Intellectual disability

Congenital hyperthyroidism is most likely the single most preventable cause of intellectual disability, especially in the Southern African context where routine screening is not performed currently.

Anti thyroid hormone resistance

An interesting case of resistance to anti-thyroid hormone treatment in a pregnant patient

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Type 2 Diabetes in a 13year old male

HOSP #	MRN123441843	**WARD**	Paediatric Endocrine clinic
CONSULTANT	Dr. Jody Rusch	**DOB/AGE**	13 y male

Abnormal Result

HbA1c = 6.6%

Presenting Complaint

This patient self-presented to a GP and referred to the Pediatric endocrinologist at Red Cross Children's hospital.

History

The patient, an orphan, had a family history of type 2 DM. The late mother (due to breast CA) and the uncle was confirmed with Type 2 DM. The patient reported self-monitoring of glucose with a point of care device, reported having a glucose at times of 13-14mM. This was thus suspicious for DM2. He reported being active and "running 5-6km on some weekends".

The patient did not report polyuria, but there was a history of polydipsia occasionally.

Examination

BP elevated, pulse regular, BMI 28.3
Acanthosis nigricans was noted, as well as an oily skin.

The rest of the examination was essentially normal.

Anthropometry: not short, overweight

Laboratory Investigations

HbA1c = 6.6%

An OGTT was done, but unfortunately the glucose was out of stock so we needed to make another plan, thus 50% Dextrose (150ml) was given as the 75g glucose equivalent.

Baseline 4.9 mM; 2h 7.8mM

Criteria for interpretation of Oral GTT (WHO guidelines 1999/2007):

Impaired Fasting Glycaemia:
Fasting plasma glucose 6.1 – 6.9 mmol/L
2 hour glucose during 75g OGTT < 7.8 mmol/L Impaired Glucose Tolerance: Fasting plasma glucose < 7.0 mmol/L 2 hour glucose during 75g OGTT 7.8 – 11.0 mmol/L

Diabetes Mellitus: Fasting plasma glucose >= 7.0 mmol/L OR
2 hour glucose during 75g OGTT >= 11.1 mmol/L

Other Investigations

- TSH normal
- Free-T4 = 11.2 pM
- ALT = Normal and no signs of fatty liver disease (although an ultrasound was not performed).

Central hypothyroidism was also suspected. A synacthen stimulation test can be performed to assess the function, but the fact that the TSH is normal, fairly confidently excludes this diagnosis.

Urine protein:creatinine ratio = normal
Ultrasound not done yet to determine whether there's a fatty liver

Final Diagnosis

Diabetes Mellitus type 2 in a child, likely a case of MODY (maturity onset diabetes of the young), although this would likely not present itself in a child with the phenotype of a type 2 diabetic child.

Take Home Message

Diabetes Mellitus type 2 is increasing at an enormous rate, even to the extent that children are starting to become affected.

MODY is caused due to a range of genetic diseases involved in insulin signalling and control. The most wel-known gene is most likely that of glucokinase. However, the most prevalent gene affected in MODY-affected individuals is Hepatocyte Nuclear factor 1 alpha (*HNF1A*) gene. The optimal treatments differ between the different causal genetic defects.

Type	Genetic defect	Frequency	Beta cell defect	Clinical features	Risk of microvascular disease	Optimal treatment
1	Hepatocyte nuclear factor-4-alpha	<10%	Reduced insulin secretory response to glucose	Normal renal threshold for glucose	Yes	Sulfonylureas
2	Glucokinase gene	15 to 31%	Defective glucokinase molecule (glucose sensor), increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion	Mild, stable, fasting hyperglycemia, often diagnosed during routine screening. Not progressive.	Generally no	Diet
3	Hepatocyte nuclear factor-1-alpha	52 to 65%	Abnormal insulin secretion, low renal threshold for glucose	Low renal threshold for glucose, +glycosuria	Yes	Sulfonylureas
4	Insulin promoter factor 1	Rare	Reduced binding to the insulin gene promoter, reduced activation of insulin gene in response to hyperglycemia	Rare, pancreatic agenesis in homozygotes, less severe mutations result in mild diabetes	Yes	

5	Hepatocyte nuclear factor-1-beta	Rare		Pancreatic atrophy, renal dysplasia, renal cysts, renal insufficiency, hypomagnesemia	Yes	Insulin
6	Neurogenic differentiation factor-1	Rare	Pancreatic development		Yes	Insulin

Data from:Naylor R, Philipson LH. Who should have genetic testing for maturity-onset diabetes of the young? Clin Endocrinol (Oxf) 2011; 75:422.

