Severe Cerebral White Matter Involvement in a Case of Dentatorubropallidoluysian Atrophy Studied at Autopsy

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Background: The pathophysiology of white matter involvement in dentatorubropallidoluysian atrophy (DRPLA) is controversial. Moreover, the clinical repercussions and evolution of these lesions have not been well documented.

Objective: To describe a case of DRPLA with severe cerebellar white matter involvement.

Design: Case report.

Patient: A 62-year-old woman with DRPLA.

Results: When the genetic diagnosis was made, the patient manifested severe ataxia, slight dysarthria, and subcortical cognitive impairment. Cranial magnetic resonance imaging showed atrophy of the cerebellum and brainstem and moderate high-intensity signal alterations in the periventricular cerebral white matter in T2-weighted sequences. In the following 5 years, she developed uncontrolled head movements associated with severe bruxism and tetraparesis, and became deeply demented. New magnetic resonance imaging showed severe diffuse cerebral white matter alterations in T2 sequences with only slight progression of brainstem and cerebellar atrophy. After her death at 67 years of age, the autopsy study showed diffuse myelin pallor, axonal preservation, and reactive astrogliosis in the cerebral white matter, with only mild atherosclerotic changes, and moderate neuronal loss in the cerebellum and brainstem.

Conclusions: Leukoencephalopathy could be a prominent finding in some patients with DRPLA, explaining, at least in part, their clinical evolution. In our case, the disproportion between the severity of white matter damage and vascular changes does not support a cardinal role for ischemic mechanisms in leukoencephalopathy.

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DENTATORUBROPALLIDOLUYSIAN atrophy (DRPLA) is an autosomal dominant neurodegenerative disease characterized clinically by the presence of cerebellar ataxia, choreoathetosis, myoclonus, dementia, and behavioral disturbances. The genetic defect consists of an increased CAG repeat expansion in the B37 gene on chromosome 12p that leads to the production of an abnormal protein called atrophin 1, which is widely expressed in different neurons of the central nervous system. Usually, patients with large expansions have an early onset and a rapid disease progression. The diagnosis of DRPLA is more frequent in Japan than in Europe or America, where only a few cases have been reported. We describe the clinical and radiologic evolution, as well as the postmortem findings, of a patient with DRPLA who developed a severe leukoencephalopathy.

The patient belonged to a family our group has previously reported on. Her disease began at the age of 27 years with behavioral changes, irritability, depression, and gait instability. At the age of 50 years, she was unable to continue to work because of frequent falls, and she required assistance in walking. By that time she had also developed slurred speech and memory disturbances, and she had become untidy. At the age of 62 years she suddenly developed sphincteral incontinence, lost the ability to walk, and had insomnia and psychomotor agitation after a cranial trauma. Therefore, she was admitted to our hospital.

At admission she was disoriented, with low attention and slurred speech. The strength was normal, deep tendon reflexes were diminished, and plantar responses were flexion. Occasional slight choreic movements of the head and slight
intentional choreoathetoid upper limb movements were observed. Upper- and lower-limb dysmetria and dysdiadochokinesia were also prominent features. Standing up and gait testing were impossible because of marked instability. The patient showed a predominantly subcortical cognitive impairment with anterograde memory loss and slowing of verbal responses. She did not cooperate enough to permit a neuropsychological evaluation to be carried out, but language was preserved.

At that time, cranial magnetic resonance imaging (MRI) showed atrophy of the cerebellum, brainstem, and cerebral cortex; high signal intensity on T2-weighted sequences, predominantly in the periventricular white matter; and the presence of a subdural hematoma on the left cerebral hemisphere (Figure 1A-C). The subdural hematoma was drained, but the patient’s clinical status did not improve greatly. Genetic testing was performed, showing the presence of 2 alleles of 15/60 CAG repeats in the B37 gene that confirmed the diagnosis of DRPLA.

One year later, the patient presented with bruxism that initially responded well to botulinum toxin type A treatment. Her mental status had hardly worsened, but slight proximal weakness of the limbs, without apparent amyotrophy at that time, was seen. An electromyographic study only showed a moderate reduction in the recruitment of motor units without denervation signs in the proximal muscles. Results of peripheral nerve neurography were normal. In addition, the patient’s husband explained that she complained of progressive loss of vision. She had been visited by an ophthalmologist, who diagnosed bilateral corneal degeneration.

At the age of 65 years, the family reported the presence of daily abnormal movements of the head and extremities lasting for a few minutes but without loss of consciousness. At the age of 67 years, the patient was admitted again because of a worsening of these abnormal movements. On examination, she showed severe bruxism with almost continuous abnormal “no-no” movements of the head. These movements were stereotyped but could not be classified as tremorlike or choreic movements. Her speech was hypophonic, and she responded only with single words or very short sentences, so it was very difficult to make contact with her. Her visual acuity was severely impaired, and both corneas, especially the right one, showed prominent leukoma. Severe weakness, predominantly in proximal muscles, was seen in the extremities. Plantar responses were indifferent. The patient frequently experienced sudden movements of the 4 extremities consisting of flexion of thighs, knees, and elbows, as well as adduction of the shoulders, that lasted for 1 to 2 minutes. A video electroencephalogram showed generalized 4- to 7-Hz semirhythmic background activity and intermixed bilateral frontal delta activity bursts following the paroxysmal body flexion spasms, but did not disclose any epileptiform activity. A new MRI showed a slight progression of the atrophy of cerebellum, ver-

