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Clinical Report

Tachycardiomyopathy-like presentation in neonatal MCAD deficiency: A novel cardiac phenotype

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ABSTRACT

Background: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder in Europe. Clinical onset typically occurs between 3 and 24 months of life with hypoketotic hypoglycemia, while neonatal presentations are less common. Although the disorder classically manifests with metabolic decompensation, atypical cardiac involvement has occasionally been reported but remains exceedingly rare. MCADD is included in many newborn screening programs, enabling early detection and timely management.

Case presentation: We report a full-term female neonate who, at 3 days of life, developed severe metabolic decompensation with refractory supraventricular tachyarrhythmias, severe systolic dysfunction, and biventricular dilation requiring maximal inotropic support. Expanded newborn screening revealed a profile consistent with MCADD, and genetic testing identified a homozygous variant in the *ACADM* gene, described according to HGVS nomenclature as ACADM(NM_000016.6):c.985A > C p.(Lys329Gln). Disease-specific management, including high-rate intravenous glucose administration, carnitine supplementation, and a tailored low-fat diet, resulted in complete normalization of cardiac function within 48 hours.

Discussion: This case represents a tachycardiomyopathy-like presentation of neonatal-onset MCADD, a novel and rarely described cardiac phenotype. It emphasizes the importance of considering fatty acid oxidation disorders in the differential diagnosis of unexplained arrhythmias and cardiomyopathy in neonates, particularly before newborn screening results are available.

Conclusions: Early diagnosis and prompt initiation of metabolic treatment are essential to reverse potentially life-threatening cardiac manifestations in MCADD. This report highlights a novel phenotype and expands the clinical spectrum of neonatal-onset MCADD.

1. Case report

A full-term female infant was born via vaginal delivery to a febrile mother, gravida 4, para 1.

The mother had a history of several spontaneous abortions; the parents were consanguineous (first-grade cousins); familial anamnesis was negative for relevant diseases.

Right after delivery, the baby was discharged to the maternal ward.

At 48 hours of life, the patient was admitted to the Neonatology Unit for hypoglycemia (36 mg/dL), hypothermia (33.3 °C), hypotonia and metabolic acidosis, in the context of significant weight loss (−9.5 % from birth weight), associated with poor feeding and prolonged overnight fasting; the EKG performed at the admission showed phases of severe bradycardia (HR 65–68 bpm), polymorphic ventricular

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extrasystoles, and 2:1 atrioventricular block (Fig. 1).

She was then transferred to the Neonatal Intensive Care Unit (NICU), where she received glucose and bicarbonate supplementation and adrenaline boluses; however, she subsequently developed a large QRS complex tachycardia with a left bundle branch block (LBBB) pattern (Fig. 2), interpreted as a supraventricular tachycardia with aberrant conduction, and was managed with multiple adenosine boluses. The echocardiography showed severe systolic dysfunction (ejection fraction, EF, 25–30 %) and biventricular dilation without evidence of structural congenital heart disease.

She was then referred to the Pediatric Cardiology Intensive Care Unit, where she experienced multiple recurrences of supraventricular tachycardia with a lesser degree of aberrancy, all treated with adenosine administration and electrolyte correction (Fig. 3).

Given the suspicion of neonatal myocarditis, intravenous immunoglobulin (IVIG) therapy was initiated on day 5 of life. Inotropic support with dopamine and dobutamine was added due to worsening of systolic function; however, no clinical improvement was observed.

On day 5 of life, results from the metabolic screening, performed routinely at 48 hours of age using dried blood spot (DBS) sampling, revealed a profile consistent with medium-chain acyl-CoA dehydrogenase deficiency (MCADD), showing markedly elevated acylcarnitine levels: C6 = 2.82 μmol/L (reference <0.6 μmol/L), C8 = 47.35 μmol/L (reference <0.75 μmol/L), and C10 = 3.27 μmol/L (reference <0.53 μmol/L), C0 = 1.87 (reference >8.22)

In light of the metabolic diagnosis, parenteral nutrition, containing lipids, including medium-chain triglycerides (MCTs), was immediately discontinued, and specific metabolic management was initiated, including high-rate intravenous glucose infusion and carnitine supplementation.

