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CASE REPORT

# A case report of a first pregnant woman with late-onset multiple acyl-CoA dehydrogenase deficiency in Saudi Arabia

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## ABSTRACT

**Background:** Multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric aciduria II, is a rare autosomal recessively inherited disorder of inborn error of metabolism. It can mainly be presented in three phenotypes: severe neonatal onset with a dysmorphic feature, neonatal-onset without dysmorphic features, and less severe mild late-onset phenotype.

**Case presentation**: A 34-year-old Saudi female previously healthy, Para 4, with severe metabolic acidosis, rhabdomyolysis intrapartum was presented to us. Her previous pregnancy history and deliveries were unremarkable; she has three healthy sons. Since the beginning of this pregnancy, she complained of fatigability and muscle weakness which was progressive with time. At 36 weeks of gestation, she was presented to the emergency room with labor pain. She deteriorated rapidly with significant drowsiness. Her arterial blood gas showed severe metabolic acidosis with a high anion gap and normal lactate. She was intubated and underwent emergency cesarean delivery under general anesthesia. After the operation, she was sent to the intensive care unit. She passed away after a few days. A molecular test confirmed the diagnosis of MADD.

**Conclusion:** First, late-onset MADD is a rare, underdiagnosed disease in adults. Second, the biochemical diagnosis of late-onset MADD is challenging as it mimics medium chain acyl CoA dehydrogenase deficiency which makes the molecular diagnosis essential for diagnosis. Third, for any unexplained myopathy, cardiac dysfunction, encephalopathy, or metabolic acidosis, metabolic disorders must be considered as early consultation with metabolic service.

**Keywords:** Case report, pregnant, late-onset MADD, unexplained myopathy.

## Introduction

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) (OMIM 231680), also known as glutaric aciduria II (GA II), is a rare autosomal recessively inherited disorder of Inborn error of metabolism. It is due to deficiency of electron transfer flavoprotein (ETF) or ubiquinone oxidoreductase (ETF-QO), which are important mitochondrial electrons carrier for the respiratory chain and located in the mitochondrial matrix and the inner mitochondrial membrane, respectively (1-4). They play an important role in 12 enzymes (Figure 1), including several fatty acid oxidation, amino acid metabolism, and choline metabolism (1-4). ETF has alpha and beta subunits encoded by ETFA and ETFB genes, and ETF-QO is encoded by ETFDH genes (3).

MADD can mainly be presented in three phenotypes: severe neonatal onset with a dysmorphic feature, neonatal-onset without dysmorphic features, and less severe mild late-onset phenotype. The severest phenotype is the neonatal-onset form with a dysmorphic feature presented in first 28 days of life with hypoglycemia, encephalopathy, myopathy or cardiomyopathy, metabolic acidosis, and associated with dysmorphic features and congenital anomalies, predominantly cystic renal dysplasia. Those patients mostly died in the neonatal

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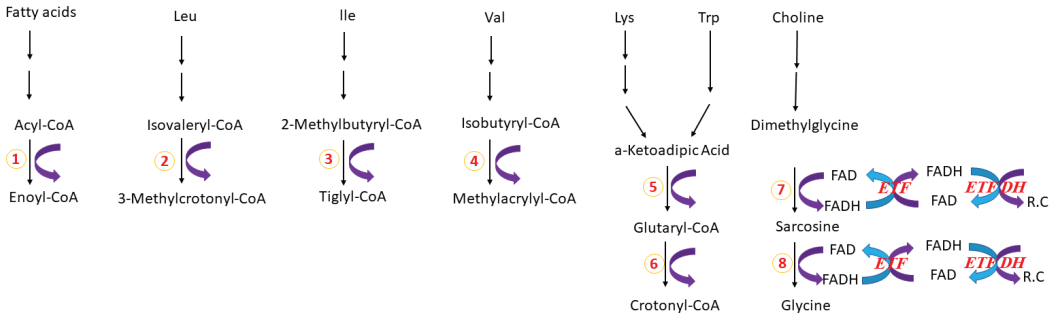


***Figure 1.*** *Pathways affected by MADD include fatty acids, amino acids, and choline metabolism 1: Very Large Acyl Co A Dehydrogenase, Large Acyl Co A Dehydrogenase, medium chain acyl CoA dehydrogenase deficiency (MCAD), Small Acyl Co A Dehydrogenase; 2: Isovalryl Co A Dehydrogenase; 3: Short Branch Chain Acyl Co A Dehydrogenase; 4: Acyl Co A Dehydrogenase family member 8; 5: alpha ketoadipic acyl Co A dehydrogenase; 6: Glutaryl Co A dehydrogenase; 7: Sarcosine dehydrogenase; and 8: Dimethylglycine dehydrogenase.*

