3- METHYLCROTONYL CoA CARBOXYLASE DEFICIENCY: DISORDER OR JUST A BIOCHEMICAL PHENOTYPE?

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INTRODUCTION

3-Methylcrotonylglycinuria (MCG) is an inborn error of the leucine catabolism resulting from isolated biotin-insensitive deficiency of 3-methylcrotonyl-CoA carboxylase (3-MCCD), the enzyme converting 3-methylcrotonoyl-CoA to 3-methylglutaconyl-CoA (1).

Before the introduction of expanded newborn screening 3-MCCD was considered extremely rare but is now found in a number of asymptomatic babies or sometimes in their mothers. This is the commonest organic aciduria found by screening, with a incidence of about 1:32 392 in our country.

The clinical phenotype has been shown to vary considerably, ranging from entirely asymptomatic to death in infancy. The metabolic phenotype characterizing 3-MCCD is the elevated excretion of the diagnostic compounds 3-methylcrotonylglycine and 3-hydroxyisovaleric acid in the urinary organic acids , and the presence of abnormally elevated blood levels of 3-hydroxyisovalerylcarnitine (C5-OH), as determined by tandem mass spectrometry (MS/MS). Many patients also develop a severe secondary carnitine deficiency.

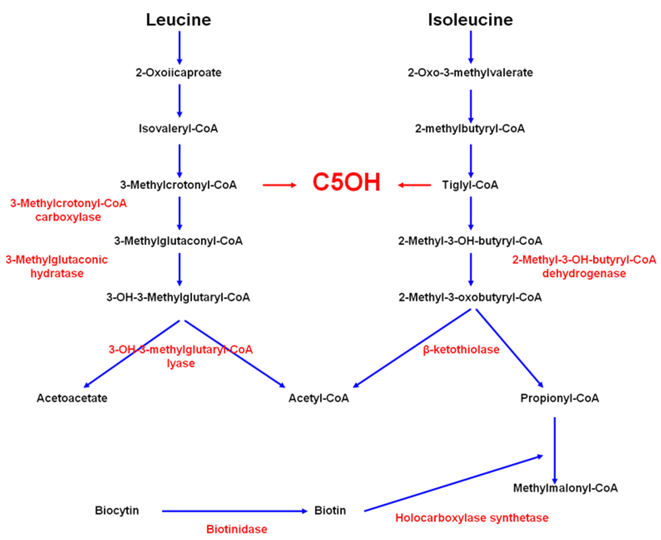

Figure 1: The L-Leucine catabolic pathway and the site of the defect in 3-methylcrotonyl-CoA carboxylase deficiency (MCC).

Increased C5OH, a side metabolic product of leucine and isoleucine metabolism (figure 1), can be associated to several diseases besides 3-MCCD, namely 3-methylglutaconic hydratase deficiency, 2-methyl-3-hydoxybutyryl-CoA dehydrogenase deficiency, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (3-HMG), β-ketothiolase deficiency, holocarboxylase synthetase deficiency, and sometimes biotinidase deficiency. Only three of this diseases are included in the Portuguese Newborn Screening panel (3-MCCD, 3-HMG and holocarboxylase synthetase deficiency).

The aim of this study is to demonstrate that although 3-MCCD has low clinical penetrance is important to identify these patients to prevent further decompensation.

PATIENT AND METHODS

The authors present a study case, a symptomatic 3-y-old-boy, of Spanish nationality, with an increase of C5-OH in the acylcarnitine profile who has a developmental delay. The genes MCCA and MCCB, encoding the 3-MCC enzyme were studied by standard methods.

Since the beginning of extended Newborn Screening in 2004, about 715.000 newborns samples collected between days 3 and 6 in Watman 903 filter paper blood spot, were tested through tandem mass spectrometry analysis of acylcarnitines as butyl esters (2).

Suspected cases were confirmed through acylcarnitines analysis in a new blood spot sample and organic acid analysis in urine.

