Malays J Pathol 2022; 44(3): 523 – 526

CASE REPORT

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) precipitating unexpected death in an infant: Report of a case and a brief review of literature

Tara KAZEMI[1], Edward FIRGAU[2], Dustin R. BUNCH[2,3]*, Samir B. KAHWASH[2,3]

[1]Purdue University, Indiana; [2]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio; [3]Department of Pathology, College of Medicine, The Ohio State University, Columbus, Ohio.

Abstract

Medium-chain acyl CoA dehydrogenase deficiency (MCADD) and other inborn errors of metabolism are common causes of Sudden Unexpected Deaths in Infancy (SUDI). If identified early or before metabolic decompensation, MCADD is manageable. In the US and other countries, identification of MCADD has improved through the routine use of newborn screening (NBS), which is able to identify most cases. This case study presented here occurred before NBS was implemented in Ohio for MCADD and outlines the typical clinical presentation, pathological features, and relevant biochemical and molecular markers for identifying MCADD. Genetic counselling should be sought for the family if MCADD is identified.

Keywords: Sudden Unexpected Death in Infancy, SUDI, MCAD

Abbreviation: Emergency department (ED), Fatty acid oxidation deficiencies (FAOD), inborn errors of metabolism (IEM), Medium-chain acyl CoA dehydrogenase deficiency (MCADD), Newborn screening (NBS), Sudden unexpected death in infancy (SUDI), Sudden infant death syndrome (SIDS)

INTRODUCTION

Sudden infant death syndrome (SIDS) is a term used for the unexpected death of seemingly "normal" infant that appears unexplained and of unknown death aetiology. Recently, the term sudden unexpected death in infancy (SUDI) has replaced SIDS. According to Horne et al.,[1] SUDI is the unexpected death of an infant, usually occurring during sleep, where a cause of death is not immediately obvious. SUDI is a research classification that encompasses a broad range of sudden and unexpected deaths, including the classical SIDS, infections, anatomical or developmental abnormalities not recognised before death, sleep accidents due to unsafe sleep environments, and sudden unexpected deaths that are revealed by investigations to have been the result of non-accidental injuries.[1] Based on a recent review, fatty acid oxidation deficiencies (FAOD) should be considered for any SUDI.[2]

FAODs as a disease class have a combined global incidence that ranges from 0.07 to 1.9 per 100,000 live births with medium-chain acyl CoA dehydrogenase deficiency (MCADD) being the most prevalent.[2] MCADD is an autosomal recessive disorder of fatty acid oxidation which historically, accounts for up to 1% of SIDS/SUDI[3] and is more prevalent in those of European descent. Enzyme defects in the mitochondrial fatty acid β-oxidation pathway specifically the Acyl-CoA Dehydrogenase Medium Chain (ACADM) cause MCADD. Defects within this enzyme prevent ketone production from very long-, long-, and medium chain fatty acids which decreased energy availability especially during fasting or acute illness such as viral infections. This energy shortage primarily affects tissues with high energy requirements such as skeletal and cardiac muscle, the liver, and others. Without ketones available, these tissues are required to consume glucose, causing hypoglycemia which greatly affects the brain and can lead to death.

Early diagnosis of MCADD relies on newborn screening (NBS), if available, with definitive diagnosis based on biochemical and/or molecular analyses. NBS is recognised internationally as an

**Address for correspondence*: Dustin R. Bunch, 700 Children's Drive, Columbus, OH, 43205-2644. Tel: (614) 722-5359. Fax: (6164) 722-5308. Email: *dustin.bunch@nationwidechildrens.org*

essential, preventative health scheme that detects and manages inborn errors of metabolism (IEM), ideally, before the onset of symptoms.[4] Screening is effective in patients with MCADD deficiency since early diagnosis reduces death and severe adverse events in children up to 4 years.[5] Despite this, NBS initiation and implementation in developing countries, especially South-East Asian and North African regions, is challenging. There are barriers to implementing sustainable national NBS programs which include limited funding, manpower shortages, inadequate support services, low public awareness, and uncertain commitment from healthcare practitioners among others.[4] Typically, NBS programs measure acylcarnitines from dried blood spots using tandem mass spectrometry.

The diagnosis of MCADD is established through clinical presentation, biochemical, and molecular genetic testing for pathogenic variants in the *ACADM* gene.[6] The clinical presentation is nonspecific with the most common symptoms including emesis, lethargy, and hypoglycemia. The typical age of presentation, if not detected by NBS, is 3-24 months, however presentation into adulthood is possible. An MCADD diagnostic work-up is initiated due to suggestive biochemical testing in a symptomatic individual that was previously healthy or after positive NBS result. The diagnostic testing for MCADD, include both biochemical assays, urine glycines (*n*-hexanoylglycine, *n*-octanoylgylcine, 3-phenylpropionylglycine, and suberylglycine), plasma acylcarnitines (octanoylcarnitine [C8], hexanoylcarnitine [C6], and decanoylcarnitine [C10]), and molecular diagnostic testing. In addition to routine diagnostic assays, there are residual enzyme activity assay, but these methods are not routinely necessary and not clinically available in many regions,[7] and unlike some IEM, the MCADD biochemical and molecular diagnostic methods do not require provocative tests to identify asymptomatic affected individuals due to their sensitivity. Due to the autosomal recessive nature of MCADD, the siblings or possible future siblings of an affected individual are at a 25% risk of being affected, a 50% risk of being asymptomatic carriers, and a 25% risk of being unaffected and not carriers.[6] Sibling testing should proceed to identify other possible MCADD individuals due to high risk of being affected.

