

# Clinical, Imaging and Electrophysiological Studies of Corticobasal Degeneration

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**Abstract-** Corticobasal degeneration (CBD) is a rare neurodegenerative disorder characterized by distinctive clinical manifestations including asymmetric akinetic-rigid syndrome and higher cortical dysfunctions. We characterized the clinical, electrophysiological and imaging presentations in four patients with CBD. All patients exhibited unilateral hand dystonia, rigidity and apraxia, but showed no significant response to levodopa therapy. Surface electromyography demonstrated short duration and stimulus-sensitive myoclonus in three of the four patients. On the other hand, there was no “giant” SEPs (somatosensory evoked potentials), and the backaveraged electroencephalography did not show any jerk-locked cortical potentials. Brain magnetic resonance imaging showed asymmetrical cortical atrophy. [<sup>99m</sup>Tc]HMPAO single-photon emission computed tomography (SPECT) revealed decreased regional cerebral blood flow in the frontoparietal areas and thalamus opposite to the more severely affected limb. [<sup>99m</sup>Tc]TRODAT-1 SPECT showed decreased uptake in the striatum of the affected hemisphere. These data supported that there are abnormal cortical excitability and asymmetric pathological change of the affected hemisphere in the patients with CBD.

**Key Words:** Corticobasal degeneration, Myoclonus, Magnetic resonance imaging (MRI), Apraxia, [<sup>99m</sup>Tc]HMPAO SPECT, [<sup>99m</sup>Tc]TRODAT-1 SPECT

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## INTRODUCTION

In 1968, Rebeiz and colleagues first described three patients with a very distinctive clinical pattern consisting of progressive asymmetric rigidity, apraxia and other cortical and subcortical features<sup>(1)</sup>. They named the disorder “corticodentatonigral degeneration with neu-

ronal achromasia”. In the following reports, the name of “corticobasal ganglionic degeneration” or “corticobasal degeneration (CBD)” was used to denote the major pathological findings in this disease. Basically, this is a neurodegenerative disorder with a relatively late age of onset at around sixty years<sup>(2)</sup>. In the study of 66 patients with CBD evaluated over 10 years, Vanek and Jankovic

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reported a female:male ratio of 2:1<sup>(3)</sup>. The cardinal signs of CBD include asymmetric akinetic-rigid syndrome and higher cortical dysfunctions such as limb apraxia or alien limb<sup>(4)</sup>. The median survival time after the onset of symptoms was  $7.9 \pm 0.7$  years<sup>(5)</sup>. The typical pathological findings in CBD include focal asymmetric cortical atrophy with ballooned neurons, nigral degeneration, tau-positive neuronal and glial lesions in both gray and white matters, and particularly astrocytic plaques in the affected cerebral cortex<sup>(6)</sup>. However, several neurodegenerative disorders may underlie CBD, leading to difficulty in diagnosis<sup>(6-10)</sup>. Pathologic heterogeneity in clinically diagnosed CBD has also been reported<sup>(11)</sup>.

In addition to typical symptoms, unusual clinical presentations including language disturbance have been reported in CBD patients<sup>(12,13)</sup>. In clinical practice, assessment of orofacial praxis may be helpful to differentiate CBD from idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy<sup>(14)</sup>. To achieve more accurate clinical diagnosis, neuropsychological, electrophysiological and imaging methods could be applied to differentiate this disease from the other parkinsonism syndrome. In a pathology-proven study, dementia was the most common presentation of CBD<sup>(15)</sup>. The neuropsychological findings in CBD represent a distinctive mixture of posterior cortical and frontal-subcortical dysfunctions<sup>(16)</sup>, and probably also depressive symptoms<sup>(17)</sup>. Abnormal magnetoencephalography<sup>(18)</sup>, electromyographic-electromyographic (EMG-EMG) coherence<sup>(19)</sup>, and paired transcranial magnetic stimulation<sup>(20)</sup> (TMS) findings were noted in patients with CBD. Recently, functional imaging has played an important role on the clinical diagnosis and even pathological evaluation of the disease<sup>(21,22)</sup>. A markedly asymmetric involvement of the parietal cortex, the thalamus, the caudate nucleus and the putamen was disclosed in a study of [<sup>18</sup>F]fluoro-DOPA positron emission tomography (PET)<sup>(23)</sup>. Lai et al. maintained that the dopamine transporter (DAT) system was abnormal in CBD patients<sup>(24)</sup>. However, heterogeneity in glucose hypometabolism in CBD was also noted with PET studies<sup>(25)</sup>.

