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Branched Chain Keto-Acid Dehydrogenase Kinase (BCKDK) Deficiency

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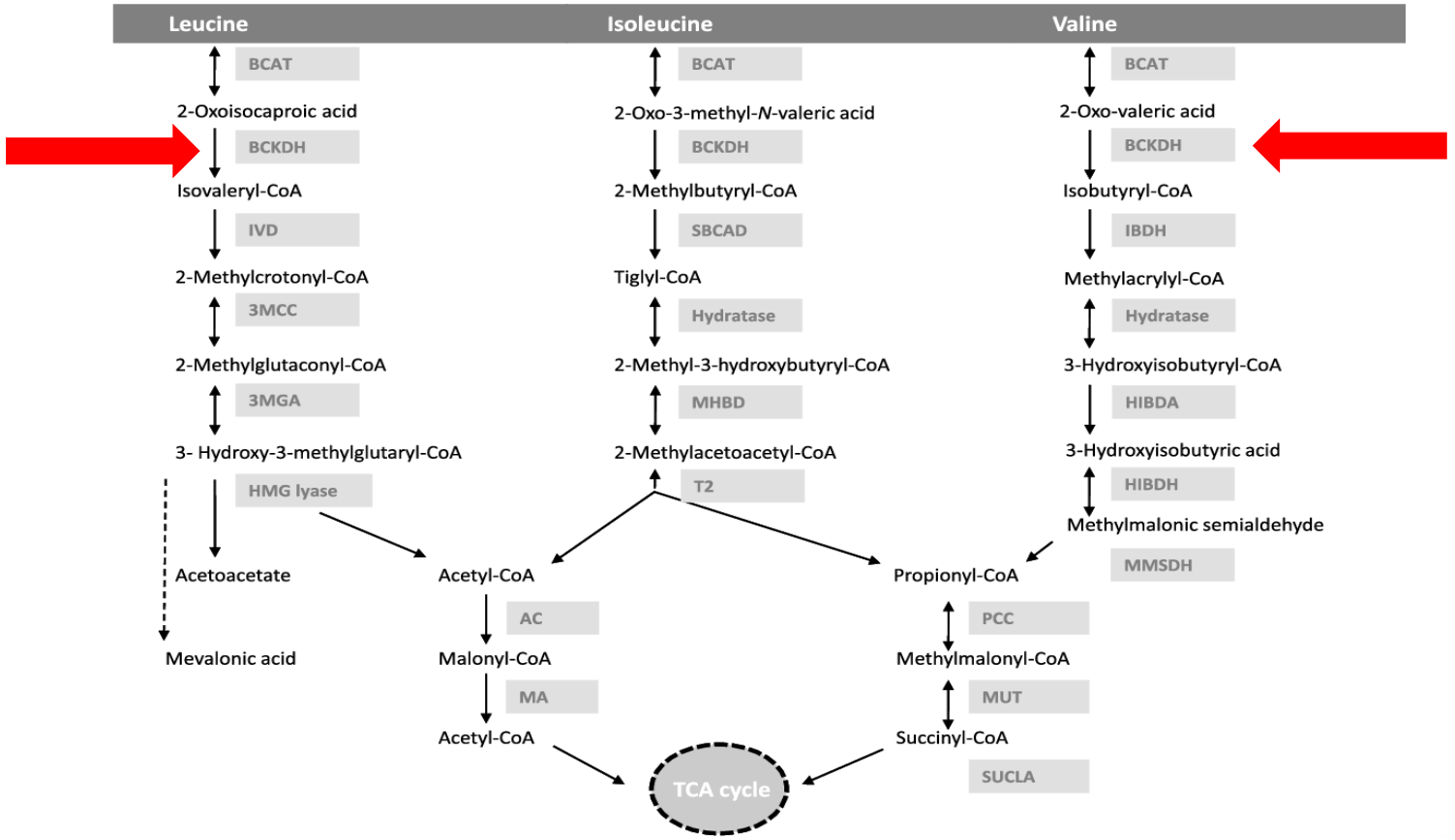
1. Branched Chain Keto-Acid Dehydrogenase Kinase Deficiency

- First described in 2012 by Novarino *et al* as a cause of autism with epilepsy and intellectual disability in three unrelated consanguineous families.
- Caused by mutations to *BCKDK* located on chromosome 16p11.2, inherited in a recessive manner.
- Exact prevalence unknown, although most recent worldwide cohort study had 21 participants.