Remarkable clinical and functional recovery occurred within 48 hours, with a rapid normalization of cardiac function. By 72 hours, inotropic support was entirely withdrawn, and echocardiographic assessment confirmed full restitution of systolic performance, without any residual cardiac dysfunction. Genetic tests confirmed the hypothesis, and we identified a homozygous variant in the *ACADM* gene, described according to HGVS nomenclature as ACADM(NM_000016.6): c.985A > C p.(Lys329Gln).

The acylcarnitine profile was found to be markedly improved at 8 days after the initiation of metabolic management.

Finally, measurement of residual MCAD enzyme activity in peripheral blood lymphocytes revealed complete absence of activity (0 %).

Long-term follow-up, now exceeding two years of age, has shown no recurrence of cardiac involvement. The patient follows a structured metabolic care plan, which includes avoiding or limiting foods and infant formula that contain MCTs, regular carnitine supplementation (three times daily), and, most importantly, strict avoidance of fasting, together with adherence to an emergency protocol during periods of illness or increased metabolic demand.

2. Discussion

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is a potentially life-threatening autosomal recessive inborn error of mitochondrial fatty acid β-oxidation, caused by pathogenic variants in the *ACADM* gene. This enzyme plays a crucial role in the metabolism of medium-chain fatty acids (typically C6–C12), affecting the body's capacity to produce energy during prolonged fasting or periods of increased energy demand, such as illnesses (Merritt et al., 2018; Adam et al., 1993).

This condition results in the accumulation of fatty acid intermediates and impaired ketogenesis, which can lead to hypoketotic hypoglycemia, vomiting, lethargy, seizures, coma, and sudden death, particularly in young children (Merritt et al., 2018; Mayell et al., 2007; Derks et al., 2006).

The clinical presentation of MCADD is usually not highly variable and typically occurs in catabolic situations such as prolonged fasting, febrile illness, gastrointestinal infections, or vomiting, mainly in infancy and early childhood, but cases with later onset in adolescence or even adulthood have been reported (Mayell et al., 2007; Feillet et al., 2003).

Neonatal presentations, though less common, can be particularly severe and may mimic other critical conditions such as sepsis or cardiomyopathy, sometimes requiring interventions like extracorporeal life support (Kumar et al., 2014; Maclean et al., 2005). Management primarily focuses on the avoidance of fasting, the provision of emergency regimens during illness, and, in some cases, carnitine supplementation to support fatty acid transport and excretion of toxic metabolites (Treem et al., 1989).

Recent national data from Italy on expanded newborn screening have confirmed that MCADD is the most frequently detected fatty acid oxidation disorder, with an estimated incidence of 1 in 20,686 live births (Ruoppolo et al., 2022).

When evaluating neonatal emergencies such as early-onset tachyarrhythmias or cardiac dysfunction, clinicians should maintain a high index of suspicion for inborn errors of metabolism, including MCADD, which may present with atypical cardiovascular manifestations in the

