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Marked hypertrophy of the cauda equina in a patient with chronic inflammatory demyelinating polyradiculoneuropathy presenting as lumbar stenosis

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Sirs: Hypertrophy of peripheral nerves and enlargement of nerve roots have been reported in some patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [4]. We report a patient with CIDP who suffered from intermittent claudication as a rare manifestation of enlargement of the cauda equina.

A 63-year-old male was admitted to our hospital in 2001 complaining of difficulty in walking and recurrent pain in the legs. The patient had noticed slight atrophy of the muscles in the left hand in 1980. In 1996, he noticed numbness of both feet. In March 1999, intermittent claudication appeared: he noticed tingling pain in the lower thigh, which worsened after ambulation for several hundred meters and ameliorated after a rest. He was diagnosed as having lumbar stenosis by an orthopedist. However, his condition continued to worsen and he could not walk without assistance after six months.

Physical examinations showed severe wasting of muscles and distal dominant sensory loss. Drop foot was observed. Hypertrophic peripheral nerve trunks were not found. Tendon reflexes were absent without pathological reflexes.

Routine laboratory tests including serum autoantibodies against gangliosides and DNA analysis for P0, connexin 32 and PMP 22 genes were normal. Cerebrospinal fluid (CSF) contained a markedly elevated protein (952 mg/dl). Motor nerve conduction velocity of the right median nerve was extremely slowed (28.6 m/s) with marked dispersion of action potentials. Compound muscle action potentials of both lower extremities and all sensory nerve action potentials were not detectable. Needle electromyography showed typical findings of reinnervation without evidence of ongoing denervation. MRI of the lumbar spine showed marked enlargement of the cauda equina and spinal nerve roots (Fig. A, C). The spinal subdural space was occupied with enlarged cauda equina (Fig. A). Patchy enhancement of these hypertrophic tissues was observed (Fig. B). The biopsy specimen of the right sural nerve showed severe depletion of myelinated fibers with onion-bulb formations (Fig. D). Electron microscopy showed myelinated fibers surrounded by several layers of Schwann cells (Fig E).

The patient was diagnosed as having definite CIDP [7]. Initial treatment with oral prednisolone was ineffective. The patient received three courses of intravenous immunoglobulin therapy (IVIG, 0.5 g/kg), which ameliorated the weakness of the muscles and the intermittent claudication.

A diagnosis as a lumbar stenosis was initially raised when the patient complained of the slowly progressive onset of leg pain and gait disturbance including intermittent claudication. However, absence of tendon jerks and a distal weakness in the upper limbs hinted at a more diffuse neuropathy, and subsequent examinations fulfilled the criteria for the diagnosis of CIDP. Apparent effects of IVIG treatment also supported the diagnosis of CIDP.

Hypertrophy of peripheral nerves and spinal nerve roots is a well-known presentation of CIDP. However, CIDP presenting initially with symptoms of lumbar stenosis is rare; only eight cases have been reported so far [2, 3, 5, 6, 8]. Among these patients, two underwent nerve biopsy and the biopsy specimens showed marked onion-bulb formations [3, 5]. Therefore, the pathomechanism of nerve root hypertrophy may be attributed to repeated segmental demyelination and remyelination along with onion-bulb formations.

Neurogenic intermittent claudication is one of the characteristic symptoms of lumbar stenosis in which hypertrophy of osseous and soft tissue structures surrounding the lumbar canal causes entrapment of the cauda equina nerve roots [1]. As in our patient, the structures around the lumbar canal were intact in contrast to marked hypertrophy of the cauda equina, that is, occupation of lumbar canal by hypertrophic nerve roots caused relative narrowing of lumbar canal, which led to symptoms similar to "true" lumbar stenosis.

In conclusion, this case is of particular interest because it shows that "apparent" lumbar stenosis associated with marked hypertrophy of nerve roots can develop during the course of CIDP.

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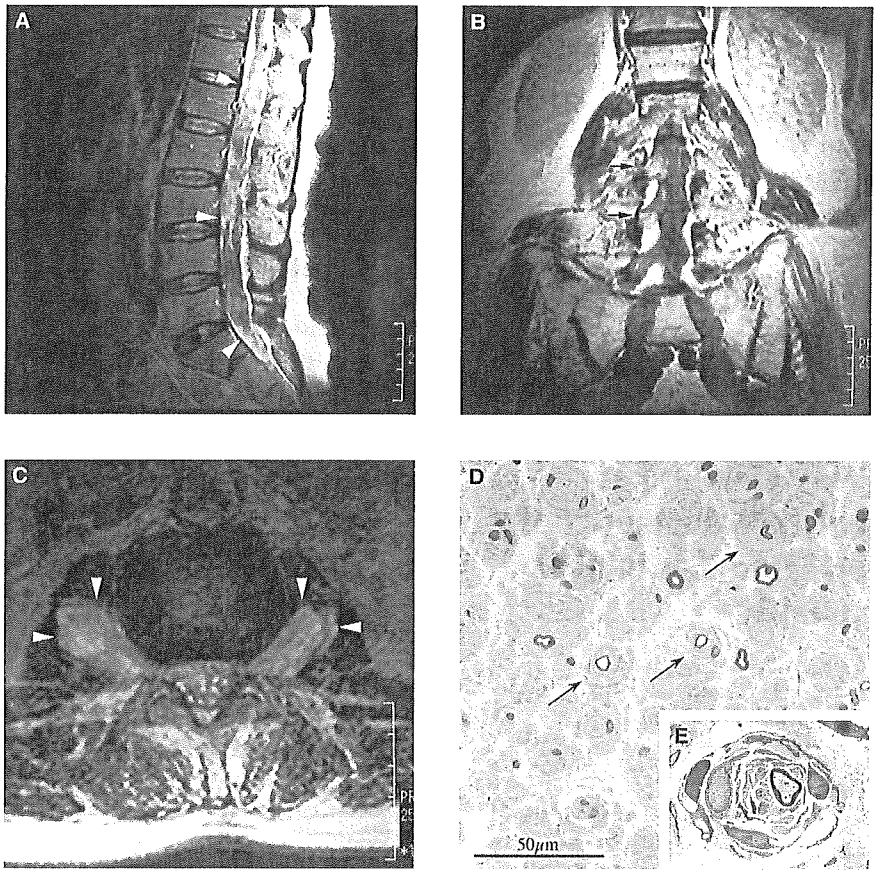

Fig. 1 MRI of the lumbar spine (**Fig. A, B, C**). T2-weighted sagittal image shows that the subdural space from Th12 to sacral canal is occupied with hypertrophic nerve roots and the cauda equina (arrowhead, **A**). Post-contrast T1-weighted coronal image shows patchy enhancement of hypertrophic nerve roots (arrow, **B**). T2-weighted axial image shows marked enlargement of nerves out from the intervertebral foramina (arrowhead, **C**). Sural nerve biopsy-specimen (**Fig. D, E**). Myelinated fibers are severely depleted. Most of remaining myelinated fibers show onion-bulb formations (arrow). Many of the onion-bulb formations are without central myelinated fibers (**D**). Electron microscopy shows layers of Schwann sells surrounding myelinated fibers (**E**)

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SHORT COMMUNICATION

Somatosensory-evoked cortical potential during attacks of paroxysmal dysesthesia in multiple sclerosis

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multiple sclerosis, paroxysmal dysesthesia, somatosensory-evoked potential

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Paroxysmal dysesthesia is considered to be one of the characteristic symptom of multiple sclerosis (MS), but the lesion responsible and the pathophysiology of this dysesthesia are not known. We report the interesting finding of somatosensory-evoked potentials (SEPs) in a patient with MS during a paroxysmal dysesthesia attack.

Case report

A 43-year-old woman developed paroxysmal dysesthesia of the left arm and leg. Four months before she experienced bilateral optic neuropathy, symptoms of transverse myelopathy at the Th5 segment, and dysesthesia in the C5 to C8 area in the left arm. She was diagnosed as MS by her recurrence and remission of the symptoms. During the recovery stage, attacks of paroxysmal dysesthesia occurred more than 20 times a day. These were induced by voluntary or passive, quick anteroflexion of the neck and lasted for 60–90 s. The attacks started in the left hand with an unpleasant tickling or electrical sensation that radiated to the left upper extremity immediately and to the left lower extremity approximately half a minute later. Most attacks were accompanied by tonic spasm in the muscles of the left extremities.

T2-weighted magnetic resonance imaging showed three small irregular areas of high signal intensity; in the base of the right pons, dorsal part of cervical spinal cord from C5 to C7, and center of the thoracic spinal cord from Th5 to Th7.

Somatosensory-evoked potentials elicited on left and right median nerve stimulation showed no abnormality when there was no attack. SEPs were recorded before and after the attacks, whilst the patient mimicked the dystonic posture and muscle contraction of a tonic spasm to exclude the effect of proprioceptive impulses from the activated muscles. The median nerve was stimulated at the wrist, and the intensity adjusted to the level that evoked a 2 mV compound muscle action potential (CMAP) from the abductor pollicis brevis muscle. CMAP size was monitored to maintain constant stimulation. The SEP data was recorded on digital audiotape before the attack induced by neck flexion until the end of the attack. More than 100 responses during attack were averaged for one test. The average N20 amplitude from the baseline during the attack was smaller (1.1 μV) than before (1.9 μV) and after (1.7 μV) the attack (Fig. 1). The reduction of N20 amplitude was statistically significant in four independent examinations ($P < 0.05$, Mann–Whitney U-test). There was no discernible difference in the N20 latencies. N13 could not be evaluated due to artifacts produced by muscle contraction.

