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

---

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

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Quadruple-H

A case of hyperparathyroidism, hyperthyroidism, hypercalcemia and hypertension

---

Possible Heterophile

antibodies

A case of possible heterophile antibodies

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).

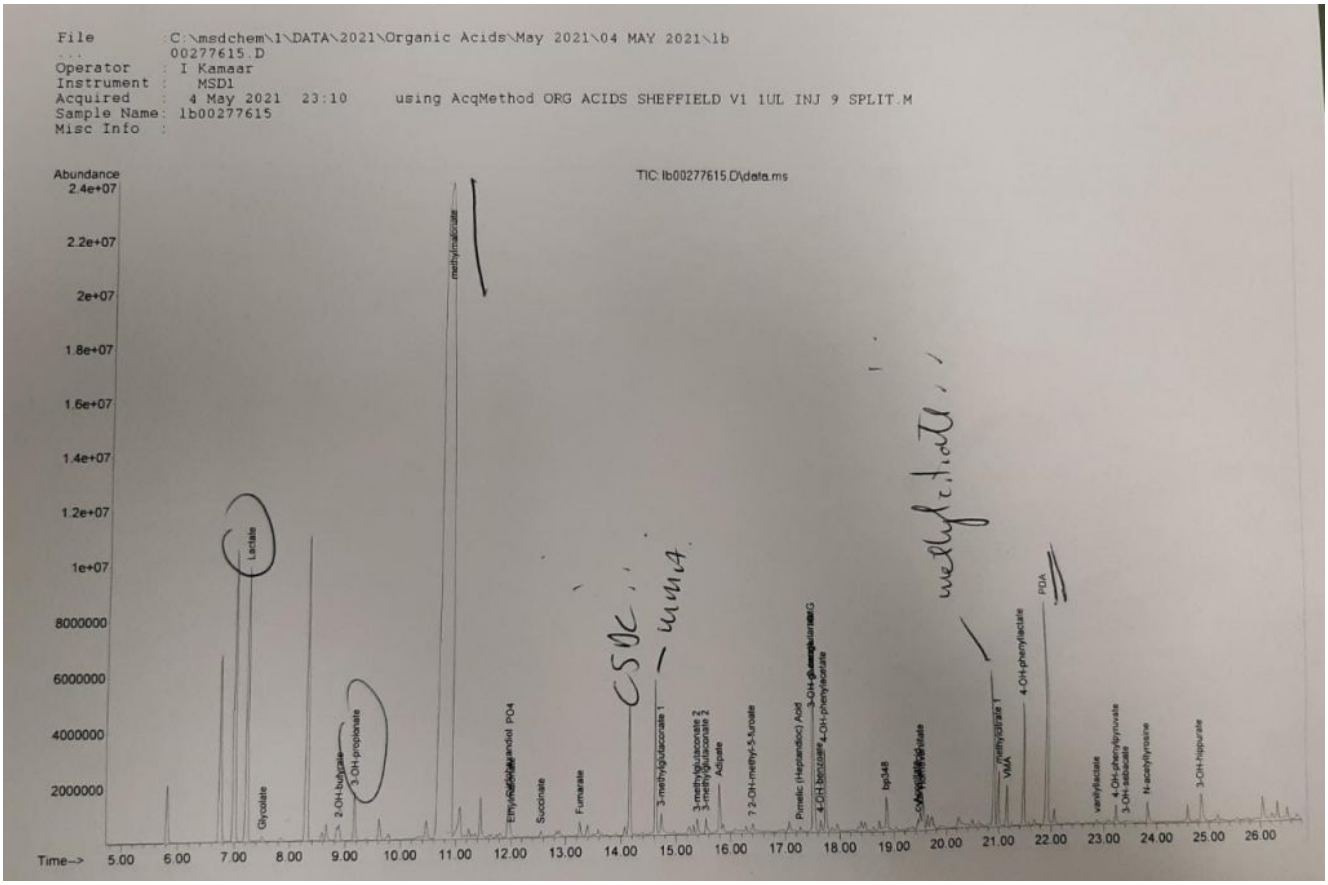

Figure 1 – Urine organic acid profile – annotated by Prof. George van der Watt

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

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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.

Falsely decreased total cholesterol

HOSP #	Req#452050196	**WARD**	Pathcare Private

CONSULTANT	John Stanfliet / Jody Rusch	**DOB/AGE**	Unknown

Abnormal Result

Presenting Complaint

This was a case discussed in consultation with a private consultant:

The patient was admitted with SARS-CoV-2.

History

The clinician was contacted regarding an extremely low LDL-cholesterol, not comparable with the other measurements.

Medication history was unknown at the time when these results became known and had to be authorized.

Examination

Not applicable and information not available.

Laboratory Investigations

Test	Result
Lipaemia	Absent
Total Cholesterol	< 0.5 mmol/L
Triglyceride	0.38 mmol/L
HDL Cholesterol	1.9 mmol/L
Non-HDL-Cholesterol	-1.40 mmol/L
Cholesterol:HDL ratio	0.3
LDL-cholesterol (calculated)	Not done

LDL-cholesterol (measured)	3.0 mmol/L
Glucose (fasting)	5.0 mmol/L

Other Investigations

From the results above it becomes clear that there are some discrepancies in the results. The total cholesterol, as measured on the Abbott Allinity (<0.5 mmol/L) does not compare against the measured LDL-cholesterol (3.0 mmol/L), which should be lower than the total cholesterol.

Other investigations to perform on this sample would perhaps be to run it on a different analyser.

Final Diagnosis

The clinician was phoned and it was found that the patient was on high doses of Vitamin C intravenously.

Take Home Message

When there’s a big discrepancy between LDL (measured – directly with a homogenous assay) and the total cholesterol, the cause should be determined, or at least investigated.

The Total cholesterol, LDL-cholesterol, Triglycerides and HDL-cholesterol all use Trinder reactions.

Vitamin C is a quencher in the reaction (likely due to its high anti-oxidant activity). Since COVID has been around, there are quite a lot of protocols of treatment with Vitamin C IV. It is likely that patients infused with IV N-acetylcysteine, also a potent anti-oxidant, will also cause spuriously low total cholesterol. Or perhaps spuriously low results in any reaction employing the trinder reaction.

It is also clear from this case how important it is to discuss

results which do not make sense with clinicians.

