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van Rijt, Willemijn J.; Jager, Emmalie A.; Spronsen, van, Francjan J.; de Koning, Tom; Heiner-Fokkema, M. Rebecca; Derks, Terry G. J.

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Neonates at risk of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency: a perinatal protocol for before population neonatal screening test results become available

Willemijn J van Rijt[1], Emmalie A Jager[1], Francjan J van Spronsen, MD, PhD[1], Tom de Koning, MD, PhD[1], M Rebecca Heiner-Fokkema, PhD[2], Terry G J Derks, MD, PhD[1]

From: [1]Section of Metabolic Diseases, Beatrix Children's Hospital and [2]Laboratory of Metabolic Diseases, Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Address correspondence to: Terry G. J. Derks, MD, PhD, Section of Metabolic Diseases, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen. PO Box 30 001, 9700 RB Groningen, The Netherlands. Phone: +31 (0)50 3614944. Fax: +31 (0)50 3611787. E-mail: t.g.j.derks@umcg.nl.

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To the Editor:

Since the 1990ies, the application of tandem mass spectrometry in population neonatal bloodspot screening (NBS) programs has improved the prognosis for many patients with treatable inherited metabolic diseases. However, clinical awareness amongst pediatricians and neonatologists remains important as ever, since severe neonatal clinical presentations can occur before population NBS test results become available.[1] In this issue of Genetics in Medicine, the authors of "Morbidity and mortality among exclusively breastfed neonates with medium-chain acyl-CoA dehydrogenase deficiency" highlight the importance of the feeding regimens for these neonates at risk.[2] In their paper, Ahrens-Nicklas *et al.* retrospectively studied a cohort of patients with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (MIM #201450) and report that 23.9% (11/46) of the infants were symptomatic before the return of the NBS results, of which four died or suffered from a cardiac arrest. All symptomatic neonates had been exclusively breastfed. This is important as it may not be known to pediatricians and neonatologists that a substantial percentage of newborns with MCAD deficiency are symptomatic during the first days of life. In addition, the authors mention six neonates with an older sibling known to have MCAD deficiency, who were carefully monitored and of which five received supplemental feeding. None of the six carefully monitored neonates suffered from metabolic decompensation.

After the pilot NBS study in our region of the Netherlands in 2003-2005, we have developed a perinatal protocol for health care providers and families to monitor neonates at increased risk of MCAD deficiency (Table 1). Parents are instructed to contact the metabolic team around the end of the first trimester of a new pregnancy. Thereafter, an information letter is shared with the parents and the health care providers (including general practitioner midwife, obstetrician and pediatrician, when applicable), which includes the perinatal

monitoring protocol and contact details of our pediatric metabolic team for 24/7 consultation. Depending on the clinical situation, parents either call us within 24 hours after birth or transfer our contact details to the involved health care providers. In agreement with the report by Ahrens-Nicklas *et al.*[2], in our protocol we emphasize the importance of a guaranteed minimal intake in milliliters during the first days. However, to date we have not communicated any preference between either formula milk or mother's milk obtained after breast pumping.

In the Dutch population NBS program in 2013, only 62% of the positive neonates have been referred to a metabolic physician before day 8. Therefore, our protocol has included analysis of dried bloodspot acylcarnitines already before NBS test results can become available. Usually, the dried blood spots are delivered to our center by family members at the second day of life and the results of acylcarnitine analysis are reported the same day. Although not formally studied, parents reported to us that the protocol importantly reduces the stress about the diagnosis and feeding regimen while awaiting the results of the national NBS program. Table 2 presents acylcarnitine concentrations in umbilical cord blood and the first days of life in two (c.985A>G *ACADM* homozygote) MCAD deficient neonates from families, in which the index patients were identified earlier by the NBS program. These results illustrate that cord blood acylcarnitines may offer a fast biochemical diagnosis in these newborns. In our (still relatively limited) experience, neonates in whom MCAD deficiency was excluded have normal (ratios of) acylcarnitines in umbilical cord blood.

Walter *et al.* studied the overall feasibility of acylcarnitine and amino acid analysis by tandem mass spectrometry in umbilical cord blood for identification of inherited metabolic diseases.[3] These authors mentioned several limitations of umbilical cord blood metabolite screening. First, depending on the nature of the metabolic defect and the role of enteral feeding and fasting, by far not all inherited metabolic diseases can be detected.[3] However, the

feasibility of more rapid identification also depends on the nature of the disorder. Walter *et al.* used only cut-off values for acylcarnitine *concentrations*, additional use of their *molar ratios* might increase the detection rate of some disorders.[3] Despite reports on age related variations in acylcarnitine concentrations comparing umbilical cord blood samples with NBS samples[4,5], dried cord blood spot acylcarnitine reference values for concentrations *including their molar ratios* are not available yet. Second, theoretically umbilical blood acylcarnitines can be influenced by the maternal (nutritional and/or disease) status.[3] This problem can be circumvented by sequential acylcarnitine (ratio) analysis. Therefore, acylcarnitine concentrations in umbilical cord blood may provide an early indication in addition to the regular NBS program.

The abnormal umbilical cord blood acylcarnitine profiles in MCAD deficient neonates may indicate the importance of mitochondrial fatty acid oxidation prenatally and during the perinatal transition. This period is characterized by important changes in cardiac energy metabolism (i.e. from predominantly carbohydrate driven towards mitochondrial fatty acid driven), besides the changes from a passive, fetal towards an active, neonatal glucose homeostasis and thermoregulation.

To summarize, a substantial percentage of newborns with MCAD are symptomatic during the first days of life. Therefore, a perinatal protocol is important and reduces the risk of early clinical ascertainment. Analysis of umbilical dried blood spot acylcarnitines (and their molar ratios) can provide rapid diagnosis.

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Legends to tables:

Table 1. Perinatal protocol for neonates at risk of MCAD deficiency pending population NBS results. Legend: day 0 is defined as the day of birth.

Table 2. Dried bloodspot acylcarnitine profiles in two neonates with MCAD deficiency. Legend: day 0 is defined as the day of birth.