

## Fatty Acid Oxidation Defects

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### Abstract

**Fatty acid oxidation defects (FAODs) are a group of inborn errors of metabolism that carry a risk for morbidity and mortality. Successful management of these conditions involves early diagnosis, proper management of clinical situations that predisposes to metabolic crisis as well as adequate treatment of a metabolic crisis. The advent of tandem mass spectrometry based newborn screening has reduced the morbidity and mortality in some FAODs. This article discusses how to recognise FAODs and how to manage them.**

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**Key words:** Newborn screening, Tandem mass spectrometry

### Introduction

Fatty acids are aliphatic monocarboxylic acids and commonly have carbon chains that range from 4 to 28 carbons. They can be saturated or unsaturated. Fatty acids serve many important biological functions. These include being a source of energy especially during prolonged fasting as well as being a vital building block in cell membrane and the production of essential molecules such as lipoproteins and cell signalers.

The main sources of fatty acids are dietary intake, release from fat stores (lipolysis) and synthesis by the human body. The human body can synthesise all fatty acids except for linolenic acid and linoleic acid. Hence the latter are also known as essential fatty acids.

There are 2 pathways for breaking down fatty acids. The main pathway is beta-oxidation and this occurs in the mitochondria. The minor pathway is omega-oxidation and this occurs in the endoplasmic reticulum. Hence, defects in fatty acid oxidation can occur either in the beta or the omega oxidation pathway. In this paper, the focus will be on defects in beta-oxidation.

### Types of Fatty Acid Oxidation Defects (FAODs)

The beta oxidation defects can involve the acyl-CoA dehydrogenases or the 3-hydroxylacyl-CoA dehydrogenases. e.g. very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), short-chain acyl-CoA

dehydrogenase deficiency (SCADD), multiple acyl-CoA dehydrogenase deficiency (MADD or GAIL) and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD).

MCADD is the most common with an incidence of 1 in 10,000 to 20,000 births. LCHADD and VLCADD are rare disorders occurring at approximately 1 in 100,000 births. There are 2 forms of SCAD deficiency: a severe form occurs approximately 1 in 100,000 and a mild form which is more common and is thought to be benign. There are also rarer FAODs but these will not be discussed here.

### Signs and Symptoms

Beta-oxidation defects can present with acute symptoms or chronic symptoms. Examples of acute signs and symptoms include

- **Encephalopathy** (e.g. lethargy which can progress to coma)
- **Urine ketones that are absent or present in small amounts (hypoketotic or non-ketotic) when large amounts are expected.** The human body is expected to produce large amounts of ketone bodies when a person is not feeding well or when a person is hypoglycemic. If urine ketones are absent or present in small amounts (e.g. + or ++ on a urine dipstick), this would generally be considered to be hypoketotic and inappropriate for the above mentioned scenarios.
- **Blood glucose level may be normal or low.** In fatty

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acid oxidation defects, the encephalopathy is usually caused by accumulation of fatty acids. Hence the blood glucose level may be normal during such episodes and the presence of a normal blood glucose level does not exclude the diagnosis of a fatty acid oxidation defect.

- **Hepatomegaly may be present**
- **Plasma ammonia may be elevated**
- **Liver transaminases may be elevated**

These clinical features are usually triggered by physiological stresses such as prolonged fasting, febrile illness, vaccinations etc. Each episode carries with it a high risk for morbidity (neurological sequelae that is usually permanent) and mortality.

There are also some symptoms which are particular to some of the conditions. For example, chronic skeletal muscle weakness can be seen in VLCADD, SCADD, LCHADD and chronic cardiomyopathy is seen in VLCADD and LCHADD.

### Diagnosis

Several tests can be used to confirm the diagnosis of an FAOD. Plasma or urine acylcarnitine analysis usually shows the characteristic abnormalities especially if the specimen was taken during an episode of a metabolic crisis. Urine organic acid analysis also frequently show the characteristic abnormalities if the specimen was taken during an episode of a metabolic crisis. It is important to note that in some individuals, these abnormalities disappear during periods of good health hence there is a risk for a false negative result. In such cases, skin fibroblasts can be sent for enzyme analysis and/or in-vitro fatty acid oxidation analysis.

As the genes for these conditions have been identified, DNA testing is also available. In general, it is relatively easy to send specimens for the above tests. However, the interpretation of their results requires domain knowledge of the disease as well as the sensitivity and specificity of each test. Hence, consultation with a metabolic physician may be wise so as to avoid misinterpreting false negatives and false positives.

