Variable lab results on an encephalopathy child

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Presentation

- *Master K is an 8 year old male who presented to a local district general hospital when he became ataxic with slurred speech and a fluctuating GCS after 4 days of vomiting with minimal oral intake.*
- *He was found to have acute encephalopathy with extensive brainstem changes on an MRI and was transferred to the Evelina London.*
- *The vomiting started 3 weeks post travel to Burkinoa Fassa where he had developed a blistering rash on his legs that was treated locally.*

Presentation

- *On admission to the Evelina he was initially treated as having acute necrotising encephalitis with IV antibiotics.*
- *He was seen and tested extensively by the Paediatric Infectious Diseases team but remained afebrile thorough out with the only positive result an elevated anti-streptolysin O titre (ASOT), suggestive of a recent streptococcus infection.*
- *He continued to vomit and have variable GCS.*

Investigation

- *An initial Amino acid sample had been sent by the local district general and was processed routinely, results showed a leucine of 1912 umol/L (50-264) and alloisoleucine of 265 umol/L (<10).*
- *These results closely matched a second amino acid sample taken on the patient's admission to the Evelina.*
- *The paediatric metabolic team at the Evelina where immediately informed and the patient was made nil by mouth and given IV N/saline + 10% dextrose*

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Diagnosis ?

- *Raised Branch Chain amino acids with detectable Alloisoleucine*
- *Symptoms; Encephalopathy, Vomiting*

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Diagnosis ?

- *Raised Branch Chain amino acids with detectable Allo-isoleucine*
- *Symptoms; Encephalopathy, Vomiting*

Maple Syrup Urine Disease

- *But age 8?*
- *No previous medical history*

Diagnosis

- *However sometime later another plasma amino acid was taken and a blood spot for branch chain amino acid monitoring and these came back with entirely normal results.*
- *Repeated amino acid and bloodspot branched chain amino acids remained within normal limits with undetectable allo-isoleucine.*
- *Over time the patients condition improved and he was restarted on his usual diet without any dietary restriction.*

Amino Acid Analysis at ST Thomas

- *Amino acids quantitation is run by LC-MS/MS*
  - *This does not separate Alloisoleucine from isoleucine*
  - *Samples with elevated Isoleucine, elevated Branch chains or an elevated isoleucine/Alanine ratio are run on a specific LC-MS/MS branch chain amino acid method*
- *MSUD Patients are Monitored with a Bloodspot LCMS/MS Branch chain method.*

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Results

Allo-isoleucine $(\mu mol/L)$	**Isoleucine** $(\mu mol/L)$ **RR: 26-159**	**Leucine** $(\mu mol/L)$ **RR: 50-264**	**Valine** $(\mu mol/L)$ **96-566 umol/L**	**Sample**	**Method**
265	625	1912	1174	Initial sample from DGH	Plasma Amino Acids by LC-MS/MS
Significant peak detected on Plasma Branch chain method	539	1691	1097	Initial smaple from Evelina	Plasma Amino Acids by LC-MS/MS
No Allo-isoleucine detected	131	220	344	+7 Days	Plasma Amino Acids by LC-MS/MS
<10	63	118	229	+8 days	Bloodspot Branch Chain amino acid monitoring

Diagnosis

- *Based on the initial amino acids results and the resolution of his metabolic disturbance with minimal active intervention he was given a diagnosis of intermittent MSUD.*
- *His presentation with encephalopathy was seemingly due to a metabolic decompensation secondary to prolonged vomiting perhaps following recent streptococcus infection.*
- *Diagnosis was confirmed by genetics.*
  - *He was found to be a compound heterozygote for two mutations.*

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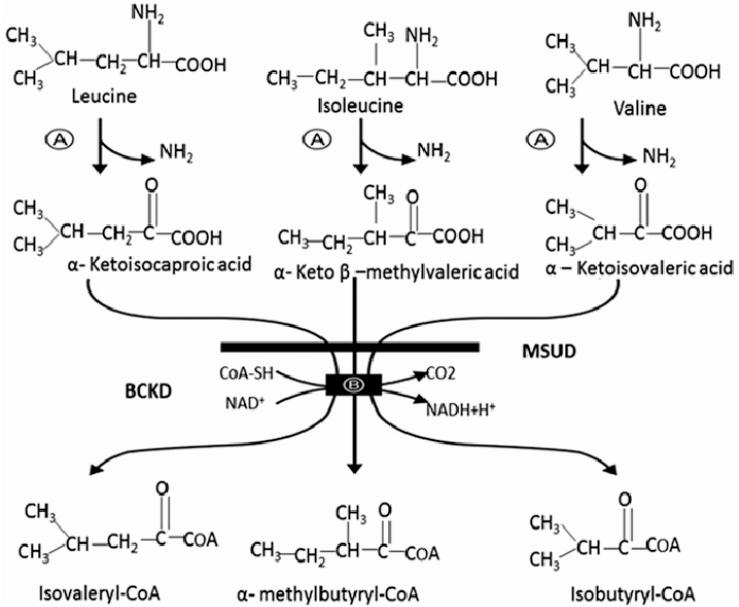
MSUD

