Methylmalonic acidemia

HOSP #	MRN123332237	WARD	
CONSULTANT	Prof. George van der Watt	DOB/AGE	5 day neonate

Abnormal Result

Grossly increased Methylmalonic acid on urine organic acid analysis

Presenting Complaint

The baby presented as a 1 day neonate at the pediatric OPD with seizures and admitted to ICU.

History

The baby was discharged being normal after birth via a normal vaginal delivery. 24 hours later was brought to the hospital with seizures

Examination

Upon admission the neonate was encephalopathic with uncontrollable seizures.

Laboratory Investigations

Test	Result (mmol/L)
Na	142
K	5,8
Cl	108
Bicarb	12 L

Anion gap	28 H
Urea	16,3 H
Creat	167 H (umol/L)

Other Investigations

Ammonia in this child was >600 umol/L according to the clinician.

The child was managed as a possible urea cycle defect:

Glucose infusion, preventing catabolism, infusion of vitamins (co-factors). It is unknown whether specifically Vitamin B12 was given as well. Child likely had persistent lactatemia, also evidenced by the high lactate peak in the urine organic acid profile.

The neonate demised after 4 days in the ICU.

Urine organic acid analysis (unfortunately only analysed 2 weeks after demise) demonstrated increased levels of methylmalonic acid, 3-OH propionate, lactate, methylcitrate and a C5 dicarboxylic acid (likely glutarate).

