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A Case Study of Very Long Fatty Acid Dehydrogenase Deficiency Presented by Irritability and Seizures

S. AlKaabi, R. Ebead, M. Khames*, M. Amin, S. Ahmed, A. Gupta, E. Marzouk

ICU Department Zayed Military Hospital Abu Dhabi, UAE
*Corresponding author: Magdy.aly@msc.mil.ae

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Abstract This case study presents the clinical course and management of an 18-year-old male patient diagnosed with very long fatty acid dehydrogenase deficiency (VLCADD). The patient exhibited recurrent episodes of rhabdomyolysis accompanied by acute kidney injury (AKI) and elevated liver enzymes. Presented to us by irritability and restlessness and 3 episodes of seizures. The purpose of this case study is to highlight the challenges in diagnosing and managing this rare metabolic disorder and to emphasize the importance of early recognition and intervention to prevent further complications.

Keywords: *VLCADD, very long fatty acid dehydrogenase (FAD), rhabdomyolysis, seizure*

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1. Introduction

Very long fatty acid dehydrogenase deficiency "VLCADD" is a rare autosomal recessive disorder characterized by impaired metabolism of fatty acids. Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD, OMIM 201475) is the second most common disorder of inborn errors of fatty acid metabolism; its incidence varies between 1:30,000 and 1:400,000 live births, with some outliers such as Saudi Arabia with reported incidence of 1:3200 and Taiwan with 1:1,400,000. In Europe incidence range from 1:77,000 in Germany and Netherlands to 1:400,000 in Czech Republic. [1,2,3,4,5] Incidence of VLCADD increased after the introduction of an expanded newborn screening program with the use of tandem mass spectrometry (MS/MS) allowing early detection of patients [1,6]. VLCADD is caused by pathogenic variants in the *ACADVL* gene and is inherited in an autosomal recessive manner, resulting in deficient enzyme in the mitochondrial β-oxidation of long-chain fatty acids. Fatty acids are an important source of energy during prolonged fasting, physical exercise, and febrile infections when the body requires more energy. In VLCADD long-chain fatty acids with chain lengths of 14–20 carbons are not metabolized, which can lead to metabolic crises due to inadequate energy supply. This lack of energy may result in symptoms such as lethargy and hypoglycemia. Fats that are not properly broken down can also build-up and damage tissues in the heart, liver, and skeletal muscles, which can cause the other clinical features observed in people with VLCADD [7]; Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD) - NORD (National Organization for Rare Disorders)].

Patients with "VLCADD" are unable to adequately break down fatty acids for energy production, leading to various clinical manifestations, including recurrent rhabdomyolysis and multi-organ involvement. [8]

There are three forms of VLCAD infant, childhood, and adult. [9,10,11,12]

Symptoms can be mild to serious.

Infant and childhood types of VLCADD may cause periods of illness called Metabolic Crises, or low blood sugar. Some of the first signs of a Metabolic Crisis are:

- Too much sleepiness
- Behavior changes (such as crying for no reason)
- Irritable mood
- Poor appetite

If a Metabolic Crisis is not treated, a patient with VLCADD can develop.

- Breathing problems and seizures
- Coma, sometimes leading to death
- Other problems include enlarged liver, cardiomyopathy and muscle problem.

We present a case of an 18-year-old male patient diagnosed with very long FAD deficiency who experienced recurrent rhabdomyolysis and AKI with increased liver enzymes.