To develop a more accurate understanding of MCADD related deaths in the general population, we must have a clear understanding of the clinical presentation and diagnostic marker of MCADD. The case report presented herein details the autopsy findings of an infant who had the homozygous mutation (K329E also known as A985G) in the ACADM gene (which accounts for 90% of MCADD in Caucasian populations).

RESULT

Clinical History

A one-year-old boy with no significant past medical history was brought to the Emergency Department (ED) with the chief complaint of lethargy. The mother reported that he vomited earlier, then felt tired, so he was put to bed to sleep while the family was preparing for his first birthday celebration. Upon arrival to the ED, the child was responsive only to deep pain. His heart showed regular rate and rhythm and his lungs demonstrated good respiratory sounds. He was placed on a cardiac monitor and IV fluids were ordered. However, soon after the physical exam was completed, the child developed cardiac and respiratory arrest. Despite vigorous resuscitation efforts, the child could not be revived.

Pathologic findings

1.1.1 Gross Examination

Upon postmortem examination, the height and weight of the child were in the 60th and 10th percentiles, respectively. Weight and measurements of all organs, including the liver were within normal ranges. The main gross pathologic findings included fatty metamorphosis of the liver and heart.

1.1.2 Microscopic Examination

Sections from liver showed preserved architecture with micro-vesicular fatty metamorphosis (Figure 1, A&B). Glycogen was markedly decreased. Electron microscopic examination of liver showed steatosis with no other specific changes. Section from heart showed fatty metamorphosis with very small lipid droplets seen within cytoplasm of myocytes (Figure 1, C&D). Rare mononuclear inflammatory cells were noted between cardiac muscle bundles. Fat-stained sections confirmed fatty deposits within myocytes. Microbiologic cultures on samples from cerebrospinal fluid and blood were negative. Lung tissue cultures for viruses, legionella and acid-fast bacilli were negative.

Other findings

Urine samples were tested for fatty acid β-oxidation screening through biochemical

