University Hospitals Bristol and Weston NHS Foundation Trust

Is it really VLCADD?

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Inspected and rated Good
CareQuality Commission

Case 1

- 1 year 4 months old female

- History
  - Born at term, 2.6 kg
  - Cleft palate noted on day 5 of life
  - Developmental delay – gross motor, fine motor, communication and speech
  - Diagnosis of Di George Syndrome
  - Limp/less responsive episodes around twice weekly on waking
  - Vacant episodes with eye deviations

Case 1

- Acute presentation
  - Limp episode
  - Fell backwards from a seated position
  - Intermittent cycling movements without recovery to normal state between episodes
  - Increased temperature
  - Admitted to local A&E with GCS 6/15
  - Eye rolling and occasional posturing noted
  - Hypoglycaemia - glucose 1.2 mmol/L
  - Oxygen saturations 54%
  - Pyrexial with temperature of 38.3°C

Case 1

- Progression
  - Glucose bolus and high flow oxygen given
  - Ongoing abnormal posturing with reduced tone
  - Normal CT
  - Ongoing reduced respiratory rate so intubated and ventilated
  - Transferred to BRHC PICU

Blood gas on arrival

- Metabolic acidosis with lactate 5.7 mmol/L

Hypoglycaemia screen sent overnight on day of arrival

- Lab glucose 3.4 mmol/L
- Lactate 7.7 mmol/L

Case 1

- On PICU
  - Persistent lactic acidosis - 8 mmol/L
  - Rising creatine kinase
  - Ongoing seizures
  - MRI head showed diffuse brain injury likely hypoxic ischaemia

Urine organic acids:

Mild lactic acidosis. Moderate ketosis and increase in dicarboxylic and 3-hydroxy dicarboxylic acids. Of note, significant excretion of longer chain dicarboxylic acids. 5-hydroxy hexanoate and 7-hydroxy octanoate also detected. Query related to sample timing relatvie to hypoglycaemic episode and / or feeds.
Increased glutarate with trace 2-hydroxy glutarate. No glycine conjugates detected in this sample. Advise repeat urine organic acids. Plasma acyl carntine profile to follow.

Case 1

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- Plasma acylcarnitine results - Sheffield

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Free carnitine 11 umol/L (ref 15-53)
      C4-OH 0.18 umol/L (ref <0.07)
      C12:1 0.25 umol/L (ref <0.10)
        C12 0.37 umol/L (ref <0.10)
      C14:1 1.20 umol/L (ref <0.18)
        C14 0.37 umol/L (ref <0.20)
      C16:1 0.20 umol/L (ref <0.08)
        C16 0.38 umol/L (ref <0.24)
      C18:1 0.49 umol/L (ref <0.28)
        C18 0.12 umol/L (ref <0.10)
Significantly increased tetradecenoylcarnitine
(C14:1) with milder increases in the other long
chain species. The C14:1 is markedly
disproportionate compared with the
hydroxybutyrylcarnitine (C4-OH), with a
C14:1/C4(OH) ratio of 6.7 (normal ref. <2.5). Free
carnitine is slightly low.
This profile is consistent with a diagnosis of
Very Long Chain Acyl CoA Dehydrogenase Deficiency
(VLCADD), and requires immediate referral to a
specialist metabolic paediatrician for management.
Recommend enzyme asaay (e.g. in cultured
fibroblasts), or mutational analysis of the ACADVL
gene for diagnostic confirmation.
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- Ongoing seizures and moved to end of life care
- Died – 1.5 weeks after admission

Case 1

Genetic results

- Fatty acid oxidation genetic testing panel
- Genes tested:
  - ACAD8, ACAD9, ACADM, ACADS, ACADSB, ACADVL, ALDH5A1, CPT1A, CPT2, ECHS1, ETFA, ETFB, ETFDH, ETHE1, FLAD1, GLUD1, HADH, HADHA, HADHB, HMGCL, HMGCS2, HSD17B10, MLYCD, NADK2, SLC22A5, SLC25A20, SLC52A2, SLC52A3, SLC25A32.
- Genetic cause not identified

Case 2

- 13 month old, male
- Acute Presentation
  - Presented to A&E
    - Reduced GCS (7-11)
    - Vomiting
    - Reduced tone
  - Metabolic acidosis with lactate of 9.4 mmol/L and pH 6.9
  - Hypoglycaemia - glucose 1.9 mmol/L
  - Glucose infusion and treated for sepsis unclear source
  - Intubated and ventilated
  - Transferred to BRHC PICU

Case 2

- History
  - Stopped night time feeding the previous night
  - Had previously gone without feeds overnight without event

- A full metabolic screen was sent

Case 2

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- Urine organic acids

Evening sample collected on day of initial acute presentation →

Mild lactic acidosis.
Moderate ketosis with increased dicarboxylic and 3-hydroxy dicarboxylic acids.
Consistent with a lipolytic and ketogenic response to a metabolic stress/hypoglycaemic episode.
Glutaric acid, 2-hydroxy glutarate and 5-hydroxy hexanoate also increased, may be secondary to ketosis. Note, no glycine conjugates detected in this sample.
Of note, longer chain dicarboxylic acids also significantly raised in this profile. Plasma acylcarnitine profile to follow to investigate the significance of this finding.
Repeat sample already recieved within laboratory.
Result to follow.

