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CASE REPORT

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Clinical and neuropathological features of a neurodegenerative disorder in the central nervous system with progressive head drooping *(Kubisagari)*

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Abstract The clinical and neuropathological features of a case of a neurodegenerative disorder with pronounced and progressive head drooping, in Japanese *Kubisagari*, are reported. This female patient died at the age of 72 years after an approximately 20-year history of peculiar posture with progressive head drooping *(Kubisagari)* and lordosis (bowed posture), parkinsonism, dysphonia and slight muscle wasting of the face, tongue, neck, and distal portions of the upper extremities. She did not display mental deterioration until the terminal stage of the illness. A simple macroscopic inspection of formalin-fixed sections of the central nervous system (CNS) showed prominent atrophic frontal and temporal lobes, brownish discoloration of the putamen and an atrophic pyramidal tract. Light microscopy revealed severe neuron loss with fibrillary gliosis at both the above-mentioned lobes and the putamen. Both the facial and hypoglossal nuclei had almost disappeared. Motor neurons in the spinal cord were moderately to markedly decreased. Neither Bunina nor Lewy bodies, senile plaque, nor Pick's argyrophilic neuronal inclusions were observed, but very occasionally ubiquitin-positive neurons were found in the temporal cortex. In conclusion, the hitherto-unrecognized neuropathological findings in the CNS corresponding to progressive head drooping *(Kubisagari)* suggest that this is a neurodegenerative disorder of the CNS, possibly an atypical form of amyotrophic lateral sclerosis.

Key words Neuropathology · Postural abnormality · Amyotrophic lateral sclerosis · Parkinsonism · Multiple system atrophy

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Introduction

Progressive head drooping (*Kubisagari* in Japanese) is clinically observed in patients with amyotrophic lateral sclerosis (ALS). This disorder was first reported in 1894 by Miura [10] in a patient who showed a peculiar progressive head drooping. Miura called this disorder *Kubisagari*; this condition seems to correspond to familial ALS or myasthenic syndrome (myasthenia gravis ?) in present-day terms. Our present report describes the first clinico-neuropathological study of a female patient with "Kubisagari" disease.

Case report

The patient was a woman who died of respiratory failure at age 72 years. She first presented at the age of 65 years with complaints of head drooping, lordosis, and difficulty in speaking. Her past history was unremarkable. No similar disorder was found in her relatives, but 2 of her 11 siblings suffered from essential tremor.

In 1975, when she was 55 years old, those around her had noticed her peculiar posture, head drooping, and upwards gaze, as well as a bowed posture (lordosis) above the breast. These changes were insidiously progressive. However, at that time, her limb and truncal muscles were well preserved.

At our initial examination at the age of 65 years, she had difficulty in speaking because of the head drooping and impaired lingual movement. She had no involuntary movements. A clinical diagnosis of parkinsonism was made, and she was treated with antiparkinsonian drugs, but the medications were ineffective. No organic lesion was found in the nose, pharynx, or larynx. By the age of 70, she was unable to pronounce words spontaneously, and at age 71, the head drooping was so pronounced that her chin appeared to be fixed to the upper chest wall (Fig.1). Objective neurological findings at that time showed that she had no dementia; she was active in organizing the family finances, communicating in

