Factors that impact the control of an ‘orphan’

and should nephrologists be concerned?

Mr A (dob 1985)

- Admitted with malaise and tetany.
- Jan 2018 2 episodes of collapse
- June 2018 Burn. Rx Flucloxacillin
- July 2018 Serum K 2.3mmol/L
  Serum Mg 0.53mmol/L

Rx iv supplements

1/52 later K 3.4 & Mg 0.67

Differential diagnosis ?

What other investigations?

Mr A

- Check serum bicarbonate
- X ray knees - ?why
- Urinary calcium – what would you expect?

Mr A

- Check serum bicarbonate 32 umol/L
- X ray knees - chondrocalcinosis
- Urinary calcium – hypocalciuria

What treatment would you advise?

- Potassium chloride syrup 25ml gds
- Magnesium lactate 5tabs bd
- Potassium chloride 600mg 2tabs qds
- Slow sodium 600mg 2 tabs qds

Gitelman Syndrome

- Caused by recessive mutations in the gene coding for the thiazide-sensitive sodium cotransporter (SLC12A3).
- Characterized by:
  - salt wasting
  - hypokalaemic metabolic alkalosis,
  - hypomagnesaemia
  - hypocalciuria

Ms B – born 1973

- 2000 & 2004 LSCS
  - Uncomplicated but low potassium noted
- 2006
  - Lethargy & cramps
- 2008
  - Referred on account of hypokalaemia

Ms B

- Past History
  Infantile epilepsy
  Right ovarian cystectomy
  Sero negative arthritis
- Cramps
  Palpitations
  Lethargy and tiredness

Ms B

- February 2008

  Na 139; K 2.5; Cl 99; Bicarb 30

  Urea 3.0; Creatinine 58

  Ca 2.25; PO4 1.2; Mg 0.5

Ms B

- Differential diagnosis
  - Gitelman's syndrome
  - Interstitial nephritis
  - Diuretic abuse
  - Vomiting

- SLC12A3 mutations
  - c. 1925A>G and c.2965G>A

Ms B
Treatment

- Slow sodium 600mg 6 tabs daily
  Potassium chloride 600mg 12 tabs daily
  Magnesium lactate 10 tablets daily

Ms B
Current biochemistry

- Na 141; K 2.5; Cl 94; Bicarb 28
  Urea 6.4; Creatinine 64
  Ca 2.25; PO4 1.13; Mg 0.49

Bartter and Gitelman syndromes

Fred Bartter 1962; Hillel Gitelman 1966
Hypokalemic alkalosis with enlarged JGA
Autosomal recessive
Many candidate genes, much diagnostic confusion
Bettinelli 1992

	Type 1 / 4 Bartter	Type 2 Bartter	Type 3 Bartter	Gitelman
Age at diagnosis	Infancy (polyhydramnios)	Infancy (polyhydramnios)	Variable	Variable
Symptoms	Dehydration Failure to thrive Deafness	Dehydration Failure to thrive	Variable	Tetany, chondrocalcinosis
K^+	Low	Low w/ salt repletion	Low	Low
Mg^{++}	Normal	Normal	Normal	Low
Urine Ca^{++}	High	High	Normal or high	Low
Nephrocalcinosis?	Yes	Yes	No	No
Gene	*NKCC2/BSND1*	*ROMK*	*CLCNKB*	*NCCT*

A Nephrologist - 2009

Hypomagnesaemia

- GI loss
- Gentamicin
- Diuretics
- Alcoholism
- Gitelman Syndrome

Hypermagnesaemia

- Renal impairment with magnesium containing medication

Mr C [born 1940]

- 2005 Presented with swollen ankles.
  Proteinuria Not diabetic
  Creatinine 366umol/L
  Calcium 2.05mmol/L
  Phosphate 3.15mmol/L
  Magnesium 0.8mmol/L
- 2005 Focal segmental glomerulosclerosis
  Haemodialysis
  CAPD
- 2011 Transplanted (LKD-daughter)

Mr C

- 2012 BMI 28
  Creatinine 91
  Glucose 12.1

  New onset diabetes after transplantation [NODAT]