Summary of the Trinder reaction

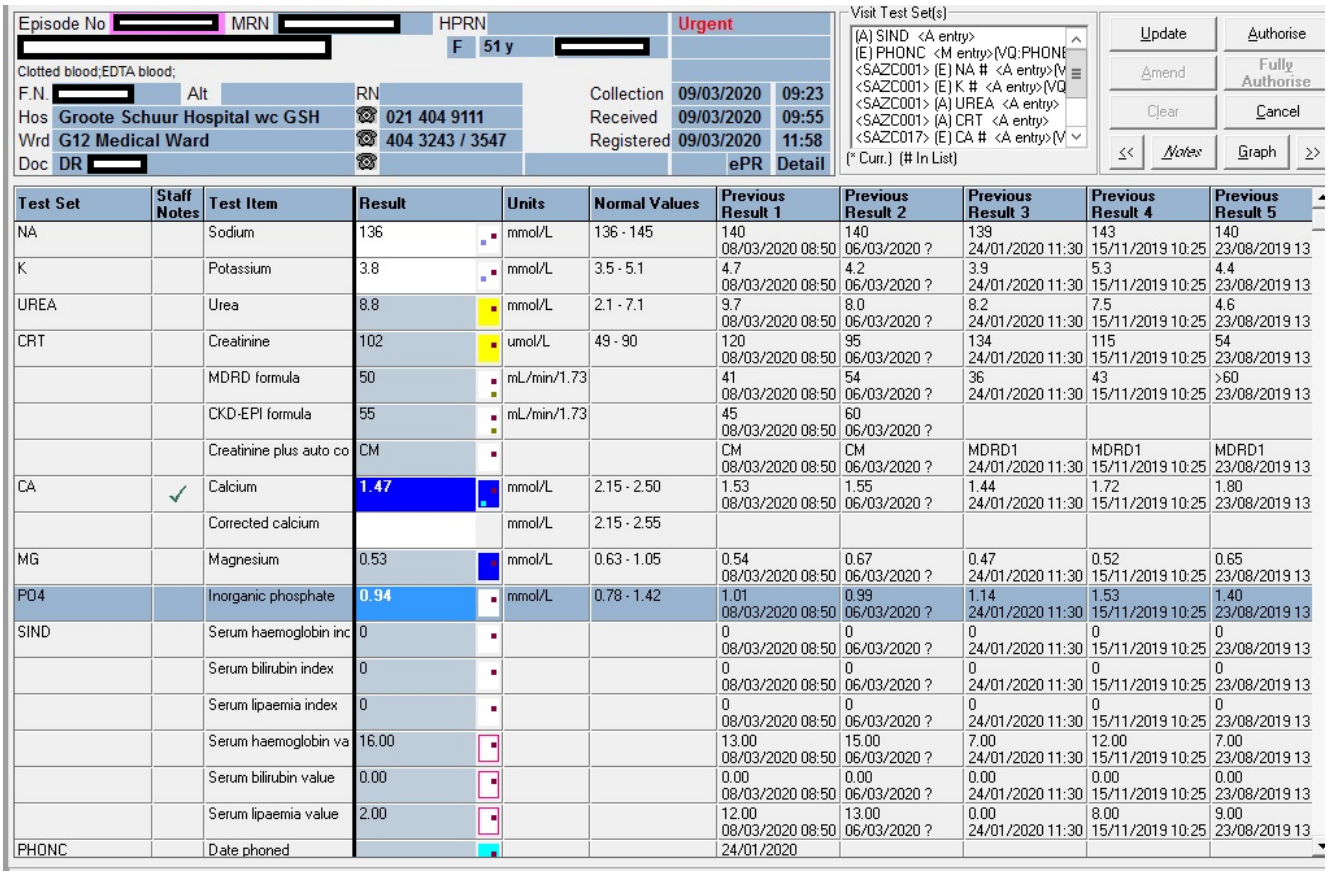
A few decades ago, Emerson presented a new color test reaction (Emerson 1943), which is still in common use for the determination of phenolic compounds (e.g. Ettinger et al. 1951; Fiamegos et al. 2002). Later, Trinder adapted this reaction for the determination of blood glucose using horseradish peroxidase (HRP), coupling the hydrogen peroxide produced from the glucose oxidase reaction, to the Emerson indicator reaction (Trinder 1969; Barham & Trinder 1972). For this reason, this reaction is also known as the Trinder reaction. The so-called Emerson–Trinder reaction, is now routinely used as a spectrophotometric indicator reaction in clinical chemistry, in which a quinoneimine dye product is produced by oxidative condensation of a phenol with 4-aminoantipyrine (4-AAP) (Emerson 1943). This indicator reaction was subsequently used for the spectrophotometric assay of a large number of substrates or enzymes (Burtis & Ashwood 1994) such as uric acid (Kabasakalian et al. 1973), cholesterol (Allain et al. 1974), free hemoglobin (Bauer 1981) or triglycerides (Fossati & Prencipe 1982) and also by using different organic hydrogen-donor compounds such as different substituted (ortho, meta and para) chloro or bromophenols, 4-hydroxybenzene-sulfonic acid (Wang et al. 1992), 2,4-dichlorophenol (Klose et al. 1978), 3,5-dichloro-2-hydroxybenzensulfonic acid (Fossati & Prencipe 1982; Fossati et al. 1980) or different aniline derivatives (Tamaoku et al. 1982).

Farzad Deyhimi, Massoud Arabieh & Lida Parvin (2006) Optimization of the Emerson–Trinder enzymatic reaction by response surface methodology, Biocatalysis and Biotransformation, 24:4, 263-271, DOI: [10.1080/10242420600661943](10.1080/10242420600661943)

A case of persistent hypocalcemia

HOSP #	MRN63985901	WARD	Medical Ward
CONSULTANT	Dr. Heleen Vreede	DOB/AGE	51 year Female

Abnormal Result



Episode No [redacted] MRN [redacted] HPRN [redacted] Urgent
[redacted] F 51 y [redacted]
Clotted blood;EDTA blood;
F.N. [redacted] Alt [redacted] RN [redacted] Collection 09/03/2020 09:23
Hos Groote Schuur Hospital wc GSH 021 404 9111 Received 09/03/2020 09:55
Wrd G12 Medical Ward 404 3243 / 3547 Registered 09/03/2020 11:58
Doc DR [redacted] ePR Detail

Visit Test Set(s)
(A) SIND <A entry>
(E) PHONC <M entry>[VQ:PHONE
<SAZC001> (E) NA # <A entry>[V
<SAZC001> (E) K # <A entry>[VQ
<SAZC001> (A) UREA <A entry>
<SAZC001> (A) CRT <A entry>
<SAZC017> (E) CA # <A entry>[V
(* Curr.) (# In List)

