Prolonged QTc Interval in Association With Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

AUTHORS: Jason R. Wiles, MD,[a] Nancy Leslie, MD,[b,c] Timothy K. Knilans, MD,[c,d] and Henry Akinbi, MD[a,c]

[a]*Perinatal Institute, Division of Neonatology;* [b]*Division of Human Genetics;* [c]*Department of Pediatrics; and* [d]*The Heart Institute, University of Cincinnati College of Medicine and Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*

KEY WORDS

medium-chain acyl-coenzyme A dehydrogenase deficiency, MCAD, neonate, prolonged QT

ABBREVIATIONS

ACADM—acyl-coenzyme A dehydrogenase for medium-chain fatty acids

ECG—electrocardiogram

MCAD—medium-chain acyl-coenzyme A dehydrogenase

VLCAD—very-long-chain acyl-coenzyme A dehydrogenase

Dr Wiles conceptualized and drafted the initial manuscript; Drs Leslie and Knilans reviewed and revised the manuscript; Dr Akinbi critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-1105

doi:10.1542/peds.2013-1105

Accepted for publication Nov 27, 2013

Address correspondence to Henry Akinbi, MD, Cincinnati Children's Hospital Medical Center, Division of Neonatology, 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229-3039. E-mail: henry.akinbi@cchmc.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Wiles is supported by National Institutes of Health grant 5T32HD069054 at Cincinnati Children's Hospital Medical Center. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

abstract

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most common disorder of mitochondrial fatty acid oxidation. We report a term male infant who presented at 3 days of age with hypoglycemia, compensated metabolic acidosis, hypocalcemia, and prolonged QTc interval. Pregnancy was complicated by maternal premature atrial contractions and premature ventricular contractions. Prolongation of the QTc interval resolved after correction of metabolic derangements. The newborn screen was suggestive for MCAD deficiency, a diagnosis that was confirmed on genetic analysis that showed homozygosity for the disease-associated missense A985G mutation in the *ACADM* gene. This is the first report of acquired prolonged QTc in a neonate with MCAD deficiency, and it suggests that MCAD deficiency should be considered in the differential diagnoses of acute neonatal illnesses associated with electrocardiographic abnormality. We review the clinical presentation and diagnosis of MCAD deficiency in neonates. *Pediatrics* 2014;133:e1781–e1786

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most common disorder of fatty acid oxidation, with an incidence of 1 in 15 000 to 1 in 20 000 births. MCAD deficiency is an autosomal recessive disorder characterized by a defect in mitochondrial fatty acid β-oxidation of medium-chain triglycerides. The most frequent disease-associated mutation is an A985G substitution in the gene that encodes acyl-coenzyme A dehydrogenase for medium-chain fatty acids (*ACADM*) located on chromosome 1p31. Clinical manifestations of MCAD deficiency include hypoketotic hypoglycemia, vomiting, lethargy, seizure, and encephalopathy and are often precipitated by prolonged fasting or increased metabolic demand (eg, infection, stress). In the era of newborn screening for common inborn errors of metabolism, diagnosis of MCAD deficiency before the onset of symptoms has become the norm. Here, we report an atypical presentation of MCAD deficiency in which the patient became symptomatic before the report of the newborn screen with a constellation of signs that included a previously unreported cardiac finding. This case reveals that individuals with MCAD deficiency are at increased risk of developing metabolic derangements that may precipitate a prolonged QTc interval.

PATIENT PRESENTATION

The patient is a product of term nonconsanguineous pregnancy born to a 29-year-old gravida 5 para 2 mother. The pregnancy was complicated by maternal premature atrial contractions and premature ventricular contractions prompting evaluation by a cardiologist. However, intervention was deferred until the postpartum period. The mother received adequate intrapartum antibiotic prophylaxis with penicillin before delivery for a genitorectal colonization with *Streptococcus agalactiae*. All other prenatal laboratory findings were unremarkable. Past obstetric history was notable for 3 spontaneous abortions. Family history was remarkable for premature atrial contractions and premature ventricular contractions in a maternal uncle but was otherwise negative for congenital heart diseases, long QT syndrome, inborn errors of metabolism, and early childhood deaths.

