

Arrhythmias and Conduction Defects as Presenting Symptoms of Fatty Acid Oxidation Disorders in Children

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Background—The clinical manifestations of inherited disorders of fatty acid oxidation vary according to the enzymatic defect. They may present as isolated cardiomyopathy, sudden death, progressive skeletal myopathy, or hepatic failure. Arrhythmia is an unusual presenting symptom of fatty acid oxidation deficiencies.

Methods and Results—Over a period of 25 years, 107 patients were diagnosed with an inherited fatty acid oxidation disorder. Arrhythmia was the predominant presenting symptom in 24 cases. These 24 cases included 15 ventricular tachycardias, 4 atrial tachycardias, 4 sinus node dysfunctions with episodes of atrial tachycardia, 6 atrioventricular blocks, and 4 left bundle-branch blocks in newborn infants. Conduction disorders and atrial tachycardias were observed in patients with defects of long-chain fatty acid transport across the inner mitochondrial membrane (carnitine palmitoyl transferase type II deficiency and carnitine acylcarnitine translocase deficiency) and in patients with trifunctional protein deficiency. Ventricular tachycardias were observed in patients with any type of fatty acid oxidation deficiency. Arrhythmias were absent in patients with primary carnitine carrier, carnitine palmitoyl transferase I, and medium chain acyl coenzyme A dehydrogenase deficiencies.

Conclusions—The accumulation of arrhythmogenic intermediary metabolites of fatty acids, such as long-chain acylcarnitines, may be responsible for arrhythmias. Inborn errors of fatty acid oxidation should be considered in unexplained sudden death or near-miss in infants and in infants with conduction defects or ventricular tachycardia. Diagnosis can be easily ascertained by an acylcarnitine profile from blood spots on filter paper. (*Circulation*. 1999;100:2248-2253.)

Key Words: metabolism ■ arrhythmia ■ fatty acids

Clinical findings in fatty acid β -oxidation deficiencies vary according to the specific enzymatic defect and even among patients with the same genotype.¹⁻³ A simultaneous dysfunction of the heart, liver, and skeletal muscle, associated with hypoketotic hypoglycemia, is highly suggestive of a fatty acid oxidation disorder. However, the clinical presentation may be puzzling. Indeed, the diversity of the presenting signs and the need to collect blood and urine specimens for metabolic investigation at an appropriate time in relation to the illness frequently limit the recognition of these diseases.^{2,4} Prompt recognition of these inborn disorders is warranted because they can often be treated. In addition, a precise diagnosis of the enzymatic defect is crucial for genetic counseling; prenatal or presymptomatic diagnosis can be performed in siblings.

Cardiac involvement is frequent in these deficiencies.^{2,5-7} Indeed, cardiomyopathy is the chief clinical manifestation of several inherited disorders of mitochondrial fatty acid β -oxidation.⁸ In addition, arrhythmias and conduction defects, in association with hepatomuscular symptoms, have

been previously mentioned in isolated cases of fatty acid oxidation disorders.⁹ Severe ventricular arrhythmias are suspected as the cause of sudden infant death syndrome or unexpected death in young children harboring these defects.^{10,11} Although neonatal ventricular or atrial tachycardias in infants with a structurally and functionally normal heart are usually considered idiopathic, we report a series of 24 children in whom arrhythmias or conduction defects were the predominant presenting symptom of various fatty acid oxidation disorders.

Methods

Over a period of 25 years, 107 children investigated at our Institution were diagnosed with an inherited mitochondrial fatty-acid β -oxidation disorder. The diagnosis was suspected because of hypoketotic hypoglycemia with hyperlactatemia or with hyperammonemia associated with the following various clinical features: neonatal distress, sudden infant death syndrome, Reye syndrome, cardiomyopathy, progressive myopathy, hypotonia, muscle pain, and myoglobinuria. A presymptomatic recognition was possible in some patients because of a previous diagnosis of fatty acid oxidation

Received April 12, 1999; revision received July 6, 1999; accepted July 22, 1999.

