Spastic tetraplegia as an initial manifestation of familial Alzheimer's disease

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Abstract

Two sisters with familial Alzheimer's disease developed spastic gait disturbance as an initial manifestation. Their gait disturbance progressed gradually, followed by dementia a few years later. Post-mortem examination of one of the patients disclosed degeneration of the thalamus and corticospinal tract in addition to numerous senile plaques and neurofibrillary tangles in the neocortex, both of which were confirmed by immunohistochemistry. This is the first report in which clinicopathological evaluation is sufficient to establish a new variant of Alzheimer's disease presenting initially as spastic tetraplegia.

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Alzheimer's disease is a degenerative disorder of the brain characterised clinically by progressive dementia and pathologically by senile plaques and neurofibrillary tangles.^{1,2} Although some cases with unusual clinicopathological features have been classified as atypical Alzheimer's disease, such diagnoses are uncertain.^{3,4} We describe the clinicopathological findings in two siblings who developed progressive spastic tetraplegia followed by dementia. Immunohistochemical examinations confirmed the diagnosis of Alzheimer's disease.

Case reports

PATIENT 1 (III-5, FIG 1)

Patient 1 had non-consanguineous parents. Her history disclosed a fracture of the fifth lumbar vertebra in a traffic accident at the age of 51, and standard radical mastectomy for left breast cancer at the age of 58. Neither was associated with neurological sequelae. Her first neurological symptom was spastic gait disturbance at the age of 57. At the age of 60, memory impairment and decreased mental activities in daily life were noted. She also showed difficulty in dressing and using instruments of daily life due to spastic paresis in her upper limbs. Her spastic tetraplegia and dementia progressed gradually. At the age of 64, she became bedridden and showed frequent nocturnal delirium and emotional incontinence. On admission, she was alert but disoriented for time and place. She correctly named only two of 10 objects presented. She answered with only a single word to some simple questions. She could not repeat a short sentence. Her score on the Mini mental state scale was 4. Cranial nerves were normal except for mild dysarthria. Weakness, atrophy, postural tremor, hyperreflexia, and muscle contracture in all limbs, and bilateral Babinski's signs were noted. There was neither sensory deficit nor cerebellar signs. She was incontinent of urine and faeces. Blood, urine, and CSF examinations were unremarkable. An EEG showed a moderate degree of generalised slowing. An EMG and nerve conduction study were normal. Brain MRI showed moderate frontotemporal atrophy (fig 2A). Single photon emission computed tomography (SPECT) showed diffuse cerebral hypoperfusion. Cervical spinal cord MRI was unremarkable except for mild spinal canal stenosis. She was diagnosed as having atypical Alzheimer's disease. During the next six months her general condition deteriorated further with decubitus ulcers and pneumonia. At the age of 65, she died of empyema. The general necropsy showed empyema, multiple erosion of the gastric mucosa, atrophy of the pancreas, small stones in the bladder, myoma uteri, and an adenoma in the thyroid.

Gross neuropathology

The weight of the unfixed brain was 1030 g. The brain showed no abnormalities externally. Coronal sections of the cerebrum, cerebellum, and brainstem were unremarkable. Purulent pachymeningitis at the lumbar level was noted. Transverse sections of the spinal cord showed no abnormalities.

Figure 1 Family pedigree.

Figure 2 (A) Axial T1 weighted MRI of the brain of patient 1 showing moderate frontotemporal atrophy. (B) Plain CT of the brain of patient 2 showing the same distribution pattern of atrophy as in patient 1.

Figure 3 Numerous senile plaques and neurofibrillary tangles in the temporal cortex; methenamine-Bodian stain; magnification originally $\times 80$; bar = 50 μm .

Figure 4 Section of the medial nucleus of the thalamus showing severe astrocytic gliosis and neuronal loss; haematoxylin-eosin stain; magnification originally $\times 50$; bar = 50 μm .