Mr C

- Drugs
  - Tacrolimus
  - Mycophenolate mofetil
  - Alfacalcidol
  - Calcium carbonate
  - Simvastatin
  - Omeprazole

Mr C

- Nov 2017 Hb 90 g/L
  MCV 122
  Vitamin B12 <100
  Rx. Hydroxocobalamin

- Jan 2018 Hb 137 g/L
  Weak; Cramp; Palpitations
  Creatinine 128
  Calcium 2.01mmol/L
  Magnesium 0.49mmol/L

Mr C

- Possible causes of hypomagnesaemia
  - Renal transplant
  - Tacrolimus
  - Omeprazole

- Omeprazole stopped
  Alfacalcidol increased
  Magnesium L-lactate dihydrate

Mr C

- March 2018
  - Admitted with fever & tender transplant
  - Loss of control of legs
  - Presumed urosepsis
    - Creatinine 312umol/L
    - Calcium 1.08 mmol/L
    - Phosphate 1.36 mmol/L
    - Magnesium 0.22 mmol/L

- Mg & Ca IV; Alfacalcidol increased; Antibiotics

- May 2018 Ca 2.38; PO4 1.14; Mg 0.62; Creatinine 124

Mr C - Summary

- 77 yr old man with renal transplant who developed NODAT and was noted to have become hypomagnesaemic

Hypomagnesaemia
Should we be concerned?

- Neuromuscular

  Tetany, Convulsions, Weakness, Apathy & Coma

- Cardiovascular

  Widening QRS & PR interval; Arrhythmias

- Abnormalities of calcium metabolism

  Hypocalcaemia and hypoparathyroidism

- Hypokalaemia
- Insulin resistance; Increase NODAT

Hypomagnesaemia in patients with a renal transplant

- 495 patients
- 303 [61%] had had a magnesium level during past 5 years.
- Of these 199 [66%] Mg > 0.6 mmol/L
- 104 [34%] Mg < 0.6 mmol/L [*Omeprazole*]
- 192 [39%] had not had a magnesium measured

Magnesium [Mg] – units of measurement

- Mg mainly intracellular principally in bone.
  In extracellular fluid Mg can be ionised, bound to anions or bound to protein.
- Serum Mg 0.7-0.85 mmol/L
  Total body Mg 11.4 – 17.5 mmol/Kg

  mmol/L = [mg/dl x 10] / mol wt [24.3]

  mEq/L = mmol/L x valence [x2]
- Daily magnesium intake 15mmol
  Daily absorption 5mmol
  Intestinal loss 0.9mmol
  Urine 4.1mmol

Regulation of plasma Mg

- Mg treated by body as an orphan – no hormones to control urinary excretion and bone does not readily exchange with circulating Mg.
- Control is dependent on urinary retention or excretion [mainly loop of Henle and distal tubule].

Regulation of Magnesium Homeostasis

GI Tract

Magnesium

(Passive diffusion)

Blood

Bones

(Glomerular Filtration)

Mg

(Passive diffusion)

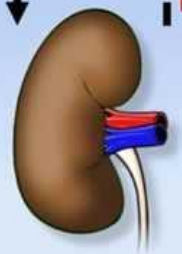
+ Claudin-16

- ↓ plasma K

- ↑ plasma Ca

- ↑ plasma Mg

- ↓ serum pH



Kidneys

There are no known hormones or enzymes that directly regulate magnesium balance

Electrolytes

Non-Hormone, Non-Enzyme Protein

Causes of Hypomagnesaemia

- Gastrointestinal [lower > upper]
  - PPI’s
- Renal losses
  - Drugs
  - Alcohol
  - Uncontrolled diabetes
  - Post transplant patients
  - Inherited tubular defects

Hospital referral (2010)

“Please see this 39yr old woman whose eGFR is 36ml/min . She has diabetes mellitus and has been investigated by the hepatologists because of abnormal LFT’s.”

Ms D – born 1971

- Portuguese
  Father recently developed DM
  Maternal aunt DM
- 1994 – developed diabetes
  No DKA but started Insulin soon.
- 1996 – bifid uterus noted on investigation of infertility.

