

muscle is involved.<sup>7</sup> Third, the discharge frequency of the EMG activity during the involuntary contractions was 40 to 50 Hz. Discharge rates in cramps are typically around 150 Hz.<sup>6</sup> Last but not least, our polymyographic recordings showed that massive electric muscle activity was not limited to one muscle. It extended over different leg muscles, even more or less simultaneously in both legs. The latter directed us to consider this mass activity as muscle spasms.

As already stated, spasms are ill defined.<sup>10</sup> That there were no clinical signs of pyramidal tract lesion provides an important argument that the involuntary painful contractions in this patient are not "conventional" spasms. In healthy subjects, motor units usually fire at 6 to 10 Hz when first recruited and at 15 to 60 Hz during maximal voluntary contractions.<sup>15</sup> Thomas and Ross showed with needle EMG studies of motor unit activity in patients after spinal cord injury that, during spasms, the motor unit firing frequencies show mean peak firing rates of  $18 \pm 9$  Hz.<sup>12</sup> Rate coding for many motor units appears to be similar whether descending motor input is intact or whether it has been reduced severely by spinal cord injury.

In 1978, Satoyoshi already described that, during the involuntary contractions in his patients, needle EMG recordings revealed synchronized motor unit discharges of 40 to 50 Hz and of 4 to 10 mV amplitude. He suggested that abnormal discharge of anterior horn cells is responsible for the mass activity.<sup>1</sup> The HD-sEMG recordings showed a stable spatial extension of such synchronized activity throughout the vastus lateralis muscle during the contractions. This finding supports and provides additional arguments for this hypothesis of massive hyperactivity or disinhibition at the alpha motor neuron level. In conclusion, although a more proximal origin cannot be excluded, the surface EMG findings strongly suggest a deregulation at the alpha motor neuron level leading to involuntary muscle contractions in Satoyoshi syndrome.

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## Alzheimer's Disease Presenting as Corticobasal Syndrome

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Video



**Abstract:** A 60-year-old man presented with slowly progressive left hemi-Parkinsonism, left hand apraxia, myoclonus, dystonia, visuospatial disturbances, and alien limb phenomenon, resembling corticobasal syndrome. Eight years later,

This article includes Supplementary Video, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat>

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**neuropathology revealed features of Alzheimer's disease, with asymmetrical (right more than left) cortical tau burden with image analysis. The videotaped clinical features, neuropsychological aspects, and neuropathological correlates are presented and discussed.** © 2006 Movement Disorder Society

**Key words:** Alzheimer's disease; corticobasal degeneration; corticobasal syndrome; myoclonus; alien limb phenomenon; neuropathology

Alzheimer's disease (AD) is the most common form of primary degenerative dementia and is characterized by a progressive amnesic disorder with subsequent involvement of other cognitive functions and personality alterations. However, AD can present with various other clinical profiles of a focal cortical degenerative syndrome with features dependent on the areas of the brain affected. Some of these syndromes include progressive aphasia, apraxia, visuospatial disturbances, and motor disturbances.<sup>1</sup> Motor disturbances in the form of Parkinsonism (i.e., bradykinesia, rigidity, postural instability, and abnormal gait) and myoclonus are well documented in AD, and their occurrence correlates with the disease duration and progression as well as with the functional and cognitive decline.<sup>1</sup> Corticobasal degeneration (CBD) is a disease with slowly progressive cognitive and motor disturbances that classically has been described to present in the sixth to seventh decade of life with an asymmetrical akinetic-rigid syndrome, myoclonus, and apraxic limb (held in a fixed dystonic position resembling the alien limb phenomenon).<sup>2</sup> Due to considerable overlap in the clinical phenotypes between CBD and other neurodegenerative disorders, such as progressive supranuclear palsy (PSP), and frontotemporal dementia (FTD), and the various underlying pathologies presenting with the classic clinical phenotype, there is a view that patients with this phenotype should be diagnosed as having corticobasal syndrome (CBS) and that neuropathology should be the only criteria to make a definitive diagnosis of CBD.<sup>2</sup>

There have been a few reports of patients with a CBS presentation who turned out to have AD at postmortem examination.<sup>3-5</sup> We present the video and clinical profiles, neuropsychological evaluation, and neuropathological features of a patient who presented with CBS and postmortem asymmetrical AD pathological involvement.

