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Maternal Glutaric Acidemia, Type I Identified by Newborn Screening*

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Abstract

We report two women with glutaric acidemia type I in whom the diagnosis was unsuspected until a low carnitine level was found in their newborn children. Both mothers had low carnitine in plasma. In the first, organic acid analysis was only done after fibroblast studies revealed normal carnitine uptake. Having learned from the first family, organic acid analysis was done immediately in the mother of family 2. In both, the plasma acylcarnitine profile was normal but both excreted the metabolites typical of their disorder. One of the women was a compound heterozygote for distinct mutations in the glutaric acid dehydrogenase gene, whereas the second was either homozygous or hemizygous for a mutation in Exon 6 of the gene.

Keywords

Glutaric Acidemia, type I; GA-I; Newborn Screening; Maternal Glutaric Acidemia

Introduction

Glutaric acidemia, referred to as type 1 because it was the first disorder in which excess glutaric acid was found in body fluids, was first described by Goodman et al in 1975 [1]. They demonstrated a deficiency in the enzyme glutaryl-CoA dehydrogenase (GCD)[1], subsequently shown to be due to mutations in the *GCD* gene[2]. All early cases were ascertained through clinically affected probands, many of whom were profoundly impaired, usually as a result of

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one or more severe metabolic crises triggered by otherwise mild or routine childhood illnesses[2,3].

It was more than a decade later that studies in the Amish population with a high frequency of a single mutation in the *GCD* gene, demonstrate that a number of individuals who were homozygous for this mutation reached late childhood and beyond with no discernable neurologic damage[4]. Others ascertained through affected siblings or through newborn screening and treated preemptively with a low lysine diet and rapid medical response to routine childhood illnesses are doing well clinically[5]. This improvement in outcome is recognized as a significant benefit of expanded newborn screening using tandem mass spectrometry (MS/MS)[5].

Within the last year, we and others have recognized that low carnitine ascertained during expanded newborn screening was sometimes associated with low maternal plasma carnitine levels and a carnitine transporter defect in the mother[6]. In this paper we report the discovery of maternal glutaric acidemia type 1 as a result of persistently low carnitine levels in the newborns and similarly low levels in the mother. These results reinforce the notion that like hyperphenylalaninemia, abnormal metabolite levels in newborns may lead to the diagnosis of maternal biochemical disorders[7].

Material & Methods

Case Report

Family 1—A male child born in late 2005 was the product of the second pregnancy to a non-consanguineous couple. There was 1 normal older sibling and an older half sibling. Pregnancy and delivery were normal and the boy is healthy and developing normally. The biochemical results are shown in table 1. The total carnitine concentration at 2 days in the newborn screening blood spot was 4μM. At day 12 it was 12 μM. The level rose rapidly on addition of carnitine to the treatment (100mg/kg/day in divided doses) and now on baby and table foods, the level remains normal without carnitine supplementation.

The mother was tested, initially for carnitine deficiency and her levels were found to be 2 μM in plasma. Skin fibroblast from the mother were shown by Dr. Nicola Longo to have normal uptake of carnitine. At this time, when her baby was 6 months old, urine organic acid analyses revealed a glutarate level of 1190 μmol/mmol creatine (nl<5) and 3-OH-glutarate was 40 (nl<6). Mutation analyses revealed compound heterozygosity for two mutations in the *GCD* gene (see below and table 1). The mother complained only of intermittent fatigue, apparently mitigated by carnitine 330 mg twice a day.

Family 2—This female was the 3rd pregnancy and delivery to a non-consanguineous couple with 2 healthy older children born in Mexico. Pregnancy and delivery were normal and the child born in July 2006 is healthy and developing normally. He was breastfed with supplementation with solid foods. The initial total carnitine level at 2 days of age was 7 μM and at 10 days was 2uM. He was started on carnitine 80 mg/kg/day and levels rose rapidly. They remain normal without carnitine supplementation.

Forewarned by family 1, we immediately obtained blood and urine from the mother. Plasma carnitine was 2 μM and urine organic acid analyses revealed glutarate 202 μmol/mmol creatinine (nl<5) and 3-OH-glutarate 38 (nl<6). Study of her DNA revealed a homozygous (hemizygous) mutation in exon 6. Mom complained of intermittent fatigue which has apparently been mitigated by carnitine 330 mg BID. She is otherwise well.

