Neuropathology 2006; **26**, 376–378 doi:10.1111/j.1440-1789.2006.00689.x

Neuropathology Education

Predominant motor symptoms in a 74-year-old man with a small elongation in the spinocerebellar atrophy type 1 gene

Toshiki Uchihara,[1] Takayoshi Kobayashi[2] and Hidehiro Mizusawa[3]

[1]Department of Neuropathology, Tokyo Metropolitan Institute for Neuroscience, Tokyo, [2]Department of Neurology, Nakano General Hospital, Nakano, and [3]Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Tokyo, Japan

CLINICAL HISTORY

The patient was a 74-year-old man who developed gait and bulbar disturbances, which progressed for several years.[1] His mother and a sister complained of a similar disturbance. On admission, generalized muscle atrophy and weakness were prominent, especially in the distal portions of the legs, with bulbar involvement. The patellar tendon reflexes were retained and the Achilles tendon reflexes were decreased with a positive right Babinski's sign. The ocular movements were restricted in vertical directions and, to a lesser extent, in horizontal directions. Sensory disturbance, ataxia, and extrapyramidal signs were not apparent on admission. A needle electromyogram demonstrated neurogenic changes. The laboratory examination was normal except for elevated blood glucose (320 mg/dL) and creatine kinase (1760 U/L). His general condition deteriorated so rapidly that intractable respiratory distress due to pneumonia led to a fatal outcome. The clinical diagnosis was motor neuron disease, although a familial background and a disturbance in ocular movements might have suggested other possibilities.

NEUROPATHOLOGICAL EXAMINATION

The fixed brain weighed 1260 g (Fig. 1A).[1] The spinal cord and pons were atrophic (Fig. 1B). In contrast, the inferior olivary nucleus and the cerebellum were relatively preserved (Fig. 1B). The substantia nigra was slightly depigmented. Except for several small necrotic areas, presumably related to marked atherosclerotic changes (Fig. 1A), the dentate nucleus, basal ganglia including subthalamic nucleus, cerebral cortex, and white matter were macroscopically unremarkable (Fig. 1C).

Microscopically, the pontocerebellar fibers and the pontine neurons were markedly degenerated. Occasionally, the pontine neurons contained intranuclear inclusions (NIs), immunopositive for ubiquitin (Fig. 1D) and expanded polyglutamine.[2] The anterior horn cells were depleted and the remaining neurons were atrophic (Fig. 1E). They sometimes contained NIs but not Bunina bodies or skein-like inclusisons. Large caliber-axons in the corticospinal tract were reduced in number. Intranuclear inclusions were absent in the Purkinje cells[3] and neuronal depletion and proliferation of Bergmann's glia were not extensive (Fig. 1F). In contrast, the degeneration was relatively mild, but consistently accompanied by a few NIs, in the inferior olivary nucleus (Fig. 1G), cerebellar dentate nucleus, spinocerebellar system including Clarke's column, and substantia nigra. Dilatation of the perineuronal space and mild spongiosis were noted in the cerebral cortex and striatum, where NIs also were identified. Neuronal atrophy and gliosis were evident in the globus pallidus, where a difference in the severity of degeneration between its external and internal segments was not apparent.

GENETIC DIAGNOSIS

With the consent of the patient's family, genomic DNA was extracted from the autopsied brain and a small elongation ($n = 41$, normal < 39) of the CAG repeat was noted in the spinocerebellar atrophy type 1 (*SCA1*) gene,[4] while the CAG repeat size was normal in the *SCA2*, *SCA3*, *SCA6*, *SCA17*, and DRPLA genes.

