

Short Communication

Lateralized Cortical Involvement and Contralateral Parkinsonism without Basal Ganglia Involvement in Two Autopsy Cases of Corticobasal Syndrome-Alzheimer's Disease

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Abstract. Corticobasal syndrome (CBS) is characterized by lateralized motor disturbance due to levodopa nonresponsive parkinsonism and progressive apraxia. Although CBS is neuropathologically heterogeneous, it remains unclear whether the clinical features of all CBS cases are the same. We report two autopsy cases diagnosed clinically as CBS and pathologically as Alzheimer's disease characterized by lateralized cerebral cortical degeneration and absence of significant nigrostriatal lesions. Cerebral cortical degeneration in both cases was contralateral to their motor disturbances. Thus, nigrostriatal lesions and contralateral cerebral cortical lesions can cause motor disturbances in CBS, necessitating the need for bedside examination in patients with CBS.

Keywords: Alzheimer's disease, cerebral cortex, corticobasal syndrome, parkinsonism, striatonigral system

INTRODUCTION

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Corticobasal syndrome (CBS) is a clinical diagnostic term, pointing to a lateralized motor disturbance caused by a mixture of levodopa nonresponsive parkinsonism and progressive apraxia [1]. In addition

to corticobasal degeneration, pathologically featured by deposition of a four-repeat tau, the underlying cytopathologies of CBS are heterogeneous [2, 3] and include Alzheimer's disease (AD) [2]. We describe two autopsy-verified AD cases that were clinically diagnosed as CBS based on such lateralized motor disturbance. Nigrostriatal degeneration was, at most, mild without laterality, whereas neurofibrillary degeneration around the pericentral area was more pronounced in the neocortex contralateral to the motor disturbances.

CASE REPORTS

Patient 1 (Pt1) [4] (67-year-old right-handed male) presented with gait disturbance and postural instability. Neurological examination revealed mask-like face, lead-pipe rigidity of the right upper limb, micrographia, and small voice; however, hallucination, personality change, and dementia were absent. Two years later, his short-term memory was slightly disturbed. Brain magnetic resonance imaging (MRI) performed three years after symptom onset showed bilateral cerebral atrophy, which was most prominent at the medial temporal region, including the hippocampus. Limb-kinetic apraxia and nonfluent aphasia supervened five years after symptom onset. Follow-up MRI showed left-side-dominant cerebral atrophy with progressive atrophy of the hippocampus and parahippocampus. Rigidity involving his trunk and extremities was more pronounced on the right side. At 74 years, he died of septicemia due to pneumonia.

Patient 2 (Pt2) [5] (60-year-old male) presented with gait disturbance and difficulty in dressing. Neurological examination revealed left-side-dominant lead-pipe rigidity of the trunk and extremities; upper limb myoclonus was observed seven years after symptom onset. Brain MRI revealed right-side-dominant cerebral atrophy. Nine years after symptom onset, he died of pneumonia and acute pancreatitis. Levodopa was not effective throughout the disease course in both cases.

The fixed brain of Pt1 weighed 1090 g. External macroscopic examination revealed mild fronto-temporo-parietal atrophy without laterality (Fig. 1a). After serial coronal slicing, left-sided atrophy involving anterior medial temporal structures such as the amygdala and hippocampus was evident. The substantia nigra (SN) and locus coeruleus (LC) were relatively preserved. Microscopically, numerous neurofibrillary tangles (NFTs) and senile plaques (SPs) were observed in the cerebral cor-

tices, corresponding to Braak NFT stage VI and Braak SP stage C [6, 7] by Gallyas–Braak staining, Methenamin–Bodian staining, and both AT8 and amyloid- β (A β) immunohistochemistries, in addition to laminar necrosis in the entorhinal cortex, which were compatible with a histological diagnosis of advanced AD. Remarkable neuronal loss and gliosis were limited to the temporal medial region, including the amygdaloid nuclei, hippocampi, entorhinal cortices, and precentral gyri, where neurofibrillary changes were more robust in the left (Fig. 1b) than the right (Fig. 1c) side (Table 1). SN was median part predominantly affected by slight neuronal loss and gliosis without laterality (Table 1, Fig. 1d). The LC and subcortical gray matter, including the caudate nuclei, putamen (Fig. 1e), and globus pallidus, were all free from neuronal loss and gliosis (Table 1).