- *Incidence of 1:200,000 (European population)*
- *Inherited in an autosomal recessive manner*
- *3 proteins coded by 4 Genes implicated in the disorder*



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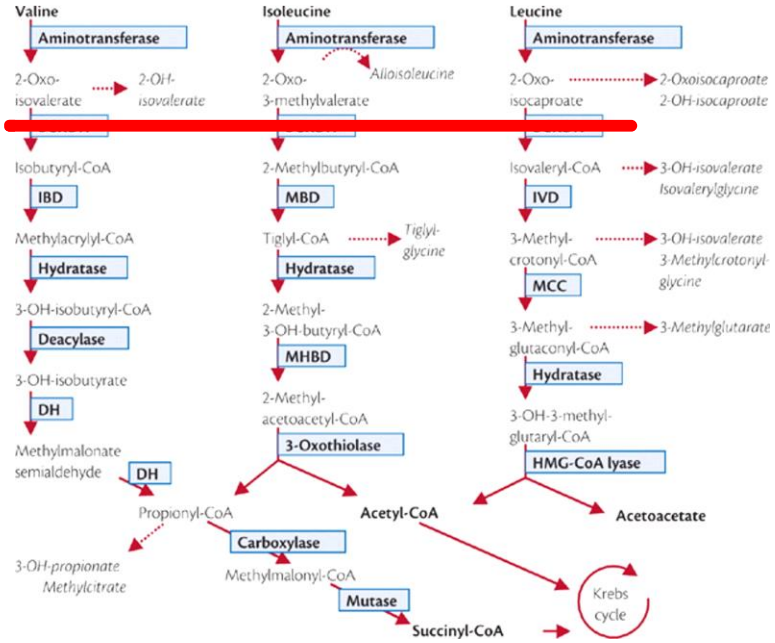
MSUD

- *Caused by an Inherited defect in branched chain 2-keto acid dehydrogenase*
- *Degradation of branched chain amino acids blocked at the 2-keto acid stage*
- *Leads to the formation of Alloisolecuine which is pathognomonic*



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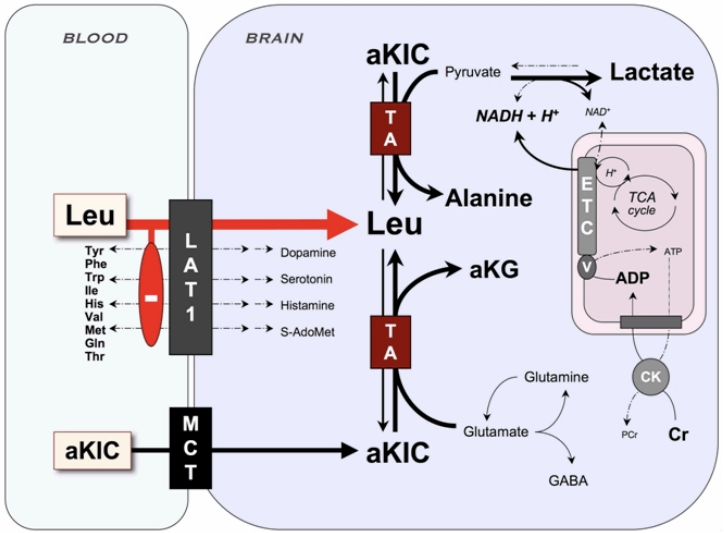
MSUD

- *Leucine and its product 2-Ketoisocaproate are neurotoxic*
- *Mechanism of brain toxicity not well understood*
- *Leads to acute and chronic brain dysfunction*
  - *Encephalopathy crisis*
  - *Normally within 2 weeks of birth*
- Classical MSUD <2% BCKAD activity