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disorder or sudden death in a sibling. A detailed distribution of the presenting symptoms of these patients was recently reported.²

A urinary organic acid profile using gas chromatography-mass spectrometry was obtained in all patients. Free and total carnitine levels in plasma and urine were measured. Functional tests (fasting, phenylpropionic acid-loading test, and long chain triglyceride-loading test) were performed when the results were incomplete or ambiguous. The precise diagnosis of the fatty acid oxidation disorder was performed by following the oxidation of [1-¹⁴C] fatty acids to ¹⁴CO₂ and the dehydrogenation of [9,10-³H] fatty acids by lymphocytes and/or fibroblasts.^{12,13} Specific assays for carnitine palmitoyl transferase types I (CPT-I) and II (CPT-II), translocase, carnitine transport defects, and specific acyl-coenzyme A (CoA) dehydrogenase were performed when necessary. In addition, since 1996, acylcarnitine profiling was performed by using tandem mass spectrometry on a blood spot collected on a Guthrie card; this allowed a retrospective diagnosis in the patients who did not survive acute neonatal distress.¹⁴ Rhythm anomalies were diagnosed on 12-lead ECG and/or Holter monitoring.

Results

Cardiac manifestations were observed in 55 patients (51%). They included cardiomyopathy in 28 patients, isolated arrhythmia in 14, arrhythmias and associated cardiomyopathy in 10, and cardiogenic shock in the remaining 3. Among the 24 patients with arrhythmia, 11 were female and 13 were male children. The mean age at admission was 3.5 ± 6 months (range, 1 day to 13 months), and 14 of the 24 were newborns. In 18 of the 24 patients with rhythm disturbances, arrhythmias and/or conduction defects were the revealing symptom of the metabolic disorder. In the remaining 6 patients, the diagnosis of the fatty acid oxidation disorder was determined before the first episode of arrhythmia.

Arrhythmias were variously associated in the same patient. Fifteen patients had ventricular tachycardia, with transition from a polymorphic ventricular tachycardia to ventricular fibrillation in 6 of the 15. One patient with neonatal ventricular tachycardia and a very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency had a ventricular flutter (Figure 1). Four patients had episodes of supraventricular tachycardia: 3 were tachysystoles and 1 was reentrant junctional tachycardia. Four patients had a sinus node dysfunction responsible for acute bradycardia with episodes of atrial tachycardia on Holter monitoring. Conduction anomalies were observed in 10 patients: 6 had atrioventricular blocks (3 first-degree blocks, 1 Mobitz I block, and 1 complete block associated with ventricular tachycardia in a patient with VLCAD deficiency) and 4 had left bundle-branch blocks. These left-bundle branch blocks were always associated with other rhythm anomalies (atrioventricular block in 3 patients and supraventricular tachycardia in 1 patient).

The relationship of the type of arrhythmia to the enzymatic deficiency is summarized in the Table. Conduction disorders and atrial tachycardias were usually observed in patients with defects of long-chain fatty acid transport across the inner mitochondrial membrane (CPT-II deficiency and carnitine-acylcarnitine translocase deficiency); they occurred in only 2 patients with other defects (1 trifunctional enzyme deficiency and 1 multiple acyl-CoA dehydrogenation deficiency [glutaric aciduria type II]). Ventricular arrhythmias were observed in all types of fatty acid oxidation deficiencies, but they were the main arrhythmias in VLCAD deficiencies. Arrhythmias

