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Screening of a healthy newborn identifies three adult family members with symptomatic glutaric aciduria type I

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ABSTRACT

We report three adult sibs (one female, two males) with symptomatic glutaric acidura type I, who were diagnosed after a low carnitine level was found by newborn screening in a healthy newborn of the women. All three adults had low plasma carnitine, elevated glutaric acid levels and pronounced 3-hydroxyglutaric aciduria. The diagnosis was confirmed by undetectable glutaryl-CoA dehydrogenase activity in lymphocytes and two pathogenic heterozygous mutations in the *GCDH* gene (c.1060A>G, c.1154C>T). These results reinforce the notion that abnormal metabolite levels in newborns may lead to the diagnosis of adult metabolic disease in the mother and potentially other family members.

1. Introduction

Glutaric aciduria type I (GA I, MIM #231670) is an autosomal recessive inborn error of lysine metabolism with an estimated prevalence of 1/100.000 neonates [1]. GA I is caused by mutations in the *GCDH* gene, encoding glutaryl-CoA dehydrogenase. The natural course is usually determined by acute encephalopathic crises precipitated by e.g. infections during infancy or childhood and progressive dystonia. Treatment with a lysine-restricted diet, carnitine supplementation and aggressive emergency treatment has been shown to significantly improve outcome in GA I [2–4]. A small group of untreated GAI patients remains asymptomatic, even in adult life [5].

Since 2007, GA I is included in the Dutch newborn screening program. In this paper we report a mother and her two brothers with symptomatic GA I, who were diagnosed after a low carnitine level was found by newborn screening in the healthy newborn of this mother.

1.1. Cases

Patient 1 is a 35 year old Dutch female. Her infancy and childhood were uneventful with exception of two hospital admissions due to fainting, for which no cause was detected, in the first year of life. She always had some difficulties in performing sports because of exercise intolerance. From age 30 onwards, she complained of increasing and disabling fatigue and was diagnosed with 'burnout'. She had no intellectual problems or movement disorder.

The pregnancy of her first child was uneventful besides excessive fatigue and resulted in delivery of a healthy female newborn at term (birth weight 3840 g). The total carnitine concentration at day 3 in the newborn screening blood spot was 9.7 μmol/L (ref 20–55 μmol/L). As we are aware of maternal carnitine deficiency presenting this way, we always screen the mothers simultaneously. The maternal free (4.6 μmol/L, ref 20–55 μmol/L) as well as total carnitine levels (6.9 μmol/L, ref 25–65 μmol/L) in plasma were severely reduced. Additional investigations demonstrated elevated plasma glutarylcarnitine (1.27 μmol/L, ref < 0.06 μmol/L), urinary glutaric acid (687 μmol/mmol kreat, ref < 30) and clearly increased 3-hydroxyglutaric acid. The newborn had no elevated glutarylcarnitine of urinary glutaric acid. Glutaryl-CoA dehydrogenase activity in lymphocytes was undetectable: <1.0 nmol/h.mg protein (ref 4.8–20 nmol/h.mg). Mutation analysis of the *GCDH* gene revealed two pathogenic heterozygous mutations (c.1060A>G and c.1154C>T), which proved the diagnosis of GA I. MRI of the brain showed enlarged sylvian fissures (Fig. 1). ECG and cardiac ultrasound were normal, especially no cardiomyopathy was detected. Carnitine supplementation was started 660 mg BID with slight improvement of exercise tolerance. After starting protein-controlled nutrition she felt much better.

Patient 2 is the 33 year old brother of patient 1. During childhood he was investigated because of macrocephaly and learning difficulties. CT scan of the brain at that time showed no abnormalities besides two arachnoidal cysts. He was then lost to follow-up until the diagnosis was made in his sister. At the current age of 33 years he has no

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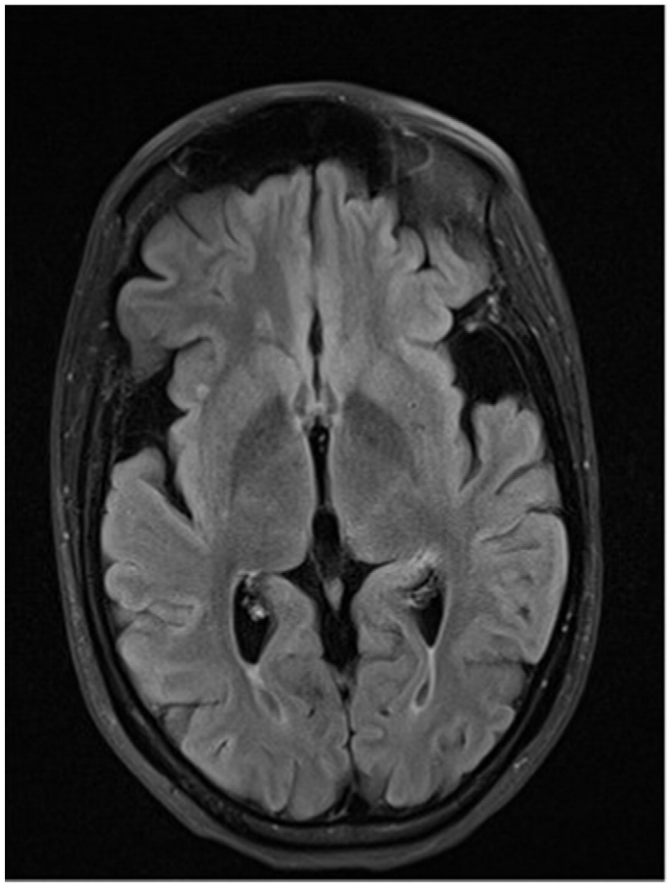