period. The second phenotype is usually started in the neonatal period but without dysmorphic features. The third phenotype is the mildest late-onset phenotype which can be presented in infantile, childhood, adolescence, or adulthood with myopathy or cardiomyopathy (5). The disease's pathophysiology is due to decreased adenosine triphosphate production, lipid accumulation in different organs, and insufficient gluconeogenesis (6). Any physical or psychological stress usually provokes metabolic crises. It is characterized by hepatic involvement as hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia with elevated liver enzymes. In addition to muscular involvement, which can involve cardiac and/or skeletal muscles (7). Diagnosis biochemically is by accumulating intermediate metabolite in acylcarnitine and urine organic acid. Biochemical diagnosis is usually difficult for late-onset phenotype, especially when the affected individual is metabolically stable. Molecular testing is necessary for confirming the diagnosis (7-10). Early diagnosis facilitates early initiation of management, which includes dietary and medical management. Dietary management is based on the restriction of fat and protein and the avoidance of fasting. The mainstay of medical management is Riboflavin at a dose of 100-400 mg/day. As the disease is associated with 2ry deficiency of Co Q 10, it is suggested to combine it with Riboflavin (11). Carnitine supplement should be started for 2ry carnitine deficiency (5). Up until now, seven cases have been reported in Saudi Arabia. Two of them were late-onset diagnosed at 1 and 7 years old (6). In this report, we present a case of a 34-year-old female with MADD in which the clinical manifestations appeared during her pregnancy with fatal acute decompensation after the delivery. This case report is for an extremely rare disease with a rare presentation with mortality post-delivery was made to increase awareness about the disease, which is important for early initiation of treatment and prevention of mortality, and also emphasizes the variability of clinical manifestation of this disease.

## Case Report

A.A is a 34-year-old Saudi female previously healthy, Para 4, with severe metabolic acidosis and rhabdomyolysis intrapartum. Her previous pregnancy history and deliveries were unremarkable; she has three healthy sons. Since the beginning of this pregnancy, she complained of fatigability and muscle weakness which was progressive with time. She was referred at gestational age (GA) of 18 weeks to physiotherapy for severe low back pain. For the last three months of her pregnancy, she had difficulty going upstairs and downstairs (she used to walk beside the wall), she could not hold an object, she used two hands to hold a glass of water instead of one to have complete control. She has had a peculiar body odor for the last 2 months of pregnancy and foul-smelling vaginal secretion. High vaginal swab (HVS) was taken at GA of 33 weeks +2 days, and culture result was reported as no N.Gonorrhea, T. Vaginalis, or Candida species isolated. She had been vomiting one to two times a day for the last two months of pregnancy. At 36 weeks of gestation, she was presented to emergency room with labor pain and admitted accordingly. She was clinically stable, and the cardiotocography (CTG) was reactive. On third day of admission, she complained of headache, dizziness, and shortness of breath, and after a few hours, she felt palpitation. She had tachycardia, hypertension, and tachypnoea with normal saturation. The impression was severe preeclampsia toxemia (PET). The internal medicine team evaluated her with suspicion of neurological disorder . At that time, CTG showed fetal distress in the form of bradycardia. The patient decided to be taken for an emergency cesarean section as a case of G4 P3, GA: 36 weeks +4 days, severe PET and fetal distress for emergency cesarean section with possibility of chorioamnionitis.

She deteriorated rapidly with significant drowsiness. Her arterial blood gas showed severe metabolic acidosis with a high anion gap and normal lactate. She was intubated and underwent emergency cesarean delivery

under general anesthesia. During operation, she has managed aggressively with sodium bicarbonate boluses and replacement besides fluid resuscitation. After the operation, she was sent to the intensive care unit.

She had elevated liver enzymes, high CK, and high uric acid. There was no hypoglycemia. Urine ketone: +3. The laboratory characteristics of the case are mentioned in detail in Table 1.

Metabolic consultation was done on the third day post-partum. The patient died less than 24 hours after consultation. Brain magnetic resonance imaging and the abdominal ultrasound were requested, diagnostic samples were taken, echocardiogram and electrocardiogram (ECG) were requested with advice to keep blood glucose more than 120 mg/ dl. The echocardiogram revealed severe left ventricular dysfunction EF: 15%-20% with dilated left atrium and ventricle, severe global hypokinesia, severely depressed systolic dysfunction, and restrictive diastolic function of the left ventricle. The right atrium and the right ventricle were normal. it also revealed moderate to severe mitral regurgitation, moderate tricuspid regurgitation and moderate pulmonary hypertension. ECG showed sinus

