

THE CHALLENGE OF RECOGNISING INHERITED METABOLIC DISEASE AS A CAUSE OF PAEDIATRIC CARDIOMYOPATHY

Rik De Decker
Liesl Zühlke

Red Cross Children's Hospital Cape Town
South Africa



Outline

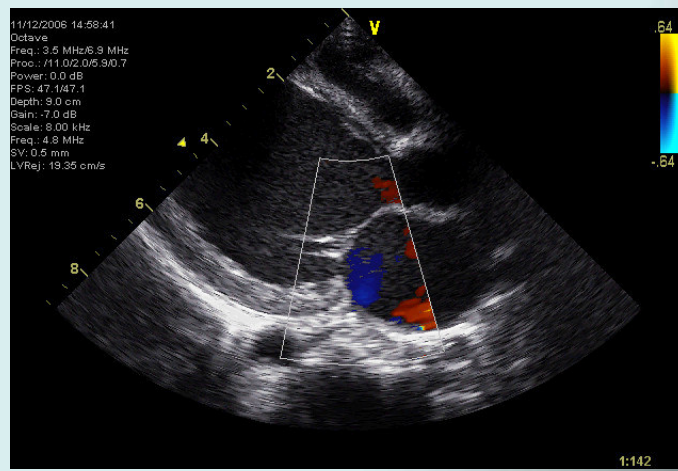
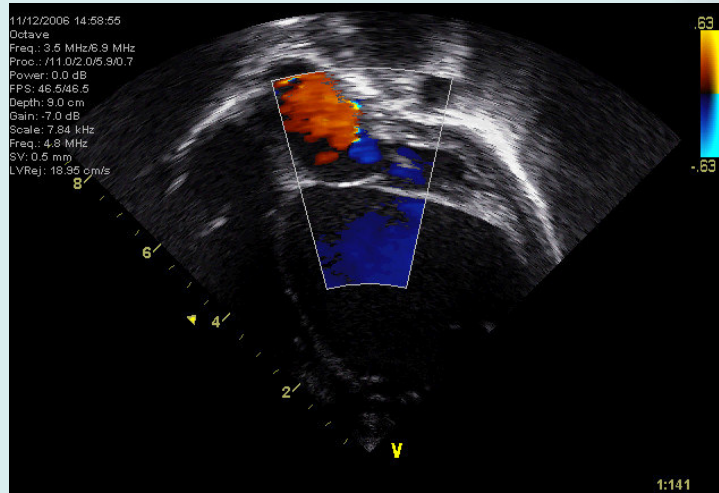
- The epidemiology of new onset cardiomyopathy
- Focus on inborn errors of metabolism
- The problem of under-diagnosis
- An approach to diagnosis
- Treatment and support

A boy presents to the emergency unit at Red Cross Hospital:

- 2 years 9 months old, first of twins
- Presented with cough, shortness of breath and lethargy
- On examination: poor perfusion, cardiomegaly and congestive cardiac failure
- Admitted to ICU for inotropic support and ventilation

