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Report of Three Cases of Alzheimer's Disease with Focal Motor Symptoms: Clinical Correlates of Neuroimaging Findings

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Summary

We report clinical and neuroimaging findings for three patients suffering from Alzheimer's disease (AD) with focal motor symptoms. These patients initially showed cognitive deficits and subsequently featured myoclonus and awkward movements in the unilateral upper limb while progressing to paresis. Paresis was noted in the unilateral upper limb. All patients held the unilateral arm flexed at the wrist and elbow, closely adducted to the body and the hand fisted and pronated. No signs of cerebellar ataxia, sensory disturbance or long tract signs were observed, nor any of the initial non-cognitive behavioural changes typical of frontotemporal dementia. EEGs of these patients showed marked slowing of basic activity without epileptic discharges. MRIs showed progressive brain atrophy in the contralateral frontoparietal lobes as well as the hippocampal formation. Cases 2 and 3 featured extensive long T2 lesions on MRI. ^{99m}Tc-HMPAO-SPECT revealed blood flow hypoperfusion in the corresponding regions. The cerebellum and brain stem showed neither morphological abnormalities nor blood flow hypoperfusion. On the basis of these clinical and neuroimaging observations, the focal motor symptoms were attributed to contralateral frontoparietal cortical atrophy with or without white matter lesion.

Key words: Alzheimer's disease, myoclonus, hemiparesis, neuroimaging, SPECT.

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Introduction

Alzheimer's disease (AD) starts with cognitive disturbance in the absence of any apparent neurological deficits. The symptoms and signs then progress, including disorientation as to time and place, profound memory disturbance, lexical anomia, visuospatial disturbance and constructional apraxia. Pathological substrates for AD are neurofibrillary tangles (NFT) and senile plaques in the cerebral cortex. In neuropathological terms, Braak and Braak (1991) established a sequence of AD-related changes in which NFT start in the entorhinal cortex, then spread to the cornu ammonis and subiculum, and finally to the cerebral association cortex. NFT develop extensively with the progression of the illness, so that brain atrophy can be observed on MRI or CT in parallel with this pathological progression (De Leon et al 1989, 1993; Lehericy et al 1995). The symptomatology, pathological findings and clinical course of AD are otherwise heterogeneous (Schuttleworth 1989; Chui et al 1985; Mayeux et al 1985; Klatka et al 1996). Many case studies have described focal symptoms in individuals with relatively mild cognitive impairment, which have been designated as focal variants of AD (Mayeux et al 1985).

These focal variants of AD include posterior cortical atrophy (Benson et al 1988; Aharon-Peretz et al 1999), progressive aphasia (Pogacar et al 1984), progressive apraxia (Crystal et al 1982; Kaida et al 1998) and progressive hemiparesis (Jagust et al 1990). Jagust et al (1990) first reported a demented patient who initially featured myoclonus and clumsiness that progressed to paresis of the left upper limb. Autopsy revealed focal accentuation of NFT in the right perirolandic somatosensory cortex and hippocampal Alzheimer changes. This case was given the name "focal AD". Subsequently Golaz et al (1992) reported an autopsied case with focal accentuation of NFT in the primary motor cortex. These two cases exhibited unusual localisation of Alzheimer-related changes in the cerebral cortex. It thus appears that AD patients

with focal motor symptoms are extremely rare, and neuroimaging of focal AD has not been fully explored.

In the study presented here, we report on the clinical features and neuroimaging studies of three AD patients who showed initial myoclonus and limb apraxia and subsequent paresis of the unilateral upper limb.

Patients and methods

We could examine three AD patients who were subjected to neurological, psychiatric and neuropsychological examination. Cognitive disturbance was evaluated with Mini-mental status examination (MMSE). Diagnosis of AD was confirmed by the presence of clinical features relevant to NINCDS-ADRDA criteria (McKhann et al 1984). Regional cerebral blood flow was examined with ^{99m}Tc -HMPAO-SPECT study, and brain morphology was studied with MRI and CT.