Although the features of CBD are well-described in western countries, they have been rarely addressed in

Taiwan. In 1998, Lu et al. first reported the electrophysiological findings of early stage CBD in two Asian patients<sup>(26)</sup>. We herein describe the clinical manifestations, electrophysiological and imaging features in four Taiwanese patients with CBD to add more information on this intriguing disease entity in the Asian people.

## MATERIALS AND METHODS

### Patients

Four patients with the clinical diagnosis of CBD were studied (Table). All of them were regularly followed up for at least two years.

Patient 1 is a 74-year-old, right-handed woman with progressive gait and behavior disturbances for six years. Her family noticed that she developed slowness of motion and slurred speech in the early years, followed by clumsiness of the left upper limb. She usually exhibited forced groping with her hands while paying attention to something. Inappropriate behaviors including doing exercise all night and a strong tendency of left-turning

**Table.** Demographic and clinical features of the four CBD patients

Patient number	1	2	3	4
Age (yr)/Sex	74/F	61/M	60/F	79/M
Disease duration (yr)	6	5	4	6
Affected side	left	left	left	right
Rigidity	+	++	+	++
Postural instability	++	++	++	—
Unilateral hand dystonia	+	++	++	++
Tremor	—	—	—	+
Myoclonus	—	++	++	++
Dysarthria	++	++	+	+
Hyperreflexia	—	—	—	—
Extensor plantar response	—	—	—	—
Alien hand/limb phenomenon	++	—	++	—
Cortical sensory loss	+	++	++	+
Apraxia	++	+	++	+
Primitive reflex	+	—	+	++
Response to levodopa	—	—	—	—
Score of CASI (MMSE)	ND	83 (24)	49 (16)	36 (16)

—: absent; +: present; ++: prominently present; CASI: Cognitive Abilities Screening Instrument (full score: 100); MMSE: Mini-Mental Status Examination (full score: 30); ND: not done.

while walking were noticed by her family. There are also emotional fragility with easy crying and slight memory impairment. A tentative diagnosis of frontal-temporal dementia was made in the first visit. Because of the aggravated gait unsteadiness, she was re-evaluated 3 years ago. Neurological examination (NE) disclosed mild disorientation, preservation, dysarthria, bradykinesia, rigidity, left hand apraxia, left arm dystonia, and postural instability. Her speech was characterized by an unusual prolongation of word phonation. There was no limitation of eyes movement. She received levodopa treatment, but adverse effects such as restlessness and psychosis has limited the maximal dosage to 375 mg daily and no significant clinical effect was observed.

Patient 2 is a 61-year-old, right-handed man whose major symptom was an akinetic-rigid left hand for five years. He felt cramping pain in the left fingers initially, followed by progressive stiffness and clumsiness of the left hand. Deterioration in manual dexterity such as difficulty in buttoning became manifest two years later. In the past two years, his left upper extremity gradually took a fixed posture of flexion of the elbow, metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints, and stiff extension of the first interphalangeal joint of the thumb. The left thumb therefore extruded between the index finger and the middle finger (Fig. 1). Such a posture significantly interfered with the function of the hand. Slurred speech and limping gait with unsteadiness were also noticed. Neurological examination revealed cortical sensory loss with prominent focal dystonia (bird-beak like posture), akinetic rigidity, and stimulus-sensitive myoclonus of the left hand. Dysarthria and poor balance were also noted. He took daily medications of sinemet 750 mg and pergolide 1.5 mg, which have only a very limited clinical effect.