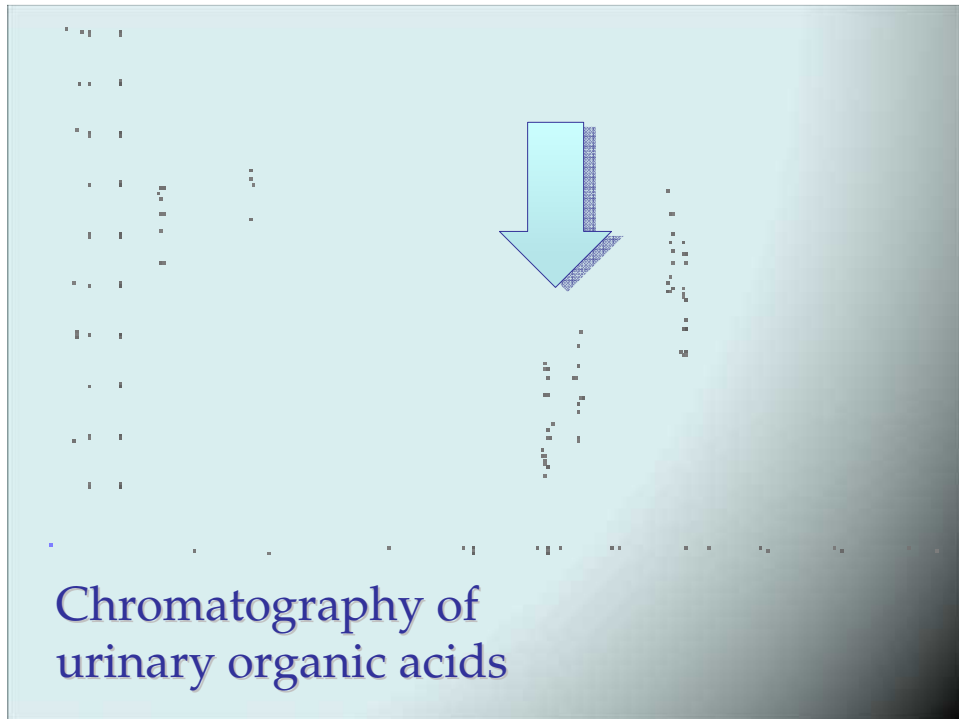
Investigations

- **FBC:** Hb 10.9, no neutropaenia
- **CXR:** cardiomegaly, no pneumonia
- **ECG:** moderate BVH
- **ESR, CRP and procalcitonin:** all low
- **Creatine kinase:** 448mmol/l (2-163)
- **Viral panel:** no acute viral infection
- **Broncho-alveolar lavage:** no infection
- **Echocardiogram**



Special investigations

- **Fasting lipogram:** hypocholesterolaemia
- **Endomyocardial biopsy:** no evidence for acute myocarditis, no lymphocytosis
- Screen for organic aciduria...



Clues to the diagnosis of Barth Syndrome

- Non-acute dilated cardiomyopathy
- Some skeletal muscle wasting
- Hypocholesterolaemia
- Typical organic aciduria

BUT

- No neutropaenia

EPIDEMIOLOGY

Epidemiology of new onset heart failure

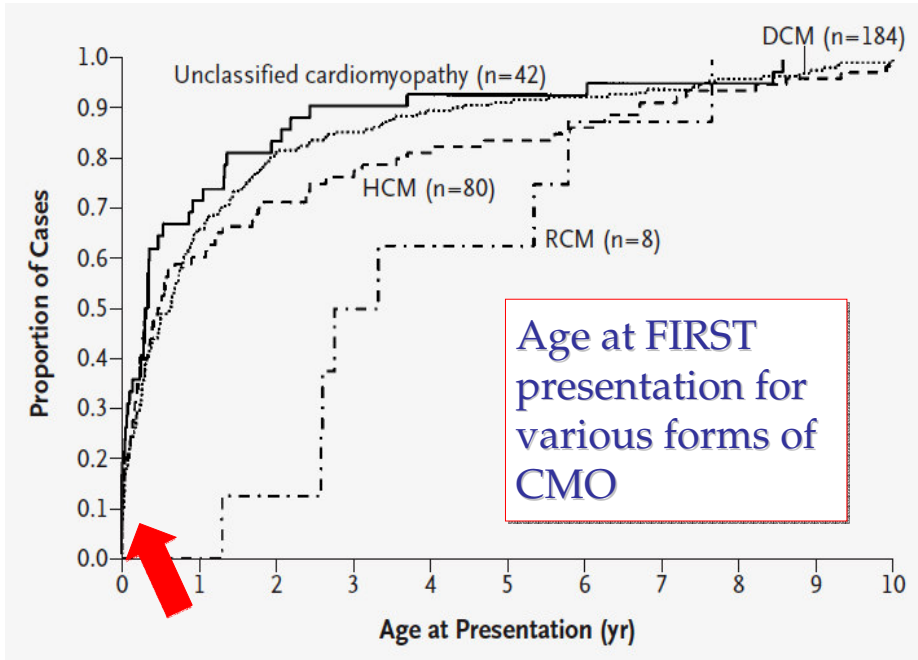
- Incidence: 0.87 per 100 000 Andrews et al. 2008
 - Dilated CMO: 0.57 per 100 000 Towbin et al. 2006
 - Hypertrophic CMO: 0.47 per 100 000 Colan et al. 2007
- Excellent agreement in retrospective and prospective surveys in USA, Australia, UK
- Africa and South Africa: unknown
- Red Cross Hospital:

New patients with CMO at RXH in 2008

TOTAL: 26 patients

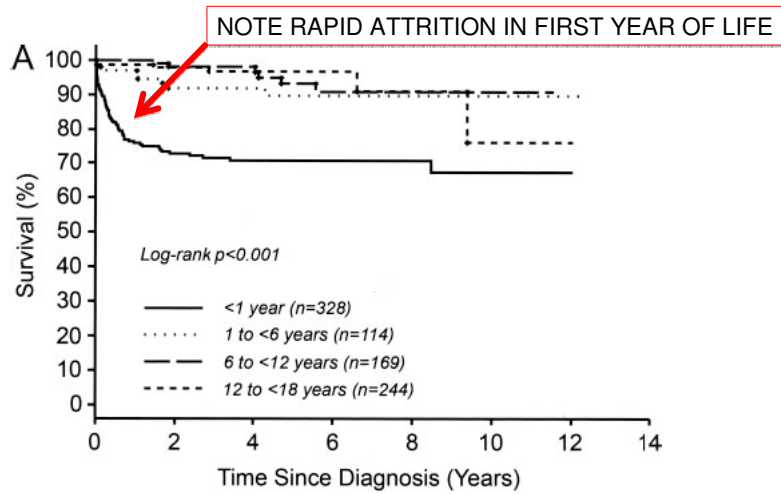
- | | |
|---------------|-------------------|
| • Dilated: 24 | • Hypertrophic: 2 |
| – Girls: 13 | – Girls: 1 |
| – Boys: 11 | – Boys: 1 |

- very few with a firm aetiology
- mostly viral myocarditis



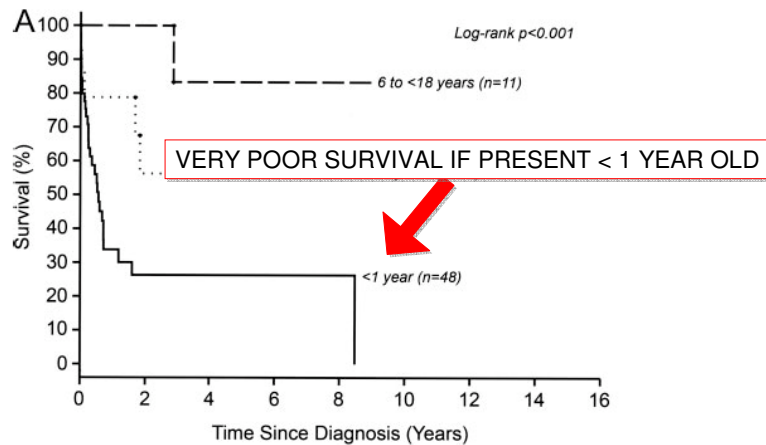
Colan SD et al. Circulation 2007;115:773-781.

Survival rate from diagnosis to death:
all CMO



Colan SD et al. Circulation 2007;115:773-781.

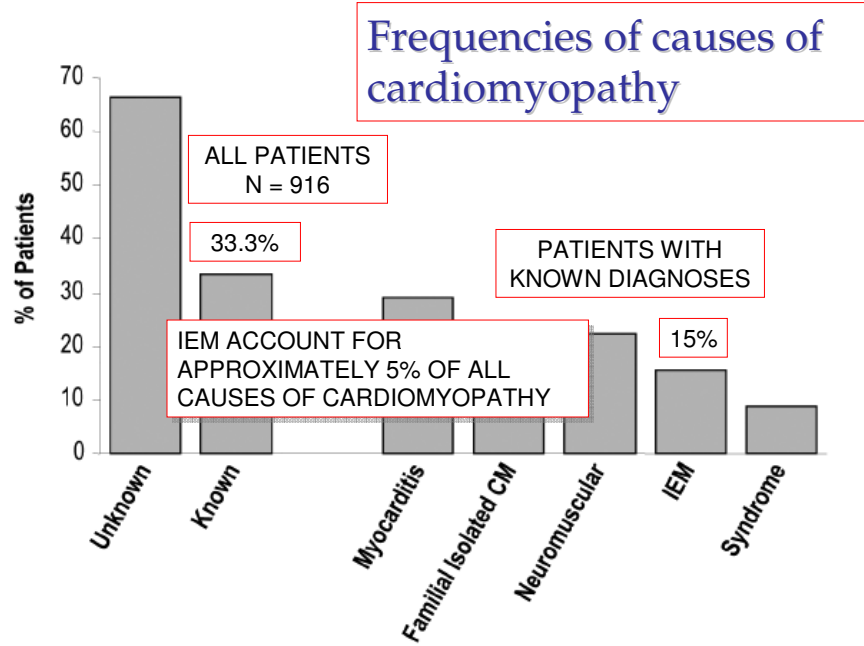
Survival rate from diagnosis to death: CMO due to IEM