Discussion

The pathophysiology of paroxysmal dysesthesia is proposed to be the generation of ectopic impulses and ephaptic transmission in a focal demyelinated lesion in a tract of the central nervous system (Osterman and Westerberg, 1975; Rasminski, 1981). Ectopic impulses were shown to proceed from a lesion both rostrally and caudally in an experimental animal model (Smith and McDonald, 1982). We think this impulse is generated at axons of the posterior column of the cervical cord because (i) there is a lesion in the posterior part of the cervical cord on MRI; (ii) the attack was induced by neck flexion; and (iii) dysesthesia begins in the hand and does not involve the area innervated by cranial nerves. We speculate that three mechanisms are responsible for the attenuation of N20 size during an attack. First,

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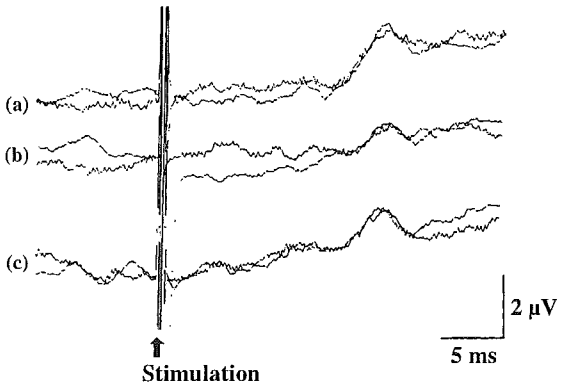

Figure 1 Somatosensory-evoked cortical potentials by left median nerve stimulation before (a), during (b) and after (c) a dysesthesia attack. Recording site: 2 cm posterior to C4. Reference site: Fz (International 10–20 system).

descending impulses are generated abnormally in dorsal column axons of a cervical lesion and collide with afferent impulses evoked by stimulation of the nerve. Secondly, ectopic impulses produce presynaptic modification on synaptic transmission of posterior column cells or thalamic neurons, which is similar to the gating mechanism seen in the spinal cord. Thirdly, the ectopic impulses have a direct or indirect inhibition of N20 generation (Abbruzzese *et al.*, 1980).

We consider that the attenuation of N20 on SEPs during a dysesthesia attack supports the hypothesis that the ectopic impulse generated in the posterior column causes paroxysmal dysesthesia in MS.

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REGULAR PAPER

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Constant and severe involvement of Betz cells in corticobasal degeneration is not consistent with pyramidal signs: a clinicopathological study of ten autopsy cases

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Abstract This report concerns a clinicopathological study of three additional patients with corticobasal degeneration (CBD), described here for the first time, and a clinicopathological correlation between pyramidal signs and upper motor neuron involvement, in ten autopsy cases of CBD, including seven cases reported by us previously. We investigated pyramidal signs, including hyperreflexia, Babinski sign, and spasticity, and involvement of the primary motor cortex and pyramidal tract, focusing on the astrocytosis of the fifth layer of the primary motor cortex. Pyramidal signs were observed in six (60%) of the ten cases. Hyperreflexia was evident in six patients (60%), with spasticity being observed in three patients (30%). Loss of Betz cells associated with prominent astrocytosis and presence of ballooned neurons in the fifth layer of the primary motor cortex was observed in all ten cases. In all cases, involvement of the pyramidal tract was obvious in the medulla oblongata, without involvement of the pyramidal tract in the midbrain. Constant and severe involvement of the fifth layer of the primary motor cortex, including the Betz cells, has not previously been reported in CBD. We suggest that the pyramidal signs in CBD have been disregarded.

Keywords Betz cells · Charcot-Rebeiz disease · Corticobasal degeneration · Pyramidal signs · Pyramidal tract degeneration

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Introduction

Corticobasal degeneration (CBD) [3, 9, 10, 11, 16, 17, 20, 21, 28, 29, 31, 38, 42, 43, 51, 56, 58, 59, 72, 73, 74] or cortical-basal ganglionic degeneration [4, 5, 37] was first described by Rebeiz et al. in 1967 and 1968 [52, 53] as corticodentatonigral degeneration with neuronal achromasia. It is a rare neurodegenerative disorder and can be classified as "Parkinson plus" together with multiple system atrophy and progressive supranuclear palsy [22, 23, 24, 25, 30]. CBD may occur more frequently as initially thought, as indicated by the growing number of reported cases since the report of three autopsy cases of CBD by Gibb et al. [18] in 1989. With

more autopsy cases and clinicopathological studies of CBD, Goetz [19] in 2000 noticed that the CBD prototype may be the "atypical Parkinson's disease" described by Jean-Martin Charcot. In 2000, Agid [1] proposed that the clinical diagnosis of CBD was evident when the following features were observed in a given patient: an akineto-rigid syndrome unresponsive to L-DOPA associated with dystonic postures, apraxia, and a marked asymmetry of symptoms. Furthermore, Agid noted that if Jean-Martin Charcot was really the first to point out this form of parkinsonism (atypical Parkinson's disease) at the end of the last century, that is, 75 years before Rebeiz et al. described the three cases that became the archetype of the syndrome, it might perhaps be more reasonable to name this affliction Charcot-Rebeiz disease, at least until its mechanism and causes are discovered. In 1999, Tsuchiya et al. [65] found that basal ganglia lesions of Group B Pick's disease, which have prominent degeneration of the pallidum and substantia nigra, and those classified by Constantinidis et al. [8] in 1974 and Constantinidis [7] in 1985, which macroscopically show frontal atrophy and histologically cortical degeneration characterized by ballooned neurons without Pick bodies, are fundamentally consistent with the basal ganglia lesions of CBD elucidated by Tsuchiya et al. in 1997 [63]. Recently, CBD has been regarded a member of the "Pick complex" [13, 60], a "unifying concept of overlapping clinical syndromes and neuropathological findings of neurodegenerative diseases causing focal cortical atrophy", as proposed by Kertesz and Munoz, emphasizing the similarities, rather than the differences, between them [32, 33, 44].

It is generally believed that pyramidal signs, including hyperreflexia, Babinski sign, and spasticity, are usually observed in cases of CBD [6, 36, 54, 55, 76]. Furthermore, it has been reported that the frequency of pyramidal signs in cases of CBD, ranged from extremely common [37] to about 27% [57]. In contrast, clinicopathological correlation studies of pyramidal signs with the lesions of the primary motor cortex and pyramidal tract in CBD have been rare [27, 53].

The purpose of this report is to describe the clinicopathological features of CBD in ten Japanese autopsy cases, including pyramidal signs and involvement of the primary motor cortex and pyramidal tract, focusing on the presence or absence of astrocytosis in the fifth layer of the primary motor cortex associated with presence of ballooned neurons and loss of Betz cells; i.e., small groupings of fat granule cells in the spaces in which Betz cells were present [66, 70]. We investigated the clinicopathological correlation between pyramidal signs and involvement of the pyramidal tract in ten autopsy cases. In addition, we address in the discussion the pathological heterogeneity in the primary motor cortex among multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS) with dementia, and CBD, paying attention to the clinicopathological dissociation of the pyramidal signs and lesions of the Betz cells and pyramidal tract in CBD, compared with those of MSA and ALS with dementia.

Materials and methods

The present investigation was carried out on ten autopsy cases from three Japanese institutions. The clinical records and tissue specimens in cases 1, 3, 6, 7, 8, and 9 were from the Department of Neuropathology, Tokyo Institute of Psychiatry. Those in cases 2, 5, and 10 were from the Department of Neuropathology, Tokyo Metropolitan Gerontology, and those in case 4 were from the Department of Laboratory Medicine, National Center Hospital for Mental, Nervous, and Muscular Disorders.

After fixation in formalin, the brains of the ten cases were sectioned in the coronal plane. The cerebral hemisphere and/or small blocks, including the frontal, temporal, parietal, and occipital lobes, and the striatum, pallidum, subthalamic nucleus, thalamus, amygdala, and hippocampus, were taken. Additional tissue blocks were taken from the midbrain, including the substantia nigra, brain stem, and cerebellum. The brains were embedded in paraffin and cut at a thickness of about 10 μm. The sections were stained with hematoxylin-eosin (HE), 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), polyclonal neurofilament (200 kDa), and glial fibrillary acidic protein (GFAP).

The neuropathological diagnosis in the ten cases was made on the basis of the findings described below, which included many astrocytic plaques and ballooned neurons [14, 15, 34, 35] in the cerebral cortex and the widespread presence of argyrophilic threads in the central nervous system (Figs. 1, 2, 3). The neuropathological features of all ten cases were fundamentally consistent with the recently proposed neuropathological criteria for CBD by Dickson et al. [12].