The nursery course was remarkable for parental concerns of feeding difficulty on the day of discharge. The mother had successfully breastfed the infant's sibling and elected to exclusively nurse the patient. Nineteen breastfeeding attempts with sessions lasting 10 to 30 minutes, 5 stools, and 5 wet diapers were documented during the ~40-hour hospitalization, satisfying hospital-established discharge criteria. The family was reassured that urine and stool outputs were adequate and that the patient's feeding skills would improve. The patient, however, began to take progressively longer periods of time between feedings at 48 and 72 hours of age. On the day after discharge from the nursery, the patient was noted to be drowsy, with decreased urine output and prolonged intervals between feedings (5–6 hours). No improvement was observed in response to supplementation of breastfeeding with formula. The infant presented to the emergency department at almost 72 hours of age with lethargy, a hoarse cry, low body temperature, and decreased urine output in addition to difficulty with feeding. Pertinent findings on physical examination included an axillary temperature of 35.7°C and a blood pressure of 42/17 mm Hg. Although the infant's body weight was only 3% less than that at birth, the findings of a sunken anterior fontanel and dry mucous membranes suggested possible dehydration. No arrhythmia was appreciated on cardiac auscultation.

The differential diagnoses entertained at admission included sepsis, congenital heart disease, inborn errors of metabolism, dehydration, and electrolyte abnormality. The initial laboratory studies were notable for hypoglycemia, hypernatremia, hypocalcemia, mildly elevated transaminases, compensated large anion gap metabolic acidosis, an elevated lactate level, and a mild unconjugated hyperbilirubinemia (Table 1). Urine analysis showed trace ketones with no reducing substances. Cultures of the blood, urine and cerebrospinal fluid were negative for bacterial pathogens. A prolonged QTc of 517 milliseconds (normal <440 milliseconds) was noted on electrocardiogram (ECG) (Fig 1A). The initial management comprised intravenous fluid resuscitation, dextrose infusions to correct hypoglycemia, calcium gluconate for hypocalcemia, empirical intravenous antibiotics (ampicillin, cefotaxime, and acyclovir) for possible early-onset neonatal sepsis, and serial ECGs. Poor feeding, lethargy, and hypotonia resolved after correction of hypoglycemia. Similarly, the prolonged QTc interval noted on admission ECG (72 hours of life) normalized within 30 hours after correction of the metabolic derangements and did not recur on follow-up ECGs (Fig 1B). The remainder of the hospital course was uneventful.

TABLE 1 Initial Laboratory Findings

Laboratory Test	Result	Reference Range
Glucose, mg/dL	<20	65–115
Sodium, mmol/L	147	133–146
Potassium, mmol/L	6.6	3.2–5.5
Calcium, mg/dL	6.7	7.9–10.7
Ionized calcium, mmol/L	0.83	0.85–1.45
AST, U/L	155	20–60
ALT, U/L	119	5–45
pH	7.39	7.35–7.45
P_{CO_2}, mm Hg	28	35–45
Bicarbonate, mmol/L	17.2	22–28
Base excess, mmol/L	−8	−2 to 2
Anion gap, mmol/L	22	4–15
Lactate, mmol/L	3.9	0.7–2.1
Unconjugated bilirubin, mg/dL	9.7	0.6–10.5

ALT, alanine transaminase; AST, aspartate transaminase.