Microscopic neuropathology

Numerous senile plaques and neurofibrillary tangles were found in the whole cortical grey matter, caudate nucleus, putamen, hippocampus, parahippocampus, and amygdala on methenamine-Bodian stain (fig 3). There were neurofibrillary tangles but no senile plaques in the locus coeruleus and neither in the substantia nigra. Numerous neuropil threads, diffuse plaques, ghost tangles, and amyloid angiopathy were also seen in the cerebrum. Some senile plaques contained degenerative neurites. There was no definite spongy change except patchy microspangiosis in the insula and motor cortex. In the thalamus, there were neither senile plaques nor neurofibrillary tangles. Severe astrocytic gliosis and neuronal loss had occurred in the medial part of the bilateral thalamus, especially the medial nucleus (fig 4). Neuronal loss in the cortical grey matter, amygdala, locus coeruleus, basal nucleus of Meynert, putamen, caudate nucleus, and hippocampus was mild. Neurons in the substantia nigra were preserved. The cerebral white matter was normal. There were no senile plaques or neurofibrillary tangles in the cerebellum. Betz cells of the motor cortex, the internal capsule, and pyramidal tract in the brainstem were preserved (fig 5A). Neuronal loss, mild astrocytic gliosis, and slight spongiform change, however, were found in the external granular layer of the motor cortex (fig 5B). The corticospinal tract showed pronounced symmetric pallor at all levels of the spinal cord (fig 6). A similar change was found in the bilateral anterior funiculus. Anterior horn cells were intact except for mild gliosis and some central chromatolysis.

To characterise senile plaques and neurofibrillary tangles, immunohistochemical studies using antibodies to amyloid β protein,⁵ human tau protein,⁶ and prion protein⁷ were performed as previously described.^{7,8} Senile plaques and the walls of the vessels were immunostained by antibody to amyloid β

Figure 5 Section of the motor cortex. (A) Betz cells were well preserved. The amount of lipofuscin deposited in the cytoplasm of Betz cells is consistent with the patient's age; haematoxylin-eosin stain; magnification originally $\times 50$; bar = 50 μm . (B) Neuronal loss, mild astrocytic gliosis, and slight spongiform change in the external granular layer are shown; haematoxylin-eosin stain; magnification originally $\times 20$; bar = 200 μm .

protein, but not by antibody to prion protein. Degenerative neurites of senile plaques and neurofibrillary tangles were labelled by antibody to human tau protein. Western blot analysis of the brain tissue excluded the presence of an abnormal prion protein.⁷

PATIENT 2 (III-3, FIG 1)

The elder sister of patient 1 developed spastic gait disturbance at the age of 53. At the age of 59, memory impairment, lack of initiation, and deterioration in homemaking performance were noted. Neurological evaluation at the age of 60 disclosed remarkable spasticity

in the lower extremities, diffuse hyperreflexia, bilateral Babinski's sign, and dementia (a total IQ on the WAIS was 65). No sensory deficit was detected. Laboratory investigation was unremarkable and EEG, EMG, and a nerve conduction study were normal. Brain CT showed moderate frontotemporal atrophy (fig 2B). Her neurological symptoms worsened gradually. At the age of 64, she became bedridden. She could follow only simple commands and showed frequent emotional incontinence. On neurological examination at the age of 67, she had lost all ability to communicate. She followed objects with her eyes and responded to her name. She mumbled incomprehensible words and could not follow any commands. Cranial nerves were normal except for mild dysarthria. She lost the ability of voluntary movement of all limbs, which showed severe contracture and muscle atrophy.

There was no similar disease in other members in our patients' pedigree (fig 1). HTLV-1 antibody was not detected in either patient. Sequencing analysis of the prion protein gene open reading frame in both patients and exons 16 and 17 of the amyloid β protein precursor gene in patient 2 showed no mutation.^{9,10}

Discussion

Our patients were clinically characterised by familial occurrence of progressive spastic tetraplegia before dementia developing in their 50s, and pathologically by degeneration of the thalamus and corticospinal tracts. Although clinicopathological features in our patients are far from those of typical Alzheimer's disease,^{1,2} the neuropathological

Figure 6 Section of the thoracic spinal cord showing symmetric pallor of the corticospinal tract and anterior funiculus; Klüver-Barrera stain; magnification originally $\times 3.3$; bar = 1 μm .

findings met the diagnostic criteria for Alzheimer's disease,² and the deposition of amyloid β protein was immunohistochemically confirmed.

