

Enzyme activity and brain anatomy: lessons from HPRT deficiency



Lesch-Nyhan disease is a rare, X-linked disorder, related to deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). In addition to uric acid overproduction, HPRT deficiency affects motor and cognitive function and is associated with behavioural disturbances caused by unknown pathophysiological changes.¹

Since it was first described,² it has been known that one of the most conspicuous manifestations of Lesch-Nyhan disease is self-injurious behaviour, which manifests between 18 months and 13 years of age, causing severe lesions, mainly on the lips, tongue, and fingers. This behaviour is of an obsessive-compulsive nature and is not present in patients with partial HPRT deficiency (those with Lesch-Nyhan variant disease).^{3,4} Differences between patients with the classic Lesch-Nyhan disease phenotype and Lesch-Nyhan variant disease might help to elucidate the pathophysiological changes behind the neurological manifestations, including self-injurious behaviour. In *The Lancet Neurology*, David Schretlen and colleagues⁵ report results of their study of regional brain abnormalities in Lesch-Nyhan disease and its variants to identify affected brain regions and regions that differ between the two disease forms.

Previous autopsy and imaging studies have focused on the basal ganglia because the main clinical manifestations implicate basal ganglia dysfunction. Various results have been reported, including decreased dopamine concentrations, a mean 17% reduction of total cerebral volume, and reduced basal ganglia volume.^{6,7} However, the brain structure in patients with HPRT deficiency has not been fully described. Schretlen and colleagues⁵ report for the first time brain regional volumes, examined by voxel-based morphometry, in a complete range of HPRT-deficient patients (21 with classic Lesch-Nyhan disease and 17 with Lesch-Nyhan variant disease). Since 1995, voxel-based morphometry has been used to define structural patterns of brain damage in patients with movement disorders.⁸ The results of Schretlen and colleagues' study⁵ show a mean 20% decrease in intracranial volumes (17% in grey matter and 26% in white matter) in patients with classic Lesch-Nyhan disease compared with healthy controls,

and a mean 14% reduction (16% in grey matter and 14% in white matter) in patients with Lesch-Nyhan variant disease, which directly correlated with the severity of the clinical manifestations. Detailed anatomical brain regional analysis showed not only basal ganglia reductions, but also reductions in other connecting cortical and subcortical cerebral regions, such as limbic and frontotemporal structures, without affecting the occipital and parietal cortical areas. Unfortunately, no anatomical lesions could clearly distinguish patients with classic disease from those with the variant form.

These findings suggest that the clinical manifestations related to HPRT deficiency are associated with specific anatomical modifications that might be related to impaired brain development. The neurological indications of HPRT deficiency have been associated with dopaminergic system impairment.⁶ However, the extensive neuroanatomical abnormalities shown by Schretlen and colleagues⁵ cannot be explained by an isolated nigrostriatal dopamine pathway disturbance; other neurotransmitters, such as serotonin or adenosine, might also be pathogenic.⁹ This result renders a crucial unanswered question: what is the relation between HPRT deficiency and regional brain volume reduction?

The results of this study provide insight into this association. First, the investigators present new information for enhanced assessment of the neuroanatomical phenotype in patients with HPRT deficiency. Since 1984, we have diagnosed 45 patients with HPRT deficiency (32 [70%] of whom had classic Lesch-Nyhan disease). Most of these patients presented before their first birthday with reddish sandy urine, hyperuricaemia, or neurodevelopmental retardation. Some patients had a normal *HPRT1* coding region but decreased *HPRT1* mRNA expression of unknown cause.¹⁰ To the parent of such a patient, we could not readily answer questions such as: "Will my son bite himself?" The considerable overlap in grey matter reduction between classic and variant Lesch-Nyhan disease does not allow these disease types to be distinguished. However, the comparison of affected brain regions in both groups in this study showed several areas, including the posterior cingulate, the ventral striatum,

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and the orbitofrontal cortex, that tended to differentiate the groups of patients.

Second, from our 30 years of clinical experience, with follow-up of 20 patients, we have seen that Lesch-Nyhan disease gets worse over time; others have also noted evidence of progression of the disease (Nyhan W, University of California San Diego, personal communication). The results of Schretlen and colleagues' cross-sectional study⁵ do not support accelerated brain ageing. Longitudinal studies will be needed to assess individual neuroanatomical and functional variations over time to delineate whether HPRT deficiency is in fact a progressive disease.

Finally, although Lesch-Nyhan disease is a rare disease, self-injurious behaviour is a manifestation of many neuropsychiatric disorders. Therefore, there is much value in studying a rare disease that might ultimately shed light on more common disorders. Lesch-Nyhan disease was the first neurogenetic disorder for which the responsible enzyme was identified.¹¹ Close to the 50th anniversary of its first description in two siblings,² we continue to learn much from HPRT deficiency, an enzyme defect that substantially modifies brain anatomy.

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