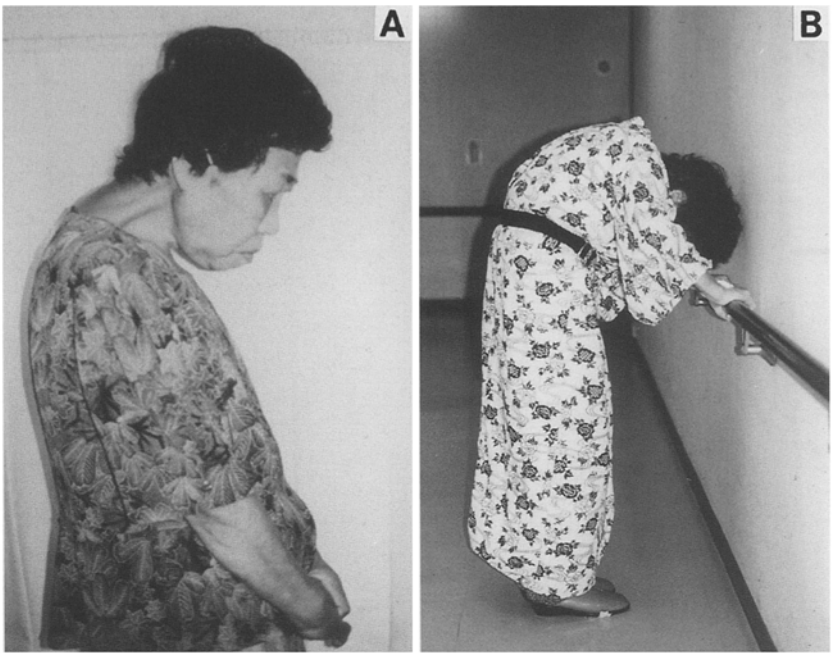


Fig. 1 A, B Facial expression, Kubisagari (head drooping) and bowed posture. **A** At 67 years of age; **B** at 72 years of age