### Newborn Screening for FAODs

The strategy of waiting for these affected individuals to present symptomatically and then diagnosing and treating them is unsatisfactory as it carries with it a risk of morbidity and mortality. Thus, the advent of screening to diagnose these conditions pre-symptomatically is an important step preserving good health in these affected individuals.

The leading way to screen for these disorders is during the newborn period through tandem mass spectrometry acylcarnitine analysis. Each of the above disorder has a relatively distinct pattern of abnormalities and hence a

baby with an abnormal profile would be flagged for further evaluation.

For most paediatricians, their participation in the screening process will involve sending the sample and following up a positive screen. In the event of a positive screen, the parents should be contacted and informed of the screening result. An assessment of the baby's status should be done as a matter of urgency e.g. is the baby feeding poorly or vomiting or lethargic? The family should be educated on the need for regular feeds and to avoid fasting, as fatty acid oxidation only occurs during fasting. If the baby is ill (even if it is mildly ill), treatment must be started immediately (IV 10% glucose) and a paediatric metabolic specialist contacted. If the infant is well, referral to metabolic specialist for diagnostic/confirmatory testing should occur.

The main advantage of screening is the reduction in morbidity and mortality. For example, the MCAD screening programme has been shown to be effective in reducing deaths and severe adverse events in children up to the age of 4 years<sup>1</sup> and suggests that the neurological outcome is better in those who were diagnosed through screening.<sup>2</sup> Screening is also more cost effective.<sup>3-5</sup> There are some limitations to screening.<sup>6</sup> There is a risk for false negatives ("normal" result in an affected person) and this can occur if the screening test was done when the baby was not metabolically stressed (e.g. beyond the testing window) or if the baby was carnitine deficient. There is also a risk for false positives ("abnormal" result in an unaffected person) and these can result in parental anxiety, unnecessary testing, detection of carriers and the detection of benign variants e.g. mild SCAD. High quality laboratories have minimum false positive and false negative results. Finally, screening programmes are costly to set up and require much expertise if it is to be well run.

### Management of FAOD

After a patient has been diagnosed to have an FAOD, each family should have a written action plan for management of illnesses and this should be available to all services involved in the child's care.

In managing an individual with an FAOD, the main principles are (i) avoiding situations/conditions that predispose to a metabolic crises and (ii) starting treatment before they get into a crisis. Hence, avoid fasting and consider restricting the fat intake to <25% of total caloric intake. Medium chain triglyceride (the predominant fat in coconut milk) should be restricted in MCADD. The patient may need carnitine supplementation (except in VLCAD where this is controversial). During periods that predispose to metabolic crises, increased calories and frequency of feeding and close observation are required.

If a child is not feeding well or is showing early signs of

crisis (e.g. lethargy), the child must be admitted for further management. The cardinal principle revolves around stopping catabolism, in particular, lipolysis. This means giving glucose (which will stimulate insulin production and insulin will inhibit lipolysis) and high calories (but avoiding IV lipids!). As specific therapies may be indicated for a particular FAOD, such as riboflavin for MADD, involvement of a specialist metabolic physician is recommended.

#### RESOURCES

1. Newborn Screening Fact Sheets. Available at: <http://www.pediatrics.org/cgi/content/full/118/3/1304>. Accessed 11 November 2008.
2. Acute Metabolic Illness Protocols. Available at: [http://www.childrenshospital.org/newenglandconsortium/NBS/Emergency\\_Protocols.html](http://www.childrenshospital.org/newenglandconsortium/NBS/Emergency_Protocols.html). Accessed 11 November 2008.

#### REFERENCES

1. Wilcken B, Haas M, Joy P, Wiley V, Chaplin M, Black C, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet* 2007;369:37-42.
2. Joy P, Black C, Rocca A, Haas M, Wilcken B. Neuropsychological functioning in children with medium chain acyl coenzyme a dehydrogenase deficiency (MCADD): the impact of early diagnosis and screening on outcome. *Child Neuropsychol* 2008;1-13.
3. Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr* 2007;151:121-6.
4. van der Hilst CS, Derks TG, Reijngoud DJ, Smit GP, TenVergert EM. Cost-effectiveness of neonatal screening for medium chain acyl-CoA dehydrogenase deficiency: the homogeneous population of The Netherlands. *J Pediatr* 2007;151:115-20.
5. Venditti LN, Venditti CP, Berry GT, Kaplan PB, Kaye EM, Glick H, et al. Newborn screening by tandem mass spectrometry for medium-chain acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Paediatrics* 2003;112:1005-15.
6. Wilcken B. Recent advances in newborn screening. *J Inherit Metab Dis* 2007;30:129-33.

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