Case reports

Case 1

A 63-year-old, right-handed man noticed forgetfulness at age 57. There was no family history of psychiatric or neurological illness. His cognitive decline developed insidiously until he could no longer pass on any information, and he retired from his work at age 59. Neurological examination disclosed memory disturbance and MRI showed predominant right hemispheric cerebral atrophy. Memory disturbance progressed gradually, and at age 60 he became aware of clumsiness of his left upper extremity, which led to inability to control it, so that he frequently bumped his left hand against surrounding objects. In conjunction with the gradual worsening of his motor signs, he sometimes could not recognise his family members. He was admitted to our clinic at age 63. He was almost totally disorientated and delayed recall was particularly impaired. He

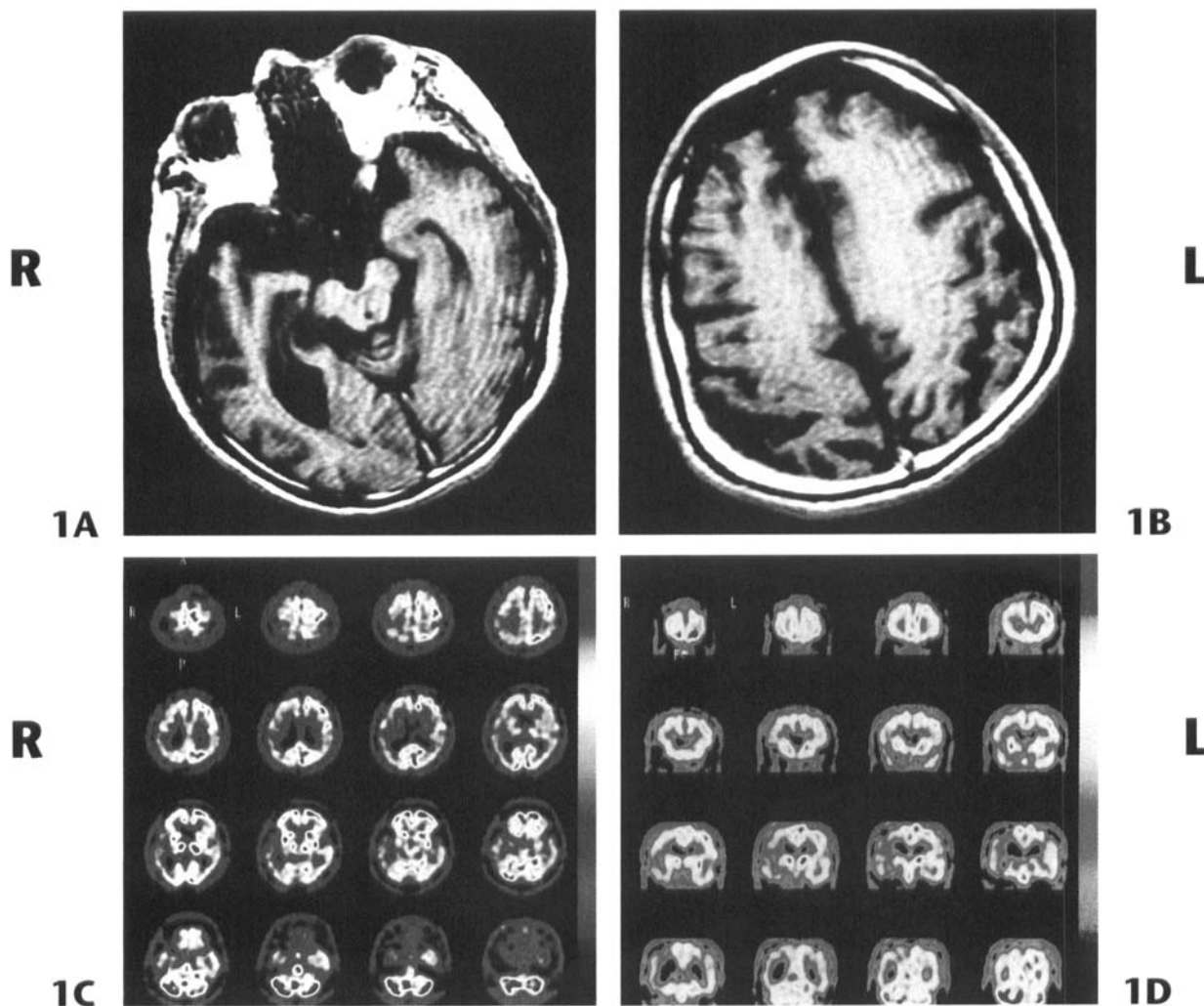


Figure 1

MRI of Case 1 shows atrophy of the cornu ammonis and parahippocampal gyrus with right-sided predominance (1A) and marked atrophy of the parietal lobe (1B). ^{99m}Tc -HMPAO-SPECT findings of the horizontal (1C) and coronal (1D) planes show marked blood flow hypoperfusion in the frontal and parietal lobes with right-sided predominance.