Symptoms

- *Classically*
  - *Maple syrup odour from urine*
    - *Earwax soon after birth*
  - *Ketonuria, irritability and poor feeding within 48 hours*
  - *Lethargy, intermittent apnoea, stereotyped movements by 4-5 days*
  - *Coma and central respiratory failure.*

Diagnosis

- *Elevated Branch chain amino acids in plasma amino acids*
  - *Detectable Allo-isoleucine*
  - *Low Alanine (high Alanine/isoleucine ratio)*
- *Branch Chain Intermediates on Urine organic acids*
  - *2-hydroxy-isovaleric acid, 2-oxoisocaprioc acid*
- *Confirmation with genetics*
  - *Possible to asses 2-keto acid dehydrogenase activity in cultured cells*

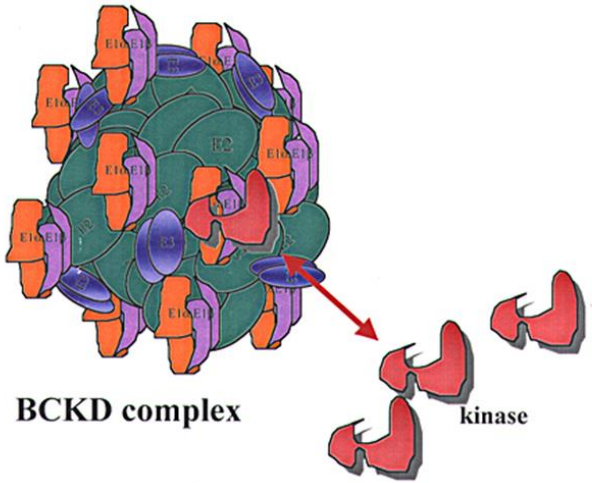
Treatment

- *Acutely*
  - *Glucose and Insulin to enhance anabolism*
  - *Ensure isoleucine and valine don't become deficient*
- *Long term*
  - *Diet low in branch chain amino acids with regular monitoring*
  - *Emergency regime if ill (glucose and amino acids)*
  - *Frequent feeds*
  - *Regular monitoring with blood spot branch chain amino acids*

Branched Chain 2-Keto acid dehydrogenase

BCKD complex

- 3 proteins from 4 genes
  - E1 (decarboxylase)
    - E1α (45% mutations)
    - E1β (35% mutations)
  - E2 (acyl transferase)
    - 20% mutations
  - E3 (flavoprotein lipoamide dehydrogen
- Classic 0-2% enzyme activity
- Intermediate 3-30% activity
- Intermittent 5-20%



Non Classical MSUD's

- *Approximately 20% of patients suffer from a non-classical variant forms of MSUD*
- *Variable residual BCKD activity from 3-40%*
- *Intermediate, Intermittent and Thiamine responsive forms*
- *Intermediate Form*
  - *Less severe presentation*
  - *Moderately increased Branch chains and presence of Allo-isolecine*

Intermittent MSUD's

- *Normal BCAA between episodes*
- *Similar picture to Classic MSUD during illness*
  - *Episodic decompensation that can be severe when patient catabolic*
  - *In rare cases can be so sever as to cause coma and death.*
- *Normal early growth and development*
- *A normal Leucine intake is tolerated when well*

Intermediate MSUD's

- *May appear well initially*
  - *Ceramen (earwax still smells sweat)*
- *Amino acids are consistently abnormal with detectable alloisoleucine*
- *Symptoms; feeding problems, poor growth, dev delay*
- *Susceptible to the same metabolic decompensation as classical MSUD*
- *Treated and monitored as if classical MSUD*
- *May be Thiamine responsive*

Follow Up

- *Master K made a full recovery and currently has no dietary restriction and only an emergency regimen.*
- *He is monitored routinely with dried blood spot branch chain amino acid analysis and has received repeat plasma amino acid profiles with no allo-isoleucine detected.*
- *He remains well*

Learning Points

- *As well as the classical form, MSUD can present with an Intermediate and Intermittent form.*
- *With Intermittent MSUD biochemistry may be normal between acute episodes*
- *Intermittent MSUD may not be picked up by Newborn Screening*

References

- Simon, E., et al. "Variant maple syrup urine disease (MSUD)—the entire spectrum." *Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism* 29.6 (2006): 716-724
- Podde-Shakked, Naomi., et al. “Clues and challenges in the diagnosis of intermittent maple syrup urine disease.” *European journal of medical genetics* 63.6 (2020): 103901

Acknowledgements

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