The clinicopathological findings in cases 1, 3, 4, 6, 7, 8, and 9 have been reported previously by Tsuchiya et al. [61], Mimura et al. [39], Arima et al. [2], Oda et al. [49], Mitani et al. [40], Miyazaki et al. [41], and Oda et al. [50], respectively. The neuropathological hallmarks of case 7, including the abnormal cytoskeletal pathology peculiar to CBD, have been described by Uchihara et al. [71]. The distribution of cerebral cortical lesions identified by light microscopy, classified into three categories in cases 1, 6, 7, 8, and 9, has been reported by Tsuchiya et al. [62]. The distribution of basal ganglia lesions, classified into three categories in cases 1, 4, 6, 7, 8, and 9, has been investigated by Tsuchiya et al. [63]. Serial brain CT of cases 1 and 8 have also been described by Tsuchiya et al. [64].

Basal ganglia lesions, including the pallidum, caudate nucleus, putamen, and subthalamic nucleus, was

Table 1 Summary of clinical and pathological features (*M* male, *F* female, + presence, − absence,*severe* severe neuronal loss, *moderate*moderate neuronal loss, *slight* slight neuronal loss,*PD* Pick's disease, *CBD* corticobasal degeneration, *PSP* progressive supranuclear palsy)

Case	1	2	3	4	5	6	7	8	9	10
Clinical diagnosis	CBD	CBD	PD or frontal lobe dementia	PD	CBD	PSP	CBD	PD	PD	Atypical PSP
Heredity	−	−	−	−	−	−	−	−	−	−
Sex	M	M	F	M	M	F	M	F	F	F
Age at onset (years)	65	71	62	64	64	45	63	58	62	67
Duration ofthe disease	2 years 1 month	4 years 8 months	2 years 9 months	9 years 2 months	5 years 8 months	8 years	3 years 10 months	3 years 7 months	7 years	11 years
Initial sign	Limbkinetic apraxia	Limbkinetic apraxia	Motor aphasia	Aphasia	Memory disturbance	Delusion of persecution	Limbkinetic apraxia	Abnormal behavior	Abnormal behavior	Memory disturbance
Muscular rigidity	+	+	−	+	+	+	+	−	+	+
Dementia	+	+	+	+	+	+	+	+	+	+
Brain weight (g)	1,370	1,345	1,200	1,120	1,100	1,050	1,040	987	940	810
Cerebral cortex										
Neuronal loss	+	+	+	+	+	+	+	+	+	+
Ballooned neurons	+	+	+	+	+	+	+	+	+	+
Astrocytic plaques	+	+	+	+	+	+	+	+	+	+
Pallidum	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Striatum (caudate nucleus and putamen)	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Subthalamic nucleus	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight	Slight
Neuronal loss in the Substantia nigra	+	+	+	+	+	+	+	+	+	+
References	[61, 62, 63, 64]		[39]	[2, 63]		[49, 62, 63]	[40, 62, 63, 71]	[41, 62, 63, 64]	[50, 62, 63]	

Table 2 Clinicopathological correlation between pyramidal signs and involvement of the primary motor cortex and pyramidal tract (+ present, – absent, *N.R.* not recorded)

Case	1	2	3	4	5	6	7	8	9	10
Pyramidal sign	+	+	N.R.	–	–	+	+	–	+	+
Hyperreflexia	+	+	N.R.	–	–	+	+	–	+	+
Babinski sign	+	–	N.R.	–	–	–	–	–	N.R.	–
Spasticity	+	+	N.R.	N.R.	–	N.R.	+	–	N.R.	N.R.
Loss of Betz cells	+	+	+	+	+	+	+	+	+	+
Astrocytosis of the primary motor cortex layer V	+	+	+	+	+	+	+	+	+	+
Degeneration of the pyramidal tract										
Midbrain	–	–	–	–	–	–	–	–	–	–
Medulla oblongata	+	+	+	+	+	+	+	+	+	+

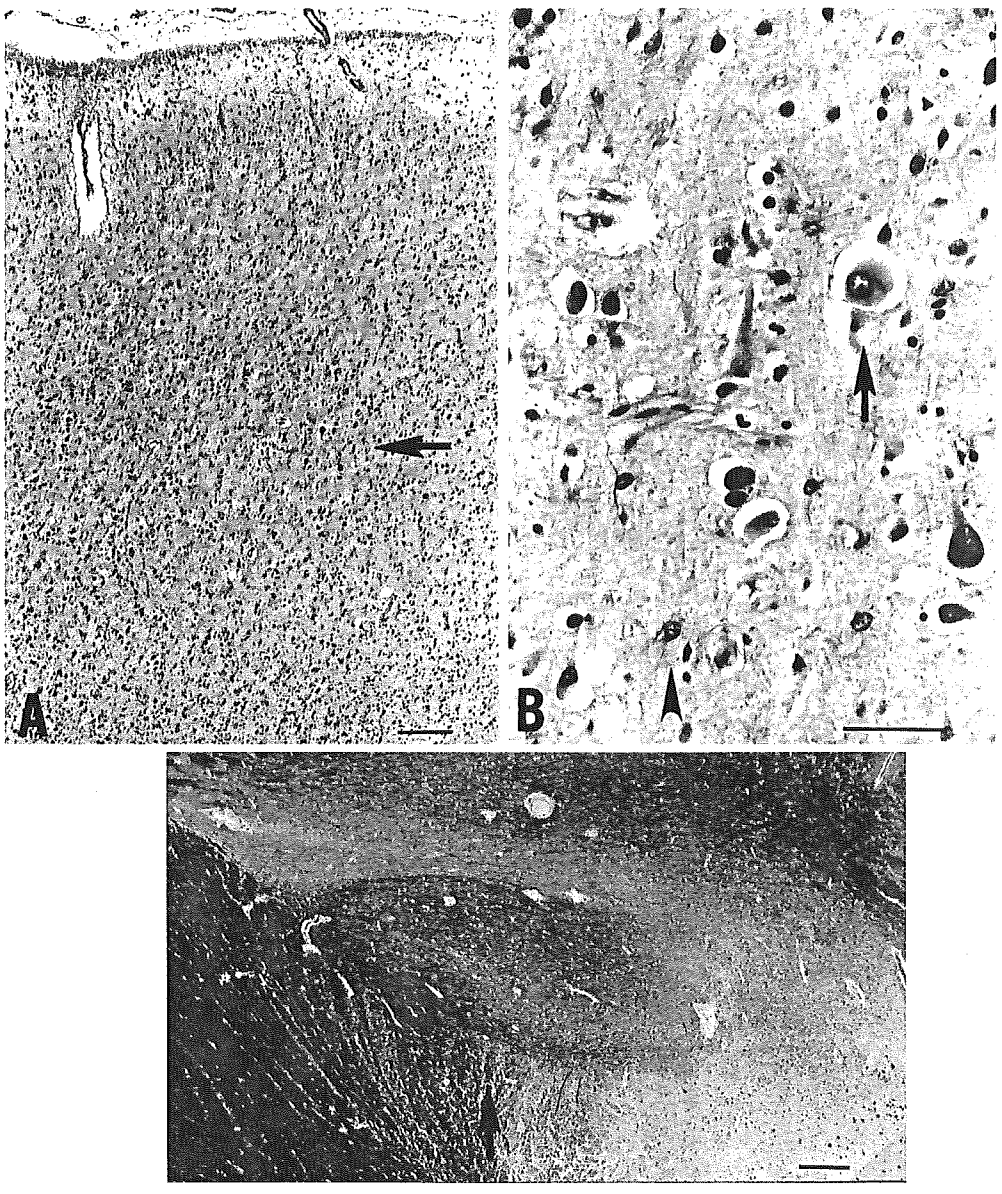


Fig. 1 **A–C** Case 2. **A** Superior frontal gyrus showing obvious neuronal loss. **B**. Enlargement of area indicated by *arrow* in **A** showing a ballooned neuron (*arrow*) and fibrillary glia (*arrowhead*). **C** Relative preservation of the subthalamic nucleus (*arrow*). **A**, **B** HE stain; **C** Klüver-Barrera stain; *bars* **A** 0.2 mm, **B** 0.05 mm, **C** 0.5 mm

classified as follows. Lesions identified by light microscopy were assigned to one of three categories: slight, showing relative preservation of the neurons with slight proliferation of the glia; moderate, showing obvious neuronal loss with evident astrocytosis and slight fibrillary gliosis; or severe, showing pronounced neuronal loss with neuropil rarefaction 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,