scored 10 on the MMSE and 4 on Hachinski's test. He appeared slightly euphoric and was unaware of his intellectual decline. His left upper extremity manifested arrhythmic myoclonic movements that were provoked easily by stimulation involving hand and elbow joints. He had severe limb apraxia predominantly in his left hand, which appeared slightly paretic. He could not imitate simple finger positions presented by examiners. He showed signs of transcortical sensory aphasia and had difficulty in naming objects. Ocular movements were not impaired but saccades were not smooth. No eyelid apraxia or palatal myoclonus was observed. Deep tendon reflexes were brisk on the left side and his left upper and lower extremities were rigid. Primitive reflexes could be elicited on both sides, but pyramidal tract signs were absent. Sensory disturbance of the limbs was absent, and ataxia was not observed. Cerebral MRI revealed widening of the sylvian fissure, atrophy of the prefrontal and parietal lobe and parahippocampal gyrus (Figure 1A-1B) with right-sided predominance. The ^{99m}Tc-HMPAO-SPECT study revealed a marked blood flow reduction in the right frontoparietal lobe (Figure 1C-1D). The apolipoprotein E (APOE) genotype was e3/e3.

Case 2

A 70-year-old, left-handed woman had begun to experience mnemonic failure at age 56. She had run a kindergarten until she was 57 years old, at which time she could no longer deal with her business because of her memory disturbance. She consulted a neurologist at age 58. Cerebral CT showed brain atrophy and she was diagnosed as AD. Subsequently she began to complain of inability to control her right hand at age 65, and she was hospitalised at age 67. At admission, arrhythmic myoclonic movements that were easily provoked by any stimuli were observed in her right upper limb. Her mental symptoms progressed with signs of severe aggression, and she frequently uttered strange sounds both during the day and at night. At age 68 she was holding her right arm flexed at the wrist and elbow, closely adducted to her body with the hand fistled and pronated. Muscle atrophy was absent, but right upper limb was spastic, and deep tendon reflexes were brisker on the right side. Babinski's sign could not be elicited. The ^{99m}Tc-HMPAO-SPECT study revealed marked blood flow reduction in the left frontoparietal lobe (Figures 2A and 2B), although the cerebellar blood flow remained normal. MRI showed

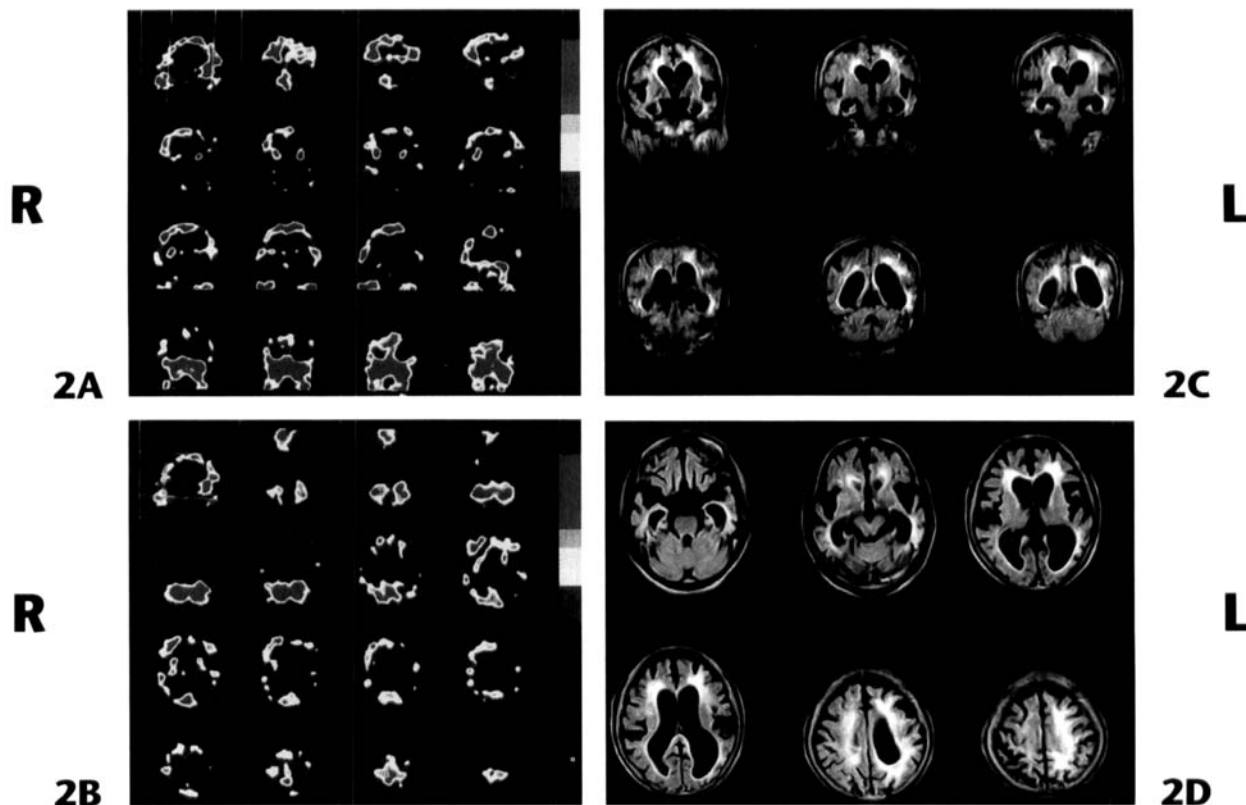
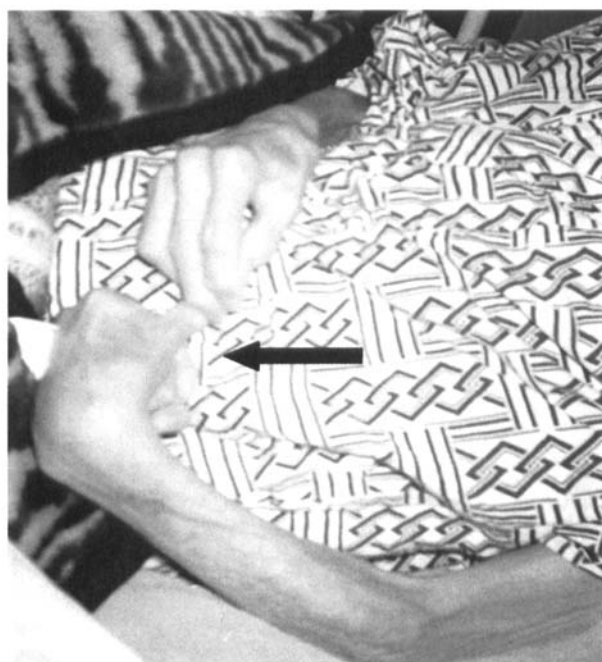