Patient 3 is a 60-year-old, right handed housewife. She was found to have difficulty dealing with her daily activities four years ago. She could not put on or take off clothes without help, and tended to spend a lot of time in the toilet room. The most notable symptom was that her left hand had a tendency of "wondering" and forced grasping beyond voluntary control. There was also difficulty fully extending her left fingers by herself.



**Figure 1.** The dystonic posture of left hand in Patient 2 ("bird-beak" like posture). The thumb extrudes rigidly between the flexed index and middle fingers.

Progressive slowing of motion, speech and mentality was noticed. Neurological examination demonstrated higher cortical dysfunctions including amnesia, dyscalculia, ideomotor and ideational apraxia, graphyesthesia, and astereognosis. Dysdiadochokinesia and paratonic rigidity were noted mainly in the left upper limb. Remarkable stimulus-sensitive myoclonus could be induced by pinpricking her left fingers. She also presented postural instability. Sinemet 750 mg per day was prescribed but did not ameliorate the symptoms.

Patient 4 is a 79-year-old man with jerky movement of the right hand for six years. In the early years, he was diagnosed as Parkinson's disease elsewhere because of the tremor. Madopar 375 mg daily was prescribed at the beginning and the daily dose was gradually increased to 750 mg 2 years later. In recent years, progressive clumsiness of the right hand with a tonic flexion posture was noticed. Rigid posture, small-step gait, slow mental response, emotional incontinence and impaired memory also developed. There was no significant response to the medications. Neurological examination showed bradyphrenia, impairment of recent memory, presence of primitive reflexes, and akinetic-rigid right upper limb. Spontaneous and stimulus-sensitive myoclonus were also present in the right hand.

### Electrophysiological studies

Multi-channel surface electromyography (SEMG) were recorded in three patients (Patient 2, 3 and 4). The signals were amplified (Digitimer 360, Welwyn Garden City, Hertfordshire, England) with a bandpass filter of 100 Hz to 1 kHz and analyzed with Spike 2 software. We were able to document electroencephalographic (EEG) recordings with jerk-locked back average in two patients (Patient 2 and 3). The trigger muscle was set on the left extensor digitorum communis (EDC). Twenty-six Ag/AgCl scalp electrodes were used for recording. We selected the EEG epoch between 84 milliseconds (ms) before to 36 ms after the EMG onset. The EEG and EMG signals were sampled by a rate of 1 kHz and band filtered (EEG: 0.05-70 Hz, EMG: 30-200 Hz. NeuroScan SynAmps, Neurosoft, Inc. Sterling, Va, USA). Somatosensory evoked potential (SSEP) was also conducted in all patients (Medtronic Dantec Keypoint DK-2740). All patients gave informed consent to the studies that they participated in.

### Imaging studies

Conventional brain magnetic resonance imaging (MRI) and Technetium-99m hexamethylpropyleneamine oxime ( $^{99m}\text{Tc}$ ]HMPAO) single-photon emission computed tomography (SPECT) were performed in all patients. Patient 2 and patient 4 also received [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methyl](2-mercaptoethyl) amino]ethyl]amino]ethanethiolato(3-)-N2,N2',S2,S2']oxo-[1R-(exo-exo)]- $^{99m}\text{Tc}$ ]technetium ( $^{99m}\text{Tc}$ ]TRODAT-1) SPET examination. Informed consent was always obtained before the examination.

