■ Mild nonketotic hyperglycinemia caused by glycine decarboxylase mutations

Novel mutations of the *GLDC* were found by Dinopoulos et al. in three adults with hyperglycinemia and mental retardation. This mild NKH phenotype is the result of the residual enzyme activity demonstrated in the in vitro expression analysis.

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■ Nonketotic hyperglycinemia in adults: Anticipating the unexpected

Commentary by Alan Percy, MD

The inherited neurometabolic disorders of organic acid metabolism typically present during infancy or early childhood, in many instances as an acute and occasionally irreversible neonatal encephalopathy. As such, approaches to diagnosis and management generally follow a predictable pathway. Diagnosis of delayed-onset forms of these disorders, in which the pattern of presentation may be insidious, is often challenging. Rather than an acute encephalopathy, the clinician is more likely to encounter altered personality or aggressive behavior, cognitive impairment, impaired school or work performance, or abnormalities of tone and movement, including gait dysfunction or dyskinesias. Despite the non-specific nature of these clinical features, advances in neuroimaging and biochemical and molecular genetics make it possible to come to a diagnosis. Furthermore, delayed onset may be due to significant residual enzyme activity as is well known in other inherited metabolic diseases such as the

mucopolysaccharidoses, the oligosaccharidoses, and the sphingolipidoses.¹⁻³ Such phenotype-genotype differences most likely relate to the type and position of the specific mutation and may have implications for treatment.

Dinopoulos et al. describe the clinical and laboratory features of delayed-onset forms of NKH. The common features of the three reported individuals include infantile hypotonia, cognitive impairment, and episodic behavior problems, especially aggressive outbursts. None had features of metabolic crisis as seen in classic NKH. Two distinct mutations (A389V and R739H) in the glycine decarboxylase (*GLDC*) gene were identified in these individuals. Each mutation was associated with significant residual enzyme activity, representing a striking contrast to the common mutation (S564I) seen in classic NKH in which no residual activity is noted. This paper underscores the need for diligent pursuit of a specific diagnosis in individuals whose pattern of presentation dif-

fers from that expected for the classic forms. We have the necessary diagnostic tools. With significant residual enzyme activity, treatments that are ineffective in classic NKH, namely low protein diet, sodium benzoate to bind glycine and facilitate its excretion, and folic acid, a necessary cofactor in the glycine cleavage system, may be helpful. It is reasonable to postulate that early diagnosis and treatment may improve outcome.

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