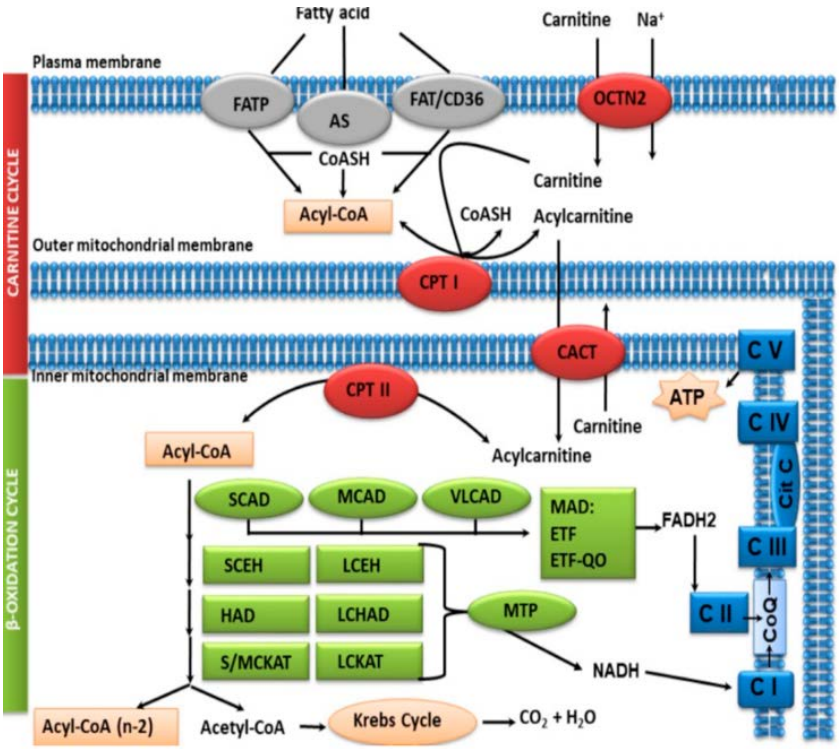

Figure 1. Main stages in carnitine and fatty acid ß-oxidation cycle. Uptake and activation of FA, in gray: FATP, FAT/CD36: fatty acid transporters; AS: acyl-CoA synthetase; Cycling of carnitine to pass the FA to the mitochondrial matrix, in red: OCTN2: carnitine transporter; CPT I: carnitine palmitoyltransferase I; CACT: carnitine-acylcarnitine translocase; CPT II: carnitine palmitoyltransferase II; β-Oxidation spiral, in green: SCAD: short-chain acyl-CoA dehydrogenase; MCAD: medium-chain acyl-CoA dehydrogenase; VLCAD: very long-chain acyl-CoA dehydrogenase; SCEH: short-chain enoyl-CoA hydratase; LCEH: long-chain enoyl-CoA hydratase; HAD (M/SCHAD): 3-hydroxyacyl-CoA dehydrogenase; LCHAD: long-chain 3-hydroxyacyl-CoA dehydrogenase; S/MCKAT: short/medium-chain 3-ketoacyl-CoA thiolase; LCKAT: long-chain 3-ketoacyl-CoA thiolase; MTP: mitochondrial trifunctional protein; MAD: multiple acyl-CoA dehydrogenase; Electron transfer and respiratory chain pathway, in blue: CoQ, CI, CII, CIII, CIV, CV: coenzyme Q and mitochondrial respiratory complexes I, II, III, IV and V. [13]

2. Case Presentation

An 18-year-old male patient presented to the emergency department with a history of recurrent episodes of muscle pain, weakness, and dark urine. Each episode lasted for approximately 2-3 days before resolving spontaneously. The patient reported no significant past medical history or family history of similar symptoms, has past history of subclinical hypothyroidism.

Investigated for myositis by MRI and muscle biopsy all was normal.

Patient admitted to the medical ward in our hospital by same presentation and diagnosed by Rhabdomyolysis associated with AKI and fatigability.

On physical examination, the patient appeared with generalized muscle tenderness. Laboratory investigations revealed elevated serum creatine kinase (CK) levels (24,000 U/L; reference range: 24-170 U/L), myoglobinuria, and acute kidney injury (serum creatinine: 3.8 mg/dL; reference range: 0.6-1.2 mg/dL).

Additionally, liver function tests showed elevated levels of liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Other laboratory parameters, including electrolytes and blood glucose, were within normal ranges

Patient managed by rehydration and discharge after 4 days.

Patient presented again to ED next day after discharge by irritability and restlessness but was conscious managed by dose of diazepam. After few hours patient complained of headache and episode of convulsions that aborted by another dose of diazepam, but he went into status epileptics and severe aspiration and desaturation required intubation and connection to MV and admitted in ICU.

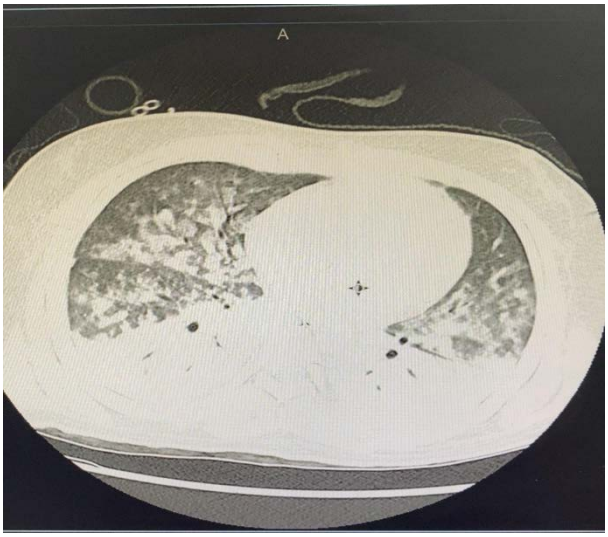

Figure 2. CT Chest at admission

3. Management and Outcome

The patient was admitted to the intensive care unit (ICU)
Patient ventilated in prone position as a case of ARDS

for 3 days, monitoring and aggressive management of ARDS, Rhabdomyolysis and AKI. Intravenous fluids were initiated to maintain hydration and prevent renal complications. Sedation and IV Levetiracetam to control seizure

EEG done and epileptic focus excluded

CT, MRV brain done, and venous sinus thrombosis excluded.