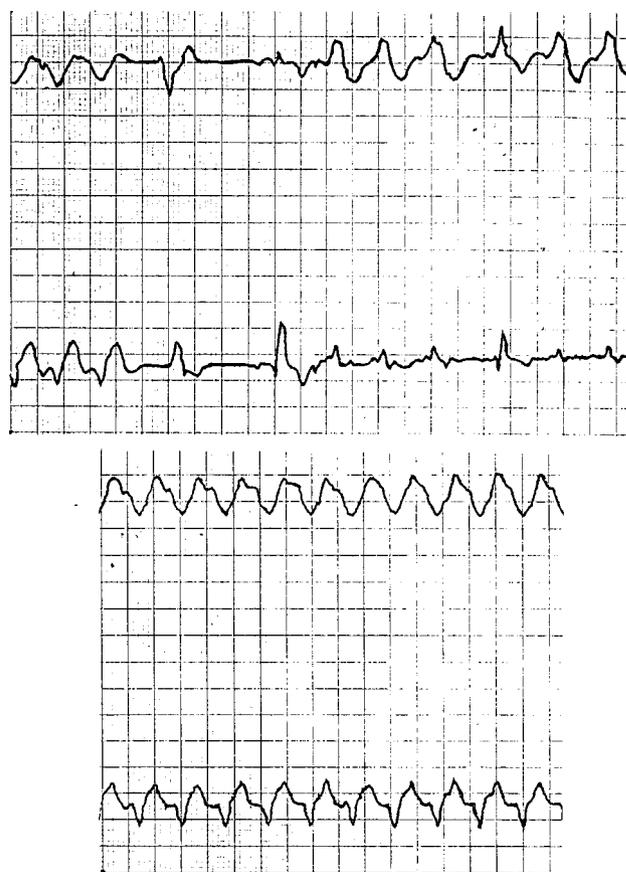


Figure 1. Neonatal ventricular tachycardia revealing VLCAD deficiency. This 1-day-old boy was referred to the neonatal intensive care unit for tachycardia. A 12-lead ECG showed polymorphic ventricular tachycardia. Echocardiography was normal, as was liver function, renal function, and neuromuscular examination. Sinus rhythm was restored by amiodarone. At 9 months of age, he had Reye syndrome, which led to the diagnosis of VLCAD deficiency.

were absent in patients with primary systemic carnitine deficiency due to carnitine carrier deficiency, CPT-I deficiency, or medium-chain acyl-CoA dehydrogenase deficiency.

Among our 24 patients with arrhythmias, only 3 are still alive with an adequate diet (1 CPT-II deficiency, 1 VLCAD deficiency, and 1 carnitine-acylcarnitine translocase deficiency). The other 21 patients died 1 day to 2 years (median, 1 month) after the diagnosis of the arrhythmia, except 1 patient with a long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency who survived 18 years and then died suddenly. Despite symptomatic therapy of the arrhythmia, 8 patients (all aged <1 year) died within the first week after the onset of the disease. The diagnosis of the fatty acid oxidation deficiency was retrospective in these latter patients. The arrhythmias were resolute in all the patients who survived the first week after the diagnosis of the defect, except in 1 patient with glutaric aciduria type II, who received antiarrhythmic medications (digoxin, amiodarone, and β -blockers) for intractable atrial arrhythmia. A stable sinus rhythm could never be obtained, and he died after 7 months (Figure 2).

Fatty Acid Oxidation Disorders and Arrhythmias in 24 Patients

Patient	Sex	Age	FAO Defect	Conduction Anomalies	Arrhythmias	Arrhythmias as		Outcome
						the First Symptom	Associated Cardiomyopathy	
1	F	1 d	CPT-II	LBBB, AVB	VT	+	—	Alive
2	M	3 mo	CPT-II	AVB	VT	+	—	† 17 mo
3	M	1 d	CPT-II		VT	+	—	† 7 mo
4	M	1 d	CPT-II		VT, VF	+	+	† 4 d
5	M	2 d	Translocase			+	—	Alive
6	F	1 d	Translocase	LBBB, AVB		+	—	† 3 d
7	M	2 d	Translocase	LBBB, AVB		+	—	† 8 d
8	F	2 d	Translocase		VT, VF	+	—	† 3 d
9	F	2 d	Translocase	Sinus node dysfunction	SVT	+	—	† 2 mo
10	F	2 d	Translocase	Sinus node dysfunction	SVT	+	—	† 2 mo
11	F	2 d	Trifunctional	LBBB	SVT	+	+	† 1 mo
12	F	6 d	Trifunctional	Sinus node dysfunction	SVT	+	+	† 11 d
13	F	2 d	Trifunctional		VT	+	+	† 1 mo
14	M	10 mo	LCHAD	Sinus node dysfunction	SVT	+	+	† 10 mo
15	M	1 d	MADD		SVT, VT	+	—	† 7 mo
16	F	12 mo	MADD		SVT, VT	+	—	† 12 mo
17	M	1 d	VLCAD		VT	+	—	Alive
18	M	9 mo	VLCAD		VT, VF	+	+	† 9 mo
19	F	9 mo	LCHAD		VT, VF	—	+	† 18 y
20	M	2 y	MADD		VT	—	—	† 4 y
21	M	2 mo	VLCAD	AVB	VT	—	+	† 5 mo
22	M	4 mo	VLCAD		VT, VF	—	+	† 5 mo
23	M	3 mo	VLCAD		VT, VF	—	+	† 3.5 mo
24	F	8 mo	Unknown		SVT	—	—	† 10 mo