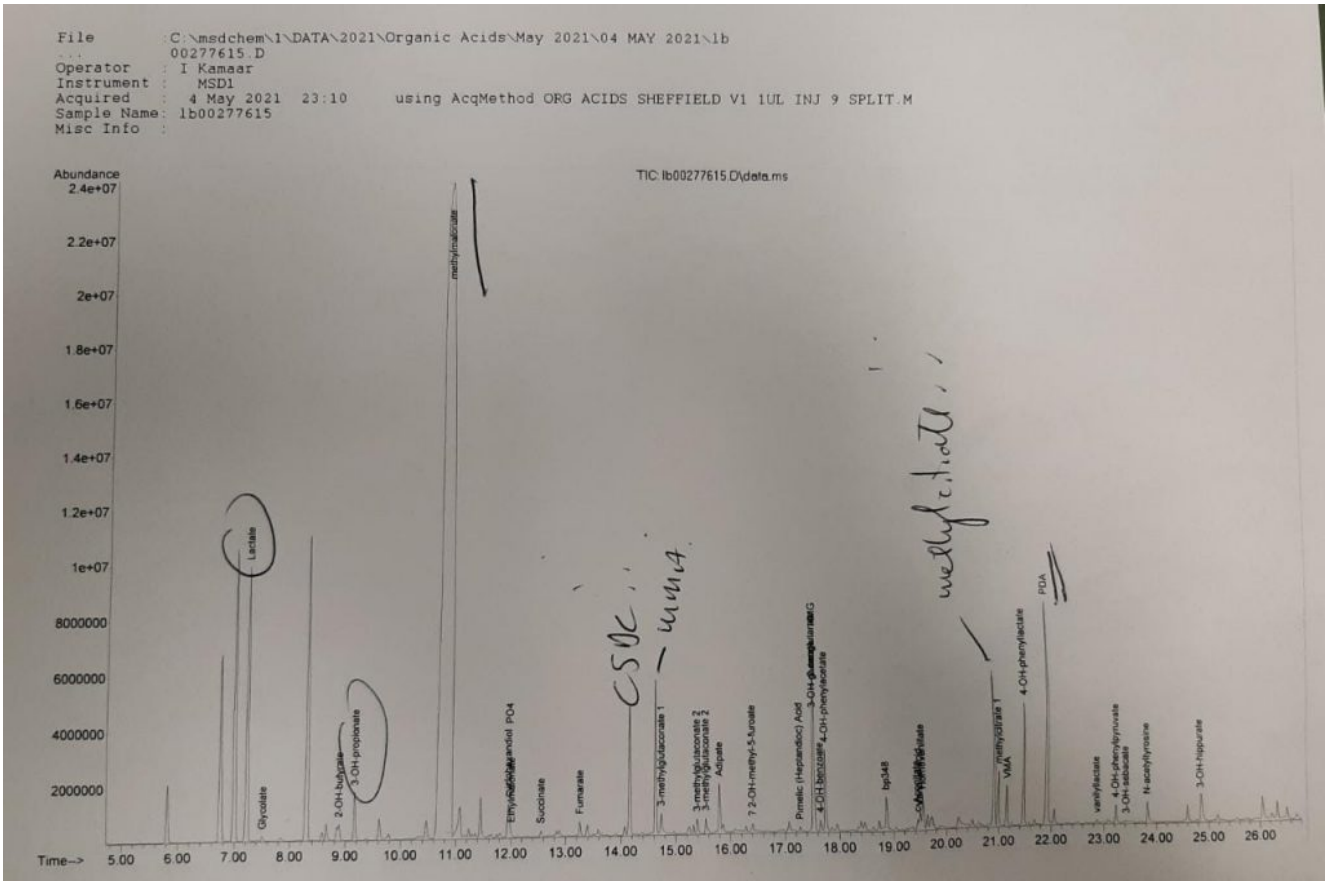

Figure 1 – Urine organic acid profile – annotated by Prof. George van der Watt

Final Diagnosis

Methylmalonic aciduria

Take Home Message

There are a range of genetic defects causing an increase in Methylmalonic aciduria, but this case likely is

Gene defects that cause elevation of methylmalonic acid

Disease (OMIM#)	Gene (OMIM#)	Protein	Inheritance	Homocystinuria
Mut^0 (#251000)	*MUT* (#609058)	Methylmalonyl-CoA mutase	AR	No
Mut$^-$ (#251000)	*MUT* (#609058)	Methylmalonyl-CoA mutase	AR	No
CblA (#251100)	*MMAA* (#607481)	Metabolism of cobalamin associated A	AR	No
CblB (#251110)	*MMAB* (#607568)	Metabolism of cobalamin associated B	AR	No
CblC (#277400)	*MMACHC* (#609831)	MMACHC	AR	Yes
CblD (#277410)	*MMADHC* (#611935)	MMADHC	AR	No for variant 2 Yes for combined type (frameshift pathogenic variants in exon 5, exon 8, and intron 7)
CblF (#277380)	*LMBRD1* (#612625)	LMBR1 domain-containing protein 1	AR	Yes
CblJ (#614857)	*ABCD4* (#603214)	Peroxisomal membrane protein 1-like	AR	Yes
CblX (#309541)	*HCFC1* (#300019)	VP16 accessory protein	XLR	Yes
Methylmalonyl-CoA epimerase deficiency (#251120)	*MCEE* (#608419)	Methylmalonyl-CoA epimerase	AR	No
Transcobalamin receptor defect (#613646)	*CD320* (#606475)	Transcobalamin receptor	AR	Yes
Transcobalamin II deficiency (#275350)	*TCN2* (#613441)	Transcobalamin II	AR	Yes
Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria) (#612073)	*SUCLA2* (#603921)	Succinate-CoA ligase, ADP-forming, beta subunit	AR	No
Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria) (#245400)	*SUCLG1* (#611224)	Succinate-CoA ligase, alpha subunit	AR	No
Malonyl-CoA decarboxylase deficiency (#248360)	*MLYCD* (#606761)	Malonyl-CoA decarboxylase	AR	No
Combined malonic and methylmalonic aciduria (#614265)	*ACSF3* (#614245)	Acyl-CoA synthetase family, member 3	AR	No

CblD variant 1 (also known as CblD homocystinuria subtype due to pathogenic missense variants in exons 6 through 8), CblE, CblG, and MTHFR deficiency do not cause elevated methylmalonic acid and are therefore not included in the table.

CoA: coenzyme A; AR: autosomal recessive; Cbl: cobalamin; *MMACHC*: metabolism of cobalamin associated C; *MMADHC*: metabolism of cobalamin associated D; *ABCD4*: ATP-binding cassette subfamily D member 4; *HCFC1*: host cell factor C1; XLR: X-linked recessive; *CD320*: CD320 molecule; MTHFR: methylenetetrahydrofolate reductase.

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Table 1- from Uptodate

Patients presenting with ketosis, acidosis, and hyperammonemia may have methylmalonic acidemia or another organic acidemia. Evaluation of plasma acylcarnitines and urine organic acids can help to make the diagnosis. Organic acidemias may have a similar presentation, although patients with propionic acidemia may have more severe hyperammonemia than patients with MMA.

Other inherited metabolic disorders that cause elevated serum methylmalonic acid include combined malonic and methylmalonic aciduria, mitochondrial depletion syndrome due to autosomal-recessive pathogenic variants in SUCLA2 or SUCLG1, and also vitamin B12 deficiency.