Patient improved and successfully extubated after 3 days.

Metabolic disorders especially Fatty acid oxidation disorders highly suspected so the following tests ordered:

- Plasma Acylcarnitine profile
- Plasma total/free carnitine levels
- Urine organic acids

The result came back:

- Tetradecenoyl carnitine(C14:1) elevated 2.15 µmol/L (ref. <0.3µmol/L)
- Tetra dienoyl carnitine (C14:2) elevated 0.56µmol/L (ref. <0.15µmol/L)
- Urine organic acid returned normal.

During the hospital stay, the patient's renal function gradually improved, and CK levels normalized. Liver enzyme levels also decreased to near-normal ranges.

Test Name	Test Result	Reference range
WBC	22.04 x 10^3/uL (High)	4.8-10.8 x 10^3/uL
Hgb	13.6 g/dL	14-18 g/dL
Neutro Auto %	87.8 % (High)	50-70
Lymph Auto %	7.1 % (Low)	20-45
ALT	277 unit/L (High)	5-40 unit/L
AST	200 unit/L (High)	5-40 unit/L
Protein Total	69.0 g/L	67-83 g/L
Albumin	38.0 g/L	35-53 g/L
Globulin	31.0 g/L	20-35 g/L
A/G Ratio	1.2	
Alkaline Phosphatase	70 unit/L	20-140 unit/L
Gamma Glutamyl Transferase	34 unit/L	7-47 unit/L
Sodium	146 mmol/L (High)	135-145 mmol/L
Potassium	4.8 mmol/L	3.5-5.2 mmol/L
Chloride	109 mmol/L (High)	96-106 mmol/L
Bicarbonate	15.0 mmol/L (Low)	22-26 mmol/L
Calcium	2.07 mmol/L (Low)	2.2-2.6 mmol/L
Creatine Kinase Total	17503 unit/L (Critical)	24-170 U/L
CRP	15.1 mg/L (High)	0-5 mg/L

Figure 3. ICU admission lab results

ABG	Normal range	Day 3	Day 2	Day 1	Admission
pH Art (POC)	7.35-7.45	7.41 - 7.44 [3]	7.39	7.20 - 7.35 [4]L07	5.99-7.27 [41[91
pCO2 Art (POC)	35-45 mmHg	43 - 45 [3]	41	144 - 68 [4]I(HI	51 - 73 (4](0)]
p02 Art (POC)	75-100 mmHg	121 - 197 (3]](H)]	149 (H)	192-139 1436H17	26 - 143 [4]](0)
Na+ Art (POC	135-145 mmol	132 - 135 BILLI	134 (L)	134 - 139 (4](L)]	135 - 143 (4}(L)]
K+ Art (POC	3.5-5.2 mmol	3.0 - 3.8 (3]](L))	3.5	3.7 - 4.5 [4]	4.3 - 5.4 1434401
Cl Art (POC)	96-106 mmol	103 - 105 (3]	104	1105 - 108 F4JIH/	103 - 108 (4]](H)]
Ca++ Art (POC)	1.15-1.30 mmol	0.99 - 1.03 (BJ](L)I	1.04 (L)	0.90 - 0.93 1[L]	0.89 - 1.12 [4}((L)J
Glu Art (POC	3.5-5.4 mmol	5.60 - 6.50 (3)	6.2	15.90 - 6.40 [4]	5.10 - 8.70 |4)((H))
Lac Art (POC)	0-2 mmol	0.70 - 0.80 [3]	0.8	0.90 - 1.00 [4)	2.40 - 12.20 (4][]
tHb Art (POC)	13-15 g			11 (L)	12.9 - 15.4 (BJC(L))
02Hb Art (POC)	95-99%	96.3 - 97.1 [3]	96.6	94.9 - 96.7 [4]I(L)]	17.7 - 96.1 (4][0)]
COb Art (POC)	1.3-1.8	1.0 - 1.8 [3)	0.9	1.1 - 2.0 (4]	1.2 - 2.0 [4]
MetHb Art (POC)	0.4-1.2	1.3 - 1.5 (3](HI!	1.3	1.4 - 1.6 [4]H)	1.0 - 2.0 [4]CHI
HCO3 Art (POC)	22-26	27.3 - 29.9 [3]](H)]	24.8	24.3 - 26.6 [4]](H)]	17.6 - 24.2 [4]](L)]

