METHYLMALONIC ACIDEMIA COMBINED WITH HOMOCYSTINURIA TYPE CblD (CblD-MMA/HC): 3rd CASE OF GYPSY ETNIA DETECTED IN OUR LABORATORY.

Tomeu Oliver Tormo[1*], **Mireia Calvo Vega**[2*], Irina Royo[2], Dra. Cristina Camprubi[2], Albert Torrents[1,2]. Dr. Valentín Cadenas García[3]

[1]**Reference Laboratory Metabolics**, [2]**Reference Laboratory Genetics**, [3]Hospital Rafael Mendez. *Coauthors.

Basis and objectives

Vitamin B12 (cobalamin) is metabolised to methylcobalamin and adenosylcobalamin, two essential coenzymes for maintaining intracellular homeostasis of homocysteine (HC) and methylmalonic acid (MMA).

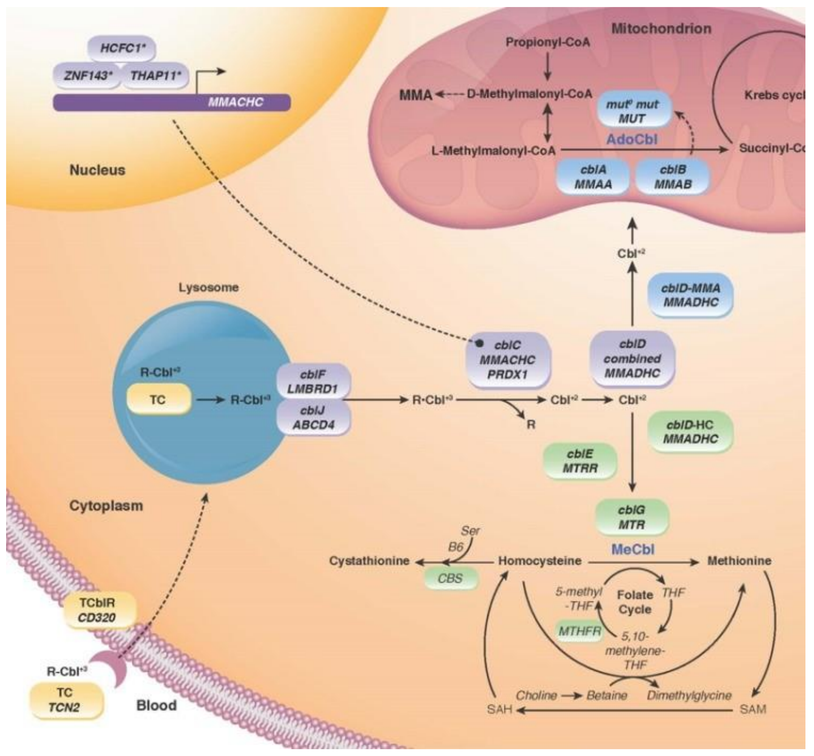
Acquired or inherited imbalances in the metabolism of cobalamin (Cbl) can lead to accumulations of HC and/or MMA in plasma and urine.

Disorders in their intracellular metabolism are classified from A to J according to clinical phenotype and genetic and complementation analyses.

CblD deficiency is one of the most rare and complex disorders of cobalamin metabolism since it can lead to patients with different biochemical variability depending on the nature and location of the variants present.

CblD-MMA/HC is caused by pathogenic variants in the *MMADHC* gene (2q23.2) that is transmitted following an autosomal recessive inheritance pattern.

Affected patients have variable symptoms: developmental delay, seizures, hypotonia, serious learning disabilities, behavioural disorders, and gait changes. The disorder can occur from early childhood through to adulthood.