Ms D

- 2000 – Abnormal liver function tests
  Liver biopsy Portugal – ‘normal’
- 2002 – Creatinine 128µmol/L
- 2010 – Multiple renal cysts (L kidney 11.8
  R kidney 10cm)
- 2010 – ALT 71; Alk Phos 182
  - MR cholangiogram – atrophic pancreas.

Clinical examination in 2010

- BMI 24.6
- BP 110/70 [No drugs]
- Urinalysis: Prot Neg; Blood Neg; Glucose ++
- No neuropathy
- No retinopathy
- Medication: Insulin
  Alfacalcidol
  Ursodeoxycholic acid
- Creatinine 144 umol/L

Assessment

- 1. Could it be diabetic nephropathy?
  Type 1 v 11
- 2. Might she have PCKD?
- 3. Is there an alternate explanation?

What other investigations might help in this scenario?

Assessment

- 1. Could it be diabetic nephropathy?
  Type 1 v 11
- 2. Might she have PCKD?
- 3. Is there an alternate explanation?

Urate 484 umol/L
Magnesium 0.58mmol/L

Ms D.

- 2012 – urinary microalbumin 2.9 (<3.5)
- 2013 – Wt 64 Kg; BP108/72 (no drugs)
  Creatinine 144µmol/L
  Alk phos 421 (35-104)
  ALT 207 (<33)
- 2019 – Creatinine 176µmol/L
  ALT 29 Alk Phos 198
  Urinary PCR 32

Summary

- 46 year old woman with:
  Progressive CKD
  DM but no proteinuria
  No neuropathy nor retinopathy
  Abnormal LFT's
  Bifid uterus; Renal cysts;
  Atrophic pancreas
  Low magnesium
  High urate

?diagnosis

Hospital referral (2016)

- ‘Please see this 20 year old lad who has diabetes and an eGFR of 26ml/min. He does not have hypertension or proteinuria but his liver function is abnormal. His BMI is 22.’

Mr E – born 1996

- Diabetes (aged 5)
- Renal dysplasia/cysts (creat 273; eGFR 26)
  Hypothyroidism (TSH > 100; T_4 6.7)
- Diabetic control recently improved
  HbA1c 120.....76
  No microalbuminuria
- Mother, maternal grandfather and paternal grandfather have diabetes
  Half sister renal cysts aged 3 & CKD
- Serum magnesium 0.63mmol/L; Urate 460

Summary

- 20 year old man with:
  Progressive CKD
  DM but no proteinuria
  No neuropathy nor retinopathy
  Abnormal LFT's
  Renal cysts
  Hypothyroid
  Low magnesium
  High urate ? diagnosis

Genetic testing (D)

- Dosage analysis of her HNF1β gene shows a heterozygous whole gene deletion (c.1-?_1674+?del).
- This mutation is predicted to be pathogenic and the result confirms a diagnosis of ‘Renal cysts and Diabetes (RCAD) syndrome’
- Each of her offspring will be at 50% risk of inheriting the mutation.

Genetic testing (E)

- Dosage analysis of his HNF1β gene shows a heterozygous missense mutation (p Arg.276GLn).
- This mutation is predicted to be pathogenic and the result confirms a diagnosis of ‘Renal cysts and Diabetes (RCAD) syndrome’
- Each of his offspring will be at 50% risk of inheriting the mutation.

HNF1-β

- Also known as transcription factor 2 is involved in early stages of embrionic development of several organs including the kidney, liver, pancreas and genital tract.

Phenotype of individuals with RCAD (HNF1beta) mutation.