Correspondence: Toshiki Uchihara, MD, PhD, Department of Neuropathology, Tokyo Metropolitan Institute for Neuroscience, 2-6 Musashi-dai, Fuchu, Tokyo 183-8526, Japan.
Email: uchihara@tmin.ac.jp

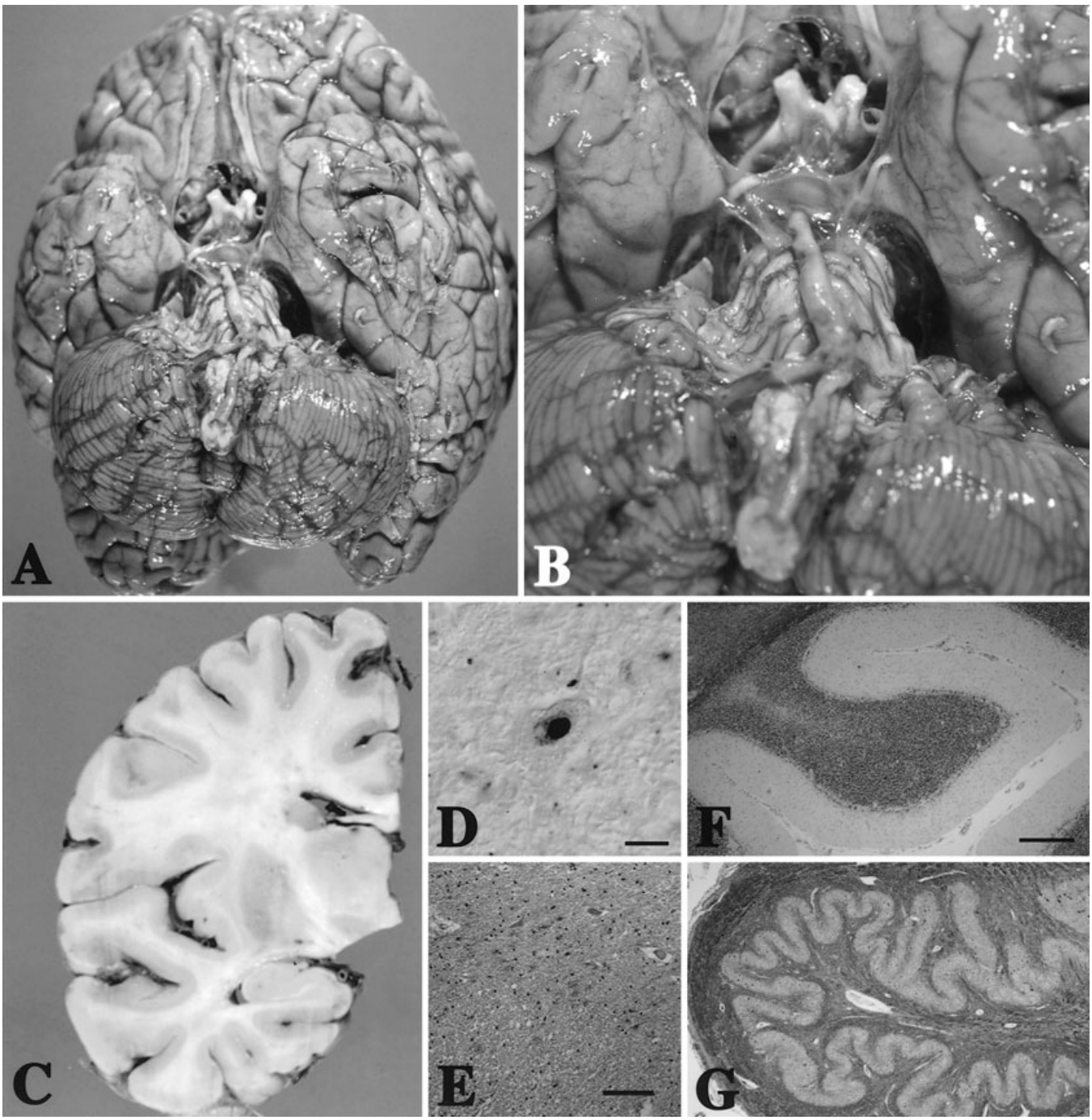

Fig. 1 (A,B) Marked atherosclerotic changes in the basilar artery. A pronounced pontine atrophy and relative preservation of cerebellar hemisphere. (C) Putamen, pallidum, thalamus, and subthalamic nucleus are macroscopically unremarkable. (D) Nuclear inclusion in a pontine neuron (ubiquitin immunostaining, bar = 10 μm). (E) Anterior horn of the cervical cord. Neurons are depleted and the remaining neurons are atrophic (HE, bar = 100 μm). (F) Cerebellar cortex (hemisphere). The Purkinje cells are affected, while the molecular and granular layers are relatively preserved (KB stain). (G) Inferior olivary nucleus. The width of the ribbon is slightly reduced, but the entire structure is relatively preserved (KB stain). Figure part (G) is reproduced from Uchihara *et al.*,[1] with permission.

DISCUSSION

Systems involved in SCA1 typically include the pontine nucleus, spinocerebellar system, substantia nigra, and lower motor neurons in the presence of NIs, as noted in this patient.[2,5] In addition, the involvement of the inferior olivary nucleus and dentate nucleus is found in most of the cases with SCA1.[5–7] Neither of them was evident in this case. Although preferential involvement of the external segment of the globus pallidus[5] is a distinguishing feature of SCA1 and DRPLA, this gradient was not evident in this case. The presence of NIs positive for ubiquitin and expanded polyglutamine in relation to a background of familial occurrence strongly suggested CAG/polyglutamine repeat expansion as a candidate abnormality linked to this phenotype. However, neither the clinical picture nor the distribution of the lesions in this patient was readily comparable to any of those described previously.[5] A small expansion of the CAG repeat in the *SCA1* gene of this patient might be linked to the late onset of the disease.