Detection of Neonatal Carnitine Palmitoyltransferase II Deficiency by Expanded Newborn Screening With Tandem Mass Spectrometry

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ABSTRACT. The introduction of tandem mass spectrometry to newborn screening has substantially expanded our ability to diagnose metabolic diseases in the newborn period. We report the first case of neonatal carnitine palmitoyltransferase deficiency II detected by expanded newborn screening with tandem mass spectrometry. The neonate presented with dysmorphic facial features, structural malformations, renal failure, seizures, and cardiac arrhythmias and died on the third day of life. This experience illustrates the importance of expanded newborn screening to avoid missing a metabolic diagnosis in early infantile death. Pediatrics 2001;107(6). URL: http://www.pediatrics.org/cgi/content/full/107/6/e103; fatty acid oxidation, dysmorphic, calcification, neonatal death.

ABBREVIATIONS: MS/MS, tandem mass spectrometry; CPT, carnitine palmitoyltransferase.

The introduction of tandem mass spectrometry (MS/MS) to newborn screening has substantially improved our ability to detect metabolic diseases in the newborn period. The combined MS/MS analysis of acylcarnitines and amino acids allows for the identification of >20 inborn errors of metabolism in a single assay. These include disorders traditionally screened for, such as phenylketonuria and maple syrup disease, but also numerous other disorders of amino acid, organic acid, and fatty acid metabolism previously not detectable by newborn screening. Although the technology was first applied to the newborn screening specimen in 1990, only recently has it been used in routine screening, first in Pennsylvania and, subsequently, in North Carolina, Germany, Saudi Arabia, Australia, and, most recently, in Massachusetts and Wisconsin. We report the first case of neonatal carnitine palmitoyltransferase (CPT) II deficiency, an autosomal recessive disorder of fatty acid oxidation, detected by expanded newborn screening.

RESULTS

Newborn screening by MS/MS, reported on the day after death, revealed an elevation of acylcarnitines, notably of C16 and C18:1, suggestive of a defect in mitochondrial β-oxidation that could be CPT II, glutaric acidemia II, or carnitine-acylcarnitine translocase deficiency (Fig 2).

The urine organic acid profile revealed increased lactic and pyruvic acid, as well as increases in saturated and unsaturated dicarboxylic acids C10>C8>C6. Glutaric acid was not elevated and no unsaturated forms were found, making glutaric acidemia type II an unlikely diagnosis. Increases in the tyrosine metabolites 4-OH-phenylpyruvic and 4-OH-phenylactic acid were also detected, but succinylacetone was not present, excluding the probability of tyrosinemia I.

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Analysis of blood acylcarnitines later confirmed markedly increased C12 to C18 acylcarnitines. The urinary acylglycine profile revealed increased excretion of long-chain dicarboxylic acids with concentrations of C12, 11.1 μg/mg of creatinine; C14, 8.4 μg/mg of creatinine; and C16, 2.4 μg/mg of creatinine (normal levels for all of these metabolites: <0.01–1.1 μg/mg of creatinine).

The results of other investigations included a normal blood amino acid profile, normal karyotype, negative screen for prenatal infections, and normal very long-chain fatty acids.

Autopsy confirmed bilateral dysplastic, multicystic kidneys with double ureters. Bilateral cataracts were also present. There was marked lipid accumulation in the liver, muscle, and brain. Microscopic examination of the brain revealed multiple developmental anomalies. Myofibrillar disarray in skeletal muscle was consistent with a myopathic process.

CPT II activity was 1.15 nmol/minute/mg of pro-
tein (6% of controls) in cultured skin fibroblasts and 0.02 nmol/minute/mg of protein (18% of controls) in skeletal muscle, establishing the diagnosis of CPT II deficiency. CPT I activity was normal in both tissues.