Fig. 1. MRI features of patient 1. Fluid attenuated inversion recovery image demonstrating enlarged sylvian fissures.

complaints at all. He works as a mechanic. Metabolic investigations in plasma demonstrated low free carnitine (7.7 μmol/L, ref 20–55 μmol/L) as well as total carnitine (10.6 μmol/L, ref 25–65 μmol/L), elevated glutarylcarnitine (1.55 μmol/L, ref <0.06 μmol/L) and in urine glutaric- and 3hydroxy-glutaric aciduria. Glutaryl-CoA dehydrogenase activity in lymphocytes was <1.0 nmol/h.mg protein (ref 4.8–20 nmol/h.mg protein). DNA investigations revealed the same two heterozygous mutations as detected in patient 1.

Patient 3, the youngest brother, is 24 years old. He only complains of intermittent fatigue. He also had a low free (7.5 μmol/L) and total carnitine (10.4 μmol/L), elevated glutarylcarnitine in plasma and glutaric acid and 3hydroxy-glutaric acid in urine, decreased glutaryl-CoA dehydrogenase activity in lymphocytes and the same two heterozygous mutations. Fatigue disappeared on carnitine 660 mg BID supplementation.

Evaluation of the healthy parents of the three patients revealed only a slightly elevated glutarylcarnitine in the mother. No metabolic abnormalities were found in the father, both had one heterozygous mutation in GCDH.

2. Discussion

Newborn screening has allowed the early identification of patients with GA I [3] and thereby improved the outcome of affected individuals [2,5]. Incidentally, maternal GA I is diagnosed based on the findings in their offspring. Until now, seven cases of maternal GA I are reported in the literature [6–10]. There is only one more detailed case description of a mother with a history of hypotonia, macrocephaly, learning disabilities (IQ 75) and a typical MRI [9]. Also two mothers are reported with intermittent fatigue mitigating on carnitine supplementation [10]. For the other four cases, no details about the clinical presentation are provided [5,6]. To the best of our knowledge, in contrast to e.g. maternal phenylketonuria, maternal glutaric aciduria does not affect the health and development of the offspring [9]. The child of our patient 1 shows a normal development during 12 month follow-up.

For the first time we present a family of three affected adult family members identified by an abnormal newborn screening. Isolated carnitine deficiency was found in the unaffected newborn of patient 1, which lead to the diagnosis of GA I in herself and subsequently in her two brothers. The identified mutations have been previously reported [11].

Since the extension of the new born screening in the Netherlands we, and others, have experienced that low carnitine ascertained during new born screening can be associated with low maternal plasma carnitine levels [12]. This finding can be due to maternal conditions e.g. the pregnancy itself [12], nutritional state (vegetarian) [13], primary carnitine deficiency [14,15] or 3-methyl-crotonyl-CoA-carboxylase deficiency [16].

As in most inborn errors of metabolism, the phenotypic spectrum of GA I is broad. It ranges from severely affected individuals to asymptomatic adults [17]. Neurological damage can be prevented with adequate crisis management and a lysine-restricted diet [2–4]. Inter- and intrafamilial variabilities in clinical presentations are described and raise important questions in terms of incidence and prevalence, pathogenesis and patient management. In only a few patients the diagnosis was made after the age of 18 years [18]. GA I is thought to be rare in adults, but it has been suggested that there are almost certainly unrecognized cases among populations of adults with stable neurological deficits acquired in childhood or even with only complaints of fatigue [19,20].

Our patients underline the clinical and neuro-radiological variability of this disorder. All three patients had the typical metabolites in blood and urine, including low serum carnitine levels. The latter is due to years of excretion of excessive levels of glutarylcarnitine. Their clinical signs and symptoms, however, differed. Patient 1, mother of the unaffected newborn who led to the diagnosis, suffered debilitating fatigue which improved on carnitine supplementation and a protein restricted diet. Metabolic decompensation never occurred, not even during the delivery. She also showed MRI described in patients with GA I before [21–23]. From her two younger brothers affected, one had no complaints at all and one had intermittent fatigue improving on only carnitine supplementation.

Our findings reinforce two notions. Extended newborn screening can detect symptomatic maternal disorders or even more affected family members with treatable metabolic disorders. Low serum carnitine levels are a rare, but treatable cause of excessive fatigue.

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