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A new case of Congenital Hyperinsulinemic Hypoglycemia due to M/SCHAD deficiency: the contribution of metabolic and molecular diagnosis for the management

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Congenital Hyperinsulinemic Hypoglycemia (CHH) is a rare metabolic disease (prevalence <1/1.000.000) characterized by a persistent hypoglycemia and high secretion of insulin in the neonatal and infancy period. An early management of patients with CHH is mandatory to avoid brain damage. Recent advances in molecular analysis have linked CHH to mutations in nine genes: ABCC8, KCNJ11, GCK causing either diazoxide-responsive or diazoxide-unresponsive Hyperinsulinemic Hypoglycemia, and GLUD1, HADH, SLC16A1, UCP2, HNF4A and HNF1A, causing generally diazoxide-responsive CHH. However, HADH defect is the most common form in presence of consanguinity and diazoxide-responsiveness. The HADH gene codifies the M/SCHAD mitochondrial enzyme, which catalyses the penultimate reaction in the β-oxidation of medium and short-chain fatty acids, causing in some affected individuals an elevated plasmatic hydroxybutyrylcarnitine and urinary medium-chain dicarboxylic, and 3-hydroxydicarboxylic metabolites. To date about 40 cases of M/SCHAD defect have been reported in literature.We report here a new case of CHH due to M/SCHAD deficiency. The index case was a Pakistan infant, born from consanguineous parents, showing a diazoxide-responsive hyperinsulinism and organic aciduria. The M/SCHAD deficiency was confirmed by the molecular diagnosis performed by sequencing of HADH gene, which revealed the presence of the nonsense mutation c.706C>T (p.R236*) in HADH gene, at homozygous state, while both parents were heterozygous for the mutated allele. The patient started diazoxide treatment at the maximum dose of 10 mg/kg/day, which resulted in adverse drug reactions (hypertrichosis, peripheral edemas and persistent hypertension) gradually solved with antihypertensive regimen. Diazoxide was progressively titrated to 2 mg/kg/day with good results in glycemic control and no hypertensive crisis. Low organic aciduria was followed.In conclusion, when the metabolic profile suggests a CHH disorder, the molecular analysis is necessary for the precise diagnosis and the appropriate counseling to the parents, also for the possibility of a prenatal diagnosis. In this setting, the definitive diagnosis of CHH, due to M/SCHAD deficiency, may suggest also the most appropriate therapeutic intervention to avoid both risk of worsening or adverse drug effect.

References

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