Fatty Acid Oxidation Disorder

Case Study by

Muhammad Ali Pervaiz, MD
Clinical Biochemical Genetics Fellow.

FOD/OAA Family Support Groups
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Topics Discussed

Pathophysiology of VLCAD Deficiency.

Clinical subtypes and features.

Medical Management.

Dietary Management (to be discussed by Dr Singh).

Case discussions.

Fatty acid oxidation

Important for energy production and homeostasis once glycogen stores are depleted.

Provides up to 80% of energy to heart and liver.

Sequential cleavage of fatty acids to generate ketone bodies which are used as an alternative energy source by extrahepatic organs, esp. the brain.

Occurs in mitochondria.

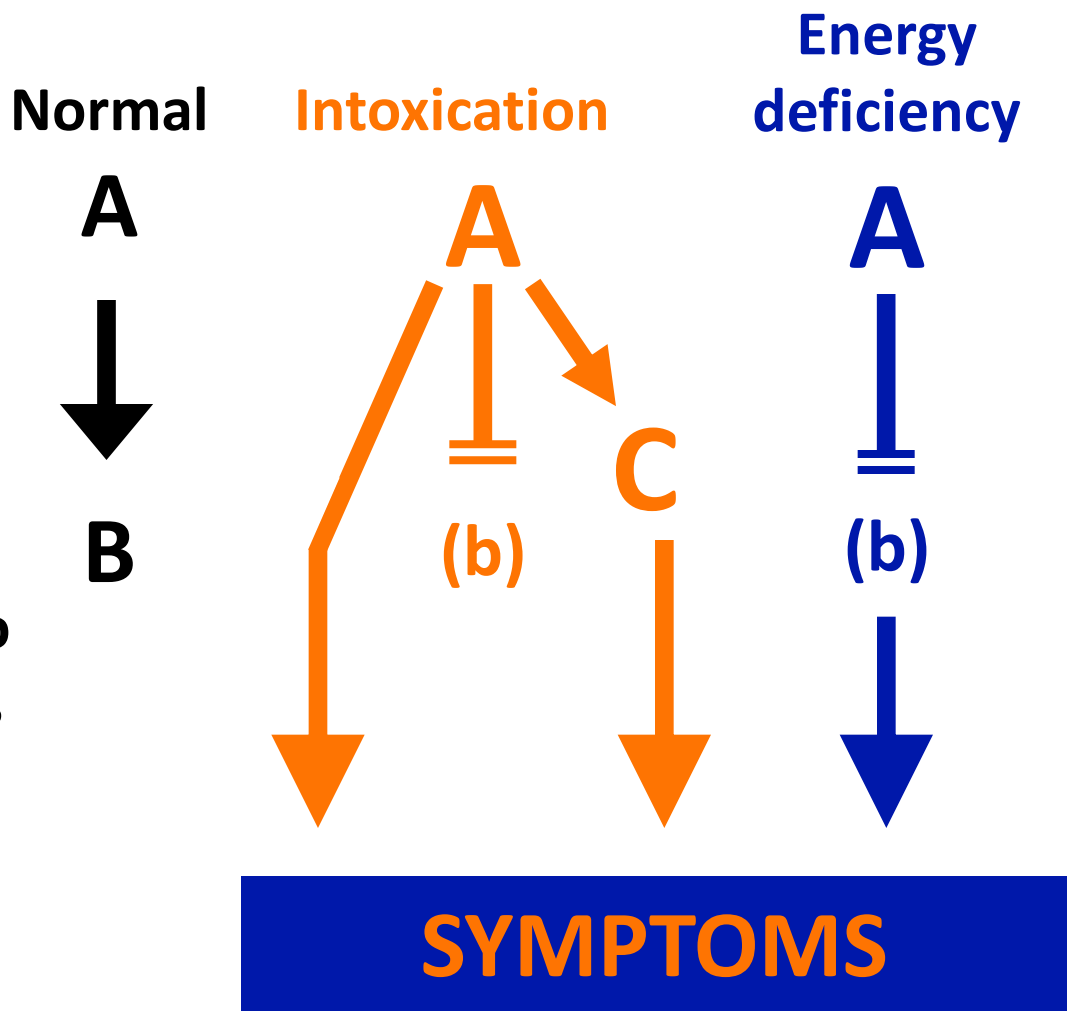
Metabolic effects of impaired fatty acid metabolism