Ramesh SC, Marshall I. Clinical suspicion of Maturity Onset of Diabetes of the Young in pediatric patients diagnosed with diabetes mellitus. Indian J Pediatr 2012; 79:955.

Thanabalasingham G, Owen KR. Diagnosis and management of maturity onset diabetes of the young (MODY). BMJ 2011; 343:d6044.

Graphic 83071 Version 5.0

Quadruple-H

A case of hyperparathyroidism, hyperthyroidism, hypercalcemia and hypertension

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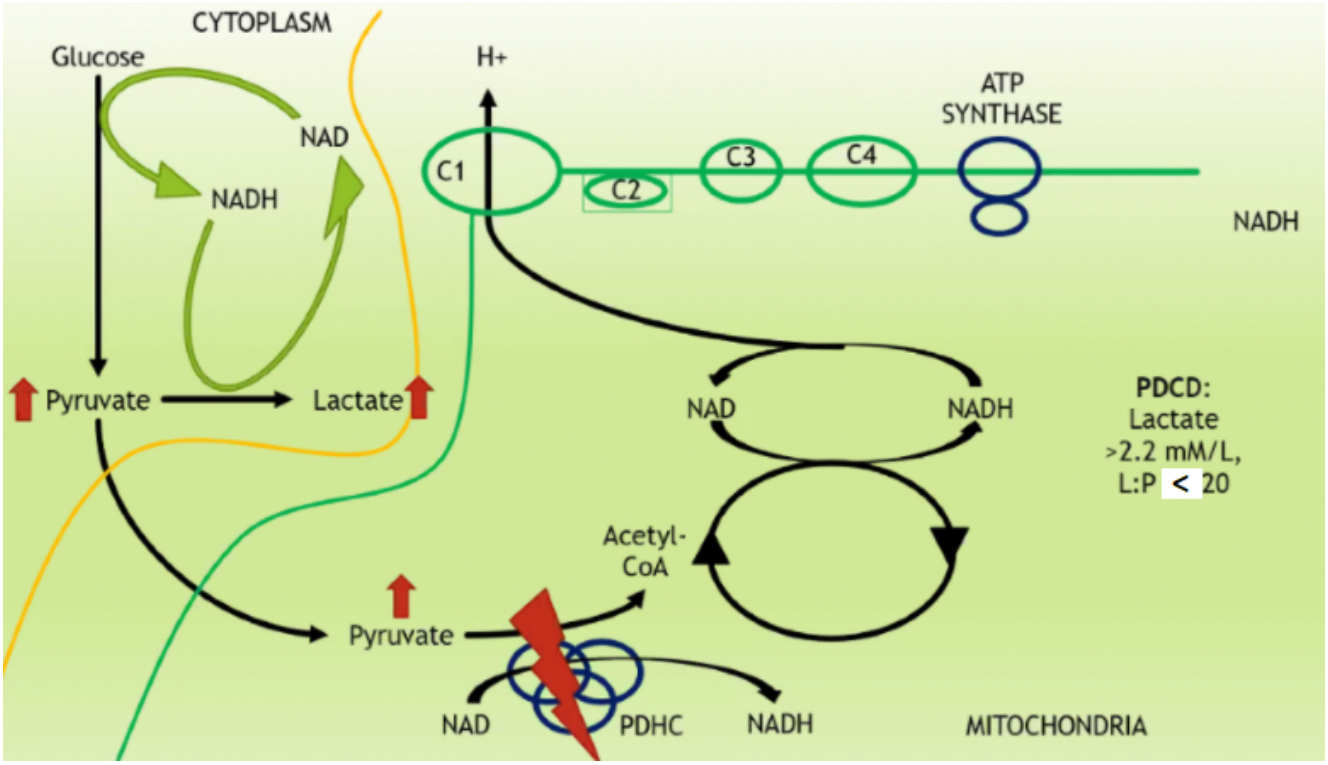
Possible Heterophile

antibodies

A case of possible heterophile antibodies

Lactate:Pyruvate ratio



1. Don’t measure L:P-ratio when lactate is <2.2mM

If lactate is high:

1. L:P will be high in mitochondrial problems (hypoxia, mt cytopathy, complex deficiencies) – the common ones.
2. L:P will be low (<20) in PDHC deficiency, glycogen storage disease,

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).

