the midbrain including the substantia nigra, cerebellum, and brain stem. The

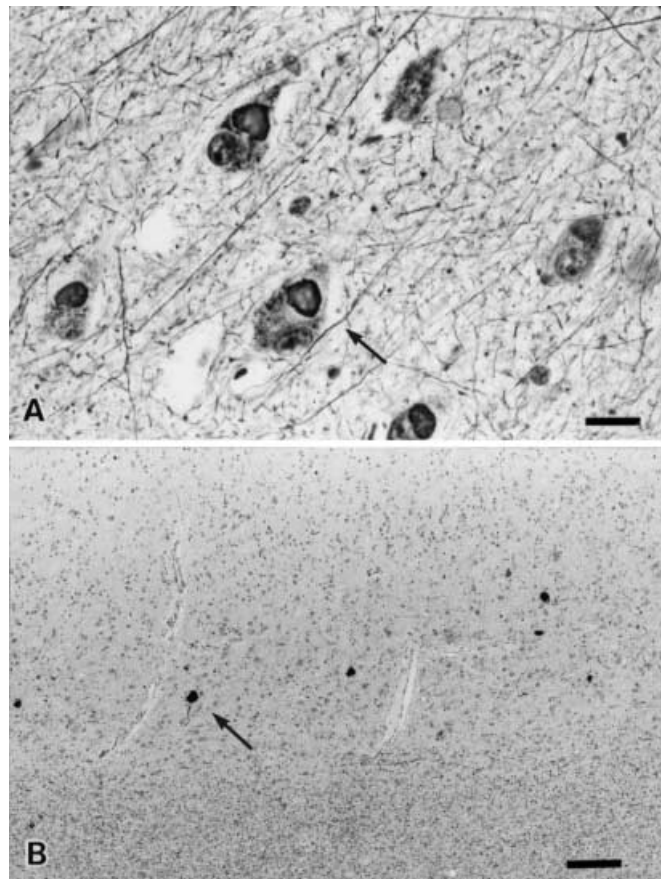


Fig. 1a, b Case 4. **a** Widespread presence of Pick bodies (arrow) in the hippocampus; Bodian stain. **b** Widespread presence of ballooned neurons (arrow) in the lateral occipitotemporal gyrus; neurofilament stain. Bars **a** 20 μ m; **b** 150 μ m

brains were embedded in paraffin and cut to a thickness of about 10 μ m. The sections were stained with hematoxylin-eosin (H&E) and also using the Klüver-Barrera, Holzer, Bodian, methenamine-silver, and modified Gallyas-Braak methods. Immunocytochemistry was performed using antibodies against human-tau pool 2 (from Dr. H. Mori; Osaka City University), paired helical filaments (PHFs; Sigma 1:50), polyclonal ubiquitin (Dako, Glostrup, Denmark), monoclonal ubiquitin (from Dr. H. Mori; Osaka City University), polyclonal neurofilament (200 kDa), and glial fibrillary acidic protein (GFAP).

In all patients, Pick bodies (Fig. 1a) were numerous encountered in the dentate granule cells and pyramidal neurons of the hippocampus, affected lesions of the cerebral cortex, prominently in cortical layers II and III, the amygdala, striatum, nucleus basalis of Meynert, and locus ceruleus. A widespread distribution of ballooned neurons (Fig. 1b) was observed in the affected neocortex, prominently in the fifth layer, parahippocampal gyrus, and amygdala in all patients examined in this study. Pick bodies in our six cases were distinctive by their large size, roughly similar to that of the cell nucleus, their often perfectly round shape, and the intense argyrophilia on the methenamine-silver or/and Bodian stain [1]. The immunoreactivity of Pick's bodies in all six patients was not only intensely positive for tau and a variable intensity-positive for ubiquitin, but also negative for neurofilament in a large number of Pick bodies, which were compatible with the study on immunoreactivity of Pick bodies reported by Murayama et al. [51] and Munoz [50], respectively. Ballooned neurons in our cases showed not only focal cytoplasmic tau immunoreactivity, but also strong neurofilament immunoreactivity, which was also fundamentally

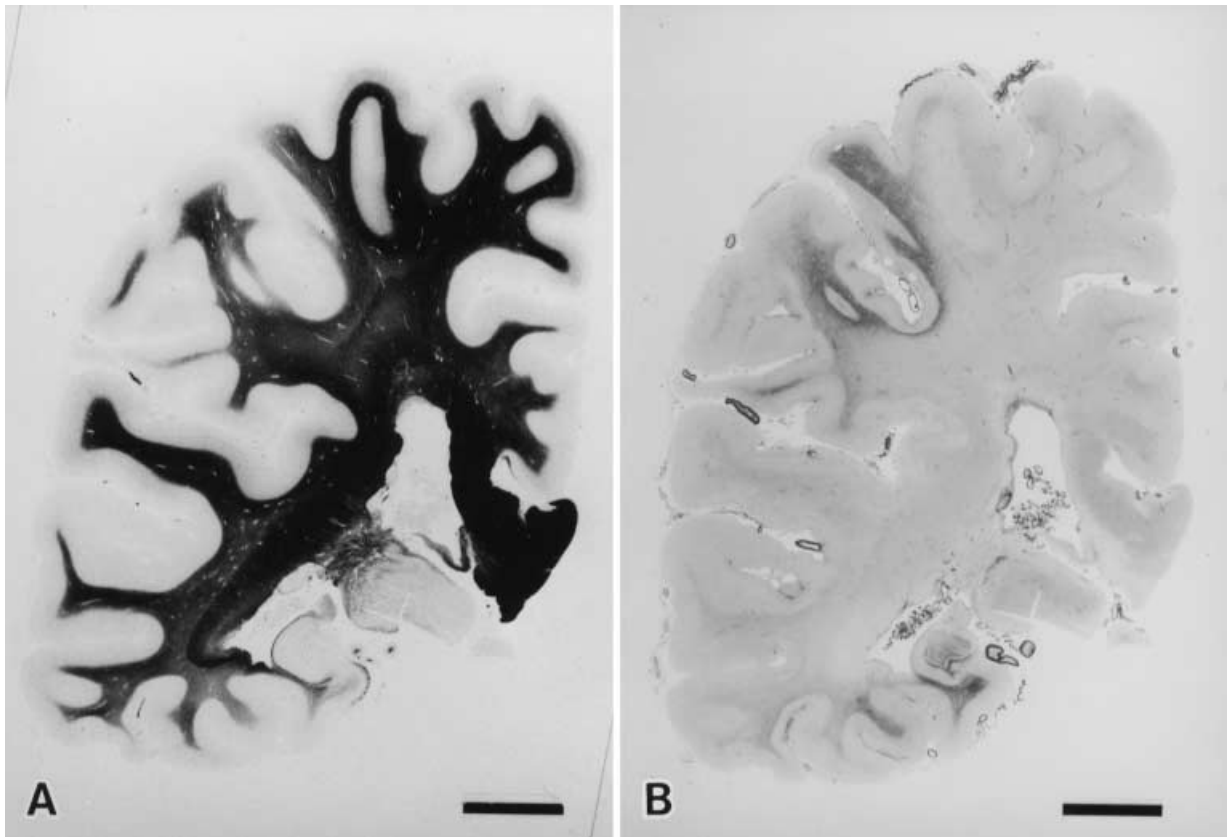


Fig. 2a, b Case 1. Coronal section through the left pulvinar showing prominent atrophy with loss of myelin and fibrillary gliosis of the parietal lobe, including the postcentral gyrus and supramarginal gyrus. **a** Klüver-Barrera stain, **b** Holzer stain; bars 10 mm

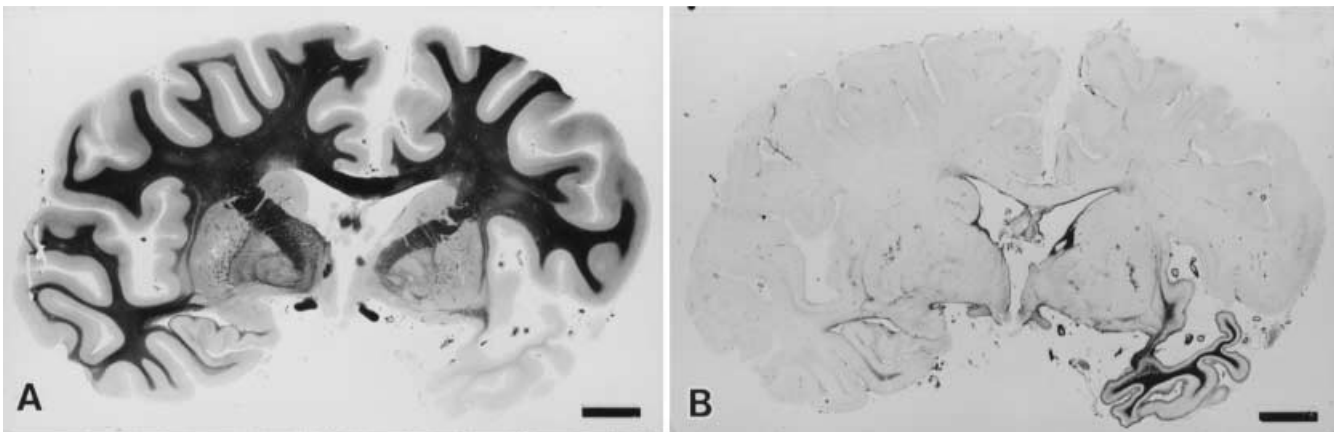


Fig. 3a, b Case 2. Coronal section through the right amygdala and anterior portion of the left temporal lobe showing prominent atrophy with loss of myelin and fibrillary gliosis in the ventral portion of the left insular gyrus and left temporal lobe. **a** Klüver-Barrera stain; **b** Holzer stain; bars 10 mm

consistent with the study on immunoreactivity of ballooned neurons reported by Murayama et al. [51] and Munoz [50]. Neuropathological features in all the patients were consistent with the pathological criteria of group A Pick's disease reported by Constantinidis et al. [11] and Constantinidis [10] and also with the pathological criteria for Pick's disease recently proposed by Dickson [15].