Intoxication

- Fatty acids
- Acylcarnitines

Energy deficiency

- **Hypoglycemia**
- **No ketone bodies to extrahepatic tissues**



Courtesy: SIMD NAMA

Types of VLCADD

Severe, Early Onset	First months of life	Cardiomyopathy, Pericardial effusion, Arrhythmia, Hypotonia, hepatomegaly and intermittent hypoglycemia
Hepatic	Early Childhood	Hypoketotic hypoglycemia hepatomegaly, but without cardiomyopathy.
Episodic Myopathic Form	Later onset	Intermittent rhabdomyolysis, muscle cramps and/or pain, and/or exercise intolerance. No Hypoglycemia

Principles of Treatment

1: Avoid Fasting.

2: Limit long chain fatty acids in diet.

3: Supplement diet with MCT.

4: Increase calorie intake before high energy demand process.

5: Supplement carnitine to appropriate levels?

Monitoring Parameters

Acylcarnitine Profile

Total Carnitine Levels

Liver Function Tests

CPK esp. CK-MB fraction should be monitored aswell.

Echocardiogram

EKG

Essential Fatty Acids

Before the implementation of expanded newborn screen…

Case Study

1. Two and half month old baby boy.
2. Genetics consulted for hepatomegaly and cardiomyopathy.
3. Persistent emesis with dehydration for 1 day.
4. Hyponatremic dehydration along with hypotension.
5. Anemia.
6. Persistent elevation of Liver function tests.
7. Abdominal U/S detected hepatomegaly and pleural effusion.
8. CXR showed enlarged heart.

9. Echocardiogram:
    1. Biventricular hypertrophy.
    2. Moderate Pericardial Effusion.
    3. Ejection Fraction of 47%.

10. EKG: Sinus tachycardia with RBBB.

11. Intermittent problems with vomiting since birth.

12. Recently more somnolent as per parents report.

13. Normal developmental milestones.

Physical Examination

Hepatomegaly 8 cm below the costal margin.

Splenomegaly ~ 3 to 4 cm below the costal margin.

No cardiac murmur.

Hypotonia.

Lab results

AST	156-404	(11-39)	U/L
ALT	103-243	(22-58)	U/L
Alkaline Phosphatase	290	(40-150)	U/L
Ammonia	44-74	(22-48)	umol/L
Blood Glucose	128-195	(65-100)	mg/dl

