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Molecular analysis has allowed the definitive diagnosis of multiple acyl-CoA dehydrogenase deficiency (MADD)

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Multiple acyl-CoA dehydrogenation deficiency (MADD) is a rare autosomal recessive disorder due to defects in the electron transfer flavoprotein (ETF) or in the electron transfer flavoprotein dehydrogenase (ETFDH) enzymes, involved in the mitochondrial electron transport chain. Patients with MADD fall into different clinical phenotypes, ranging from a severe neonatal presentation, with metabolic acidosis, cardiomyopathy and liver disease to a mild childhood/adult disease, with episodic metabolic decompensation, muscle weakness and respiratory failure.Nowadays, the MADD diagnosis is established by the presence of dicarboxylic organic acids and acylglycine derivatives in the urine and increased levels of medium-and long-chain acylcarnitines in the blood. Mutations in ETFA, ETFB, ETFDH genes, encoding for alpha and beta subunits of ETF and for ETF-dehydrogenase are associated with MADD. We report the case of a three years old child, affected by lethargy and asthenia associated with anorexia. Biochemical analyses showed hypoketotic hypoglycemia with remarkable increments in transaminases, lactic dehydrogenase, aldolase and creatine kinase. The chromatographic layout of urinary organic acids showed a typical dicarboxylic aciduria. Thus, based on these features, MADD was suspected. Fifteen years later, at the age of 19, MADD diagnosis was confirmed by molecular analysis, showing a compound heterozygosity for the mutations c.1074G>C (p.R358S; HGMD: CM031670 in HGMD database) and c.1073G>A (p.R358K) in the ETFDH gene. The c.1073G>A (p.R358K; rs796051959) mutation is reported in ClinVar database as pathogenic allele, although lacking link to a specific clinical condition. However, familial segregation study and in silico analysis, performed by bioinformatics tools, confirmed that this substitution is likely pathogenetic. Her parents were healthy carriers of one of the two mutations. It is known that the severity of the clinical phenotype of MADD may be related to the type of mutation in the ETFA/ETFB/ETFDH genes. Particularly, missense mutations in the ETFDH gene, leaving a detectable residual enzyme activity, may account for the milder form of the disease, as is the case here. In conclusion we suggest that molecular analysis is essential to the definitive diagnosis of MADD and to direct the adequate therapeutic management. Thus, through a close nutritional follow up, a few months ago the patient gave birth to a healthy boy.

References

Olsen et al. Clear relationship between ETF/ETFDH genotype and phenotype in patients with multiple acyl-CoA dehydrogenation deficiency. Hum Mutat. 2003; 22:12–23.