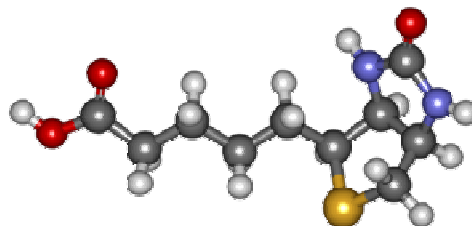


## Biotinidase Deficiency: A preventable cause of neurological impairment



David Haarburger  
Division of Chemical Pathology  
Red Cross Children's Hospital

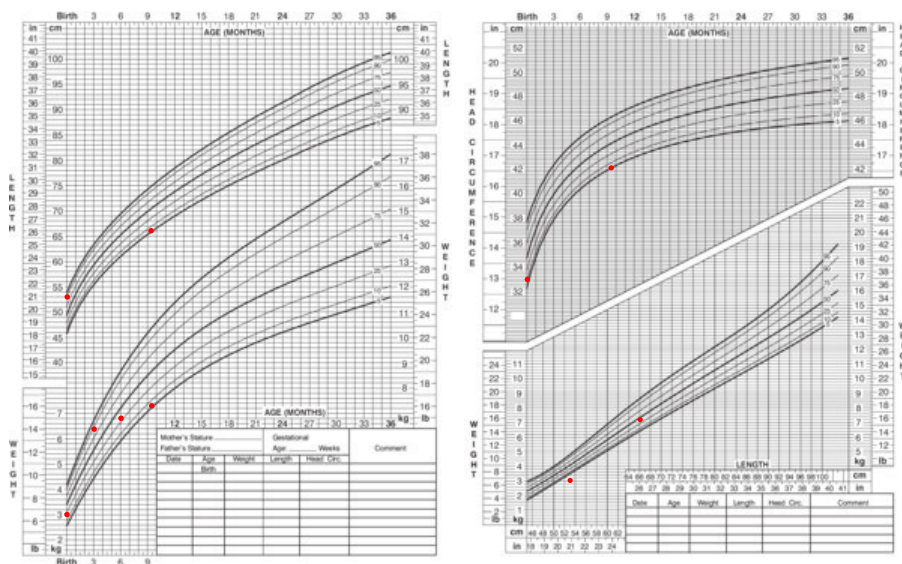
### Case History

- 9 month old baby girl
- Near daily seizures from  $\pm$  1 month
  - Bilateral
  - Legs and arms extended and stiff
  - Eyes roll back
  - Child unresponsive
- Birth history
  - NVD at term
  - Apgar scores – 8, 10
  - Weight 3060 g
  - Head circumference 33cm
- Developmental history
  - Smiles and laughs
  - Unable to sit
  - No respond to voice
  - No response to visual stimuli
- Family History
  - Mother
    - 15 years old
    - First pregnancy
    - HIV negative
  - Non-consanguineous relationship
  - No history of epilepsy
  - No history of alcohol

## Examination

- Alert
- Well hydrated
- Not dysmorphic
- Apyrexial
- CVS, Chest, Abdomen
  - Unremarkable
- Neuro
  - Moves all four limbs
  - Hypotonic
  - Poor head control
  - Brisk reflexes
  - Decreased plantar response
  - Opisthotonus

## Growth Charts



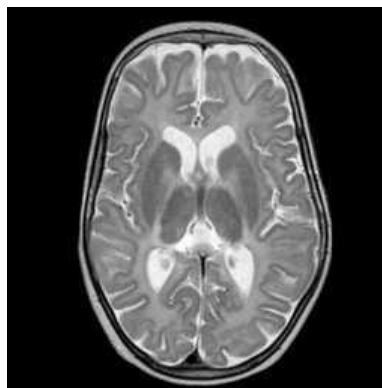
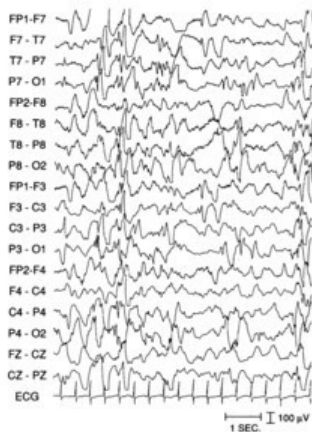
## Assessment and Plan