AVB indicates atrioventricular block; LBBB, left bundle-branch block; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; †, deceased; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; and MADD, glutaric aciduria type II.

Discussion

Since the recognition of systemic carnitine deficiency, at least 14 inborn errors of fatty acid oxidation have been described.^{1,2} Acute neonatal distress is frequently revealing and usually precipitated by an infectious illness or fasting. In fact, the impaired long-chain fatty acid oxidation activity in these patients causes a shortage of energy, particularly in circumstances that increase reliance on fatty acids as the main energy substrate, such as during the immediate postnatal period.¹⁵ Indeed, their misleading clinical presentation and the poor prognosis probably impair the recognition of these disorders. For these reasons, the frequency of inborn errors of fatty acid oxidation is probably higher than recorded cases. In our experience, fatty acid oxidation disorders and disorders of mitochondrial oxidative phosphorylation account for ≈15% of cardiomyopathies in infants.¹⁶ In addition, sudden or unexpected death has been recognized as a presenting symptom of fatty acid oxidation disorders. The prevalence of fatty acid oxidation disorders in the different reported series of

sudden infant death is variously appreciated, and the diagnosis is usually retrospective, either by studying fatty acid oxidation by skin fibroblasts or by postmortem acylcarnitine profiling.^{10,11,17,18}

The mechanism of sudden death in children harboring a fatty acid oxidation deficiency is unclear. It is, however, obvious that acute arrhythmia may account for these unexpected deaths. In our series, 6 patients experienced acute, severe arrhythmia during the course of their disease and could be resuscitated. Rare case reports noticed conduction anomalies or ventricular arrhythmias as a major feature of these defects. Pande et al⁹ reported the first case of carnitine-acylcarnitine translocase deficiency in a newborn infant with severe hypoglycemia and atrioventricular block (patient 1, Table). de Lonlay-Debeney et al¹⁹ reported the case of a 9-month-old child with VLCAD deficiency who presented with severe heart failure and polymorphic ventricular tachycardia masquerading as fulminant myocarditis. Although a cardiomyopathy was present in 10 of our 24

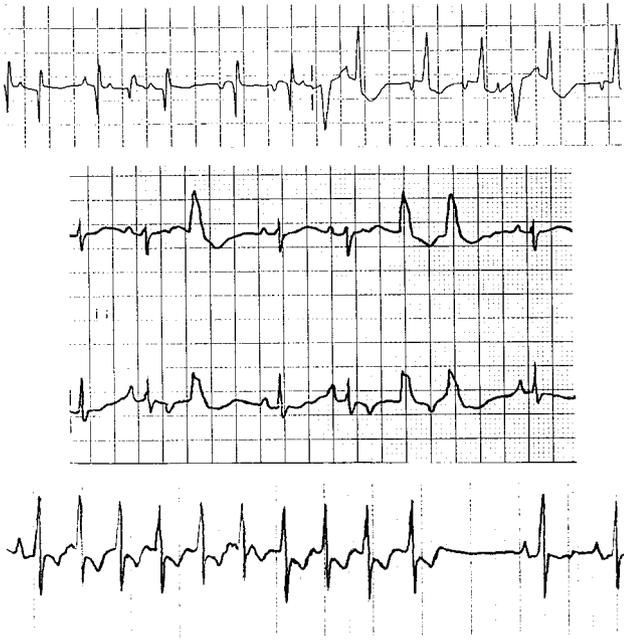


Figure 2. Arrhythmias and conduction anomalies in a newborn infant with glutaric aciduria type II. This 1-day-old child was referred for neonatal cardiac control because fetal echocardiography diagnosed atrial bigeminy during routine follow-up. Echocardiography was normal, and 12-lead ECG showed premature atrial and ventricular beats (top). During his first month of life, the patient experienced many episodes of atrial tachycardia (bottom). The diagnosis of fatty acid oxidation disorder was suspected because of neonatal recurrent hypoglycemia. At 4 months of age, hypertrophic hypokinetic cardiomyopathy was diagnosed; the child died at 7 months of age during cardiogenic shock.

patients, the arrhythmia was the only cardiac symptom in the remaining 14 when they were referred to the emergency or metabolic wards.