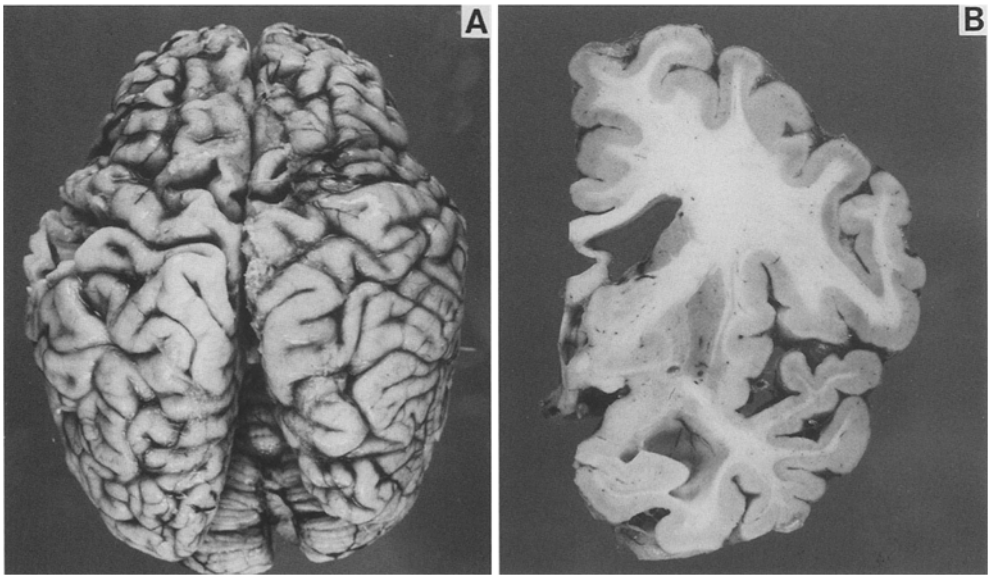
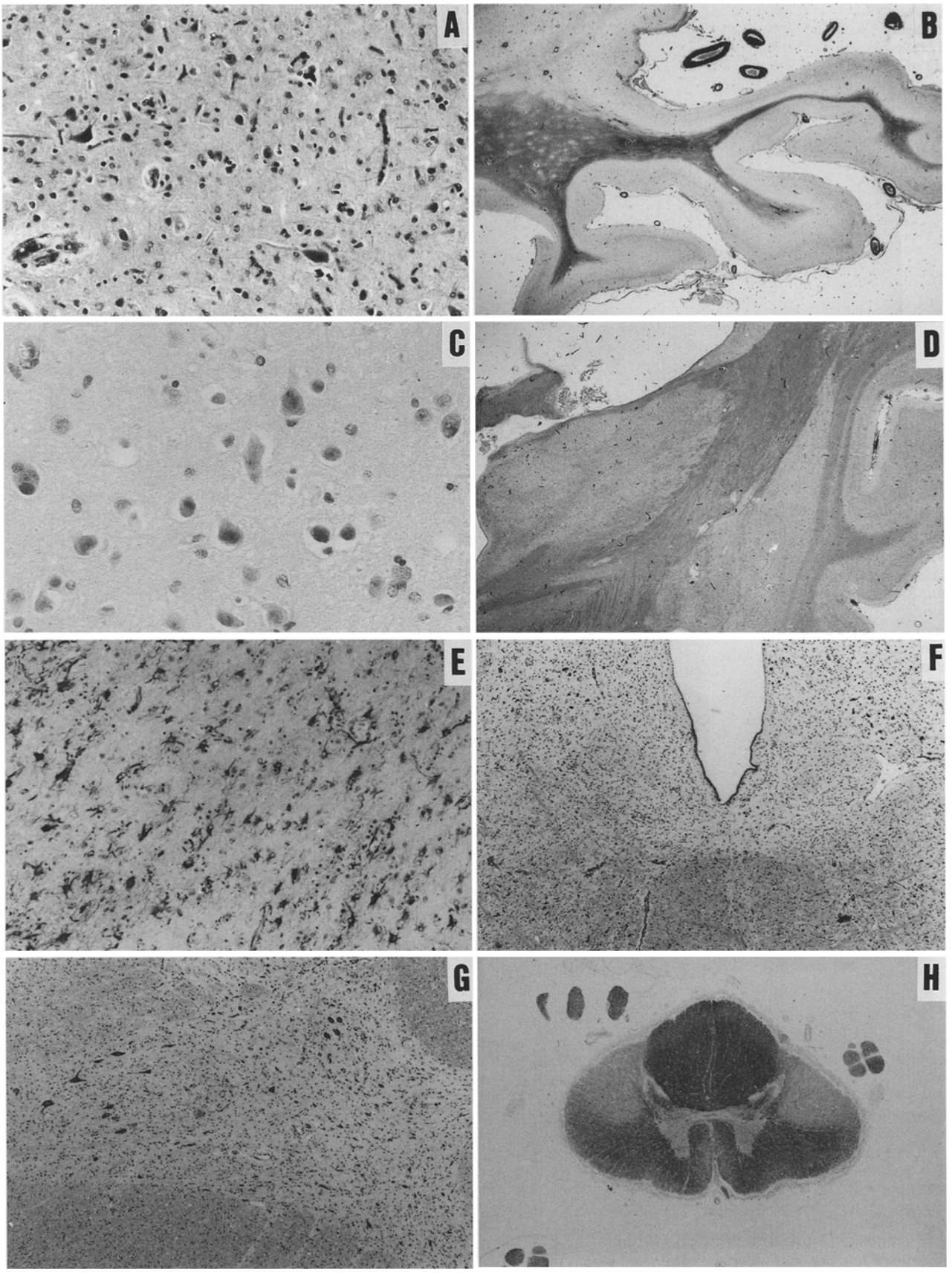


Fig. 2 A, B Macroscopic observation of brain. **A** More markedly atrophic brain at the frontal lobe. **B** Coronal section, showing severe atrophy of temporal lobe and putamen and regions of brown discoloration due to lipofuscin deposits

handwriting. Her performance-intelligence quotient (P-IQ) score was then 98. Ocular findings revealed limited upward gaze, apraxia of lid-opening, and decreased blinking. The tongue was slightly atrophic and difficult to move voluntarily. She ate in the prone position, using a spoon. The cervical muscles were slightly atrophic, but rigid, like a leadpipe. Extension of the neck was impossible. The limb muscles were rigid, moderately spastic, and atrophic, predominantly in the distal portions of the four extremities. She was not ataxic. For walking alone, she needed a cane. Deep reflexes were a little hyperactive. Both the sucking reflex and the Babinski response were positive. There was no sensory deficit. In regard to autonomic functions, the skin was cold, but values for recto-urinary function and blood pressure were within the normal limits.