### CASE REPORT

A 60-year-old, right-handed male high school teacher presented with slow loss of function in his left arm. Initial evaluation by a neurologist documented a left

hemi-Parkinsonism and a left upper extremity myoclonus. His family history revealed that his mother had a 3-year history of dementia and died at 83 years of age. Brain computed tomography and magnetic resonance image (MRI) scans were normal for his age. During the first year, the patient noted progressive difficulties in dressing, reading a map, mental slowness, writing, and recognizing where his left hand was in space. A neuropsychological evaluation revealed mild deficits in attention, complex reasoning, visual perception, and visual constructive skills, as well as moderate to severe visual memory impairment. His performance and full-scale IQ scores were considered below expectation given his premorbid functioning (Table 1; Year 1). Three years after symptom onset, the patient was examined for the first time at the National Institutes of Health (NIH). He was alert and oriented with immediate memory 3/3, delayed recall 2/3, ability to follow three-step commands and anomia with a good interpretation of proverbs and social situations. He had left visual field neglect, left ideomotor apraxia, and an alien limb phenomenon manifested as intermanual conflict and inability to differentiate his limb from the examiner's limb. Cranial nerves were normal. He had bilateral bradykinesia and rigidity, more evident on the left; stooped posture; and decreased associated movements when walking. He had a left upper extremity and occasionally right upper extremity action and stimulus sensitive myoclonus. There was a left pronator drift and a positive left Babinski sign. There was a palmo-mental reflex, but no grasp or snout. MRI of the brain showed asymmetrical cerebral cortical and subcortical atrophy, more pronounced on the right (Fig. 1). An electroencephalogram (EEG) showed mild background disorganization but no focal abnormalities or periodic discharges. The sensory evoked potentials confirmed the presence of cortical originated myoclonic movements. Neuropsychological tests showed impairment in multiple cognitive domains consistent with mild dementia (Table 1; Year 3). He was markedly impaired on the Benton Visual Form Discrimination and Judgment of Line Orientation Tests. His drawings were remarkable for their dramatic neglect of the left visual hemi-field. Five years from symptom onset, he started to drag his left foot and myoclonus spread to all extremities. His posture became more stooped, and he required assistance for activities of daily living. On examination, the degree of his cognitive impairment and aphasia had worsened (Table 1; Year 5). He showed a bilateral ideomotor apraxia, more evident on the left, for both transitive and intransitive actions. He had a dystonic posturing of the left hand and difficulty in finding and controlling the left hand that seemed to move on its own (see video Segment 1, alien limb phenome-

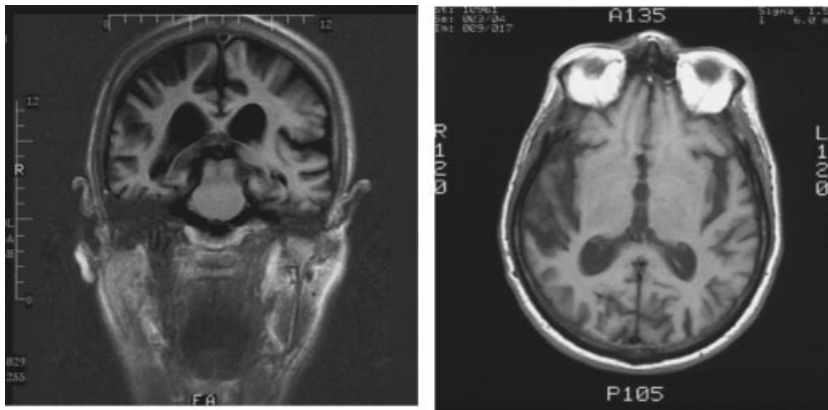
**TABLE 1.** Neuropsychological evaluation

Neuropsychological test	Year 1 evaluation	Year 3 evaluation	Year 5 evaluation
Wechsler Adult Intelligence Scale-Revised			
Score (Percentile)			
Full Scale IQ	96 <sup>a</sup> (40)	80 (9)	Untestable
Verbal IQ	113 (81)	94 (34)	76 (5)
Information		11	7
Digit Span		5	2
Vocabulary		11	9
Arithmetic		5	2
Comprehension		12	10
Similarities		10	7
Performance IQ	78 (7)	61 (1)	Untestable
Picture Completion		4	
Picture Arrangement		2	
Block Design		2	
Object Assembly		2	
Digit Symbol		1	
Wechsler Memory Scale-Revised Raw			
Score (Percentile)			
General Memory Index		<50	Untestable
Delayed Recall		81	
Digit Span Forward		4 (<5%)	
Visual Memory Span Forward		1 (<1%)	
Visual memory Span Backward		1 (<1%)	
Logical Memory I		8 (<3%)	
Logical memory II		7 (<9%)	
Visual reproduction I		10 (2%)	
Visual reproduction II		17 (17%)	
Mattis Dementia Rating Scale			
Total Raw Score		118	71
Attention		30	25
Initiation/Perseveration		31	14
Construction		3	0
Conceptualization		37	26
Memory		17	6
Benton Judgment of Line Orientation		25/60	
Benton Facial Recognition Test		35/54 (<37)	Untestable
Benton Visual Form Discrimination		6/16	6/16
Western Aphasia Battery			60/100

