Fatty Acid Oxidation Disorders- an update

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An update….

- Overview of metabolism
- Clinical presentation and outcome
- Diagnostic approach
- Monitoring disease progression
- ACAD 9
- SCADD

Fatty Acid Oxidation

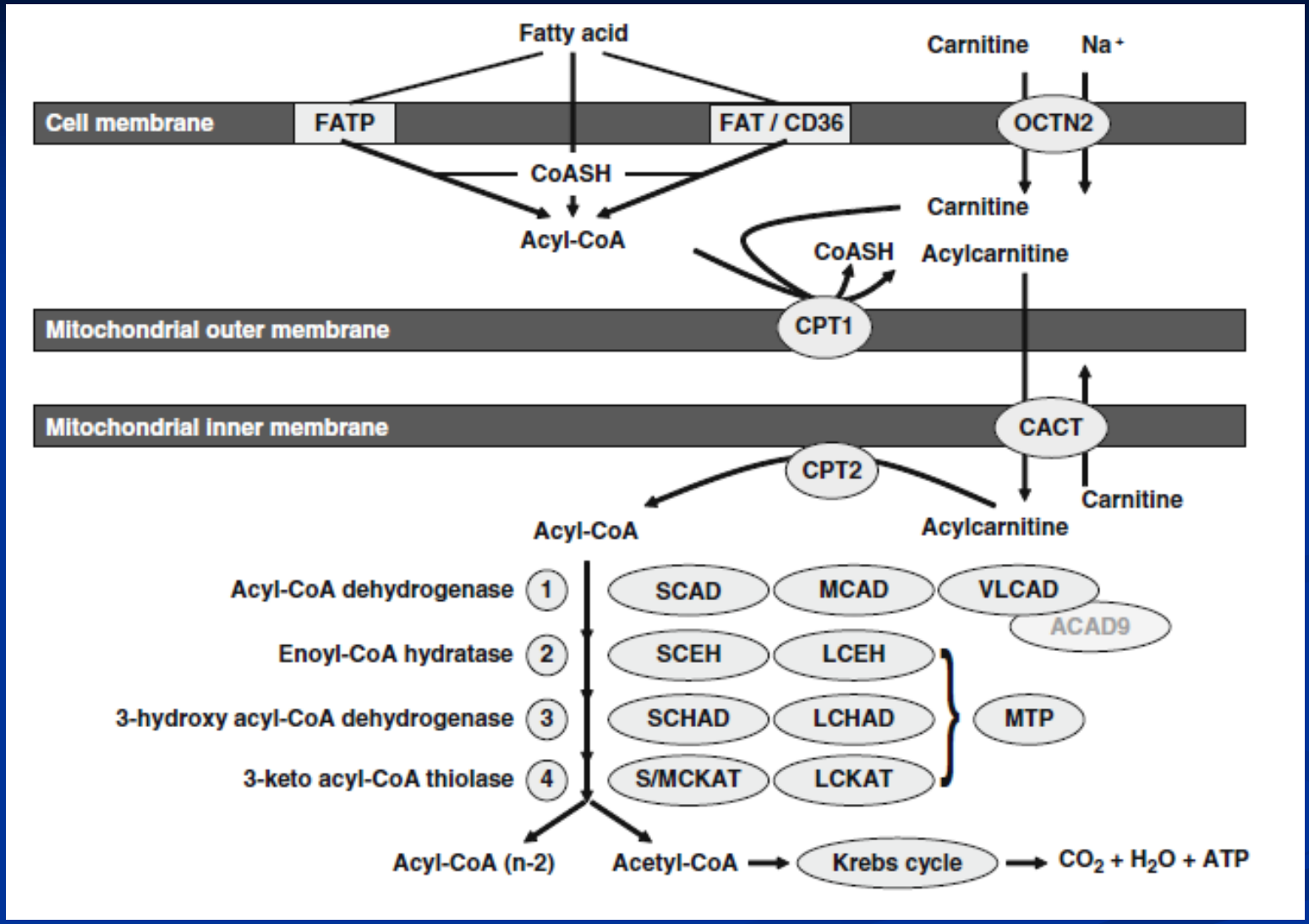
- 1904 Georg Knoop first described B-oxidation
- Pivotal role in energy homeostasis
  - Gluconeogenesis via production of acetyl-CoA
  - Electrons for respiratory chain
  - Ketogenesis