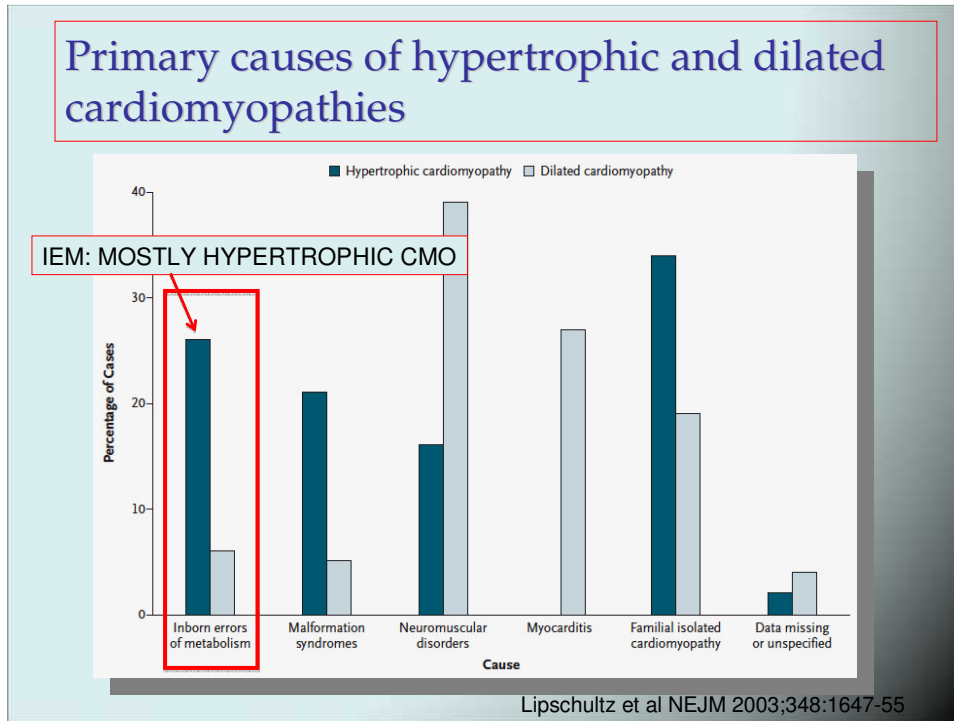
Colan SD et al. Circulation 2007;115:773-781.

Major groups of cardiomyopathy

- Myocarditis
 - e.g. Coxsackie virus
- Neuromuscular diseases
 - e.g. Duchenne muscular dystrophy
- Malformation syndromes
 - e.g. Noonan syndrome
- **Inborn errors of metabolism**
- Familial isolated cardiomyopathy



Cox GF Prog Ped Cardiol 2007; 24: 15-25



Lipschultz et al NEJM 2003;348:1647-55

IEM that cause cardiomyopathy

Disorders of:

A Substrate

- amino acid and organic acid metabolism
- fatty acid metabolism
- glycogen metabolism
- glycoprotein metabolism

B Organelles

- lysosomes
- mitochondria
- peroxisomes

Pathophysiology

1. Storage causing tissue disruption
 - triglycerides
 - glycogen
 - lysosomal substrates
2. Impaired energy metabolism
 - shortage of free fatty acids and glycogen
3. Toxic metabolites
 - organic acidaemias
 - amino acidurias
 - disorders of oxidative phosphorylation

Why the poor diagnostic rate?

- **Huge** number of genetic and acquired causes of cardiomyopathy
 - bewildering complexity of approaches to diagnosis
 - more than 40 due to IEM *per se*
- Diagnostic tests not widely available
- Slow translation of research techniques to clinical application
- Lack of a systemic approach to diagnosis
- Lack of a team approach to diagnosis

CLINICAL

Two approaches...

1. Screen for cardiomyopathies in children with known IEM

EASY

OR

2. Screen for IEMs in children with cardiomyopathies

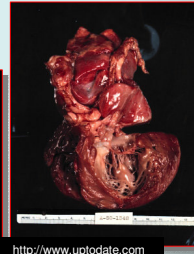
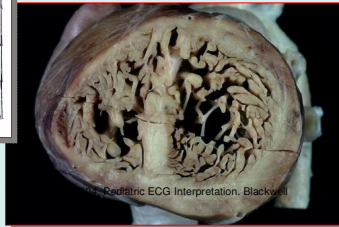
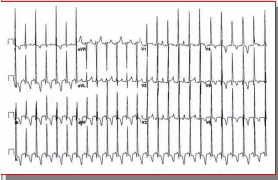
TRICKY!