Mild lactic acidosis. Moderate ketosis with increased dicarboxylic and 3-hydroxy dicarboxylic acids. Trace 5-hydroxy hexanoate also detected.
Consistent with a lipolytic and ketogenic response to a metabolic stress/hypoglycaemic episode.
Of note, longer chain dicarboxylic acids detected in the previous sample for this patient are no longer detectable in this profile. Query response to treatment?
Please note, this was a dilute urine sample (urine creatinine = 0.9 mmol/L). Organic acids present at low concentrations may not be detected.

← Morning sample collected the following day

Case 2

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- Bloodspot acylcarnitines – Southmead Bristol.

Bloodspot Free Carnitine	*	5.92	umol/L	10.3 - 54.7
C2		7.16	umol/L	5.0 - 34.2
C3		0.50	umol/L	0.47 - 3.50
C4		0.19	umol/L	0.00 - 0.58
C5:1		0.04	umol/L	0.00 - 0.06
C5		0.13	umol/L	0 - 0.30
C4-OH		0.29	umol/L	0.00 - 0.50
C6		0.06	umol/L	0.00 - 0.21
C5-OH		0.19	umol/L	0.00 - 0.40
C8		0.12	umol/L	0.00 - 0.21
C3DC		0.09	umol/L	0 - 0.11
C10:1		0.13	umol/L	<0.21
C10		0.28	umol/L	0 - 0.30
C4DC		0.48	umol/L	0.00 - 1.29
C5DC		0.09	umol/L	0.00 - 0.11
C12:1	*	0.25	umol/L	0 - 0.19
C12	*	0.37	umol/L	0 - 0.31
C6DC		0.06	umol/L	0.00 - 0.09
C6DC-OH		0.02	umol/L	0 - 0.03
C14:2	*	0.26	umol/L	0 - 0.06
C14:1	*	1.02	umol/L	0 - 0.23
C14		0.42	umol/L	0 - 0.43
C8DC	*	0.07	umol/L	0.00 - 0.06
C14:1-OH	*	0.08	umol/L	<0.07
C14-OH		0.05	umol/L	0 - 0.05
C16:1		0.17	umol/L	<0.2
C16		1.13	umol/L	0.35 - 1.71
C10DC		0.11	umol/L	0 - 0.13
C16:1-OH		0.06	umol/L	0.00 - 0.22
C16-OH		0.04	umol/L	0.00 - 0.11
C18:2		0.16	umol/L	0.04 - 0.60
C18:1		0.93	umol/L	0.3 - 2.00
C18		0.59	umol/L	0.25 - 1.28
C18:1-OH	*	0.05	umol/L	0 - 0.04
C18:OH		0.02	umol/L	0.00 - 0.03
FC/(C16+C18)		3.44		<100
(C16+C18:1)+C2	*	0.29		<0.22

Free carnitine (C0) = 5.92 umol/L
(ref range 10.3 - 54.7)
Low free carnitine noted. Acylcarnitine profile shows increases in tetradecenoylcarnitine (C14:1), 1.02 umol/L (ref range < 0.23) and tetradecadienoylcarnitine (C14:2), 0.26 umol/L (ref range < 0.06). Together with increases in C14:1/C16 and C14:1/C2 ratios, these results are consistent with a diagnosis of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency.
Recommend mutational analysis to confirm.
Report to be emailed to Dr Germaine Pierre (paediatric metabolic team).

Sample collected morning on day of initial acute presentation

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Case 2

- Repeat plasma acylcarnitines – Sheffield

Free carnitine = 7 umol/L (ref. 15-53)
C5:1 = 0.05 umol/L (ref. <0.04)
C4-OH = 0.16 umol/L (ref. <0.07)
C5-DC = 0.08 umol/L (ref. <0.06)
C6-DC = 0.08 umol/L (ref. <0.02)
C14:1 = 0.19 umol/L (ref. <0.18)
C16:1 = 0.10 umol/L (ref. <0.08)
C16 = 0.31 umol/L (ref. <0.24)
C16-OH = 0.04 umol/L (ref. <0.02)
C18:1 = 0.38 umol/L (ref. <0.28)
Plasma acylcarnitine profile shows increased hydroxybutyrylcarnitine together with a generalised increase of medium to long chain acylcarnitines. These findings are indicative of a lipolytic and ketogenic response to a metabolic stress.
Free carnitine is low which may give false negative results. Suggest check urine organic acids and repeat plasma acylcarnitines when carnitine replete.

