Newborn Screening for MCAD Deficiency

Experience of the First Three Years in British Columbia, Canada

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ABSTRACT

Background: Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency is an autosomal recessive disorder of fatty acid oxidation, with potential fatal outcome. MCAD deficiency is diagnosed by acylcarnitine analysis on newborn screening blood spot cards by tandem mass spectrometry. Early diagnosis of MCAD and presymptomatic treatment can potentially reduce morbidity and mortality.

Objectives: To evaluate incidence, clinical outcome, biochemical and molecular phenotype of MCAD cases detected in the first three years of newborn screening in British Columbia (BC).

Methods and Results: Medium chain length acylcarnitines, octanoylcarnitine (C8) and decanoylcarnitine (C10), were measured on newborn screening blood spot cards. Out of 121,000 live births, 17 newborns had C8 values above the screening cut-off of 0.38 $\mu\text{mol/L}$. Ten newborns had elevated C8 on repeat cards and were investigated further. Both C8 and C8/C10 ratios remained abnormal in all confirmed MCAD cases. Positive predictive value of screening was 58% with no false negative results. Seven patients were homozygous for the common c.985A>G MCAD mutation and three others were compound heterozygous for the c.985A>G and a second mutation. Two novel mutations were identified (c.260T>C and c.382T>A). The estimated incidence of MCAD was ~1:12,000 live births. Upon frequent feeding and carnitine supplementation, none of the patients had metabolic crises or adverse outcomes.

Conclusion: Frequency of MCAD in BC is comparable to reports from other newborn screening programs. Persistence of elevated C8 levels and C8/C10 ratios in confirmed MCAD cases suggest that these are sensitive markers for newborn screening. Early detection and treatment have successfully prevented adverse health outcomes in patients with MCAD.

Key words: Neonatal screening; fatty acid oxidation complex; Acyl-CoA dehydrogenase; medium chain Acyl-CoA dehydrogenase; sudden infant death

La traduction du résumé se trouve à la fin de l'article.

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Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency (McKusick 201450)

is an autosomal recessive disorder affecting the mitochondrial beta-oxidation of medium-chain fatty acids. Clinical manifestations include hypoketotic hypoglycemia, Reye syndrome and/or sudden death, provoked by prolonged fasting or catabolic stress during episodes of infection. Patients are asymptomatic in the interval between episodes of decompensation, but survivors of metabolic crisis may have severe neurological sequelae. MCAD deficiency may mimic sudden infant death syndrome although steatosis of the liver is a common finding on autopsy.¹ A study of the natural history of the disease in 120 affected children showed that 23 (19%) were diagnosed after death, and 19 of these children had no prior clinical symptoms before their final illness.² A large retrospective analysis of 155 Dutch patients with MCAD deficiency also showed a mortality rate of 22% at the acute presentation before the diagnosis was made, and 21% developed disabilities after the diagnosis.³ Biochemically the disease is characterized by elevated medium-chain acylcarnitines in blood (marked elevation of octanoylcarnitine (C8), increases in hexanoyl (C6) and decanoyl (C10) and elevated C8/C10 ratio). Affected children may also have an increased urinary excretion of dicarboxylic acids, which are alternative omega oxidation products from accumulating medium-chain fatty acids. Secondary carnitine depletion is observed in some patients as a result of increased requirement for the production of acylcarnitines.¹ A common mutation (c.985A>G) in the MCAD gene accounts for 80% of clinically ascertained cases.^{4,5}

Treatment guidelines generally include frequent feeds with complex carbohydrates, avoidance of fasting, moderate restriction of dietary fat, and in some centres, supplementation with oral carnitine.

Early recognition by newborn screening and presymptomatic therapy can potentially prevent fatal outcome. Since the availability of tandem mass spectrometry (TMS), several newborn screening programs have included MCAD screening in their programs.⁶⁻¹¹ In British Columbia, newborn screening for MCAD has been performed since January 2003. The objective of the study was to evaluate the health

benefit of MCAD neonatal screening through an evaluation of test performance, molecular and biochemical characterization, and clinical outcome of the 10 patients detected in the first three years of screening.