Regulation of FAO

- Normal/well fed-
  - glucose preferred substrate
- Fasting/exercise/illness
  - Adrenaline/NorAdr/Glucagon/ACTH
  - Activate Hormone sensitive lipase
  - Lipolysis induced
  - Release of Free Fatty Acids to feed FAO

Mitochondrial FAO

- Transport of fatty acids across plasma membrane
  - Fatty Acid Transport Proteins (FATP1-6)
  - Fatty Acid Binding Protein (FABP)
  - Fatty acid Translocase (FAT)
- Carnitine Shuttle
  - Imports acyl-CoA into mitochondria
- B-Oxidation
  - Classic 4 enzyme reaction


Fatty acid
Carnitine
Na+
Cell membrane
FATP
FAT / CD36
OCTN2
CoASH
Carnitine
Acyl-CoA
CoASH
Acylcarnitine
Mitochondrial outer membrane
CPT1
Mitochondrial inner membrane
CACT
CPT2
Carnitine
Acyl-CoA
Acylcarnitine
Acyl-CoA dehydrogenase
1
SCAD
MCAD
VLCAD
ACAD9
Enoyl-CoA hydratase
2
SCEH
LCEH
3-hydroxy acyl-CoA dehydrogenase
3
SCHAD
LCHAD
MTP
3-keto acyl-CoA thiolase
4
S/MCKAT
LCKAT
Acyl-CoA (n-2)
Acetyl-CoA
Krebs cycle
CO2 + H2O + ATP

FAO defects

- Individually rare, collectively common
- Typically autosomal recessive
- Generally episodic symptoms during catabolism
- Impaired oxidative capacity is overwhelmed
- Significant morbidity/mortality if undiagnosed

Clinical Presentation

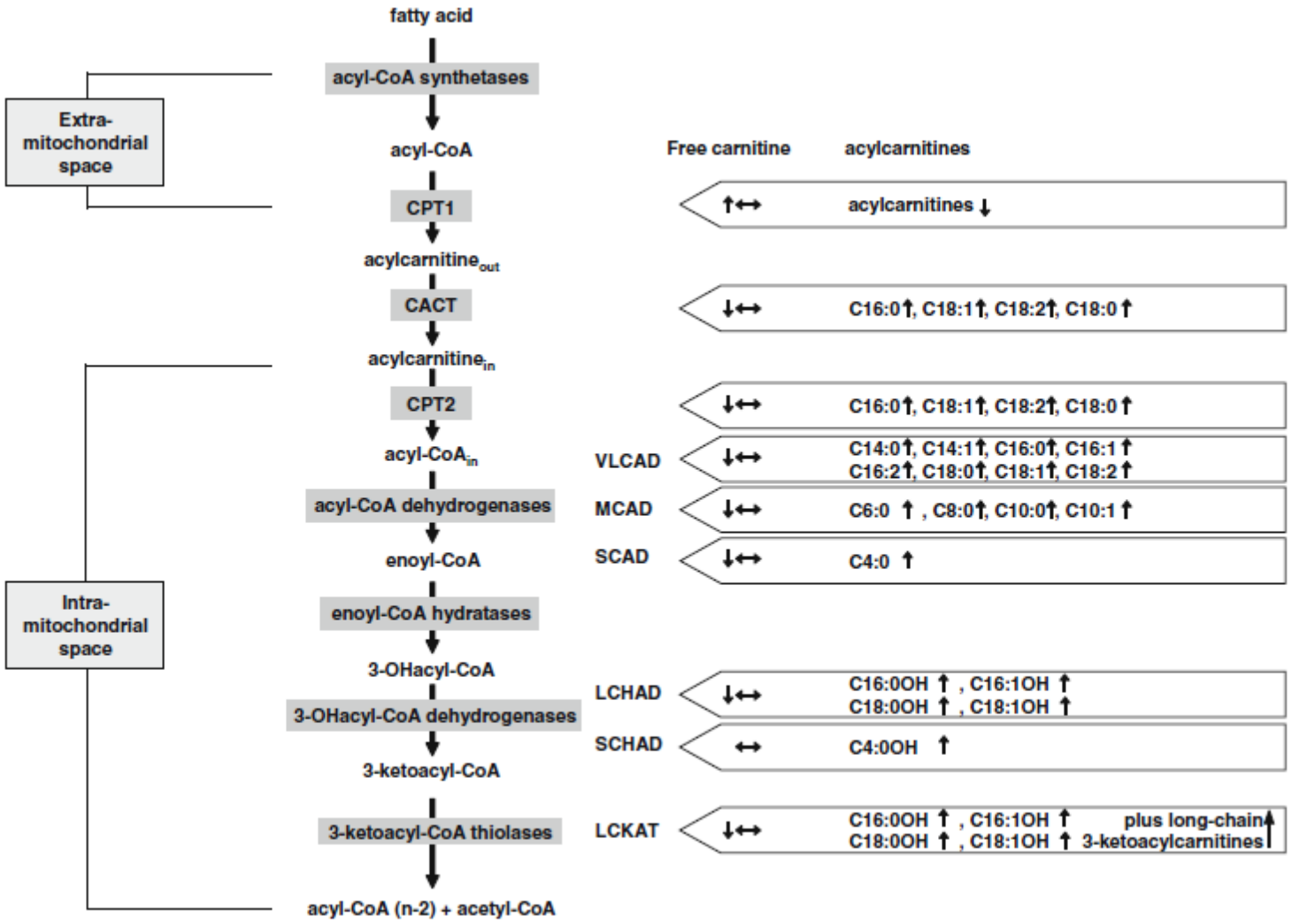
- Hepatic Presentation
  - Severe often lethal
  - Infancy/neonate
  - Hypoketotic hypoglycaemia
  - Reye-like illness
  - Triggered by catabolic state
- Cardiac presentation
  - Dilated or hypertrophic cardiomyopathy
- Milder/later (adult)
  - Exercise induced myopathy
  - rhadomyolysis