***Table 1.*** *Laboratory characteristics of the case.*

| Complete blood count | | Chemistry | |
|---|---|---|---|
| WBC differential | 6.6 X10^3/uL (4 - 10) | ALT | 49 U/L ( 15 - 60) |
| Neutrophil | 88.7% | AST | 164 U/L (5 - 37) |
| lymphocyte | 8.4% | GGT | 13 U/L (5 - 85) |
| Monocyte | 2.6% | Total protein | 58 g/L (64 - 82) |
| Eosinophil | 0% | Albumin | 235 g/L (35 - 52) |
| Basophil | 0.3% | Bilirubin (total) | 12 umol/L (0 - 20.52) |
| RBC | 2.7X10^6/uL (3.8 - 4.8) | Bilirubin (conjugated) | 4.31 umol/L (0 - 5.13) |
| Hemoglobulin | 7.6 g/dL (12 - 15) | Alkaline phosphatase | 78 U/L (50 - 137) |
| MCV | 81 fL (78 - 96) | BUN | 3.9 mmol/L (2.5 - 6.43) |
| MCH | 27.8 PG (27 - 32) | Creatinine | 60 umol/L (44 - 88) |
| MCHC | 34.4 g/dL (31.5 - 34.5) | Sodium | 144 mmol/l (135 - 153) |
| RDW | 14.7 % | Potassium | 4.2 mmol/l (3.5 - 5.3) |
| Platelet count | 86 X10^3/uL (150 - 430) | Chloride | 107 mmol/l (97 - 107) |
| MPV | 11.5 FL (7.4 - 10.9) | Calcium | 1.85 mmol/L (2.1 -2.55) |
| **Coagulation profile** | | | Phosphorus |
| PT | 13.8 Sec (11.5 - 15.5)<br>INR 1.03<br>Control :14.1 Sec | Magnesium | 1 mmol/L (0.7 - 0.99) |
| PTT | 27 Sec (0.85 - 1.15)<br>Control: 29.9 | ammonia | 111 umol/l (11 - 51) |
| **Reticulocyte count** | 0.79 % (0.5-2.5) | CK | 1088-1857 U/L (26 - 192) |
| **ESR** | 19 mm /hour (2-20) | CK-MB | 149.2 U/L (7 - 25) |
| **Peripheral blood film** | Toxic granulation, band cells, shift to left with leucoerythroblastic blood picture | Uric acid | 370 umol/L (142.7 - 339) |
| **Arterial blood gas** | PH: 6.8 (7.35-7.45)<br>HCO3: 6.5 mEQ/L (22-28)<br>PaCO2: 2 mm Hg (35-45)<br>Base excess: -24<br>AG:26.6 | LDH | 774 U/L (81 - 230) |
| **Microbiology** | Blood culture: No growth<br>Urine culture: No growth<br>HVS : Normal | C-REACTIVE PRO-TEIN | 21 mg/dl (0 - 0.8) |
| **Urine ketone:** | +++ | Glucose | 6.1 mmol/L |
| **Placental pathology:** | No signs of chorioamnionitis, normal placenta | Lactate | 2.5 MMOL/L (0.5 -2.2) |

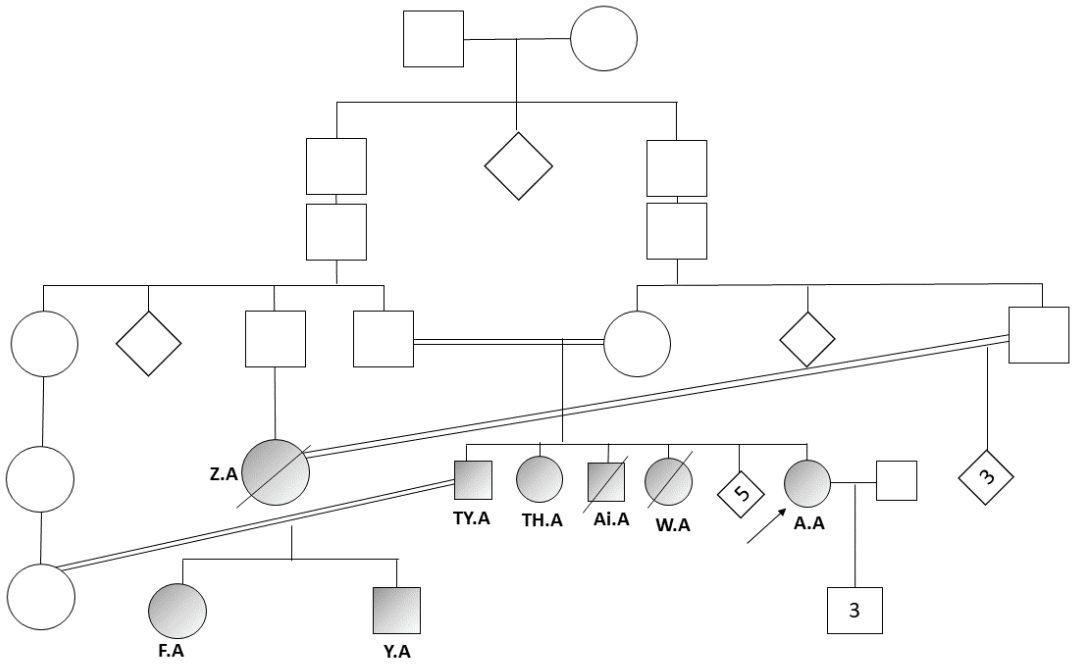


***Figure 2.*** *The family Pedigree with high consanguinity, affected individuals are labeled with black colored (filled) symbols.*