Figure 2 ^{99m}Tc-HMPAO-SPECT of the coronal (2A) and horizontal (2B) planes showing marked reduction in blood flow in the frontal and parietal lobes with left-sided predominance. MRI of coronal (2C) and horizontal (2D) sections show dilatation of the lateral ventricle with left-sided predominance, severe atrophy of the bilateral hippocampus and extensive T2 hyperintensity covering the cerebral white matter. The left parietal lobe features marked dilatation of the lateral ventricle, which is surrounded by a hyperintensity lesion.

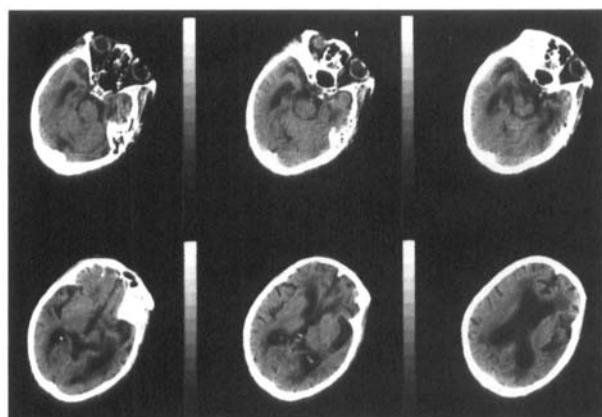
progressive cerebral atrophy, especially in the left frontal and parietal lobes and bilateral hippocampal formation. On T2-weighted images, high intensity areas were seen to cover all of the cerebral white matter particularly of the left frontoparietal lobes (Figures 2C and 2D). The APOE genotype was e4/e4. She was treated with oral risperidone administration that was effective to her behavioural changes.