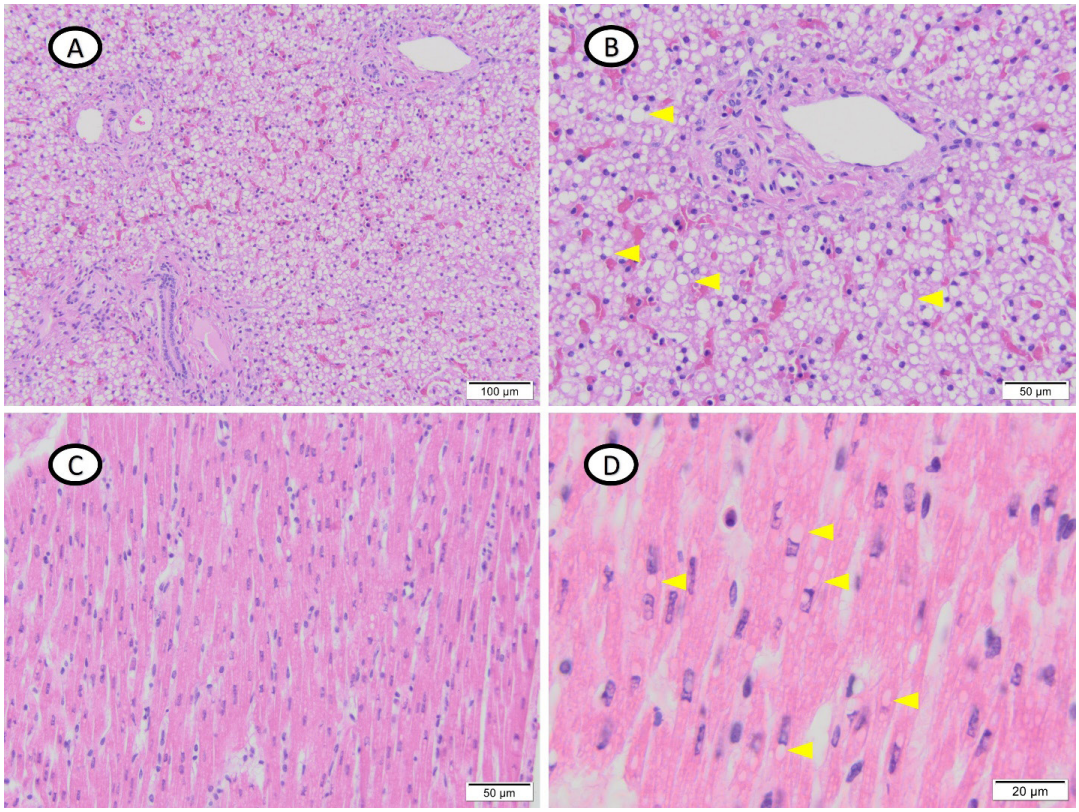

FIG. 1: Composite of microscopic findings in Liver (A, 20X magnification; B, 40X magnification) and Heart (C, 40X magnification; D, 100X oil magnification) showing fatty metamorphosis and prominent cytoplasmic lipid droplets (arrow heads) in hepatocytes and myocardial cells.

and molecular methods. Urine analysis showed markedly elevated acylglycines (n-hexanoylglycine, n-octanoylgylcine, 3-phenylpropionylglycine and suberylglycine). These results were consistent with MCADD deficiency. Molecular genetic analysis revealed a homozygous A985G mutation in MCADD gene.

DISCUSSION

In this case review, a child diagnosed with MCADD prior to the availability of routine NBS screening was characterized. Muscle (cardiac and skeletal) and liver tissues sampled during autopsy contained increased fat deposits and the urine acylglycine conjugates were elevated levels (*n*-Hexanoylglycine, *n*-Octanoylgylcine, 3-Phenylpropionylglycine and suberylglycine), which is a typical presentation for MCADD.

Often MCADD is silent and affects individuals who appear clinically normal until an intercurrent illness triggers hypoglycemia and fatty acid discharge.[8] This case study is a classic example of an intercurrent illness precipitating metabolic decompensation leading MCADD symptomology presenting. Due to the prolonged fasting state IV fluids were recommended, however, before the IV fluids could be administered the child developed cardiac and respiratory arrest, which subsequently lead to the child's death. If the presence of MCADD was diagnosed sooner, the family would have been aware of the risk of fasting for the child and they might not have died. The major recommendation to prevent death in individual diagnosed with MCADD is to avoid a fasted state. To prevent individuals from entering a fasted state varies as an example Merritt *et al*. outline frequent feeding of infants, and a relatively low-fat diet (e.g., <30% of total energy from fat) for toddlers, and administration of simple carbohydrates by mouth or intravenous if needed to reverse catabolism and sustain anabolism in emergent cases.[6] Not only can decompensation of a patient arise due to prolonged fasting (e.g. sleep, emesis), viral infection, as presented by this case study, can result in depleted glucose stores. Viral infections reduce appetite, promote sleep, and can lead to emesis and diarrhea, all of which promote catabolic processes.

Individuals with MCADD should discuss with their reproductive partners, genetic counselors, and doctors the likelihood of transmitting MCADD to their progeny. Additionally, all SUDI cases should be followed up with molecular testing based on the prevalence and impact IEM especially FAODs. If a known IEM is identified, the family should be tested to identify carrier status and consult with genetic counselors concerning future progeny and possible preemptive testing to manage possible disease states. After MCADD diagnosis for the case study child, genetic was arranged for the family.

Acknowledgement: None

Conflict of interest: The authors declared no conflict of interest.

REFERENCES

1. Horne RSC. Sudden infant death syndrome: Current perspectives. Intern Med J 2019;49:433-8.
2. Marsden D, Bedrosian CL, Vockley J. Impact of newborn screening on the reported incidence and clinical outcomes associated with medium- and long-chain fatty acid oxidation disorders. Genetics in Medicine 2021;23:816-29.
3. McConkie-Rosell A, Iafolla AK. Medium-chain acyl coa dehydrogenase deficiency: Its relationship to sids and the impact on genetic counseling. J Genet Couns 1993;2:17-27.
4. Leong YH, Gan CY, Tan MAF, Majid MIA. Present status and future concerns of expanded newborn screening in malaysia: Sustainability, challenges and perspectives. Malays J Med Sci 2014;21:63-7.
5. Wilcken B, Haas M, Joy P, *et al*. Outcome of neonatal screening for medium-chain acyl-coa dehydrogenase deficiency in australia: A cohort study. Lancet 2007;369:37-42.
6. Merritt JL, Chang IJ. Medium-chain acyl-coenzyme a dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. Genereviews((r)) Seattle (WA); 1993.
7. Goetzman ES. Chapter 10 - modeling disorders of fatty acid metabolism in the mouse. In: Chang KT, Min K-T, editors. Progress in molecular biology and translational science, Vol. 100: Academic Press; 2011. p. 389-417.
8. Schatz UA, Ensenauer R. The clinical manifestation of mcad deficiency: Challenges towards adulthood in the screened population. J Inherit Metab Dis 2010;33:513-20.