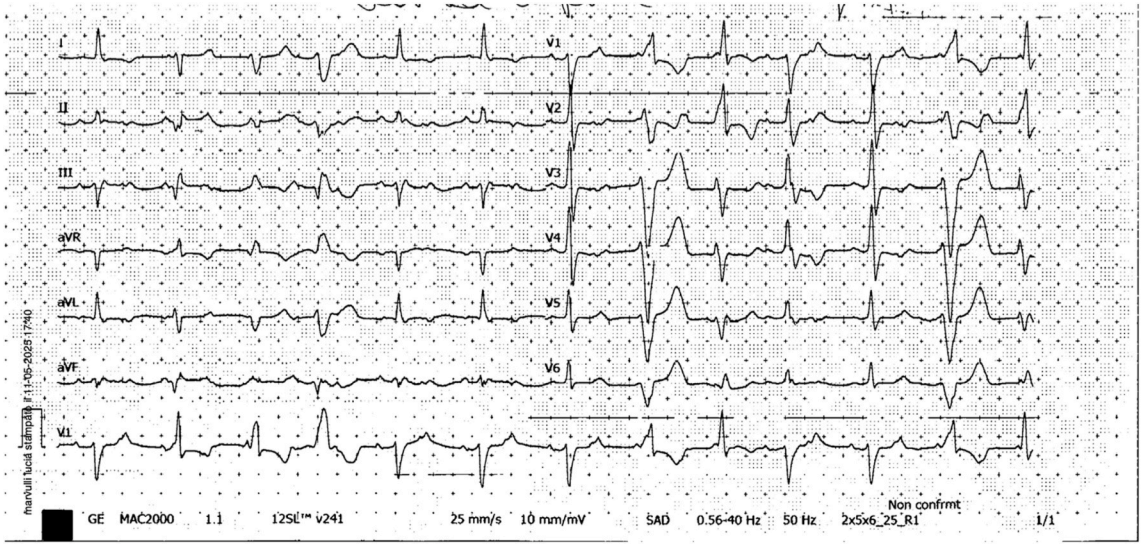

Fig. 1. Admission electrocardiogram showing severe bradycardia with polymorphic ventricular extrasystoles and 2:1 atrioventricular block.

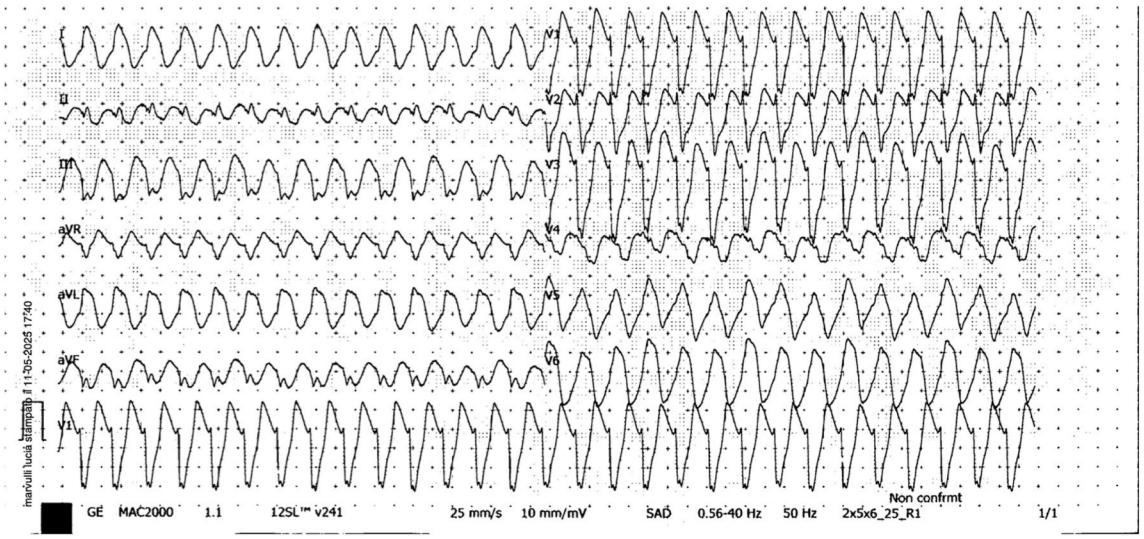

Fig. 2. ECG demonstrating wide-complex tachycardia with a left bundle branch block (LBBB) pattern, consistent with supraventricular tachycardia with aberrant conduction.