Update | Authorise | Amend | Fully Authorise | Clear | Cancel | << | Notes | Graph | >>

Test Set	Staff Notes	Test Item	Result	Units	Normal Values	Previous Result 1	Previous Result 2	Previous Result 3	Previous Result 4	Previous Result 5
NA		Sodium	136	mmol/L	136 - 145	140 08/03/2020 08:50	140 06/03/2020 ?	139 24/01/2020 11:30	143 15/11/2019 10:25	140 23/08/2019 13
K		Potassium	3.8	mmol/L	3.5 - 5.1	4.7 08/03/2020 08:50	4.2 06/03/2020 ?	3.9 24/01/2020 11:30	5.3 15/11/2019 10:25	4.4 23/08/2019 13
UREA		Urea	8.8	mmol/L	2.1 - 7.1	9.7 08/03/2020 08:50	8.0 06/03/2020 ?	8.2 24/01/2020 11:30	7.5 15/11/2019 10:25	4.6 23/08/2019 13
CRT		Creatinine	102	umol/L	49 - 90	120 08/03/2020 08:50	95 06/03/2020 ?	134 24/01/2020 11:30	115 15/11/2019 10:25	54 23/08/2019 13
		MDRD formula	50	mL/min/1.73		41 08/03/2020 08:50	54 06/03/2020 ?	36 24/01/2020 11:30	43 15/11/2019 10:25	>60 23/08/2019 13
		CKD-EPI formula	55	mL/min/1.73		45 08/03/2020 08:50	60 06/03/2020 ?			
		Creatinine plus auto co	CM			CM 08/03/2020 08:50	CM 06/03/2020 ?	MDRD1 24/01/2020 11:30	MDRD1 15/11/2019 10:25	MDRD1 23/08/2019 13
CA	✓	Calcium	1.47	mmol/L	2.15 - 2.50	1.53 08/03/2020 08:50	1.55 06/03/2020 ?	1.44 24/01/2020 11:30	1.72 15/11/2019 10:25	1.80 23/08/2019 13
		Corrected calcium		mmol/L	2.15 - 2.55					
MG		Magnesium	0.53	mmol/L	0.63 - 1.05	0.54 08/03/2020 08:50	0.67 06/03/2020 ?	0.47 24/01/2020 11:30	0.52 15/11/2019 10:25	0.65 23/08/2019 13
PO4		Inorganic phosphate	0.94	mmol/L	0.78 - 1.42	1.01 08/03/2020 08:50	0.99 06/03/2020 ?	1.14 24/01/2020 11:30	1.53 15/11/2019 10:25	1.40 23/08/2019 13
SIND		Serum haemoglobin inc	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum bilirubin index	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum lipaemia index	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum haemoglobin va	16.00			13.00 08/03/2020 08:50	15.00 06/03/2020 ?	7.00 24/01/2020 11:30	12.00 15/11/2019 10:25	7.00 23/08/2019 13
		Serum bilirubin value	0.00			0.00 08/03/2020 08:50	0.00 06/03/2020 ?	0.00 24/01/2020 11:30	0.00 15/11/2019 10:25	0.00 23/08/2019 13
		Serum lipaemia value	2.00			12.00 08/03/2020 08:50	13.00 06/03/2020 ?	0.00 24/01/2020 11:30	8.00 15/11/2019 10:25	9.00 23/08/2019 13
PHONC		Date phoned				24/01/2020				

Total calcium of 1.47 mmol/L (2.15 – 2.50)

Presenting Complaint

The patient has been having persistent hypocalcemia despite supplementation with calcium.

History

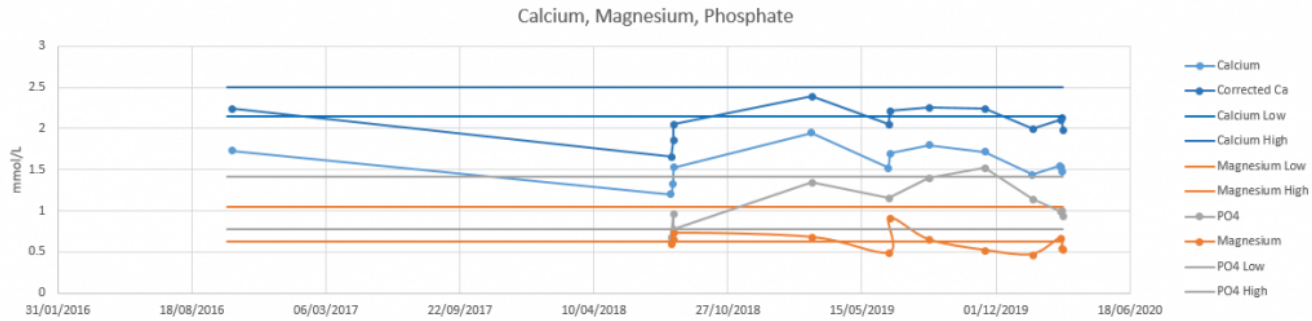


Figure 1 – Illustration of the patient's CMP over time: Calcium: blue; Magnesium: orange; Phosphate: grey
Reference ranges are the horizontal lines without dotted markers

Examination

Not available.

The typical findings in a patient with true hypocalcemia (low ionised calcium) are

Trouseau's sign

Chvostek's sign

Laboratory Investigations

Arguably, the first important consideration in patients with low calcium is the albumin. The patient had a mean albumin of 12 g/L, significantly lower than normal (40-50g/L). Arguably, the calcium can be corrected with the well known Payne's formula to then be 1.47 + (0.02 x (40-12) = 2.03 mmol/L:

> *Albumin-adjusted calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)])*

> *Payne RB, Little AJ, Williams RB, Milner JP. Interpretation of serum calcium in patient with abnormal serum proteins. Br Med J. 1973;4:643-646. DOI: 10.1136/bmj.4.5893.643. (View)*

Measurement of serum intact parathyroid hormone (PTH) should be performed in all patients with hypocalcemia; it is the most valuable laboratory test for determining the etiology of hypocalcemia:

	2019/11/15	2019/06/28	2018/08/03
PTH (pmol/L)	21,8 H	15,5 H	25,8 H

Reference interval: (1.6-6.9 pmol/L)
Vitamin D

	09/09/2020	15/11/2019	03/08/2018
Total Vitamin D (25-OH VitD)	20.5 nmol/L	45.4 nmol/L	23.2 nmol/L