Why is a diagnosis important?

- Treatment by cause is frequently possible
- Evidence that a diagnosis is significantly associated with a better prognosis Cox et al. 2006
- Genetic counselling
 - Future reproductive options
 - Antenatal screening
 - Cascade screening

Approach to diagnosis

- Very few pathognomonic features
 - LV hypertrophy and ECG in Pompe disease
 - Infiltrative signs in mucopolysaccharidoses
 - LV noncompaction or undulating phenotype in Barth syndrome
- Must look for associated signs and symptoms...



<http://www.som.tulane.edu/classware/>

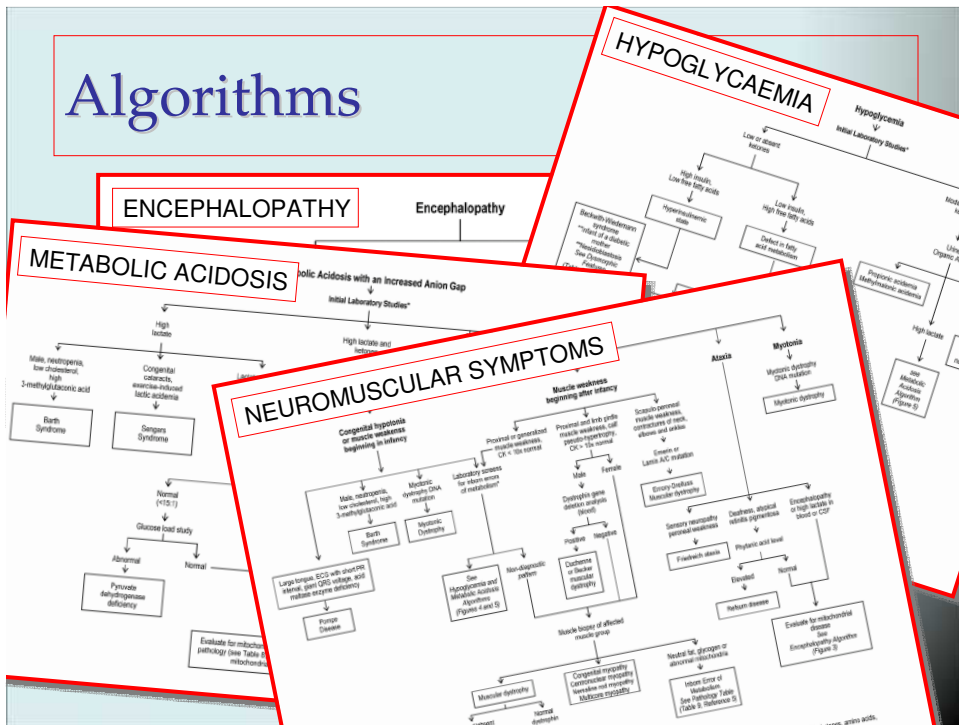
Associated features

Suggestive of a metabolic cause:

- Encephalopathy
- Hyperammonaemia
- Hypoglycaemia (nonketotic) or hyperglycaemia
- Metabolic acidosis with an increased anion gap
- Neuromuscular symptoms

INVESTIGATIONS

Algorithms



Important special investigations

- **FAMILY HISTORY**
 - Cot deaths
 - Still births
 - Sudden deaths
- Blood and urine metabolic screen
- Viral serology
- Biopsy
 - Skeletal muscle
 - Skin
 - Endomyocardial

| CARDIOMYOPATHY WORKUP | | |
|-----------------------|--------------------------|---------|
| INVESTIGATION | DATE | RESULTS |
| ECG | | |
| ECHOCARDIOGRAM | | |
| BLOOD: Chemistry | glucose | |
| | Mg, Ca, Pi | |
| | TFT | |
| | Lactate | |
| | Carnitine | |
| | CPK (inc MB%) | |
| | Troponin | |
| | CRP | |
| | Autoimmune screen | |
| Haematology: | ESR | |
| Viral serology: | Coxsackie A & B | |
| | Echovirus | |
| | Mumps | |
| | Rubella | |
| | Parvovirus B19 | |
| | CMV | |
| | EBV | |
| Bacterial: | bloodculture | |
| NPA: | RSV, adenovirus | |
| | Influenza, Parainfluenza | |
| URINE: Chemistry: | ketones | |
| | reducing substances | |
| | amino- and organic acids | |
| STOOL: | enteroviruses | |
| MUSCLE BIOPSY | | |
| ENDOMYOCARDIAL BIOPSY | | |

Cardiomyopathy: what if.....?

