Renal Tubular Disease

There are various disorders of tubular function, both generalised and specific. These disorders may be isolated defects, generalised tubular defects, as in Fanconi’s syndrome, or associated with more generalised disease processes.

Presentation[1]

Clinical features suggestive of renal tubular disorders include:

- Growth restriction, failure to thrive.
- Polyuria, polydipsia.
- Refractory rickets.
- Renal calculi, nephrocalcinosis.
- Unexplained hypertension.

Laboratory features include:

- Hyperchloraemic metabolic acidosis.
- Metabolic alkalosis with or without hypokalaemia.
- Hyponatraemia with hyperkalaemia.
- Hypercalciuria with normal serum calcium.

Fanconi's syndrome

See separate Renal Fanconi Syndrome article.

Renal tubular acidosis

Type 1 (classic distal) renal tubular acidosis[2]

- Inability to form an acid urine in the distal tubule[3].
- May be inherited as a primary disorder or associated with autoimmune disorders (eg, Sjögren's syndrome, systemic lupus erythematosus (SLE)) [4], hyperparathyroidism, analgesic nephropathy, renal transplant rejection, obstructive uropathy and chronic urinary tract infections (UTIs).
- Without treatment, it leads to growth restriction and progressive renal failure.
- Presentation:
  - Hyperventilation, muscle weakness, cardiac arrhythmias (hypokalaemia) and bone pain (due to rickets or osteomalacia).
  - Renal calculi, recurrent UTI, chronic kidney disease.

- Investigations:
  - Hypokalaemia, hyperchloraemic metabolic acidosis.
  - Urinary pH is above 6, hypercalciuria.

- Treatment[5]
  - Acute: correct hypokalaemia before acidosis.
  - Chronic: oral bicarbonate; long-term potassium supplements are usually not required, as alkali therapy prevents excessive urinary potassium loss.
Type 2 (proximal) renal tubular acidosis
- May occur in isolation but is more often associated with other tubular defects as part of Fanconi's syndrome.
- Defective bicarbonate reabsorption in the proximal tubule leads to an excess of bicarbonate in the urine\[^6\].
  - Presentation:
    - Polyuria, polydipsia, proximal myopathy.
    - Osteomalacia or rickets.
  - Investigations:
    - Hypokalaemia, hyperchloremic metabolic acidosis.
  - Treatment:
    - High doses of bicarbonate are required but the prognosis is good. Correcting acidosis and low potassium levels allows normal growth and prevents bone disease; however, vitamin D supplements may also be required.
    - Hydrochlorothiazide can be added to create mild volume depletion and increase proximal tubular resorption if bicarbonate level fails to rise; however, if this is done, potassium supplementation needs to be increased\[^5\].

Type 3 renal tubular acidosis\[^7, 8\]
It is not clear whether this is a specific entity in itself or a combination of type 1 and type 2.
- There is impaired proximal bicarbonate resorption and impaired distal acidification. It is a rare entity. An inherited form due to recessive mutation has also been reported. Iatrogenic causes include acetazolamide and topiramate.
- Osteopetrosis marble bone disease) and cerebral calcification can occur, in association with renal tubular acidosis. This is called Guibaud-Vainsel syndrome, or marble brain disease. Conductive hearing loss and sight impairment can occur due to excessive bone growth and nerve pressure.
- Treatment:
  - Needs to be individualised to the patient's biochemical status, depending on whether proximal or distal renal tubular acidosis predominates.

Type 4 (hyperkalaemic) renal tubular acidosis\[^7\]
- Occurs in diseases associated with reduced aldosterone activity; causes include:
  - Addison's disease, inborn errors of steroid metabolism, diabetes mellitus, SLE, amyloidosis, chronic tubulointerstitial disease.
  - Drugs: angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, potassium-sparing diuretics, non-steroidal anti-inflammatory drugs (NSAIDs).
  - Mineralocorticoid deficiency: reduced hydrogen secretion in the distal nephron causes reduced ammonium excretion.
  - Presentation:
    - Urinary pH below 5.4.
    - Hyperkalaemia\[^8\], hyperchloremic metabolic acidosis.
  - Treatment:
    - Fludrocortisone is required if there is acidosis or hyperkalaemia\[^10\].

Glycosuria
See separate Glycosuria article.
Nephrogenic diabetes insipidus

See also separate Diabetes Insipidus article.