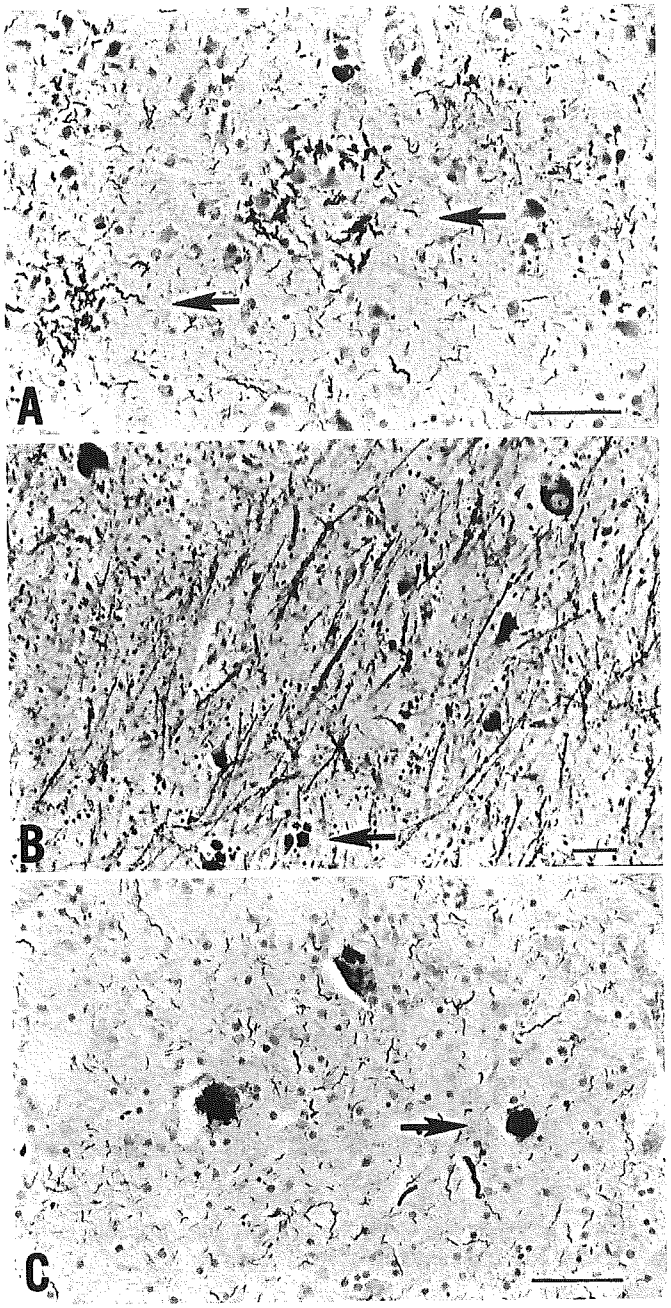


Fig. 2 A–C Case 5. **A** Astrocytic plaque (*arrow*) in the cerebral cortex. **B** Substantia nigra showing prominent neuronal loss with free melanin (*arrow*). **C** Substantia nigra showing neurofibrillary tangles (*arrow*). **A** modified Gallyas-Braak stain, **B** Klüver-Barrera stain, **C** modified Gallyas-Braak stain; *bars* **A–C** 0.05 mm

Pick's disease with Pick bodies (PDPB) [65], a generalized variant of Pick's disease (gvPD) [67], diffuse neurofibrillary tangles (NFT) with calcification, reported by Tsuchiya et al. [63, 65, 67, 69], respectively. The clinical and pathological features of all cases are summarized in Table 1.

Pyramidal signs were judged to be present in patients who showed one or more signs of hyperreflexia in the extremities, Babinski sign, and spasticity in the extremities. Loss of Betz cells was judged to be present in cases that showed small groupings of lipofuscin-laden macrophages in the holes, from which Betz cells had presumably disappeared, in the primary motor cortex with the presence of normal and degenerated Betz cells in the absence of an internal granular layer [26, 45, 46, 47, 48, 75] (Fig. 4). Astrocytosis of primary motor cortex layer V was considered present in cases showing definite astrocytosis determined using HE and Holzer staining or immunohistochemistry using an antibody against GFAP (Fig. 4). Pyramidal tract degeneration was also judged as present in cases showing definite loss of myelinated fibers shown by Klüver-Barrera stain, accompanied by gliosis revealed using Holzer stain and immunohistochemistry using an antibody against GFAP (Fig. 5). The determination of loss of Betz cells, astrocytosis of primary motor cortex layer V, and the pyramidal tract degeneration described above was fundamentally consistent with that in MSA and ALS with dementia, as described by Tsuchiya et al. [66, 70]. The pertinent data are summarized in Table 2.

Case reports

Clinical course and neuropathological findings in case 2

The patient was a Japanese man aged 76 years at the time of death. He was in good health until the age of 71, when he became aware of clumsiness of the right hand and action tremor of the right upper extremity, followed by bradykinesia 3 months later and action tremor of the left upper extremity 7 months after the onset of the disease. A neurological examination at the age of 72 years (8 months after the disease onset), revealed right limbkinetic apraxia, mild agraphia, bilateral action myoclonus on the upper extremities, prominent on the right, muscular rigidity, bradykinesia, and hyperreflexia in the upper and lower extremities without Babinski sign. At this stage, obvious dementia was not observed. Neurological examination 1 year after disease onset disclosed evident dementia. At 2 years after the disease onset, he could no longer walk without assistance. Vertical ocular movement involvement and dysphagia were noticed 3 years after disease onset. During this period, he was bed-ridden. At 3 years 10 months after disease onset, severe dementia and spasticity were obvious. He died of pneumonia at age 76, 4 years 8 months after the onset of the disease. He was clinically diagnosed as having CBD.

The brain weighed 1,345 g. Macroscopic examination revealed atrophy of the posterior portion in the superior frontal gyrus abutting the precentral gyrus, atrophy of the pallidum, and depigmentation of the substantia nigra. A histological examination showed neuronal loss with astrocytosis, status spongiosus, many ballooned neurons, and astrocytic plaques in the cerebral cortex of the frontal and parietal lobes (Fig. 1A, B). In the primary mortor cortex layer V, there was loss of Betz cells associated with prominent astrocytosis and ballooned

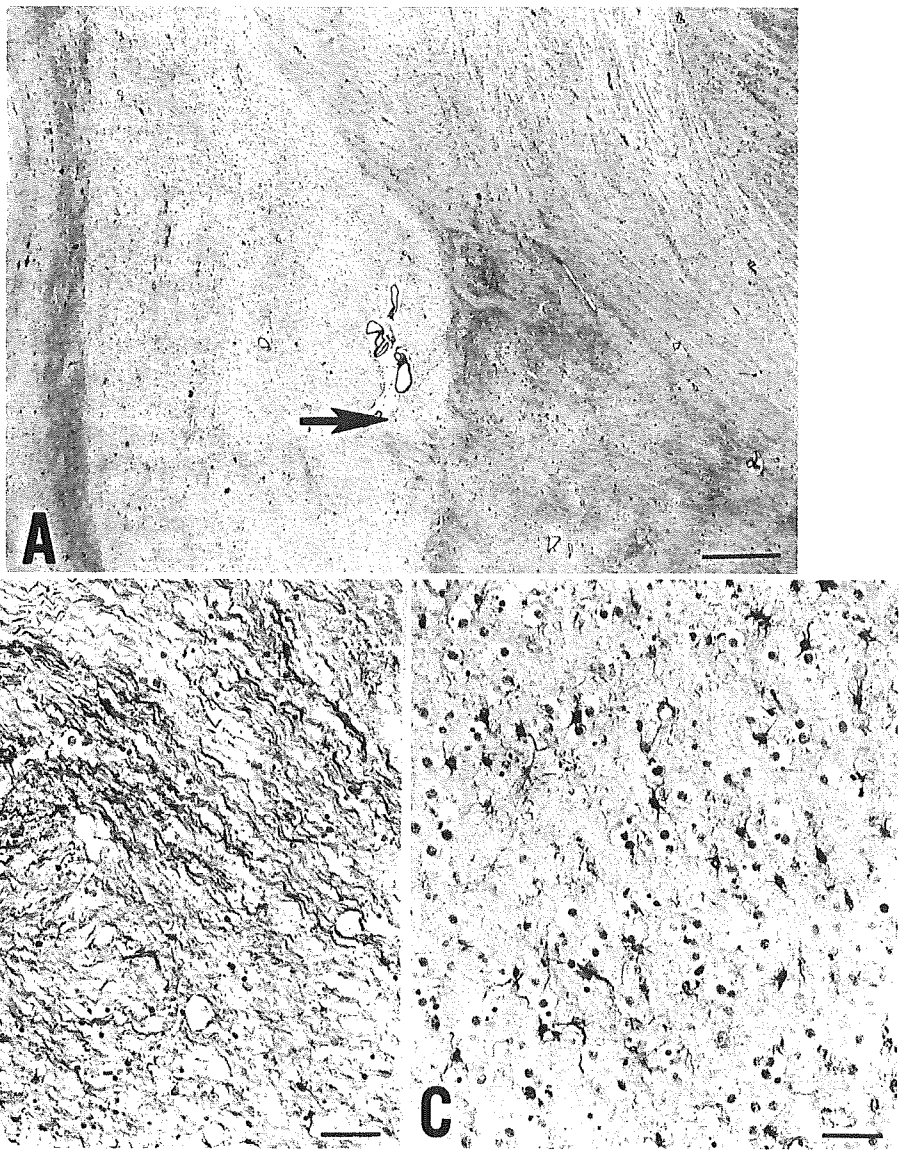


Fig. 3 A–C Case 10. **A** Obvious fibrillary gliosis in the pallidum (*arrow*), in contrast to slight fibrillary gliosis in the putamen. **B** Obvious fibrillary gliosis in the pallidum. **C** Slight fibrillary gliosis in the putamen. **A**, **B**, **C** Holzer stain; *bars* **A** 1 mm; **B**, **C** 0.05 mm

