MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY (MAD)

WHAT IS MAD DEFICIENCY?

It is an inborn error of metabolism of autosomal recessive inheritance. In most cases, multiple acyl-CoA dehydrogenase deficiency (MAD) is caused by the defect of electron transfer flavoprotein (ETF) or its oxidoreductase [ETF-QO: electron transferring flavoprotein to ubiquinone (CoQ)].

WHAT ARE FLAVOPROTEINS?

They are proteins that require a derivative of the riboflavin (vitamin B2) cofactor for its function. They consist of a nucleic acid bound to flavin: flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN). Flavoproteins are involved in a wide range of biological processes, including those of redox or dehydrogenation.

WHAT IS THE ROLE OF ELECTRON TRANSFER FLAVOPROTEINS (ETF / ETF-QO)?

These flavoproteins (ETF/ETF-QO) lose electrons from redox processes catalyzed by dehydrogenases to the mitochondrial electron transport chain (respiratory chain), i.e. they link redox reactions of dehydrogenase flavoproteins to the oxidative phosphorylation and thereby contribute to the production of cell energy (ATP) in the mitochondria.

HOW DO THE ACYL-COA DEHYDROGENASES FUNCTION?

During dehydrogenation reactions (redox), the reduced FAD (FADH2) transfers its electrons to oxidized ETF and hence to the mitochondrial electron transport chain for energy production. Reduced ETF (ETF H2) is recycled through ETF-QO oxidoreductase (ETF dehydrogenase). ETF or ETF-QO deficiency leads to a defect in many FAD-dependent dehydrogenases.

Some MAD-deficient patients show no changes in ETF or ETF-QO, so it is assumed that there may be other yet unknown proteins involved.
WHY DOES A HEREDITARY DEFECT OF MAD OCCUR?

Each of the flavoproteins involved in redox processes (ETF/ETF-QO) is genetically determined (encoded). When a mutation (stable and heritable change) in one of the genes encoding any of these proteins occurs, this protein shows changes in the concentration or structure that can alter its function.

All MAD causing defects are inherited in an autosomal recessive way, i.e., parents carry mutations in one of these genes, but they do not suffer the effects of the deficiency. If both parents pass on a mutation to the child, the baby will suffer multiple dehydrogenase deficiency (MAD).

WHAT HAPPENS IN MAD DEFICIENCY?

As noted above, MAD deficiency causes a blockage at various points of the β-oxidation of fatty acids, of the metabolism of leucine, lysine and sarcosine, among others. All these blockages involve a major interference in the production of energy, in the formation of ketone bodies in the fasting state, and the accumulation of various compounds involved in these metabolic pathways.

WHAT IS THE CLINICAL PRESENTATION OF MAD DEFICIENCY?

The clinical characteristics of MAD deficiency are heterogeneous, but can be grouped in three main forms:

1. **Severe neonatal form**, characterized by hypoketotic hypoglycemia, metabolic acidosis, and multisystem involvement. It can be associated with congenital malformations such as facial dysmorphism, indicating that the damage is already prenatal. Excretion of metabolites derived from fatty acids and amino acids are abundant.

2. **Late-onset form**, appearing at a variable age, is characterized by recurrent episodes of lethargy, vomiting, hypoglycemia, metabolic acidosis and hepatomegaly, often triggered by a metabolic decompensation.

3. **Myopathic form**, of late presentation sometimes even in adulthood, involving the muscle as pain, weakness and lipid storage myopathy. The organic aciduria only reveals in decompensation periods.

HOW IS MAD DEFICIENCY DIAGNOSED?

Diagnosis is based on clinical presentation (hypoketotic hypoglycemia) or by extended neonatal screening of fatty acid β-oxidation defects.

The study of **organic acids** in urine shows a characteristic profile of dicarboxylic acids, among them ethylmalonic and glutaric acid. A typical acylglycines profile is also observed (isovalerylglucose and hexanoylglycine). In blood, apart from **hypoketotic hypoglycemia**, free fatty acids, and acylcarnitines are high, while lactic acidosis, secondary carnitine deficiency, and variable increase in
hepatic enzymes and CK were detected. In the late form this profile is only evident during periods of metabolic decompensation.

**Diagnosis of MAD deficiency**

**Neonatal screening** for MAD deficiency, with initiation of appropriate treatment, prevents decompensation and possible sequels, so it is currently being applied in many countries.

The diagnosis is confirmed by the study of the oxidation of labeled palmitate in cultured fibroblasts.

The study of mutations in the genes encoding the α and β subunits of ETFα/ETFB and ETF-QO definitely confirms the diagnosis. Genotype-phenotype correlation was observed, since two severe mutations involve severe neonatal presentation, while mild mutations that allow some residual activity lead to a late presentation form.

Genetic testing allows the family genetic counseling and prenatal diagnosis, if required.

**MAY MAD DEFICIENCY BE TREATED?**

Although there is no effective treatment for severe neonatal forms, early diagnosis and early introduction of dietary treatment (restriction of protein and fat) supplemented with riboflavin and coenzyme Q10 can improve prognosis, especially in the late-onset and myopathic forms.

As MAD deficiency affects the oxidation of fats and amino acids, a fat-low protein-low diet should be applied.

Riboflavin treatment is associated to clinical improvement and normalization of lactate and CK in the late and myopathic forms although neonatal severe forms usually are unable to respond to such supplementation. A positive effect Coenzyme Q10 supplementation is also observed.

**Treatment of MAD deficiency**

Carbohydrate-rich, fat-low, protein low diet

Furthermore, the common treatment of all defects of β-oxidation based on preventing hypoglycemia should be applied. It is achieved by:

1. **Avoiding prolonged fasting**, by fractional diet.

2. Using a carbohydrate-rich diet, using slow carbohydrate absorption products (see “Avoiding hypoglycemia”).

3. In situations of stress (infections, fever) avoid prolonged fasting ensuring an adequate intake of carbohydrates (based on beverages or foods rich in carbohydrates) (see Guideline for decompensation).

**Translation**

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