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Purkinje Cell Loss is the Major Brain Pathology of Spinocerebellar Ataxia Type 10

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Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant cerebellar degenerative disorder, variably associated with epilepsy¹. The mutation responsible for SCA10 is an expansion of an ATTCT repeat in intron 9 of the *ATXN10* gene on chromosome 22q13.3². Although brain MRI of SCA10 patients show isolated cerebellar atrophy, histopathological changes in the brain of SCA10 patients remain unknown. Here, we report the post-mortem neuropathologic findings of an SCA10 patient and compare these to a normal age and gender-matched control subject.

Subject and Methods

The patient was a 42 year-old Mexican-American male with the diagnosis of SCA10 based on the presence of 2,350 ATTCT repeats. Gait ataxia started at 26 years of age followed by the development of complex partial seizures with occasional secondary generalization. An examination at age 30 showed normal mental status and typical symptoms and signs of cerebellar ataxia with MRI findings showing cerebellar atrophy without other abnormalities. Ataxia progressed and his seizures were poorly controlled even with multiple anticonvulsants and a vagal nerve stimulator. Shortly before his death, he was wheelchair bound. He developed aspiration pneumonia, which was subsequently complicated by multiple organ failure, and died after staying in the ICU for 7 days. With family's consent for autopsy, the brain was removed three hours postmortem. Samples were taken from cerebral cortex, hippocampus, brainstem and cerebellum. A normal postmortem control brain was obtained from a 38 year-old male who died from pulmonary emboli. We performed gross and microscopic examinations, immunohistochemistry/immunofluorescence for Calbindin, Neurofilament-H, NeuN, GAD, and VGULT2, and transmission electron microscopy and compared to the normal control. This is the first neuropathological description of an SCA 10 patient.

Results

We found that Purkinje cell (PC) loss is the primary pathology in SCA 10 cerebellum. The cerebellum showed marked, symmetrical atrophy of the hemispheres with the vermis being less affected. Hematoxylin and eosin staining of the cerebellum revealed striking PC loss with a corresponding reduction in the molecular layer volume (Figure AB). Bergmann

gliosis was present in areas of PC loss. The internal granular layer was also affected but not as extensive as PC cells. PC cell linear density (PC number per centimeter of PC layer) and molecular layer thickness (the distance from the PCs to the cerebellar surface in micrometer) were significantly reduced compared to normal control (16.9 ± 7.1 vs 58.6 ± 9.4 , $P < 0.01$ and 244.8 ± 41.7 vs 387.3 ± 27.1 , $P < 0.01$). The residual PCs were dysmorphic with poor dendritic arborization and abnormally widened residual dendrites near the pial surface as demonstrated by calbindin and Neurofilament-H staining (Figure C, D). Marked PC loss with decreased cellularity of internal granular layer was confirmed by double immunofluorescence studies for calbindin and NeuN (Figure E, F). The control brain showed normal arborization of PC dendrites (data not shown). Anti-GAD immunohistochemistry also revealed marked PC loss in the cerebellar cortex (Figure 1G) with a decrease of GAD staining (decreased projection from PCs) in dentate nucleus area (Figure H). GAD-positive neurons in the dentate nucleus are mostly preserved (Figure H, and the projection to the inferior olivary nucleus in Figure I). The corresponding staining in normal cerebellar cortex (Figure J), dentate nucleus (Figure K) and inferior olivary nucleus (Figure L) are included for comparison.

Examination of the cerebral cortex, hippocampus, midbrain, and pons revealed no apparent pathological change. No developmental abnormality or gray matter heterotopia was found. A subtle increase in subcortical white matter neurons was suggested by NeuN immunohistochemistry but this was not quantitatively verified.

Discussion

The core clinical manifestation of SCA10 is cerebellar ataxia, which can be caused by an impairment of either the cerebellum or its afferent or efferent pathways.¹ Our study clearly showed that the primary histopathological feature of SCA10 is PC degeneration with early deformities of dendrites. The pathology in the SCA10 cerebellum is similar to SCA 1, 2 and 6 but is in contrast to SCA 3 in which PC cells are relatively spared.² While we cannot exclude the effect of antiepileptics on this particular case, the fact that his brain MRI showed cerebellar atrophy at early stage of his disease suggests a primary cerebellar degeneration. Immunohistochemistry with anti-GAD antibodies revealed dendritic atrophy in dentate nucleus which was not associated with neuron loss. Neuronal loss in the inferior olivary nuclei was mild and could be caused by a retrograde neuronal loss secondary to the extensive PC loss. These findings suggest that the loss of PCs could be the primary and initial pathologic change in SCA10 and is consistent with the clinical classification as an autosomal dominant cerebellar ataxia type III (ADCA III) by Harding's criteria. The mechanism of PC loss is unclear. Our previous study with transgenic model suggested a RNA gain-of function.³ As intronic non-coding tandem repeats are gaining more and more attention in neurodegenerative disorders,⁴ further investigation of PC loss in SCA10 may shed light into our understanding of neurodegeneration.

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Abbreviations

SCA	spinocerebellar ataxia
PC	Purkinje Cell
NeuN	neuronal nuclear antigen

NeuH   Neurofilament-H
GAD   Glutamic Acid Decarboxylase

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Figure 1. Purkinje cell changes in the SCA10 cerebellum

(A) Hematoxylin and eosin (H&E) staining reveals extensive Purkinje cell loss with a reduction in volume of the molecular layer. (B) A normal cerebellar cortex is shown for comparison. (C) Calbindin immunohistochemical study confirms loss of Purkinje cells. The remaining Purkinje cells are dysmorphic with markedly reduced dendrites in the molecular layer. (D) Neurofilament-H immunostaining confirms the loss of Purkinje cells with an aberrant arborization of residual dendrites. Some dendritic processes are abnormally widened near the surface of molecular layer (asterisk). (E,F) Double staining of Calbindin (green) and NeuN (red) in SCA10 cerebellum (E) reveals sparsely distributed PCs and thinning of molecular layer in contrast to normal control (F) cerebellum. The poor staining in PC dendrite trees in normal control may result from the longer postmortem interval. (G-L) Immunohistochemical staining with anti-GAD reiterates PC loss in SCA 10 cerebellar cortex (G) and also demonstrates a loss of projection to dentate nucleus (H). The anti-GAD positive neurons in dentate nucleus (H) are GABA-ergic neurons (arrows), which project to inferior olivary nucleus (I). Normal control cerebellar cortex (J), dentate nucleus (K) and inferior olivary nucleus (L) are included for comparison.