- Renal dysplasia / cysts
- Diabetes 58% (Mean age of diagnosis 25yrs)
- Uterine malformations 14%
- Male genital malformation 5%
- Hyperuricaemia 20%
- Abnormal LFTs 13%
- Mutations in HNF1beta are the most common genetic cause of hypomagnesaemia

Maturity onset diabetes of the young [MODY]

Classification	Gene mutation	Comments
MODY 1	HNF 4 alpha	Responsive to sulphonylureas. May later need Insulin
MODY 2	Glucokinase	Often asymptomatic. May not require treatment
MODY 3	HNF1 alpha	Most common form of MODY in UK
MODY 5	HNF1 beta	Associated with renal cysts, uterine abnormalities, gout

Maturity onset diabetes of the young (MODY) – monogenic diabetes

- Autosomal dominant
- Mutations of HNF-1α on chromosome 12q is the commonest cause of MODY
- The HNF-1α and HNF-1β proteins show >80% homology and bind to the same DNA sequence.
- HNF-1β (located on chromosome 17q) mutation first demonstrated in Japanese family in 1997.
- HNF-1β mutations rare cause of MODY (1%) in UK....known as MODY5
- HNF-1β mutations responsible for Renal Cysts and Diabetes syndrome…..as well as other systemic manifestations.

Message

- Consider RCAD / MODY5 in patients with diabetes and structural abnormalities of the kidney.
- Get U/S in patients with impaired renal function who have diabetes but not microalbuminuria or hypertension.
- Consider genetic abnormalities as cause of hypomagnesaemia

E.
MODY 5 and hypothyroid

‘value of Smartphone text message’

and impact of hypothyroidism on renal function

Date	TSH	T4	Creatinine
04/16	**>100**	4.1	273
05/17	**>100**	3.2	322
12/17	**>100**	7.2	267
02/18	**0.26**	38.1	224
04/19	**4.27**	21.1	226

Ms F (born 1967)

- October 2001
  Right loin pain; Febrile
  Blood cultures – E coli

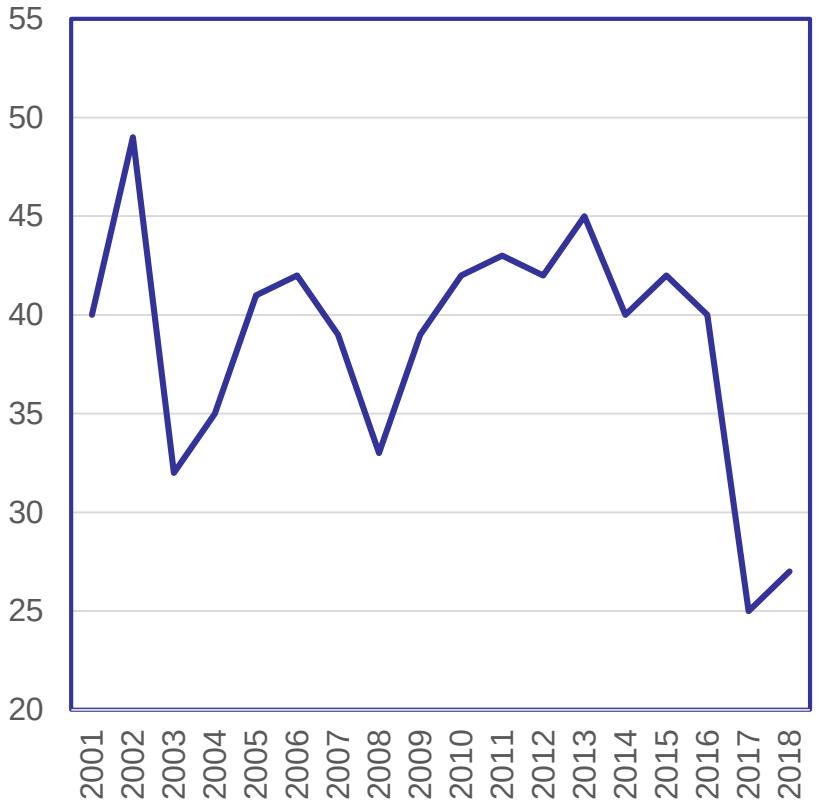
  Na 137; K 3.0; Cl 74; HCO3 46
  Urea 10; Creatinine 107; Urate 710
  Ca 2.3; PO4 1.1; Mg 0.56
- Pyelonephritis – treated antibiotics