Acylcarnitine Profile

species	(ACYL GROUP)	normal range (nmol/mL)	RESULT (nmol/mL)	status
C2	(ACETYL)	2.0 - 15.7	0.81	LOW
C3:1	(PROPENOYL)	< 0.03	(BQL)	NL
C3	(PROPIONYL)	< 0.75	0.06	NL
C4	(BUTYRYL/ISOBUTYRYL)	< 0.43	(BQL)	NL
C5:1	(TIGLYL/ME-CROTONYL)	< 0.03	0.07	ELEVATED
C5	(ISOVALERYL/2ME-BUTYRYL)	< 0.37	0.06	NL
OH-C4	(3-OH-BUTYRYL)	* < 0.21	(BQL)	NL
C6	(HEXANOYL)	< 0.25	(BQL)	NL
OH-C5	(3-OH-ISOVALERYL)	* < 0.08	(BQL)	NL
BZL	(BENZOYL)	* < 0.03	(BQL)	NL
C4DC	(METHYLMALONYL/SUCCINYL)	* < 0.04	(BQL)	NL
C8:1	(OCTENOYL)	< 0.52	0.06	NL
C8	(OCTANOYL)	< 0.22	0.03	NL
C5DC	(GLUTARYL)	* < 0.03	(BQL)	NL
C6-DC	(ADIPOYL/ME-GLUTARYL)	* < 0.08	0.07	NL
C10:1	(CIS-4-DECENOYL)	< 0.30	0.05	NL
C10	(DECANOYL)	< 0.34	0.12	NL
C8-DC	(SUBERYL)	* < 0.08	0.03	NL
C12:1	(DODECENOYL)	< 0.24	0.13	NL
C12	(DODECANOYL)	< 0.17	0.25	ELEVATED
C14:2	(TETRADECADIENOYL)	< 0.15	0.73	ELEVATED
C14:1	(TETRADECENOYL)	< 0.28	3.18	ELEVATED
C14	(TETRADECANOYL)	< 0.10	2.02	ELEVATED
OH-C14:1	(3-OH-C14:1)	* < 0.05	0.17	ELEVATED
OH-C14	(3-OH-C14)	* < 0.03	0.06	ELEVATED
C16	(PALMITOYL)	< 0.27	4.89	ELEVATED
OH-C16	(3-OH-PALMITOYL)	* < 0.03	0.06	ELEVATED
C18:2	(LINOLEOYL)	< 0.27	1.58	ELEVATED
C18:1	(OLEOYL)	< 0.42	5.68	ELEVATED
OH-C18:2	(3-OH-LINOLEOYL)	* < 0.03	0.04	ELEVATED
OH-C18:1	(3-OH-OLEOYL)	* < 0.03	0.06	ELEVATED
C16-DC	(C16-DICARBOXYLIC)	* < 0.03	0.07	ELEVATED
C18:1-DC	(C18:1-DICARBOXYLIC)	* < 0.03	0.10	ELEVATED

Marked elevations of long chain species.

Total and free Carnitine levels were low.

ACADVL sequencing

- c.1141_1143delGAG in frame deletion in exon 11.

- A deletion mutation encompassing exon 8 to exon 18 (partial) with approximate genomic breakpoints at nucleotide positions g.7,065,899 in intron 7 and g.7,068,084 in exon 18 was detected in this individual.

Initial Management

IV fluids resuscitation including dextrose (D10).

Dopamine for a very short period for cardiac support.

Blood Transfusion for Anemia.

Cardiology consulted and patient started on

- Captopril
- Lasix.
- Carvedilol.
- Potassium chloride.
- Aldactone.
- L-carnitine ~ 75mg IV twice a day.
- Riboflavin 25 mg by NG tube twice a day.

Pericardiocentesis.

Initial Dietary Management

Portagen (20 calories/oz)

1 cup portagen powder = 136 grams

29 oz of water.

12ml of canola oil (EFA).

2/3 cup of Polycose powder (carbohydrates).

Carnitine PO ~ 50 mg/kg.

Lasix, aldactone and KCl was stopped after 2 months.

(to be discussed further by Dr Rani Singh).

Echocardiogram at 18 months

Normal biventricular size.

No pericardial effusion.

Normal systolic function and ejection fraction.

Present Management

Remaining cardiac medications were discontinued.

At 5 years of age he is at the 50th percentile for height and weight and has normal development.

He continues to be on his current diet with high MCT oil.

Plasma carnitine:	WNL
Liver Enzymes:	WNL
CPK:	Fluctuations can be seen.

After the implementation of expanded newborn screen

Case Study 2

Possible VLCAD detected

	Value	H	L	CH	CL
C16	4.48	8	0.19	16	0.09
C14:1	**3.37**	0.49	-	**0.98**	-
C14:2	0.58	0.33	-	-	-
C14:1/C12:1	6.72	4.5	-	-	-
C14	2.03	0.8	-	-	-
C12:1	0.5	0.37	-	-	-
C12	0.82	0.4	-	-	-