METHODS

Specimens

Newborn screening for MCAD deficiency was performed on the same blood spot filter paper sample collected by heel prick from virtually all (99.94%) infants born in the province of British Columbia and the Yukon for routine newborn screening. Most specimens were collected in hospital prior to discharge between 24-48 hours after birth. Testing was performed in the Newborn screening laboratory, Department of Pathology and Laboratory Medicine, Children's & Women's Health Centre, Vancouver, BC. Once newborn screening is complete, cards are stored at room temperature indefinitely. Any further use of stored cards is for clinical purposes only.

Lab methods (see Appendix)

The screening protocol was developed through consultation with NBS programs currently screening for MCAD. The screening cut-off was set for high sensitivity in order not to miss any cases with the understanding that as experience is gained over time, the cut-offs may be adjusted. Results were considered positive when the octanoyl-carnitine (C8) concentration was >0.38 $\mu\text{mol/L}$ which is the 99.994th percentile. A repeat card was requested and received within 2-5 days. If the repeat C8 value was >0.3 $\mu\text{mol/L}$, the patient was considered presumptive positive for MCAD. Results were considered false positive when the repeat C8 concentration on the second card was less than 0.3 $\mu\text{mol/L}$. If the C8 value was >0.3 $\mu\text{mol/L}$, the infant was referred for further investigation (Figure 1).

The outcomes of the NBS-detected MCAD cases were compared with historical MCAD cases (N=2) clinically ascertained between 1999 and 2002. Diagnostic workup: DNA analysis for the common c.985A>G mutation was done on all presumptive positive cases. No further diagnostic testing was performed in the patients who were homozygous for the c.985A>G mutation. In those patients

Legend:

NBS: Newborn Screening program

MCAD: Medium Chain Acyl-CoA

Dehydrogenase deficiency

Figure 1. MCAD Newborn Screening Algorithm

Presumptive positive MCAD screens are followed up initially by ascertainment of clinical status. Wellness is defined as asymptomatic infants who are either formula fed or breastfed, likely meeting caloric requirements based on a clinical history checklist (no fasting stress).

with one copy of c.985A>G, further mutation analysis was performed, by sequencing all exons (laboratory of Dr. B.S. Andresen) as previously described.¹⁴ Beta-oxidation flux studies using [9,10-³H] myristate were performed in the laboratory of Dr. S. Olpin¹⁵ in the cases where a novel mutation was identified and thus the genotype alone was insufficient to confirm the diagnosis. Organic acids in the urine were measured by GC mass spectrometry.

Management

Families were instructed to feed their newborn every three hours for the first 3 months, then every four hours until the child is 12 months of age. Oral carnitine (100 mg/kg/day) and a moderate (35% of calories) fat intake were prescribed. At age one year, uncooked cornstarch 2 g/kg/dose was prescribed before bedtime to maintain carbohydrate supply through the night.

TABLE I

Acylcarnitine Results on Initial Newborn Screening Blood Spot Cards from 10 MCAD Patients Diagnosed in BC in the Period of January 2003-January 2006

	Initial NBS Blood Spot Acylcarnitines/Ratios		
	C8 (umol/L)	C10 (umol/L)	C8/C10
Classical c.985A>G homozygous MCAD cases (n=7)			
Minimum	2.2	0.2	10.4
Median	13.2	1.1	14.3
Maximum	26.5	1.7	16.0
Compound heterozygous MCAD cases (n=3)			
Pt1: c.985A>G / c.977T>C	3.2	0.2	15.1
Pt2: c.985A>G / c.260T>C	9.2	3	8.7
Pt3: c.985A>G / c.382T>A	1.1	3.3	3.8
Screening cut-off	<0.38	N/A	N/A

Seven patients were homozygous for the c.985A>G mutation. The remaining three patients were compound heterozygous for c.985A>G and a second mutation.