Ms F

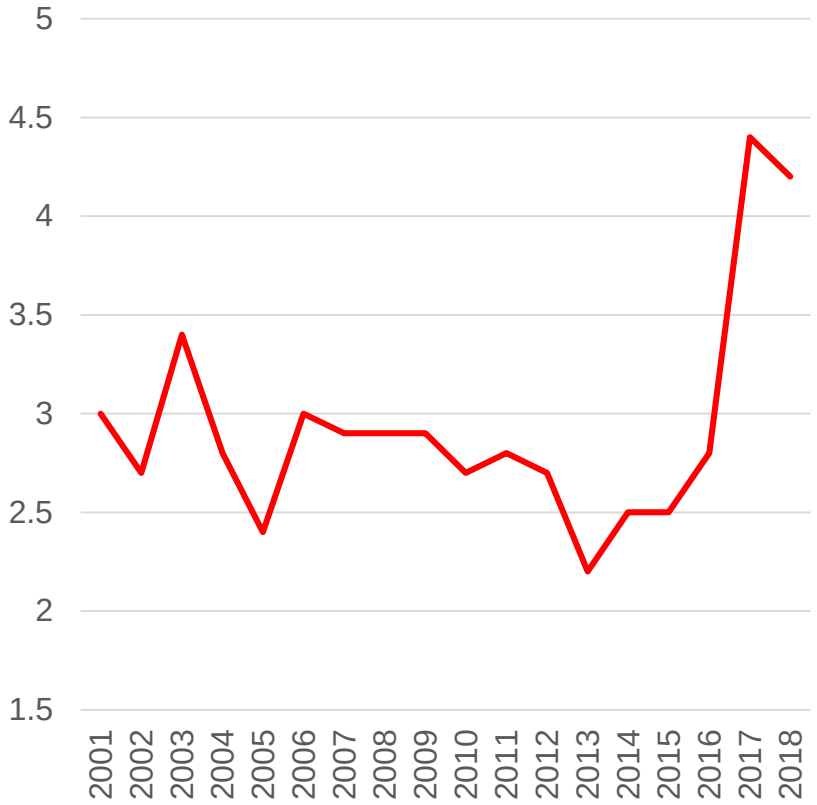
- 2001 – 2016
  Persistent hypokalaemic hypochloraemic metabolic alkalosis with hyperuricaemia and low magnesium.

Ms F

Serum Bicarbonate



Serum Potassium



Ms F

- April 2018
  - Sodium 134 mmol/L
  - Potassium 4.2 mmol/L
  - Chloride 96 mmol/L
  - Bicarbonate 27 mmol/L
  - Urea 7.3 mmol/L
  - Creatinine 90umol/L
  - Magnesium 0.89 mmol/L
  - Urate 310

Hypomagnesaemia for the nephrologist

- Drugs
  - Diuretics (Thiazides & Loop diuretics)
  - PPIs (Omeprazole)
  - Antibiotics (Gentamicin)
  - Calcineurin inhibitors (Tacrolimus)
- Genetic causes
  - Gitelman's syndrome
  - Hypercalciuric hypomagnesaemic syndrome.
  - Renal cyst / diabetes syndrome
- Others
  - Recovery from AKI and urinary obstruction
  - Renal transplant

Inherited hypomagnesaemia

- Familial renal magnesium wasting
- Gitelman and Bartter syndrome
- EAST syndrome [Epilepsy, Ataxia, Sensorineural deafness, Tubulopathy]
- Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis
- Hepatocyte nuclear factor-1-beta gene mutations
- Epidermal growth factor gene mutation

Other Drugs causing hypomagnesaemia

- Aminoglycosides
- Amphotericin
- Cisplatin
- Pentamidine
- Calcineurin inhibitors [Tacrolimus>CiA]
- Epidermal growth factor receptor [EGFR] Ab [cefuximab; panitumumab colorectal]
- EGFR tyrosine kinase inhibitors [afatinib; erlotinib lung]
- Human epidermal growth factor receptor 2 [HER2] inhibitors [trastuzumab; pertuzumab breast]
- ? Vascular endothelial growth factor [VEGF] pathway inhibitors

Hypomagnesaemia

Should we pay more attention to it?