Neurodegenerative Diseases: The Clinician's Dilemma—The Forest, Trees, or Roots

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In this issue of the Journal of Child Neurology, Percy reviews several categories of inherited neurodegenerative disorders of childhood, emphasizing the latest developments in the clinical assessments of these complex diseases. Within this ever-expanding field of pediatric neurology, the forest is no less bewildering now than ever before, requiring of the clinician astute, careful observation and continued understanding of the trees and the roots from which they spring.

In the beginning, only a few such disorders had been characterized. Diagnosis and classification of these disorders were based on careful clinical descriptions, sometimes supplemented with morphologic or microscopic studies of biopsy or postmortem material. Such studies have been gradually supplemented and eventually replaced by biochemical analysis of body fluids and organs.

In 1908, Garrod first proposed the concept of an enzyme blocking a single metabolic step as the basis for some inherited diseases. It was not until 50 years later, however, that Cori and Cori demonstrated the first enzyme deficiency in disease resulting from a single gene mutation. Current practice now includes identification of accumulated abnormal metabolites, definition of biochemical etiology, and methodologies for the identification of affected individuals and asymptomatic carriers. With increasing definition of the biochemical basis of these diseases has come the recognition and characterization of even greater numbers of distinct disorders. The current status of neurogenetics now permits meaningful genetic counseling and prenatal diagnosis for many of these conditions, and, as pointed out by Percy, enzyme replacement therapy is now under active clinical study.

Clinical and biochemical heterogeneity within an inborn error of metabolism may be imposed by quantitative differences in the activity of individual mutant enzymes or by deficient activities involving different mutant isoenzymes. Such differences are then reflected in changes expressed through the maturing nervous system, in which lesions incurred early in development might not become manifest until later in life. Although Percy addresses several complex categories of biochemical abnormalities, the array of diagnostic possibilities encountered by the clinician is much greater, including the disorders of lipid, pyruvate, purine, and pyrimidine metabolism, the aminoacidopathies and the mucopolysaccharidoses, other distinct leukodystrophies without known metabolic cause, and a variety of diseases in which the metabolic abnormality is incompletely defined, such as Wilson's disease, Menkes' syndrome, Canavan's disease, Leigh's disease, Lowe's syndrome, and the Zellweger syndrome, which has recently been defined as a disorder of peroxisomal function.

When faced with such a diagnostic task, the clinician must find the tree within the forest by means of a multiparameter evaluation, using a combination
of careful history, accurate pedigree, clinical findings, and screening tests, followed by chemical analysis of urine and blood, and comprehensive biochemical and structural analyses of brain and peripheral tissues, in addition to available neuroimaging and neurophysiologic techniques.\textsuperscript{5–11}

It is tempting when undertaking such a task to seek the roots or causes immediately. Although such disorders of metabolism may be common in childhood, some cases defy attempts at screening or definitive diagnosis.

There is no simple solution, but centralized registries and increased numbers of geographically identifiable centralized tertiary care facilities for such patients would greatly facilitate their evaluation, diagnosis, and management.

\textbf{References}