<sup>a</sup>A premorbid-full scale IQ of 116/117 was estimated, based on familiarity with terms and concepts and demographic variables. Untestable: Test was attempted but discontinued due to multiple errors.

non). He also showed a stimulus-sensitive myoclonus (see video Segment 1). Seven years after symptom onset, he developed severe difficulties ambulating and eventu-

ally became bedridden; his left arm became severely dystonic and contracted. His speech became almost incomprehensible, and he was mute a few months before



**FIG. 1.** Coronal and axial T1-weighted sequence of magnetic resonance imaging scan of the brain, showing diffuse cerebral atrophy and ventriculomegaly, being more prominent on the right fronto-temporo-parietal area.

**TABLE 2.** Neuropathology: lesion counts of senile plaques and neurofibrillary tangles in cerebral cortical sections

Area	Senile plaques		Neurofibrillary tangles		Amyloid angiopathy	
	Left	Right	Left	Right	Left	Right
Frontal	50	50	9.5	11.5	3	3
Temporal	50	50	8	16.5	0	1
Parietal	50	50	2.5	11	0	2
CA4	11.5	12	5	4.5		
CA2	1	6.5	13.5	14		
Subiculum	19	40	11.5	27.5		
Entorhinal cortex	20.5	41	19.5	22		

The tau burden was based upon image analysis of PHF-1 immunostained sections. The regions studied were from the superior frontal and superior parietal sections. The thickness was 5 microns. The fields were chosen at random in the region of interest, and the analysis was performed blinded to side. The senile plaques were counted and counts truncated at 50, because this is more than twice the maximum needed for the Khachaturian criteria for AD. The senile plaques were frequently neuritic in type with dense amyloid cores. Amyloid angiopathy was noted in the frontal section and was scored by a three-point system as mild, moderate, or severe, based upon the density of affected vessels in the leptomeninges and parenchyma.

his death. Laboratory studies were always normal. He died at age 68, 8 years after initial symptom onset.

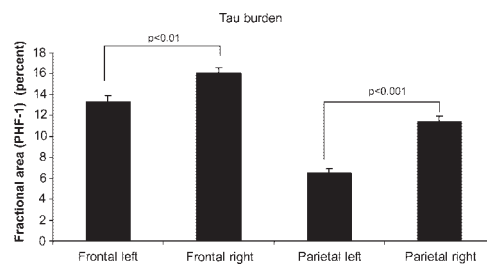
### Neuropathology

The brain weighed 1,225 grams and displayed moderate atrophy in the frontal, parietal, and superior temporal lobes. Minimal atherosclerosis was apparent in the arteries of the circle of Willis and their major branches. Microscopic sections of the neocortex, hippocampus, basal ganglia, midbrain, pons, medulla, and cerebellum were examined with hematoxylin and eosin (H&E), thioflavin-S fluorescent microscopy and all sections were immunostained with tau antibodies (PHF-1) by standard methods.<sup>6</sup> The neocortex on H&E stain displayed neuronal loss, slight vacuolar change in the upper cortical layers and gliosis. With thioflavin-S stains, many senile plaques (SP) and neurofibrillary tangles (NFT) were noted. Lesion counts are shown in Table 2. The tau immunostaining showed extensive NFTs in the neocortex, including the primary visual cortex, and was thus consistent with “Braak stage VI.”<sup>7</sup> Patchy neuronal loss in Sommer’s sector with NFT in residual neurons, SP in the pyramidal cell and molecular layers of the dentate fascia, and granulovacuolar degeneration or Hirano bodies were seen in the hippocampus, but there was no hippocampal sclerosis. The entorhinal cortex had loss of neurons in layer II with many NFT and SP (15–26 per 10× field). NFT were present in both layer II (14–25 per 40× field) and the deeper cortical layers (10–12 per 40× field). The NFT lesion counts in the various cortical sections (Fig. 2) showed a significantly greater increased right side involvement in CA1 ( $P < 0.004$ ) and subicu-

lum of the hippocampal sectors ( $P < 0.003$ ) and the right temporal ( $P < 0.048$ ) and parietal ( $P < 0.008$ ) areas (Mann–Whitney rank sum test). However, the counts were not adjusted for atrophy.