Guidelines for assessment of Vitamin D status:
<30 nmol/L <12 ng/mL Deficient
30-50 nmol/L 12-20 ng/mL Insufficient
>50 nmol/L >20 ng/mL Sufficient
125-150 nmol/L 50-60 ng/mL Safe upper limit
Reference: Revised South African Clinical Guideline for the diagnosis and management of osteoporosis (NOFSA 2017), endorsing the institute of Medicine Dietary Reference intakes for calcium and vitamin D (2010). Note regarding conversion of units:
Divide result in nmol/L by 2.496 to convert to ng/mL
Multiply result in ng/mL by 2.496 to convert to nmol/L

Other Investigations

Anti-Tissue Transglutaminase antibodies: **Negative**: repeated 3 months apart, with sufficient IgA levels in the serum): 0.9 & 0.8 U/mL (EliA c/o: 6.9)

Anti-Gliadin antibodies: **Equivocal**: 7.8 & 9.6 U/mL (EliA c/o: 6.9)

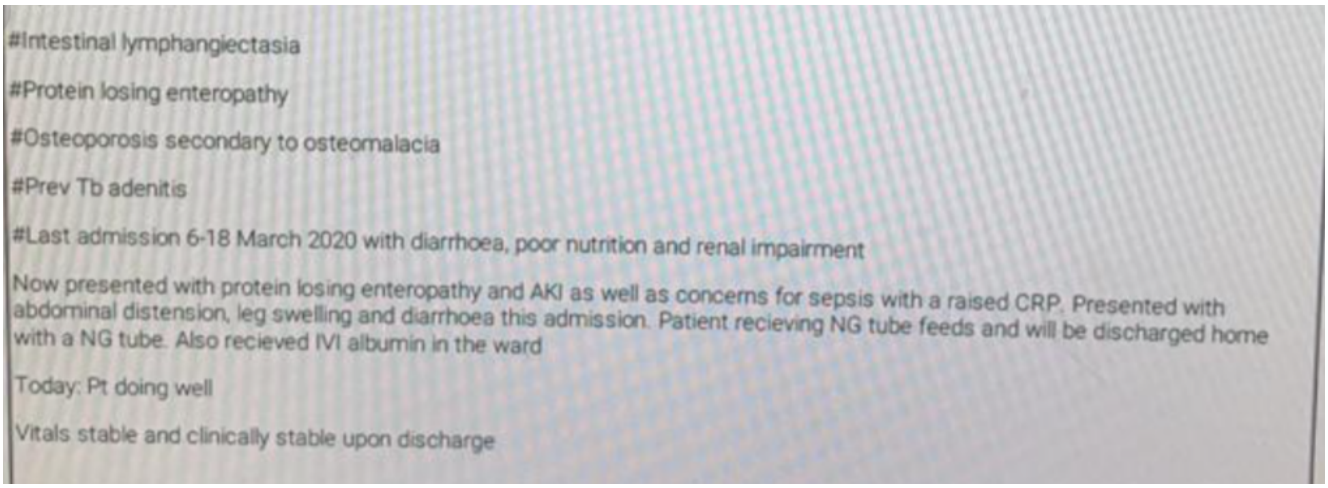
Anti-endomysial antibodies: **Negative**

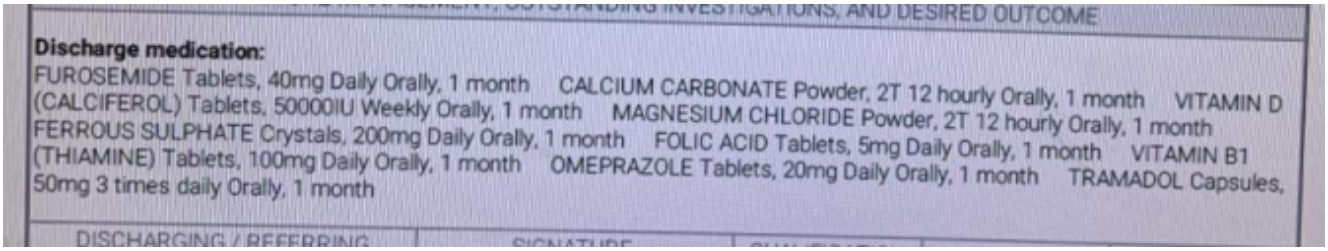
HLA-DQ2: **Positive**

HLA-DQ8: **Negative**

Final Diagnosis

Hypocalcemia likely due to malabsorbtion (telangiectasia stated by the clinicians).





Take Home Message

According to International guidelines the following association is expected for patients with Coeliac Disease:
Positive for HLA-DQ2 (HLA-DQA1*05, DQB1*02)
Positive for HLA-DQ8 (HLA-DQA1*03, DQB1*03:02)

Considering the fact that the albumin was high with an increased PTH, the calcium very likely was physiologically also low (bioactive Ca). The Payne's formula also failed to correct the calcium to the normal reference range.

Cumulative History:Download

Cystine crystals in the urine

The patient, a 16 y female presented with signs and symptoms of an upper urinary tract infection.

High succinate in the urine

A case of falsely raised succinate

3D Printing in the laboratory

Although not strictly a patient case, I will discuss the applicability of 3D printing in the laboratory in two particular problems which presented itself in our laboratory.

Hypernatremia with hypokalemia

This patient likely has a combination of aetiologies accounting for the deranged electrolytes.

Raised fecal osmolar gap

A child with an increased fecal osmolar gap

Raised fecal calprotectin

HOSP #		WARD	GIT clinic
CONSULTANT	Dr. Heleen Vreede	DOB/AGE	59 y male

Abnormal Result

Faecal calprotectin >6000 ug/g stool

Presenting Complaint

59 y male, presenting with diarrhoea and bloody mucus per rectum

History

This is a 59 year old male known with ulcerative colitis proctitis who now has a suspected flare.

Ulcerative colitis (pancolitis) diagnosed 2009.

Histological history

2017: Mild focal active colitis noted on Histology

2019: Sections of rectal mucosa showed features of active chronic proctitis. The crypts showed distortion with focal areas of crypt abscesses noted. The lamina propria was expanded by reactive polymorphous mature lymphocytes with conspicuous eosinophils.

Examination

Unknown

One would look for especially extra-intestinal manifestations of Ulcerative Colitis

Laboratory Investigations

Histology: Sections of colon demonstrate a severe acute colitis with cryptitis , crypt abscess and numerous neutrophils in the lamina propria on a background of chronic changes illustrated by architectural disarray and glandular atrophy.

Other Investigations

Apart from the colonoscopy and histology, one needs to evaluate for other autoimmune disorders in the gastro-intestinal tract, especially complications of primary sclerosing cholangitis. No biochemical signs thereof was present.