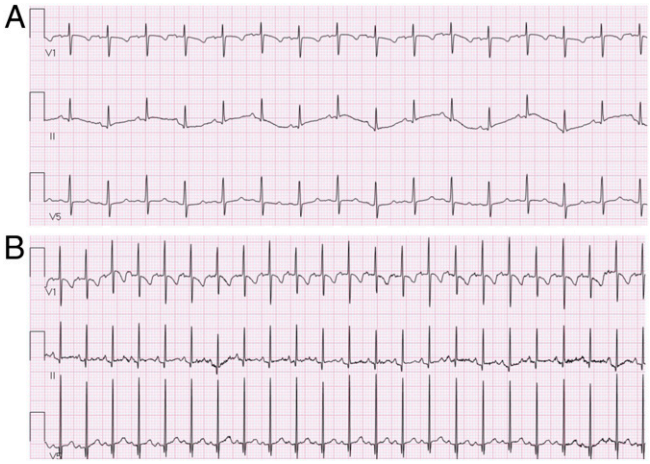

FIGURE 1

A, ECG leads of rhythm obtained on the day of presentation that show prolonged QTc interval (25 mm/second, 10 mm/millivolt; R-R = 468 milliseconds, QT = 354 milliseconds, QTc = 517 milliseconds). B, Normal ECG obtained on the 41st day of life indicative of resolution of prolonged QTc interval (25 mm/second, 10 mm/millivolt; R-R = 366 milliseconds, QT = 244 milliseconds, QTc = 403 milliseconds).

Samples for the newborn metabolic screening were obtained at 28 hours of life, and results were received at 93 hours of life (Table 2). These revealed an octanoylcarnitine level of 19.35 μmol/L (normal $<$0.6), suggestive of MCAD deficiency. A plasma acylcarnitine profile obtained at 101 hours of life revealed accumulation of C6 to C10 acylcarnitine species with predominance of C8 (Table 3). There were large 5-hydroxy-hexanoic and hexanoylglycine peaks, but the lactate and ketone excretion was normal on urine organic acid analysis. Urine concentrations of medium-chain dicarboxylic acids were elevated in a pattern consistent with MCAD deficiency (adipic acid [281 μmol/mmol creatinine] was greater than suberic acid [92 μmol/mmol creatinine], which was greater than sebacic acid [2 μmol/mmol creatinine]). Genetic analysis revealed homozygosity for the disease-causing c.985A$>$G mutation of the *ACADM* gene, the most frequent mutation reported in MCAD deficiency.

DISCUSSION

In the era of newborn screening for metabolic and endocrine disorders, it is unusual for infants with MCAD deficiency to present with manifestations of the disease before diagnosis. However, in a study from The Netherlands, 15 of 120 individuals were diagnosed with MCAD deficiency on the basis of clinical presentation before the availability of newborn screen results.[1] The importance of prompt recognition of MCAD deficiency in the symptomatic neonate is underscored by a 5% risk of mortality.[2] Therefore, a high index of suspicion for inborn errors of metabolism in critically ill neonates should be maintained, because results from the blood spot newborn screen are often not available until after 72 hours of life.

In addition to the very early onset of symptoms attributable to MCAD deficiency, this infant presented with cardiac electrical disturbance. Although various cardiac arrhythmias and cardiomyopathy have been reported in MCAD deficiency, to our knowledge the association of a prolonged QTc interval has not been described.[3–7] QTc interval prolongation may be secondary to congenital or acquired abnormalities and is significant in that it may progress into life-threatening cardiac arrhythmia.

Congenital long QT syndrome is a well-described, genetically determined condition that predisposes affected individuals to prolongation of ventricular repolarization, which can result in early after depolarizations, induce reentry, and provoke torsade de pointes and fatal ventricular arrythmia.[8] This condition may be inherited in an autosomal dominant (Romano-Ward syndrome) or an autosomal recessive (Jervell and Lange-Nielsen syndrome) fashion.[9] Many subtypes of these conditions have been described and are the result of mutations in ion channel subunits or regulatory protein coding genes.[10]

Several common genetic variants within the general population have been associated with QT interval variation. Some of these sequence variants involve genes with established long QT syndrome associations (eg, *KCNQ1, KCNH2, SCN5A, KCNE1*), whereas many recent discoveries implicate genes with no previously recognized relationships with cardiac electrophysiology (eg, *NOS1AP, NDRG4, PLN, LITAF, LIG3, RFFL*).[11,12]

TABLE 2 State Newborn Screening

Test	Result	Reference Range	Risk Level
Amino acid profile	All within range	Profile	Low
TSH, μIU/mL	7.2	$<$34	Low
Fatty acid profile	Abnormal	Profile	N/A
Octanoylcarnitine (C8), μmol/L	19.35	$<$0.6	Elevated
All others	Within range	Profile	Low
Organic acid profile	All within range	Profile	Low
Biotinidase, MRU	123.1	$>$20	Low
Galactose-1-P04-urdyl transferase, U/g Hb	14.1	$>$2.0	Low
Hemoglobin	FA	FA	Low
17-OH progesterone, ng/mL	7	$<$35	Low

Blood specimen was obtained at 28 hours of life. FA, fetal and adult; Hb, hemoglobin; N/A, not applicable; MRU, microplate response units; THS, thyroid stimulating hormone.