On laboratory examination, erythrocyte sedimentation rate, complete blood count, urinalysis, feces, endocrine tests, and cerebrospinal fluid were all normal, but GOT, GPT, and Al-P in serum were slightly elevated due to a liver cyst and cholelithiasis. Antinuclear antibody was positive. ECG showed the first degree of A-V block. Needle EMG showed neurogenic changes in the cervical and forearm muscles. Nerve conduction, evoked responses in peripheral nerves, and auditory brain stem evoked response were normal. Brain computed tomography and magnetic resonance imaging showed markedly atrophic frontal cortices. Biopsy of the biceps brachii revealed type 2b fiber atrophy (disuse atrophy), and slight neurogenic changes.

Clinically, the head drooping and stooped posture became very conspicuous. The patient was able to walk alone, to read and to understand speech completely up until 5months before she died. No decubitus appeared. She died of aspiration pneumonia.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◀ **Fig. 3 A–H** Microscopic observation of brain and spinal cord. **A** Precentral gyrus of the frontal lobe reveals neuronal cell loss, simple atrophy of the remaining cells, and proliferation of astroglia; H&E. **B** Subcortical white matter of the temporal pole has no senile plaques, Alzheimer-type neurofibrillary tangle, or Pick's argyrophilic neuronal inclusions, but shows severe gliosis; Holzer stain. **C** Ubiquitin-positive neurons in temporal cortex; ubiquitin immunostaining. **D, E** In the atrophic putamen (**D**), moderate neuronal cell loss, gliosis, and deposits of lipofuscin pigment and iron are observed (**E**); **D** Klüver-Barrera stain (K-B), **E** glial fibrillary acidic protein immunostain. **F** Hypoglossal nuclei have pronounced neuronal cell loss; K-B. **G** Cervical cord (C8) shows marked loss of motor neurons, and gliosis is evident; K-B. **H** Pyramidal tract of the middle thoracic cord is degenerating. The number of motor neurons is reduced; K-B. **A** × 135, **B** × 3, **C** × 270, **D** × 3, **E** × 96, **F, G** × 32, **H** × 7.1

Neuropathological findings

Autopsy was performed within 2h after death. The formalin-fixed nervous tissues were stained with hematoxylin-eosin (H&E), Holzer, Klüver-Barrera (K-B), and Gallyas stainings, and immunostaining for GFAP, tau and ubiquitin was performed. Apart from in the CNS, the pathology was not exceptional, although muscles in the extremities showed moderate neurogenic changes.

The brain weighed 930 g. On gross observation, both the frontal and temporal lobes (poles) were highly atrophic (Fig. 2A). The other lobes, brain stem, cerebellum and spinal cord showed no exceptional findings on simple inspection. When the brain was cut, the bilateral fronto-temporal cortices and putamen were markedly atrophic and showed a brown discoloration (Fig. 2B). The cerebral peduncles, the pyramis at the medulla, and the lateral column of the spinal cord were gray and atrophic. The anterior root was not atrophic.

On microscopic observation, loss of large neurons and proliferation of astrocytes were observed in the fronto-temporal cortices (Fig. 3A). All cortical layers were involved, particularly the third, fifth, and sixth layers. Ballooned cells (Pick cells) were not observed, and severe neuron loss was often accompanied by aggregations of macrophages containing lipofuscin. Such lesions were prominent in the precentral, rectal, orbital, and superior frontal gyri, and in the left temporal pole (Fig. 3B). Fibrillary gliosis was observed in the subcortical white matter. No spongy degeneration, senile plaque, or Pick's argyrophilic neuronal inclusions were found.

