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Case Report

Late-onset Very long-chain acyl-CoA dehydrogenase deficiency diagnosis complicated by fulminant myocarditis in adult patient

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Introduction

A 21-year-old woman presented to the emergency department with fatigue, abdominal pain and diarrhea. Her physical activity in school was strictly normal.

She had no family medical history and no personal history but reported frequent episodes of nausea and vomiting lasting 2 to 7 days during the past two years, as well as a weight loss of 9 kg due to reactive anorexia (Body Mass Index 17.5), without triggering factors or self-medication. These gastrointestinal symptoms led to the detection of isolated elevated transaminases (aspartate aminotransferase [AST] 190 U/L and alanine aminotransferase [ALT] 170 U/L); however, the patient did not pursue the proposed etiological investigation. She has been using cannabis once a day for several years, with an increase in consumption over the past year, but no co-intoxication. She reported no other recent change in her habits.

At the emergency department, she was polypneic without any other sign of respiratory distress, no fever and her hemodynamic status were preserved. The clinical examination was normal, especially abdominal, neuromuscular and cardiological examinations as were the echocardiographic findings. The laboratory test showed a lactic metabolic acidosis (lactatemia 4.6 mmol/L) with respiratory compensation, elevated aminotransferase enzymes (AST 4093 U/L > ALT 891 U/L), rhabdomyolysis with creatine phosphokinase (CPK) 80,000 U/L, an oliguric acute renal failure (Kidney Disease: Improving Global Outcomes [KDIGO]) III and without inflammatory syndrome. The pregnancy test was negative. Toxicologic screening was negative except for cannabis. She required daily intermittent hemodialysis with ultrafiltration due to persistent acute renal failure with oliguria.

A cannabinoid hyperemesis syndrome was suspected but the intense rhabdomyolysis with acute renal failure, the duration of the attacks of more than 2 days, the lack of relief from hot showers and the diarrhea were unusual.[1] We therefore suspected an inherited metabolic disease especially a long-chain fatty acid (LCFA) oxidation disorder. Therefore, before receiving the results of biochemical tests, specific metabolic management was initiated. It consisted of a restricted long-chain triglycerides intake (i.e. limited natural fat intake of 20 g/day), but with a high carbohydrate diet combined with supplementation in medium-even-chain triglycerides (MCT) 40 g per day. The total calorie intake aim was close to 30 kcal/(kg·day). Calcium supplementation was initiated for slight hypocalcemia.

Analysis of the acylcarnitines profile by mass spectrometry from dried blood spots on blotting paper allowed the diagnosis of a very long chain acyl-CoA dehydrogenase deficiency (VLCADD): C14: 0.74 μmol/L (0.02-0.21 μmol/L), C14:1: 2.65 μmol/L (0.02-0.28 μmol/L), C16: 1.11 μmol/L (0.06-0.41 μmol/L), C16:1: 0.81 μmol/L (0.01-0.22 μmol/L), high ratio C14:1/C16: 2.89. These results confirmed the dietary instructions. The venous glucose intake was increased on day 4 as the patient developed anorexia.

Thereafter, the CPK level decreased, as did the intensity of vomiting, but the troponin I ultra sensible level increased from 80 ng/L to 1500 ng/L. Echocardiograms and electrocardiograms were regularly performed, and did not reveal any cardiac abnormality, from day 1 to day 4.

At day 5 the patient presented with rapidly progressive respiratory distress due to an acute lung edema. Despite depletion by hemodialysis and non-invasive ventilation initiation, the patient was intubated on day 6. The left

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ventricular ejection fraction was estimated at 15% with septal akinesia and lateral and global hypokinesia, without pericardial effusion, with a dilated left ventricle needing dobutamine. The patient was transferred to a referral center for veno-arterial extracorporeal membrane oxygenation if needed. Management consisted of enteral nutrition with formula monogen (1300 kcal/day [close to 30 kcal/(kg·day)]), including 42 g fat (29% Daily Caloric Intake [DCI] in which 86% MCT), 36 g protein (11% DCI), 194 g glucides (3 mg/(kg·day), 60% DCI), vitamin B2 (BEFLAVINE® 50 mg/day) and sodium beta-hydroxybutyrate at 15 g/day.

The left ventricular systolic function rapidly normalized. Weaning from catecholamines was done on day 7, extubation on day 9 and weaning from hemodialysis on day 12. This specific metabolic management was associated with a significant improvement of the acylcarnitine profile two weeks after initiating the changes in diet (C14:1 decreased to 1.05 μmol/L, C16 normalized [0.18 μmol/L]). The diagnosis of VLCADD was molecularly confirmed, with the pathogenic variant c.577G>C and the probably pathogenic variant c.680C>T for the *ACADVL* gene. The favorable evolution led to the recommendation of the current maintenance treatment: (1) a diet containing 30% of the fat DCI, divided into 1/3 of the ration as long-chain triglycerides (restricted dietary lipids) and 2/3 of the ration as MCT, delivered as oil (40 g/day); (2) LEVOCARNIL® 2 g/day; (3) Avoidance of any prolonged fasting situations (patient carries an emergency certificate to optimize management in case of urgent hospitalization for suspected metabolic decompensation).