Acylcarntine Profile

	umol/L	Normal range	Comment
Acetyl-, C2	4.97	0 - 26.9	
Propionyl-, C3	0.46	0 - 0.88	
Iso-/Butyryl-, C4	0.21	0 - 0.91	
Isovaleryl-/2-Methylbutyryl-, C5	0.13	0 - 0.45	
Hexanoyl-, C6	0.06	0 - 0.17	
3-OH-Isovaleryl-, C5-OH	0.05	0 - 0.12	
Octenoyl-, C8:1	0.32	0 - 0.61	
Octanoyl-, C8	0.12	0 - 0.21	
Decenoyl-, C10:1	0.14	0 - 0.34	
Decanoyl-, C10	0.26	0 - 0.35	
Glutaryl-, C5-DC	0.09	0 - 0.19	
Dodecenoyl-, C12:1	0.18	0 - 0.17	H
Dodecanoyl-, C12	0.47	0 - 0.25	H
3-OH-Decanoyl-, C12-OH	0.05	0 - 0.07	
Tetradecadienoyl-, C14:2	0.58	0 - 0.09	H
Tetradecenoyl-, C14:1	1.84	0 - 0.24	H
Tetradecanoyl-, C14	0.70	0 - 0.19	H
3-OH-tetradecenoyl-, C14:1-OH	0.24	0 - 0.13	H
3-OH-tetradecanoyl-, C14-OH	0.03	0 - 0.05	
Hexadecenoyl-, C16:1	0.26	0 - 0.22	H
Hexadecanoyl-, C16	0.40	0 - 0.69	
Hexadecenoyl-, C16:1-OH	0.03	0 - 0.07	
Hexadecanoyl-, C16-OH	0.03	0 - 0.09	
Linoleyl-, C18:2	0.15	0 - 0.45	
Oleyl-, C18:1	0.31	0 - 0.82	
Stearoyl-, C18	0.14	0 - 0.19	
3-OH-Linoleyl-, C18:2-OH	0.02	0 - 0.09	
3-OH-Oleyl-, C18:1-OH	0.02	0 - 0.05	

ACADVL sequence analysis:

Identified two disease causing changes.

Present Status:

- Pt with no history of metabolic decompensation.
- No hypoglycemic events.
- Normal cardiac echo.
- Variable CPK.

Mutation types in 3 VLCAD deficiency phenotypes

Type of mutations	Group 1: severe childhood form	Group 2: mild childhood form	Group 3: adult form
Missense mutations, one amino acid del/ins	14	31	13
"Truncating mutations," nonsense mutations, out of frame del/ins, splice mutations	34	7	1

81% of all truncating mutations in VLCAD found in the severe childhood form

76% of missense, small insertion/deletions found in mild childhood or adult form

Andresen et al. Am J Hum Genet 1999; 64:479–94

Newer therapies

Triheptanoin

- Source of 7-carbon fatty acids.
- May be superior to medium chain triglycerides as they provide a 3-carbon chain to promote ‘anaplerosis’ or ‘filling up’ of the citric acid cycle.
- Study by Roe et al in 2007 showed improvement in signs and symptoms in patients with VLCAD, LCHAD and TFP deficiencies.

Dantrolene Sodium

- Muscle relaxant
- Useful as an adjunctive therapy in adult-onset rhabdomyolysis

Bezafibrate

Used to decrease cholesterol levels.

Increases VLCAD enzyme activity in vitro in fibroblasts cultured from individuals with *ACADVL* missense mutations.

Improves residual enzyme activity.

Current Research: Rigshospitalet, Denmark and Institut de Myologie, Pitié-Salpêtrière Hospital, France are currently recruiting patients for

> "Effect of Bezafibrate on Muscle Metabolism in Patients With Fatty Acid Oxidation Defects".

MCAD Deficiency

Clinical Presentation:

Hypoketotic hypoglycemia, lethargy, seizures, and coma triggered by a common illness.

Hepatomegaly and acute liver disease.

Sudden and unexplained death.

Treatment:

Avoidance of fasting for more than 12 hours.

Infants require frequent feedings.

Hypoglycemia must be avoided, if necessary by intravenous administration of glucose.

LCHAD Deficiency

Clinical Presentation:

During infancy with hypoglycemic coma, hepatic steatosis, and hypocarnitinemia.

Cardiomyopathy.

Rhabdomyolysis.

Specific features namely peripheral neuropathy and chorioretinopathy.

Female carriers of LCHAD deficiency are prone to have preeclampsia-related pregnancy complications.

Treatment:

Avoidance of fasting

MCT oil as supplement

EFA

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