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50 Years Ago in *The Journal of Pediatrics*

Diazoxide-Induced Hyperosmolar Nonketotic Coma: Contemporary Genetic Insights

Balsam MJ, Baker L, Kaye R. Hyperosmolar nonketotic coma associated with diazoxide therapy for hypoglycemia. J Pediatr 1971;78:523-5.

Diazoxide has been used for the treatment of hypoglycemia since the 1960s.[1] In 1971, Balsam et al published this case report, noting the rare association of a child receiving treatment with diazoxide for hyperinsulinemic hypoglycemia and the development of nonketotic hyperosmolar coma in the setting of *Hemophilus influenza* bacteremia.[2] Nearly 35 years later, Pearson et al examined birth weight and hypoglycemia in infants born to families with mutations in the maturity-onset diabetes of the young (MODY) genes: HNF4A and HNF1A/TCF1. In addition, they studied pancreatic beta-cell deletion of HNF4A in mice that developed hyperinsulinemia in utero and hyperinsulinemic hypoglycemia at birth. They discovered HNF4A to be a cause of neonatal hypoglycemia.[3] Based on this novel observation, Flanagan et al further explored the HNF4A mutations in a large cohort of patients with diazoxide-responsive hyperinsulinemic hypoglycemia, not just those with family history of the MODY gene mutation. The team found HNF4A mutations to be commonly associated with diazoxide responsiveness in the treatment of hyperinsulinemic hypoglycemia.[4] Taking this correlation a step further, Arya et al reported that the HNF4A mutation is associated with exceptional sensitivity to diazoxide therapy and thus serves as a risk factor for the development of nonketotic hyperosmolar coma. Their group suggests lower doses of diazoxide (1.5 mg/kg/d), instead of traditional dosing (5 mg/kg/d), in patients with this mutation to prevent this rare complication.[5] It is now worth considering screening for HNF4A mutations before initiating diazoxide treatment. Kudos to Balsam et al, who identified a rare but serious complication of diazoxide treatment that may now be preventable.

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