The clinicopathological findings in cases 1, 2, 4, and 6 were reported previously by Fukui et al. [17], Ikeda et al. [25], Masaki et al. [47], and Oyanagi et al. [55], respectively (Figs. 2, 3, 4, and 5). The clinicopathological findings and electron microscopic features of Pick bodies in case 6 were also reported by Oyanagi et al. [55] and Oyanagi [54]. The distribution of Pick bodies in the central nervous system and the presence of ghost Pick bodies in case 6 were reported by Arima et al. [2] and Izumiyama et al. [28]. The distribution of basal ganglia lesions in cases 1, 2, 3 and 5 were previously reported by Tsuchiya et al. [70]. The classification of basal ganglia lesions, including the amygdala, striatum, and pallidum, was carried out as follows. Lesions identified by light microscopy were classified into three categories: mild, relative preservation of the neurons with slight proliferation of the glia; moderate, obvious neuronal loss with obvious astrocytosis and slight fibrillary gliosis;

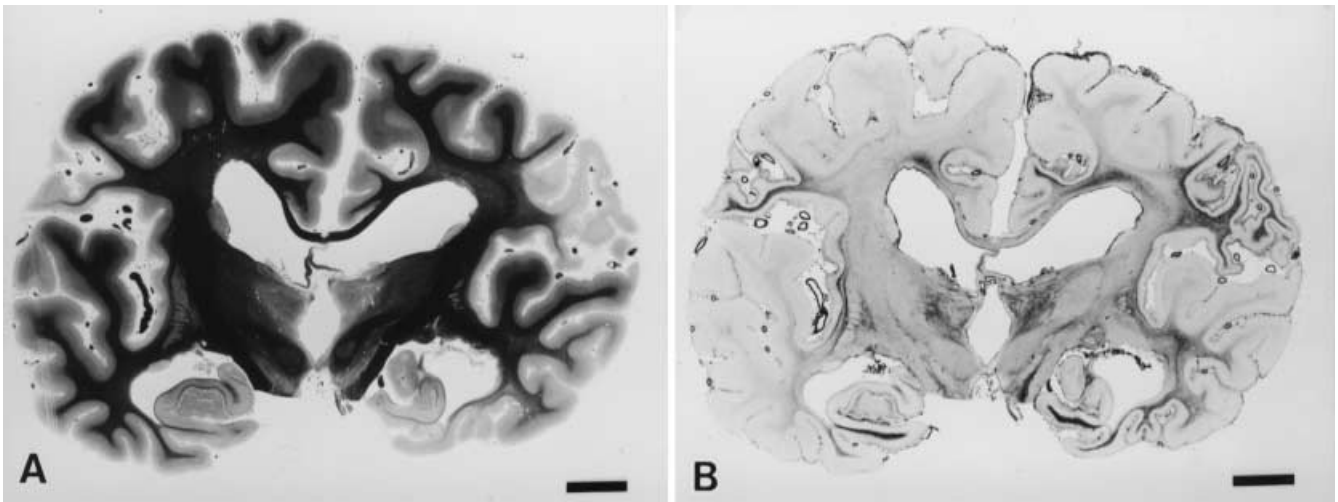


Fig. 4a, b Case 4. Coronal section through the bilateral thalamus showing prominent atrophy with loss of myelin and fibrillary gliosis in the bilateral postcentral gyri. **a** Klüver-Barrera stain; **b** Holzer stain; bars 10 mm

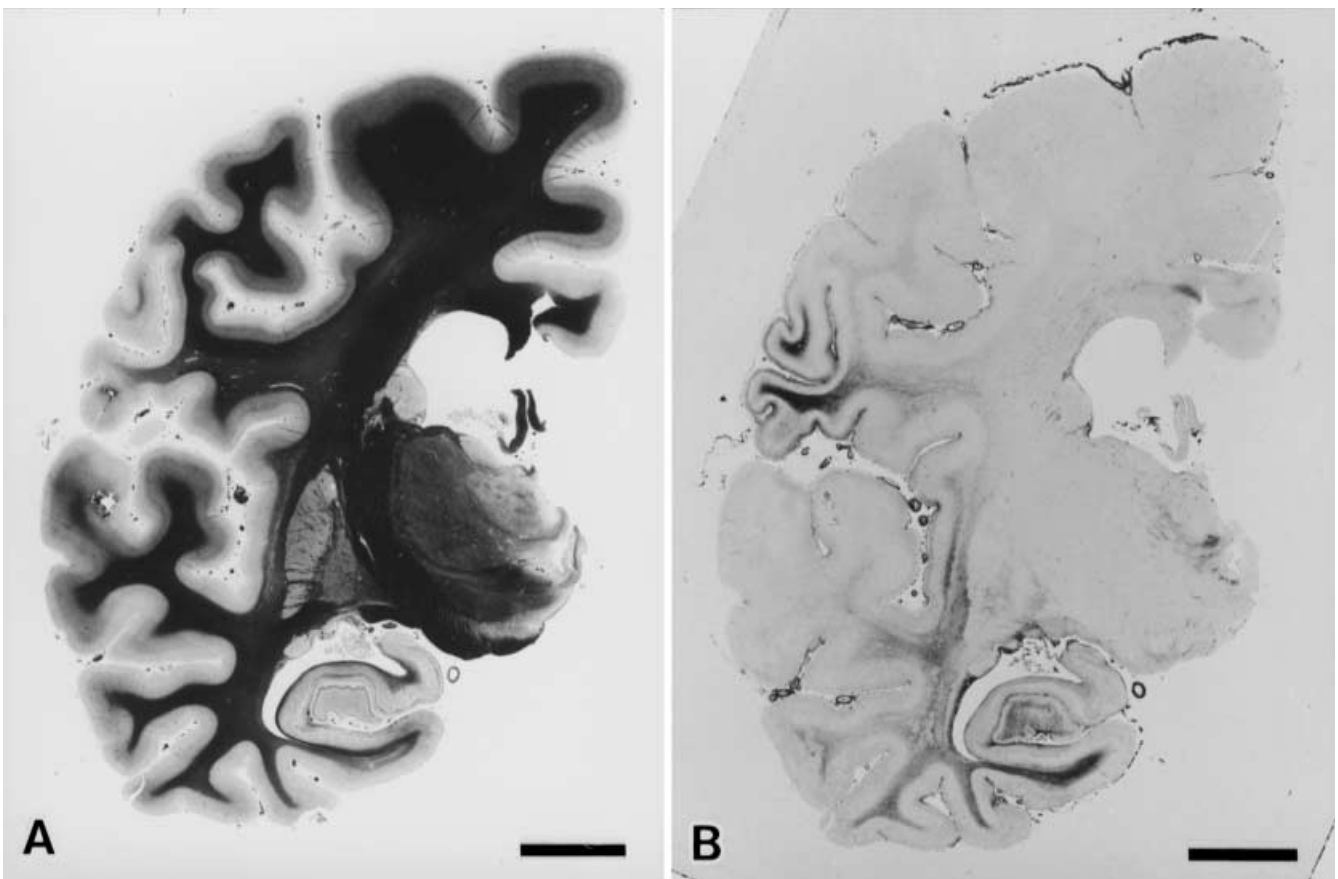


Fig. 5a, b Case 6. Coronal section through the right thalamus showing prominent atrophy with loss of myelin and fibrillary gliosis in the parietal lobe, including the postcentral and supramarginal gyrus. **a** Klüver-Barrera stain; **b** Holzer stain; bars 10 mm

and severe, pronounced neuronal loss with rarefaction of the neuropil and/or prominent fibrillary gliosis. The classification of basal ganglia lesions described above is fundamentally consistent with

the classification of basal ganglia lesions in CBD and PDPB reported by Tsuchiya et al. [68, 70].

Case reports

Clinical course and neuropathological findings in case 3

The patient presented with a depressive state, including abulia, asponaneity, and logopenia, when he was 54 years old. Thereafter,