[4] Furthermore, this small expansion, if related to the preservation of some systems usually affected in SCA1, might account for the predominant manifestation of lower motor involvement without any apparent abnormalities of motor control (ataxia, extrapyramidal features). In contrast with the relative preservation of some of the systems, NIs were present in the cerebral cortex and striatum. This indicates that a degenerative process with NIs extended to these areas, not described in detail so far in SCA1 brains, which awaits confirmation with other SCA1 cases.

In conclusion, this patient with predominant motor weakness was unexpectedly found to harbor a small elongation of the CAG repeat in the *SCA1* gene. This atypical case demonstrated that the phenotype linked to an elongation of the *SCA1* gene could be variable, not only in clinical but, also, in pathological aspects. As we so far have no explanation for selective vulnerability in any of the neurodegenerative disorders, the comparison of clinical and pathological phenotypes linked to the same mutation might potentially give an insight into which are modified factors and which are modifying factors.

REFERENCES

1. Uchihara T, Takeda Y, Kobayashi T *et al.* Unexpected clinicopathological phenotype linked to small elongation of CAG repeat in SCA1 gene. *J Neurol* 2006; **253**: 396–398.
2. Duyckaerts C, Dürr A, Cancel G, Brice A. Nuclear inclusions in spinocerebellar ataxia type 1. *Acta Neuropathol (Berl)* 1999; **97**: 201–207.
3. Koyano S, Iwabuchi K, Yagishita S, Kuroiwa Y, Uchihara T. Paradoxical absence of nuclear inclusion in cerebellar Purkinje cells of hereditary ataxias linked to CAG expansion. *J Neurol Neurosurg Psychiatry* 2002; **73**: 453–455.
4. Orr HT, Chung MY, Banfi S *et al.* Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nat Genet* 1993; **4**: 221–226.
5. Iwabuchi K, Tsuchiya K, Uchihara T, Yagishita S. Autosomal dominant spinocerebellar degenerations. Clinical, pathological, and genetic correlations. *Rev Neurol (Paris)* 1999; **155**: 255–270.
6. Robitaille Y, Schut L, Kish SJ. Structural and immunocytochemical features of olivopontocerebellar atrophy caused by the spinocerebellar ataxia type 1 (SCA-1) mutation define a unique phenotype. *Acta Neuropathol* 1995; **90**: 572–581.
7. Schut JW. Hereditary ataxia: clinical study through six generations. *Arch Neurol Psychiat* 1954; **63**: 535–567.