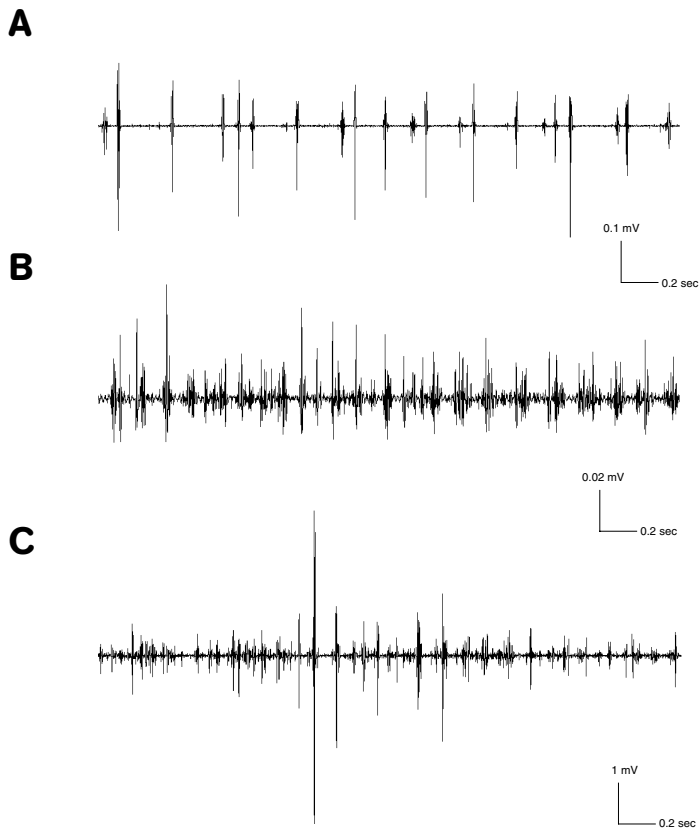
## RESULTS

The mean age of the current four patients was  $68.5 \pm 9.5$  years. The mean duration of the disease was  $5.3 \pm 1.0$  years. All patients presented asymmetrical clinical manifestations and higher cortical dysfunction (Table). None of them had explicit response to levodopa treatment. The SSEP findings are similar among Patient 1, 2 and 3. It revealed normal latencies of N9, N13 and N20

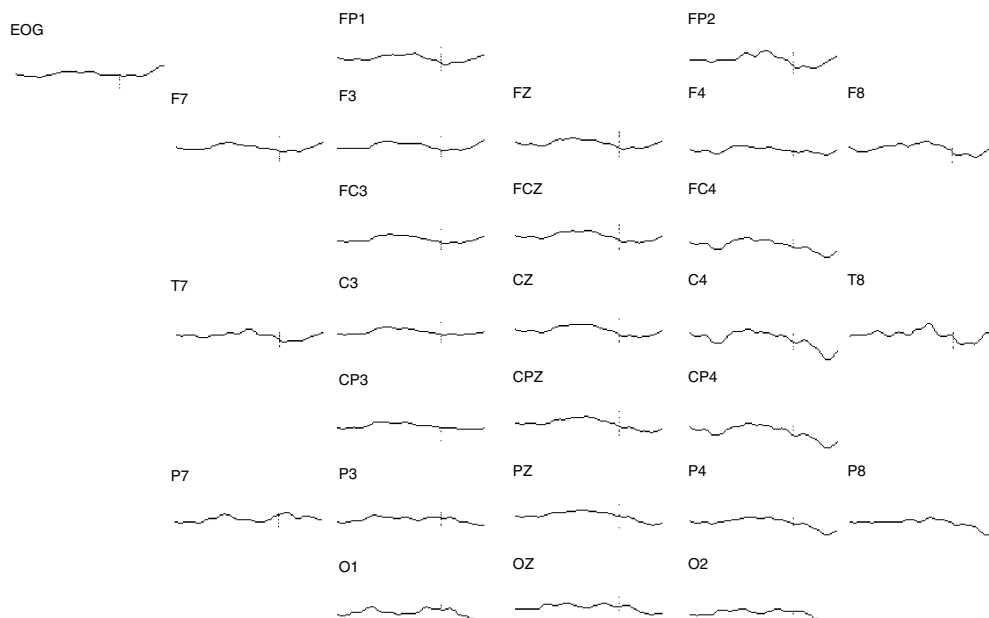
waves, and no "giant" SEPs were found. Patient 4 showed borderline prolongation of N20 latency, but still without "giant" SEPs on bilateral median nerve stimulation. The SEMG recordings in Patient 2, 3, and 4 revealed short duration of EMG burst (30-100 ms) over multiple forearm or hand muscles of the affected limb (Fig. 2). The frequency ranged from 5 Hz to 12 Hz with individual variations. In Patient 2 and 3, the EEG recordings with jerk-locked back average did not found any jerk-locked cortical potentials (Fig. 3). Conventional brain MRI showed mild to moderate cortical atrophy, particularly in the hemisphere opposite to the (more severely) affected limb (Fig. 4A).  $^{99m}\text{Tc}$ ]HMPAO SPECT revealed mild degree of cerebral hypoperfusion in the right frontoparietal region in Patient 1, hypoperfusion in the left temporal, right inferior temporal, right posterior parietal regions, and the right basal ganglia in Patient 2, hypoperfusion in the right temporoparietal region and right thalamus in Patient 3 (Fig. 4B), and hypoperfusion in bilateral temporal, left fronto-temporoparietal, left parieto-occipital regions and left thalamus in Patient 4.  $^{99m}\text{Tc}$ ]TRODAT-1 SPECT demonstrated significantly decreased uptake in the right striatum in Patient 2 (Fig. 4C) and severely decreased uptake in bilateral striatum in Patient 4.