The case met the Consortium to Establish a Registry for AD (CERAD) and NIA-Reagan criteria for “definite” and “high likelihood AD,” respectively. The tau stains showed Alzheimer’s type NFT in the expected distribution, but no evidence of ballooned neurons, astrocytic plaques, or tau immunoreactivity in the white matter, lower brainstem, or cerebellum, which are hallmarks of CBD.<sup>8,9</sup>

The basal nucleus of Meynert was not available for study, but the diagonal band of Broca had only a few



**FIG. 2.** Tau burden in frontal and parietal lobes with image analysis. Sections from frontal and parietal cortices of right and left sides were immunostained with a monoclonal antibody to tau (PHF-1). Thirty nonoverlapping microscopic fields were photographed from each section, and the burden of tau immunoreactivity was determined from each captured image using image analysis software (SigmaScan Plus). The proportion of the area occupied by tau-immunoreactive neurons and neuronal processes ranged from 2.7% to 22.7%. The tau burden was significantly greater in frontal than parietal lobes for both sides. There was a significantly greater tau burden in both frontal and parietal lobes on the right compared with the left.



NFT. The basal ganglia had many non-neuritic SP and Alzheimer's type II astrocytes. There were a few NFT in the striatum, substantia nigra, dorsal raphe, and tectum, but no significant neuronal loss or Lewy bodies. The locus ceruleus and the central raphe had NFT. The lower brainstem and brainstem fiber tracts were unremarkable, except for scattered NFT in the reticular formation. The cerebellum had unremarkable Purkinje and internal granular cell layers, no NFT, and many diffuse amyloid plaques.

### DISCUSSION

The clinical CBS presentation in this case of an alien left hand phenomenon, cortical myoclonus, Parkinsonism, bilateral parietal lobe dysfunction, and apraxia with preserved initial language skills was highly suggestive of CBD, but at autopsy, 8 years after symptom onset, the pathology was that of AD together with some scattered ballooned pale neurons in the cerebral cortex. The CBS-like presentation in AD is rare,<sup>4,5</sup> and the alien limb phenomenon has been reported only once before in AD<sup>3</sup> and is an illustration of the clinical heterogeneity that may occur in AD. In retrospect, the early marked impairment of memory is unusual for CBD and should raise the suspicion of AD with an atypical presentation. Our patient showed the characteristic findings reported in the neuropsychological testing in CBD such as asymmetrical limb apraxia (usually ideomotor), constructional and visuospatial difficulties, acalculia, a dys-executive syndrome, and a nonfluent aphasia.<sup>10</sup> He showed impairment in multiple cognitive domains consistent with a mild dementia.

Quantitative comparative neuropathologic studies showed a predominance of lesions in the right frontoparietal region that could correlate with the signs of apraxia, visual neglect, and alien limb phenomenon on his left side. The tau stains showed AD-type NFT in the expected distribution, but no evidence of the hallmarks of CBD.<sup>9</sup> The SP and NFT found in the striatum, substantia nigra, dorsal raphe, and even the midbrain tectum are known to occur in advanced AD and are likely to have contributed to the clinical signs of dystonia, Parkinsonism, and myoclonus in our patient, leading to the CBS phenotype. It is interesting to note that AD and CBD are now classified as tauopathies—as the main proteinaceous component of NFTs is the abnormally phosphorylated microtubule associated protein tau. The extent to which the molecular structure of the tau aggregates varies in these diseases is just beginning to be understood. Although the characteristic tau abnormality and the sites of lesions vary among the tauopathies, there may be considerable overlap in the clinical signs between them. One possible explanation for this clinical diversity may be that the clinical profile is related to the

location of the tau neuropathology, which may vary among patients with the same tauopathy as exemplified in the present case. Except for this patient's mother, there were no other family members with a clinical diagnosis of AD. Further research is needed to better understand the reasons for the various underlying pathologic CBS presentations and the diverse clinical AD phenotypic presentations.

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### LEGEND TO THE VIDEO

The videotape shows the patient executing a series of commands first with the right hand and then with the left hand: (1) bang a gavel, (2) saw a board, (3) stir a gallon of paint, (4) snap fingers, (5) dial a phone, and (6) tap a telegraph. During the execution of these commands, the patient displays considerable intermanual conflict, ideomotor apraxia, and action myoclonus. The left hand is held in a dystonic posture. Despite the dystonia, he is able to execute some commands, such as tapping a telegraph, but he is unable to perform others, such as dial a phone or stir paint. He is unable to snap fingers with the left hand and says that he cannot find his hand (alien limb phenomenon).

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