The fixed brain of Pt2 weighed 1037 g. Cerebral atrophy was more prominent in the right side, especially in the right parietal lobe and post- and precentral gyri (Fig. 1f). After coronal slicing, right-sided atrophy became more evident in the occipital lobe and right pericentral gyrus. The temporal medial region, including amygdaloid nuclei, hippocampi, and entorhinal cortices, showed atrophy without laterality. Mild depigmentation was observed in the SN and LC. Microscopically, numerous NFTs and SPs were observed in the cerebral cortices, corresponding to Braak NFT stage VI and Braak SP stage C [6, 7] by Gallyas–Braak staining, Methenamin–Bodian staining, and both AT8 and A β immunohistochemistries, in addition to laminar necrosis in the entorhinal cortex and both superior and inferior parietal lobules, which were compatible with AD. However, NFTs were more abundant in the right parietal area (Fig. 1h) than the left counterpart (Fig. 1g, Table 1). In Pt2, remarkable neuronal loss and gliosis affected the temporal medial regions, including amygdaloid nuclei, hippocampi, and entorhinal cortices, and the right-side-dominant pericentral regions and cerebral cortices of the parietal lobe (Fig. 1g and h) (Table 1). In the SN, mild neuronal loss and gliosis were median to lateral part predominantly noted, without laterality (Table 1, Fig. 1i). The LC and subcortical gray matter, including the caudate, putamen (Fig. 1j), and globus pallidus, showed mild-to-no-gliosis; no remarkable neuronal loss was observed in those nuclei (Table 1).

By phosphorylated α -synuclein immunohistochemistry, several Lewy bodies were observed only in the amygdaloid nuclei of Pt1, whereas none were observed in Pt2. There was neither astrocytic plaques nor tufted astrocytes in both cases.

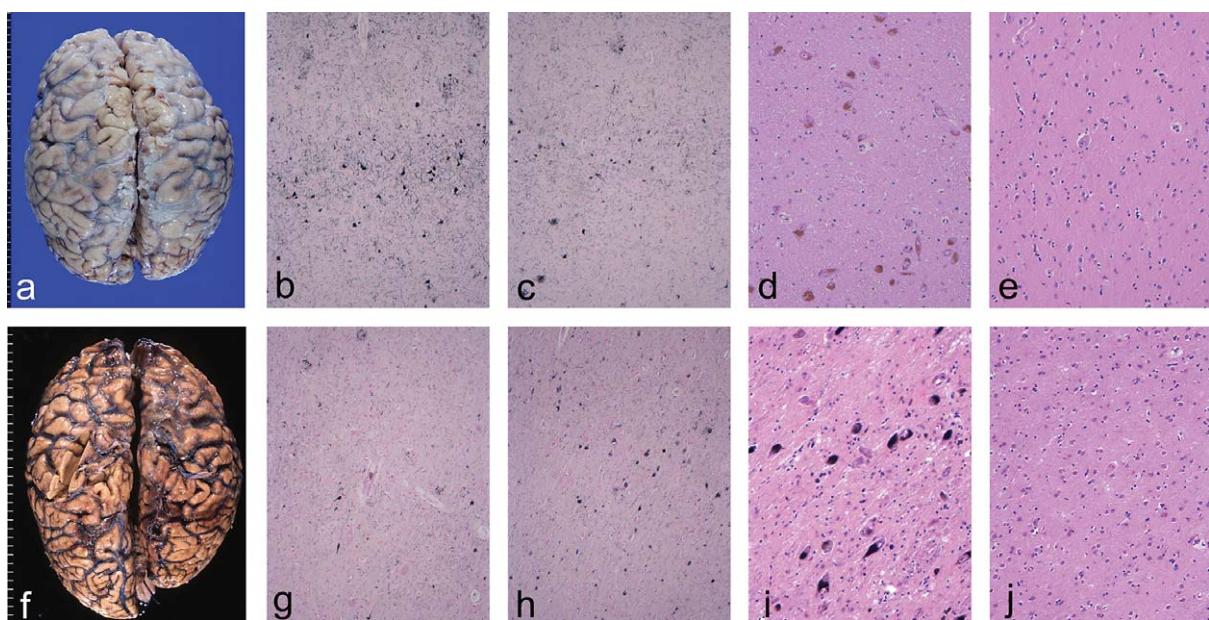


Fig. 1. Macroscopic and microscopic symmetry of cortical lesions. a) Symmetrical cerebrum with mild fronto-temporo-parietal atrophy. b, c) Compared with the right side (c), the left precentral cortex (b) was affected by numerous NFTs (Gallyas–Braak). d, e) The substantia nigra (d) and putamen (e) were well preserved (H&E). f) Marked cerebral atrophy with right-side laterality, which was most prominent in the right occipital lobe and the right pericentral sulcus region. g, h) Compared with the left side (g), the right precentral cortex (h) was affected by numerous NFTs (Gallyas–Braak). i, j) The substantia nigra (i) and putamen (j) were well preserved (H&E).

In the present report, semiquantitative analyses for neuronal loss and gliosis in the peri-sylvian fissure region, basal ganglia, and substantia nigra were performed. In addition, the average number ($/\text{mm}^2$) of both NFTs and SPs per 10 fields (200 power fields) was calculated. These data are described in Table 1.