RESULTS

This patient in acylcarnitines profile has a concentration of 3.7μM C5OH (N<0.52 μM) and in profile of urinary organic acids only has excretion 3-hydroxyisovaleric acid without excretion of 3-methylcrotonylglycine.

The molecular study has allowed the identification in the *MCCB* gene of the *frameshift* mutation p.S173FfsX25 and the *missense* mutation p.V339M. Both mutations are described in the literature (3,4).

The screening of 715.000 newborns lead to the identification of 31 patients with high concentrations of C5OH (0.85 a 14.5 for normal until 0.57 μM).

The organic acid analysis in urine and in some cases molecular studies allowed to establish a differential diagnosis in these patients (fig. 2).

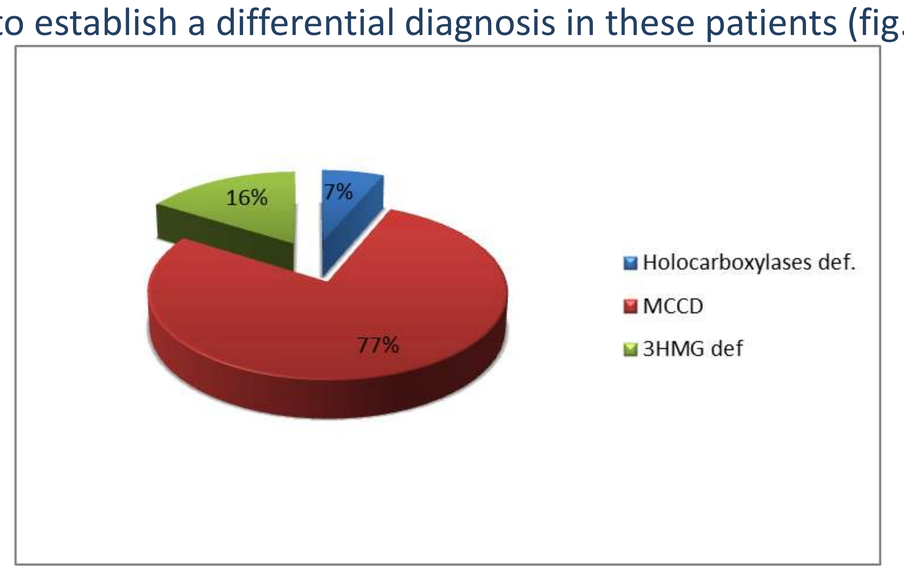

Figure 2-Distribution of patients according to differential diagnosis.

DISCUSSION

The 3-MCCD is a pathology not completely understood and its clinical phenotype is very heterogeneous, and often highly variable even within the same family. The phenotype ranges from neonatal onset with severe neurological involvement and even lethal cases to asymptomatic adults. Some patients develop an acute metabolic crisis usually triggered by intercurrent infections or introduction of a protein-rich diet in early childhood. A review of the literature on 37 individuals indicates that only 27% developed normally and stayed completely asymptomatic. Approximately 30% were reported to suffer from muscular hypotonia and psychomotor retardation, respectively, and almost half suffer from various other neurological symptoms. Even a lethality of 11% was observed. (1)

Most patients show private mutations in compound heterozygosity making the phenotype-genotype correlation difficult.

The newborn screening identification of patients which can develop symptoms seems to indicate that this disease should be included in NBS programs. More studies are needed to find genetic and/or biochemical markers that explain why a relatively small number of individuals are at risk of developing a severe disease phenotype.

This study demonstrated that an important reason to include 3-MCCD in our panel is that there are other disorders, some of which with severe phenotype, detected by the marker C5OH. If 3-MCCD was not part of the NBS panel, these patients would only be identified by the first symptoms, hindering the possibility to start early therapy and the aim of NBS is primarily to produce a good clinic outcome for babies by early diagnosis of treatable disorders, and facilitation of appropriate treatment.

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