2. Branched Chain Keto-Acid Dehydrogenase



2. Branched Chain Keto-Acid Dehydrogenase

- Complex of 3 catalytic components located in inner mitochondrial membrane
- Primary function is catabolism of branched chain amino acids
- Regulated by a phosphorylase/kinase pair – phosphorylated = inactivated, dephosphorylated = active
- Deficiency of the enzyme complex as a whole leads to MSUD.
- Deficiency of branched chain keto-acid dehydrogenase kinase results in unregulated overactivity of branched chain keto-acid dehydrogenase complex, and thus increased catabolism of branched chain amino acids.

2. BCKDK Deficiency

- Deficiency of BCKDK results in reduced phosphorylation of BCKDH and thus increased enzyme activity
- Leads to reduced branched chain amino acids (BCAAs)
- BCAAs are required for protein synthesis and growth, autophagy signalling, mitochondrial function and neurotransmitter metabolism

3. Clinical Features

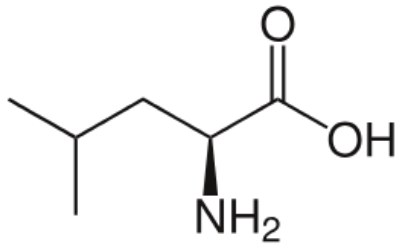
- Global developmental delay, including motor delay, language delay, and learning difficulties present in all reported patients.
- 95% patients had reported behavioural differences, most notably ASD.
- Progressive microcephaly (not present at birth) was reported in 85% patients at time of diagnosis.
- Just under half (9/21 patients) experienced seizures

Tangeraas et al (2023)

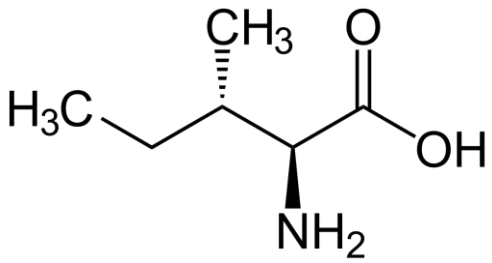
BCKDK deficiency: a treatable neurodevelopmental disease amenable to newborn screening

4. Diagnosis

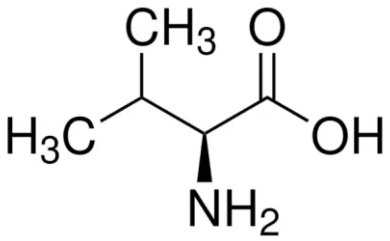
- Diagnosis often takes some time due to low prevalence and awareness.
- Typically patients are noticed to be falling behind in development, and are falling behind their predicted growth curves (particularly for head circumference).
- Plasma amino acid analysis will typically show decreases in the branched chain amino acids (leucine, isoleucine and valine).
- Definitive diagnosis is by molecular genetic analysis of *BCKDK* gene.



Leucine



Isoleucine



Valine

4. Treatment

- Main aim of treatment is to restore BCAA depletion
- This is with specific BCAA supplementation and increasing natural dietary protein.
- Blood BCAA concentrations typically peak ~2hrs after ingestion, returning to baseline within 3-5 hours.
- This typically means supplementation several times a day, often via PEG
- Treatment started early (typically before 2 years) can reduce the severity of symptoms, and some improvements in language development were seen.
- However, there is limited evidence on effects of treatment due to such low prevalence.