## DISCUSSION

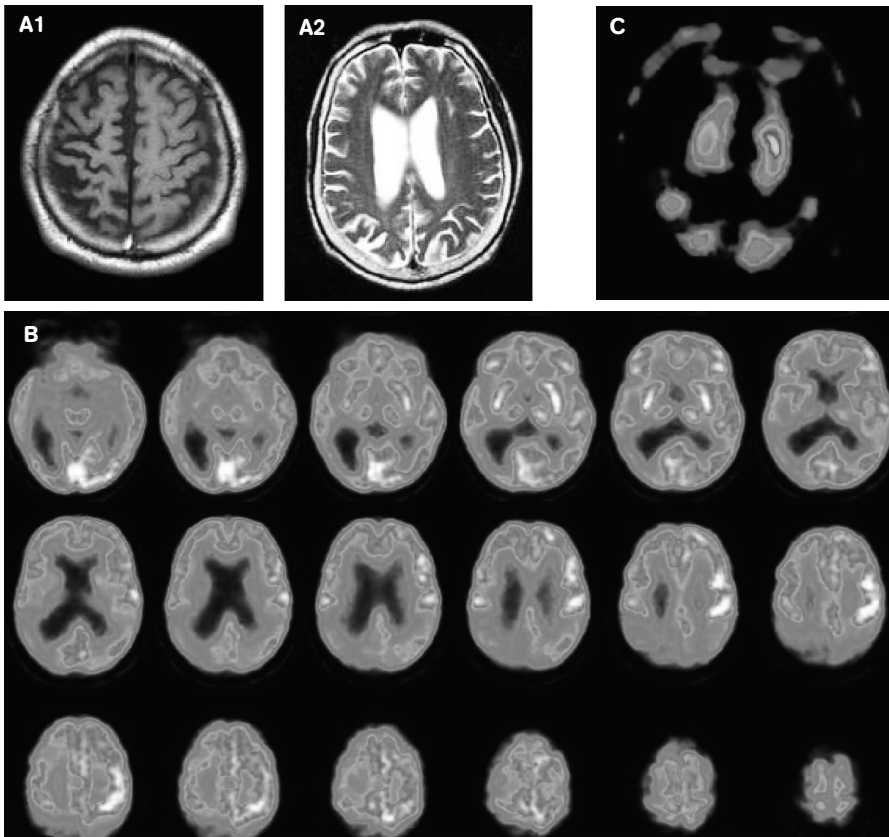
The current patients all presented asymmetric akinetic-rigid syndrome with higher cortical dysfunctions, which are consistent with the clinical diagnosis of CBD. It is not always straightforward to differentiate CBD from the other Pick complex, such as frontotemporal dementia, primary progressive aphasia, and progressive supranuclear palsy (PSP), because there are significant overlaps of clinical and pathological manifestations among these diseases<sup>(27)</sup>. The current concept is that the clinical syndrome of prominent apraxia, unilateral extrapyramidal syndrome, and alien hand phenomenon should be designated as CBD syndrome regardless of the pathology<sup>(28)</sup>. Those patients with vertical gaze palsy, axial dystonia, falls, or bilateral rigidity would be considered as typical cases of PSP<sup>(29)</sup>. We did not document