Neonatal ventricular arrhythmias are usually considered idiopathic when they are not associated with primary cardiac tumors, cardiac malformations, or a prolonged QT interval.²⁰ In addition, idiopathic ventricular tachycardia is rare in neonates, is usually monomorphic, and has a good prognosis.²¹ Regarding the conduction defects, the main cause of

atrioventricular block in newborn infants is lupus or Gougerot-Sjögren disease in the mother.²² Our series suggests that metabolic screening should be performed to exclude a fatty acid oxidation disorder in atypical and severe cardiac arrhythmias in newborn infants. The most convenient metabolic investigations of urine and plasma to determine the diagnosis of fatty acid oxidation disorders are as follows: determination of urinary acid organic profile, which can give a highly specific pattern or nonspecific dicarboxylic aciduria; plasma and urine free and total carnitine concentrations; and plasma acylcarnitine profile by tandem mass spectrometry.¹⁴

Clearly, such a metabolic screening should not be performed in all infants with arrhythmias, but preserving urine and plasma samples and a blood spot on a Guthrie card for infants with unusual arrhythmias, conduction defects, or associated symptoms (acidosis or hypoglycemia) is warranted to allow a retrospective diagnosis of the defect. These metabolic tests should be performed in patients with a clinical presentation suggestive of a fatty acid oxidation defect and also when atypical arrhythmias look isolated. This is well illustrated in patient 15 (Table), in whom the first symptom was fetal atrial bigeminy, which revealed glutaric aciduria type 2, and in patient 17 (Table), who experienced a transient neonatal ventricular tachycardia that was related to a VLCAD deficiency diagnosed when he presented with Reye syndrome at 9 months of age (Figures 1 and 2).

Inborn errors of fatty acid oxidation result in metabolite buildup proximal to the enzyme defect and in deficient formation of energy-yielding substrates after the block. In the defects downstream from CPT-I (Figure 3), the acylcarnitine that accumulates has detergent properties, which may explain its toxicity. Indeed, amphiphilic lipid metabolite, long-chain acylcarnitine, and lysophosphatidylcholine accumulate during myocardial ischemia and play a pivotal role in the production of arrhythmias. Incorporation of long-chain acylcarnitine in the sarcolemma elicited electrophysiological anomalies analogous to those seen in acute myocardial ischemia.²³ The cellular electrophysiological bases of the proarrhythmic effects of long-chain acylcarnitine seem to be multifactorial. First, reduction of the single-channel conduc-