DISCUSSION

The prevalence of AD pathology in CBS patients is estimated to be 5.2–50% in prospective [2, 8–10] and 17.6–23.8% in retrospective [8, 11, 12] studies. However, this overall prevalence does not clarify the relation between AD pathology and this characteristic mixture of ipsilateral parkinsonism and apraxia. Either parkinsonism or apraxia could be independently manifested in AD [13, 14]. In accordance with the conventional framework of neurology, parkinsonism is ascribed to nigrostriatal lesions possibly with tau deposition [13], and apraxia is usually ascribed to cortical lesions [14] in AD. On the other hand, extrapyramidal features in the absence of significant nigral lesion have been reported in AD patients [2, 4, 5, 10, 15–20]. Among them, some exhibited extranigral lesions in the basal ganglia [2, 19], which may explain the extrapyramidal symptoms [2]. Even after exclud-

ing AD cases with significant lesions in the SN or basal ganglia, there still remain some autopsy-verified AD patients who developed some motor disturbance [2, 4, 5, 15, 17, 18, 20] with more or less extrapyramidal features. It is also being recognized that extrapyramidal symptoms in CBS are not necessarily accompanied by a reduced uptake of FP-CIT in the nigrostriatal system by FP-CIT single photon emission computed tomography (SPECT) [21, 22]. These clinicopathological and SPECT results suggest that the so-called extrapyramidal features may be evident even in the absence of functional or pathological involvement of the nigrostriatal system, as confirmed here. Motor disturbances in AD patients without significant lesions in the SN or basal ganglia are lateralized frequently [2, 4, 5, 15, 17]. In such cases, the cortical asymmetry represented by macroscopic atrophy or NFT abundance is always contralateral to the motor disturbance, with extrapyramidal and apraxic features [2, 4, 5, 15, 17]. It is plausible that this unique mixture of extrapyramidal and apraxic features originates in the contralateral cortex, at least in CBS-AD patients. This is one of the potential explanations as to why two apparently distinct manifestations, extrapyramidal and apraxic features, develop ipsilaterally.

Because lateralized cortical lesions not accompanied by basal ganglia lesions may develop in

Table 1
Clinico-pathological characteristics of two CBS-AD cases

	Case 1		Case 2	
Clinical features				
Gender	Male		Male	
Age at onset	67		60	
Duration of illness	7		9	
Parkinsonism	Rt side-dominant		Lt side-dominant	
	Gait disturbance		Gait disturbance	
	Postural instability		Postural instability	
	Lead pipe rigidity		Lead pipe rigidity	
	Myoclonus		Myoclonus	
Dementia	+ (short-term memory)		–	
Apraxia	Hand-finger apraxia		Dressing apraxia	
Brain MRI	Lt side-dominant cerebral atrophy, including hippocampus and parahippocampus		Rt side-dominant cerebral atrophy	
Effect of L-dopa	–		–	
Pathological features				
	Left	Right	Left	Right
Brain weight (g)	1090		1037	
Macroscopic cerebral atrophy	Lt=Rt		Lt < Rt	
Braak NFT stage [6, 7]	VI		VI	
Braak SP stage [6]	C		C	
Laminar necrosis	ER		Occ, ER	
Peri-sylvian region	PreMo			
	Neuronal loss	–	–	++
	Gliosis	–	+	++
	NFT (/mm ²)	54	55	137
	SP (/mm ²)	17	14	14
	Mo			
	Neuronal loss	+	±	++
	Gliosis	+	+	++
	NFT (/mm ²)	88	36	97
	SP (/mm ²)	20	16	19
Basal ganglia	Se			
	Neuronal loss	–	+	+++
	Gliosis	–	++	+++
	NFT (/mm ²)	27	28	59
	SP (/mm ²)	9	10	23
	Caud			
	Neuronal loss	–	–	–
	Gliosis	–	+	+
	NFT (/mm ²)	2	1	4
	SP (/mm ²)	NA	0	0
Substantia nigra	Put			
	Neuronal loss	–	–	–
	Gliosis	–	+	+
	NFT (/mm ²)	1	2	2
	SP (/mm ²)	NA	0	0
	GP (e/i)			
	Neuronal loss	–/–	–/–	–/–
	Gliosis	–/–	–/–	–/–
	NFT (/mm ²)	0/0	0/0	0/0
	SP (/mm ²)	NA	0/0	0/0

Lt, left; Rt, right; PreMo, premotor cortex; Mo, motor cortex; Se, sensory cortex; Caud, caudate nucleus; Put, putamen; GP, globus pallidus; NFT, neurofibrillary tangle; SP, senile plaque; e, external segment; i, internal segment; ER, entorhinal cortex; Occ, occipital cortex. Degrees of neuronal loss and gliosis are described as follows: –, none; ±, slight; +, mild; ++, moderate; +++, severe.

contralateral CBS in situations other than AD [2, 20, 23], this clinical presentation is not unique to AD. However, it remains to be clarified by autopsy whether an isolated cortical lesion due to cerebral infarction may mimic CBS, although there is one clinical investigation in which anterior cerebral artery territory infarction was described as the cause of CBS [24]. Awareness of CBS with or without basal ganglia lesions will challenge the conventional framework of clinical neurology if these apparently different pathological conditions cannot be distinguished. CBS patients should be reexamined at the bedside while keeping this awareness in mind to allow clinical distinction of these conditions in the future.

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