Case Study

Case: Presentation and Medical History

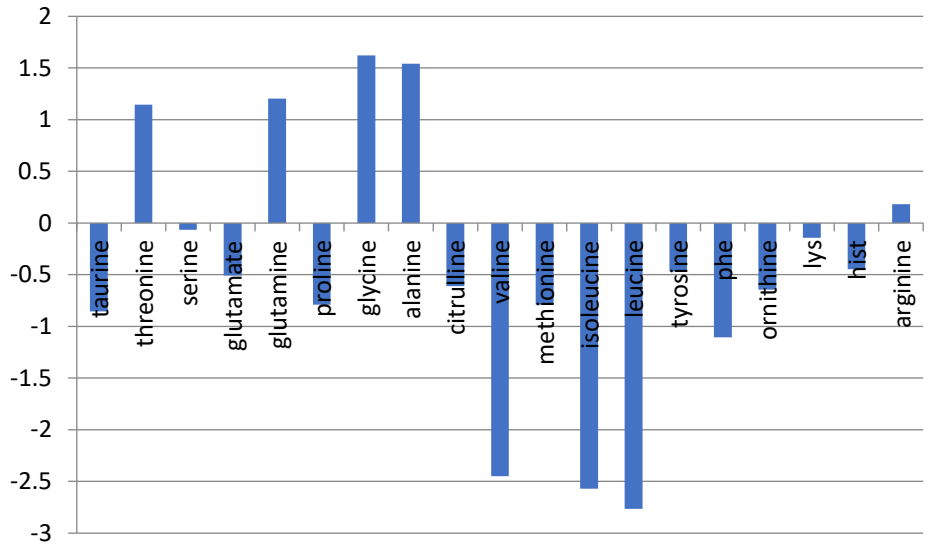
- A 2 year old boy presented to his local paediatric outpatients department with global developmental delay, seizures, microcephaly and faltering growth.
- He is the second child to consanguineous (2nd cousin) parents. His elder brother, age 4, is well.
- He had been born at 37/40 by emergency C-section, following failed IOL, due to poor growth.
- He had also been noted to have unilateral ventriculomegaly at the 20 week scan.
- By 2 years, he was not yet standing and had limited verbal communication.
- He had previously had a 6 minute febrile seizure, but in the weeks preceding his outpatients appointment had been “twitchy” whilst awake.

Case: Metabolic Investigations

- A plasma sample for amino acid analysis and a urine sample for organic acid analysis were sent at the patient's initial outpatients appointment.
- The urine profile was normal.

Case: Plasma Amino Acids

Description	Value	Units	Ref range
Taurine	63	umol/L	19 - 173
Threonine	196	umol/L	38 - 239
Serine	138	umol/L	51 - 231
Glutamate	78	umol/L	21 - 174
Glutamine	676	umol/L	307 - 768
Proline	168	umol/L	45 - 452
Glycine	282	umol/L	81 - 303
Alanine	620	umol/L	112 - 686
Citrulline	25	umol/L	8 - 57
Valine	**43**	umol/L	96 - 566
Methionine	23	umol/L	10 - 53
Total Isoleucine	**7**	umol/L	26 - 159
Leucine	**<25**	umol/L	50 - 264
Tyrosine	75	umol/L	26 - 154
Phenylalanine	51	umol/L	34 - 110
Ornithine	62	umol/L	20 - 144
Lysine	189	umol/L	61 - 337
Histidine	80	umol/L	40 - 143
Arginine	110	umol/L	26 - 180