neurons were present. Fibrillary gliosis was observed in the cerebral white matter. Neuronal loss was not observed in the hippocampus, parahippocampal gyrus, amygdala, nucleus basalis of Meynert, oculomotor nucleus, pontine nucleus, Purkinje cells, hypoglossal nucleus, dorsal motor nucleus of the vagus, or inferior olive. Severe neuronal loss was observed in the pallidum, prominently in the dorsal part. The caudate nucleus and putamen showed moderate neuronal loss, but the subthalamic nucleus disclosed relative preservation of the neurons with slight proliferation of the glia (Fig. 1C). In the substantia nigra, there was prominent neuronal loss with melanin pigment incontinence. In the dentate nucleus, there was mild neuronal loss and "grumose degeneration". Senile plaques were not observed using methenamine silver staining. Using modified Gallyas-Braak methods, a few NFT in the hippocampus CA1 and a small quantity of NFT in the parahippocampal gyrus were seen, compatible with stage II of Braak's classification, and many argyrophilic threads were encounterd in the central nervous system.

Clinical course and neuropathological findings in case 5

This autopsy case was a Japanese man who was 70 years old at the time of death. He was well until the age of 64, when he developed memory disturbance, followed by topographical disorientation 10 months later and aspontaneity 1 year 6 months after the onset of the disease. A neurological examination when the patient was 69 years old (4 years 4 months after the disease onset) revealed severe dementia (revised Hasegawa dementia rating scale 0), vertical ocular movement involvement, rigidity of the right upper and lower extremities, absence of Babinski sign and hyperreflexia in the upper and lower extremities. At 4 years 7 months after disease onset, he

could walk and eat a meal with assistance, but he was doubly incontinent. Dysphagia became evident 5 years 2 months after the onset of the disease. Severe dysphagia very often caused misswallowing, which necessitated a gastrostomy, performed 5 years 5 months after the disease onset. He died of repeated pneumonia, probably due to severe dysphagia, 5 years 8 months after the onset of the disease. He was clinically diagnosed as having CBD, mainly because of prominent dementia and obvious rigidity in the clinical stage without difficulty in walking, by one of the authors (K. Tsuchiya).

Fig. 4 Involvement of the primary motor cortex. **A**, **B** Case 1; **C**, **D** case 3; **E**–**G** case 7; **H**, **I** case 10. **A** Ballooned neuron (*large arrow*) and hypertrophic glia (*arrowhead*) in the primary motor cortex, including Betz cell (*small arrow*). **B** Loss of Betz cell (*large arrow*) in the primary motor cortex, including Betz cell (*small arrow*). **C** Ballooned neuron (*arrow*) in the primary motor cortex. **D** Loss of Betz cell (*large arrow*) in the primary motor cortex, including Betz cell (*small arrow*). **E** Obvious involvement of the primary motor cortex, including degenerated Betz cell (*arrow*), showing prominent spongy state in the upper cortical layers. **F** Enlargement of the area indicated by *arrow* in **E**, showing degenerated Betz cell (*arrow*) and hypertrophic glia (*arrowhead*). **G** Hypertrophic glia (*arrowhead*) in the primary motor cortex, including degenerated Betz cell (*arrow*). **H** Deep layer of the primary motor cortex, including Betz cell (*arrow*). **I** Enlargement of the area indicated by *arrow* in **H**, showing loss of Betz cell (*arrow*) and hypertrophic glia (*arrowhead*). **A**, **B**, **E**, **F**, **H**, **I** H.E. stain; **C**, **D** K-B stain; **G** Holzer stain; *bars* **A**–**D**, **F**, **G**, **I** 0.04 mm; **E**, **H** 0.2 mm

The brain weighed 1,100 g before fixation. Macroscopic examination revealed atrophy of the frontal and parietal lobes, with depigmentation of the substantia nigra. A histological examination showed neuronal loss with astrocytosis, status spongiosus, many ballooned neurons, and astrocytic plaques in the cerebral cortex of the frontal and parietal lobes (Fig. 2A). In the primary morter cortex layer V, there was loss of Betz cells associated with obvious astrocytosis and presence of ballooned neurons. In the cerebral white matter, hyalinosis of the small vessels was obvious. Neuronal loss was not observed in the hippocampus, parahippocampal gyrus, amygdala, pontine nucleus, Purkinje cells, hypoglossal nucleus, dorsal motor nucleus of the vagus, or inferior olive. Severe neuronal loss was encountered in the pallidum, prominently in the dorsal part. The caudate nucleus and putamen showed moderate neuronal loss, but the subthalamic nucleus disclosed relative preservation of the neurons with slight proliferation of the glia. In the substantia nigra, there was prominent neuronal loss with leakage of melanin pigment and the presence of NFT (Fig. 2B, C). In the dentate nucleus, there was mild neuronal loss and grumose degeneration. Senile plaques were not observed using methenamine silver staining. Using modified Gallyas-Braak staining, a few NFT in the hippocampus CA1 and a small quantity of NFT in the parahippocampal gyrus were seen, con-