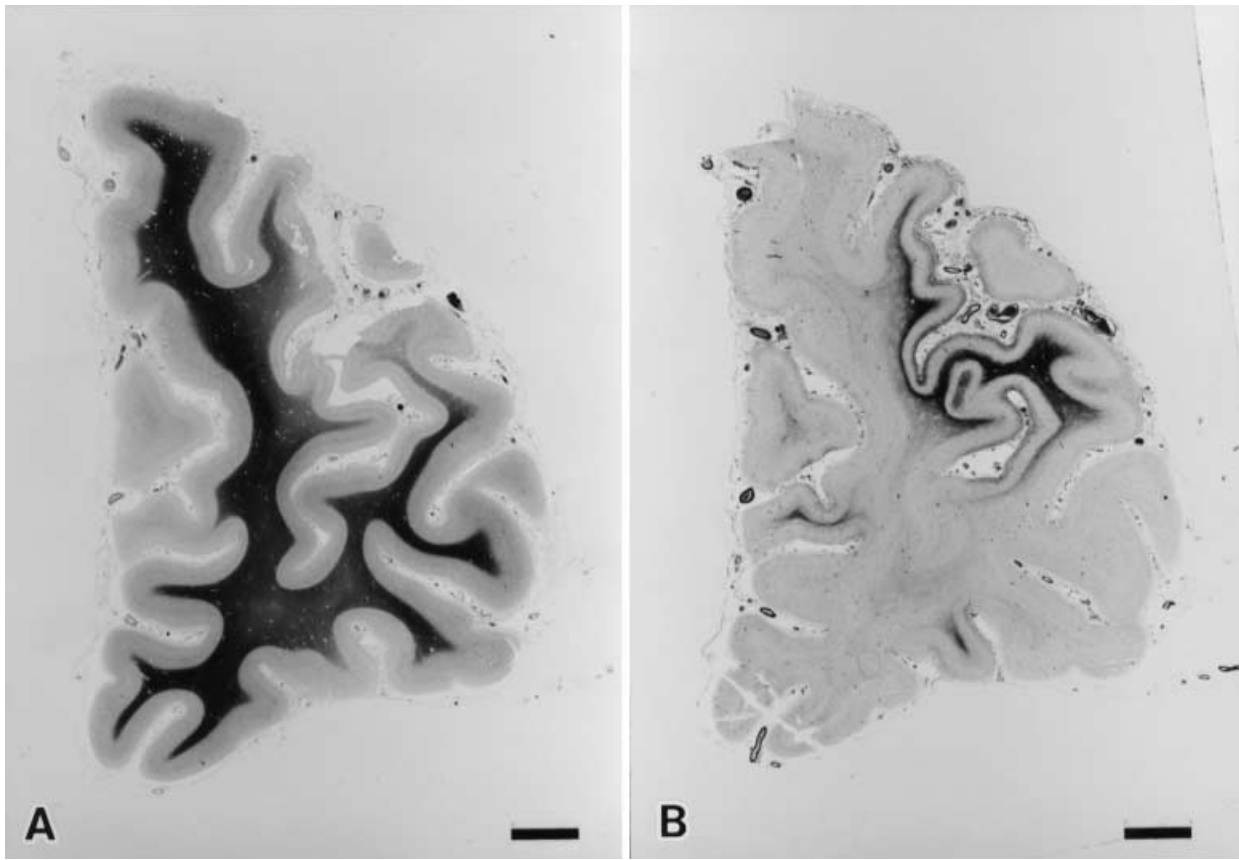


Fig. 6a, b Case 3. Coronal section through the left frontal lobe showing prominent atrophy with loss of myelin and fibrillary gliosis, prominently in the convexity. **a** Klüver-Barrera stain; **b** Holzer stain; bars 5 mm

he did not go to work and conversation with the family prominently decreased. At age 56, 2 weeks before his death, he fell upstairs. After that, he became bedridden and suffered double incontinence. Psychiatric and neurological examinations when the patient was 56 years of age, 4 days before his death, revealed a depressive state, absence of dementia, aimless wandering, changes in dietary habits, and absence of neurological signs. The patient died of cardiac arrest at age 56. The total duration of his disease was 1.5 years, and the clinical diagnosis was depression. There was no family history of dementia.

The weight of the brain was 1,090 g. Macroscopic examination revealed atrophy of the frontal lobes (Fig. 6). Histological examination revealed neuronal loss with astrocytosis, status spongiosus, Pick bodies, and ballooned neurons in the cerebral cortex, prominently in the frontal lobe. Neuronal loss was not found in the hippocampus. Moderate neuronal loss was evident in the amygdala, with slight neuronal loss in the caudate nucleus, putamen, and pallidum. Neuronal loss was obvious in the thalamus, but was not seen in the substantia nigra.

Clinical course and neuropathological findings in case 5

The patient developed memory disturbance when she was 62 years of age, followed by spatial disorientation and paraphasia about 1 year later. At age 63, she could not go to the hospital by herself, and was diagnosed as having Alzheimer's disease. Psychiatric and neurological examinations when the patient was 65 years old revealed severe dementia, sensory aphasia, and ideational apraxia. However, even during this period, abnormal behavior and disinhi-

bition, which are compatible not only with Pick's disease but also with frontotemporal dementia, were not found. There were no neurological signs. Brain magnetic resonance imaging during this period revealed prominent atrophy of the bilateral frontal and temporal lobes, compatible with Pick's disease. She died of pancreatic cancer at age 67. The total duration of her disease was 5 years, and she was suspected as having Alzheimer's disease. There was no family history of dementia.

The weight of the brain was 1,050 g. Macroscopic examination revealed atrophy of the bilateral frontal and temporal lobes, with atrophy of the amygdala and caudate nucleus (Fig. 7). Histological examination disclosed neuronal loss with astrocytosis, status spongiosus, Pick bodies, and ballooned neurons in the cerebral cortex, prominently in the frontal and temporal lobes. Neuronal loss was not found in the hippocampus, but was severe in the amygdala, moderate in the caudate nucleus and putamen, and slight in the pallidum. Neuronal loss was obvious in the thalamus, but was not seen in the substantia nigra.

Classification of cerebral cortical lesions

The lesions identified by light microscopy were classified into three categories: **slight**, showing slight neuronal loss and gliosis of the superficial layers; **moderate**, showing obvious neuronal loss with gliosis of the second and third layers, often accompanied by status spongiosus and relative preservation of the neurons of the fifth and sixth layers; and **severe**, showing pronounced neuronal loss with gliosis of the second to sixth layers with prominent fibrillary gliosis in the subjacent white matter (Fig. 8). The primary motor area, including Betz cells, was identified on the hemisphere and/or bisphere specimens of the six cases [72]. The classification of cerebral cortical lesions described above is consistent with that of cerebral cortical lesions in CBD elucidated by Tsuchiya et al. [69]. The data obtained for each patient are depicted schematically in Figs. 9, 10, 11, 12, 13, 14.

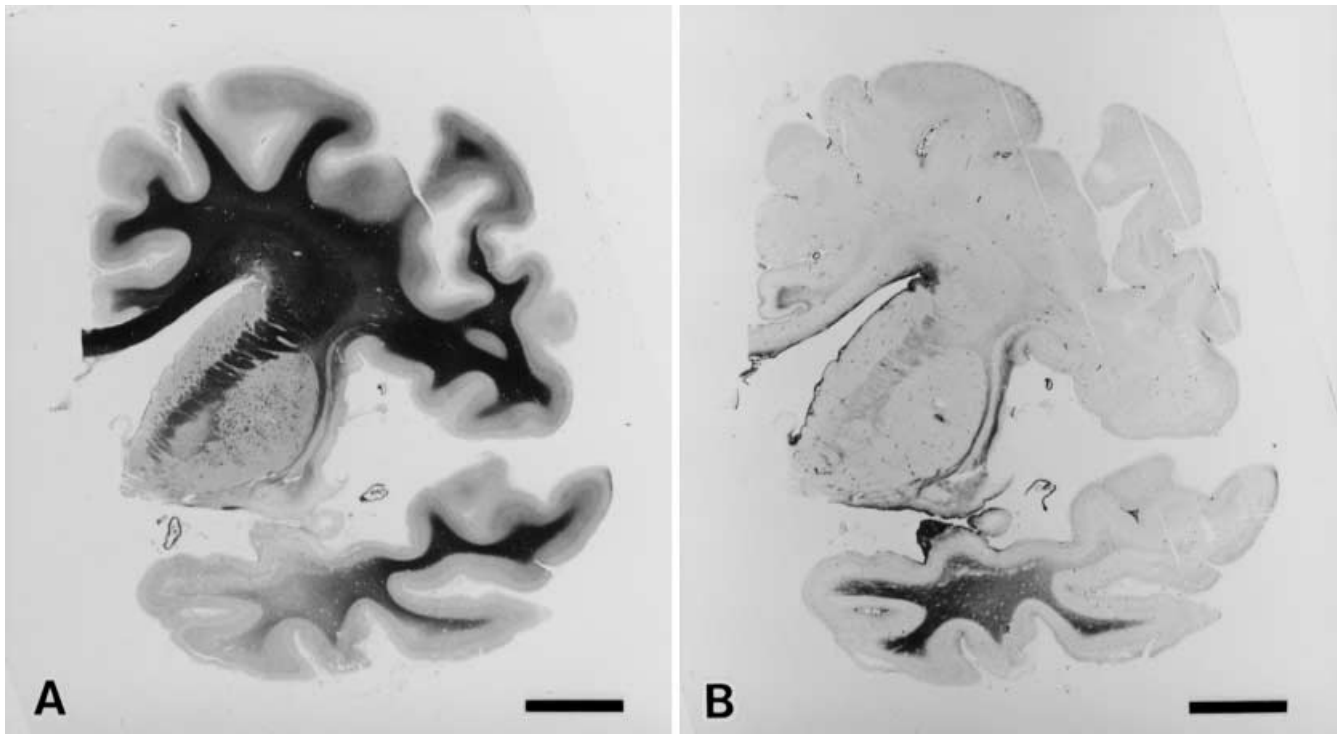


Fig. 7a, b Case 5. Coronal section through the anterior portion of the left temporal lobe showing prominent atrophy with loss of myelin and fibrillary gliosis in the ventral portion of the insular gyrus and medial portion of the first temporal gyrus. **a** Klüver-Barrera stain; **b** Holzer stain; bars 10 mm

Results

Clinical features

The main clinical information on the six patients (three male, three female) is summarized in Table 1. The patients had no hereditary burden. The age at onset of symptoms was from the fifth to seventh decade of life, with an average of 55 years. The duration of the disease ranged from 1 year 6 months in case 3 to 19 years in case 2, with the mean duration being 8 years 9 months. Two patients had speech apraxia as their initial sign, and two patients developed memory disturbance as the initial sign. Dementia was observed in five patients. Extrapyrarnidal signs were observed in four patients, including the two whose the initial signs were speech apraxia. Two patients were suspected as having Alzheimer's disease, with the clinical diagnosis of the other four patients being primary progressive apraxia, presenile dementia, depression, and slowly progressive aphasia, respectively.

