PROTEIN MISLOCALIZATION AND LONG TERM FOLLOW-UP OF A PATIENT WITH MALONYL-CoA DECARBOXYLASE DEFICIENCY

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Malonyl CoA decarboxylase (MLYCD) plays a potential role in fatty acid metabolism in mitochondria. MLYCD deficiency is an inherited autosomal recessive disorder present in infancy or childhood with seizures, central nervous system involvement, cardiomyopathy and excretion of excess malonic acid. Several subcellular localizations for MLYCD have been suggested. However, the localization is still controversial because its canonical targeting sequence is peroxisomal. We present a long-term follow-up of a patient with MLYCD deficiency caused by protein mislocalization. Neonatally the patient had feeding difficulties, failure to thrive and somnolence. Urinary organic acid analysis showed malonic aciduria and tandem mass spectrometry profile showed elevated malonylcarnitines. Malonic acid and methylmalonic acid levels were high in cerebrospinal fluid than in blood serum. At age 2, brain MR imaging showed delayed myelination and abnormal signal in cerebral white matter. At age 5, moderate problems in motor coordination and balancing were observed. Neuropsychological testing showed mild mental retardation. Sequencing of genomic DNA extracted from fibroblasts revealed only one heterozygous mutation at exon 1 region of second methionine codon of MLYCD gene which was also detected in mother DNA but not in father DNA. Immunocytochemistry analysis showed that patient fibroblasts have diffused cytoplasmic and a more pronounced nuclear staining whereas control and maternal fibroblasts showed mitochondrial/peroxisomal staining. Although the clinical and biochemical findings are consistent with MLYCD deficiency, only a single heterozygous mutation was found suggesting that mislocalization of the protein into the cytoplasm and potentially to the nucleus could be the cause for developmental delay.