CHAPTER 11

PATHOLOGY OF NEUROACANTHOCYTOSIS
AND OF HUNTINGTON’S DISEASE

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Abstract. The pathology of Huntington’s disease is well characterized by atrophy, neuronal loss and gliosis of the striatum, with preferential damage of the small and medium spiny neurons. The surviving cells show nuclear and intracytoplasmic inclusions that stain with antibodies against ubiquitin and huntingtin. Involvement of other brain regions is common for the cerebral cortex (loss of the pyramidal glutamate bearing neurons, projecting to the striatum) and less frequent in other brain regions (globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cerebellum). In neuroacanthocytosis there is a more selective involvement of the striatum and globus pallidus, though the substantia nigra and medial thalamus may be affected in some cases. Involvement of the anterior horn cells and of the peripheral nerve is also described, and myopathic changes have been reported. No inclusions or specific immunocytochemical patterns have yet been reported in neuroacanthocytosis.

INTRODUCTION

The pathology of Huntington’s disease (HD) is well known through hundreds of pathological studies in patients in different disease stages that had molecular confirmation of the diagnosis. More recently the initial changes in histology have been studied in transgenic models that allow for investigation of cellular changes before the presence of clinical abnormalities. The pathology of neuroacanthocytosis, however, presently is limited to a small number of cases without molecular confirmation and without complementary data provided by transgenic animals.
Table 1. Grading of striatal pathology (according to Vonsattel et al 1985 [17]).

- Grade 0 (1% of HD brains):
  No macroscopic changes, loss of 30-40% neurons without gliosis in the head of the caudate nucleus.
- Grade 1 (4% of HD brains):
  Atrophy of the tail of CN and 50% neuronal loss with gliosis in the head of the caudate nucleus.
- Grade 2 (16% of HD brains):
  Striatal atrophy is mild to moderate. Severe neuronal loss and gliosis.
- Grade 3 (54% of HD brains):
  Striatal atrophy is severe. Very severe neuronal loss and gliosis.
- Grade 4 (25% of HD brains):
  Loss of 95% of striatal neurons, preservation of accumbens nucleus in 50% of cases.

PATHOLOGY IN HD

Brain

There is great variability in the severity of changes in the brains of patients with HD, depending on disease duration and the size of the CAG expansion [16,17]. A grading system, proposed on the basis of the severity of striatal atrophy and the percentage of loss of striatal neurons, has been proposed (summarized in Table 1).

In general, gross striatal atrophy is considered to be present in around 95% of the patients with HD at the time of death (Figures 1a and b). Frontal atrophy is present in 80% of the patients. Morphometric studies reveal that the regional percentage of volume loss in different brain areas is the following: cerebral cortex 25%, thalamus 28%, caudate nucleus 57%, putamen 64%, globus pallidus pars medialis 27%, globus pallidus pars lateralis 50%, white matter 32% [17]. Cerebellar atrophy is often found in patients with juvenile onset or in those with advanced disease. Pathological changes in other brain areas, such as the limbic system or the hippocampus are rare, unless there is associated pathology, such as Alzheimer changes.

Microscopically, there is neuronal loss and gliosis of the striatum (Figures 2a and b). The severity of striatal changes has a regional gradient, increasing gradually along the antero-posterior, latero-medial, and ventro-dorsal axes. So, the neuropathological changes are more severe in the tail than in the body, and more severe in the body than in the head of the caudate nucleus, and the paraventricular portion is almost always more severely affected. Also, the dorsal portion of the putamen is much more involved than the ventral one. The nucleus accumbens is usually well preserved. The severity of gliosis in different brain areas parallels the loss of neurons [17].