Figure 2. Initial and follow-up C8 levels

C8 values on the initial newborn screening cards show higher levels in the homozygous (c.985A>G/c.985A>G) patients compared to the compound heterozygous patients. C8 values decline by 5-7 days of age on follow-up newborn screening cards but remain above the screening cut-off for infants >1 week of age (>0.3 umol/L). No evidence of MCAD: 5 out of 7 false-positive patients initially had levels just slightly above the cut-off value of 0.38 umol/L, which upon repeat testing fell below the screening cut-off for infants >1 week of age.

At times of intercurrent illness, the infant's parents were advised to give glucose polymer-containing fluids (1 tsp Polycose/100 mL EBM or formula every 2-3 hours when <1 year old, and 1 Tb Polycose/120 mL juice every 2-3 hours when >1 year old). In case of persisting illness and refusal of feeds or persistent vomiting, parents were instructed to take the child to the nearest hospital's Emergency Department. All families were given a letter to be shown to the Emergency nurse or physician on arrival. The letter advised that treatment should be started without delay with IV 10% glucose solution at a rate sufficient to provide 5 mg/kg/min of glucose, and to add IV Carnitine at 50 mg/kg slow infusion over 2-5 minutes.

Follow-up

Confirmed MCAD cases were monitored with monthly blood spot card acylcarnitines (C8, C10, and C8/C10 ratio) and urine organic acids (hexanoylglycine, suberylglycine, 3-phenylpropionylglycine). Serum carnitine was also collected at the same time. Patients were seen at the Biochemical Diseases Clinic twice in the first 6 months, then at 6-month intervals.

Surveillance of missed cases (false negatives)

In British Columbia, all pediatric deaths are referred to Children's Hospital for review by a pathologist. Since 2001, acylcarnitine profiling has been part of the

investigation of sudden unexpected death. The acylcarnitine profiles are reviewed by a Biochemical Geneticist to assess whether there is evidence of an underlying fatty acid oxidation disorder such as MCAD.

RESULTS

During the 36 months between January 2003 and January 2006, 10 patients were confirmed positive for MCAD deficiency out of 121,000 live births (incidence: 10/121,000 = 1/12,100 with a 95% confidence interval between 0.3:10,000-1.3:10,000).

Acylcarnitine results and the mutations found in the affected patients are shown in Table I.

In the 10 confirmed MCAD cases, the second blood spot card had lower but persistently elevated C8 levels, all above the screening cut-off and ranging between 0.9-3.9 umol/L (Figure 2). C8 values declined with treatment as compared to the pre-treatment diagnostic samples but still remained above the 95th percentile (data not shown). Both initial and follow-up C8/C10 ratios are clearly distinguished from the false positive cases (Figure 3). Overall, test sensitivity was 100%, specificity 99%, and the positive predictive value was 58%. Applying ROC analysis, the performance of the screening test using C8 alone gave us an area under the curve (AUC_{ROC}) of 0.993 $\pm$ 0.033 and was improved further to an AUC_{ROC} of 1.0 when the C8/C10 ratio was utilized (complete discrimination of true and false positives).

Organic acids showed hexanoylglycine, suberylglycine and 3-phenylpropionylglycine excretions of variable degree in all true positive cases.

Seven out of ten patients were homozygous for the c.985A>G mutation. This corresponds to the amino acid substitution Lysine at position 304 to Glutamate (p.K304E), and is present in most of the clinically presenting cases.⁸ One patient was compound heterozygous for c.985G>A and a c.977T>C missense mutation [p.M301T] which has previously been identified in clinically affected patients.¹⁶

Two other patients were found to be compound heterozygotes for the common mutation c.985G>A and novel missense

mutations: [c.985G>A / c.260T>C] and [c.985G>A / c.382T>A]. The c.260T>C mutation changes Methionine 62 to Threonine (p.M62T), and the c.382T>A results in substitution of Leucine 103 to Methionine (p.L103M). Fatty acid oxidation measurement in cultured fibroblasts using [9,10-³H]myristate confirmed that both patients had a defect in oxidation of medium chain fatty acids.