**Figure 2.** The surface electromyography recorded in Patient 2 (A), Patient 3 (B) and Patient 4 (C). Intermittent short-duration EMG bursts were noted in the three patients. The EMG duration ranged from 30 ms to 100 ms and the frequency ranged from 5 to 12 Hz with individual variations. Patient 2 and Patient 3 (A and B) were recorded in the left first dorsal interosseous muscle and Patient 4 (C) in the right abductor pollicis brevis muscle.



**Figure 3.** The EEG recordings of jerk-locked back average in Patient 2. The whole epoch period was 120 ms and the vertical dash marked the burst onset in EMG (left EDC muscle). Over 60 artifact-free epochs were averaged. There were no notable jerk-locked cortical potentials.



**Figure 4.** (A) Asymmetric cortical atrophy in the right hemisphere of Patient 2 (A1, T1WI) and Patient 3 (A2, T2WI) in conventional brain MRI. (B) [ $^{99m}\text{Tc}$ ]HMPAO SPECT image in Patient 3. Regional hypoperfusion was noted in the right temporoparietal area and right thalamus. (C) [ $^{99m}\text{Tc}$ ]TRODAT-1 image in Patient 2. Evident decrease of uptake was noted in the right striatum.

any limitation of voluntary eye movement in all of the four patients. The mean age of onset of the symptoms in our patients was  $63.3 \pm 8.6$  years, which is similar to the previous reports<sup>(2,3,5)</sup>. A major complaint in our patients was “hand clumsiness” in the affected limb, but the manifestation was quite different from the “clumsiness” caused by muscle weakness. In fact, we could not detect pyramidal signs in any of the four patients. By contrast, hand apraxia is a constant and distinctive sign. CBD patients usually present a type of apraxia known as “limb-kinetic apraxia” which is more evident distally than proximally and is most notable for incoordination between fingers<sup>(30)</sup>. To detect limb-kinetic apraxia in CBD is sometimes difficult, because it is not always easy to differentiate this apraxia from the clumsiness caused by rigidity, bradykinesia and dystonia<sup>(3,30)</sup>. The underlying pathophysiology of the apraxia remains unclear. A case study reported that the features of the apraxia are markedly different from those associated

with lesions in the left parietal lobe<sup>(31)</sup>. One possibility is that lesions affecting the globus pallidus and the supplementary motor area (SMA) pathway might contribute to the apraxia<sup>(32,33)</sup>. By applying TMS, the silent period was significantly shorter in the apraxic limb of the CBD patients<sup>(26,34)</sup>. Leiguarda et al. suggested that disruption of the frontoparietal circuit and defective cortical inhibition might contribute to this manifestation. The result from paired TMS studies also supported this hypothesis<sup>(20)</sup>.

The alien limb behavior is present only in the patients with ideomotor apraxia<sup>(33)</sup>. Our finding in the current study supported this observation. Two patients (Patient 1 and 3) with severe apraxia showed prominent alien limb phenomenon. A prevalence rate of ~50% is also similar to the literatures reported<sup>(2,5)</sup>. Three varieties of alien hand syndrome (AHS) have been reported, including lesions of the corpus callosum alone, of the corpus callosum plus dominant medial frontal cortex, and of the posterior cortical or subcortical areas<sup>(35)</sup>. The