tachycardia. A mitochondrial cocktail was ordered to be started, but unfortunately patient passed away. Reviewing family history, a nephew Y.A and a niece F.A have MADD. Their parents are 3rd-degree cousins once removed. They were diagnosed by a national newborn screening program with MCAD deficiency based on elevated C8 and C10. They had been followed up in the clinic with continuous monitoring of free carnitine. They received l carnitine supplement once there was carnitine deficiency and were advised to avoid hypoglycemia. They had never been admitted with metabolic crises. Recently molecular tests revealed that they have MADD with homozygous mutation (c.1418C>T:p.P473L) on the ETFDH gene.

Biochemical Metabolic workup came after the patient died, including Tandem MS, which showed low C2, low C3, low free Carnitine :1.8. The diagnosis was confirmed by Urine organic acid that showed significant elevation of glutaric acid and 2 -glutaric hydroxy acid. A molecular test further confirmed the diagnosis. The family met, and extensive family history was taken besides clinical and laboratory assessment, and genetic counseling was provided.

The family pedigree shows the high consanguinity in the family (Figure 2). Her parents were second cousins from the paternal side. Her sister W. A died at the age of 15 years. She was previously healthy. She started to have progressive myopathy. She was unable to walk. She developed difficulty swallowing and required gastrostomy and tracheostomy. Two months later, she died with a diagnosis of myopathy, inconclusive the type. Her brother Ai.A died at the age of 9 years with a similar course to his sister W.A after two months of deterioration. Her paternal first cousin Z.A started to have manifestations at 40 years of age. She underwent three cesarean sections. Post last delivery, she started to have progressive myopathy. She became wheelchair-bound with no precise diagnosis and died after 20 years as a complication of cancer. After laboratory screening of the family members, two cases were confirmed to have the disease, including her sibling TY.A and TH.A.

## Discussion

MADD, also known as glutaric aciduria II (GA II), is a rare autosomal recessively inherited disorder of Inborn error of metabolism. Its prevalence is unknown. Its estimated incidence at birth is 1:250,000 (12). It can be mainly presented in three phenotypes: severe neonatal onset with dysmorphic features, neonatal-onset without dysmorphic features, and less severe mild late-onset phenotype. Late-onset MADD is underdiagnosed. Up until now, seven cases have been reported in Saudi Arabia. Two of them were late-onset diagnosed at 1 and 7 years (6). Over the world, 350 cases have been reported, 2 of them develop crises during pregnancy (7,14,15). Age of presentation is variable even within the same family as in our case. As early as Ai.A who started manifestation at the age of 9 years and late as Z.A started to have manifestation at 40 years. Provoking factors are variable. Pregnancy and delivery were the provoking factors for A.A and Z.A despite passing through normal and smooth delivery before. A.A showed typical manifestations, including hepatic involvement, hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia with elevated liver enzymes. In addition to muscular involvement, which can involve cardiac and/or skeletal muscles.

Diagnosis of MADD biochemically is by increasing dicarboxylic acids, glutaric acid, ethylmalonic acid, 2-hydroxyyglutarte, and glycine conjugates in urine organic acid. Urine organic acid was diagnostic for our case A.A as it shows the typical metabolites. Her sibling TY.A and TH.A had normal urine organic acid, which

makes molecular testing essential for diagnosis. Typical blood acylcarnitine of MADD is the elevation of C4 to C18 species with deficiency of free carnitine. A.A had a severe deficiency of l carnitine and all other acylcarnitine. Her siblings TY.A, TH.A, her nephew Y.A and her niece F.A had an elevation of C8 and C10 only, which mimics MCAD deficiency.

## Conclusions

First, late-onset MADD is a rare, underdiagnosed disease in adults. Second, the biochemical diagnosis of late-onset MADD is challenging as it mimics MCAD deficiency which makes the molecular diagnosis essential for diagnosis. Third, for any unexplained myopathy, cardiac dysfunction, encephalopathy, or metabolic acidosis, metabolic disorders must be considered as early consultation with metabolic service.


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**Ethical approval**
This study was approved by the Qatif Central Hospital ethics committee, and the patient's guardian signed informed consent.

**Consent for publication**
Informed consent was obtained from the patient's guardian.


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