The causes of acquired long QT may include medications, electrolyte disturbances (hypokalemia, hypomagnesemia, and hypocalcemia), increased thyroid hormone concentrations, left ventricular hypertrophy, ischemia, and slow heart rate.[13] Treatment of the underlying etiology in these cases ultimately results in resolution of the condition. Of note, due to the increased appreciation for the numerous medications associated with acquired long QT, an extensive list of potentially offending medications is maintained by an online registry (http://www.crediblemeds.org).

We postulate, although we cannot conclusively state, that this case is likely one of an acquired prolonged QTc interval resulting from hypocalcemia that accompanied an acute metabolic crisis as evidenced by the normalization of the QTc interval on ECGs obtained after correction of the metabolic derangement (Tables 4 and 5). There was no observed hypokalemia or history of exposure to medications associated with increased risk of developing prolonged QTc interval. Furthermore, differential diagnoses such as cardiomyopathy and familial long QT syndrome were not substantiated by additional studies. The infant's cardiac structure and function were normal on echocardiography and follow-up ECGs on the infant and parents did not support a diagnosis of familial long QT syndrome.

Definitive conclusions regarding the etiology of prolonged QTc interval in this infant could not be made because his magnesium level was not monitored, no further genetic testing was performed, and mild elevations in the very long acylcarnitines were noted on the acylcarnitine profile. Hypomagnesemia remains an unlikely cause because the ECG findings resolved without the administration of magnesium while the patient was receiving intravenous fluids containing only dextrose. Genetic testing for known variants associated with prolonged QTc interval was not conducted due to the very transient nature of the presentation; however, it is possible that the patient was genetically predisposed to prolonged QTc while under physiologic stress. Very-long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency has been associated with prolonged QTc intervals, and the acylcarnitine profile did show evolving increases in some of the longer chain acylcarnitines when compared with the newborn screen (Table 3). However, these elevations are observed in much lower quantities than traditionally seen in VLCAD deficiency and would be anticipated for an individual with MCAD deficiency who is acutely catabolic, lipolytic, and hypoglycemic. Unfortunately, it is difficult to ascertain the full clinical magnitude of this finding because recent mouse models of VLCAD deficiency have not revealed a correlation between blood and tissue free carnitine concentrations and blood concentrations are inadequate markers of carnitine biosynthesis.[14,15]

There are several additional clinical observations and associations reported in MCAD-deficient patients that merit discussion. Laboratory findings during an acute metabolic crisis commonly include hypoketotic hypoglycemia, elevated uric acid, increased anion gap, elevated transaminases, and mild hyperammonemia. Initially characterized as a nonketotic hypoglycemic

TABLE 3 Extended Newborn Screen and Plasma Acylcarnitines

Acylcarnitine	Newborn Screen			Plasma		
	Patient value, μM	Population mean, μM	MOM	Patient value, μM	Population mean, μM	MOM
C0	15	22	0.67	17	38	0.45
C2	13	24	0.5	17	11	1.55
C4	0.32	0.24	1.5	0.18	0.21	0.86
C5-OH	0.105	0.18	0.58	0.02	0.03	0.67
C6	2.58	0.05	51	1.33	0.05	26.6
C8	19.35	0.07	276	9.39	0.11	85
C10:1	0.435	0.05	8.7	0.71	0.13	5.46
C10	1.275	0.09	14	0.91	0.15	6.07
C12	0.18	0.12	1.5	0.13	0.06	2.17
C14:2	0.015	0.03	0.5	0.04	0.04	1
C14:1	0.115	0.13	0.88	0.34	0.06	5.67
C14	0.195	0.23	0.8	0.12	0.04	3
C14-OH	0.015	0.02	0.75	0.02	0.04	0.5
C16	2.575	2.83	0.9	0.36	0.08	4.5
C16:1-OH	0.03	0.04	0.75	—[a]	—	—
C16-OH	0.02	0.02	1	0.06	0.01	6
C18:2	0.08	0.23	0.35	0.07	0.01	7
C18:1	0.88	1.31	0.67	0.2	0.1	2
C18	0.65	0.88	0.74	0.07	0.03	2.33
C18:1-OH	0.015	0.2	0.75	0.01	0	—
C18-OH	0.01	0.01	1	0.01	0	—

