A case of Seizures with a Rash

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Presentation

- 8.5 month old boy presented to A&E with twitching
- Initially fine tremor of upper limbs
- Followed by jerking of lower limbs with extension of his back
- Four 10 minute episodes
- During one episode bit through his lip

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Past medical history

- Born at term, weight 3.16 kg, no complications of labour, routine neonatal examination normal
- Conjunctivitis shortly after birth
- One previous episode of twitching at 6 weeks old
- Measles 2 weeks prior to admission
- Following measles less active, developed cough
- Previously could sit unaided but not able to do so after measles
- ? Deterioration in development

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Family history

- Parents non-consanguineous
- Mother and father well
- Two half-siblings: brother 10 years old, sister 8 years old, both well
- Maternal grandmother possible epilepsy

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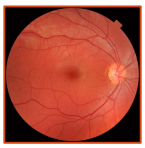
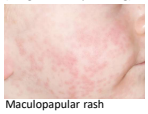
On examination

- Alert and oriented
- Slight tremor of fingers
- Slightly increased reflexes in lower limbs
- Unable to sit reliably on his own
- Immature palmar grasp
- Pink maculopapular rash on both cheeks
- Fundoscopic appearances normal



Fundus photograph showing normal right eye (Image: en.Wikipedia.org)



Maculopapular rash (Image: Dr P. Marazzi/Science Source)

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Initial investigations

NORMAL RESULTS	ABNORMAL RESULTS
• FBC • U&E • Bone profile • Magnesium • Glucose • TFTs • CSF protein glucose and microbiology • Head X-ray • Electroencephalogram (EEG) • Chromosome karyotyping studies • Urine mucopolysaccharides	• Rubella titre increased

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Two weeks later

- Readmission to A&E - twitching right side of face
- Twitching became bilateral then spread to all 4 limbs persisted intermittently for 2 hours
- No cyanosis, no difficulty breathing
- Mild pyrexia 37.5ºC
- Given rectal Valium – twitching stopped
- Started on phenobarbitone
- EEG repeated – no significant abnormality
- Discharged home

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One month later

- Readmission with twitching
- Twitching started in fingers but then became generalised
- Extremely hypotonic and ataxic
- Kept in for further investigations

Hypotonia (Image: http://casemed.case.edu/clerkships/neurology/NeurLrngObjectives/Floppy%20Baby.htm)

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During admission

- Day after admission - acutely unwell
- Blood gases – metabolic acidosis
- Unable to feed, wheezy, pyrexial, laboured respiration
- Chest X-ray showed consolidation of left lung
- Treated with antibiotics – improved within 3 days but still intermittently acidotic
- Developed almost total alopecia

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Investigations during admission

Test	Result	Reference Interval
Urea and electrolytes	Normal	
Bone Profile	Normal	
Lipid Profile	Normal	
Glucose	Normal	
Ammonia	80	<50
Urinary porphyrins	Normal	
White cell enzymes	Normal	

Test	Result
Multiple carboxylase activity in fibroblasts	Normal

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Further investigations

Test	Result	Repeat 1	Repeat 2	Reference Interval (units)
Fasting Lactate	3.4	4.2	4.75	0.5-2.2 (mmol/L)
Pyruvate	172	225	230	80-160 (µmol/L)
CK	491	56		25-200 (IU/L)
Ammonia	37			<50 (µmol/L)
Serum Copper	14.6			11-22 (µmol/L)
Caeruloplasmin	0.42			0.14-0.39 (g/L)
Blood Lead	3			<5.0 (µg/100mL)
Urine Amino Acids	normal	normal		
Plasma Amino Acids	normal	normal		

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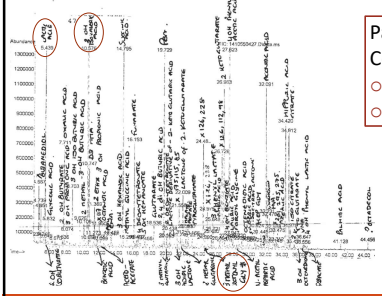
Urinary organic acid analysis



Patient organic acid results
Compounds detected:
- 3-OH isovaleric acid
- 3-methylcrotonylglycine

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Suggestive clinical and biochemical findings

- Recurrent episodes of infantile spasms
- Rash*
- Respiratory infection
- Hypotonia
- Ataxia
- Alopecia
- Deteriorating development/developmental delay
- Metabolic acidosis
- 3-OH isovaleric acid and 3-methylcrotonylglycine detected in urine

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Differential Diagnosis

- Nutritional biotin deficiency
- Biotinidase deficiency
- *Holocarboxylase synthetase deficiency* (excluded by fibroblast analysis)*

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Biotin commenced - 10mg per day

Test	Result	Repeat 1	Repeat 2	Reference Interval (units)
Fasting Lactate	0.75	0.75	1.15	0.5-2.2 (mmol/L)
Pyruvate	68	66	88	80-160 (µmol/L)

- 1 day post biotin improvement in condition
- Tone in trunk and limbs improved
- Hand coordination improved

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Diagnostic investigations

Biotinidase deficiency confirmed

	Biotinidase (µmol/mL)	Reference Range	Classification
Patient	0.106	6-10	Deficient
Patient's mother	4.0	6-10	Heterozygote