**DISCUSSION**

To our knowledge, this is the first report of neonatal CPT II deficiency detected through expanded newborn screening with MS/MS. The case illustrates the value of expanded newborn screening in an infant with an unusual clinical presentation, including dysmorphic features, structural malformations, renal failure, seizures, and cardiac arrhythmias that might not lead to the suspicion of an inborn error of metabolism. Establishing a genetic diagnosis, although untreatable, provides important information to medical providers and the family. With the application of a technology such as MS/MS to newborn screening, these rare diagnoses can be made without additional costs because the same assay as used for traditionally screened treatable metabolic disorders like phenylketonuria detects many other inborn errors of metabolism.3

The MS/MS acylcarnitine profile revealed marked elevations of C16 and C18:1, suggestive of a defect in mitochondrial β-oxidation. The differential diagnosis included CPT II deficiency, glutaric acidemia type II, or carnitine-acylcarnitine translocase deficiency. Glutaric acidemia type II, caused by a deficiency of electron transfer flavoprotein or electron transfer flavoprotein-ubiquinone oxidoreductase, can present with a neonatal picture similar to that of CPT II with dysmorphic facial features, cystic renal dysplasia, and central nervous system abnormalities.4 However, the urinary metabolites, such as glutaric and 3-OH-glutaric acid, characteristic of glutaric acidemia type II, were not present in this patient, although the urine sample was collected during acute metabolic decompensation. Carnitine-acylcarnitine translocase deficiency, another rare autosomal-recessive disorder of fatty acid oxidation that leads to a failure to transport long-chain acylcarnitines into mitochondria, can also present with neonatal seizures, hypoketotic hypoglycemia, hyperammonemia, dicarboxyluria, cardiac arrhythmias, and sudden death.5 However, affected infants have not had dysmorphic facial features or structural malformations of the inner organs. The diagnosis of CPT II deficiency was proven by enzyme analysis in cultured fibroblasts and skeletal muscle.

Two clinical phenotypes of CPT II deficiency have been reported: an adult muscular form characterized by exercise intolerance and myoglobinuria6 and a more severe, infantile hepatocardiomyoskeletal form. In the latter, a neonatal presentation invariably leads to early infantile death,7 whereas a later presenting form has a more variable clinical course and outcome.8–10 To the best of our knowledge, only 7 cases of neonatal CPT II deficiency have been reported, all of which resulted in death in the early infantile period.7,11–16 The primary biochemical abnormalities have been nonketotic hypoglycemia, elevated liver transaminases, and carnitine deficiency. Clinical features included cardiomyopathy associated with arrhythmias, seizures, and liver disease. Structural malformations, specifically cystic renal disease, were reported in several cases.11–13

Our patient demonstrated the classical features of neonatal CPT II deficiency, including nonketotic hypoglycemia, cardiac arrhythmias, seizures, and liver disease. Moreover, he had dysmorphic facial features as well as structural malformations of inner organs, only described in 2 previous cases.7,11 He also presented with calcifications of the brain and liver. The 2 reported patients with facial dysmorphisms also had intracerebral calcifications.7,11 In addition, our patient had bilateral cataracts, not previously reported. It has been hypothesized that the structural malformations could be explained based on impaired mitochondrial β-oxidation of long-chain fatty acids that could lead to abnormal organogenesis.11 Accumulation of intermediary metabolites in utero might also exert toxic effects on mitochondrial function during crucial stages of development.11 The pathogenesis of organ calcifications is unknown.

As treatment options, early administration of intravenous glucose and carnitine, avoidance of fasting, and restriction of long-chain triglycerides have been discussed.7,10 Whether early initiation of this treatment can prevent death in the early and rapidly progressing neonatal presentations is unknown. In the later presenting infantile form, however, such treatment can probably prevent the sudden death and the developmental problems secondary to recurrent metabolic decompensations. Early recognition and treatment of cardiac arrhythmias associated with accumulation of long-chain acylcarnitines may also prevent infantile death.

Expanded newborn screening serves 2 important goals. One goal is presymptomatic treatment of inborn errors of metabolism, thus preventing death or neurologic impairment. This purpose can probably be achieved for the late infantile and adult forms of CPT II deficiency. Another important goal, however, is to avoid missing the diagnosis of a metabolic disorder. The traditional criteria of Wilson and Jungner18 do not include this goal as a screening criterion. However, it is common to encounter families who had the tragedy of a newborn dying of an undiagnosed disorder and who desperately seek an explanation for their child’s death, even if this information reveals an untreatable disorder. We believe that “treatment” for the family is also important and that, therefore, the traditional criteria of Wilson and Jungner need to be reexamined.2

Nevertheless, future research needs to focus on obtaining additional information about the nature of the disorders identifiable by MS/MS newborn screening and on developing new treatment options for these rare and frequently fatal metabolic disorders.

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