Figure 1. Cerebral magnetic resonance images showing progression of white-matter changes after 5 years of follow-up. A-C, Images at the age of 62 years. T1-weighted sequences show atrophy of cerebellum and basal pons (A); T2-weighted sequences show a subdural hematoma and periventricular white-matter high intensities (B and C). D-F, Images at the age of 67 years. T1-weighted sequences demonstrate mild progression of brainstem and cerebellar atrophy and marked thinning of the corpus callosum (D). T2-weighted sequences show severe spreading of the white-matter signal alterations to the corona radiata and centrum semiovale (E and F).
mis, brainstem, and cerebral cortex, but most noticeable was the severe spread of leukoencephalopathy throughout the corona radiata and centrum semiovale (Figure 1D-F).

On the last visit, the patient showed a posture in flexion of the head, severe proximal weakness with amyotrophy, and almost complete inability to speak or eat. The abnormal movements of the head and extremities had diminished after treatment with tetrabenazine, risperdone, bromazepam, and gabapentin.

The patient died suddenly at the age of 67 years. A neuropathological study was carried out in the Brain Bank of the University of Barcelona, Barcelona, Spain.

The brain weight was 1010 g. Gross examination disclosed mild atrophy of the cerebrum and moderate atrophy of the cerebellum and brainstem, enlargement of the ventricles, and mild atherosclerosis (degree I/II) of the cerebral blood vessels.

Moderate neuronal loss accompanied by astrogliosis was observed in the dentate nuclei, subthalamus, and outer globus pallidus. Mild neuronal loss and reactive gliosis occurred in the tectum and tegmentum, olivary nuclei, red nuclei, and substantia nigra. No abnormalities were seen in the hippocampus, entorhinal cortex, and neocortex. The thalamus and striate complex were not affected.

Severe myelin loss and gliosis without significative axonal loss were seen in the centrum semiovale (Figure 2A). This was accompanied by slight vascular atherosclerosis. No amyloid deposits or abnormal products were found in the meningeal and encephalic blood vessels. The posterior columns of the upper cervical spinal cord exhibited myelin pallor. Infra-cervical spinal cord, nerve, and muscle were not available for the study.

Rare fibrillar ubiquitin-positive intracytoplasmic inclusions reminiscent of skeinlike inclusions were seen in the dorsal nuclei of the medulla oblongata. More importantly, round homogeneous ubiquitin-positive intranuclear inclusions were encountered in individual neurons of the dentate nuclei, mesencephalon, and pons (Figure 2B).

**COMMENT**

Our patient developed a picture of severe ataxia, quadriplegia, bruxism, uncontrolled stereotyped head movements, dementia, and loss of vision. The MRIs showed a marked spreading of leukoencephalopathy through the 5 years of follow-up (Figure 1). Previous MRI studies in DRPLA have usually shown atrophy of the cerebral cortex, cerebellum, and brainstem and, in some instances, white matter signal alterations in T2 and fluid-attenuated inversion recovery sequences.10-12 These white matter changes seem to be more frequent in older patients, indicating old age as a risk factor for the development of such alterations, and they appear earlier in patients with higher CAG repeats.10 However, to our knowledge, there are no longitudinal studies correlat-
ing the clinical evolution and radiologic findings in patients with DRPLA. Therefore, the clinical relevance of leukoencephalopathy has yet to be well documented.

The neuropathological findings in the present case are similar to those reported in other cases of DRPLA, mainly consisting of neuronal loss and gliosis in dentate nucleus, subthalamus, brainstem, and globus pallidus, as well as typical ubiquitin-positive intranuclear inclusions in scattered neurons. In addition, in our case, dramatic myelin loss in the cerebral white matter was accompanied by axonal preservation and mild atherosclerotic changes in vascular blood vessels. White matter involvement was not uncommon in a number of autopsy specimens of Japanese and non-Japanese patients with DRPLA. However, the origin of these white matter lesions in DRPLA is obscure, as they resembleBinswanger disease. Atherosclerotic changes in cerebral blood vessels have been reported in some Japanese cases but not in others. Atherosclerosis degree I/II in the large basal cerebral arteries and slight atherosclerotic changes in the medium and small cerebral blood vessels in the present case demonstrate the apparent lack of a close relationship between white matter and vascular changes in DRPLA.

In our case, clinical worsening seemed to run more in parallel with the progression of white matter changes than with brainstem and cerebellar atrophy, which showed only a slight progression on the MRIs throughout the follow-up period. Moreover, the neuropathological findings in our patient were consistent with only moderate neuronal loss in the brainstem and cerebellum in contrast to the severe demyelination observed in the cerebral white matter.

Although it is difficult in a single case to make a correlation between clinical and radiologic or neuropathological findings, our case highlights the fact that structures other than brainstem and cerebellum may play an important role in disease progression in some patients with DRPLA. The cellular distribution of atrophin 1 in the human brain and the impact of mutated forms of atrophin 1 in neuroectodermal cells other than neurons are now beginning to be understood. The presence of corneal endothelial degeneration has been reported in some patients with DRPLA, as was the case with our patient, who showed important loss of visual acuity related to corneal degeneration. The presence of mutant atrophin 1 in glial cells and endothelial corneal cells in patients with DRPLA suggests a potential role for the mutated protein in white matter and corneal degeneration.

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