On immunostaining, the remaining cells of the temporal lobe, the granular layer of the ammon nuclei, and the anterior horn in the spinal cord were shown to contain occasional punctate ubiquitin-positive neurons (Fig. 3C), while tau-positive Alzheimer neurofibrillary tangles were observed in a very small number of neurons in the pyramidal layers of the temporal lobe. No pathological senile plaque was observed. In the basal ganglia, cell loss and reactive gliosis of the putamen were severe, these features being prominent in the posterior part of the putamen, and associated with deposits of lipofuscin and iron. Pathological changes in the caudate nuclei were far less marked than those in the putamen. In the outer segment of the pallidum, gliosis and slight neuronal cell loss were present (Fig. 3D, E). Both the thalamus and subthalamus showed slight gliosis without neuronal loss, and the Meynert nuclei appeared normal. The posterior part of the internal capsule looked pale on myelin staining, and was massively invaded by macrophages.

In the brain stem, approximately a third of the middle portion of the cerebral peduncle, the corticospinal tract at the pons, and the pyramis at the medulla were atrophic, and they revealed loss of myelin and axons with abundant macrophage invasion. Pigmented cells in the zona compacta of the substantia nigra were well preserved, and without Lewy bodies. Cellular populations of the oculomotor and trochlear nuclei, locus ceruleus, and pontine nuclei were normal. On Gallyas staining [2, 17], there were no cytoplasmic inclusion bodies, a feature observed in multiple system atrophy (MSA), whereas the facial and hypoglossal nuclei had almost disappeared (Fig. 3E). Slight gliosis was seen in the inferior olivary nuclei. In the cerebellum, the white matter and the density of Purkinje cells, granular cells and dentate nuclei were well preserved.

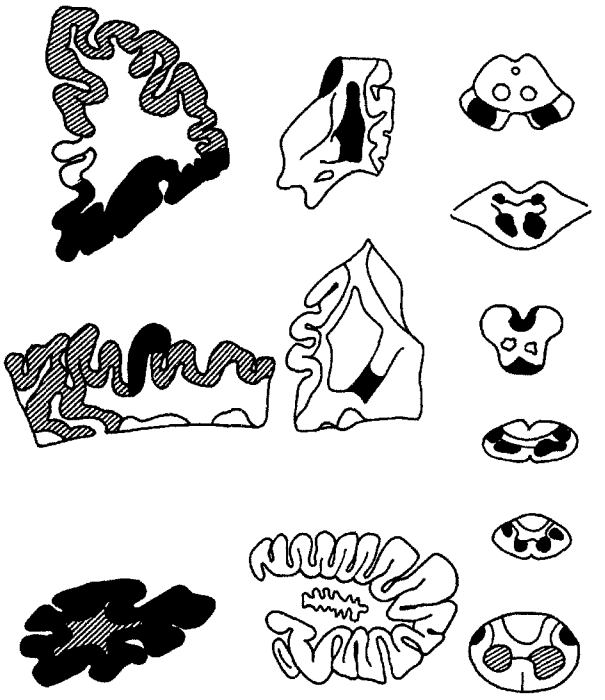

Fig. 4 Schematic representation of neuropathology in central nervous system (*solid area* severe lesions, *oblique line* moderate to slight lesions, *empty area* no lesions)

In the cervical to the thoracic cord regions, loss of motor neurons and reactive gliosis were pronounced (Fig. 3F). In the lumbar cord region, neuron loss was slight, but there was a slight decrease in the cell population and some macrophage invasion. The dorsal nucleus of Clarke, the nucleus intermediolateralis cells and the Onufrowitz nuclei were preserved. The pyramidal tract had degenerated, and exhibited macrophage invasion (Fig. 3G). The posterior column and spinocerebellar tract were almost normal, and the anterior roots in the thoracic and lumbar cord regions showed minimal loss of large myelinated fibers. Bunina bodies [4, 12, 13] were not observed in any segments of the spinal cord. A schematic representation of the neuropathology in the CNS is shown in Fig. 4.