Blood specimens were obtained at 28 hours of life except for plasma acylcarnitine concentrations, which were obtained at 101 hours of life. MOM, multiple of the mean.

[a] Value unreliable due to ceftriaxone interference.

TABLE 4 Clinical Resolution of Abnormal ECG

ECG Timing (Day of Life)	ECG Timing, Hours of Life	HR, beats per minute	QT, ms	QTc, ms
3	72	128	354	517
4	102	145	268	417
6	140	139	272	413
41	984	164	244	403

HR, heart rate.

TABLE 5 Sequence of Capillary Blood Gases

	Hours of Life					Reference Range
	72	76	84	95	99	
Hours from presentation	0	4	12	23	27	N/A
pH	7.39	7.35	7.43	7.3	7.3	7.35–7.45
P_{CO_2}, mm Hg	28	22	18	39	38	35–45
P_{O_2}, mm Hg	56	57	76	60	49	35–45
Bicarbonate, mmol/L	17	12	12	19	20	22–28
Base excess, mmol/L	−8	−13	−12	−7	−7	−2 to 2
Sodium, mmol/L	145	145	147	148	146	133–146
Potassium, mmol/L	6.4	6.5	4.4	3.9	3.3	3.2–5.5
Ionized calcium, mmol/L	0.83	0.85	1.15	1.28	1.26	0.85–1.45
Glucose, mg/dL	<20	107	90	80	94	50–115

N/A, not applicable.

disorder, it is now apparent that affected individuals are capable of producing ketones.[16–19] However, such patients are hypoketotic relative to their severity of presentation. There is a family history of unexplained childhood deaths in 20% of patients with MCAD deficiency.[20] Severe ventricular arrhythmias have been suggested to be the underlying cause of sudden or unexpected infant death in individuals with fatty oxidation disorders secondary to the toxic effects of fatty acids perturbing the ion channels of the myocardium, but electrolyte abnormality may also contribute to the pathogenesis.[21] Our case suggests that prolonged QTc interval could play a role in some fatal cases of MCAD deficiency. Patients who survive acute decompensation remain at risk of subsequent psychomotor developmental delays and behavioral problems.[1]

When MCAD deficiency is suspected as a result of clinical presentation or from an abnormal newborn screen, confirmatory testing including plasma acylcarnitines, urine acylglycines, and urine organic acids should be assessed. Diagnosis can also be confirmed via mutation analysis of the *ACADM* gene. The outcome of MCAD deficiency is generally favorable if the disorder is identified early, treatment is implemented, and prompt interventions occur during times of illness.[22,23] Medical management strategies include avoidance of medium-chain triglycerides, frequent feeding to shorten periods of fasting, and prompt medical attention during conditions of increased metabolic demand such as infection.

In cases of MCAD deficiency and acute metabolic crisis, prolonged QTc interval and cardiac arrhythmia may coexist. This case underscores the need for prompt recognition of an underlying metabolic defect in an ill-appearing neonate. The results of newborn screening are often unavailable in the first several days of life. Therefore, a high index of suspicion is needed to institute timely intervention that would mitigate the possible cardiac dysfunction. To our knowledge, this is the first report of an association of prolonged QTc interval with MCAD deficiency.