Laboratory Analysis

Analytes—Expanded newborn screening was carried out by the California Newborn Screening program which operated with contracts to six independent laboratories. Perkin-Elmer tandem mass spectrometers and reagents supplied by the manufacturer are used.

Followup testing was performed by Quest Laboratories (San Juan Capistrano, CA using their usual methods).

Carnitine Uptake Studies—These were done in skin fibroblasts in the laboratory of Dr. Nicola Longo by his usual methods[6].

Mutation Analysis—Mutation analyses were carried out in the University of Colorado at Denver and Health Sciences Center (Denver, CO) by sequencing all eleven exons and the exon/intron borders as described previously[2].

RESULTS AND DISCUSSION

Both mothers described in the paper had glutaric acidemia, type 1. Although plasma and urinary metabolite levels do not describe the potential severity of the genetic defect or the vulnerability of the person carrying them, the analyte levels are high enough, in urine, to suggest that the mutations are consequential and cause a severe disruption in the glutaryl-CoA catabolic pathway. On the other hand the normal results of the plasma glutarylcarnitine measurements underscores what is known from newborn screening, that affected individuals may not be ascertained by this method[8]. Whether the majority of older patients gradually evolve normal plasma levels of glutarylcarnitine is unknown to us at this time.

The mutations involved are consistent with the biochemical inference that these are severe mutations. In family 1, one allele is null as a consequence of a one base pair deletion in exon 1 (c11delG) and the second allele has cysteine substituted by phenylalanine at position 228 due to a T>G mutation in exon 7 (C228F:c682T>G). Although not previously reported, this substitution caused a significant change in amino acid properties and was likely, as reflected in the analytes, to cause a severe diminution in enzyme activity.

In family 2 the mother carried a single A>G mutation in exon 6 in apparent homozygousity (or hemizygosity), causing a glutamine at position 181 to be changed to a glycine (E181G:c542 A>G). Although not reported previously, this change from a larger charged amino acid to a smaller uncharged one and was likely to disrupt the protein structure greatly. Other known mutations causing changes in this amino acid residue have been associated with severe disease and positive enzymatic and biochemical analyses[2].

The fact that both women who were untreated were apparently unaffected by their condition is not surprising, given our knowledge of patients homozygous for these mutations who have not been treated[2]. A biochemically more mild condition is a plausible, but unlikely explanation. Neither is it surprising that the very low carnitine levels were either asymptomatic or minimally so. Although the plasma levels were as low or lower than patients affected with carnitine transporter deficiency, the presence of a normal transporter system likely resulted in a more favorable intramuscular carnitine level. Although this low carnitine level is presumably due to years of excretion of excessive glutarate as glutarylcarnitine, this was not pursued aggressively as it didn't impinge on the main purpose or conclusion of the paper.

It was the hyperphenylalaninemias that first establish the precedent of detecting maternal biochemical perturbations during newborn screening[7]. We have since added maternal methylcrotonyl-CoA carboxylase to this list[9] and we added at least two more, systemic

carnitine deficiency earlier this year[6] and now glutaric acidemia, type 1. This latter conclusion is supported by a similar observation made in 2 affected probands from Portugal and now published online prior to appearing in print[10]. Surely the list is not complete.

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TABLE 1

Clinical Biochemical and Molecular Results in Newborns and their Mothers

Individual	Carnitine µM Newborn screen	Early Followup*	Latest off carnitine*	Plasma glutarylcarnitine	Urine glutarate µmol/m mol creat	Urine-hydroxylgluta rate	Mutation consequence
Newborn M	4.8	7/5; 12/9	43/34	normal	normal	Normal	Not done
Mother M	---	2/1	On carnitine-12/7	normal	1190(nl<5)	40(nl<6)	Chain terminating/C228F
Newborn B	2/1	7.7	64/13	normal	Not done		Not done
Mother B	---	2/1	On carnitine-normal	normal	202(nl<5)	38(nl<6)	E181G/E181G

* Total/Free