Test (units)	Result
Creat (umol/L)	122 H
MDRD	53
CKD-EPI	56
Alb (g/L)	44
Total bili (umol/L)	4 L

Conj bili (umol/L)	2
ALT (U/L)	18
AST (U/L)	30
ALP (U/L)	77
GGT (U/L)	16
CRP (U/L)	2

Final Diagnosis

Inflammatory Bowel Disease (Ulcerative colitis)

Take Home Message

We have in recent years started to offer this test. One of our recently qualified pathologists, Dr. Justine Cole, was responsible for the method validation of this assay at our laboratory. There were quite a few difficulties with the validation, mainly due to stool being a difficult to work with matrix and sample stability when transported.

In summary:

Faecal calprotectin is excreted in excess into the intestinal lumen during the inflammatory process and so can act as a marker for inflammatory diseases of the lower gastrointestinal tract. Faecal calprotectin testing is recommended in patients with recent onset lower gastrointestinal symptoms, if cancer is NOT suspected, for the
differential diagnosis of inflammatory bowel disease (IBD e.g., Chrohn’s disease, ulcerative colitis) or irritable bowel syndrome (IBS).

Faecal calprotectin <=50 ug/g stool is negative, i.e., supports IBS.

Faecal calprotectin >50 ug/g stool is positive, i.e., supports

IBD.

Primary amenorrhoea with ulcerative colitis

HOSP #		WARD	
CONSULTANT		DOB/AGE	15 y girl

Abnormal Result

This patient was discussed at a combined Endocrinology / Chemical Pathology meeting.

Total bilirubin: 281 umol/L

Presenting Complaint

The patient was a candidate for a liver transplant, but was referred to the endocrinology department for the short stature and primary amenorrhoea prior to surgery.

History

She was diagnosed with ulcerative colitis in 2016 (@ 12y age) and primary sclerosing cholangitis. Breast development started in 2018 (@14 years), but no menstrual cycles started ever since.

She has one younger sister which is well currently at 4 y age.

Birth weight was 3.8 kg.

Medication

Patient was receiving steroids and sulfasalazine intermittently.

For portal hypertension she is also receiving furosemide and spironolactone

Vitamin D supplements are also given

Examination

Height (114cm) for age: <3rd percentile

Weight 35 kg

Breasts well developed – Tanner IV,

No armpit hair growth, parse pubic hair – Tanner II

Laboratory Investigations

Test	Result
Total bili (umol/L)	281 H
Conj bili (umol/L)	246 H
ALT (U/L)	58 H
AST (U/L)	151 H
ALP (U/L)	524 H
GGT (U/L)	65 H
TSH mIU/ml	1,74
Free T4 (pmol/L)	16,4
Free T3 (pmol/L)	2,8 L
FSH (IU/L)	8,2
LH (IU/L)	6,2
E2 (pmol/L	462

Prog (nmol/L)	0.9
Prolactin (ug/L)	15,4
INR	2.09
IGF-1 (ug/L) 107.8 – 541.5 Tanner stages: Boys Girls Stage I 63 – 271 ug/L 71 – 394 ug/L Stage II 114 – 411 ug/L 122 – 508 ug/L Stage III 166 – 510 ug/L 164 – 545 ug/L Stage IV 170 – 456 ug/L 174 – 480 ug/L Stage V 161 – 384 ug/L 169 – 400 ug/L	**23.5**

Table 1 – Results

Other Investigations

Histology (Colonoscopy)

MICROSCOPIC:
Right, transverse and left colon:
Sections show large bowel type mucosa with maintained crypt architecture with no cryptitis or crypt abscess formation noted. No significant increased intra epithelial lymphocytes or subepithelial collagen deposition is present. The lamina propria shows normal inflammatory cells with no giant cells, granulomas, infective organisms, viral inclusions, epithelial atypia or malignancy identified. Colon mucosa morphologically within normal limits

Rectum:
Sections show large bowel mucosa with preserved crypt architecture and increased chronic inflammation in the lamina propria. Active inflammation is absent. There is no evidence of granulomas, viral inclusions, parasites or dysplasia. Non-specific increase in chronic inflammation in the lamina propria.

The other proposed additional examination is a pubic ultrasound to evaluate the ovaries, fallopian tubes and uterus.

It was also proposed that IGF binding protein 3 be measured, as low levels may yield IGF-1 shorter biologically active.

Final Diagnosis

Primary amenorrhoea most likely due to a physiological delay. Although the pelvic ultrasound hasn't been done at the time of writing, the low IGF-1 likely indicates a low growth due to chronic systemic disease – see other possible aetiologies below.

Take Home Message

Amenorrhea can be a condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina.

The most common aetiologies include:

- Gonadal dysgenesis, including Turner syndrome – 43%
- Müllerian agenesis (absence of vagina, sometimes with absence of uterus) – 15%
- Physiological delay of puberty (constitutional delay of puberty, chronic systemic disease, acute illness) – 14%
- Polycystic ovary syndrome (PCOS) – 7%
- Isolated gonadotropin-releasing hormone (GnRH) deficiency – 5% (possible selection bias)
- Transverse vaginal septum – 3%
- Weight loss/anorexia nervosa – 2%
- Hypopituitarism – 2%

Hyperprolactinemia >1000

HOSP #		WARD	Neurosurgery
CONSULTANT	Dr. Jody Rusch	DOB/AGE	10 year female

Abnormal Result

Prolactin >1000 ug/L

Presenting Complaint

Patient presented at 7 years of age with galactorrhea and visual field defects.

History

Patient had a craniotomy for debulking of the adenoma. This was opposed to the usual transsphenoidal more non-invasive route of pituitary adenoma surgery. She was initiated on Cabergoline 1 g twice weekly for suppression of the tumour size.

It was also noted during surgery that the tumour was extremely vascular with much bleeding and the neurosurgeons struggled to mobilize it to adequately get it separated from the optic chiasm. Some portion of the tumour was left in situ during surgery as this was too big a risk for trying to excise.

A biopsy was also taken.

Examination

Patient subsequently developed severe intracranial edema after surgery in the ICU.