- Caused by renal insensitivity to antidiuretic hormone.
- It may be primary (familial, X-linked) or secondary to a number of causes:
  - Drugs - eg, lithium, diuretics.
  - Metabolic: hypokalaemia, hypercalcaemia.
  - Tubulointerstitial disease: partial obstruction, pyelonephritis, cystic diseases, granulomatous diseases, sickle cell disease.
- Presents with polyuria, hypernatraemia and uraemia.

Phosphate-handling disorders\[11\]

- The kidney is largely responsible for controlling extracellular phosphate levels, under the control of parathyroid hormone.
- There are several types of phosphate transport defect causing hypophosphataemia and inappropriate phosphaturia\[12\]. The most common forms include:
  - Hereditary hypophosphataemic rickets (vitamin D-resistant rickets).
  - Hypophosphataemia with rickets or osteomalacia.
- Presents with growth restriction and early bone deformity.
- Does not respond to vitamin D but resistance to 1,25-dihydroxyvitamin D only occurs with functional defects of the vitamin D receptor.
- Treatment is with 1,25-dihydroxyvitamin D plus amiloride and thiazide to reduce calcium reabsorption.
- X-linked hypophosphataemic rickets:
  - Is the most common cause of an isolated defect in tubular phosphate reabsorption.
  - Presentation is with poor growth and rickets in early childhood.
  - There is a defect in proximal tubular phosphate transport that results in persistent hypophosphataemia and inappropriate phosphaturia.
  - Large doses of oral phosphate supplements are required, together with 1,25-dihydroxyvitamin D.
  - Hypoparathyroidism and pseudohypoparathyroidism (renal resistance to parathyroid hormone) causing reduced renal phosphate excretion.

Calcium-handling disorders

Relatively common disorders causing hypercalciuria and, less commonly, hypocalciuria:

- Idiopathic hypercalciuria\[14\]:
  - High risk of calcium stone formation with hypercalciuria but normal blood calcium.
  - Usually results from calcium hyperabsorption in the intestine with hypercalciuria being of overspill type.
  - Hypercalciuria is treated with dietary restriction of calcium intake (plus careful monitoring of bone formation in children). Thiazide diuretic is used where this fails.

- Hereditary hypercalciuric nephrolithiasis\[15\]:
  - A rare disorder associated with proteinuria, nephrocalcinosis, renal stones and frequently chronic kidney disease.

- Familial hypocalciuric hypercalcaemia\[16\]:
  - An autosomal-dominant disorder following a generally benign course, associated with a defective extracellular sensing receptor.
  - Hypercalciuria and hypercalcaemia are accompanied by hypermagnesaemia with parathyroid hormone levels in the normal range.
  - In general, treatment is not required.
Aminoacidurias
See separate Aminoacidurias article.

Hereditary hypokalaemic tubulopathies[17]
See also separate Hypokalaemic Alkalosis article. Examples include:

- Bartter's syndrome: caused by a gene mutation affecting potassium transport at the ascending limb of the tubule.
- Gitelman's syndrome:
  - A rare inherited autosomal-recessive disorder caused by a defect in the renal tubule.
  - It causes the kidneys to pass excess sodium, magnesium, chloride and potassium into the urine.
  - Gitelman's syndrome is linked to a loss of function of the encoded thiazide-sensitive sodium chloride co-transporter.
  - People with Gitelman's syndrome present with hypochloraemic metabolic alkalosis, hypokalaemia and hypocalciuria. Hypomagnesaemia is present in many but not all cases.
  - Carriers of Gitelman's syndrome-linked mutations are often asymptomatic while some complain of mild muscle cramps or weakness fatigue.
  - Bartter's syndrome causes hypocalcaemia, but Gitelman's syndrome causes hypercalcaemia.
  - In both Bartter's syndrome and Gitelman's syndrome, NSAIDs in combination with potassium-sparing diuretics usually bring the plasma potassium concentration into the low normal range.

Pseudohypoaldosteronism and Liddle's syndrome[18]

- Pseudohypoaldosteronism and Liddle's syndrome cause abnormal function of the sodium channel in the renal cortical collecting tubule.
- Pseudohypoaldosteronism:
  - Inherited by either autosomal-recessive or autosomal inheritance.
  - Usually presents in infancy with hyponatraemia and hyperkalaemia.
  - The lung sodium channel is also impaired leading to lower respiratory tract infections.
  - Management consists of a high-salt diet with fludrocortisone.
- Liddle's syndrome:
  - A rare autosomal-dominant condition causing an increase in sodium reabsorption and often an increase in potassium excretion.
  - It presents with hypertension, hypokalaemia and metabolic alkalosis.
  - Management includes sodium restriction and amiloride.

Further reading & references