Discussion

The notable clinical features in the patient during the 17-year course of the illness were head drooping *(Kubisagari)*, aphonia, the absence of dementia, rigospasticity, and slight muscle atrophy in the extremities. In clinical neurology, such patients are extremely rare, with only one brief report of such a patient appearing in the Japanese literature; details of the neuropathology are unknown [6].

In general, *Kubisagari*, followed by cervical muscle atrophy and weakness, is occasionally observed in chronic neurogenic muscular disorders such as the common or bulbar forms of ALS and related disorders. Therefore, we believe that, neuropathologically, this patient should be regarded as having atypical ALS, a category which includes juvenile ALS [13, 14], ALS with dementia [9, 18],

and ALS in patients on long-term treatment with a respirator [15]. Three aspects of this case require discussion.

First, the prominent macro- and microscopic changes in this patient, localized in the motor neurons and the pyramidal tract, had the following characteristics: neuron loss in the cortex and gliosis in the subcortical white matter, predominantly in the frontal and temporal lobes, degeneration of the pyramidal tract, severe selective loss of the facial (VIIth) and hypoglossal (XIIth) nuclei, and moderate loss of the anterior horn cells. However, other cranial nerve nuclei, except for the VIIth, XIIth, Clarke's and the Onufrowitz nuclei, were well preserved. This pathology is not necessarily dissimilar to that seen in common ALS, except for the severe cortical lesions. So-called atypical ALS, found in patients with a long duration of illness [1] and in those with dementia [9, 18], also shows such cortical lesions. However, Bunina bodies [3, 8, 9], which are a hallmark of ALS, were not observed in this patient.

Second, severe lesions of the putamen are not seen in ALS, although this phenomenon is often observed in the striatonigral degeneration (SND) of MSA. However, in this patient, there were no SND-specific pathological changes in the sustantia nigra, the olive, the pontine nuclei or the cerebellum, and no glial cytoplasmic MSA-specific inclusion bodies were found using Gallyas staining [2, 17]. Therefore, although SND, which is usually associated with rigospasticity, can be ruled out, it is possible that the rigospasticity in the neck and extremities in this patient may have been due to this lesion of the putamen.

Third, some aspects of the microscopic pathology of the fronto-temporal lobe are particularly notable: (a) the cortical atrophy brought about by severe neuron loss and gliosis in the subcortical white matter, which is prominent at the frontal orbital surface, the sub-rectal/cingulate/superior frontal gyri, and the temporal pole region; (b) the lack ofsenile plaques, but the presence of a few tau-positive Alzheimer-type neurofibrillary tangles; and (c) no argyrophilic inclusions (Pick bodies) or Lewy bodies, but occasional ubiquitin-positive neurons in the temporal cortex.

The distribution and nature of the lesion in the frontotemporal lobes suggest the pathology of a syndrome associated with dementia [3, 5, 7] such as Pick's disease or ALS with dementia. Compared to the neuropathology found in long-surviving patients with such disorders [3, 8], the pathology in the present patient was not markedly severe, in that the abundance of the ubiquitin-positive substances was much lower than that normally seen in ALS [16], and that no senile plaques or argyrophillic neuronal inclusions were seen. In addition, although we recognize that the clinical evaluation of dementia is controversial, clinically we found that this patient retained normal mental capacity until the terminal stage of the illness. In conclusion, the pathology of this patient appeared to be related to atypical ALS syndromes, although there were many features that differed from these syndromes. The clinical manifestation of the peculiar posture was probably a result of the combined effects of the lesions of the frontal lobe and putamen, the degeneration of the pyramidal tract, and the selective loss of some lower motor neuron sites.

"Kubisagari" disease is an extremely rare neurodegenerative disorder of the CNS; it appears to resemble an atypical ALS syndrome, but MSA including SND and dementia syndromes such as Pick's disease must be carefully ruled out.

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