

Late-onset MADD: a rare cause of cirrhosis and acute liver failure?

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Late-onset multiple acyl-CoA dehydrogenase deficiency (MADD) is a severe in-born error of fat metabolism. In late-onset MADD, hepatopathy in the form of steatosis is commonplace and considered a benign and stable condition that does not progress to more advanced stages of liver disease, however, progression to cirrhosis and acute liver failure (ALF) has been reported in two previous case reports. Here, we report a 22-year-old man, who suffered from late-onset MADD and died from cirrhosis and ALF. In the span of three months repeated clinical examinations, blood tests, and diagnostic imaging as well as liver biopsy revealed rapid progression of hepatopathy from steatosis to decompensated cirrhosis with portal hypertension. Routine studies for recognized etiologies found no evident cause besides MADD. This case report supports the findings of the two previous case reports and adds further evidence to the suggestion that late-onset MADD should be considered a rare cause of cirrhosis and ALF.

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Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD; OMIM 231680) is an autosomal recessive inherited disorder of the mitochondrial electron transfer flavoprotein (ETF) chain causing dysfunction of fatty acid, amino acid, and choline metabolism¹. The clinical presentation varies widely from fatal, neonatal-onset phenotypes to milder, late-onset phenotypes². Patients with late-onset MADD commonly present with liver steatosis and lipid storage myopathy as well as recurrent episodes of hypoglycemia and metabolic decompensation due to their impaired fat oxidation and consequently greater dependence upon carbohydrate oxidation³. Treatment of MADD is to prevent attacks of metabolic decompensation by means of dietary fat and protein restriction along with supplementation of riboflavin and L-carnitine, while the mainstay of hypoglycemic attacks is oral or intravenous glucose⁴. The liver steatosis in these patients is considered a benign and stable condition that does not progress to more advanced stages of liver disease and thus does not need specific treatment. However, since 2013, two patients with late-onset MADD have been described with inexplicable, sudden, and rapid progression of hepatopathy to cirrhosis and acute liver failure (ALF)^{5,6}.

Here, we present a third late-onset MADD patient, who suddenly and rapidly progressed to decompensated cirrhosis with portal hypertension and died from acute liver failure (ALF) with no evident cause besides MADD.

Case report

A 22-year-old man suffered from late-onset MADD. He was born from healthy parents, who were of Palestinian ethnicity and first cousins. He was the fourth of seven siblings. His three older siblings had all died from MADD at ages 10 months, 3 years, and 10 years respectively, in emergencies of acute hypoglycemia and metabolic decompensation. Of his three younger siblings, the oldest, aged 21, also suffers from MADD, but is well treated by fat and protein restriction and supplementation with riboflavin and L-carnitine. On this treatment, she has not experienced any recurrent episodes of hypoglycemia or metabolic decompensation, but she does have liver steatosis and lipid storage myopathy. For further details, she is described as patient #2 in the study by Madsen K. L. et al.⁷. The last two siblings do not suffer from MADD.

The parents received genetic counseling and were given prenatal diagnostic testing. DNA sequencing of placental tissue from chorionic villus sampling was performed and the index patient and his affected siblings were diagnosed with MADD subsequent to the finding of a novel homozygous c.1074G > C variant in the *ETFDH* gene leading to a substitution of the evolutionary conserved arginine in position 358 of the ETF dehydrogenase with serine. The variant leads to an expressed ETF dehydrogenase and is associated with a reduction of myristate oxidation at about 40%⁸.

From birth, the index patient was closely followed with biannual routine exams at the Centre for Inherited Metabolic Diseases. He was given the standard treatment of diet along with supplements of riboflavin and L-carnitine. Especially as a smaller child, he had numerous crises of hypoglycemia and metabolic decompensation often preceded by various trivial infections. All incidents were treated successfully with intravenous glucose. On a few occasions he advanced in metabolic decompensation to an extent that led to acute kidney failure and acute respiratory distress syndrome needing hemodialysis and assisted ventilation, but he always made a full recovery. The routine exams showed no other manifestations of MADD than moderate liver steatosis and lipid storage myopathy causing mild exercise intolerance as well as muscle weakness and pain. As expected for MADD, he had consistently – though rather varied – elevations of plasma-creatinine kinase (250–2500 U/L; normal 22–198 U/L) and an acyl-carnitine profile with normal concentration of free carnitine and markedly increased concentrations of acyl-carnitines of all lengths. He never showed any symptoms or signs of any other disease.

At age 21, after several years without having experienced a single hypoglycemic event, he was hospitalized with acute hypoglycemia and metabolic acidosis. Investi-

gations revealed intestinal *Clostridium difficile* infection (CDI) as the root cause and he soon recovered on intravenous glucose and antibiotics. However, in the following four months he was hospitalized and treated for acute hypoglycemia and metabolic acidosis two more times due to recurrent CDI. At the third admission, he also presented with abdominal pain and therefore a CT scan of the abdomen was performed (Figs. 1A-B). The scan was normal except for a significantly enlarged spleen measuring 18 cm in craniocaudal length (normal < 13 cm) with otherwise normal morphology. Following the third hospitalization he underwent fecal microbiota transplantation, which ended his recurrent CDI.