first two are characterized by intermanual conflict and compulsive manipulation of tools, respectively<sup>(36)</sup>. In the current two patients with AHS, we find no signs of intermanual conflict or compulsive manipulation clinically, nor any lesions in the corpus callosum by MRI. By contrast, hemispatial neglect with variable degrees of hand sensory ataxia was noted in our patients. The presentations were compatible with the “posterior AHS”, which may occur without involvement of the corpus callosum<sup>(35,37)</sup>. Some investigators assumed that a distorted body scheme caused by a disrupted integration of somatosensory input is a possible mechanism underlying the “posterior AHS”<sup>(35,38)</sup>. Although the pathogenesis of AHS in patients with CBD remains unclear and highly speculative<sup>(38)</sup>, it is intriguing to note that the two patients with alien limb phenomenon had less severe rigidity. This might imply that AHS and rigidity involve conflicting contributory factors. The gender ratio of the development of alien limb phenomenon is also interesting. In the current study, the two patients with AHS are women. Whether gender plays a role in the occurrence of alien limb behavior in CBD needs more observations to draw a conclusion.

All of the current patients exhibited unilateral hand dystonia with rigidity and bradykinesia. Limb dystonia was reported to happen in 43% to 83% CBD cases<sup>(3)</sup>. Typical dystonic posture of the involved hand is characterized by flexion of the metacarpophalangeal joints and extension or flexion of the proximal interphalangeal and distal interphalangeal joints. As the disease advanced, the patient may develop more rigid postures. It is not clear why the dystonic posture would be so frequently observed in CBD. Since the corticostriatal connections have been proved to be topographically organized<sup>(39)</sup>, a damage of the vulnerable hand area in the cortex or basal ganglia of the patients with CBD might contribute to the dystonic posture.

The myoclonus found in the current patients is a type of action and reflex myoclonus, which is usually induced by sensory stimulation of the affected limb. The cortical SEPs are not enlarged as that in cortical reflex myoclonus, and backaveraged cortical potentials do not precede each myoclonic jerk<sup>(26,40,41)</sup>. Clinical and imaging

evidence suggested that the localized parietal cortical damage is a pivotal factor for the absence of a giant SEP in these patients with CBD<sup>(42)</sup>. In the CBD patients with myoclonus, facilitation of long latency reflexes (LLR) could be noted in the myoclonic arm<sup>(41,43)</sup>. An alternation of inhibitory and excitatory balance at the level of cortical neurons, particularly enhanced cortical excitability, may be induced due to the pathology of CBD and play an important role in the generation of myoclonus<sup>(40,41)</sup>. Strafella et al. have furthermore proposed three possibilities to explain the abnormal cortical excitability, namely loss of inhibitory neurons in the cortex or thalamus, effect of morphologic changes in cortical neurons, and effect of gliosis<sup>(44)</sup>.

The abnormal findings in conventional MRI in CBD patients are usually subtle and are not specific. These may include ventricular enlargement, asymmetrical cortical atrophy, and increased T2-weighted lenticular signal hypointensity<sup>(45)</sup>. Hyperintense lesion in the primary motor area contralateral to the affected side has been reported in two patients by T2-weighted imaging<sup>(46)</sup>. We can only find asymmetrical cortical atrophy and slight ventricular enlargement in three of the current patients. Consistent with previous reports<sup>(26,47)</sup>, the SPECT study here also showed decreased regional cerebral blood flow in the frontoparietal areas and thalamus opposite to the (more severely) affected limb. Those with dementia may show relatively reduced regional cerebral blood flow in the inferior prefrontal region in the more severely affected hemisphere<sup>(4)</sup>. The findings of [<sup>99m</sup>Tc]TRODAT-1 SPECT image in the current study were in general similar to those in the previous report<sup>(24)</sup>, strongly supporting the clinical diagnosis of CBD. In positron emission tomography (PET), a pattern of increased microglial activation in cortical regions and the basal ganglia has been documented in CBD patients<sup>(21)</sup>. The progress in functional imaging technique may advance our understanding of CBD in either the diagnostic or the pathophysiological domain.

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