Case: Follow Up

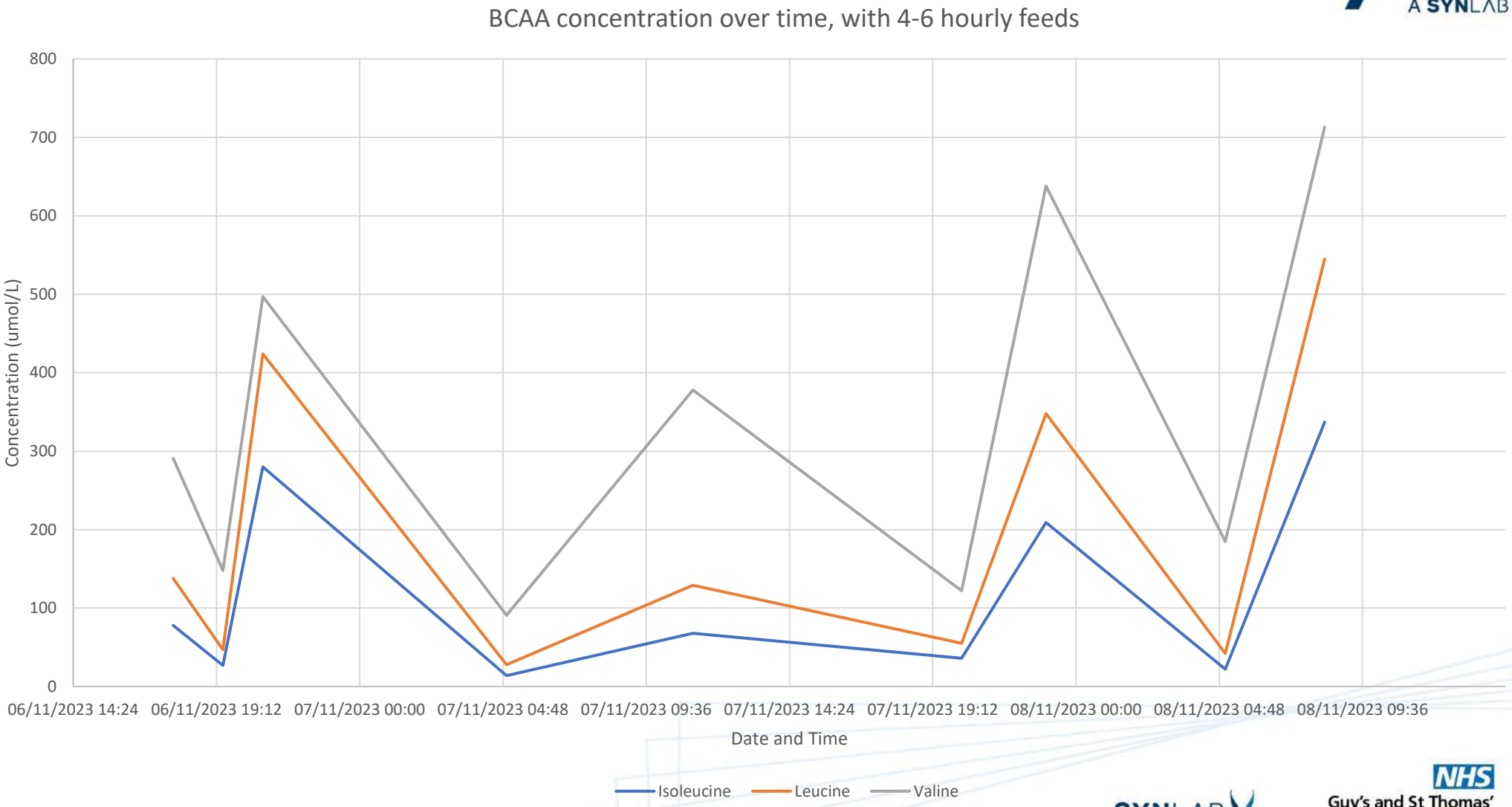
- The boy was referred to the paediatric metabolic team at the Evelina London Children's Hospital.
- Based on clinical and laboratory findings, he was diagnosed with BCKDK deficiency (DNA analysis pending).
- He was commenced on BCAA supplementation every 4 hours
- Initial bloodspot BCAA monitoring performed to determine rate of decrease following supplementation

Case: BCAA monitoring

- He has 4.5g BCAA supplements at 05:00, 08:00, 12:00, 16:00, 20:00, 23:00

Date/Time	Isoleucine	Leucine	Valine
06/11/2023 17:45	78	138	291
06/11/2023 19:25	27	47	148
06/11/2023 20:45	280	424	497
07/11/2023 04:55	14	28	91
07/11/2023 11:10	68	129	378
07/11/2023 20:10	36	55	122
07/11/2023 23:00	209	348	638
08/11/2023 05:00	22	42	185
08/11/2023 08:20	337	545	713

All concentrations (umol/L)


BCAA concentration over time, with 4-6 hourly feeds
800
700
600
500
400
300
200
100
0
Concentration (umol/L)
06/11/2023 14:24
06/11/2023 19:12
07/11/2023 00:00
07/11/2023 04:48
07/11/2023 09:36
07/11/2023 14:24
07/11/2023 19:12
08/11/2023 00:00
08/11/2023 04:48
08/11/2023 09:36
Date and Time
Isoleucine
Leucine
Valine

Case: On-Going Care

- The boy is now being monitored by the metabolic dietician team.
- He is sending a pre- and 1hr post-dose bloodspot card for BCAA analysis every fortnight.
- He receives 3g BCAA every 4 hours during the day and 4.5 before going to bed.
- Despite initial concerns, he is taking it well orally, so NG feeding has not been necessary.
- He is being seen by speech and language therapy, and by neurophysiology.
- Final genetic confirmation showed he was homozygous for a frameshift nonsense mutation, and both his parents were identified as carriers.
- Long term prognosis is as of yet unknown.

Thank you!