Neuropathological features

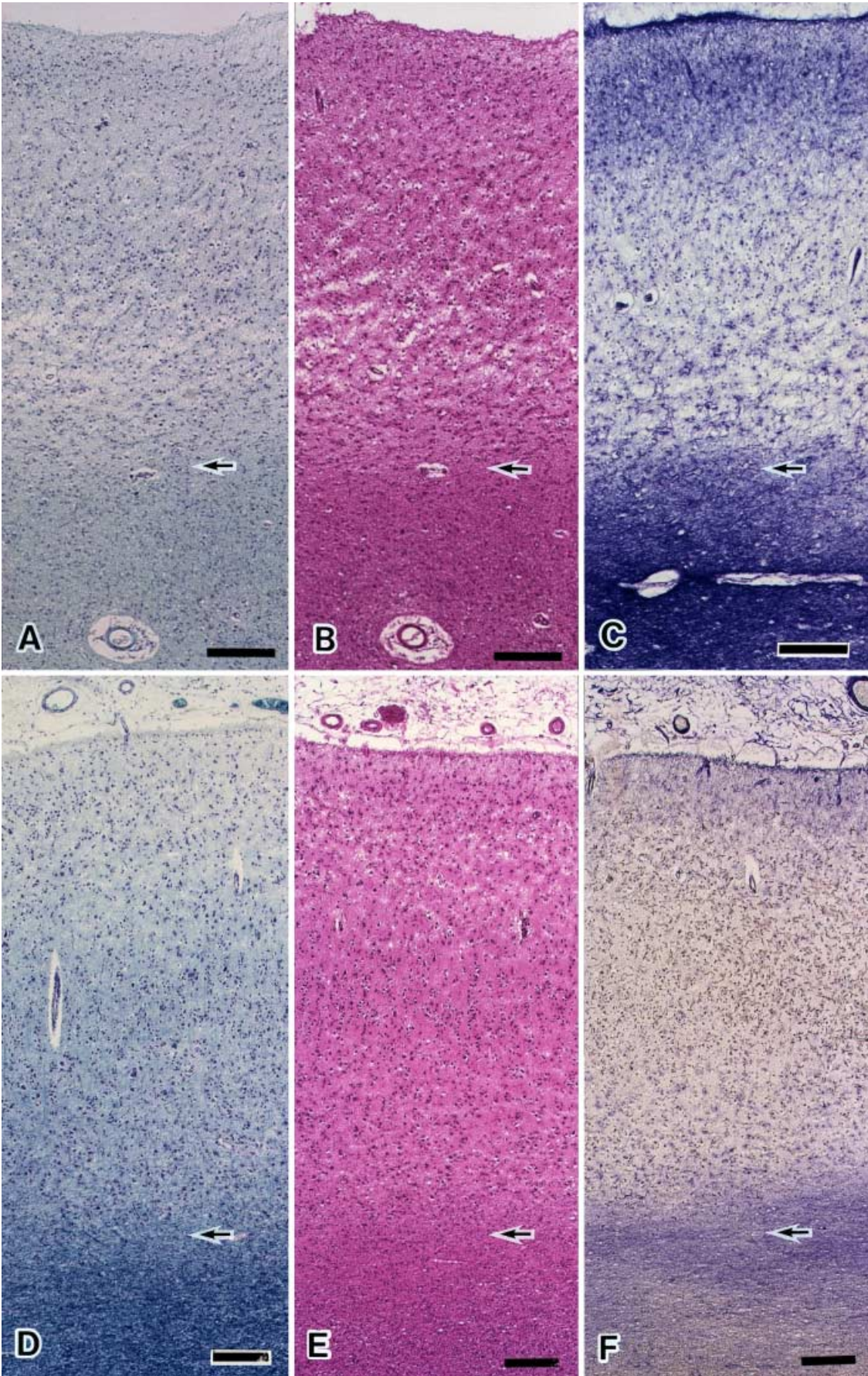
The neuropathological data are summarized in Table 2. Brain weights at autopsy ranged from 950 g to 1,350 g (average 1,105 g). Widespread presence of Pick bodies

and ballooned neurons in the central nervous system were evident in all cases. Amygdala showed severe to moderate neuronal loss, with the striatum having moderate to slight neuronal loss. In all six cases, the pallidum revealed slight neuronal loss. Obvious neuronal loss was seen in the thalamus in all six cases. In the substantia nigra, there was no neuronal loss in any of the six cases.

Distribution of cerebral cortical lesions

The data obtained are schematized in Figs. 9, 10, 11, 12, 13, 14. In case 1, whose initial sign was speech apraxia and who was clinically diagnosed as having primary progressive apraxia, we found severe lesions in the posterior part of the insular gyrus, posterior portion of the inferior frontal gyrus, including the pars opercularis, parahippocampal gyrus, primary motor area, postcentral gyrus, and supramarginal gyrus (Figs. 2, 9c–f). Severe lesions were seen in the medial part of the right superior temporal gyrus, left orbital gyrus, left insular gyrus, left first temporal gyrus, left parahippocampal gyrus, left lateral occipitotemporal gyrus, and left inferior temporal gyrus of case 2,

Fig. 8 Neuronal loss with gliosis in the cerebral cortex (**a–c** from case 3; **d–i** from case 4). **a–c** Severe: pronounced neuronal loss with gliosis of the second to sixth layers with prominent fibrillary gliosis in the subjacent white matter. **d–f** Moderate: obvious neuronal loss with gliosis of the second and third layers accompanied by status spongiosus and relative preservation of the neurons of the fifth and sixth layers. **g–i** Slight: slight neuronal loss and astrocytosis of the superficial layers. The demarcation between the cerebral cortex and cerebral white matter is represented by an arrow. **a, d, g** Klüver-Barrera stain; **b, e, h** H&E stain; **c, f, i** Holzer stain; bars **a–i** 200 μ m



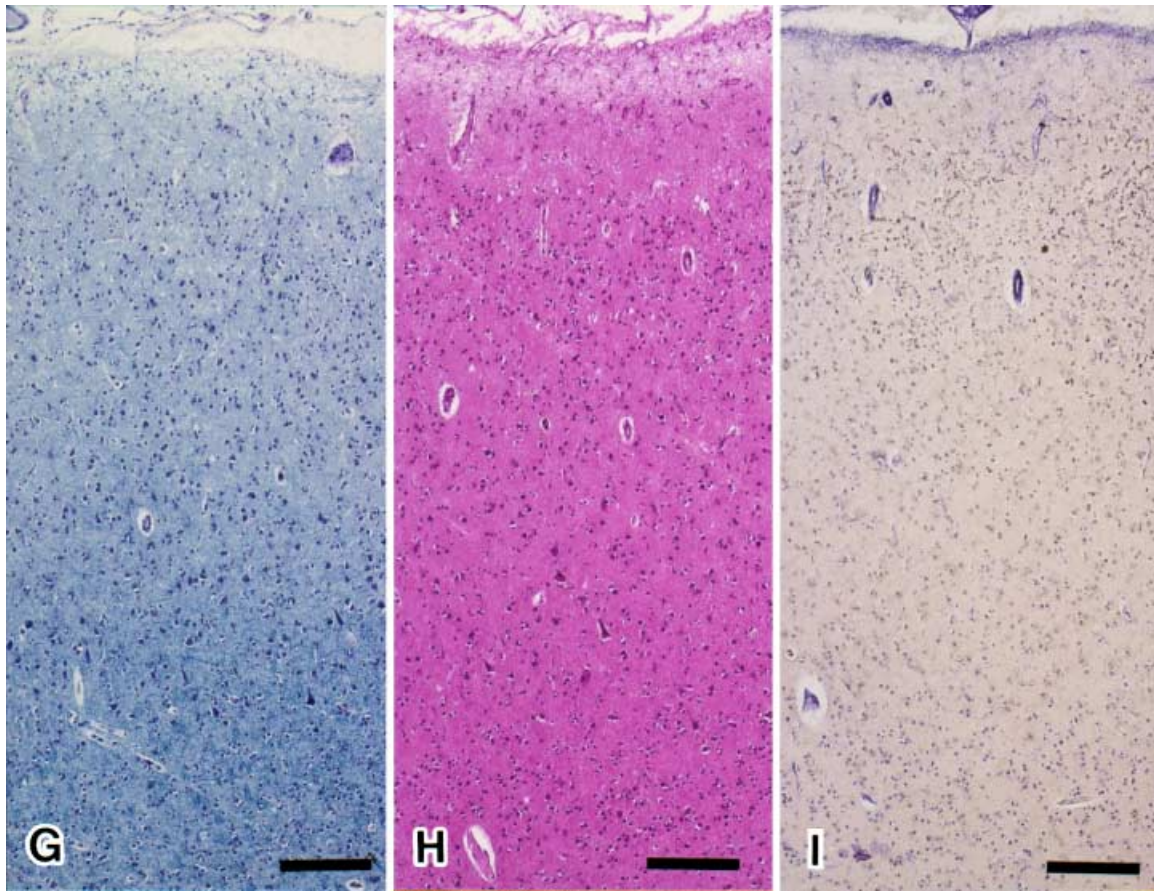


Fig. 8g-i (continued)

who had delusions of persecution as the initial sign and was diagnosed as having presenile dementia with a very long clinical course (Figs. 3, 10b–e). The primary motor area of this patient showed slight lesions (Fig. 10d, e). Case 3, who presented with a depressive state as the initial sign and was clinically diagnosed as having depression, had severe lesions in the left parahippocampal gyrus and anterior portion of the left frontal lobe, prominently in the convexity (Figs. 6, 11a–c). The lesions in the primary motor cortex of this patient were mostly slight (Fig. 11b–e). In case 4, whose initial sign was speech apraxia and whose clinical diagnosis was slowly progressive aphasia, widespread severe lesions were found in the bilateral frontal, temporal, and parietal lobes, including the primary motor area, postcentral gyrus, and supramarginal gyrus (Figs. 4, 12a–e). Severe lesions were found in many portions of the right frontal lobe, right insular gyrus, right parahippocampal gyrus, left first temporal gyrus, left insular gyrus, left second temporal gyrus, and left third temporal gyrus of case 5, who had memory disturbance as the initial sign and was clinically suspected as having Alzheimer's disease (Figs. 7, 13a–e). The lesions in the primary motor cortex of this patient were slight (Fig. 13d–f). Case 6, who had the same initial sign and clinical diagnosis as case 5, had severe lesions in the anterior portion of the right frontal lobe and right parietal lobe, including the

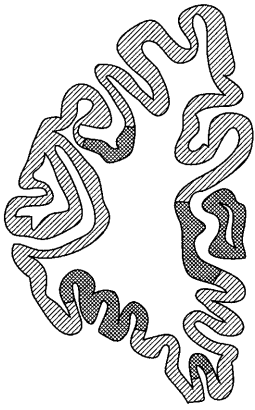
postcentral and supramarginal gyrus (Figs. 5, 14a, c, d). The lesions in the primary motor area of this patient were slight (Fig. 14c).