Clinical Presentation

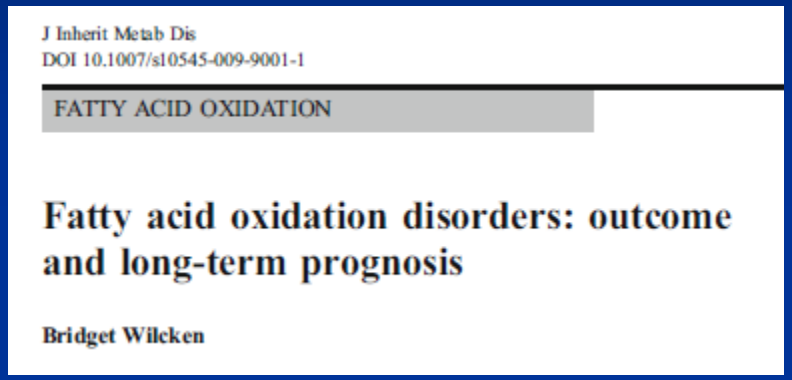
Major Clinical presentation	FAO disorder
Fasting hypoketotic hypoglycaemia	PCD, CACT, CPT1, CPT II, LCHAD, MCAD, SCAD, MTP, VLCAD, ACAD9
Rhadomyolysis, muscle weakness, myalgia	CPT II, VLCAD, ACAD9, LCHAD, MTP
Cardiomyopathy	PCD, CACT, CPTII, VLCAD, ACAD9, MTP, LCKAT
Peripheral neuropathy	LCHAD, MTP
Maternal HELLP/AFLP	LCHAD, MTP

Diagnostic approach (?FAOD)

- Routine biochemistry
- Urine organic acids
- Blood lactate
- Plasma carnitine and acylcarnitine profile
- Serum CK
- Fibroblast culture for enzyme analysis
- DNA analysis


fatty acid
acyl-CoA synthetases
Extra-mitochondrial space
acyl-CoA
CPT1
acylcarnitine$_{out}$
CACT
acylcarnitine$_{in}$
CPT2
acyl-CoA$_{in}$
acyl-CoA dehydrogenases
enoyl-CoA
enoyl-CoA hydratases
3-OHacyl-CoA
3-OHacyl-CoA dehydrogenases
3-ketoacyl-CoA
3-ketoacyl-CoA thiolases
acyl-CoA (n-2) + acetyl-CoA
Intra-mitochondrial space
Free carnitine
acylcarnitines
↑↔
acylcarnitines ↓
↓↔
C16:0↑, C18:1↑, C18:2↑, C18:0↑
VLCAD
C14:0↑, C14:1↑, C16:0↑, C16:1↑
C16:2↑, C18:0↑, C18:1↑, C18:2↑
MCAD
C6:0 ↑ , C8:0↑, C10:0↑, C10:1↑
SCAD
C4:0 ↑
LCHAD
C16:0OH ↑ , C16:1OH ↑
C18:0OH ↑ , C18:1OH ↑
SCHAD
↔
C4:0OH ↑
LCKAT
C16:0OH ↑ , C16:1OH ↑
C18:0OH ↑ , C18:1OH ↑
plus long-chain
3-ketoacylcarnitines ↑