- Infantile spasms
  - Regression
  - Impaired vision and hearing
- Plan
  - Basic chemistry
  - CSF analysis
  - Urgent EEG
  - MRI brain
  - Metabolic disease screen
    - Organic and amino acids
- Treatment
  - ACTH
  - Valproate



## Investigations

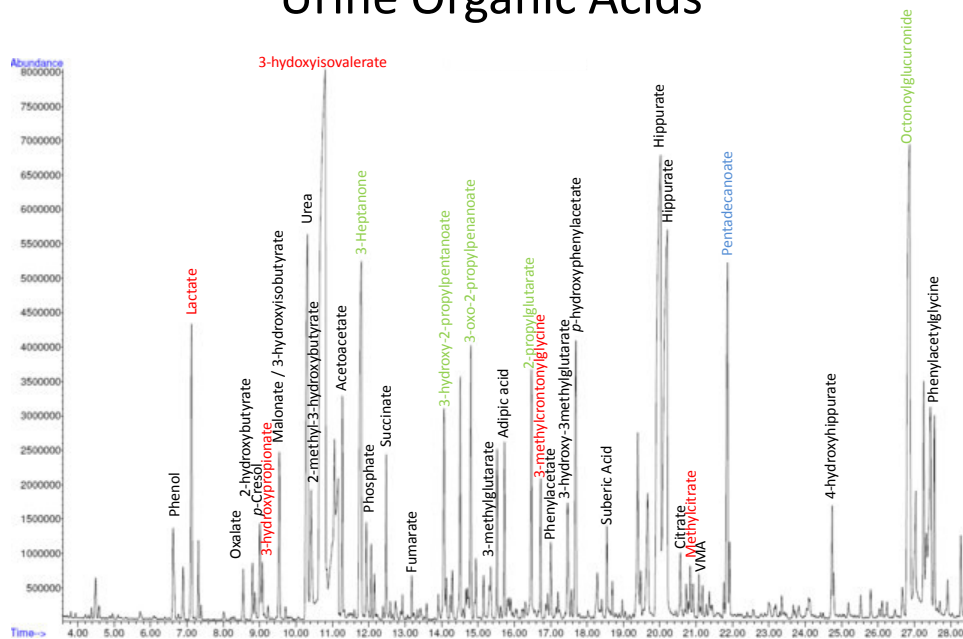
- Interictal EEG
- MRI Brain



# Investigations

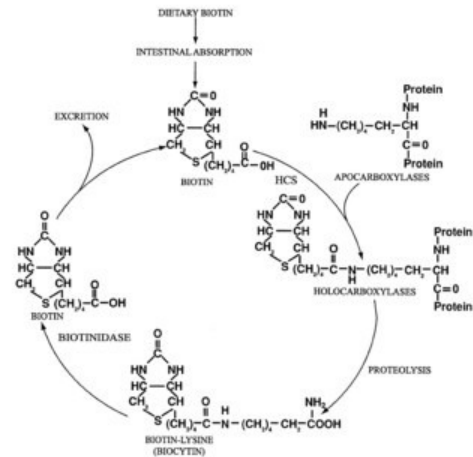
- Chemistry
  - Normal electrolytes, urea and creatinine
  - Normal liver function tests
  - Normal calcium, magnesium and phosphate
  - Lactate 3,8 mmol/l (0,5 – 2,2)
  - Ammonia 58 µmol/l (20 – 50)
- Full blood count
  - Hb 114 g/l (101 – 129)
  - WCC  $9,5 \times 10^9/l$  (6 – 18)
  - Plts  $439 \times 10^9/l$  (140 – 350)
- CSF
  - Clear and colourless
  - Protein 0,14 g/l (0,15 – 0,45)
  - Glucose 1,7 mmol/l (2,2 – 3,9)
  - Lactate 4,36 mmol/l (<2,89)
  - Cells
    - Neutrophils 0
    - Lymphocytes 0
    - Erythrocytes 8/µl
  - No bacteria or growth after 3 days

