METHYLMALONIC ACIDEMIA COMBINED WITH HOMOCYSTINURIA TYPE CblD (CblD-MMA/HC): REGARDING TWO CASES

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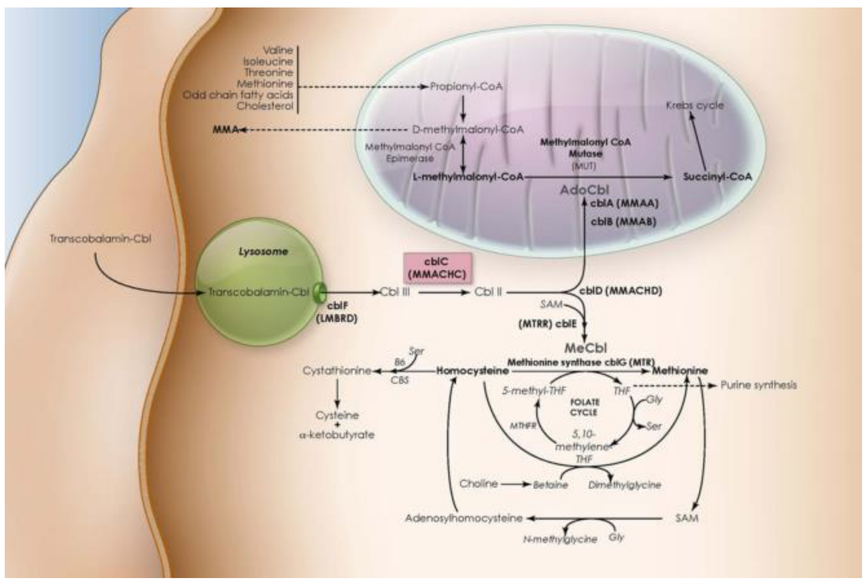
Basis and objectives

Methylmalonic acidemia with homocystinuria, included in the remethylation disorders of homocysteine to methionine, is a rare congenital error of vitamin B12 metabolism (cobalamin). There are four complementation groups of cobalin defects (cblC, cblD, cblF and cblJ), associated with methylmalonic acidemia with homocystinuria (MMA/HC). The defect causes decreased levels of the coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl), which lead to decreased activity of the respective enzymes methylmalonyl-CoA mutase and methionine synthase. CblD-MMA/HC is caused by mutations in the MMADHC gene (2q23.2) with an autosomal recessive inheritance pattern.

The objective of this presentation is to describe 2 cases of methylmalonic acidemia combined with homocystinuria type cblD-MMA / HC with late debut in the same family .



Castillo-Carrasco 2012

Case 1

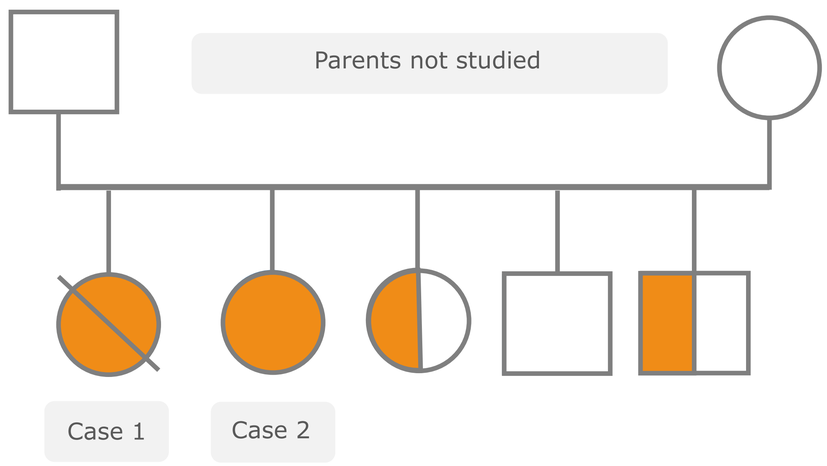
First daughter of healthy non-consanguineous parents. A wholesome girl and with adequate academic performance. At age 18, she presents an encephalopathic condition with an episode of 38'5 fever. TAC SNC: normal. Suspicion of herpetic encephalitis: acyclovir. Good and high cognitive evolution. She does not go to periodic reviews. Spasticity 10 months later: gait disorder with EEII. Cognitive impairment, bradypsychia and severe mixed demyelinating and axonal polyneuropathy with cerebral and corpus callosum atrophy. The patient presents a massive pulmonary thromboembolism. Irreversible deterioration and *exitus* without confirmed diagnosis.

Case 2

Second daughter (Case 1 sister): at age 15, a few months before her sister's death, begins, in a more subtle and slow way, a very similar picture associated with a cervical dystonia with tonic-clonic seizures. Poor academic performance and marked bradypsychia. The picture is superimposable to that of the sister, both clinically and radiologically (cerebral and corpus callosum atrophy) without polyneuropathy. Ataxic gait with spasticity. The metabolic study reveals increases in methylmalonic acid (urine, serum). Total homocysteine and propionylcarnitine (C3) elevated in plasma. Suspicion of Methylmalonic Acidemia with Homocystinuria.

Genetic study

The genetic study (NGS) confirms the presence of a homozygous c.748>T mutation (p.Arg250Ter) in *MMADHC* gene in both sisters. Diagnosis: Methylmalonic Acidemia with Homocystinuria.



Conclusions

Methylmalonic acidemia with homocystinuria is a rare, severe and difficult to diagnose clinical entity. The existence of an acquired or genetic remethylation disorder should be considered in those cases with neurological, visual and/or hematological symptoms of uncertain etiology, as well as in unexplained thromboembolic phenomena. Total homocysteine and methylmalonic acid are the main diagnostic metabolites in these types of disorders. High values of these parameters require a careful differential diagnosis because they can be observed in other more frequent conditions. It is essential to characterise the different complementation groups, since the treatment and response to it may be different. Molecular confirmation allows genetic counselling, highly reliable prenatal diagnosis in case of new pregnancy and determination of healthy carriers.

Bibliography

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