Long-term follow-up

Five episodes of febrile illness in four patients were reported to us, and managed according to our preplanned protocol. None of these episodes resulted in metabolic decompensation or other sequelae. At the mean age of 20.5 months (range 5 months to 3 years), all patients have normal psychomotor development. In contrast, one of the two clinically-ascertained cases had a severe hypoglycemic episode and cardiac arrest during the neonatal period prior to diagnosis and has learning disabilities at age 6. The other case was diagnosed after an episode of hypoglycemia and lethargy associated with a viral illness at 6 months of age and is developing normally.

Missed cases

No children with MCAD were identified through the systematic investigation of sudden unexpected death cases during the study interval and up to the time of submitting this paper for publication.

DISCUSSION

The results of this study allow us to draw the first conclusions on the frequency of MCAD deficiency in BC. The incidence of 1:12,100 live births is in the range of reports from other newborn screening programs in the world – 1:15,600 (Heidelberg), 1:6,600 (Munich), 1:19,700 (Vienna), 1:21,000 (Australia), 1:16,400 (New England).⁶

In terms of test performance, C8 and the C8/C10 ratio are sensitive and specific markers for MCAD detection. The positive predictive value of 58% is comparable to the experience of other screening centres using TMS to screen for MCAD.⁷ With increasing experience, the recall rates may even decrease further over time, by changing the cut-off values and algorithms.⁶ By applying ROC analysis, the C8/C10 ratio

Figure 3. Initial and follow-up C8/C10 ratios

C8/C10 ratios on initial and follow-up newborn screening cards are all elevated in the confirmed MCAD cases. There is clear discrimination between the true and false positives using the C8/C10 ratio on both the initial and follow-up newborn screening cards.

was identified as the best screening parameter and could be incorporated into the diagnostic algorithm.

Seven out of ten patients (70%) diagnosed by newborn screening were found to carry two copies of the common mutation (c.985A>G). The literature suggests that 80% of patients who present clinically are homozygous for this mutation, compared to about half of those detected by screening.^{4,8} Evidence for a correlation between the biochemical phenotype and genotype was described in a recent article in which higher levels of octanoylcarnitine on the initial newborn screen were found in homozygous cases.⁴ This is in agreement with our results, which show higher levels of C8 in the homozygous cases compared to the compound heterozygotes, although there was some overlap between the two groups. Given the excellent clinical outcome so far in all our cases, no predictions can be made regarding genotype-phenotype correlation.

Two MCAD patients were ascertained by clinical means between 1999 and 2002 prior to the introduction of screening, corresponding to an estimated incidence of MCAD of 1:43,000 live births (about 25% of the neonatally-detected cases). The apparent higher incidence of MCAD since neonatal screening began is not surprising, and could reflect missed (undiagnosed)

sudden unexpected death cases as well as asymptomatic MCAD cases in the community. These results are also in keeping with the suggestion that less than half of proven MCAD cases ever become symptomatic with hypoglycemic episodes and/or sudden unexpected death.^{2,3,9}

Long-term follow-up of the 10 neonatally screened and treated MCAD patients showed normal psychomotor development and no acute episodes of metabolic decompensation. This is in contrast to the published outcome of patients who were diagnosed after having presented with clinical manifestations.^{2,3} Iafolia et al. studied 120 MCAD cases diagnosed clinically, in which 16% had muscle weakness, 14% had seizure disorder, 10% had failure to thrive and 9% had cerebral palsy. Thirty-two percent of the children had abnormal psychodevelopmental test results, 22% had speech difficulties, and 11% had attention deficit disorder.²

Our results are encouraging and are consistent with findings from other programs, indicating that MCAD neonatal screening and early institution of medical surveillance and management can prevent adverse health outcomes.

Limitations of study

We are only aware of two historical clinically-ascertained MCAD cases. It is

Appendix

Materials: Acylcarnitine standards were obtained for C0 and C2 from Sigma-Aldrich (catalog # C0283 and A6706, respectively), for C3-C18 from the VU University Medical Center Metabolic Laboratory in Amsterdam, deuterated acylcarnitine reference standards (NSK-B) from Cambridge Isotope Laboratories, and butanolic hydrochloride for derivatization from Regis Technologies Inc.