Discussion

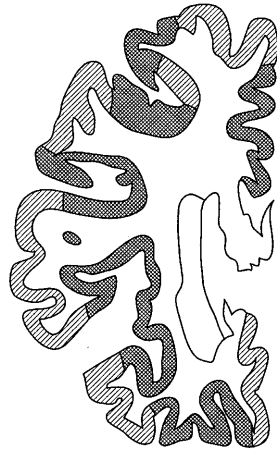
Clinical features

The prominent clinical hallmark in cases 1 and 4 was speech apraxia, also called aphemia and anarthria. Case 1 developed speech apraxia as the initial sign, followed by loss of manual dexterity 2 years later. Buccofacial apraxia, complex limb apraxia, myoclonus, rigidospasticity, and increased deep tendon reflexes in the upper and lower extremities developed about 4 years after the disease onset. Case 4 presented with speech apraxia as the initial sign at age 56, and transcortical motor aphasia with ideomotor apraxia and rigidity in four limbs appeared 4 years later. At this time, dementia was not found. Examination with WAIS (Wechsler adult intelligence scale revised) revealed

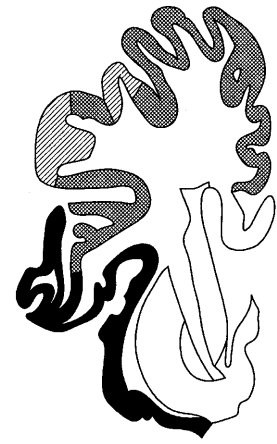
Fig. 9 Distribution of cerebral cortical lesions in case 1. The lesions are classified into three categories: slight (*hatched*), moderate (*cross-hatched*), severe (*black*). The normal cerebral cortex is also depicted (*white*). The primary motor areas are between the *arrows*. The left side of the brain is represented by *L* (left) in the photograph. The right side of the brain is represented by *R* (right) in the photograph



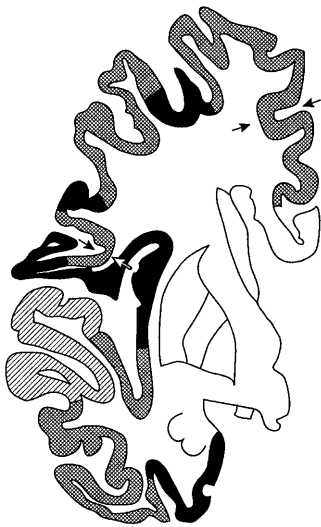
A L



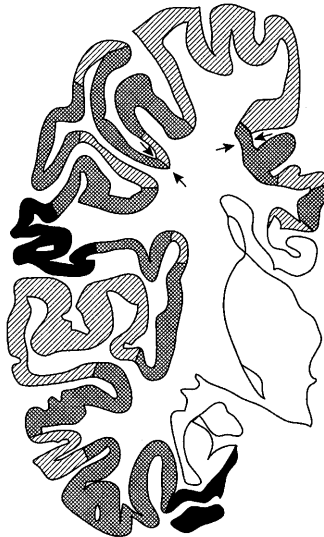
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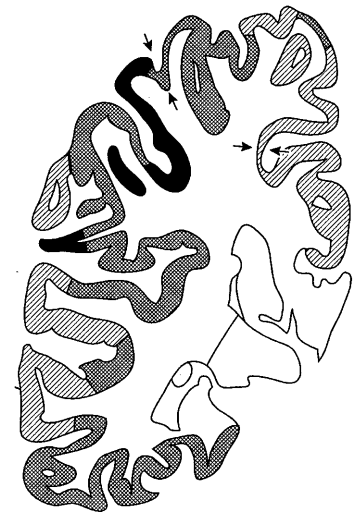
C L



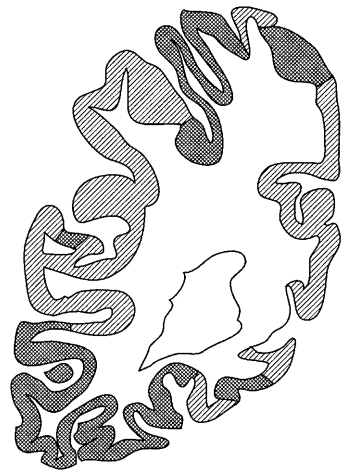
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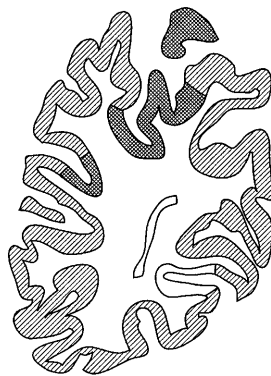
E L