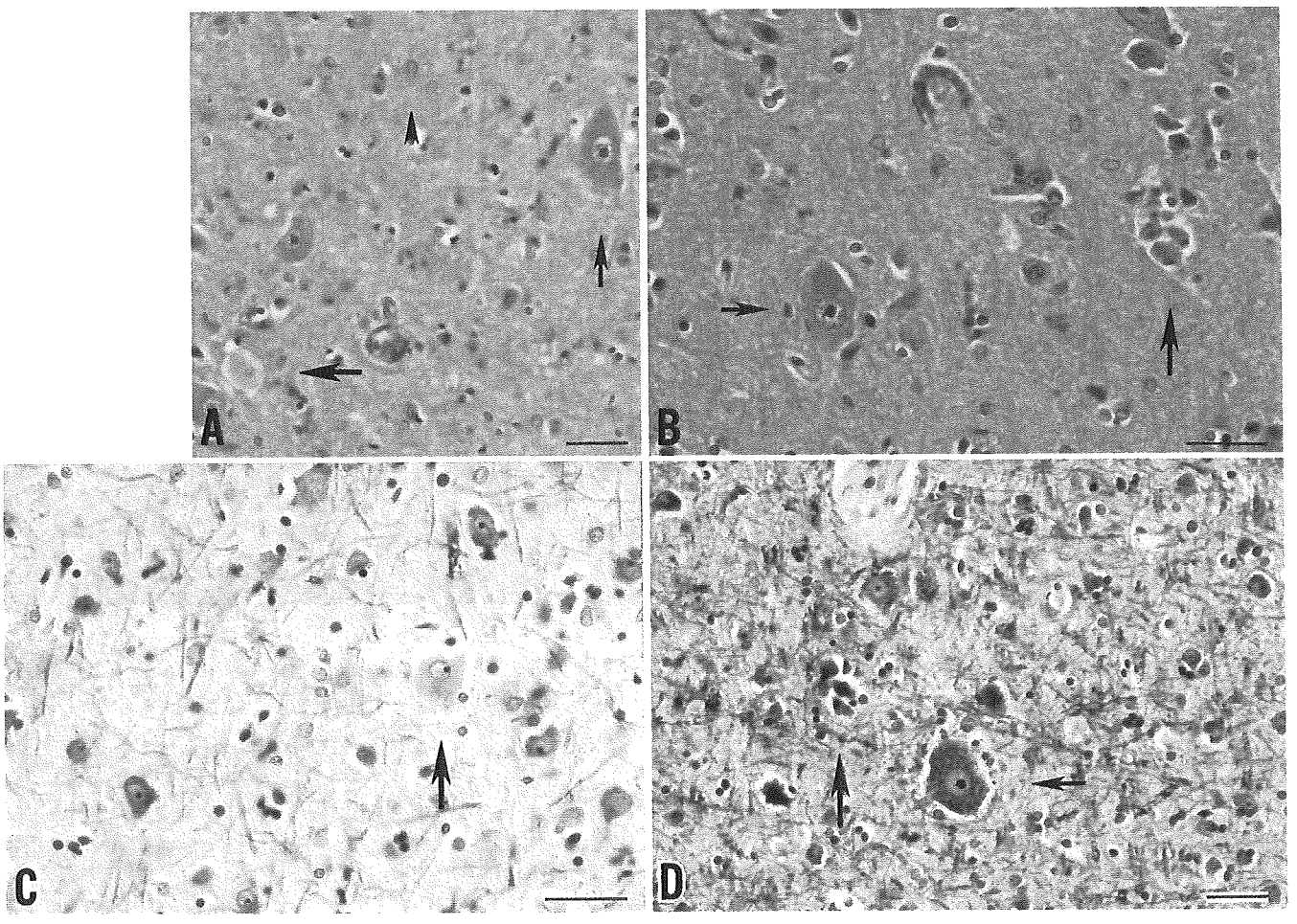
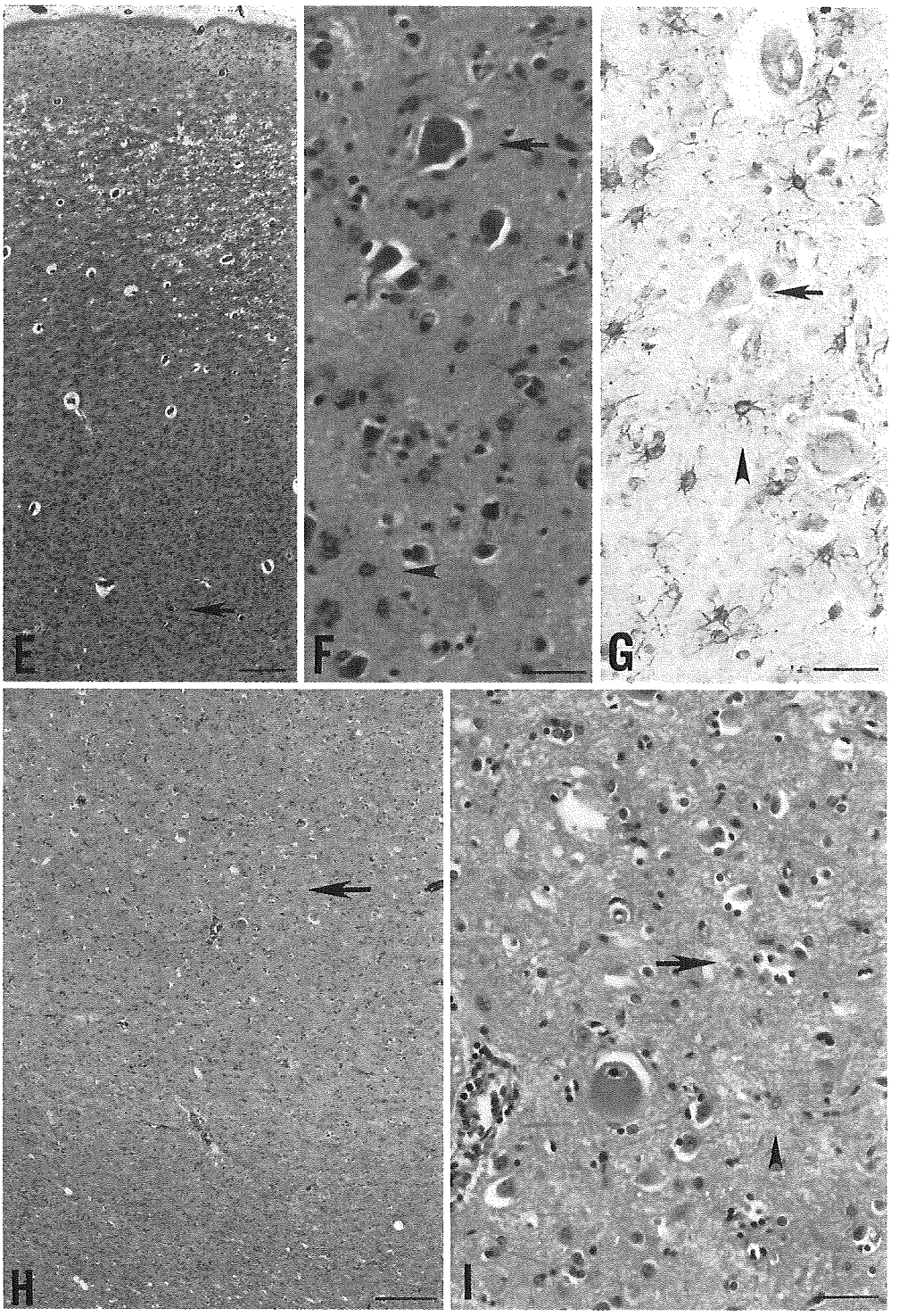


Fig. 4 (Contd.)



sistent with stage II of Braak's classification, as well as many argyrophic threads.

Clinical course and neuropathological findings in case 10

This patient was a Japanese woman aged 78 years at the time of death. She was in good health until the age of 67, when she developed memory disturbance, followed about 2 year later by action tremor, and at 3 years after the onset of the disease by difficulty in walking. At 5 years after the disease onset, memory disturbance worsened, followed by dyskinesia in the upper extremities. A neurological examination at the age of 75, 8 years after the disease onset, disclosed severe dementia, dyskinesia in the upper and lower extremities, hyperreflexia in the four extremities without Babinski sign. She died of

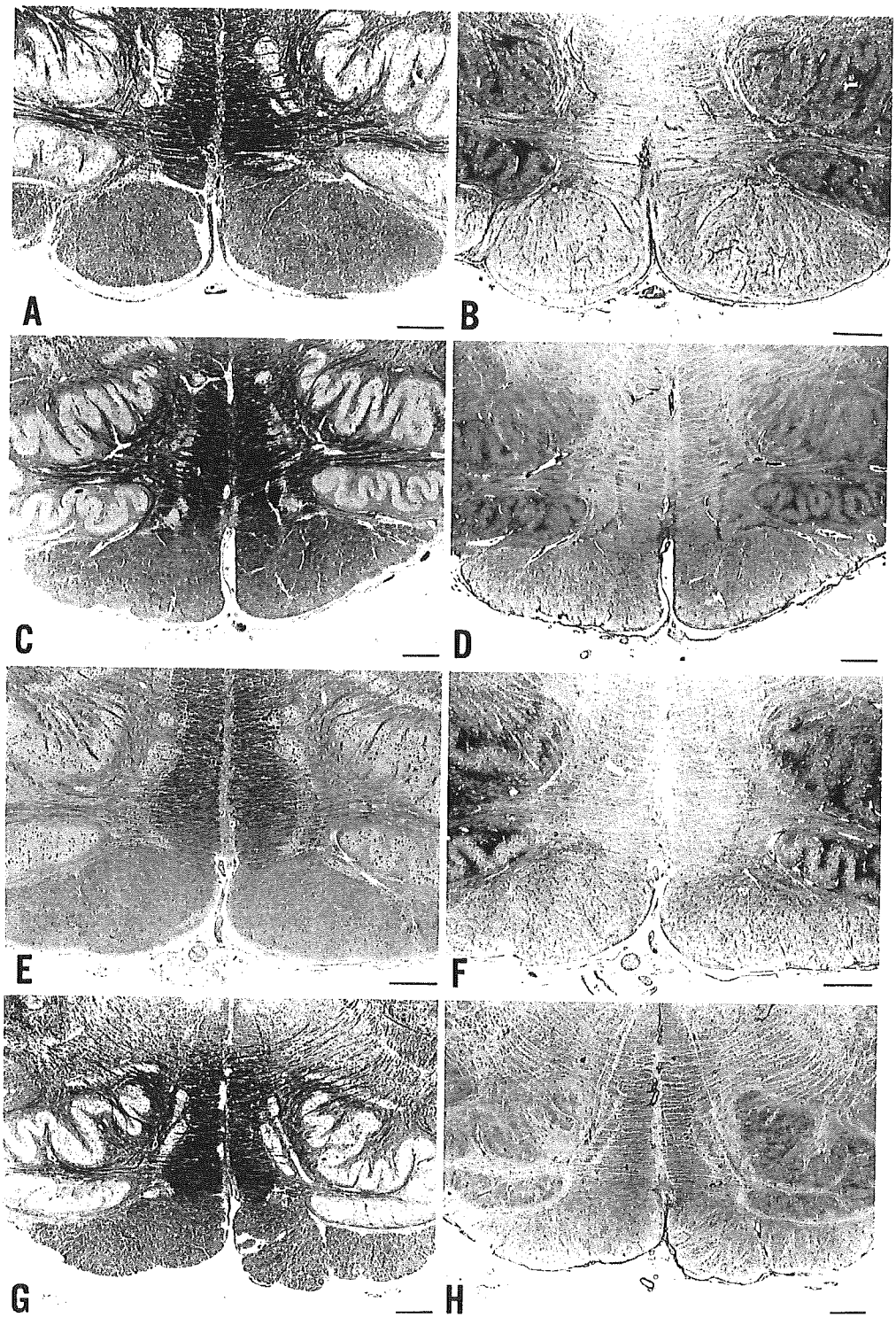


Fig. 5 A–H Involvement of the pyramidal tract in the medulla oblongata. **A**, **B** Case 1; **C**, **D** case 6; **E**, **F** case 7; **G**, **H** case 8. **A**, **C**, **E**, **G** Klüver-Barrera stain; **B**, **D**, **F**, **H** Holzer stain; *bars* **A–H** 1 mm

pneumonia at age 78, 11 years after the onset of the disease. She was clinically diagnosed as having atypical progressive supranuclear palsy.