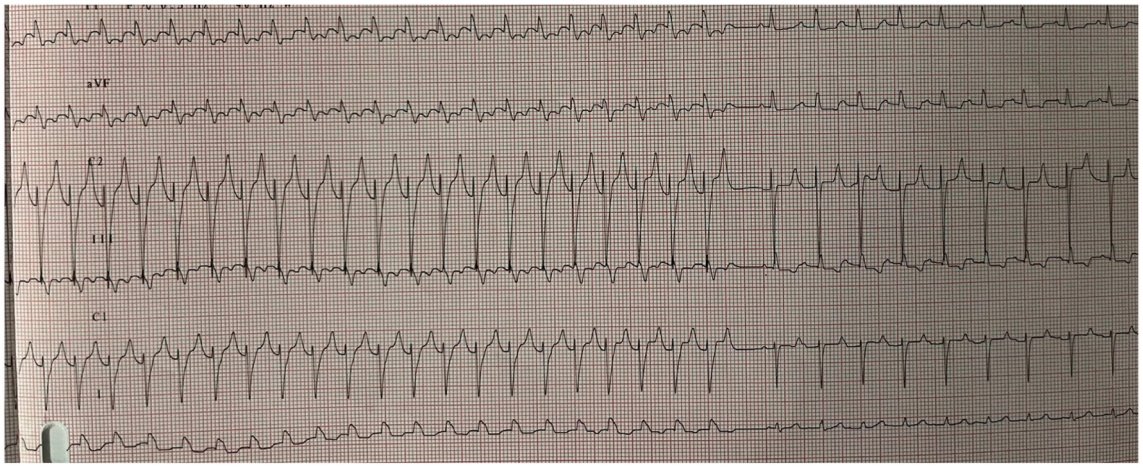

Fig. 3. Recurrent supraventricular tachycardia with reduced aberrancy observed during Pediatric Cardiology Intensive Care Unit admission.

first hours of life. The pathogenesis of the cardiac complications in this disease is thought to be related to the accumulation of fatty acids and acylcarnitine: high plasma levels may generate cytosolic calcium overload, reentry mechanisms, and activation of voltage-dependent calcium channels, which may lead to arrhythmic events (Feillet et al., 2003).

Nevertheless, cardiac involvement in MCADD is not traditionally considered a hallmark of the disorder. In 1999, Saudubray et al. described a series of 107 patients with FAODs: 97 patients died (30 % of them in the first 24 hours of life) within the first year of life. Cardiac presentation was observed in 51 % of patients: 47 % of them showed arrhythmias as the first symptom of the syndrome. None of the patients presenting cardiac involvement was affected by MCADD (Saudubray et al., 1999).

Only a limited number of case reports and clinical series have described associations with ventricular arrhythmias, dilated cardiomyopathy, and ECG abnormalities such as Brugada-like patterns in neonates and infants (Table 1) (Yusuf et al., 2010; Bala et al., 2016; Sanatani et al., 2005; Rice et al., 2007; Marcí and Ajovalasit).

To date, the arrhythmic presentation in MCADD has been documented in only seven cases in the literature, occurring both during the neonatal period and in adulthood (Table 1).

Conversely, to the best of our knowledge, a ‘cardiomyopathy-like’ phenotype has been reported only once in the literature in association with MCADD: a two-month-old female infant referred for heart transplant for idiopathic dilated cardiomyopathy; her twin sister died suddenly in the first days of life without a clear cause.

During her hospital stay, a comprehensive screening was conducted to identify the etiology of the cardiomyopathy, including metabolic screening, that resulted consistent with MCADD. Her conventional diet was suspended, and she started a low-fat diet and carnitine supplementation, resulting in gradual improvement: a dramatic reduction in her left ventricle end-diastolic volume, LVEDD, and an improvement in her EF.

She was eventually discharged after 90 days in good clinical conditions (Marcí and Ajovalasit).

Our patient showed the first symptoms at 48 hours of life and, despite a rapid glycemic correction, she experienced several episodes of tachyarrhythmias along with systolic dysfunction and biventricular dilation, mildly responsive to medical therapy.

The metabolic and cardiac decompensation in our neonate was primarily triggered by catabolic stress due to poor feeding and prolonged overnight fasting, which are typical risk factors in MCADD patients. Only after the appropriate metabolic diet and management were administered, we observed an improvement in cardiac function, which

Table 1
MCADD cases with arrhythmic presentation described in the literature.