F L



G L



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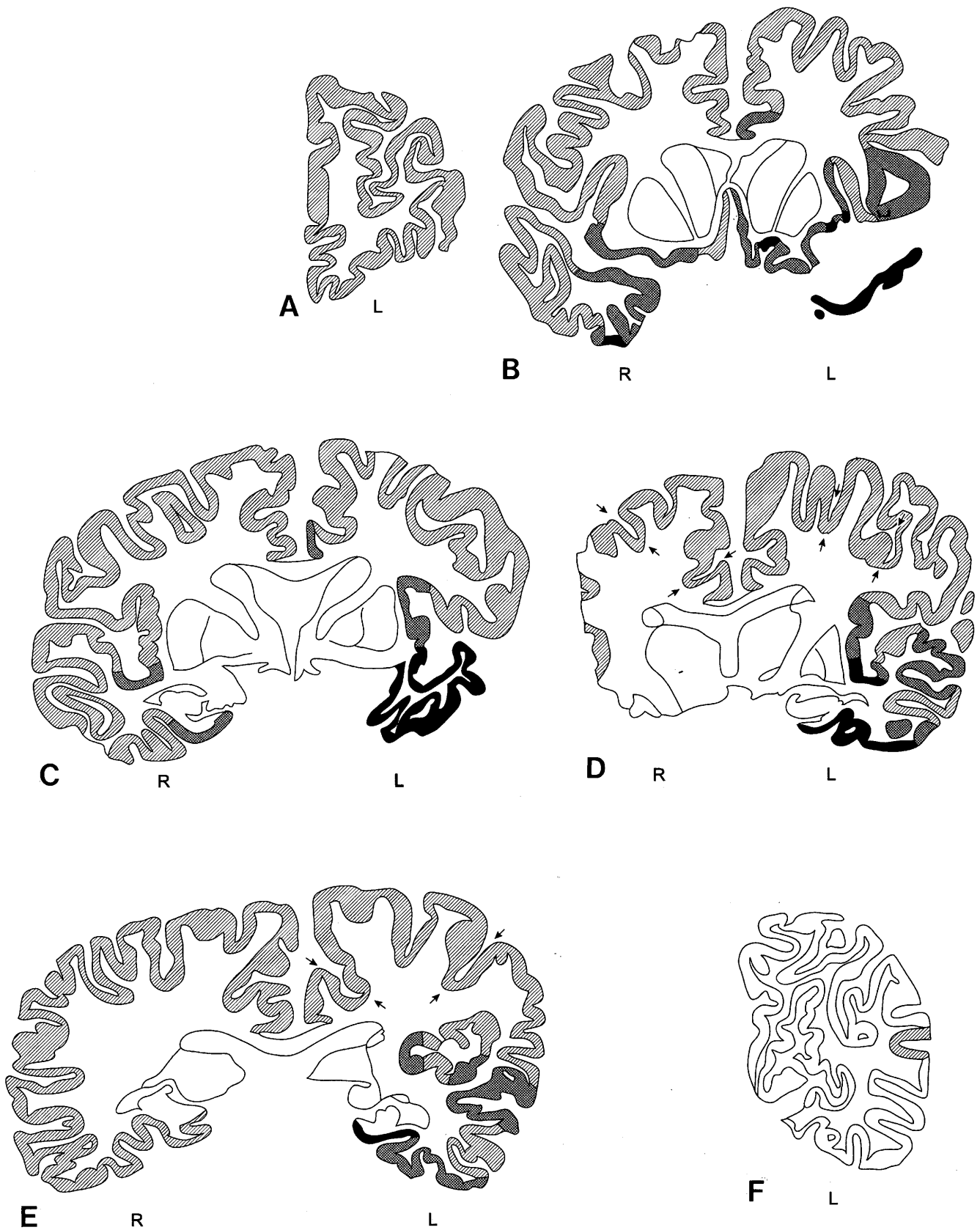
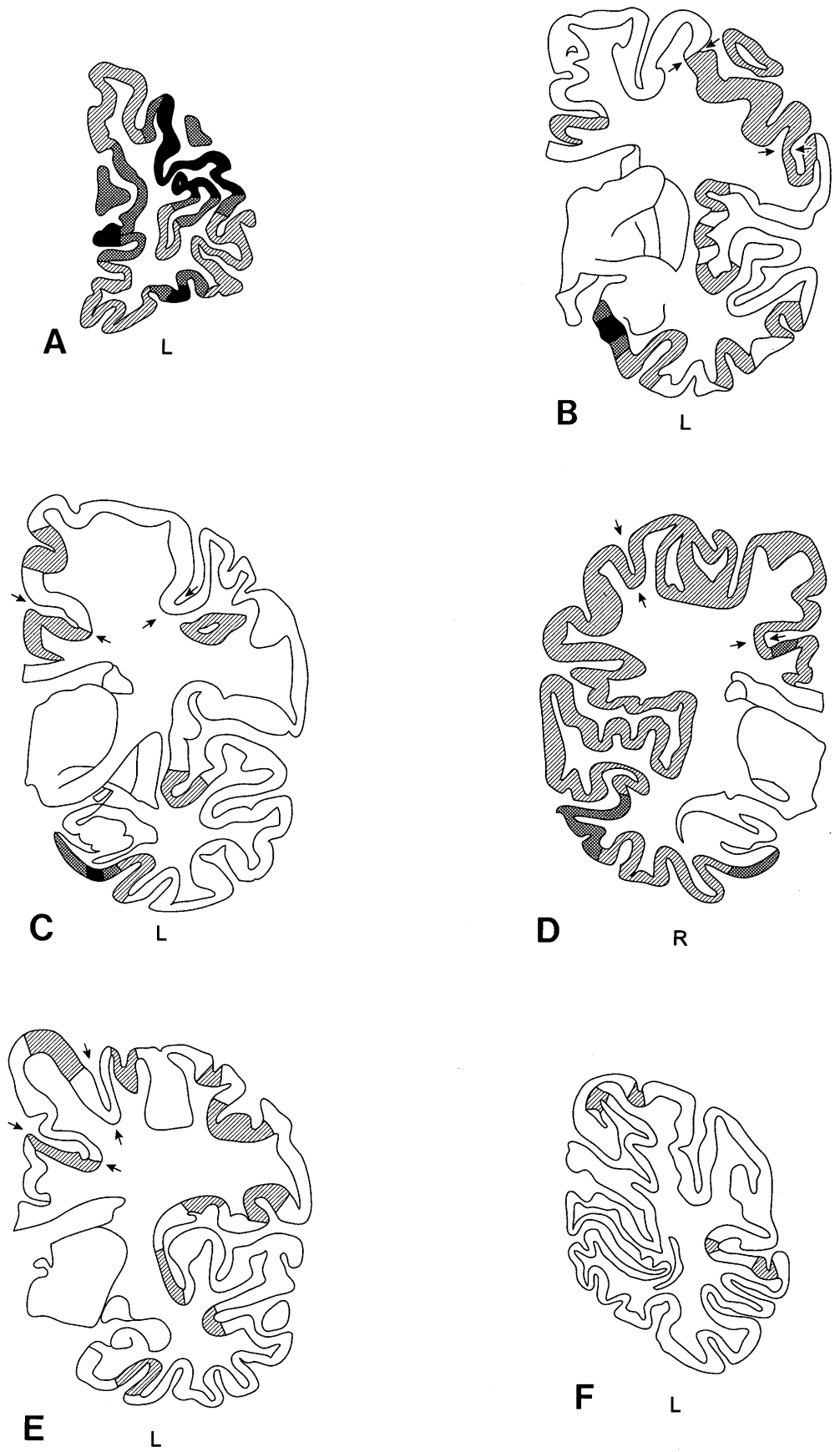


Fig. 10 Distribution of cerebral cortical lesions in case 2. For details see Fig. 9

Fig. 11 Distribution of cerebral cortical lesions in case 3. For details see Fig. 9



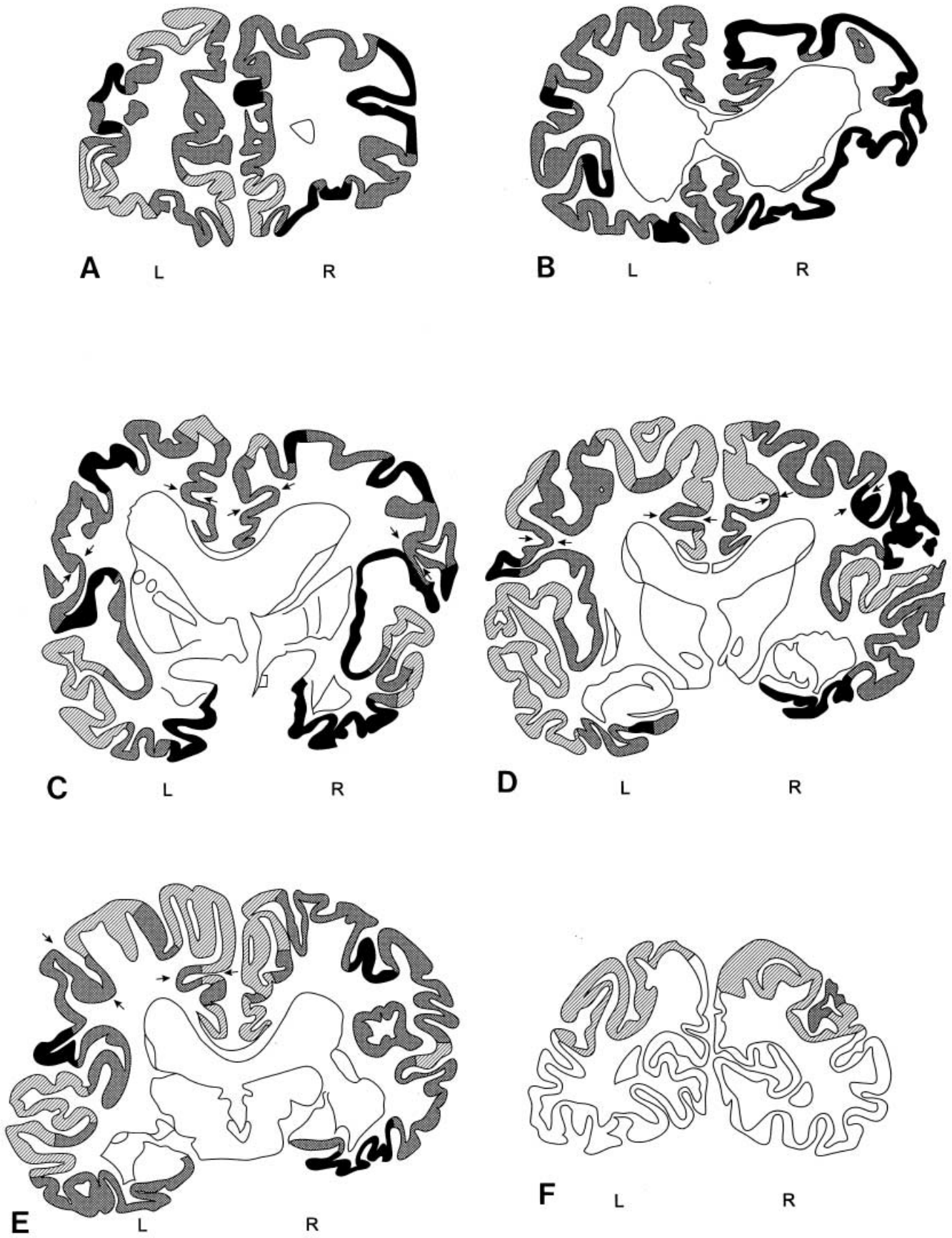


Fig. 12 Distribution of cerebral cortical lesions in case 4. For details see Fig. 9