Immunohistochemical findings also clearly differentiated the disease affecting our patients from some variants of familial prion disease that show development of dementia with degeneration of the corticospinal tract,^{8,9,11-13} or motor disturbances and dementia with thalamic degeneration.^{14,15} Because the SPECT study of severely affected patients with Alzheimer's disease often shows diffuse cerebral hypoperfusion,^{16,17} the SPECT findings obtained for patient 1 do not conflict with the diagnosis of Alzheimer's disease. Therefore, the disease affecting our patients could be placed within the range of Alzheimer's disease.

Pyramidal signs are rarely noted in Alzheimer's disease. Hyperreflexia was found in 18.5% of patients with Alzheimer's disease, and Babinski's signs in 2.7%.¹⁸ Severe spastic tetraplegia early in the disease is exceptionally rare in Alzheimer's disease.¹ Moreover, Alzheimer's disease with spastic paresis is generally considered to occur in younger persons than classic Alzheimer's disease, and many patients with Alzheimer's disease showing spastic paresis reported in the medical literature have cerebellar signs; different from our patients' clinical findings.³

Thalamic degeneration with spastic paresis was reported in thalamic dementia associated with motor neuron disease,¹⁹ familial multiple system atrophy,²⁰ fatal familial insomnia,¹⁵ and primary degeneration of the thalamus.^{21,22} Pronounced degeneration of the medial thalamus in familial juvenile Alzheimer's disease with spastic paresis was reported by Fukutani *et al.*²³ Although their patient and ours showed degeneration of the bilateral pyramidal tracts in the distal spinal cord, considerable myelin loss and axonal damage in the cerebral white matter of their patient were not found in ours. Both patients in our study developed emotional incontinence and dementia without sensory disturbance. Although delirium and dementia are often noted in cases of bilateral thalamic degeneration, sensory deficit is not found in many such cases.¹⁸⁻²² The associated delirium and dementia might mask sensory deficit.

In our patients, degeneration of the corticospinal tract in the spinal cord was apparent, whereas Betz cells, the internal capsule, and anterior horn cells were preserved as found in atypical Alzheimer's disease associated with motor neuron disease reported by Matsuoka *et al.*²⁴ and Barrett *et al.*²⁵ The causal relation of neuronal loss, mild astrocytic gliosis, and slight spongiform change in the external granular layer of the motor cortex and spastic tetraplegia is unclear, and this pattern of abnormalities in Alzheimer's disease or similar disorders has not been previously reported. In a case of atypical Alzheimer's disease reported by Aikawa *et al.*,³ degeneration of the corticospinal tract spread to the cerebral white matter, brainstem, and spinal cord.

Cases of Alzheimer's disease or similar disorders associated with spastic paralysis have been reported by some authors, including Fukutani *et al.*, Matsuoka *et al.*, Barrett *et al.*, and Aikawa *et al.*, as mentioned above.^{3,23-30} In these patients, however, the evidence is insufficient to make a clear diagnosis of Alzheimer's disease. No case of this kind should be categorised as atypical Alzheimer's disease unless both the presence of amyloid plaques containing amyloid β protein and the absence of prion disease are confirmed immunohistochemically.⁴

The changes in the thalamus and corticospinal tract in our patients were sufficiently severe that they could be considered not to be secondary effects of degeneration of other structures. The neuropathological findings of patient 1—namely, the combination of the corticospinal tract and thalamic degeneration, and the presence of senile plaques and neurofibrillary tangles—well explain the clinical features of the case. The presence of similar clinical features in her sibling (patient 2) suggests that the combination of neuropathological findings is hardly explained by chance. Therefore all clinicopathological findings in our patients should originate from familial Alzheimer's disease.

Alzheimer's disease is generally thought to represent several different biological disorders.³¹ Spastic tetraplegia of presenile onset cannot be sufficient evidence to exclude the diagnosis of this type of Alzheimer's disease. This is the first report in which clinicopathological evaluation is sufficient to establish a new variant of familial Alzheimer's disease showing spastic tetraplegia.

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