Onset	Cardiac involvement and associated symptoms	Author
72h	Male neonate, cardiac arrest after several **ventricular tachyarrhythmias**. Extracorporeal life support was performed, resulting in gradual clinical improvement.	Kumar, 2013 (Kumar et al., 2014)
12h	Female neonate, several episodes of **ventricular tachycardia and fibrillation,** resistant to anti-arrhythmic therapy and defibrillation. The patient **died** at 68 hours of age, despite maximal cardiopulmonary support.	Yusuf et al., 2010 (Yusuf et al., 2010)
48h	Female neonate with hypoglycemia and hyperammonaemia; generalized seizures and **pulseless ventricular tachycardia**. She **died** after several relapses.	Bala et al., 2016 (Bala et al., 2016)
72h	A male neonate with metabolic acidosis developed pulmonary hemorrhage and cardiac arrest. He was resuscitated but had several relapses of **ventricular tachycardia and ventricular fibrillation**, and recovered after cardioversion.	Maclean et al., 2005 (Maclean et al., 2005)
48h; 72h	Two neonates with severe hypoglycemia later developed **ventricular tachyarrhythmias**.	Sanatani,2005 (Sanatani et al., 2005); Rice et al., 2007 (Bala et al., 2016)
Adult onset	A male adult with vomiting, hypoglycemia, and hyperammonemia. He later developed **ventricular tachycardia and fibrillation, and atrial fibrillation**, which recovered after cardioversion.	Feillet et al., 2003 (Feillet et al., 2003)

led to gradual clinical improvement and discharge after 23 days. According to the literature, patients should avoid prolonged fasting and can continue breastfeeding while taking oral carnitine supplementation (Treem et al., 1989). To our knowledge, this is the first case described with supraventricular tachyarrhythmias along with systolic dysfunction and biventricular dilation at the onset.

The complete and sustained normalization of cardiac function with specific metabolic management, including dietary therapy and carnitine supplementation, strongly supports MCADD as the sole underlying cause of the cardiac phenotype, making the coexistence of another primary cardiac disorder highly unlikely.

Newborn screening programs have significantly improved the early detection and prognosis of MCADD, enabling timely interventions before the onset of clinical symptoms in most cases (Kumar et al., 2014). Despite the undeniable efficacy of newborn screening in preventing severe outcomes in metabolic disorders, clinical symptoms may still manifest before DBS results are available. This highlights the critical importance of sustained continuous clinical vigilance, especially among healthcare providers in delivery centers, who must be prepared to suspect and promptly manage rare metabolic conditions that may initially present with unusual clinical phenotypes, as exemplified by the case reported.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Statements

Supplementary Materials: No supplementary materials.

Institutional review board statement

Written informed consent was obtained from the patient for publication of this case series. Ethical review and approval were waived for this study because we report a clinical series and we have not included any identifiable information. We obtained written consent for publication of this case report from the patient's parents according with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective review of patients' data did not require ethical approval in accordance with local guidelines. For the literature review an ethics statement is not applicable because this study is based exclusively on published literature.

Data statement

All clinical data and material are available in our Pediatric Unit.

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CRediT authorship contribution statement

Elisabetta Morana: Conceptualization, Data curation, Investigation. **Federico Baronio:** Conceptualization, Writing – review & editing. **Marcello Lanari:** Supervision, Writing – review & editing. **Egidio Candela:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing – original draft. **Rita Ortolano:** Writing – review & editing. **Simone Bonetti:** Conceptualization, Writing – original draft. **Gabriele Bronzetti:** Validation, Writing – review & editing. **Giacomo Biasucci:** Writing – review & editing. **Tammam Hasan:** Data curation, Investigation, Methodology, Project administration. **Luca Ragni:** Resources, Validation, Writing – review & editing. **Andrea Donti:** Supervision, Writing – review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2026.105070.

Data availability

Data will be made available on request.

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