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Unexpected clinicopathological phenotype linked to small elongation of CAG repeat in SCA1 gene

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Sirs: We report a patient with spinocerebellar ataxia type 1 (SCA1), whose clinical and pathological pictures are not expected from the genetic abnormality [4, 5]. The patient was a 74-year-old man, who developed progressive gait disturbance, dysphagia and dysarthria for several years, as noted in his mother and a sister. He was fully conscious and well oriented. Extraocular movements were restricted in vertical directions and to a lesser extent in horizontal directions. Generalized muscle wasting and weakness involving bulbar muscles were prominent especially in the distal portion of the lower extremities. Patellar tendon reflexes were normal and Achilles tendon reflexes were decreased with positive right Babinski sign. Sensory disturbance, ataxia and extrapyramidal signs were not evident. Needle electromyogram demonstrated neurogenic changes. 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 severe respiratory distress led to a fatal outcome. The clinical diagnosis was motor neuron disease.

The brain weighed 1260 g. The pons and spinal cord was atrophic while inferior olives (Fig. 1A) and cerebellum were relatively preserved. The brain was otherwise normal except for nigral discoloration.

Marked degeneration of the pontocerebellar fibers and of pontine neurons, occasionally containing intranuclear inclusions (NIs) immunopositive for ubiquitin and expanded polyglutamine (1C2, Fig. 1B) was noted [1]. By contrast, degeneration was relatively mild but consistently accompanied by a few NIs, in the inferior olives, dentate nucleus, substantia nigra and lower motor neurons including those in the oculomotor nucleus. Depletion of Purkinje cells and glial reactions were mild to moderate. NIs were absent in Pj cells [3]. Dilatation of perineuronal space and mild spongiosis was noted in the cerebral cortex and striatum, where NIs were identified (Fig. 1C). Neurons were mildly degenerated in the subthalamic nucleus, where gliosis was slight (Fig. 1D). Neuronal degeneration and gliosis were evident in the globus pallidus, where difference between its external and internal segments was not apparent. Neither Bunina bodies nor skein-like inclusions were detected and anterior and lateral corticospinal tracts were preserved relative to the spinocerebellar tracts. Skeletal muscles exhibited neurogenic changes. With the consent of the family, genomic DNA was extracted and a small elongation (n = 41, normal < 39) of CAG repeat was noted in SCA1 gene [4], while CAG repeat size was normal in SCA2, SCA3, SCA6, SCA17, DRPLA genes.

Preferential involvement of pontine nucleus, spinocerebellar system, substantia nigra and lower motor neurons in the presence of NIs, noted in this patient are compatible with reported autopsy findings of SCA1 [1]. In typical SCA1 cases, apparent involvement of inferior olivary nucleus and cerebellar cortex and dentate nucleus, is the rule [2], all of which were not evident in this case (Table). Al-

Table Regional distribution of lesions and their severity

Area	representative SCA1 cases [2]	this case
Cerebellar system including its afferents and efferents		
Purkinje cells	± – ++	+
Dentatofugal system	+ – ++	+
Pontocerebellar system	± – ++	++
Inferior olivary nucleus	+ – ++	+
Spinocerebellar tracts	+++	++
Clarke's column	++	+++
Extrapyramidal system		
Substantia nigra	± – ++	++
Pallidum interna	–	++
Pallidum externa	± – ++	++
Subthalamic nucleus	± – +	+Oculomotor system + – + + + +
Anterior horns	+ – ++	++
Dorsal column	– ++	+

ext external; *int* internal; *nucl.* nucleus; – absent; ± very mild; + mild, ++ moderate; +++ severe

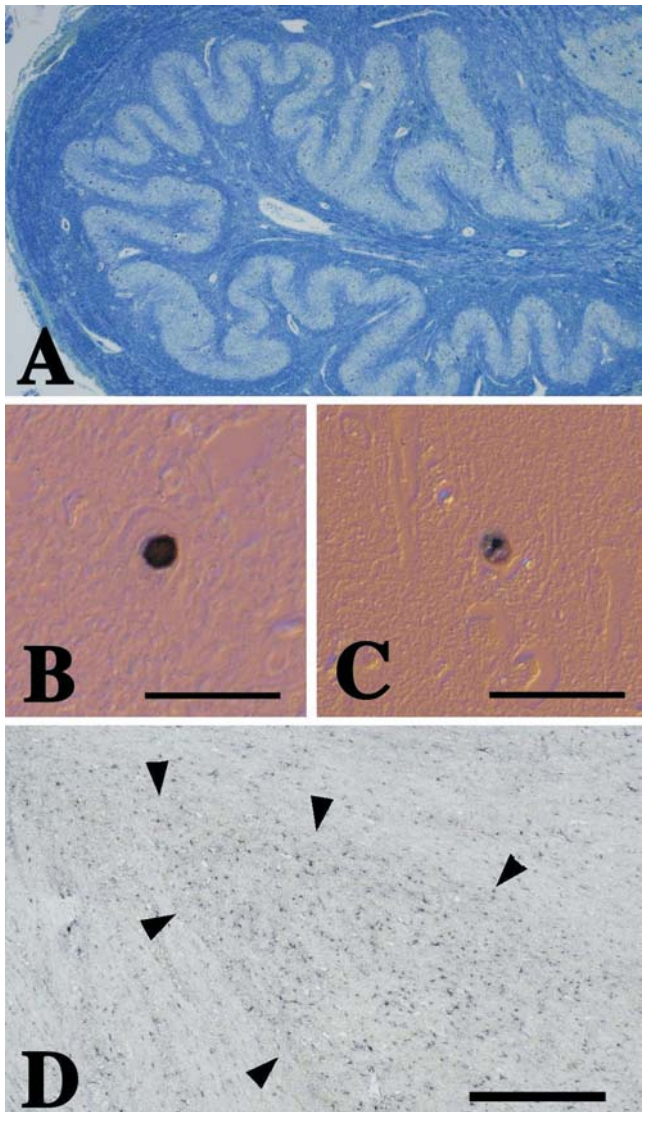

Fig. 1 **A:** Inferior olivary nucleus. The width of ribbon is slightly reduced, but the entire structure is relatively preserved. (Klüver-Barrera stain). **B:** Nuclear inclusion in a pontine neuron (1C2 immunostaining after pretreatment with formic acid, bar = 25μm). **C:** Nuclear inclusion in cerebral cortex (ubiquitin immunostaining, bar = 25μm). **D:** Subthalamic nucleus (arrowheads, GFAP immunostaining, bar = 50μm). Atrophy is not evident and proliferation of GFAP-positive cells is slight

though the lesion in the globus pallidus is one of the pathological features of SCA1, typical SCA1 cases are characterized by preferential involvement of its external segment [2], again not detectable in this case. Mild spongiosis with minimal glial proliferation may represent an influence not directly linked to degeneration but possibly related to circulatory disturbance in the agonal state. However, identification of NIs in these areas (Fig. 1C), as well as in the thalamus indicates that degenerative process with NI is extended to these areas, not described so far in SCA1 brains. Small expansion of the CAG repeat in this patient may be correlated not only with late disease onset [4] but also with relative preservation of these regions, which may explain predominant manifestation of lower motor involvement without apparent abnormality on motor control. Variability of pathological lesion as seen in this case may provide an opportunity to gain further insight into how lesions are engendered in human brains.

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