REFERENCES

1. Derks TG, Reijngoud DJ, Waterham HR, et al. The natural history of medium-chain acyl CoA dehydrogenase deficiency in The Netherlands: clinical presentation and outcome. *J Pediatr*. 2006;148(5):665–670
2. Wilcken B. More on medium-chain acyl-coenzyme a dehydrogenase deficiency in a neonate. *N Engl J Med*. 2008;358(6):647
3. Rice G, Brazelton T III, Maginot K, Srinivasan S, Hollman G, Wolff JA. Medium chain acyl-coenzyme A dehydrogenase deficiency in a neonate. *N Engl J Med*. 2007;357(17):1781
4. Maclean K, Rasiah VS, Kirk EP, et al. Pulmonary haemorrhage and cardiac dysfunction in a neonate with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. *Acta Paediatr*. 2005;94(1):114–116
5. Yusuf K, Jirapradittha J, Amin HJ, Yu W, Hasan SU. Neonatal ventricular tachyarrhythmias in medium chain acyl-CoA dehydrogenase deficiency. *Neonatology*. 2010;98(3):260–264
6. Sanatani S, Mahkseed N, Vallance H, Brugada R. The Brugada ECG pattern in a neonate. *J Cardiovasc Electrophysiol*. 2005;16(3):342–344
7. Marci M, Ajovalasit P. Medium-chain acyl-CoA dehydrogenase deficiency in an infant with dilated cardiomyopathy. *Cardiol Res Pract*. 2009;2009:281389
8. van Noord C, Eijgelsheim M, Stricker BHC. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol*. 2010;70(1):16–23
9. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348(19):1866–1874
10. Lehnart SE, Ackerman MJ, Benson DW Jr, et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation*. 2007;116(20):2325–2345
11. Newton-Cheh C, Eijgelsheim M, Rice KM, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet*. 2009;41(4):399–406
12. Pfeufer A, Sanna S, Arking DE, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet*. 2009;41(4):407–414
13. Al-Khatib SM, LaPointe NMA, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA*. 2003;289(16):2120–2127
14. Spiekerkoetter U, Tokunaga C, Wendel U, et al. Tissue carnitine homeostasis in very-long-chain acyl-CoA dehydrogenase-deficient mice. *Pediatr Res*. 2005;57(6):760–764
15. Spiekerkoetter U, Wood PA. Mitochondrial fatty acid oxidation disorders: pathophysiological

studies in mouse models. *J Inherit Metab Dis*. 2010;33(5):539–546

16. Gregersen N, Rosleff F, Kølvraa S, Hobolth N, Rasmussen K, Lauritzen R. Non-ketotic C6-C10-dicarboxylic aciduria: biochemical investigations of two cases. *Clin Chim Acta*. 1980;102(2-3):179–189
17. Iafolla AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr*. 1994;124(3):409–415
18. Leonard JV, Dezateux C. Newborn screening for medium chain acyl CoA dehydrogenase deficiency. *Arch Dis Child*. 2009;94(3):235–238
19. Fletcher JM, Pitt JJ. Fasting medium chain acyl-coenzyme A dehydrogenase–deficient children can make ketones. *Metabolism*. 2001;50(2):161–165
20. Ding JH, Roe CR, Iafolla AK, Chen YT. Medium-chain acyl-coenzyme A dehydrogenase deficiency and sudden infant death. *N Engl J Med*. 1991;325(1):61–62
21. Bonnet D, Martin D, Villain E, et al. Arrhythmias and conduction defects as presenting symptoms of fatty acid oxidation disorders in children. *Circulation*. 1999;100(22):2248–2253
22. Wilcken B, Haas M, Joy P, et al. Expanded newborn screening: outcome in screened and unscreened patients at age 6 years. *Pediatrics*. 2009;124(2):e241–e248
23. Wilcken B. Fatty acid oxidation disorders: outcome and long-term prognosis. *J Inherit Metab Dis*. 2010;33(5):501–506

Prolonged QTc Interval in Association With Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Jason R. Wiles, Nancy Leslie, Timothy K. Knilans and Henry Akinbi

Pediatrics 2014;133;e1781
DOI: 10.1542/peds.2013-1105 originally published online May 5, 2014;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Prolonged QTc Interval in Association With Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Jason R. Wiles, Nancy Leslie, Timothy K. Knilans and Henry Akinbi

Pediatrics 2014;133;e1781
DOI: 10.1542/peds.2013-1105 originally published online May 5, 2014;