Nonetheless, two months later he was admitted to the hospital in a state of hypoglycemia and metabolic decompensation for the fourth time. This time investigations revealed septicemia caused by two staphylococcal bacteria (*s. epidermidis* and *s. capitis*). Once again he was treated with glucose and antibiotics. He recovered well but one month later he was hospitalized due to two weeks of progressive abdominal pain, bloating, and mushy stools. On clinical exam, he was jaundiced, febrile, and his abdomen was notably distended. Blood tests showed prolonged coagulation and elevated transaminases and bilirubin suggesting impaired synthesis function and acute necrosis of liver cells. A new CT scan of the abdomen was performed (Figs. 1C-D). It showed a cirrhotic-looking liver containing multiple small hypodense lesions implying parenchymal micro-abscesses along with clear signs of liver decompensation in the form of large-volume ascites and rectal portosystemic shunt with collaterals to the inferior mesenteric vein. Consistent splenomegaly and severe colitis were also found. On clinical and biochemical reevaluation, he had no stigmata of chronic liver disease and routine hepatitis tests were negative. Profiles of amino acids and acylcarnitines remained unchanged. Ultrasound images and CT angiography of the liver further revealed patent vessels and no biliary dilatation but the most severe degree of portal hypertension with hepato-fugal portal venous flow. The liver biopsy showed parenchymal damage with severe macro- and micro-vesicular steatosis along with accumulation of glycogen, copper, and Mallory bodies superimposed on a cirrhotic liver. There were no signs of malignancy or infection.

Hereafter the patient's liver function rapidly deteriorated and he died two months later in the intensive care unit from ALF. In this period the patient was not a candidate for neither liver transplant surgery or trans-jugular intrahepatic portosystemic shunt insertion as his short-term and long-term survival chances were considered too poor. His family declined autopsy and thus the patient could not be further examined.