Sample collected evening on day of initial acute presentation

Case 2

- Progression
  - Extubated and stepped down to HDU the day after transfer to PICU
  - Episodes of bradycardia during sleep
  - Prolonged QT interval on repeated ECG
  - Mild dilated left ventricle and mild impaired function

  - Discharged with a VLCADD management plan
  - Cardiac follow up 3 weeks later – normalised cardiac function
  - VLCADD Genetics – cause not identified

TANGO2 genetics

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- Case 1

Heterozygous deletion at 22q11.21 (consistent with 22q11.2 deletion syndrome) with homozygous deletion of part of the TANGO2 gene
arr[hg19] 22q11.21(18877787_20025652)x1, 22q11.21(20037315_20060137)x0, 22q11.21(20073773_21461607)x1

- Case 2

In addition, a homozygous minimum deletion of ~23 kb was detected within the larger 22q11.2 deletion region. This imbalance encompasses exons 4-9 of the TANGO2 gene within the minimal deletion region (NM_152906.6)

Genetic diagnosis of *TANGO2*-related metabolic encephalopathy

Result

is homozygous for a pathogenic *TANGO2* deletion variant (details below) previously reported by Mingirulli *et al* 2019 PMID:31339582. Biallelic pathogenic *TANGO2* variants cause recurrent metabolic encephalomyopathic crises, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN) (MIM 616878).

Variant details

Gene	Zygosity	Inheritance	Location: GRCh37 (hg19)	Classification
TANGO2	Homozygous	Biparental	Chr22:g.(?_20030878)_(20052185_?)del Deletion of exons 3-9 of TANGO2 (NM_152906.7)	Pathogenic

TANGO2 deficiency

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- Transport and Golgi organisation 2 gene
- Autosomal recessive
- Variable disorder

Non-acute	Acute
Developmental delay and regression	Hypoglycaemia
Poor coordination and unsteady gait	Lactic acidosis
Speech difficulties	Elevated transaminases
Hypothyroidism	Elevated CK (rhabdomyolysis)
Seizures	Hyperammonaemia
Benign Paroxysmal Torticollis (Head Tilt)	Arrhythmias/cardiomyopathy
Episodic muscle weakness and fatigue	Risk of sudden cardiac death
Increased tone	

TANGO2

Mitochondrial dysfunction associated with TANGO2 deficiency

Paige Heiman[1], Al-Walid Mohsen[1,2], Anuradha Karunanidhi[1], Claudette St Croix[3], Simon Watkins[3], Erik Koppes[1], Richard Haas[4], Jerry Vockley[1,2] & Lina Ghaloul-Gonzalez[1,2]✉

- Studies on fibroblasts of 3 TANGO2 deficiency patients
- TANGO2 protein
  - At least partially localised to the mitochondria in control fibroblasts
  - Has considerable effects on mitochondrial bioenergetics and structure
- TANGO2 deficient fibroblasts
  - Changes in fatty acid oxidation and oxidative phosphorylation
    - Decreased mitochondrial respiration under stress
    - Greater dependency on glycolysis to meet energy needs
    - Increased ATP requirement leading to an ATP deficit
    - Decreased fatty acid oxidation flux
      - Findings specifically identify a defect in long chain fatty acid oxidation, medium and short chain FAO require further studies
  - Alterations in protein level and mRNA expression of various proteins involved in both pathways

TANGO2

JIMD REPORTS SSIEM

JIMD Rep. 2023 Jan; 64(1): 3–9.
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PMID: 36636595

Transport and Golgi organization 2 deficiency with a prominent elevation of C14:1 during a metabolic crisis: A case report

Katsuyuki Yokoi,[1,2] Yoko Nakajima,[1] Yoshihisa Takahashi,[3] Takashi Hamajima,[3] Go Tajima,[4] Kazuyoshi Saito,[1] Shunsuke Miyai,[2] Hidehito Inagaki,[2] Tetsushi Yoshikawa,[1] Hiroki Kurahashi,[2] and Tetsuya Ito[1]

- Japanese case report
  - Prominent elevation of C14:1, suggesting very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.
  - Worsening rhabdomyolysis was observed after intravenous administration of L-carnitine
  - Improved on medium chain triglyceride (MCT)
- Avoid L-carnitine during metabolic crises

Case 2 outcomes

- 2 neurological presentations with admission
  - Lethargic affecting strength and balance with head tilting
  - Vacant and tired
- A few admissions related to D&V/viral illness
- Improvement on B vitamin and CoQ10
- Moved away from MCT onto normal diet
- Limited fasting time and remains on emergency regime
- Stable currently with no recent admissions
- Stable cardiac function
- Some developmental delay
- Referred to speech and language therapy

Summary

- Consider TANGO2 deficiency as an alternative diagnosis to very long chain acyl-CoA dehydrogenase deficiency (VLCADD)
- Abnormal acylcarnitines and organic acids during acute episode only
- Findings may normalise rapidly post treatment

- Research ongoing to determine functions of TANGO2
- Increasing number of case reports