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Neuropathology Education

A 76-year-old woman presenting with adult-onset, slowly progressive cerebellar symptoms

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CLINICAL HISTORY

A female patient, healthy until the age of 56 years, developed unsteady gait and slurred speech. Horizontal gaze-evoked nystagmus was also present and all deep tendon reflexes were slightly hyperactive. Computed tomography revealed atrophy of the cerebellar vermis and hemispheres. There was a family history of the disease, the patient's father and three siblings, uncle and three first cousins having been affected by an almost identical disorder; the disease is apparently inherited as an autosomal dominant trait. Subsequently, there was an insidious progression of the gait ataxia and dysarthria. At the age of 63 years, the patient was unable to walk without assistance and virtually chair bound and at the age of 76, she died of aspiration pneumonia, approximately 19 years after onset of the disease. During the course of her illness, pollakisuria, pyramidal signs (Babinski's sign was present on both sides), and muscle weakness of the neck and upper limbs were noticed. Since the age of 73, she was sometimes incoherent and suffered delusions, but there was no obvious evidence of dementia.

NEUROPATHOLOGICAL EXAMINATION

The brain weighed 1035 g (brain stem + cerebellum = 95 g) before fixation. The cerebellum appeared to be very small and atrophic. During sectioning, the cerebellum exhibited atrophy of the folia with open fissures, being more marked in the superior parts of the vermis and hemispheres. The cerebrum, brain stem and spinal cord were of normal appearance. Histologically, the significant changes were confined to the cerebellar cortex and inferior olivary nucleus. The cerebellar cortex showed severe loss of Purkinje cells with proliferation of Bergmann glia (Fig. 1). Loss of granule cells was also seen. The molecular layer was atrophic and reduced in width. These changes were more pronounced in the superior parts of the vermis and hemispheres, the cerebellar tonsil being relatively well preserved. Myelin pallor and fibrillary gliosis were observed in the affected folial white matter. The dentate nucleus was relatively well preserved, although gliosis was evident within the nucleus itself and in the surrounding white matter (amiculum). In the olivary nucleus, mild to moderate loss of neurons with gliosis was observed, being more pronounced in the dorsal band.

The formalin-fixed, paraffin-embedded sections of the vermis and hemisphere were immunostained by the avidin-biotin-peroxidase complex method, using a monoclonal antibody against calbindin-D-28k (Sigma, St. Louis, MO; 1:400) (Fig. 2). The sections were also immunostained similarly, using a polyclonal antibody against human α_{1A} voltage-dependent Ca^{2+} channel (Gift of Dr H. Mizusawa; 1:100) (Fig. 3a) and a monoclonal antibody against expanded polygutamine stretches (1C2, Chemicon, Temecula, CA; 1:16 000) (Fig. 3b), as described previously.[1,2]

DIAGNOSIS

Spinocerebellar ataxia 6 (SCA6).

DISCUSSION

Spinocerebellar ataxia 6 (SCA6) is one of the hereditary neurodegenerative diseases caused by the expansion of a CAG repeat encoding a polyglutamine tract in the disease protein. In 1997, Zhuchenko *et al.* reported that expansion of a CAG repeat in the gene encoding the α_{1A} voltage-dependent Ca^{2+} channel was the cause of late-onset dominantly inherited ataxia.[3] At present therefore, this disease can be diagnosed genetically before death. At the age of 73, this patient was diagnosed genetically as having SCA6

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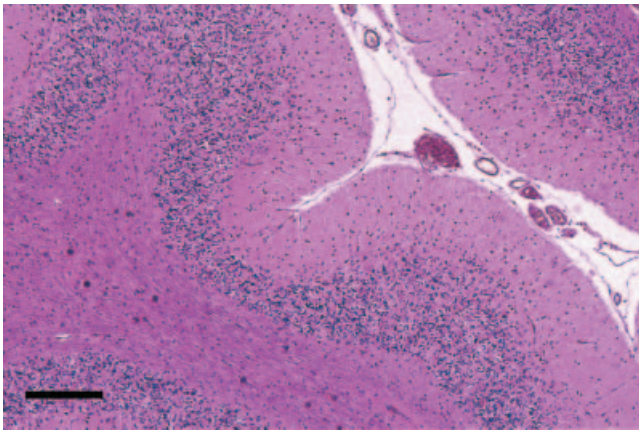

Fig. 1 The superior part of the vermis, showing complete loss of Purkinje cells (H&E). Scale bar = 200 µm.

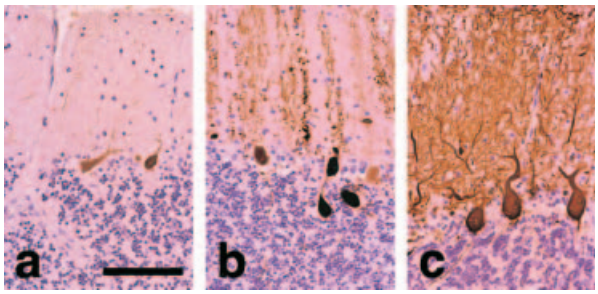

Fig. 2 The cerebellar hemisphere immunostained with anti-calbindin-D28k antibody, showing the topographical severity of the Purkinje cell involvement in the disease: (**a**) superior; (**b**) inferior; (**c**) the tonsil. Scale bar = 100 µm.

by analyzing the peripheral leukocyte DNA. The number of CAG repeats were 14 and 22 (normal allele <20).[4] Clinically, this patient also showed urinary disturbance, pyramidal signs and muscle weakness in addition to the cerebellar symptoms. Such clinical manifestations are rare in SCA6.[4]

The neuropathological phenotype of SCA6 is cerebello-olivary atrophy[5] as in the present case. In addition, it was confirmed that loss of neurons in the inferior olivary nucleus was not diffuse with preference to the dorsal band. It is of diagnostic importance that loss of neurons is much milder in the inferior olivary nucleus than in the cerebellar cortex. It is likely that this type of neuronal loss in the inferior olivary nucleus represents retrograde trans-synaptic degeneration secondary to the cerebellar cortical lesions.[5]

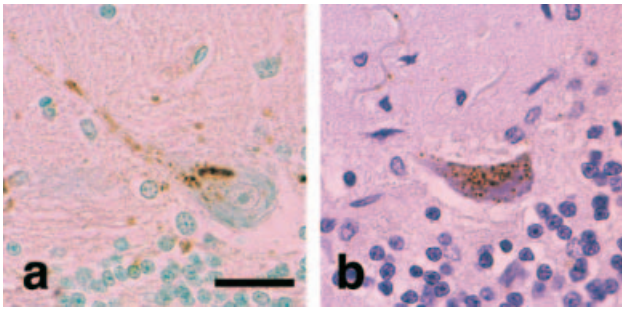

Fig. 3 The remaining Purkinje cells often contain filamentous and granular aggregates of mutant disease protein (**a**), as well as fine granular aggregates of expanded polyglutamine stretches in their cytoplasm (**b**). Scale bar = 25 µm.

As shown in other CAG-repeat diseases, including dentatorubral-pallidoluysian atrophy,[2] immunohistochemical examination with antibodies against the disease protein or expanded polyglutamine stretches is necessary for the definitive pathological diagnosis of SCA6.[1] In the present case, cytoplasmic aggregates of α_{1A} voltage-dependent Ca^{2+} channel and of expanded polyglutamin stretches were clearly demonstrated in the remaining Purkinje cells. Such pathological aggregates were not observed in other neurons, such as the inferior olivary nucleus neurons, further indicating that, in a strict sense, SCA6 is a form of cerebellar cortical atrophy[5] affecting the Purkinje cells.

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