Analytical methods: Dried blood spot cards were punched into 96-well filtration plates and extracted (by centrifugation) with methanol containing deuterated acylcarnitine internal standards. The extract was evaporated, derivatized with butanolic hydrochloride, evaporated again, reconstituted in 30% aqueous acetonitrile (v/v) and the supernatant transferred to a 96-well microtitre plate. Samples were analyzed by flow injection electrospray tandem mass spectrometry (MS/MS). Free carnitine and acylcarnitines (C2, C3, C4, C6... to C18) were determined by multiple reaction monitoring (MRM) of parents of *m/z* 85 using a Micromass Quattro MS/MS. The carnitines were quantitated from their ratios with labeled internal standards using whole blood spots spiked with known amounts of carnitines. For MCAD detection, octanoyl (C8) and decanoyl (C10) were measured. The ratio of C8/C10 was calculated.^{12,13}

likely that there are children with MCAD deficiency in the community who have not come to medical attention. These children may or may not have had signs and symptoms of MCAD such as hypoglycemia and the sequelae of hypoglycemic episodes such as developmental disability.

Clinical outcomes of the MCAD cases detected through newborn screening have been excellent. However, ongoing assessment is required to determine long-term outcomes.

In conclusion, the incidence of MCAD in BC, Canada is similar to that in other countries around the world. Our results suggest that early recognition of MCAD and presymptomatic treatment of intercurrent illness prevents acute decompensation and death. These results support the continuation of MCAD neonatal screening in BC.

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RÉSUMÉ

Contexte : Le déficit en acyl-coenzyme A déshydrogénase (DACAD) des acides gras à chaîne moyenne est un trouble autosomique récessif d'oxydation des acides gras qui peut être mortel. Ce déficit est diagnostiqué par spectrométrie de masse en tandem des acylcarnitines dans le sang du nouveau-né (une tache de sang est recueillie sur une fiche en papier). Il est possible que le diagnostic précoce et le traitement avant l'apparition des symptômes réduisent la morbidité et la mortalité liées au DACAD.

Objectifs : Évaluer l'incidence, les résultats cliniques et les phénotypes biochimiques et moléculaires des cas de DACAD décelés au cours des trois premières années du programme de dépistage des nouveau-nés en Colombie-Britannique (C. B.).

Méthode et résultats : Deux acylcarnitines à chaîne moyenne, l'octanoylcarnitine (C8) et le décanoylcarnitine (C10), ont été mesurés sur les fiches de taches de sang des nouveau-nés. Sur 121 000 naissances vivantes, 17 nouveau-nés affichaient des valeurs supérieures au seuil de dépistage de 0,38 umol/L pour le C8. Dix nouveau-nés avaient un C8 élevé sur plusieurs fiches de suite et ont fait l'objet d'examen plus poussés. Le niveau de C8 et le ratio C8/C10 demeuraient anormaux dans tous les cas confirmés de DACAD. La valeur prédictive positive du dépistage était de 58 %, sans résultat faussement négatif. Sept patients étaient homozygotes pour la mutation commune c.985A>G du DACAD et trois autres étaient hétérozygotes composites pour la mutation c.985A>G et pour une deuxième mutation. Deux nouvelles mutations ont été repérées (c.260T>C et c.382T>A). L'incidence estimative du DACAD était de ~1:12 000 naissances vivantes. Avec une alimentation fréquente et une supplémentation en carnitine, aucun patient n'a subi de crise métabolique ni de résultat défavorable.

Conclusion : La fréquence du DACAD en C.-B. est comparable à celle d'autres programmes de dépistage des nouveau-nés. La persistance d'un C8 et d'un ratio C8/C10 élevés dans les cas confirmés de DACAD donne à penser que ce sont des indicateurs sensibles pour le dépistage des nouveau-nés. Le dépistage et le traitement précoces ont réussi à prévenir des résultats cliniques défavorables chez les patients atteints de DACAD.

Mots clés : dépistage néonatal; trouble d'oxydation des acides gras; acyl-CoA déshydrogénase; acyl-CoA déshydrogénase à chaîne moyenne; mort subite du nourrisson