The brain weighed 810 g. Macroscopic examination revealed atrophy of the frontal and parietal lobes, with depigmentation of the substantia nigra. A histological examination showed neuronal loss with astrocytosis, spongy state, many ballooned neurons, and astrocytic plaques in the cerebral cortex of the frontal and parietal lobes. In the primary motor cortex layer V, there was loss of Betz cells associated with prominent astrocytosis, and ballooned neurons were present. Fibrillary gliosis was observed in the cerebral white matter. Neuronal loss was not observed in the hippocampus, parahippocampal gyrus, amygdala, nucleus basalis of Meynert, oculomotor nucleus, trochlear nucleus, pontine nucleus, Purkinje

cells, hypoglossal nucleus, dorsal motor nucleus of the vagus, or inferior olive. Severe neuronal loss was observed in the pallidum, prominently in the dorsal part (Fig. 3A, B). The caudate nucleus and putamen (Fig. 3C) showed moderate neuronal loss, but the subthalamic nucleus disclosed relative preservation of the neurons with slight proliferation of the glia. In the substantia nigra, there was prominent neuronal loss with leakage of melanin pigment. In the dentate nucleus, there was mild neuronal loss and grumose degeneration. Senile plaques were not observed with methenamine silver staining. A few NFT in the hippocampus CA1 and a small quantity of NFT in the parahippocampal gyrus, compatible with stage II of Braak's classification, and many argyrophilic threads were encountered using modified Gallyas-Braak methods.

Results

Clinical features

The main clinical information on the ten patients (five males, five females) is summarized in Table 1. The patients had no hereditary burden. The age at onset of symptoms was from the fifth to eighth decade of life (average of 62 years 1 month). The duration of the disease ranged from 2 years 1 month in case 1 to 11 years in case 10 (mean duration 5 years 9 months). Three patients presented with limbkinetic apraxia as the initial sign (cases 1, 2, and 7). Two patients initially developed aphasia and motor aphasia (cases 3 and 4). Memory disturbance was observed in two patients as the initial sign (cases 5 and 10). Delusion of persecution was noted as the initial sign in case 6. Abnormal behavior, reminiscent of Pick's disease, was noticed as the initial sign in cases 8 and 9. Muscular rigidity was noted in eight patients during the clinical course, but in cases 3 and 8, with relative shorter clinical courses, muscular rigidity was not noticed. All ten cases presented with dementia during the clinical course.

Pathological features

The neuropathological data are also summarized in Table 1. Brain weights at autopsy ranged from 1,370 to 810 g (average 1,096.2 g). In the cerebral cortex of all ten cases, neuronal loss and gliosis associated with the presence of ballooned neurons and astrocytic plaques were encounterd in the frontal and parietal lobes. In all cases, the pallidum revealed severe neuronal loss and prominent gliosis, while moderate lesions were evident in the caudate nucleus and putamen. In the subthalamic nucleus, slight lesions were found in each CBD case examined in this study. Neuronal loss of the substantia nigra was prominent in all cases.

Clinicopathological correlation between pyramidal signs and involvement of the primary motor cortex and pyramidal tract

Pyramidal signs and involvement of the primary motor cortex and pyramidal tract are summarized in Table 2. Pyramidal signs, including hyperreflexia and Babinski sign, were noted in six cases (cases 1, 2, 6, 7, 9 and 10). Spasticity was noticed in only three cases (cases 1, 2, and 7). Loss of Betz cells was observed in all ten cases (Fig. 4). Furthermore, astrocytosis of the primary motor cortex layer V, detected by HE, Holzer, and GFAP staining, was obvious in all ten cases (Fig. 4). Degeneration of the pyramidal tract was found in each case, and the distal portion (medulla oblongata) was more affected than the proximal portion (midbrain), suggestive of a dying back phenomenon (Fig. 5).

Discussion

Clinical features

Pyramidal signs, including hyperreflexia, Babinski sign, and spasticity, are said to be common in CBD cases, but the frequency of pyramidal signs in CBD patients remains unclear to date. In 1990, Riley et al. [54], who designated CBD as cortical-basal ganglionic degeneration, described 15 patients with CBD, including 2 autopsy-confirmed CBD cases (patients 1 and 2 in their report), noticed that in their 15 patients, hyperreflexia associated with Babinski sign was observed in 5 patients (33%), but that hyperreflexia without Babinski sign was found in 7 patients (47%). Rinne et al. [55], in 1994, conducted a clinical study of 36 CBD cases, including 6 pathologically confirmed CBD cases, noted that hyperreflexia was observed in 26 patients (72%), with Babinski sign in 17 patients (47%). In 1997, Schneider et al. [57], who investigated clinical and neuropathological heterogeneity in 11 cases of pathologically diagnosed CBD, observed that 3 patients manifested Babinski sign (27%). Kompoliti et al. [36], in 1998, who examined the clinical presentation and pharmacological therapy in 147 CBD patients, including 7 autopsy-proven CBD cases, noted that pyramidal signs were observed in 84 CBD patients (57%), but that they were encountered in 6 cases (86%) of the 7 autopsy-proven CBD cases. In 1998, Wenning et al. [76] analyzed the natural history and survival of 14 patients with CBD confirmed at postmortem examination, and noticed that hyperreflexia was observed in 5 cases (36%), with Babinski sign being found in 3 cases (21%), about 3 years after the disease onset, but that hyperreflexia was observed in 7 cases (58%), with Babinski sign being found in 5 cases (42%), respectively, about 6.1 years after the disease onset. Boeve et al. [6], in 1999, investigated the pathological heterogeneity in 13 clinically diagnosed CBD patients and found 7 autopsy CBD cases among

these patients. Furthermore, Boeve et al. noted that in their 7 autopsy CBD cases, pyramidal signs were obvious in 4 cases (57%).

Reviewing the literature regarding the frequency of the pyramidal signs in CBD, including hyperreflexia, Babinski sign, and spasticity, it becomes clear that there are many discrepancies between the frequencies of the pyramidal signs in CBD cases reported to date.

Pathological features

Neuropathological studies of CBD, focusing on the primary motor cortex and pyramidal tract, are very rare. Rebeitz et al. [53] noticed that in their three autopsy cases, in which case 1 had a very brisk left patellar reflex with cases 2 and 3 having prominent Babinski sign, there was evident pyramidal tract involvement in cases 2 and 3, but that in case 1 the Betz cells in the precentral cortex appeared normal with a good complement of Nissl granules. Gibb et al. [18] described three autopsy cases of CBD, in which three cases clinically presented with brisk tendon reflexes, but Babinski sign was only encountered in case 2. In their pathological findings, Gibb et al. noted that their three cases had mild to moderate corticospinal tract involvement, but they did not notice whether or not there was loss of Betz cells. In contrast, Horoupian and Chu [27] reported an autopsy case of CBD, in which bilateral Babinski signs, more prominent on the right, were clinically observed, and the pathological examination revealed prominent neuronal loss of the primary motor cortex, including Betz cells, associated with astrocytosis and presence of ballooned neurons.

From the literature concerning the involvement of the primary motor cortex and pyramidal tract in CBD, it becomes obvious that there have been few reports showing loss of Betz cells in the primary motor cortex and involvement of the pyramidal tract of CBD patients. Thus, our data, showing constant and severe involvement of Betz cells associated with constant involvement of the pyramidal tract in the medulla oblongata in ten cases of CBD, are important.

Clinicopathological correlation and pathological heterogeneity in the primary motor cortex among MSA, ALS with dementia, and CBD

Tsuchiya et al. [66] investigated the pyramidal signs, including spasticity, hyperreflexia, and Babinski sign, and the involvement of the primary motor cortex and pyramidal tract, in seven Japanese autopsy cases of MSA. In that study, pyramidal signs were observed in six (86%) of the seven MSA autopsy cases. Hyperreflexia and Babinski sign were each evident in five patients, but spasticity was observed in only one patient. Loss of Betz cells and presence of glial cytoplasmic inclusions (Papp-Lantos inclusions) in the primary motor cortex were noticed in all seven MSA autopsy cases. Astrocytosis in the fifth layer of the primary motor cortex was noted in five (71%) of the seven MSA autopsy cases. Involvement of the pyramidal tract in the medulla oblongata was observed in all seven MSA autopsy cases, but no involvement of the pyramidal tract in the midbrain was evident in any of the six autopsy cases in which this structure was examined.

Subsequently, Tsuchiya et al. [70] explored the pyramidal signs, including hyperreflexia, Babinski sign, and spasticity, as well as the involvement of the primary motor cortex and pyramidal tract, in eight Japanese autopsy cases of ALS with dementia. Pyramidal signs were observed in seven (88%) of the eight autopsy cases. Hyperreflexia and Babinski sign were evident in seven (88%) and three (38%) patients, respectively, but spasticity was not observed in any of the eight patients. Loss of Betz cells in the primary cortex was evident in all seven autopsy cases in which this structure was examined. In contrast, astrocytosis in the fifth layer of the primary motor cortex was noticed in only three cases (38%). Involvement of the pyramidal tract in the medulla oblongata was observed in all eight ALS with dementia autopsy cases, but no involvement of the pyramidal tract in the midbrain was found in any of the eight autopsy cases.

Given the high frequency of pyramidal signs in MSA (86%) [66] and ALS with dementia (88%) [70], the relatively low frequency of pyramidal signs (60%) in the ten CBD autopsy cases seen in the present study deserves a mention.