Long term outcome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FATTY ACID OXIDATION

Fatty acid oxidation disorders: outcome and long-term prognosis

Bridget Wilcken

- Prognosis for an individual often uncertain
- Genotype/phenotype correlation tenuous
- Far more cases now diagnosed by screening

MCAD deficiency

- Presents clinically as episodes of hypoketotic hypoglycaemia during catabolic stress
- Studies pre-screening
  - mortality 16-25%
  - morbidity (intellectual impairment) 20-25%
- episodes of decompensation >6yr rare
- No deaths after diagnosis
- Adult undiagnosed deaths may be underdetected

Now screening is established

- Australia wide review of outcome
- Risk of death
  - unscreened cohort 14% (5/35- 2 neonate)
  - Screened cohort 4% (1/24 – neonate)
- Risk of death in first 72 hr
- Very little risk post-diagnosis of death with good management
- 1 patient (unscreened) had mild learning difficulties
- No other identified problems

Monitoring

- Evidence based guidelines lacking
- Clinical monitoring most important
  - Check growth and development
  - Support families re risk of acute episode
  - Control adequacy of treatment
- Biochemical monitoring less clear
  - Free carnitine to monitor supplementation
  - ? Use of essential fatty acids

Strategies for monitoring

Table 1 Strategies of monitoring. Abbreviations: ECHO, echocardiogram; ECG, electrocardiogram; CK, creatine kinase; US, ultrasound

Disorder	Frequency	Clinical	Paraclinical	Biochemical
MCADD	0–1 year: 4 visits/year 1–18 years: 1 visit/year > 18 years: 1 visit/2 years	Growth, development Informal dietary record Update of acute regimen Informal dietary record Update of acute regimen	None	Plasma free carnitine
Long-chain disorders and MADD[a]	0–18 years: 4 visits/year	Growth, development. Ask for symptoms from eyes and muscles. Pain? Formal dietary record Update of acute regimen and advice concerning physical exercise	Once a year: Eye examination In some: ECHO, ECG US abdomen	Plasma free carnitine Acylcarnitines CK Erythrocyte fatty acid profile
CTD	0–1 years: 4 visits/year 1–18 years: 1 visit/year > 18 years: 1 visit/2 years	Growth, development Update of acute regimen	Once a year: ECHO, ECG (including 24 h monitoring)	Plasma free carnitine

[a] Excluding mild, late-onset variants of VLCAD and CPT2 as well as riboflavin-responsive MADD

ACAD9- a new disorder

A New Genetic Disorder in Mitochondrial Fatty Acid β-Oxidation: ACAD9 Deficiency

M. He, S. L. Rutledge, D. R. Kelly, C. A. Palmer, G. Murdoch, N. Majumder, R. D. Nicholls, Z. Pei, P. A. Watkins, and J. Vockley

Am. J. Hum. Genet. 2007;81:87–103.

- ACAD9 recently recognised (2005)
- Optimal activity to unsaturated LC-acylcoA (C16:1, C18:1)
- High degree of homology to VLCAD, but unable to compensate for each other in patients with either deficiency
- 3 patients described with deficiency in ACAD9 protein

Case Presentation (1)

- Patient 1
- 14yr old boy Reye like episode
- Triggered by aspirin during mild viral illness
- Haemodialysis instituted
- But child unresponsive

- NH3 >700 umol/L
- AST 3355 U/L
- Glu normal
- Lactate 10.8 mmol/L
- CK 2824 U/L

Biochemical findings patient 1

- Urine Organic Acids
  - Grossly elevated lactate/ketones with dicarboxylic and hydroxydicarboxylic acids, notably 3-hydroxysebacic
- Liver acylcarnitines increased C18:1 and C18:2
- Normal fibroblast B-oxidation studies

Case Presentation (2)

- 10yr old girl
- Initially presented fulminant liver failure 4 months
- Responded to IV glu therapy
- Recurrent episodes hepatocellular dysfunction with hypoglycaemia
- Acute episodes less severe as she has aged

- Initial presentation
- AST >100,000 U/L
- Glu undetectable
- Persistently low platelets

Case (3)

