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CASE REPORT

Genotype–phenotype correlations: sudden death in an infant with very-long-chain acyl-CoA dehydrogenase deficiency

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Abstract Very-long-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (VLCADD) is an autosomal recessive disorder of fatty acid oxidation. The phenotype of VLCADD is heterogeneous, and patients are typically classified into three categories based upon onset of symptoms and clinical findings. As a result of early diagnosis and treatment, many patients with VLCADD have remained asymptomatic. A general genotype–phenotype correlation has been elicited. A genotype that is associated with residual enzyme activity is more likely to present with an attenuated phenotype. One prevailing mutation, the c.848T>C (p.V283A), has been associated with residual enzyme activity and has been identified in many asymptomatic individuals diagnosed through either newborn or family screening. We present a patient who died as a result of fatal hypoglycemia at 38 h of life before diagnosis of VLCADD could be established by newborn screening. Despite the early onset of the disease, the patient was found to have a missense mutation within the *ACADVL* gene with a c.848T>C, c.342+1G>C genotype. Genotype alone remains limited in its predictive ability to determine which affected individuals are at risk for fatal complications.

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Abbreviations

VLCAD	Very-long-chain acyl-CoA dehydrogenase
VLCADD	Very-long-chain acyl-CoA dehydrogenase deficiency

Introduction

Very-long-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (VLCADD) (OMIM #201475) is an autosomal recessive disorder of fatty acid oxidation. The phenotype of VLCADD is heterogeneous, and patients are typically classified into three categories based upon onset of symptoms and clinical findings. The neonatal form presents with cardiomyopathy, liver disease, and myopathy; a childhood onset form is characterized by hypoketotic hypoglycemia, and a late-onset form presents with recurrent rhabdomyolysis and myoglobinuria (Gregersen et al. 2001). If undiagnosed, VLCADD may present with sudden infant death as a result of fatal cardiac or hepatic involvement (Boles et al. 1998; Roe et al. 2000; Chace et al. 2001). Newborn screening through tandem mass spectrometry techniques is able to detect asymptomatic individuals with VLCADD as a result of increased tetradecanoyl-carnitine (C14:1) levels in dried blood spots (Wood et al. 2001; Zytkovicz et al. 2001). Early diagnosis allows for effective treatment to be initiated, including a low-fat diet supplemented with medium-chain triglycerides (MCT) and fasting precautions. Primarily as a result of the wide acceptance of screening programs, the incidence of VLCADD has risen from 1:125,000 to as high as 1:31,500 (Boneh et al. 2006; Spiekerkoetter et al. 2003). Many individuals identified through screening programs have remained asymptomatic

as a result of the initiation of early treatment. We also recognize identification of patients with a late-onset form of VLCADD through newborn screening, and these patients may have remained asymptomatic throughout childhood.

The first patient with VLCADD was identified in 1993, and the complementary DNA (cDNA) of human very-long-chain acyl-CoA dehydrogenase (VLCAD) was cloned in 1995 (Bertrand et al. 1993; Strauss et al. 1995). Null mutations in *ACADVL* (OMIM #609575), the gene that encodes VLCAD, have been associated with undetectable enzyme activity and early onset of severe disease, whereas missense mutations and in-frame deletions that result in measurable residual enzyme activity generally have milder clinical phenotypes (Andresen et al. 1999; Gregersen et al. 2001). Although a general genotype–phenotype correlation was able to be elicited, genotype analysis alone has been unable to predict which patients with residual enzyme defects will remain asymptomatic and which patients are at a significant risk for hypoketotic hypoglycemia.

Case report

A boy was born at 39 weeks gestation following an unremarkable pregnancy in a local community hospital. On the first day of life, maternal concern about the child's poor feeding of breast milk was noted. At 38 h of life, the baby was unresponsive to touch and noted to have a mottled appearance. His blood glucose level was <10 mg/dl (normal range 30–90 mg/dl). Despite resuscitation attempts in the nursery, the patient died. An autopsy was performed and revealed hepatic steatosis. There was no evidence of other organ involvement, such as cardiomyopathy, noted on the patient's autopsy. A postmortem blood spot was sent to a commercial newborn screening laboratory where the following levels were reported: C14 of 3.17 μmol/L, C14:1 of 1.35 μmol/L ,and C16 of 11.69 μmol/L. Normal value for the acylcarnitine analysis was not available, although the absolute values were consistent with previously published reports of postmortem screening in patients with VLCADD (Chace et al. 2001). Molecular genetic testing for VLCADD was performed and revealed two mutations associated with VLCADD. A c.848T>C (p.V283A) mutation of maternal origin and a novel splice-site mutation (c.342+1G>C) of parental origin were identified.

Discussion

We present a patient who passed away at 38 h of life as a result of fatal hypoglycemia before diagnosis of VLCADD could be established by newborn screening. Despite the early onset of the disease, the patient was found to have a missense mutation within the *ACADVL* gene, with a c.848T>C, c.342+1G>C genotype. The c.848T>C mutation was first identified in 1996 and was originally reported in approximately 10% of VLCADD alleles, with no specific ethnic predisposition (Andresen et al. 1996; Andresen et al. 1999). Significant residual enzyme activity has been associated with the c.848T>C mutation (Andresen et al. 1999; Goetzman et al. 2007). As a result of the residual enzyme activity, the majority of patients with the c.848T>C mutation have remained asymptomatic, even in the absence of treatment (Spiekerkoetter et al. 2003). Despite the many asymptomatic patients with c.848T>C alleles, individuals with the c.848T>C alleles have also been reported to be symptomatic, complicating treatment recommendations for patients with this genotype (Andresen et al. 1999; Boneh et al. 2006).

The c.342+1G>C is a novel splice-site mutation located in the invariant splicing site of the *ACADVL* gene and was categorized as a deleterious mutation based upon current recommendations for reporting sequence variations (Richards et al. 2008). More than ten other splice-site mutations have been identified in patients with VLCADD and associated with a significant decrease in residual enzyme activity (Andresen et al. 1999; Cox et al. 1998, Mathur et al. 1999; Strauss et al. 1995).

Although patients who are compound heterozygous complicate genotype-phenotype correlations, individuals with at least one c.848T>C allele are hypothesized to have enough residual enzyme activity to present with a mild phenotype. Recent evidence shows that partial deficiencies in two closely related fatty acid oxidation enzymes could result in a fatty acid disorder phenotype (Schuler et al. 2005; Vockley 2008; Vockley et al. 2000). It is possible that additional mutations in other genes of fatty acid oxidation might have influenced the fatal course of disease in our patient.

Conclusion

The onset of symptoms in VLCADD can be brought on suddenly and may often result in sudden infant death syndrome or fatal hypoglycemia. Despite the presence of the c.848T>C allele in many asymptomatic individuals, our case demonstrates that genotype alone remains limited in its predictive ability to determine which affected individuals are at risk for fatal complications. Although genetic analysis in itself is valuable, as it allows for accurate genetic counseling of at-risk couples and family members, there should be caution in labeling a genotype as mild in a patient affected with VLCADD.

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