GeneReviews: Disorders of Intracellular Cobalamin Metabolism

Clinical case

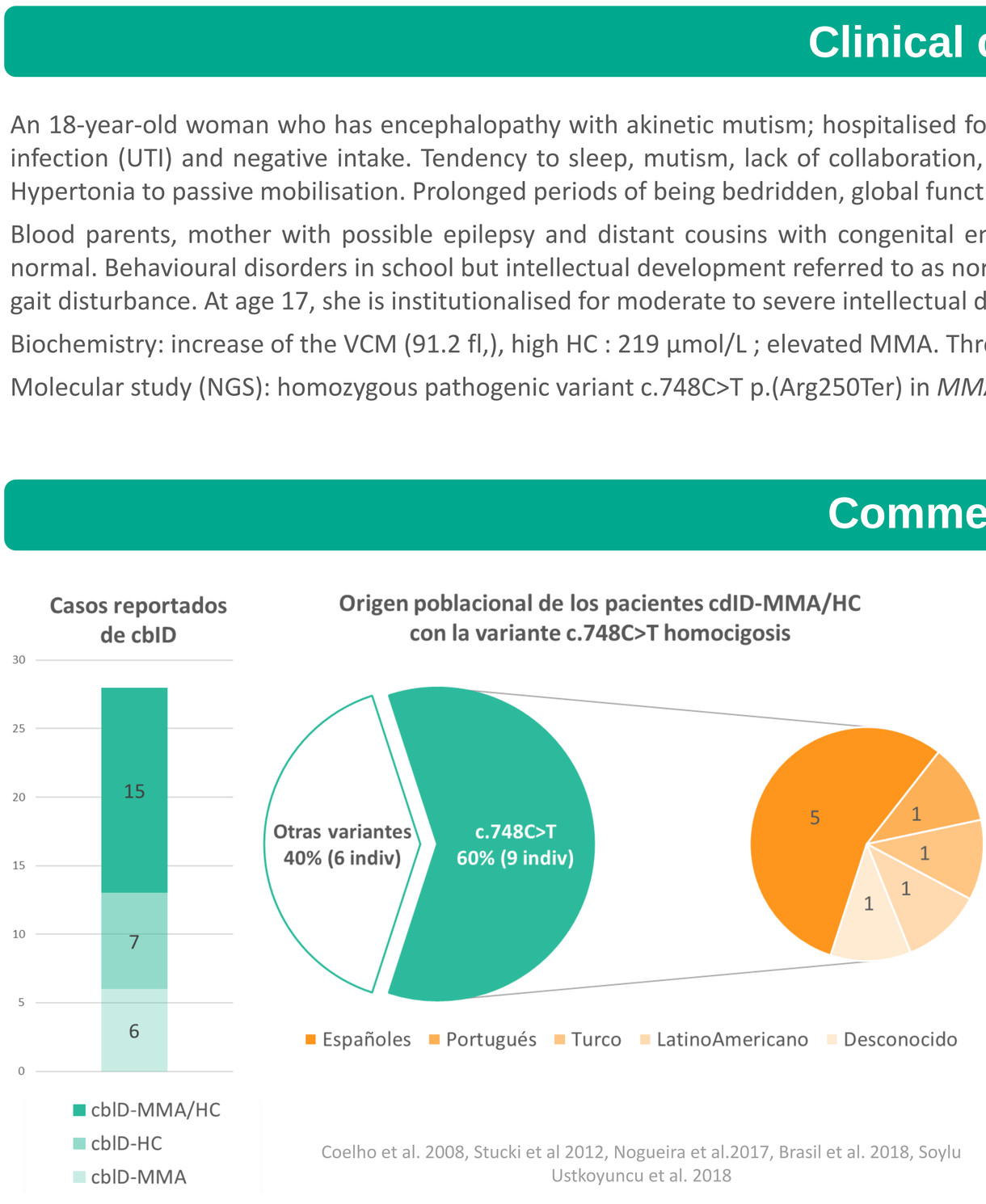
An 18-year-old woman who has encephalopathy with akinetic mutism; hospitalised for progressive deterioration of the general condition in relation to urinary tract infection (UTI) and negative intake. Tendency to sleep, mutism, lack of collaboration, and does not obey orders. Hypokinetic disease, decreased limb mobilisation. Hypertonia to passive mobilisation. Prolonged periods of being bedridden, global functional deficit.

Blood parents, mother with possible epilepsy and distant cousins with congenital encephalopathies. High family consanguinity. Early Psychomotor Development-normal. Behavioural disorders in school but intellectual development referred to as normal. Pregnant at age 14, after childbirth she had agitation and depression with gait disturbance. At age 17, she is institutionalised for moderate to severe intellectual disability, not associated with behavioural and heteroaggressive alterations.

Biochemistry: increase of the VCM (91.2 fl,), high HC : 219 µmol/L ; elevated MMA. Thrombosis in jugular vein.

Molecular study (NGS): homozygous pathogenic variant c.748C>T p.(Arg250Ter) in *MMADHC* gene.

Comments



Coelho et al. 2008, Stucki et al 2012, Nogueira et al.2017, Brasil et al. 2018, Soylu Ustkoyuncu et al. 2018

We have detected 9 cases of disorders related to intracellular metabolism of cobalamin in our laboratory : 6 cases of CblC disorder (most common of all) and 3 cases of CblD-MMA/HC. In the latter, we identified two sisters in 2017 and this third case in 2019. In all three, the same pathogenic variant was found, giving the circumstance that they are two families of gypsy ethnicity settled in 2 different Spanish autonomous communities.

Considering that the three patients diagnosed, in our Laboratory as CblD-MMA/HC with autosomal recessive inheritance have the same genetic cause, and taking into account the consanguinity that usually exists in gypsy families, It is assumed that this variant may be a predominant variant in the gypsy population in our country. However, to deepen this hypothesis, population studies would need to be carried out.