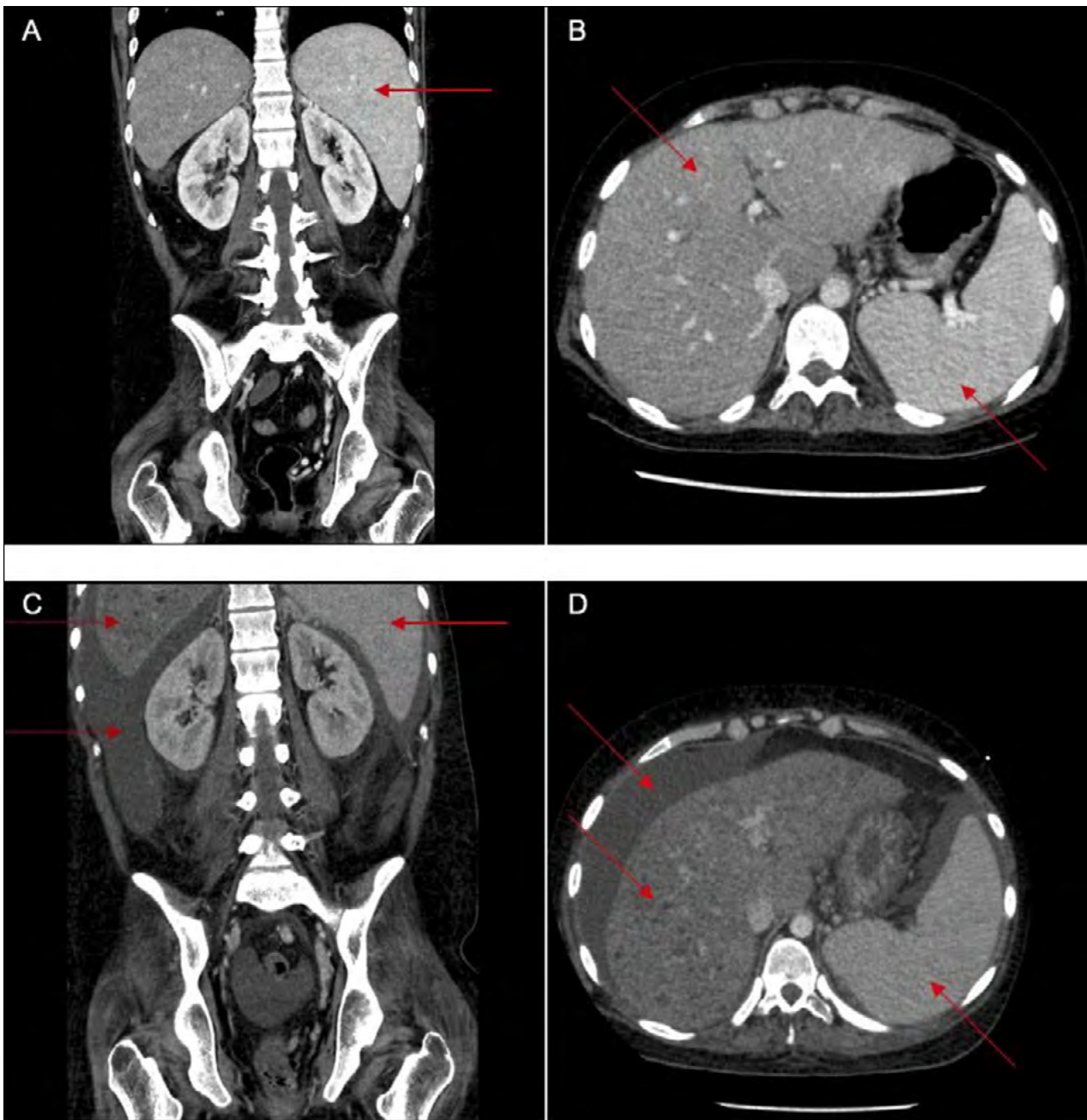


Figure 1. CT scan of the abdomen. A) Coronal scan showing normal intraabdominal conditions except for an enlarged spleen measuring 18 cm in craniocaudal length (arrow); B) Transverse scan showing normal liver and spleen tissues (arrows); C) Coronal scan showing multiple small hypodense lesions in the liver, ascites, and consistent splenomegaly (arrows); D) Transverse scan showing normal spleen tissue, but multiple small lesions in the liver tissue and ascites (arrows).

Discussion

We report the third case of a patient suffering from late-onset MADD, who suddenly and rapidly progressed in habitual hepatopathy from the state of steatosis to cirrhosis with portal hypertension, with no other evident cause than MADD. Our patient showed no other symp-

toms or signs of any other disease throughout his life except for a moderately enlarged spleen and episodes of recurrent CDI and septicemia, all this was observed and occurred prior to the diagnosis of cirrhosis with portal hypertension. CDI and septicemia are not associated with the development of cirrhosis, but splenomegaly is

frequently seen alongside cirrhosis⁹. Thus, it is most obvious that the enlarged spleen was simply a result of severe steatosis or beginning cirrhosis of the liver, and the infections merely caused by an overall immunocompromised state as seen in advanced liver disease, rather than to manifestations of another coexisting disease. Moreover, the two previously reported patients did not have either splenomegaly or events of infections prior to the onset of cirrhosis, indicating that these findings were most likely without significance to the development of cirrhosis in our patient. Our patient's liver biopsy showed accumulation of copper that could suggest Wilson's disease, but accumulation of copper is also seen in cholestatic liver disease as a consequence of decreased biliary excretion of copper¹⁰. Our patient had cholestasis with hyperbilirubinemia well explaining copper accumulation. Furthermore, he had no sign of Kayser-Fleischer ring. Therefore, further diagnostic testing for Wilson's disease was deemed unnecessary. All in all, the presence of another undiagnosed disease as a root cause or aggravating factor of the progressive liver disease in our patient cannot be ruled out with absolute certainty, but it must be considered highly unlikely.

The two previously reported patients – a German and a Chinese – who had the same age (22 years), were otherwise healthy and showed basically the same onset and timeframe of disease progression to cirrhosis and ALF as our patient. However, only the Chinese man eventually died, while the German man had a partial recovery with riboflavin and ubiquinone therapy^{5,6}. Unlike our patient who had been diagnosed prenatally and closely followed with comprehensive routine exams throughout his life, the others were unaware to suffer from MADD until their first symptoms and signs of liver disease appeared, and were subsequently diagnosed with MADD. In this way, our case report establishes with greater certainty that the onset was sudden and progression rapid in this very rare presentation of MADD. It is striking and interesting that all three cases are 22 years old, at onset. Aside from a fortuitous coincidence, we believe this simply indicates that the patients were able to compensate for gradually increasing liver steatosis during their youth and early adulthood. When the degree of steatosis eventually became too high for the liver, cirrhosis developed rapidly. Our case report, together with the two previous case reports, shows that late-onset MADD can be a rare cause of sudden and rapid development of cirrhosis and ALF. This should be kept in mind when following and treating patients with MADD. Therefore, basic biannual clinical and biochemical tests are recommended, and in case of signs of declining liver function, further investigations should be promptly conducted.

Initially our patient presented with recurring hypoglycemic events, many years after his last event in child-

hood. They were attributed solely to his simultaneous infections, but it is possible that they were – in part or in whole – actually caused by the decline in liver function and the impairment of glycogenolysis and gluconeogenesis, hence MADD patients depend heavily.

Patients with late-onset MADD have habitually elevated transaminases due to their lipid storage myopathy, but an increase in transaminases is also seen in beginning liver failure due to acute necrosis of liver cells. When our patient presented with recurrent hypoglycemic events, the increase in transaminases was entirely ascribed to the lipid storage myopathy, and therefore liver biopsy was not performed. However, it is likely that some part of the increase might have represented an early stage in development of cirrhosis. Thus, in these cases it would be an expedient measure to investigate the isoenzymes of the transaminases, in order to distinguish between if they are predominantly derived from muscle or liver tissue. If derived from the liver tissue, the liver biopsy is indicated to diagnose at an early stage the progression of the disease and to initiate the appropriate treatment as soon as possible.

In conclusion, this case supports the findings of the two previous case reports and adds further evidence to the suggestion that late-onset MADD should be considered as a rare cause of cirrhosis and ALF.

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