Maternal glutaric aciduria type 1 (GA 1) detected through newborn screening in Croatia

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INTRODUCTION:

Glutaric aciduria type 1 (GA-1; OMIM#231670) is an autosomal recessive inborn error of metabolism caused by deficiency of glutaryl-CoA dehydrogenase (GCDH) located in the catabolic pathways of L-lysine, L-hydroxylysine, and L-tryptophan. The enzymatic defect gives rise to neurotoxic metabolite glutaric acid (GA) and 3- hydroxyglutaric acid (3-OH-GA) in the urine, and to glutaryl carnitine (C5DC), the marker metabolite used for newborn screening (NBS) . As in most inborn errors of metabolism, the phenotypic spectrum of GA 1 is broad. Most untreated individuals with GA-1 experience acute encephalopathic crises during the first six years of life that are triggered by infectious diseases, febrile reaction to vaccinations, and surgery. However, a small group of untreated GA 1 patients remains asymptomatic, even in adult life. Treatment for GA-1 consists of a low lysine diet, carnitine, and high-energy intake during illness.

OBJECTIVES:

We describe a woman with GA 1 in whom the diagnosis was unsuspected until a low free carnitine level was found in her twin infants during routine newborn screening.

METHODS:

Samples for NBS were prepared using Recipe reagent kit ClinSpot ® Complete Kits, amino acids and acylcarnitines in dried blood spots (DBS) on a tandem mass spectrometer coupled with high performance liquid chromatography, LC-MS/MS (MS8050 coupled with UPLC Nexera, both Shimadzu). Samples were ionized using electrospray ionization (ESI) in positive ion mode. Concentrations of individual acylcarnitine and amino acid species were calculated using isotope-labelled internal standards of known concentration for each analyte. Urine organic acids were analyzed on capillary gas chromatography coupled with mass spectrometry (GC-MS-QP2010Plus, Shimadzu).

RESULTS:

Isolated carnitine deficiency was found in one of the twin infants (GEM 1). The free carnitine (C0) concentration at day 3 in the newborn screening was 6.2 µmol/L (cut-off >8.8) (Table 1). Confirmation tests included plasma and DBS acylcarnitine profile for infants and their mother. The maternal DBS acylcarnitine profile showed markedly elevated glutarylcarnitine (C5DC= 1.9 µmol/L, cut-off <0.35) and decreased C0 (C0=4.0, cut-off >10). All of the metabolic findings of the baby were normal except for very low free carnitine level (Table 2). Additional metabolic testing for mother showed clear elevations of glutaric and 3-hydroxyglutaric acid in urine organic acid analysis (Figure 1). Neonatal parameters normalized during the following weeks and confirmatory work-up of the non-affected neonates is negative.

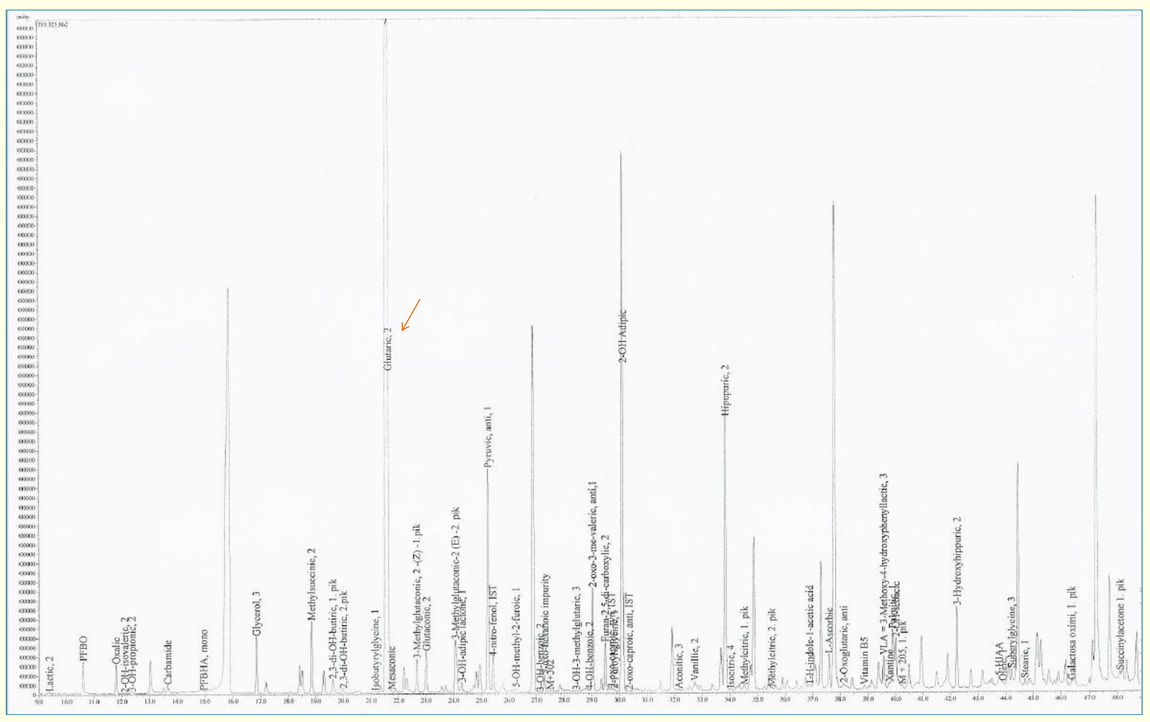

Figure 1. GC-MS total ion chromatogram of organic acid extracted from human urin

Acylcarnitines (µmol/L)	C0	C5DC
Cut-off	8,8	0,5
Gem 1	6,2	0,15
Gem 2	9,4	0,16

Table 1: Concentrations and range of acylcarnitines in newborn screening dried blood spot (DBS).

Acylcarnitines (µmol/L)	DBS		Plasma	
	C0	C5DC	C0	C5DC
Cut-off	10	0,350	10	0,350
Gem 1	7,6	0,095	9,3	0,095
Mother	4,0	1,9	/	/

Table 2: Concentrations and range of acylcarnitines in dried blood spot (DBS) and plasma.

CONCLUSION:

An asymptomatic woman with GA 1 was detected through her infant´s newborn screening. This case has confirmed that expanded NBS may, besides expected reduction in the number of deceased or affected children, also yield other useful results: It can detect certain diseases in a mother, some acquired diseases in newborns and diseases in siblings of ill children detected by screening.

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