Laboratory Investigations

Collection date time Requisition number Status	*Reference range unit*	2020-03-11 12:48 713553140	2020-03-13 09:45 713555581	2020-11-26 00:00 713573116	2020-11-26 13:07 713573113	2020-12-03 05:43 713573635	2020-12-21 15:38 713578670	2020-12-21 15:43 713578671	**2021-02-03 15:10 713583689**
BIOCHEMISTRY									
LIPAEMIC		1+		ABSENT		ABSENT		ABSENT	ABSENT
ICTERIC		ABSENT		ABSENT		ABSENT		ABSENT	ABSENT
HAEMOLYSIS		ABSENT		ABSENT		ABSENT		ABSENT	ABSENT
S-SODIUM	136-146 mmol/L	137		136		141		141	138
S-POTASSIUM	3.5-5.1 mmol/L	3.7		3.8		4.4		3.4 L	3.8
S-CHLORIDE	101-109 mmol/L	105		98 L		105		104	99 L
S-BICARBONATE	21.0-31.0 mmol/L	25.0		25.0		30.0		28.0	31.0
ANION GAP	3-15 mmol/L	7		13		6		9	8
S-UREA	2.1-7.1 mmol/L	4.8		2.2		3.6		3.0	2.2
S-CREATININE	23-68 umol/L	48		40		38		48	
C-REACTIVE PROTEIN	< 5.0 mg/L	3.6		2.8					
S-TOTAL PROTEIN	57-80 g/L	76		76		66		72	72
S-ALBUMIN	35-52 g/L	46		44		38		39	39
GLOBULIN	21-35 g/L	30		32		28		33	33
ALB./GLOB. RATIO	0.9-2.7	1.5		1.4		1.4		1.2	1.2
S-TOTAL BILIRUBIN	5-21 umol/L	5		9		4 L		6	5
S-CONJ. BILIRUBIN	< 3.4 umol/L	1		2		1		1	1
UNCONJ. BILIRUBIN	2-17 umol/L	4		7		3		5	4
S-ALK. PHOSPHATASE	51-332 IU/L							129	135
S-ALK. PHOSPHATASE	69-325 IU/L	144		149		111			
S-gamma GT	4-22 IU/L	10		9		9		7	10
S-ALT	< 35 IU/L	15		11		23		12	12
S-AST	15-60 IU/L	28		29		33		16	18
P-GLUCOSE RANDOM	mmol/L		3.7						
ENDOCRINOLOGY									
INSULIN-LIKE GROWTH FACTOR 1	57-277 ng/mL			32.40 L					
INSULIN-LIKE GROWTH FACTOR 1	80-233 ng/mL		93.70						
FREE T4	7.2 - 16.4 pmol/L	5.8*L		8.3		8.1		14.5	13.7
FREE T3	3.88 - 8.02 pmol/L	3.44*L		2.43*L		2.42*L		3.31*L	
S-TSH	0.79 - 5.85 mIU/L	0.96		1.52				0.02*L	0.01*L
PROLACTIN	3.3 - 26.7 ug/L	613.5*H		1892.1*H		948.2*H		726.4*H	
FSH	0.03 - 3.9 IU/L	1.2		0.7					
LH	0.7 - 6.7 IU/L	0.4 L		0.8					
17B OESTRADIOL (E2)	< 60 pmol/L	< 55		< 55					
CORTISOL RANDOM*	nmol/L			126					
CORTISOL 08H00	184 - 618 nmol/L		85*L						
ACTH	1.6 - 13.9 pmol/L		2.7	1.4 L					

Collection date time Requisition number Status	Reference range unit	2021-02-10 05:35 713583939	2021-02-10 13:38 713584112	2021-02-19 11:43 713585065	2021-03-15 00:00 712530075	2021-03-16 00:15 713586569	2021-03-16 00:15 713586570	2021-04-08 21:40 713588757	2021-04-08 21:40 713590857
Biochemistry									
LIPAEMIC		ABSENT	ABSENT	ABSENT		ABSENT			ABSENT
ICTERIC		ABSENT	ABSENT	ABSENT		ABSENT			ABSENT
HAEMOLYSIS		ABSENT	ABSENT	ABSENT		ABSENT			ABSENT
S-SODIUM	136-146 mmol/L	136	136	142		141			138
S-POTASSIUM	3.5-5.1 mmol/L	4.8	4.1	4.4		3.8			3.8
S-CHLORIDE	101-109 mmol/L	101	99 L	105		104			102
S-BICARBONATE	21.0-31.0 mmol/L	30.0	30.0	28.0		31.0			28.0
ANION GAP	3-15 mmol/L	5	7	9		6			8
S-UREA	2.1-7.1 mmol/L	3.8	4.7	3.5		3.1			3.2
S-CREATININE	23-68 umol/L	40	38			44			48
S-CALCIUM (total)	2.20-2.70 mmol/L					2.39			2.24
CALCIUM (corrected)	2.20-2.70 mmol/L					2.49			2.34
S-PHOSPHATE	1.20-1.80 mmol/L					1.48			1.51
S-OSMOLALITY	280-295 mOsm/kg	294				299 H			292
U-OSMOLALITY	mOsm/kg	545			91				
C-REACTIVE PROTEIN	< 5.0 mg/L								5.4 H
S-TOTAL PROTEIN	57-80 g/L					77			67
S-ALBUMIN	35-52 g/L					36			36
GLOBULIN	21-35 g/L					41 H			31
ALB./GLOB. RATIO	0.9-2.7					0.9			1.2
S-TOTAL BILIRUBIN	5-21 umol/L					5			4 L
S-CONJ. BILIRUBIN	< 3.4 umol/L					1			1
UNCONJ. BILIRUBIN	2-17 umol/L					4			3
S-ALK. PHOSPHATASE	51-332 IU/L					124			109
S-gamma GT	4-22 IU/L					8			8
S-ALT	< 35 IU/L					10			10
S-AST	15-60 IU/L					14 L			16
Endocrinology									
VITAMIN D (25 OH)	ng/mL					23			
FREE T4	7.2 - 16.4 pmol/L								12.6
FREE T4	8.5 -15.7 pmol/L					13.6			
FREE T3	4.3 - 6.8 pmol/L								3.0 L
S-TSH	0.79 - 5.85 mIU/L					<0.01*L			
PROLACTIN	4.0-23.0 ug/L					1055.2*H			791.2*H
FSH	0.03 - 3.9 IU/L								0.3
LH	0.7 - 6.7 IU/L								< 0.2 L
17B OESTRADIOL (E2)	< 60 pmol/L								< 55
PARATHYROID HORMONE	1.6-6.9 pmol/L					0.3 L			
PARATHYROID HORMONE	15.2-65.7 pg/mL					2.9 L			

Other Investigations

Histology

Frozen section – pituitary adenoma. GROSS DESCRIPTION: Specimen labelled tumour. Specimen consists of 2 fragments of tissue, larger measuring 4x3mm. HISTOLOGY: Sections show tumour tissue composed of nests of monotonous cells with intervening fibrous septae. The cells have round nuclei and abundant eosinophilic cytoplasm. The nuclei have stippled chromatin with inconspicuous nucleoli. No mitotic activity or necrosis is seen. Immunohistochemistry: Synaptophysin:Positive Prolactin: Positive LH: Negative FSH: Negative GH: Negative

TSH: Negative ACTH: Negative CONCLUSION: Pituitary, mass, excision: – Pituitary adenoma with an immunohistochemical profile compatible with a prolactinoma.