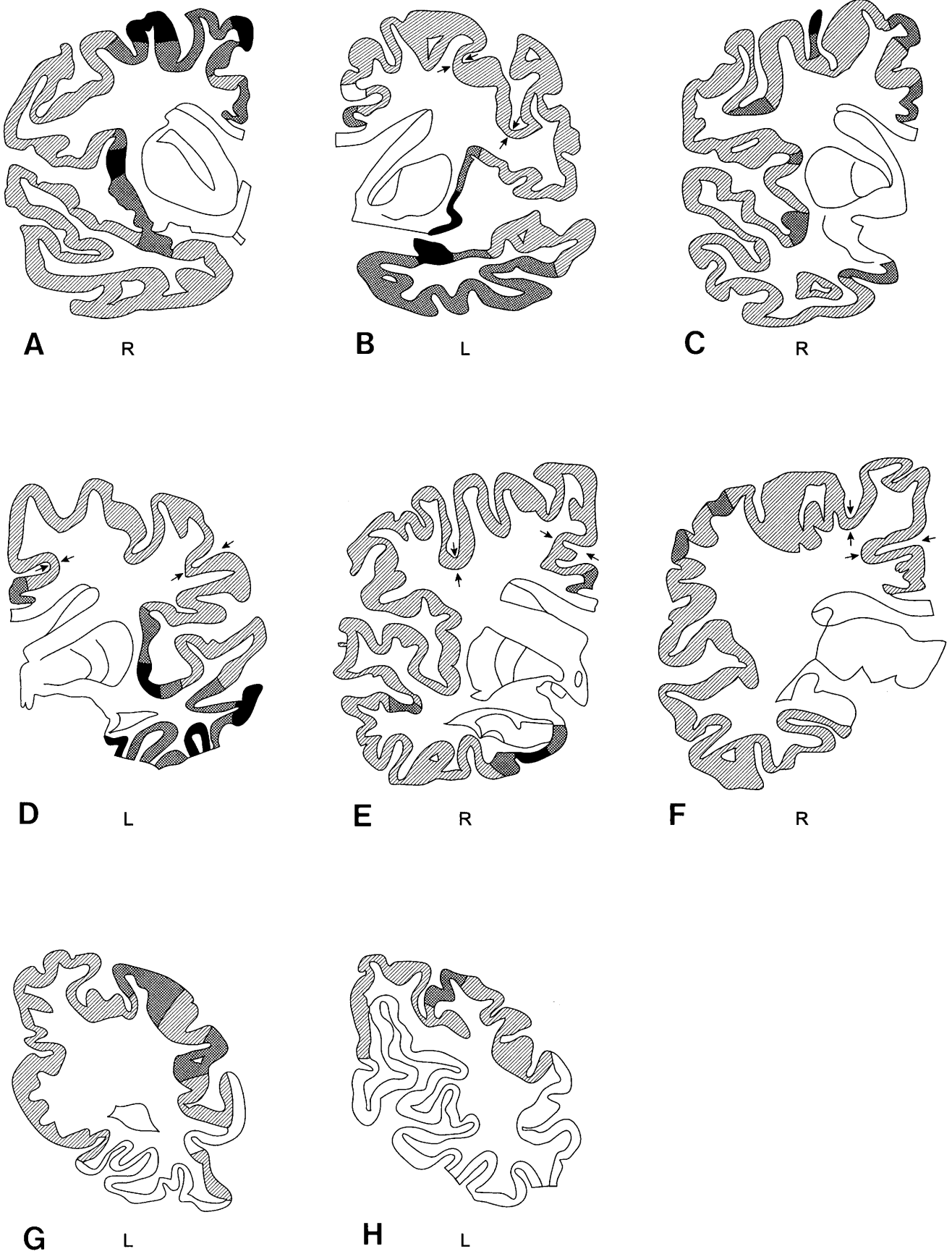


Fig. 13 Distribution of cerebral cortical lesions in case 5. For details see Fig. 9

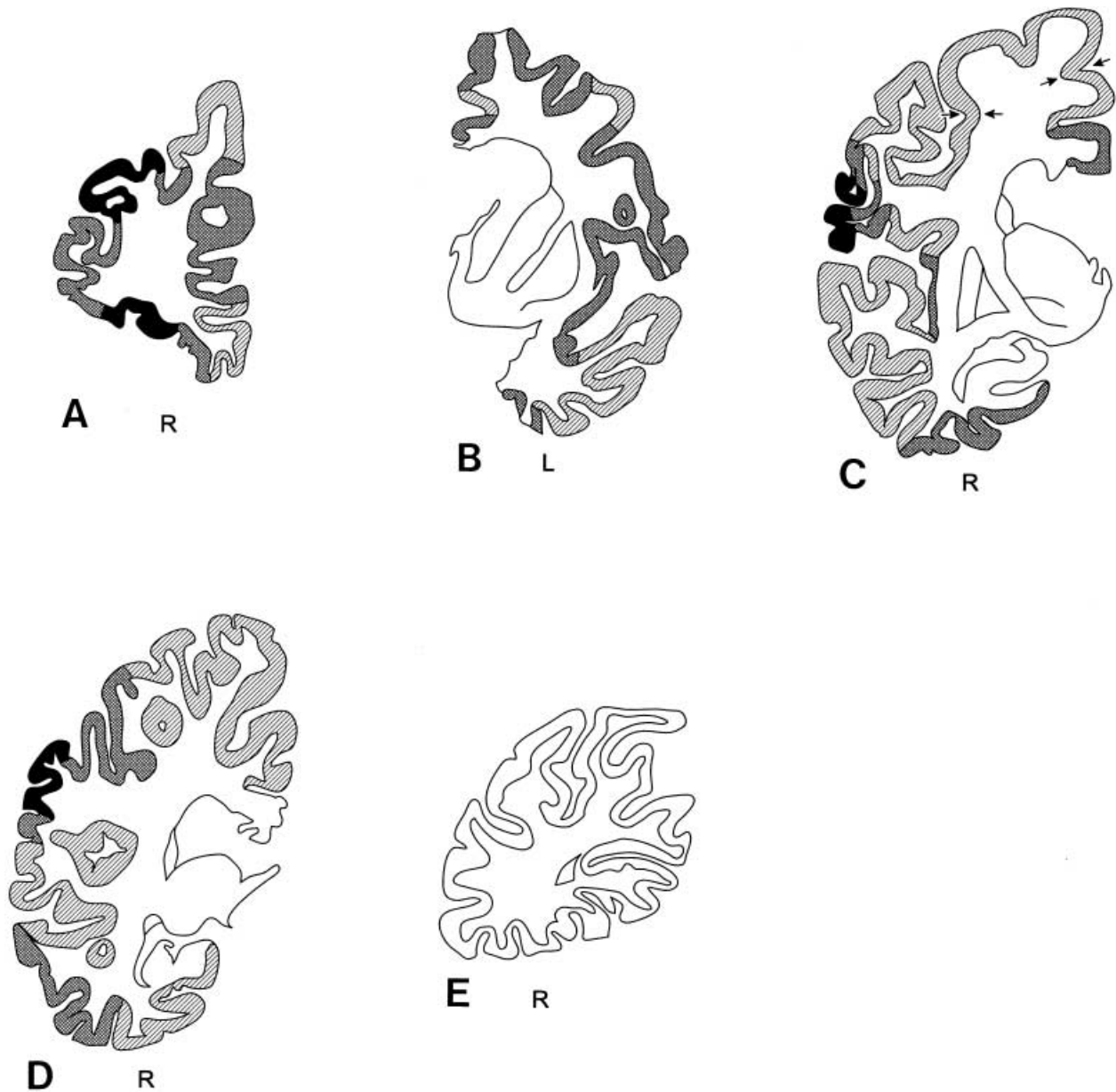


Fig. 14 Distribution of cerebral cortical lesions in case 6. For details see Fig. 9

a total IQ of 81 (Verbal IQ 78, performance IQ 92). At age 63, ideational and limbkinetic apraxia were found. Speech apraxia is a rare disorder of speech production, usually resulting from vascular lesions, affecting the inferior premotor cortex of the left hemisphere. However, it is known that, in a very few cases, progressive speech apraxia without obvious aphasia have occurred in the initial stage of degenerative disorders [5, 9, 60]. Broussolle et al. [5] described eight cases of slowly progressive speech production deficit, initially with no other deficit in other language and non-language neuropsychological domains, in which two cases had autopsy-proven dementia lacking distinctive histology (DLDH) [39]. Broussolle et al. [5] proposed that their eight cases exhibited “slowly progres-

sive anarthria with late anterior opercular syndrome”. In addition, Sakurai et al. [60] described an autopsy case of PDPB developing progressive aphemia as the initial clinical manifestation. As mentioned in the introduction, it has also been reported that in some patients with autopsy-proven PDPB, slowly progressive aphasia is an early, prominent and progressive manifestation. Based on our clinicopathological findings of cases 1 and 4, and on the recently reported atypical cases of PDPB clinically showing slowly progressive aphasia and/or progressive speech apraxia, we postulate that slowly progressive aphasia and/or progressive speech apraxia is one of the clinical manifestations of PDPB.

The noteworthy clinical signs in case 2 were a slowly progressive clinical course with a clinical course of 19 years and absence of “triebhafter Hemmungslosigkeit”, “stehenden Symptome”, “Denkfaulheit”, or semantic dementia, which are the relatively pathognomonic signs of the tem-

Table 1 Summary of clinical features (*M* male, *F* female, *P* present, *NP* not present)

Case	1	2	3	4	5	6
Sex	M	F	M	M	F	F
Hereditiy	NP	NP	NP	NP	NP	NP
Age at onset (years)	62	48	54	56	62	48
Duration of the disease (years)	8	19	1.5	12	5	7
Initial signs	Speech apraxia	Delusion of persecution	Depressive state	Speech apraxia	Memory disturbance	Memory disturbance
Dementia	P	P	NP	P	P	P
Extrapyramidal signs	P	P	NP	P	NP	P
Clinical diagnosis	Primary progressive apraxia	Presenile dementia	Depression	Slowly progressive aphasia	Alzheimer's disease (?)	Alzheimer's disease (?)

Table 2 Summary of neuropathological features (*P* present, + loss of neurons, – absence of neuronal loss)

Case	1	2	3	4	5	6
Brain weight (g)	1,350	1,120	1,090	1,070	1,050	950
Pick bodies	P	P	P	P	P	P
Ballooned neurons	P	P	P	P	P	P
Hippocampus	–	–	–	–	–	–
Amygdala	Severe	Moderate	Moderate	Severe	Severe	Moderate
Striatum (caudate nucleus, putamen)	Moderate	Slight	Slight	Moderate	Moderate	Slight
Pallidum	Slight	Slight	Slight	Slight	Slight	Slight
Thalamus	+	+	+	+	+	+
Substantia nigra	–	–	–	–	–	–

poral dominant type of Pick's disease [4, 58, 62, 64]. The patient developed transient delusions of persecution as the initial sign, followed by personality changes, including euphoria and puerilism. At age 62, she developed aspon-taneity and mild anomia. According to Mansvelt, who re-viewed 171 autopsy cases of Pick's disease reported until 1954, including PDPB and hereditary Pick's disease, the clinical duration of Pick's disease depends on the local-ization of the atrophic type: the majority of patients with predominant frontal atrophy have clinical courses of 3 to 4 years, while the majority of patients with predominant temporal atrophy have clinical course of 7 to 12 years [45]. Only one patient with a clinical course of more than 19 years was reported in the study by Mansvelt, belonging to the pedigree of "Schenk family", which was until re-cently regarded as hereditary Pick's disease and has now been shown to be frontotemporal dementia and parkin-sonism linked to chromosome 17 (FTDP-17) [14, 19, 21, 52, 61]. We speculate that the absence of pathognomonic signs of the temporal dominant type of Pick's disease in case 2 may be due to the benign clinical course, implying very slow destruction of the central nervous system.