Figure 4. Serial ABG results

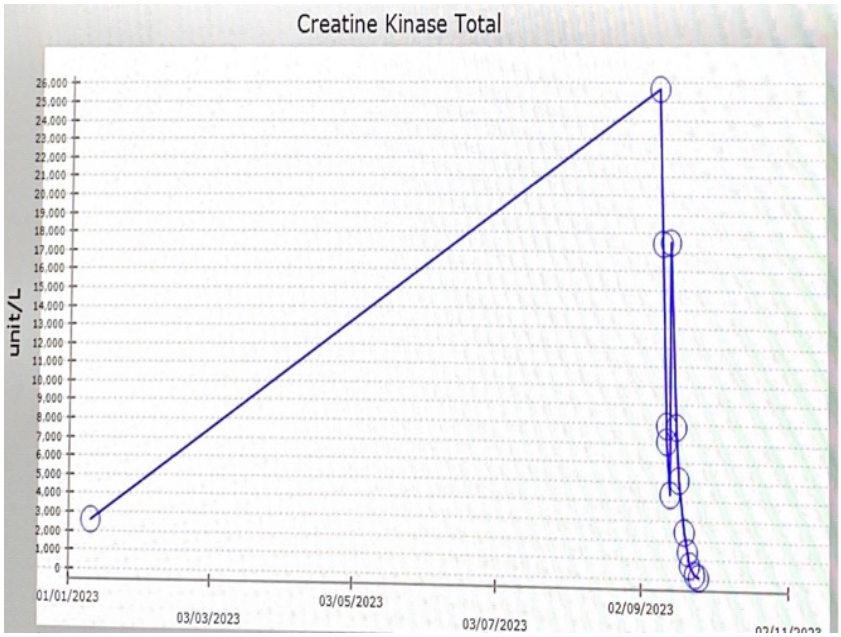

Figure 5. Creatine kinase results

Examination	Result	Unit	Ref.-Range
Acylcarnitine screening(**)			
Metabolism Diagnostics	**Result**	**Unit**	**Ref.-Range**
Acylcarnitine profile (s)(**)	Beside other acylcarnitines, significantly elevated levels of tetradecenoyl carnitine (C14:1) were detected in this serum sample:2.15 µmol/l (ref.<0.3 µmol/l).In addition tetradienoyl carnitine (C14:2) was elevated with 0.56 µmol/l (ref.:<0.15). Therefore, VLCAD (very long chain acyl Co-A dehydrogenase) deficiency must be suspected. VLCAD deficiency is a rare inherited defect of fatty acid oxidation. Clinical symptoms include cardiomyopathy, hepatopathy, hypoketotic, hypoglycemia, skeletal muscle involvement. Metabolic decompensation may occur in the neonatal period or later in life. A control from a new sample (dried blood or plasma/serum) with clinical site information would be advised. Further diagnostic measures: urine organic acids, enzyme activity in fibroblasts.		

Figure 6. Acylcarnitine screening

4. Discussion

FAD deficiency is a rare metabolic disorder that is associated with recurring episodes of rhabdomyolysis, acute kidney injury (AKI), and liver involvement. This ailment is characterized by sporadic muscle pain and weakness in mature individuals. Rhabdomyolysis, a syndrome caused by injury to the skeletal muscle, is a frequently occurring complication of FAD deficiency. It results in the release of potentially hazardous intracellular contents into the bloodstream. Complications arising from rhabdomyolysis encompass acute kidney injury, severe hyperkalemia, and hypovolemic shock. In the case of FAD deficiency, liver involvement is also observable, and the primary approach revolves around metabolic and liver-related interventions. All in all, FAD deficiency is a complex ailment that necessitates meticulous management to prevent complications and ensure optimal outcomes for patients. It is of utmost importance to promptly identify and diagnose the ailment to avert complications and long-term harm to the organs. The treatment mainly revolves around supportive measures during acute episodes, such as intravenous fluid administration and urine alkalization. Long-term management entails adhering to a low-fat, high-carbohydrate diet and avoiding triggers that could provoke rhabdomyolysis.

5. Conclusion

This case emphasizes the significance of considering VLCADD in patients who present with recurrent rhabdomyolysis, AKI, and elevated liver enzymes. Prompt

diagnosis and appropriate management are critical for preventing complications and enhancing patient outcomes. Such cases prompt healthcare systems to implement programs for early detection of these genetic diseases in newborns. Further research is necessary to gain a better understanding of the pathophysiology of this rare disorder and to develop targeted therapies for affected individuals.

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