Maternal Glutaric aciduria type I and Newborn Screening

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INTRODUCTION

Expanded Newborn Screening (NBS) programs based on MS/MS, result in a massive increase of screened metabolic disorders and detected patients. Alongside with the detection of classical forms of screened metabolic disorders, milder forms (many whose existence was unknown until now) are being detected, representing major challenges in respect to follow up protocols.

Disease spectrum of screened disorders is being stretched, through the detection of undiagnosed mothers through their son's newborn screening results. In these cases, abnormal screening results are due to maternal rather to neonatal disease. The most common examples are newborns from mothers 3-mthylcroyonyl-CoA-carboxylase deficiency (with newborns usually presenting elevated 3-hydroxy-isovalerylcarnitine and/or low free carnitine) and from mothers with Primary Carnitine Deficiency (with newborns usually presenting low free carnitine). More rarely low free carnitne values in the newborns have been associated to other maternal conditions, namely glutaric aciduria type I (1).

Glutaric aciduria type I (GAI) (MIM# 231670) is an autosomal recessive inherited metabolic caused by a defect of the enzyme glutaryl-CoA dehydrogenase. Clinically GAI, a neurometabolic disorder firstly described by Goodman (2) is characterised by a progressive neurodegeneration that typically manifests acutely in infants during a intercorrent illness. The well known phenotypic presentations are fronto-temporal brain atrophy with macrocephaly and acute encephalopathic episodes with striatal necrosis followed by dystonic-dyskinetic movement disorder (3).

The authors will present NSB data of newborns from GA I mothers and from the mothers themselves.

SAMPLE AND METHODS

Newborn Screening:

Blood spot samples from Portuguese newborns are collected between day 3 and 6 in Whatman 903 filter paper. Two triple quadrupole tandem mass spectrometers (AbSciex) are used in our laboratory to perform the routine MS-MS neonatal screening method, which includes the analysis of aminoacids and acylcarnitines as butyl esters (4). Present data results from the screening of 1,249,175 newborns.

Diagnosis confirmation:

All diagnosis were confirmed using organic acid analysis and molecular approaches..

RESULTS

Since 2004, a total of 1.249.175 Portuguese newborns were screened by MS/MS and five newborns with acylcarnitine profile abnormalities, due to maternal GA I, were detected (1:249.835) (table 1) (figure 1). All newborns present extremely low levels of free carnitine (3.36 µM +/- 0.65; normal >9.13) and only one presented a slight elevation of glutarylcarnitine (0.22 µM; normal <0.20). During this same period a total of 16 newborns with true GA I were detected (1:78.730).

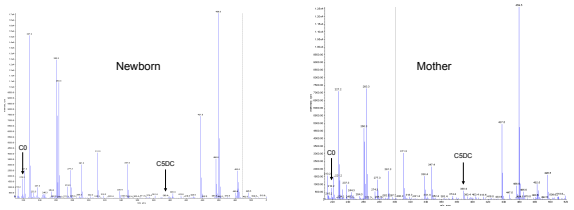

Figure 1: Example of an acylcarnitine profile of a newborn from a Glutaric aciduria type I mother and an acylcarnitine profile from his mother. C0 – free carnitine; C5DC – glutarylcarnitine.

Table1: Free carnitine and glutacrylcarnitine values of the five newborns detected as well as of theirs glutaric aciduria type I mothers.

Case	Age at sample collection	Free carnitine (C0)	Glutarylcarnitine (C5DC)
1	1 day	3,4 µM (Normal>9,13)	0,22 µM (Normal<0,20)
Mother of 1	adult	Not available	Not available
2	5 days	2,9 µM (Normal>9,13)	0,03 µM (Normal<0,20)
Mother of 2	adult	2,3 µM (Normal>16,4)	0,33 µM (Normal<0,09)
3	12 days	3,0 µM (Normal>9,13)	0,03 µM (Normal<0,20)
Mother of 3	adult	2,3 µM (Normal>16,4)	0,39 µM (Normal<0,09)
4	4 days	4,5 µM (Normal>9,13)	0,06 µM (Normal<0,20)
Mother of 4	adult	3,8 µM (Normal>16,4)	0,49 µM (Normal<0,09)
5	4 days	3,1 µM (Normal>9,13)	0,08 µM (Normal<0,20)
Mother of 5	adult	2,1 µM (Normal>16,4)	0,68 µM (Normal<0,09)

Results from the mothers of case 1 are not available, since the mother was already diagnosed with glutaric aciduria type I, but abandon treatment during all the course of the pregnancy.

DISCUSSION

These maternal cases represent milder forms of the disease, but where follow up is recommended. In order to maximize the detection of maternal conditions is advisable to test newborns mothers in all situations of unexpected findings or in situations of very low free carnitine.

The detection of affected mothers represents an important benefit of expanded newborn screening, with not only direct contributions to patients health but also creating the basis for an increasing knowledge on these disorders through the understand of their clinical spectrum.

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