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Biotinidase

- Biotinidase recycles biotin (Vitamin B7)
- Biotinyl-hydrolase and biotinyl-transferase activities
- Monomeric sialylated glycoprotein molecular mass of 76–77 kDa
- Substrates:
  - Biotinyl-peptides
  - Biocytin (biotinyl-ε-lysine)
- Encoded by BTD gene

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Biotin (Vitamin B7)

- Derived from diet
- Dietary sources:
  Liver, salmon, eggs, cheese
  Whole wheat bread, avocado, cauliflower
- Biotin is also synthesized by intestinal bacteria
- Two forms :
  - Free form (non-protein-bound)
  - Small biotinylated peptides (bound to protein)

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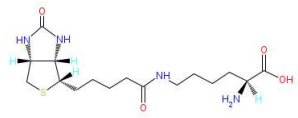
Protein-bound Biotin

- Must be proteolytically degraded to release biocytin (biotinyl-ε-lysine) and/or small biotinyl-peptides
- Further cleavage by biotinidase to release free biotin



Biotinyl-ε-lysine (Image: https://v12.chemtunes.com/biopath3/biopath/mols/N6-Biotinyl-L-lysine)

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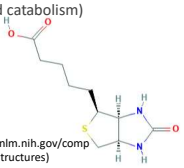
Free Biotin

- Conversion of carboxylases from apocarboxylases to holocarboxylases
- Four biotin dependent carboxylases:
  - Propionyl-CoA carboxylase (Branch chain amino acid catabolism)
  - β-methylcrotonyl-CoA carboxylase (Branch chain amino acid catabolism)
  - Pyruvate carboxylase (Gluconeogenesis)
  - Acetyl CoA carboxylase (Fatty acid synthesis)



Biotin (Image: https://pubchem.ncbi.nlm.nih.gov/compound/Biotin#section=Structures)

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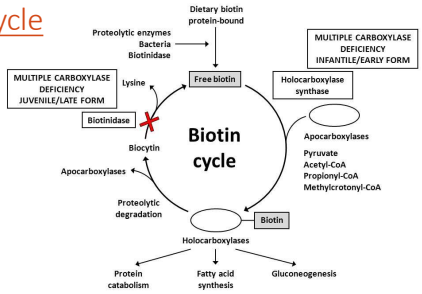
Biotin Cycle



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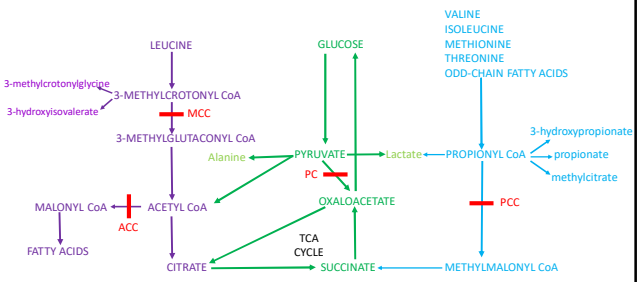
Metabolic pathways in which biotin-dependent enzymes are involved



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Biotinidase Deficiency: Clinical Features

- Seizures
- Hypotonia
- Eczematous skin rash
- Alopecia
- Respiratory problems
- Conjunctivitis
- Ataxia
- Developmental delay
- Hearing loss and optic atrophy

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Biotinidase Deficiency

- Autosomal recessive - mutations in BTD gene
- Incidence: profound/partial biotinidase deficiency 1:60K new-borns worldwide
- Mean age of presentation - 3.5 months
- Can present with a single symptom, or multiple neurological, cutaneous, or biochemical findings

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Biotinidase deficiency - biochemical features

- Organic aciduria:
  - Lactate
  - 3-OH isovalerate
  - 3-OH Proprionate
  - Methylcrotonyl glycine
  - Methylcitrate
- Mild hyperammonaemia

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Biotinidase Diagnosis

- Deficient enzyme activity in plasma/serum
  - Profound biotinidase deficiency: <10% mean normal serum biotinidase activity
  - Partial biotinidase deficiency: 10%-30% of mean normal serum biotinidase activity
- Genetic testing
- New-born screening in US

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Biotinidase Treatment

- Treated by supplementation with oral biotin in the free form
- Biotin replacement is lifelong
- All symptomatic children with biotinidase deficiency improve with treatment (↓seizures, ↓rash and ↑hair growth)
- Some of the features e.g. developmental delay, optic atrophy, and hearing loss, are irreversible once they occur

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Biotinidase: Long-term follow up

- Yearly ophthalmologic examination and auditory testing
- Yearly evaluation by a metabolic specialist
- Evaluation of urinary organic acids if return of symptoms with biotin therapy (most commonly the result of non-compliance)

Measurement of biotin concentrations in serum is not useful except to determine compliance with therapy.

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Patient update

- Patient 36 years old
- Takes 20mg biotin per day
- Patient well
- No problems with symptoms when compliant with therapy
- Hearing loss (bilateral hearing aids) due to delayed diagnosis

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References

- Scriver, Beaudet, Valle and Sly (2001*). The Metabolic & Molecular basis of Inherited Disease* 8th ed. New York: McGraw-Hill, pp3935-3956
- Wolf, B (2012)Biotinidase deficiency: "If you have to have an inherited metabolic disease, this is the one to have" *Genet Med* 14(6):565–575
- Wolf, B (2016) Biotinidase Deficiency. [online] GeneReviews® [Internet].

Available at: https://www.ncbi.nlm.nih.gov/books/NBK1322/#biotin.Management [Accessed 09/05/2021]

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Thank you
Any questions?

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