



# Medium-chain acyl-coenzyme A dehydrogenase deficiency

PROTOCOLS

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## Background

Fatty acid oxidation disorders are a common cause of unrecognized morbidity and mortality in childhood. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most frequent inherited fatty acid oxidation disorder with an incidence of about 1 in 10,000–20,000. Although the disease can occur at any time in life, the commonest presentation is during infancy and childhood (three months to two years). Usually, a relatively well child decompensates during an acute illness associated with vomiting and develops hypoglycemia, mild hepatomegaly and altered sensorium. Other biochemical features include hypoketosis, mild hyperammonemia and elevation in liver enzymes. If unrecognized, the clinical picture can worsen with seizures, coma, residual neurological deficits and subsequent developmental delay. At the initial presentation, the mortality risk is as high as 25%. Other clinical presentations include unexplained infant death, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and acute fatty liver of pregnancy. Interestingly, there is a great variability in clinical phenotypes as some individuals can remain asymptomatic.

The inheritance of MCAD deficiency is autosomal recessive with the majority of patients being homozygous for a founder mutation, 985 A>G. This mutation is



common in individuals of northern European descent. The definitive diagnosis is based on elevated plasma acylcarnitines (C6 to C10 with predominance of C8 [octanoylcarnitine]) and elevated urinary suberyl and hexanoylglycine. DNA analysis can confirm the presence of the 985 A>G mutation or other less common mutations. Measuring the MCAD activity in skin fibroblasts is another rarely required diagnostic tool.

Treatment of MCAD deficiency involves avoidance of fasting and ensuring adequate glucose intake during illnesses. If oral intake is not tolerated, intravenous glucose solution is initiated. Some infants receive cornstarch, to avoid hypoglycemia. Carnitine may be useful, but controversies persist as to the benefit of prolonged use. Prognosis is excellent once the diagnosis is made and treatment initiated early thus making a strong argument for newborn screening.

MCAD deficiency still remains underdiagnosed and there is very little incidence data for the Canadian population. With the advent of tandem mass spectrometry, neonatal screening for MCAD deficiency is now occurring in a number of countries and in some American states. Presently, four Canadian provinces (BC, SK, NS, PEI) have such programs in place and Manitoba is planning to start shortly.

Active surveillance of MCAD deficiency is timely as it will allow for comparison between provinces with and without universal newborn screening. This study will provide data on incidence, burden of illness and clinical outcome, which might guide public health policy in terms of advocating for universal newborn screening for MCAD deficiency.

### **Methods**

With the active participation of over 2,500 paediatricians, paediatric subspecialists and medical geneticists who respond monthly to the CPSP, the majority of MCAD deficiency cases will be ascertained due to the severity of the disease. Paediatric pathologists will be added to facilitate ascertainment of cases recognized post-mortem. The participation of all Canadian metabolic referral centres will also be secured. A follow-up external validation of results through specific metabolic laboratories will be undertaken to further strengthen the accuracy of study results.

### **Objectives**

- To estimate the incidence of MCAD deficiency in Canada.
- To describe the health status of children with MCAD deficiency at the time of diagnosis.
- To determine if the health status of children with MCAD deficiency differs depending on the reason for initiating investigations, such as symptoms, family history or neonatal screening.
- To determine if more children are diagnosed with MCAD deficiency in provinces with screening programs than in those without such programs.



## ***Medium-chain acyl-coenzyme A dehydrogenase deficiency (continued)***

### **Case definition**

Report any patients newly diagnosed with MCAD deficiency following investigations initiated due to any of the following: newborn screening, clinical symptoms, diagnosis in an affected family member or postmortem diagnosis.

A child will be considered to have a diagnosis of MCAD deficiency if at least **ONE** of the following biochemical/genetic diagnostic criteria are met:

- 1) Elevated plasma C6 to C10 acylcarnitines with predominance of C8 (octanoylcarnitine)
- 2) Elevated urinary organic acids: phenylpropionylglycine, suberylglycine, hexanoylglycine, and medium chain dicarboxylic acids (C6>C8>C10)
- 3) Molecular genetic studies confirming the presence of the 985 A>G mutation, or other less common mutations
- 4) Skin fibroblasts acylcarnitine probe assay demonstrating accumulation of characteristic acylcarnitines
- 5) Skin fibroblasts enzyme studies showing reduced activity of MCAD

### **in the presence of the following clinical features/biochemical findings:**

- 1) Vomiting, hepatomegaly and altered sensorium
- 2) Hypoglycemia, elevated liver enzymes

### **Duration**

September 2005 to August 2007

### **Expected number of cases**

With an MCAD deficiency incidence of 1/10,000–20,000 and a Canadian birth cohort of 330,000 per year, the expected number of cases is approximately 30 per year.

### **Ethical approval**

Research Ethics Board of the University of Western Ontario and Children's Hospital of Western Ontario, London Health Sciences Centre

### **Analysis and publication**

The incidence rate of MCAD deficiency will be calculated using national and provincial birth rates from Statistics Canada. Information on clinical features, diagnostic studies, health status at the time of diagnosis, and reason for initiating diagnostic investigations will be studied. Investigators will analyze data, interpret results and promote regular feedback to participants. Final study results will be published in a peer-reviewed journal.



### References

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Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK. *Arch Dis Child* 1998 Aug;79(2):116-9.

Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Arch Dis Child* 1994 May;70(5):410-2.

### Online resources

Matern D, Rinaldo P. Medium-chain acyl-coenzyme A dehydrogenase deficiency. Geneclinics/Gene reviews <http://www.geneclinics.org>