

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.¹ 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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The second series of 10 brains of the backlog, which were processed macroscopically, included one from an HD patient who had committed suicide, and whose father had died of the disease. On gross examination of the coronal slices, the rostral part of the neostriatum appeared normal. However, the body of the caudate nucleus was half the expected thickness, and the tail was barely distinguishable. The globus pallidus was unremarkable. Microscopic examination revealed neuronal loss and gliosis involving the dorso-paraventricular region of the head of the caudate nucleus, the nearby caudo-putaminal gray bridges, and the dorsal third of the putamen, although no volume loss was noticeable on gross examination. Furthermore, subtotal neuronal loss involved the tail of the caudate nucleus and, to a lesser extent, the body. Evidently, this brain displayed changes involving the neostriatum that were detectable in the early stage of the illness. Thus, the question was raised whether this gradient of neuronal loss and gliosis reflected the temporo-spatial, selective vulnerability of the HD striatum. Our interpretation of the findings was that the dorsal third of the rostral neostriatum is especially prone to degenerate in contrast to the relatively preserved ventral third including the nucleus accumbens. That the transition third exhibited the microscopic features of its two flanked zones supported the claim. Thus, within the degenerated part, reactive astrocytes were the predominant cells, while neurons were virtually absent. In contrast, the relatively preserved area displayed the nor-

mally expected cellular population, and was distinguishable from the intercalated zone, in which a mixture of apparently normal or degenerating neurons and reactive astrocytes were identifiable. The initial awareness of the regional heterogeneity of the cellular population of the neostriatum at different periods of the toxic process needed to be confirmed. The serial processing of a pool of brains from carefully categorised HD patients according to a strictly applied protocol did indeed allow reliable comparison of changes at different stages of the same disease.² Concomitant to these evolving observations, a group of basic scientists including Dr Nancy Wexler, James Gusella, and Marcy MacDonald were deeply involved in the search for the gene causing HD. Close interaction with members of the group contributed to the consolidation and improvement of the grading system, which has 5 grades (0-4) of severity of striatal involvement. The awareness of the dynamic research on HD steadily increased the donation of brains, which was coordinated by Tom Stevens, among others. Thus, the spectrum of the disease became gradually evident and was critically and constructively verified and improved by collaborators such as Drs. Robert Ferrante, Marian DiFiglia, and Tessa Hedley-Whyte. Dr Eric Myers assessed the hereditary and clinical features pertaining to the brains evaluated, and analysed the correlations between them and the grade assigned to the brains.³ When the candidate genes became available long before the actual gene was identified,

the samples that were most suitable for the tests were those from patients whose anterior neostriatum (e.g., at the level of the nucleus accumbens) was moderately involved. Indeed, these samples displayed within the same section the three previously mentioned zones of the neostriatum: one that was gliotic and devoid of neurons dorsally; an intermediary one less involved than the dorsal one; and the relatively preserved nucleus accumbens, which provided a kind of internal control.

The widely used grading system has helped to identify the earliest histopathological and biochemical changes in HD. For example, the analysis of low-grade HD striatum showed that immunoreactive enkephalin-containing neurons projecting to the external segment of the globus pallidus were more affected than the substance P-containing neurons projecting to the internal segment. It established that the striatal degeneration in HD appears to move simultaneously in a caudo-rostral direction and in a dorso-ventral/medio-lateral direction.

References

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Conference Report

Primary Care Neurology Society Meeting

Birmingham, UK, 17 May, 2007.

The Primary Care Neurology Society (P-CNS; www.p-cns.org.uk) seeks to develop links between primary and secondary care in order to optimise the care and management of patients with neurological disorders. A select audience (GPs and specialist nurses vastly outnumbering neurologists) converged on the Birmingham Hippodrome to hear presentations on a variety of topics of mutual interest and concern, including dementia, stroke and TIA, Parkinson's disease, epilepsy and headache.

A number of talks focused on how much GPs can and/or should do before involving secondary care, particularly in light of NICE or expert guidelines; for example whether or not to give a trial of medication in suspected Parkinson's disease prior to the recommended referral to an 'expert' for diagnosis (Paul Morrish), or diagnosing dementia and using the dreaded 'D' word (Louise Robinson). A study suggesting an average four year delay from first GP-recorded symptoms of dementia to actual diagnosis (*Fam Pract* 2007;24:108-16) may reflect, at least in part, diagnostic and therapeutic nihilism in this area, although with the latest (2006) NICE guidance on cholinesterase inhibitor use (and non-use)

such reticence may not necessarily seem inappropriate. Interestingly, an absolute criterion for referral to the speaker's clinic was GP performance of the MMSE, whereas we have found that less than 20% of referrals to a dedicated Cognitive Function Clinic report this as having been done. There was no firm guidance to GPs on the best screening or assessment tool for dementia, the MMSE being described as "the best of a bad lot". P-CNS would seem ideally placed to investigate this further, and provide advice. On the other hand, it might perhaps be seen as odd that the subject of dementia should be on the conference agenda when NICE/SCIE guidance essentially envisages no role for neurology in the diagnosis and management of this condition, despite its being the archetypal disease of higher brain function.

In a discussion on TIA/stroke (Ganesh Subramanian) it was suggested that any cerebrovascular neurological event lasting longer than one hour, rather than the current twenty-four hours, should be regarded as a stroke rather than TIA, and the ABCD2 risk stratification for TIA was promoted for wider use. Practical advice was on hand for the management of dif-

icult problems, including neuropathic pain (Chris Wells), for which codeine is apparently worse than placebo. Delegates were urged to consider the possibility of a neuropathic component to many chronic pain syndromes, including low back pain, with the therapeutic options that this may open up. The recognition of epilepsy syndromes was covered (Richard Hills) with the aid of illustrative video-EEGs, but some eyebrows were raised when the findings of the recently published SANAD trial (see *ACNR* 7(2): 39-40) were called into question on methodological grounds. A talk on the diagnosis and management of headache (Andrew Dowson) prompted lively debate. The need to recognise concurrent anxiety, depression, and social phobias which may drive the illness behaviour in chronic headache was emphasised, a point also relevant to neuropathic pain.

The need for a collaborative approach between neurologists and GPs is self-evident and will hopefully engage more practitioners, especially neurologists, in future P-CNS meetings.

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