- 4.5yr girl
- Cardiomyopathy and dilated left ventricle
- FH sibling died with cardiomyopathy at 22 months
- Acute presentation at 18mth severe left ventricular function, hepatomegaly
- Recurrent episodes of rhadomyolysis with intercurrent illness

Case (3)

- Glu undetectable during acute illness
- Plasma Carnitine 67 uM (25-79)
- Free Carnitine 16.3 uM (21-68)
- CK during illness >13000 U/L

- Carnitine supplementation- persistent neuro defects (abnormal gait), muscle weakness and hepatomegaly
- Died of congestive heart failure 4.5yr

Biochemical findings (2/3)

- Urine Organic Acids during acute episodes
  - Hypoketotic dicarboxylic aciduria with prominent unsaturated species and 3-hydroxyadipic, 3-OH suberic, 3-OH sebacic
- Total Carnitine low during illness
- Fibroblast B-oxidation studies (patient 2 only)
  - Reduced myristate/palmitate oxidation ?defect in long chain FAO

ACAD 9 deficiency

- Should be considered if other FAOD not identified
- Challenge to distinguish from other ACADs on basis of metabolites
- Suggested most likely in unexplained liver failure, cerebellar stroke and cardiomyopathy of unknown origin

SCAD deficiency


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FATTY ACID OXIDATION

Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency

Bianca T. van Maldegem · Ronald J. A. Wanders · Frits A. Wijburg

- Biochemical features
  - C4 carnitine
  - Ethylmalonic aciduria
  - Butryl-glycine
  - Butyrate
- Diagnosis confirmed by DNA analysis

???Clinical relevance

- Many studies in recent years
- SCADD generally presents early in life
- Broad spectrum of clinical presentation
  - Developmental delay
  - Hypotonia
  - Epilepsy
  - Behavioural disorders
  - Hypoglycaemia

But....

- Signs and symptoms often disappear
- Or explained by other causes
- Individuals diagnosed through sibling studies or newborn screening are asymptomatic
- Could association of signs/symptoms to SCADD be coincidental?

Comparison of symptoms

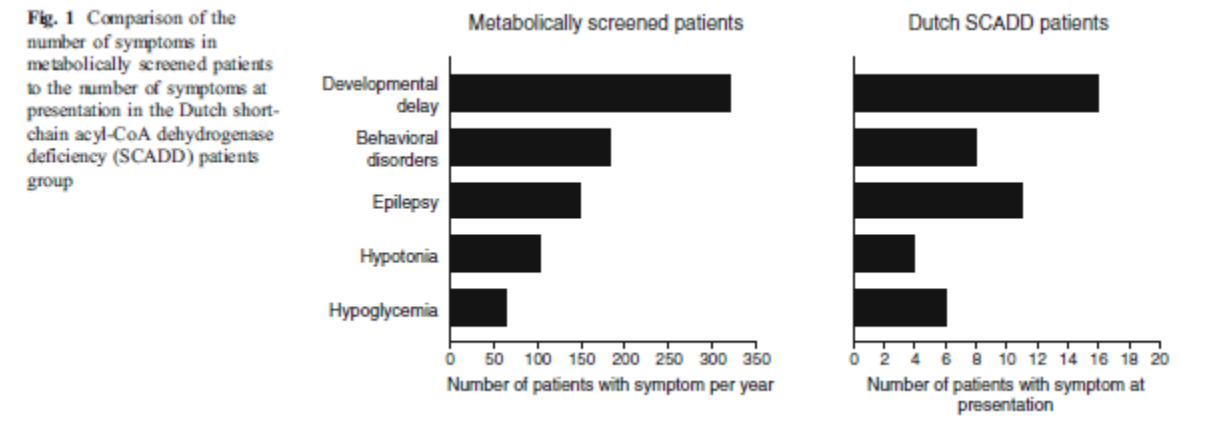

Fig. 1 Comparison of the number of symptoms in metabolically screened patients to the number of symptoms at presentation in the Dutch short-chain acyl-CoA dehydrogenase deficiency (SCADD) patients group

- Incidence of symptoms in metabolically screened patients is comparable to SCADD
- No specific cluster of clinical signs and symptoms

The implication

- Diagnosis of SCADD should not preclude a full diagnostic workup for other causes
- Patients and parents should be informed of potential lack of clinical relevance of SCADD
- SCADD is not a candidate for Newborn Screening
- Is SCADD a multifactorial disease