

# Pathologic Staging of Huntington Disease

The grading system or pathologic staging applies to the postmortem categorisation of brains from individuals who carried the clinical diagnosis of Huntington disease (HD). The development of this grading system is the result of a widespread collaboration. It included the participations of families, clinicians, pathologists, and neuroscientists. This grading system stages the extent of striatal changes and is widely used as a research tool. The hallmark of HD is the gradual atrophy of the striatum, which is the only site where neuronal loss is associated with 'active' reactive, fibrillary astrocytosis. The degeneration has an ordered, topographic distribution. The tail of the caudate nucleus shows more degeneration than the body, which in turn is more involved than the head. Similarly, the caudal portion of the putamen is more degenerated than the rostral portion, and the dorsal regions are more involved than the ventral ones.

Most investigations using HD postmortem brain samples since 1985, when the findings were published, include a correlation between results and grade or neuropathologic severity.<sup>1</sup> I discuss here how this grading system was developed, and how it happened that I had the opportunity to participate in its crystallisation.

My training in neuropathology started in 1978, in the 'Division Autonome de Neuropathologie' in Lausanne, Switzerland. The late Dr Theodore Rabinowicz, then director of the Division, encouraged me to join the Massachusetts General Hospital (MGH) in Boston to expand my professional experience. The late Dr Edward Pierson Richardson Jr was then the director of the laboratory of neuropathology at the MGH. In February 1981, I joined Dr Richardson's team. From the outset, Dr Richardson's scientific rigour and dedication profoundly impressed me.

In 1978, Harvard University had recruited Dr Edward Denis Bird to establish what is now known as the Harvard Brain Tissue Resource Center (or BTRC, as it was then called). The BTRC was not fully functional during its construction. Nonetheless, brains were collected for research. Each brain obtained was sectioned fresh sagittally through the corpus callosum. One-half was frozen en bloc as soon as possible after death, and stored at -80°C. The contralateral half was immersed in formalin and kept in storage until the logistics were in place for performing the neuropathological evaluation. Thus, fixed, half-brains accumulated. Each one was to be thoroughly evaluated to reach the best diagnostic categorisation through a rigorous clinicopathological correlation. Unless indicated otherwise by the clinical history, it was assumed that the changes observed in the fixed half-brain would be representative of the changes involving the frozen contralateral half. The frozen brains in storage were not eligible for disbursements to investigators, as definite diagnoses were not assigned to them. In June 1981, while Dr Richardson



The late Dr Edward Pierson Richardson Jr, and Jean Paul Vonsattel, MD.

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and I were evaluating surgical specimens microscopically at the MGH, Dr Bird brought a set of histology slides. He was anxious to find out whether the histology sections exhibited the changes confirming the clinical diagnosis, which would determine whether a request of tissue samples for research could be fulfilled. Kindly, Dr Richardson provided Dr Bird the response he sought. This event triggered the fruitful collaboration between Dr Bird, Dr Richardson, and me that led to the neuropathological staging of HD.

In the meantime, up to 80 formalin-fixed half-brains, including more or less 65 that were from individuals who carried the clinical diagnosis of HD, had to be evaluated neuropathologically.

Dr Richardson suggested that I perform the examination of these brains under his supervision. At first, I hesitated, especially given the number of brains involved and my conviction

to return to Switzerland within the next six months. My doubt about the value of the effort increased when a senior scientist from whom I sought advice stated: "Once you've seen one HD brain, you've seen them all." That the brunt of the degenerative process was allegedly confined to the striatum further contributed to my indecision. However, I realised that evaluating these brains would afford the opportunity to work closely with Dr Richardson, whose extraordinary personality I gradually became aware of. Together, we designed a plan for performing the macroscopic and microscopic examinations of these brains. We employed a standardised protocol whereby each fixed half-brain would be sectioned, using external landmarks, to optimise the comparison between brains. Up to ten half-brains were sectioned during one session, each yielding 30 or more coronal slices from the cerebral hemisphere alone. Among them, four were selected for the ultimate comparisons. They were aligned on a table: a row per brain, and a column per the landmark specific to each one of the four slices. The landmarks included the nucleus accumbens, the anterior commissure, the subthalamic nucleus, and the lateral geniculate body. That most of the brains were from HD patients influenced our perception of their abnormalities. It was puzzling that among them, and despite the clinical data, were brains with apparently normal striatum on gross examination, which includes the caudate nucleus, putamen (together forming the neostriatum), and the globus pallidus. However, under the microscope, changes were detected. Initially fourteen, later eighteen, defined sites were selected for harvesting blocks to be processed for microscopic evaluation. These blocks were obtained from each of the fixed half-brains available to facilitate comparisons among brains from the same or different disease processes, and from controls. To secure diagnostic accuracy, additional blocks were harvested as per the findings during the macroscopic evaluation.

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