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Outcomes of cases with 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency - Report from the Inborn Errors of Metabolism Information System

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ABSTRACT

Introduction: 3-Methyl crotonyl CoA carboxylase (3MCC) deficiency is an inborn error of leucine metabolism whose detection was increased with the advent of expanded newborn screening. While most NBS-identified infants appear clinically normal, prior studies suggest a possible increased risk for developmental or metabolic abnormalities. As yet, no predictive markers are known that can identify children at risk for biochemical or developmental abnormalities.
Method: All available 3-MCC cases diagnosed by newborn screening in the Inborn Errors of Metabolism Information System (IBEM-IS) were reviewed for markers that might be predictive of outcome.
Results: A limited number of cases were identified with traditional biochemical symptoms including acidosis, hyperammonemia or lactic acidosis, and 15% of those with available developmental information had recorded developmental disabilities not clearly attributable to other causes. There was no correlation between newborn screening (NBS) C5OH level and presence of metabolic, newborn, later-life or developmental abnormalities in these cases.
Discussion: This sample, obtained from the IBEM-IS database, attempts to avoid some of the ascertainment bias present in retrospective studies. An increase in developmental abnormalities and in traditionally described metabolic symptoms remains apparent, although no specific biochemical markers appear predictive of outcome. The role that prevention of fasting plays in outcome cannot be ascertained. These data suggest that C5OH level found on newborn screening by itself is not sufficient for diagnostic or predictive purposes.

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1. Introduction

With the introduction of expanded newborn screening (NBS) using tandem mass spectrometry in the 1990s, the number of inborn errors of metabolism (IEMs) that could be detected soon after birth increased five-fold [6]. Now, most states screen for more than thirty disorders so that a diagnosis can be made before a child develops symptoms [27]. As a result, the clinical phenotype of IEMs has broadened to include apparently asymptomatic and more mildly affected individuals as well as those with classic severe presentations. This is particularly true for 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency (OMIM 210200), a disorder in the metabolism of leucine that causes elevations of 3-hydroxyisovalerylcarnitine (C5OH) among other substrates (Fig. 1).

3-MCC deficiency is one of the most common IEMs diagnosed by NBS with a prevalence ranging from 1:2400 to 1:68,000 depending on the population [28]. This frequency is much higher than what was predicted based on the number of cases who presented clinically before 3-MCC deficiency was added to the NBS panels [4]. Children with 3-MCC deficiency were diagnosed clinically after being evaluated for developmental delay, failure to thrive, hypotonia, seizures, or metabolic disturbances such as hypoglycemia, hyperammonemia, ketoacidosis, or Reye syndrome [3,8–10,13,19,20,24]. More than 90% of cases with 3-MCC deficiency diagnosed by NBS, however, appear to remain asymptomatic. Among the <10% who do exhibit health or developmental abnormalities these are not always obviously attributable to their 3-MCC deficiency [12,21–23], Healthy mothers have also been identified as having 3-MCC deficiency from their infant's NBS, having passed the abnormal metabolites to their infants through the placenta [18,21], again suggesting that this disorder is not always clinically significant. However, in a few cases childhood hypotonia, or maternal muscular symptoms in affected mothers have been reported [14,21]. Variation in phenotype even occurs among family members with the disorder even though they share genetics and a common environment [11].

At this time, there is no predictive factor that clinicians can use to determine which cases will be symptomatic from 3-MCC deficiency. Several retrospective studies failed to identify a correlation between genotype or biochemical phenotype and outcomes [2,15]. These studies reported cases for publication retrospectively and voluntarily. This raises concern that physicians are more likely to report symptomatic cases rather than asymptomatic cases. Also, the role fasting prevention after pre-symptomatic identification plays in suppressing symptoms is not known. Prospective studies would help to alleviate some of the data bias in outcome studies [1]. The goal of this study was to use the Inborn Errors of Metabolism Information System (IBEM-IS) (https://www.ibem-is.org) to gather outcome data on a prospective sample of cases with 3-MCC deficiency and determine if there were factors that predict the likelihood of developing symptoms secondary to this disorder.

2. Method

The Inborn Errors of Metabolism Information System (IBEM-IS) was established in 2007 to allow the capture and management of longitudinal data from individuals identified with an inborn error of metabolism (IEM) [5]. Data contained in the IBEM-IS are collected and managed using REDCap electronic data capture tools hosted at Michigan Public Health Institute (MPHI) [16]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. The goal of the Inborn Errors of Metabolism Collaborative (IBEMC) is to use the IBEM-IS to accumulate data that will inform about survival, medical status, and long-term outcomes of cases with IEMs to develop evidence-based practice in patient care (ibem-is.org). As of June 23, 2015 1896 subjects representing 41 conditions have data entered into the IBEM-IS and 1312 of these subjects were identified by NBS.

After this study was deemed to be exempt by the University of Pittsburgh's IRB (PRO13060460), anonymized data were extracted from the IBEM-IS database. These data included information about subject demographics, identification method and diagnosis confirmation, mutation status, neonatal health history, development, and interim health history including other health issues, biochemical labs, diet, and medications. Data were captured using electronic forms developed using Research Electronic Data Capture (REDCap) REFXX [16] by the IBEMC in collaboration with the Newborn Screening Translational Research Network, creating the Longitudinal Pediatric Data Resource REFXX (https://www.nbstrn.org/research-tools/longitudinal-pediatric-data-resource).

Data are reported as they were submitted to the database. In some cases the submitting centers were queried by anonymized case number in an attempt to clarify or seek additional data.

3. Results

3.1. Demographics

All available cases were ascertained from the IBEM-IS. Thirty-seven cases of 3-MCC deficiency were present in the database, including ten males and twenty females, (gender was not reported in seven cases). Diagnoses were established and confirmatory studies were done at the discretion of the submitting center. At the time of enrollment,

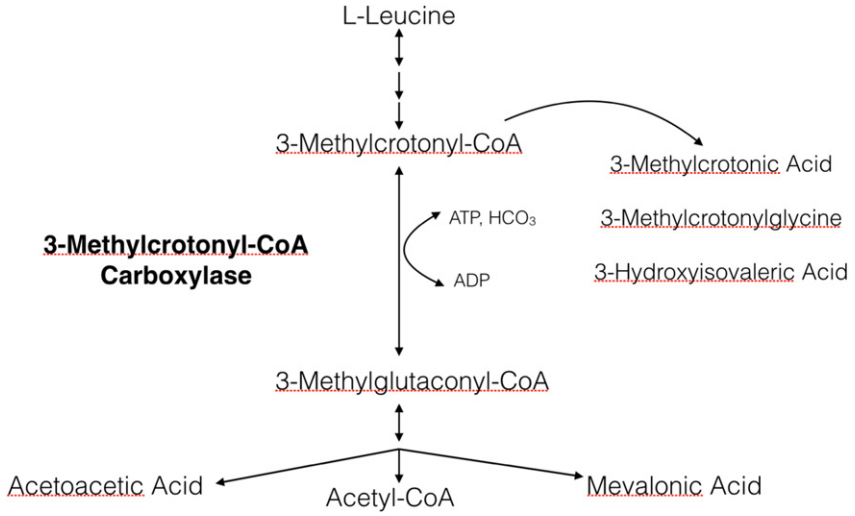

Fig. 1. Leucine metabolism. A genetic defect in 3-methylcrotonyl-CoA carboxylase leads to elevation of 3-methylcrotonyl CoA, 3-methylcrotonyl glycine and 3-OH isovaleric acid