Case 3

A 73-year-old woman began to show mnemonic failure at age 67 and consulted a psychiatrist. She had been in good health and working actively managing a store together with her husband. Her intellectual ability declined slowly leading to



3A



R

3B

L

Figure 3

The left upper limb indicated by arrow, showing flexor posture at the wrist and elbow joints (3A). Horizontal section of the CT (3B) showing hippocampal atrophy marked on the right side accompanied by periventricular low density.

complete disorientation. She began to show aggressive tendencies at age 70 and was hospitalised at age 71. At admission she scored 10 on MMSE and was neurologically normal. She showed dysfunction in naming objects and could repeat sentences. But she gradually lost the ability to control her left hand until she could not even hold a spoon. Deft movements of her left hand were impaired and she could not imitate several finger positions. She sometimes became psychotic, showing abnormal emotional changes and delusions. Her left hand became gradually paretic with showing flexor posture at the wrist and elbow joints (Figure 3A). The interosseous muscles of her hand were slightly atrophic but the nerve conduction velocity was normal. Cerebral CT showed atrophy of the hippocampal formation with right-sided predominance (Figure 3B) and T2-weighted MRI disclosed hyperintensity areas covering the white matter of the frontoparietal lobe.

Discussion

We described three rare cases of AD with initial cognitive impairment followed by focal motor signs, including myoclonus, apraxia and paresis of the unilateral upper extremity. The diagnosis of these patients meets the criteria for "probable AD" as set forth in NINCDS/ADRDA (McKhann et al 1984) and DSM-IV (American Psychiatric Association 1994) because progressive cognitive and neuropsychological deficits are compatible with AD. Klatka et al (1996) reported signs and symptoms incompatible with a diagnosis of early AD. They include tremors at rest, cogwheel muscle rigidity, long tract signs at the initial stage, ocular movement disturbance, cerebellar signs and initial non-cognitive behavioural change. Our cases lacked these clinical features, and MRI or CT revealed the progressive atrophy of the hippocampal formation related to AD (De Leon et al 1989, 1993; Fox et al 1996; Golebiowski et al 1999). Cerebral white matter lesions were noted in periventricular and deep white matter in Case 2 and 3, but they were not white matter lacunae. These white matter changes raise a possibility of cerebral infarcts combined with AD. Extensive white matter lesions have been frequently reported in AD patients with severe symptomatology (O'Brien et al 1996). These white matter lesions histologically consist of a cluster of perivascular small infarcts and/or secondary degeneration from cortical Alzheimer changes (Englund et al 1988; Englund 1998). Particularly, localised edema due to cerebrospinal fluid infiltration into the white matter is causative of periventricular white matter changes (Tomimoto et al 1997). Therefore, white matter lesions in our cases may be partly of vascular origin. Massive cerebral infarcts cannot account for the insidiously and gradually developed motor deficits and clinical features in our cases did not fit well with diagnostic criteria of vascular dementia (Román et al 1993). The SPECT study showed hypoperfusion

of these atrophied lesions, which is contradictory to evidence that vascular dementia tends to show frontal lobe hypoperfusion (Ransmayr 1998). The EEGs showed generalised slowing of background activities without focal slowing.

Predominant focal motor signs characterise corticobasal degeneration (CBD), and dementia has been recently recognised in CBD, but it usually occurs late in the clinical course and the pathological substrate for the dementia remains unclear. In fact, even macroscopic hippocampal atrophy could not be identified in a demented CBD patient (Kobayashi et al 1999). For these reasons, our cases do not fit a diagnosis of CBD. A combination of dementia and myoclonus raises the possibility of Creutzfeldt-Jakob disease (CJD), but our cases show long-term degeneration and an absence of periodic synchronous discharge. These features are not compatible with CJD.

Occurrence of myoclonus prior to limb paresis and monoplegic manifestation was a characteristic finding in our cases. Monoplegia without muscle atrophy is due to cerebral cortical lesion (Adams and Victor 1993), while monoplegia caused by a localised cortical lesion, particularly of the upper motor neuron, is usually accompanied by spasticity, hyperreflexia and an extensor plantar reflex. The position of the unilateral upper limb observed in our patients may be helpful for the diagnosis because myoclonus has been generally regarded as a late clinical feature in AD and several studies describe myoclonic AD as a distinct subtype (Chen et al 1991; Chui et al 1985; Risse et al 1990; Clark et al 1991). The neuropathological correlates of myoclonus have not been precisely determined, however aminergic neuronal cell loss in the dorsal raphe nucleus (Ebinger et al 1987; Kaye et al 1988), high density of NFT (Feldman et al 1963; Duffy et al 1988) and imbalance of neuronal population in the dentate nucleus (Fukutani et al 1999) have all been speculatively identified as loci of myoclonus. Förstl et al (1992) reported a quantitative pathological study in which myoclonus showed significant association with higher NFT density in the frontal and parietal lobe, and our result show a good match with the result of this neuropathological study. However, it did not mention any cases with focal motor symptoms. The relationship between myoclonus and limb paresis thus remains unclear.

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