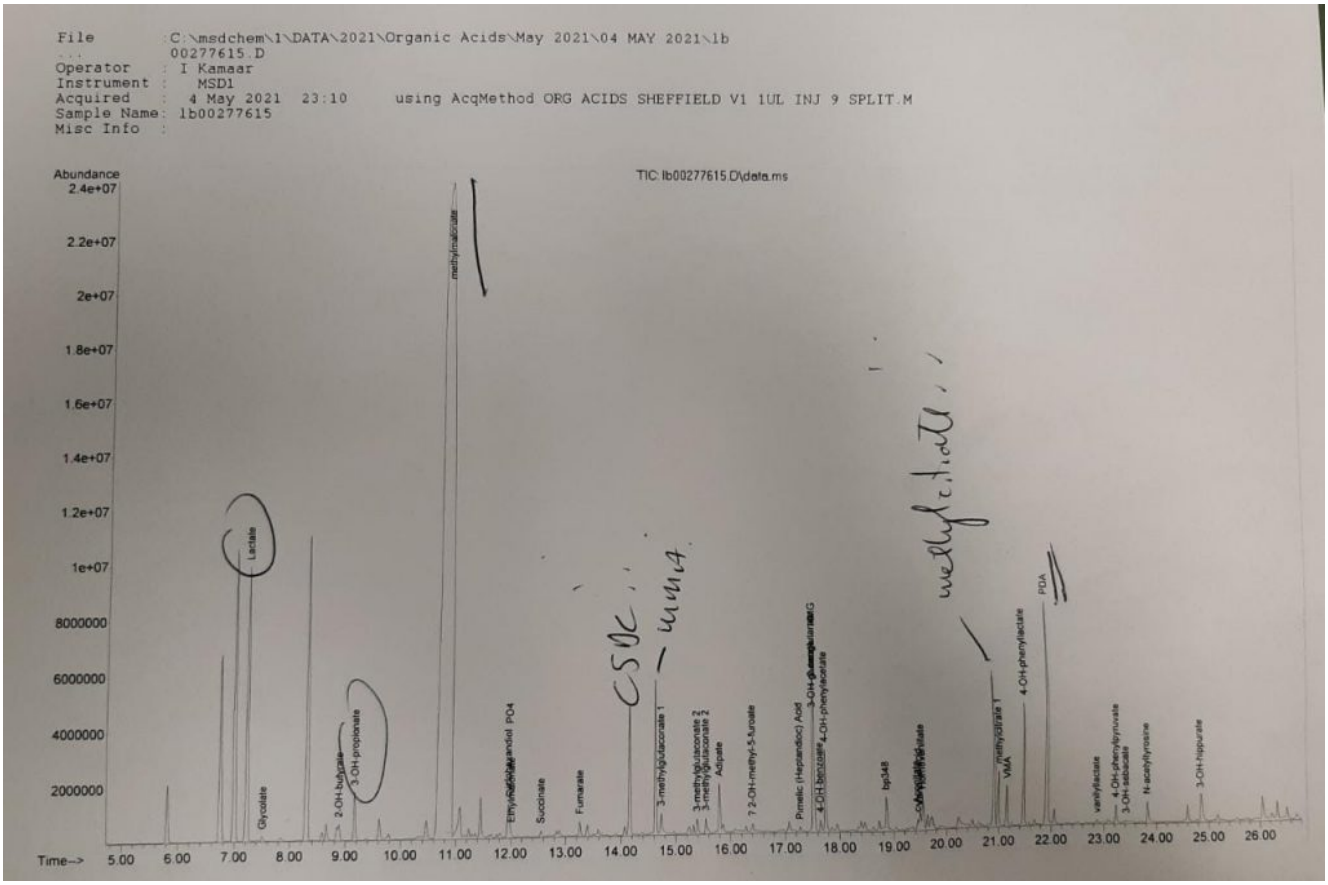


Figure 1 – Urine organic acid profile – annotated by Prof. George van der Watt

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.

Graphic 120477 Version 1.0

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.