Discussion

Inherited metabolic diseases occur mostly in childhood. Their diagnosis in adults is rarer and may be underestimated.[2] Exceptionally, these diseases can lead to the failure of an organ, such as the brain, the liver, the kidney or the heart, or multiorgan failure. Adult intensivists should be aware of these diseases.

Inherited metabolic diseases result from a genetic mutation leading to a deficiency of an enzyme or protein involved in metabolism, resulting in an accumulation or deficiency of a substrate. They are individually rare and have a very heterogeneous presentation which does not make their diagnosis obvious.[3,4] There is often a precipitating factor, like prolonged fasting or increased catabolism, such as during an infection.[5,6] Collaboration between metabolic physicians and intensivists helps to make the diagnosis.

VLCADD leads to a defect in the metabolism of very LCFA (chain lengths of 14 to 20 carbons). In a healthy subject, the production of adenosine triphosphate (ATP) in cardiac cells is 95% dependent on the beta-oxidation (BO) of fatty acids.[7] During prolonged fasting or intense effort, BO allows the metabolism of LCFA. In the case of VLCADD, LCFA accumulates in muscle, heart and liver cells.

BO deficiencies have different phenotypes depending on age and enzyme deficiency.[8,9]

The diagnosis of VLCADD is performed by the determination of the profile of blood acylcarnitines, done on plasma/serum or on a dried blood spot on a blotter. These samples must be taken during the acute phase of the disease and can be used to confirm the diagnosis. Fatty acid BO deficiencies are autosomal recessive diseases, and *ACADL* gene mutation testing can confirm the diagnosis. Other methods are possible like enzyme testing in fibroblasts and lymphocytes or flux studies in fibroblasts, but they are not routinely used.[10] Interestingly, in our patient's case, enzyme testing in fibroblasts and lymphocytes was used to confirm the diagnosis before a genetic test and allowed to rapidly institute the appropriate treatment. As it is a hereditary disease, a genetic analysis should be proposed to the family.

Acute treatment of VLCADD metabolic decompensation consists of controlling the triggering factor, providing large amounts of caloric intake with glucose, reducing the intake of LCFA (natural fat diet) and supplementation with MCT.[11] Sometimes, in the acute phase, this treatment is associated with ketone bodies, to quickly compensate for the energy deficiency due to ATP deficiency as well as the inability to produce sufficient ketone bodies due to intramitochondrial blockage of BO. L-carnitine supplementation is not recommended in acute metabolic crisis as it has not been proven to be effective and may increase the risk of arrhythmia in severe metabolic decompensation by accumulating long-chain acylcarnitines.[12] Other treatments such as triheptanoin and bezafibrate are currently being studied.

Rare cases of acute cardiopathy have also been reported but this is the second case report of acute heart disease in adults with VLCADD to our knowledge.[13] Moreover, while a treatment had been started, the patient worsened a second time and presented a fulminant myocarditis, which is a rare complication in this disease and described only in children.[7,14] It is possible that cardiac deterioration is due to a delay in increasing carbohydrate intake, and insufficient intake which is 150 g/day of carbohydrate (196 g theoretically recommended). In our opinion, this complication should justify an early and adequate carbohydrate intake, regular questioning, and clinical examination in search of arguments in favor of cardiac decompensation, monitoring of biological markers such as troponin during the stay, and frequent evaluation by echocardiography of cardiac function. Due to the rapid onset of heart failure, hospitalization in intensive care could be justified, particularly in the event of an increase in markers of cardiac distress such as troponin.

In our case, the differential diagnosis of cannabinoid syndrome could have been misleading. Indeed, several elements could have led to this diagnosis, such as the daily use of cannabis, recurrent nausea and vomiting, and elevated CPK, since rhabdomyolysis has been described with this entity.[15,16] The use of cannabinoid derivatives is increasing worldwide and cannabinoid syndrome is increasingly described, but it is important to evoke differential diagnoses, especially in this case where the duration of the attacks is not typical, nor is the absence of relief from hot showers.[17]

In conclusion, a CPK elevation without an obvious diagnosis should raise the suspicion of metabolic disease, especially in the case of associated organ failure. The expertise of metabolic physicians allows us to orientate the diagnosis and to set up an early and appropriate therapy, in order to avoid severe complications, such as myocarditis. The suspicion of cannabinoid syndrome needs a rigor-

ous analysis to unmissed alternative diagnoses like metabolic disorders.

Author Contributions

Martin GÉRARD: conceptualization, funding acquisition, writing- original draft, writing- review and editing. **Claire DOUILLARD:** funding acquisition, writing original draft. **Julien POISSY:** writing original draft. **Mehdi MARZOUK:** funding acquisition, writing original draft. **Christophe VINSONNEAU:** conceptualization, writing-original draft, writing-review and editing

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Ethics Statement

As this was a case report, there was no need for an ethics committee. We have got an oral consent from the patient.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. interest.

Data Availability

Details of the data can be requested from the corresponding author.

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