## Urine Organic Acids

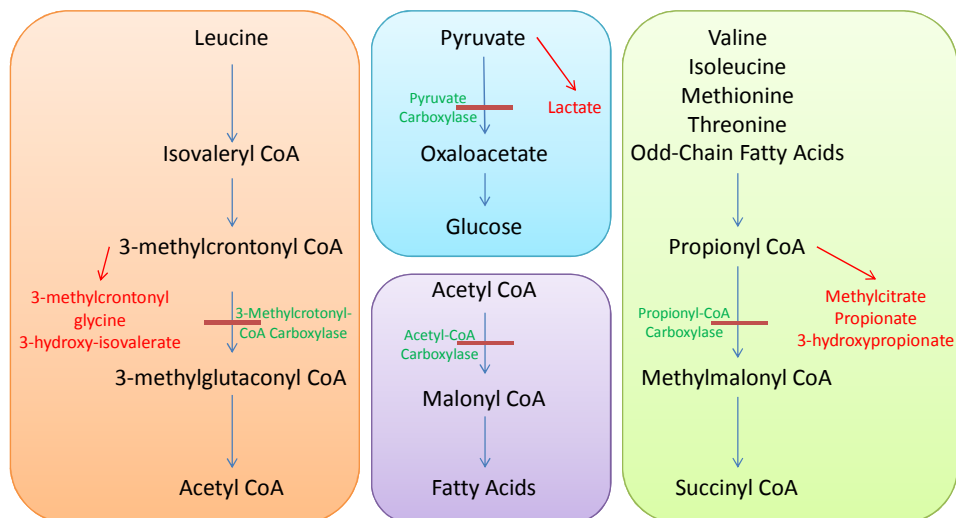


# Biotin

- Biotin is a water-soluble B vitamin
  - Vitamin B<sub>7</sub>
  - Vitamin H
- Essential cofactor for four carboxylase enzymes
  - Pyruvate carboxylase
  - Propionyl-CoA carboxylase
  - 3-Methylcrotonyl-CoA carboxylase
  - Acetyl-CoA carboxylase
- Must be derived from dietary sources and *de novo synthesis* by intestinal bacteria



## Role of carboxylases



## Biotinidase deficiency

- Autosomal recessive disease caused by the partial or total absence of biotinidase
- Incidence 1:60000
- Onset from a few weeks to several years
  - Median 3 months
  - Late-onset multiple carboxylase deficiency
- Imaging
  - Cerebral oedema or atrophy
  - low attenuation of white matter signal
  - Compensatory ventricular enlargement

### Presentation

Alopecia  
 Developmental delay  
 Hypotonia  
 Ketolactic acidosis  
 Organic aciduria  
 Seizures  
 Skin rash  
 Ataxia  
 Conjunctivitis  
 Hearing loss  
 Lethargy  
 Mild hyperammonaemia  
 Tachypnea/apnea  
 Visual abnormalities  
 Coma  
 Vomiting/diarrhoea  
 Fungal infections  
 Hepatomegaly  
 Speech problems  
 Splenomegaly

## Biotinidase deficiency

- Diagnosis
  - Urine organic acids
    - 3-hydroxyisovaleric acid
  - Enzyme activity in serum
    - Artificial substrate gives a coloured product
- Treatment
  - Biotin (free) 5-20mg/day
  - Skin manifestations, seizures and ataxia resolve quickly
  - Hearing loss and optic atrophy are irreversible
  - Developmental catch up may occur



## Outcome

- Undetectable biotinidase activity on serum testing
- No reported seizures since starting medication
  - ACTH
  - Valproate 80mg/8hrs
- Started on Biotin 10mg/day
- No immediate neurological improvement
- Discharged on treatment
  
- Did not return for follow up appointment or to collect further meds



### Take home message



- Always look for treatable metabolic diseases
- Urine organic acid analysis is an essential screening tool for the workup of neurological disease
- If metabolic disease is suspected provide nutritional support and vitamin B and carnitine supplementation
- Biotinidase deficiency can be treated easily and cheaply
- The diagnosis must be made early before the onset of irreversible complications

## Thank You

- Dr W Breytenbach
- Dr A Ndondo
- Dr G van der Watt
- Prof H Henderson
- Dr J Stanfliet



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- Barry Wolf *Disorders of Biotin Metabolism* in *The Metabolic & Molecular Bases of Inherited Disease* Scriver, Beaudet, Valle, Sly 8<sup>th</sup> Edition 3935-3962
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