

## Genetic renal tubule and metabolic disease

Including: Proximal renal tubular acidosis (RTA); distal RTA; nephrogenic diabetes insipidus  
Cystinosis; atypical haemolytic uraemic syndrome (HUS); Fabry's disease; Batter's syndrome; Gitelman's syndrome; Liddle's syndrome

### Proximal renal tubular acidosis (RTA)

- The proximal tubule is responsible for reabsorbing filtered bicarbonate, no acid is excreted
- Thus, you get bicarbonate wasting and consequent systemic acidosis
- Genetics of proximal renal tubular acidosis
  - Autosomal recessive if "proximal RTA syndrome"
  - Hypophosphatemic rickets can be AR or XD
  - Renal glucosuria is AR
  - Cystinosis is AR
  - Wilson's disease AR
- Presentation of proximal renal tubular acidosis
  - Normal anion gap acidosis with hyperchloraemia
  - If other features of proximal dysfunction (glycosuria, phosphaturia and aminoaciduria) then termed Fanconi syndrome
- Investigations of proximal renal tubular acidosis
  - Urine pH <5.3
  - Low serum potassium – as a larger sodium load hits the distal nephron (due to proximal dysfunction) you get hyperaldosteronism and consequent attempts to increase sodium intake and wasting of potassium.
  - Low serum bicarbonate (10-20mmol/L)
  - If tested may find high urinary glucose, phosphate, amino acids, urinary citrate (which all may be low in serum)
  - If you give a bicarbonate challenge then the bicarbonate will overload the already struggling proximal tubule and urinary pH will increase to >7 (done by specialist centre)
- Treatment of proximal renal tubular acidosis
  - Allow acidosis if mild
  - Thiazide diuretics
  - Potassium bicarbonate
  - Giving sodium bicarbonate (much like the investigative test) serves to make things worse by driving the process as described above, worsening hypokalaemia)

### Distal renal tubular acidosis (RTA)

- Failure of hydrogen ion excretion (alpha intercalated cells of distal nephron)
- Nephrocalcinosis is a cause, rarely inherited
- Presentation of distal renal tubular acidosis (RTA)
  - Normal anion gap metabolic acidosis with hyperchloraemia and hypokalaemia
  - Hypophosphataemia (phosphate is used to buffer the acidaemia) – this is leached from the bones along with calcium and leads to metabolic bone disease, renal stones and nephrocalcinosis
- Investigations in distal renal tubular acidosis (RTA)
  - Low serum potassium
  - Low bicarbonate <12mmol/L

- Raised urinary calcium
- Low urinary citrate (this is a buffer so is used up systemically)
- Raise urinary pH
- The commonest causes are autoimmune disease esp Sjorgens so ANA, anti-Ro/La, Rf etc.
- Specific tests to unmask distal RTA:
  - Furosemide and fludrocortisone challenge OR
- Acid loading test
- Treatment of distal renal tubular acidosis (RTA)
  - Potassium citrate OR sodium bicarbonate

### **Nephrogenic diabetes insipidus**

- XD or AR
- Causes defects in AVPR2, arginine vasopressin receptor 2 or aquaporin-2
- Presents as polyuria and polydipsia (from childhood)
- Investigations:
  - Measure serum and urine osmolality = raised plasma osmolality with inappropriately dilute urine
  - Definitive testing with water deprivation test
    - After 8 hours of water deprivation if urine osmolality <600 Osmol/kg then desmopressin given – if urine concentrates then it is cranial DI, if no effect it is Nephrogenic
- Treatment: Thiazide diuretics (induce mild hypovolaemia ) or NSAIDS (interfere with ADH functioning) – note if not a major problem then conservative management could be indicated.

### **Cystinosis (NOT cystinuria)**

- AR
- Gene encodes: CTNS, lysosomal membrane protein
- Presents as: Renal Fanconi's syndrome, renal failure in childhood
- Cystine deposits in all major tissues giving ocular problems, organomegaly, hypothyroidism and diabetes.
- Treat with cysteamine which complexes with cystine

### **Atypical haemolytic uraemic syndrome**

- AR
- Incorrectly coded proteins: Complement factor H; complement factor H-related 1; complement factor H-related 3; CD46; ADAMTS13 (AD)
- Presents with: Thrombocytopenia, haemolytic anaemia and acute renal failure
- Investigations: bloods including clotting and platelet count, blood film for MAHA, renal function etc
- Treatment: Includes plasma exchange - controversial, Eculizumab (humanized anti-C5 monoclonal antibody) is licensed (blocks complement activation)

### **Fabry's disease**

- XR (Xq22)
- $\alpha$ -galactosidase A protein encoded
- Lysosomal storage disease
- Presents with: Angiokeratoma, FSGS, adult-onset CKD but also cardiac, CNS, ophthalmic and pulmonary disease
- Treatment: Recombinant alpha-Gal A enzyme replacement therapy

### **Barter's syndrome – like a LOOP DIURETIC**

- AR
- A number of types affecting a host of tubular transport proteins (sodium-potassium-chloride transporter, chloride channel Kb, potassium inwardly rectifying channel; barttin)
- Pathology arises from Thick ascending loop of Henle
- Salt wasting, volume deplete state leads to hyperaldosteronism and hyper-reninism.
- Presents with: Hypokalaemic alkalosis, hypercalcuria, polyuria, growth retardation, hypomagnesaemia. May have mildly low BP.
- Note BP is low/normal (as opposed to high) as there is a concurrent prostaglandin increase (PGE) to offset raised angiotensin II (via increased RAAS)
- Treatment: Amiloride and potassium supplementation 1<sup>st</sup> line. Can treat with NSAIDS to counter prostaglandin synthesis if troublesome
- Gordon's syndrome is the polar opposite syndrome and very rare

### **Gitelman's – like a THIAZIDE DIURETIC**

- AR
- Defect in SLC12A3; thiazide-sensitive sodium-chloride cotransporter
- Encoding in the distal convoluted tubule
- Presents with hypokalaemic metabolic alkalosis, hypocalciuria, hypomagnesaemia and hypotension
- Note no raise in urinary PGE unlike Bartter's
- Treat with Amiloride and potassium supplements

### **Liddle's – like LIQUORICE POISONING**

- AD
- Gain of function mutation in epithelial sodium channel (ENaC) in the collecting duct
- Overexpression leads to huge reabsorption of sodium ions and consequent hypertension
- Large sodium influx leads the tubular lumen electronegativity leading to potassium influx to correct this – thus hypokalaemic metabolic alkalosis
- Presents with hypertension, hypokalaemia and LOW aldosterone. Aldosterone is appropriately suppressed due to sodium uptake being normal (as detected by JGA) – this is a cause of pseudohyperaldosteronism
- Treat with low salt-diet and Amiloride.
- Liquorice poisoning:
  - If you eat liquorice you inhibit the function of 11-beta-hydroxysteroid dehydrogenase
  - This enzyme is responsible for inactivating cortisol
  - Cortisol has a potent effect on mineralocorticoid receptors but the normal function of 11-beta-hydroxysteroid dehydrogenase acts to inactivate it prior to working. The concentration of cortisol is significantly greater than that of mineralocorticoids in the body.
  - Thus, if you inhibit 11-beta-hydroxysteroid dehydrogenase by eating a large amount of liquorice (note it must be "natural" liquorice containing glycyrrhizic acid which is the compound inhibiting the enzyme) you allow unopposed cortisol action on mineralocorticoid receptors.
  - In the tubular cells this leads to pseudohyperaldosteronism and the same effects as Liddle's