In this study, constant and severe involvement of the primary motor cortex, including loss of Betz cells and obvious astrocytosis of the fifth layer of the primary motor cortex, was observed in all ten CBD cases, suggesting that in CBD there is a clinicopathological dissociation between the involvement of the primary motor cortex and pyramidal tract, and pyramidal signs. In contrast, in seven MSA autopsy cases reported by Tsuchiya et al., astrocytosis in the fifth layer of the primary motor cortex was noticed in five cases (71%), consistent with the high frequency of pyramidal signs (86%), and in eight ALS with dementia cases reported by Tsuchiya et al., astrocytosis in the fifth layer of the primary motor cortex was noted in only three cases (38%), inconsistent with the high frequency of the pyramidal signs (88%).

On the basis of our data showing that pyramidal sign were observed in six (60%) of the ten CBD autopsy cases, and that astrocytosis in the fifth layer of the primary motor cortex and loss of Betz cells were obvious in all ten CBD autopsy cases, we believe that the pyramidal signs in CBD have been disregarded.

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An Autosomal Dominant Cerebellar Ataxia Linked to Chromosome 16q22.1 Is Associated with a Single-Nucleotide Substitution in the 5′ Untranslated Region of the Gene Encoding a Protein with Spectrin Repeat and Rho Guanine-Nucleotide Exchange-Factor Domains

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Autosomal dominant cerebellar ataxia (ADCA) is a group of heterogeneous neurodegenerative disorders. By positional cloning, we have identified the gene strongly associated with a form of degenerative ataxia (chromosome 16q22.1–linked ADCA) that clinically shows progressive pure cerebellar ataxia. Detailed examination by use of audiogram suggested that sensorineural hearing impairment may be associated with ataxia in our families. After restricting the candidate region in chromosome 16q22.1 by haplotype analysis, we found that all patients from 52 unrelated Japanese families harbor a heterozygous C→T single-nucleotide substitution, 16 nt upstream of the putative translation initiation site of the gene for a hypothetical protein DKFZP434I216, which we have called "puratrophin-1" (Purkinje cell atrophy associated protein-1). The full-length *puratrophin-1* mRNA had an open reading frame of 3,576 nt, predicted to contain important domains, including the spectrin repeat and the guanine-nucleotide exchange factor (GEF) for Rho GTPases, followed by the Dbl-homologous domain, which indicates the role of puratrophin-1 in intracellular signaling and actin dynamics at the Golgi apparatus. Puratrophin-1—normally expressed in a wide range of cells, including epithelial hair cells in the cochlea—was aggregated in Purkinje cells of the chromosome 16q22.1–linked ADCA brains. Consistent with the protein prediction data of puratrophin-1, the Golgi-apparatus membrane protein and spectrin also formed aggregates in Purkinje cells. The present study highlights the importance of the 5′ untranslated region (UTR) in identification of genes of human disease, suggests that a single-nucleotide substitution in the 5′ UTR could be associated with protein aggregation, and indicates that the GEF protein is associated with cerebellar degeneration in humans.

Introduction

Autosomal dominant cerebellar ataxia (ADCA) is a clinical entity of heterogeneous neurodegenerative diseases that show dominantly inherited, progressive cerebellar ataxia that can be variably associated with other neurological and systemic features (Harding 1982). Circumscribed groups of neurons in the cerebellum, brainstem, basal ganglia, or spinal cord are selectively involved in different combinations and to varying extents among diseases (Graham and Lantos 2002). ADCA is now classified by the responsible mutations or gene loci. To date, 24 subtypes have been identified: spinocerebellar ataxia type (SCA) 1, 2, 3 (or, Machado-Joseph disease [MJD]), 4–8, 10–19/22, 21, 23, 25, 26; dentatorubral and pallidoluysian atrophy (DRPLA); and ADCA with mutation in fibroblast growth factor (FGF) 14 (Stevanin et

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al. 2000, 2004; Margolis 2002; van Swieten et al. 2003; Yu et al. 2005). Among these, mutations in SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA17, and DRPLA have been identified as the expansion of a trinucleotide (CAG) repeat that encodes the polyglutamine tract, uniformly causing aggregation of polyglutamine-containing causative protein (Ross and Poirier 2004). Expansion of noncoding trinucleotide (CAG or CTG) or pentanucleotide (ATTCT) repeats are involved in SCA8, SCA10, and SCA12 (Holmes et al. 1999; Koob et al. 1999; Matsuura et al. 2000). Very few families are affected by missense mutations in the protein kinase Cγ (PKCγ) (SCA14 [see Chen et al. 2003]) and *FGF14* genes (ADCA with *FGF14* mutation [see van Swieten et al. 2003]). However, genes or even their loci remain unidentified for >20%–40% of families with ADCA (Sasaki et al. 2003).

We had previously mapped mutations in six Japanese families with ADCA to a 10-cM interval in human chromosome 16q13.1-q22.1, identifying 16q-linked ADCA type III, or spinocerebellar ataxia 4 (SCA4 [MIM 600223]) (Ishikawa et al. 2000). Clinically, our families show cerebellar ataxia without obvious evidence of extracerebellar neurological dysfunction (i.e., "pure cerebellar ataxia," or "ADCA type III") (Harding 1982; Ishikawa et al. 2000). The average age at onset of ataxia was >55 years (Ishikawa et al. 1997), which suggests that this disease shows the oldest age at onset among ADCA types with assigned loci. Another important clinical feature of this disease is that a substantial number of patients show progressive sensorineural hearing impairment (Owada et al., in press). Since the hearing impairment can be very mild and of later onset, presence of hearing impairment can be easily overlooked. However, this finding may indicate that the mutated gene could cause hearing impairment as well as ataxia. In this sense, it would be more appropriate to use the term "chromosome 16q22.1–linked ADCA" instead of "ADCA type III" to describe our families. Neuropathological examination showed peculiar degeneration of Purkinje cells that was not described in other degenerative ataxias (Owada et al., in press). Many Purkinje cells undergo shrinkage and are surrounded by amorphous materials composed of Purkinje-cell somato-dendritic sprouts and an increased number of presynaptic terminals. These findings may indicate that certain proteins involved in the cytoskeleton of Purkinje cells are disturbed in chromosome 16q22.1–linked ADCA.

Chromosome 16q22.1–linked ADCA has been assigned to the same locus as another ADCA, SCA4 (Flanigan et al. 1996; Hellenbroich et al. 2003). Although SCA4 and chromosome 16q22.1–linked ADCA may be allelic, SCA4 is clinically distinct from chromosome 16q22.1–linked ADCA, because SCA4 shows prominent sensory axonal neuropathy and pyramidal tract signs, with an age at onset earlier than that of chromosome 16q22.1–linked ADCA (Flanigan et al. 1996; Hellenbroich et al. 2003). Several groups, including ours, have refined the loci of SCA4/chromosome 16q22.1–linked ADCA and have, so far, excluded repeat expansions as mutations (Hellenbroich et al. 2003; Li et al. 2003; Hirano et al. 2004). The minimum candidate region of SCA4 and chromosome 16q22.1–linked ADCA is set at the region between markers *D16S3031* and *D16S3095*. A strong founder effect has been observed for chromosome 16q22.1–linked ADCA (Li et al. 2003), which indicates the need to recruit a large number of families to narrow the critical region.

To discover the causative gene of chromosome 16q22.1–linked ADCA, we embarked on a positional cloning study by recruiting 52 families from diverse regions of Japan. Here, we describe the identification of a strong association between a single-nucleotide change and chromosome 16q22.1–linked ADCA and show the consequence of this genetic change on mRNA and protein levels. The data presented here also suggest that a single-nucleotide change in the 5′ UTR could be associated with aggregation of the gene product.

Patients, Material, and Methods

Recruitment of Families with Chromosome 16q22.1–Linked ADCA

We attempted to include families clinically diagnosed with late-onset ADCA type III from a wide region of Japan. Fifty-two families, including 109 affected individuals and 48 at-risk individuals, were ultimately recruited. These families originated from seven of eight districts of Japan (Hokkaido, Tohoku, Kanto, Chu-bu, Kinki, Chu-goku, and Kyu-shu), which indicates that their origins are widespread. Clinical features of these patients were consistent with those of families described elsewhere (Ishikawa et al. 1997, 2000; Li et al. 2003).

Detailed neuro-otological examinations, including pure-tone audiometry, were performed on 13 families at the Departments of Neurology and Otolaryngology, Tokyo Medical and Dental University. Progressive hearing impairment was assessed when the pure-tone average calculated from thresholds at the frequencies of 0.5, 1, and 2 kHz was more severe than the mean +2 SD of age-matched normal Japanese population (Tsuiki et al. 2002). By that criterion, 6 (42.9%) of 14 families had a hearing impairment other than age-related hearing loss. When we used the recommendations for the description of genetic and audiological data composed by the GENDEAG study group (see The Hereditary Hearing Loss Homepage), all of the patients with the hearing impairment were confirmed to have bilateral sensorineural hearing loss of mild-to-moderate severity. The audiometric configurations of these patients include mid-fre-