Final Diagnosis

Pituitary Macroadenoma

Take Home Message

Cabergoline, sold under the brand name Dostinex among others, is a dopaminergic medication used in the treatment of high prolactin levels, prolactinomas, Parkinson's disease, and for other indications. It is taken by mouth. Cabergoline is an ergot derivative and a potent dopamine D_2 receptor agonist.

Lactotroph adenomas (prolactinomas) are more amenable to pharmacologic treatment than any other kind of pituitary adenoma because of the availability of dopamine agonists, which usually decrease both the secretion and size of these tumors. For the minority of lactotroph adenomas that do not respond to dopamine agonists, other treatments must be used. Hyperprolactinemia due to nonadenoma causes should also be treated if it causes hypogonadism.

There are two principal reasons why patients with hyperprolactinemia may need to be treated: existing or impending neurologic symptoms due to the **large size** of a lactotroph adenoma, and **hypogonadism** or other symptoms due to hyperprolactinemia, such as galactorrhea.

A third indication is in women with mild hyperprolactinemia and normal cycles who are trying to conceive as they may have subtle luteal phase dysfunction.

Bilateral adrenal vein sampling

HOSP #	Mr JB	**WARD**	Endocrine Department – CathLab – UCT private Hospital
CONSULTANT	Dr Jody Rusch	**DOB/AGE**	53y Male

Abnormal Result

Upon authorizing blood results I came across a aldosterone result of 23300 pmol/L.

After a moment of brief anxiety, luckily I realized this was part of a series of tests performed by my colleagues in the Department.

Presenting Complaint

Medical complaint: Suspected Conn's disease – right adrenal lesion/ irregular left adrenal gland.

History

The patient was confirmed to have primary hyperaldosteronism.

Unfortunately more information is not known. We were asked to assist with the sampling and the whole history weren't available.

Examination

Not available

Laboratory Investigations

Sample	Time	Episode	Aldosterone result pmol/L	Coritsol result nmol/L	Selectivity Index Cortisol AV/PV	ACR A/C	Lateralisation Index Dom A/C : nonDom A/C	Mean Aldo/Cort RAV	Aldo/Cort LAV
RAV 1	12:23	SA04663261	794	429	0.9	1.9			
RAV 2	12:39	SA04663254	887	520	1.1	1.7			
RAV 3	12:55	SA04663249	771	486	1.0	1.6			
Mean RAV			817.3	478.3	1.0				
LAV 1	12:50	SA04663243	22000	7325	15.3	3.0	1.8		3.0
LAV 2	12:51	SA04663239	23300	8449	17.6	2.8	1.6		2.8
LAV 3	12:51	SA04663234	17900	11550	24.1	1.5	0.9		1.5
Mean LAV			21066.7	9108	19.0		1.4	1.7	2.3
PIVC 1	12:53	SA04663214	865	480	1.0	1.8			
Peripheral 1	11:56	SA04663228	331	146	0.3	2.3			
Peripheral 2	12:35	SA04663189	850	518	1.1	1.6			

Key:	
RAV	Right Adrenal Vein
LAV	Left Adrenal Vein
PIVC	Peripheral Inferior Vena Cava
PFEM	Peripheral Femoral Vein
UTC	Unable to calculate
*	Not assayed in dilution
AV/PV	Adrenal Vein to Peripheral Vein Ratio
ACR	Adrenal to Cortisol Ratio

Mean peripheral	
Aldosterone	865
Cortisol	480

Table 1 – Results and calculations done in Excel.

Other Investigations

Not available for this patient.

Ideally one would need a CT with contrast beforehand to adequately visualize the positions of the adrenal veins, as this may aid in the canulation, especially of the right adrenal vein.

One needs to diagnose hyperaldosteronism (by an appropriate salt loading test) before proceeding to bilateral adrenal vein sampling.

Final Diagnosis

Interpretation

Definition	Formula	Clinical significance

Selectivity index	PCC(side) / PCC (ivc)	>cutoff **confirms canulation** of adrenal vein >3 stimulated >2 unstimulated
Lateralization index	PAC/PCC (dom) : PAC/PCC (non-dom)	>cutoff **confirms laterilization** of hyperaldo secretion >4 stimulated >2 unstimulated
Contralateral suppression index (used if inadequate canulation)	PAC/PCC (non-dom) : PAC/PCC (ivc)	<cutoff (<1 or <0.5 – sources differ) **indicate ipsilateral suppression** and suggest contralateral aldosterone overproduction.

Table 1 – Interpretation of bilateral adrenal vein sampling. PCC: plasma cortisol concentration, PAC: plasma aldosterone concentration, ivc: inferior vena cava or peripheral vein, dom: dominant side, non-dom: non-dominant side.

Selectivity index

Right: 1.0 (mean)

Left: 19.0 (mean)

These two results indicate that the left adrenal has been canulated adequately, but the right vein inadequately.

Lateralization index

Unable to comment because of the inadequate canulation of the right adrenal vein. If determined, it would very likely provide a false result.

Contralateral suppression index

1.5 : 1.8 = 0.8

This falls in between some of the referenced cutoffs (<1 and <0.5)

All of the other samples also fall somewhere in this range. Biochemically, these results suggests inadequate right sided venous sampling (a commonly described problem)

Take Home Message

- Procedure is done in the Cath Lab
- The patient received continuous synacthen infusion – as this improves the sensitivity (or perhaps rather specificity) of the test.
- Done under imaging with contrast used for the localisation of the adrenal gland and adrenal vein
- Sequential sampling technique used, generally > 20 mins infusion
- Multi-disciplinary: nurses, anaesthetist, radiographer, intervention radiologists, students, chemical pathologists
- Difficulty with sampling right side for both patients
- Difficulty with interpreting results – most likely due to inadequate canulation of the right adrenal vein

Some important learning points

1. Adrenal vein sampling may be a valuable tool that is underutilised
2. Careful selection of patients essential – also patient should consent to surgical removal of the affected adrenal before this invasive procedure is initiated
3. Inter-disciplinary approach is necessary
4. Obtaining cosyntroponin (aka synacthen) can be difficult (Section 21), but recommended.