The marked clinical features in case 3 were a depres-sive state, including abulia, aspon-taneity, and logopenia, and no dementia at the time of death, probably reflecting the short duration of his clinical course. In 1994, Sparks et al. [65] described an autopsy case of PDPB without overt intellectual decline or depression. They speculated that histological pathology occurred in advance of behavioral

and cognitive disturbances in Pick's disease. Furthermore, it is reported that patients with Pick's disease occasionally exhibit an apathetic, amotivational, and pseudo-depressed state. Therefore, it is speculated that, because of the ab-sence of typical clinical signs compatible with Pick's dis-ease, including "triebhaftige Hemmungslosigkeit", "stehen-den Symptome", and "Denkfaulheit", he was diagnosed as having depression.

The noteworthy clinical hallmarks of cases 1, 2, 4, and 6 were the presence of extrapyramidal signs without obvi-ous neuronal loss in the substantia nigra. It is generally believed that extrapyramidal signs are rare in PDPB. Con-stantinidis et al. [11] and Constantinidis [10] conducted a clinicopathological study on 32 autopsy cases of Pick's disease and divided it into three types: group A (Pick's disease with Pick bodies and ballooned neurons), group B (Pick's disease with ballooned neurons and without Pick bodies), and group C (Pick's disease without Pick bodies or ballooned neurons). Furthermore, they noted that in group A Pick's disease (PDPB) extrapyramidal symptoms were not observed. It has also been reported that very few patients with PDPB developed extrapyramidal signs in the early to late stages of the disease. Lang et al. [42] reported an autopsy case of PDPB having dyspraxia, bradykinesia, and rigidity as the initial clinical signs, in which patho-logical examination disclosed "knife-edge" atrophy of the right precentral gyrus and right parietal lobe, including the postcentral gyrus, with preservation of pigmented neurons in the substantia nigra. According to Sakurai et

al. [60], who described an autopsy case of PDPB with pure aphemia as the initial sign, bradykinesia was obvious in the late stage of the disease. In a study on “slowly progressive anarthria with late anterior opercular syndrome”, Broussolle et al. [5] noted that most patients present with extrapyramidal signs in the middle to late stage of the disease. Our cases 1 and 4, who had speech apraxia as the initial sign, developed rigidity in the middle to late stages of the disease. We speculate that, in patients with PDPB having an “atrophic center” in the precentral gyrus and/or pars opercularis in the left third frontal gyrus, extrapyramidal signs may develop, probably due to widespread involvement of the precentral gyrus, considering the absence of neuronal loss in the substantia nigra. However, the extrapyramidal signs in cases 2 and 6, with neither severe lesions in the precentral gyrus nor neuronal loss in the substantia nigra, remain to be elucidated.

Pathological features

The prominent pathological features in cases 1, 4, and 6 were the presence of severe lesions in the precentral gyrus and parietal lobe, including the postcentral gyrus in cases 1 and 4, and severe lesions in the parietal lobe, including the postcentral gyrus, in case 6. It is thought that the precentral and postcentral gyri are usually preserved in Pick’s disease. According to Mansvelt [45], a macroscopically distinct atrophy of the whole precentral gyrus was found in 10 of 171 autopsy cases he reviewed, in which only 1 case had Pick bodies. Lüers and Spatz [44], who compiled the neuropathology of Pick’s disease with and without Pick bodies, noticed that involvement of the precentral gyrus was relatively rare and that in such circumstances the precentral gyrus was involved via the extension of the lesion in the pars opercularis of the inferior frontal gyrus. According to Seitelberger et al. [63], who investigated neuropathologically 29 autopsy cases of Pick’s disease with and without Pick bodies, the precentral gyrus was affected only slightly. Furthermore, Constantinidis et al. [11] and Constantinidis [10] noted that the precentral gyrus was well preserved in 10 cases of group A Pick’s disease (PDPB). It is thought that in Pick’s disease, involvement of the postcentral gyrus is rarer than that of the precentral gyrus. Mansvelt [45] noted that atrophy of the postcentral gyrus was very rarely reported. In addition, Constantinidis et al. [11] and Constantinidis [10] described that in group A Pick’s disease (PDPB) the parietal cortex finally became atrophic in extremely advanced cases. Recently, it has been elucidated that the distribution of cerebral cortical lesions in PDPB is more widespread than previously assumed. Cambier et al. [8] reported a purely parietal form of PDPB, the clinical picture of which was that of a unilateral, parietal, focal neurological syndrome for many years, finally becoming bilateral. In contrast, Holland et al. [22] reported a patient with autopsy-proven PDPB who presented with slowly progressive aphasia as the initial sign. They noticed that marked atrophy of the bilateral first temporal gyrus, prominently

in the posterior part of the left first temporal gyrus, usually believed to be spared in Pick’s disease, was obvious. Karbe et al. [32] described an autopsy case of PDPB with slowly progressive aphasia as the initial sign, in which focal marked atrophy was found in the left parietal lobe. Based on our pathological findings of cases 1, 4, and 6, and on the atypical autopsy cases of PDPB described previously, pathologically showing marked atrophy of the posterior portion of the first temporal gyrus and parietal atrophy, we conclude that distribution of cerebral cortical lesions in PDPB is more widespread than previously believed.

The prominent pathological hallmark of case 3 was preferential involvement of the convexity of the left frontal lobe. It is well known that in the frontal lobes of Pick’s disease, the orbital portion is more involved than the convexity. According to Spatz [66], who conducted a clinicopathological study on “basal Rinde”, in 11 cases of Pick’s disease the orbital portion of the frontal lobe was more involved than the convexity of the frontal lobe, with a few exceptional cases. Mansvelt noted that predominant atrophy in the orbital portion of the frontal lobe was found in 52 of 171 autopsy cases (30%), with predominant atrophy in the convexity evident in 24 of 171 cases (14%). Furthermore, Lüers and Spatz noted that the frontal convexity type of Pick’s disease was rare. Constantinidis et al. and Constantinidis reported that in group A Pick’s disease (PDPB), the atrophic center was present in hippocampo-limbic structures with temporo-insulo-orbito-frontal diffusion. In addition, they noticed that in group B Pick’s disease with ballooned neurons but without Pick bodies, which is now speculated to be CBD, the atrophic center was found in the frontal convexity [15, 70].

Clinicopathological correlation between unusual clinical presentation and distribution of cerebral cortical lesions

The clinicopathological correlation between speech apraxia followed by various apraxia in the middle stage and topographic distribution of the cerebral cortical lesions in cases 1 and 4 is to some extent unequivocal. In both cases, severe lesions were found in the posterior portion of the left third frontal gyrus, usually believed to be the lesion responsible for motor aphasia. Furthermore, severe lesions were present in the primary motor area and postcentral gyrus, generally believed to be the lesion responsible for limbkinetic apraxia, in both cases.

With regard to the clinicopathological correlation between a depressive state and topographic distribution of the cerebral cortical lesions, our case 3 deserves mentioning. There have been many discussions concerning the clinical features of orbitofrontal lesions and those of frontal convexity lesions. Kleist [36] reported that involvement of the frontal convexity caused “Antriebsmangel”, including spontaneity, abulia, and logopenia, but that involvement of the orbital portion of the frontal lobe gave rise to emotional and character changes, including euphoria, distractibility, and disinhibition. Spatz [66] reported that pa-

tients with Pick's disease with preferential involvement of the orbital portion of the frontal lobe presented with clinical features compatible with the disinhibited type. According to Klages [35], who conducted a psychopathological study on Pick's disease and Alzheimer's disease, patients with Pick's disease showing preferential involvement of the orbital portion of the frontal lobe developed the disinhibited type, but patients with Pick's disease exhibiting preferential involvement of the frontal convexity presented with the apathetic type. In contrast, some researchers insisted that the difference between the apathetic and disinhibited types was not dependent on the localization of the frontal lesion, but rather on the volume of the frontal lesion. Recently, Snowden et al. [64] noted that in patients with the "apathetic type" of frontotemporal dementia there was predominant atrophy of the dorsolateral convexity of the anterior hemispheres. In our case 3, severe lesions were found in the left frontal lobe and left parahippocampal gyrus, prominently in the convexity of the left frontal lobe. The distribution of the cerebral cortical lesions in our case 3, showing severe lesions more widespread in the frontal convexity than in the orbital portion of the frontal lobe, indicates that frontal convexity lesions cause the apathetic type.

The clinicopathological correlation between clinical features mimicking Alzheimer's disease, including memory disturbance, and topographical distribution of the cerebral cortical lesions in cases 5 and 6 is not so clear. Neuropathological examination of cases 5 and 6 showed no neuronal loss in the hippocampus, usually believed to be the lesion responsible for memory impairment. It is also known that the responsible lesion for memory impairment is heterogeneous, composed of the fornix, mammillary body, thalamus, cingulate gyrus, temporal stem, and temporal neocortex, but not the hippocampus. Furthermore, it has been reported that extensive damage to the frontal lobes bilaterally can give rise to not only memory impairment, but also an unusual type of Korsakoff syndrome with confabulation and relative preservation of memory on standard tests [6]. We speculate that the memory impairment in cases 5 and 6 may be due to widespread lesions in the frontal lobe, including the bilateral cingulate gyri, in which widespread moderate lesions were found in both cases.

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