Without associated abnormalities:

- Consider familial idiopathic cardiomyopathy
- Repeat studies
 - when child is stressed

Moribund patient:

- Collect:
 - serum, urine, bile specimens
 - photographs, skeletal Xrays
 - skin biopsy
 - autopsy

TREATMENT

Treatment

- Resuscitation and ICU support
- Management for acute or chronic cardiomyopathy
- Cause-specific treatment
- Cardiac transplantation
- Genetic counselling
- Antenatal testing

The boy with dilated cardiomyopathy...

- Bloodspots for MLCL:CL ratio sent to AMC in Amsterdam
- Result within 10 days!
 - did NOT have Barth syndrome
- Was discharged from ICU, but required readmission and ventilation again
- Unfortunately died after 3 weeks in hospital
- Parents counseled with the blood spot result
- Twin brother echoed to reassure parents

- Always consider inborn errors of metabolism as part of the differential diagnosis of critical illness, particularly in young infants.
- Collect appropriate specimens at the time of the acute illness, and thereafter liaise with a specialist laboratory for diagnostic routes.
- Consult specialist teams early in the course of the illness, as very few ... will develop expertise in the management of inborn errors of metabolism.
- A multidisciplinary team approach is essential to successful care for affected children.

in CONCLUSION

Clinical cardiology is typically focused on *doing something* - usually surgically.

Searching for a specific aetiology for cardiomyopathy is like looking for a needle in a haystack - but having to use many tools to look for something that you are not sure is there!

There's the challenge!

The new bloodspot screening test

Clinical Chemistry 54:2
371-378 (2008)

Automation and Analytical Techniques

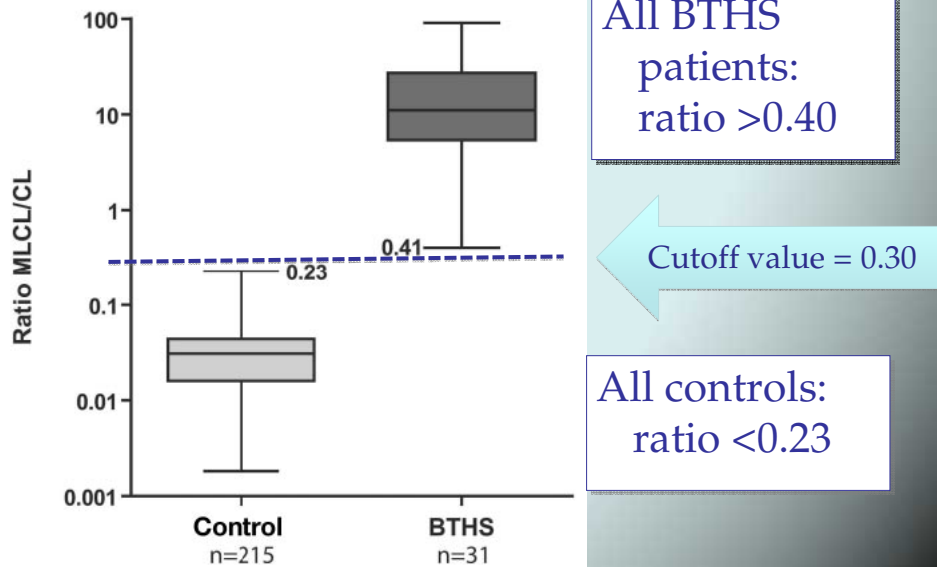
Bloodspot Assay Using HPLC-Tandem Mass Spectrometry for Detection of Barth Syndrome

Willem Kulik,^{1*} Henk van Lenthe,¹ Femke S. Stet,¹ Riekelt H. Houtkooper,¹ Helena Kemp,² Janet E. Stone,³
Colin G. Steward,³ Ronald J. Wanders,¹ and Frédéric M. Vaz¹

...simple, cheap and effective.

Sensitivity and specificity of 100%!

MLCL to CL ratios



The test...

- Based on monolysocardiolipin:cardiolipin ratio in bloodspots
- Developed on 215 men and 31 proven BTHS patients
- Blind tested on 206 specimens
 - 199 controls
 - 7 BTHS patients

Sensitivity and specificity of 100%!