5. Right adrenal access difficult: may require specific imaging. Recommended to start on the right or do simulataneous sampling.
6. Adrenalectomy may be curative or help achieve better control of BP thus decrease associated morbidity and mortality in those with unilateral adenoma

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A likely case of thyrotoxic periodic paralysis

Patient presented with a few isolated episodes of muscle weakness. This progressed from 2 weeks before, during the index episode, to become so severe that he couldn’t walk.

Conn’s syndrome with a focus on a unilateral adrenal gland

HOSP #	Mrs DW	**WARD**	Endocrine Department – CathLab – UCT private Hospital
CONSULTANT	Dr Jody Rusch	**DOB/AGE**	49y Female

Abnormal Result

49yr old female

Presenting Complaint

Medical complaint: Suspected Conn’s disease – right adrenal lesion/ irregular left adrenal gland

History

Past Medical History: Resistant Hypertension, primary hyperaldosteronism (confirmed previously with saline infusion test), hypokalaemia, hypercholesterolaemia, newly diagnosed DM.

Family History: Hypertension – Mother.

Past Surgical History: TAH – 7 years ago.

Allergies: Nil known

Smoker

Meds: Amlodipine/Valsartan 10/320 daily, Doxazosin 8mg daily, Furosemide 40mg daily, Spironolactone 25mg daily, Carvedilol 25mg daily, Metformin 1g nocte, Simvastatin 20mg nocte, Zolpidem 10mg nocte.

Examination

Not available

Laboratory Investigations

	A	B	C	D	E	F	G	H	I	J
1		Time	Aldosterone	Aldosterone	Cortisol	Selectivity Index	ACR	Lateralisation Index		
2			Episode	pmol/L	nmol/L	Cortisol AV/PV		Dom A/C : nonDom A/C	Mean Aldo/Cort RAV	Aldo/Cort LAV
3	RAV 1	10:10	SA04663221	1310	659	0.2	2.0			
4	RAV 2	10:36	SA04663224	1490	681	0.2	2.2			
5	RAV 3	10:36	SA04663229	INS	712	0.2	#VALUE!			
6	RAV 4	10:39	SA04663232	771	340	0.1	2.3			
7	RAV 5	10:49	SA04663235	1470	692	0.2	2.1			
8	Mean RAV			1260.25	616.8	0.2			2.0	
9	LAV 1	10:01	SA04663256	2160	10790	3.0	0.2	0.1		0.2
10	LAV 2	10:02	SA04663250	3210	14540	4.0	0.2	0.1		0.2
11	LAV 3	10:03	SA04663242	5260	2621	0.7	2.0	1.0		2.0
12	LAV 4	10:59	SA04663238	2760	11870	3.3	0.2	0.1		0.2
13	LAV 5	10:03	SA04663246	3590	10770	3.0	0.3	0.2		0.3
14	Mean LAV			3396	10118.2	2.8				0.3
15	PIVC 1	11:00	SA04663213	2540	3609					
16	PFEM 1	9:43	SA04663217	803	301					
17	Arm	10:12	SA04663208	1330	724					
18										
19	Key:									
20	RAV	Right Adrenal Vein								
21	LAV	Left Adrenal Vein								
22	PIVC	Peripheral Inferior Vena Cava								
23	PFEM	Peripheral Femoral Vein								
24	UTC	Unable to calculate								
25	*	Not assayed in dilution								
26	AV/PV	Adrenal Vein to Peripheral Vein Ratio								
27	ACR	Adrenal to Cortisol Ratio								

Peripheral	
Aldosterone	2540
Cortisol	3609

Other Investigations

Not available for this patient.

Ideally one would need a CT with contrast beforehand to adequately visualize the positions of the adrenal veins, as this may aid in the canulation, especially of the right adrenal vein.

One needs to diagnose hyperaldosteronism (by an appropriate salt loading test) before proceeding to bilateral adrenal vein sampling.

Final Diagnosis

Interpretation

Definition	Formula	Clinical significance
Selectivity index	PCC(side) / PCC (ivc)	>cutoff confirms canulation of adrenal vein >3 stimulated >2 unstimulated

Lateralization index	PAC/PCC (dom) : PAC/PCC (non-dom)	>cutoff confirms laterilization of hyperaldo secretion >4 stimulated >2 unstimulated
Contralateral suppression index	PAC/PCC (non-dom) : PAC/PCC (ivc)	<cutoff indicate ipsilateral suppression and suggest contralateral aldosterone overproduction.

Table 1 – Interpretation of bilateral adrenal vein sampling. PCC: plasma cortisol concentration, PAC: plasma aldosterone concentration, ivc: inferior vena cava or peripheral vein, dom: dominant side, non-dom: non-dominant side.

Selectivity index

Right: 0.2 (mean)

Left: 2.8 (mean)

These two results indicate that the left adrenal has likely been canulated adequately, but the right vein inadequately.

Lateralization index

Unable to comment because of the inadequate canulation of the right adrenal vein. If determined, it would very likely provide a false result.

Contralateral suppression index

616.8 /1260.25 : 2540/3609

= 0.70

This falls in between some of the referenced cutoffs (<1 and <0.5)

All of the other samples also fall somewhere in this range. Biochemically, these results suggests inadequate right sided venous sampling (a commonly described problem)

Take Home Message

- Procedure is done in the Cath Lab
- The patient received continuous synacthen infusion
- Done under imaging with contrast used for the localisation of the adrenal gland and adrenal vein
- Sequential sampling technique used, generally > 20 mins infusion
- Multi-disciplinary: nurses, anaesthetist, radiographer, intervention radiologists, students, chemical pathologists
- Difficulty with sampling right side for both patients
- Difficulty with interpreting results – most likely due to inadequate canulation of the right adrenal vein

Some important learning points

1. Adrenal vein sampling may be a valuable tool that is underutilised
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3. Inter-disciplinary approach is necessary
4. Obtaining cosyntroponin (aka synacthen) can be difficult (Section 21), but recommended
5. Right adrenal access difficult: may require specific imaging. Recommended to start on the right or do simulataneous sampling
6. Adrenalectomy may be curative or help achieve better control of BP thus decrease associated morbidity and mortality in those with unilateral adenoma

Amiodarone-induced hyperthyroidism

An interesting case of Amiodarone – induced hyperthyroidism