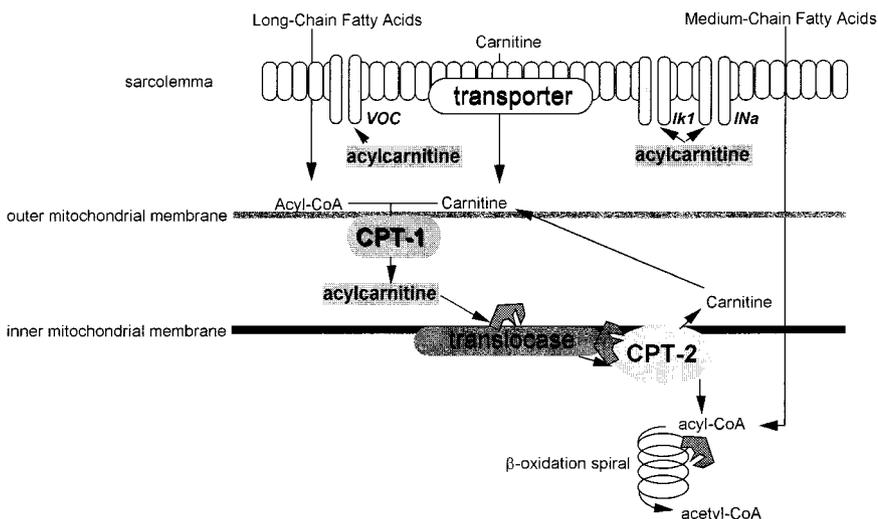


Figure 3. Hypothetic mechanism for cardiac arrhythmias in fatty acid oxidation disorders. In defects downstream from CPT-I, the accumulation of acylcarnitine may have toxic effects on the phospholipids of the sarcolemma and may interact with different ionic channels.

tance of the inward-going rectifier K current by amphipathic lipid metabolites may account for automatic action potential discharges from the resting and plateau potentials, leading to ventricular tachycardia. Second, retardation of conduction velocities by the decrease of the excitatory Na current could produce conduction anomalies and yield to reentry.²⁴ Third, nonesterified fatty acids directly activate voltage-dependent calcium currents in cardiac myocytes, inducing cytotoxic calcium overload.²⁵ Finally, amphipathic metabolites may interfere with the gap junctions and disturb the lipid-protein interface of the cell membrane and, thereby, impair gap-junction channels.²⁶ These toxic effects on ionic currents were not observed with short- and medium-chain acylcarnitine, demonstrating that the proarrhythmic effects of lipid metabolites depend on chain length and require a free carboxyl group.²³

These results are consistent with our observations. No patient harboring a fatty acid oxidation defect upstream of CPT-I, in which no accumulation of acylcarnitines occurs, experienced arrhythmias. Similarly, we did not observe any arrhythmia in patients with a medium-chain acyl-CoA dehydrogenase deficiency because these fatty acids do not use carnitine-acylcarnitine shuttling to reach the mitochondrial matrix. With regard to these hypothetical mechanisms, the prophylactics of malignant arrhythmias in fatty acid oxidation disorders should rely on the prevention of long-chain acylcarnitine accumulation, either by increasing acyl compound transport out of the cell by L-carnitine administration or by inhibiting acylcarnitine production.

L-carnitine administration plays a key role in the treatment of fatty acid oxidation deficiencies. Some have proposed using it to prevent arrhythmias in acute myocardial infarction.²⁷ Along the same line, free polyunsaturated fatty acids have a protective effect on ischemia-induced ventricular fibrillation by inhibiting the electrical automaticity/excitability of the cardiac myocyte.²⁸ The inhibition of CPT-I prevents the accumulation of long-chain acylcarnitines in the sarcolemma and, as a consequence, the incidence of lethal arrhythmias induced by ischemia in the rat heart.²⁹ Such an approach is promising because various antiarrhythmic drugs, namely perhexiline and amiodarone, inhibit CPT-I.³⁰ Metabolic interventions with targeted drugs enhancing glucose use and pyruvate oxidation at the expense of fatty acid oxidation could be a reasonable approach to prevent arrhythmias in these disorders.³¹ Today, the treatment of fatty acid oxidation disorders aims to provide sufficient glucose to prevent adipose tissue lipolysis. Carnitine therapy is also useful in lowering the accumulation of acyl-CoA and restoring the CoA pool in the mitochondria. Long-term dietary therapy is aimed at preventing any period of fasting that would require the use of fatty acids as a fuel by continuous nocturnal intragastric feeding or by the use of uncooked corn starch at bed time.²

Fatty acid oxidation disorders are rare, often misdiagnosed, inborn errors with an equivocal clinical presentation. Arrhythmias may be the presenting symptom of such deficiencies, particularly in newborn infants. Our series raises awareness for preserving tissue samples and performing a metabolic screening in cases with unusual childhood arrhyth-

mia. The investigation and diagnosis of fatty acid oxidation have been simplified by the profile of the blood acylcarnitine level by fast atom bombardment-mass spectrometry or electrospray-mass spectrometry. This technique allows the diagnosis of most fatty acid oxidation disorders from blood spots collected on a Guthrie card, which can easily be mailed to reference labs.

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