Renal tubular disorders

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Abstract

Renal tubular disorders are challenging and comprise a heterogeneous group of disorders. This review concentrates on those presenting in childhood with electrolyte abnormalities. Pattern recognition of these abnormalities is important in making diagnoses and a basic understanding of renal tubular physiology is helpful to understand why these patterns occur.

Clinical cases are used as illustrations in this review, supported by physiological descriptions of the disorders and notes about their management.

Although these disorders almost invariably come under the long-term management of paediatric nephrologists, they will just as invariably present to general paediatricians. This review should equip general paediatricians with the skills to request the appropriate initial investigations to make the correct diagnosis. There is also some advice on when to suspect a diagnosis of a renal tubular disorder and how to spot a child with a genuine polydipsia.

Keywords Bartter's; cystinosis; diabetes insipidus; Fanconi; Gitelman's; polydipsia; polyuria; pseudohypoaldosteronism; renal tubular acidosis; renal tubular disorder; tubulopathy

Introduction

Paediatricians find tubular disorders challenging: some embrace them as cerebral challenges to explore when children have abnormal electrolytes; others still come out in a sweat at the thought of having to remember the classifications of renal tubular acidosis for membership!

There is a tendency for membership candidates to focus on renal tubular acidosis as the be-all and end-all of renal tubular disorders. This is unhelpful since proximal renal tubular acidosis in isolation is extremely rare and even distal renal tubular acidosis is not one of the most common tubulopathies encountered in clinical practice. It is more helpful, we believe, for the paediatrician to have a feel for the clinical features of the more common patterns of electrolyte disturbance and learn how differing diseases fit into these patterns.

In their entirety, renal tubular disorders are a heterogeneous group affecting different aspects of tubular function and as such may present in a variety of ways. Many present with growth faltering and polyuria/polydipsia as a consequence of salt-wasting but renal tubular disorders may also be responsible for renal calculi or hypertension in otherwise healthy children.

Most commonly, paediatricians encounter renal tubular disorders in the context of investigating a child with abnormal electrolytes. The disorders are caused, directly or indirectly, through dysfunction of transporter proteins which are responsible for the tubular reabsorption or secretion of various electrolytes. Within recent years many genes encoding for these transporter proteins have been located and these genetic advances have served to improve our understanding of tubular physiology. However, as yet there is no gene therapy available for these challenging disorders.

A comprehensive review of all tubular disorders takes several chapters in paediatric nephrology texts so this article will offer a flavour of tubular disorders by focussing on several of the more common tubulopathies. The individual conditions are illustrated through case presentations but the names of patients have been changed.

At the end of this article, the reader should have a basic understanding of the role of the renal tubule in homeostasis, understand how tubular disorders deviate from the norm to result in their characteristic biochemical patterns and have confidence in how to begin to investigate a child presenting with electrolytic derangement.

Renal physiology

Faced with abnormal electrolyte results, there is a need for a foundational understanding of renal tubular physiology. The three major functions of the kidneys comprise:

- Maintenance of a constant extracellular environment for optimum cell functioning (homeostasis).
- Hormone secretion (including: erythropoietin for red blood cell production; renin and angiotensin II affecting renal and systemic haemodynamics; and hydroxylated vitamin D affecting calcium, phosphate and bone metabolism).
- Miscellaneous functions including peptide hormone catabolism and gluconeogenesis.

Homeostasis is achieved through the kidney excreting waste products (e.g. urea and uric acid) and specifically adjusting the urinary excretion of water and electrolytes (solute) to match the body's dietary intake and endogenous production through metabolism.

The human body contains around one million nephrons in each kidney. This is the functional unit of the kidney and its precise homeostatic function is achieved through differing properties of cells that define each segment of the tubule as well as a number of internal feedback mechanisms which require the close juxtaposition of the distal tubule with its parent glomerulus.

Each nephron comprises a glomerulus and tubule. The glomerulus, the initial part of the nephron, is a tuft of capillaries lined by epithelial cells. The endothelial cell and epithelial cell sandwich the glomerular basement membrane and these structures together constitute a sieve which results in a glomerular ultrafiltrate passing into Bowman's space at the start of the tubule. A schematic view of the nephron is shown in Figure 1.

The average adult glomerular filtration rate (GFR) is 125 ml/min/1.73 m^2. Therefore the glomeruli of a healthy adult (of

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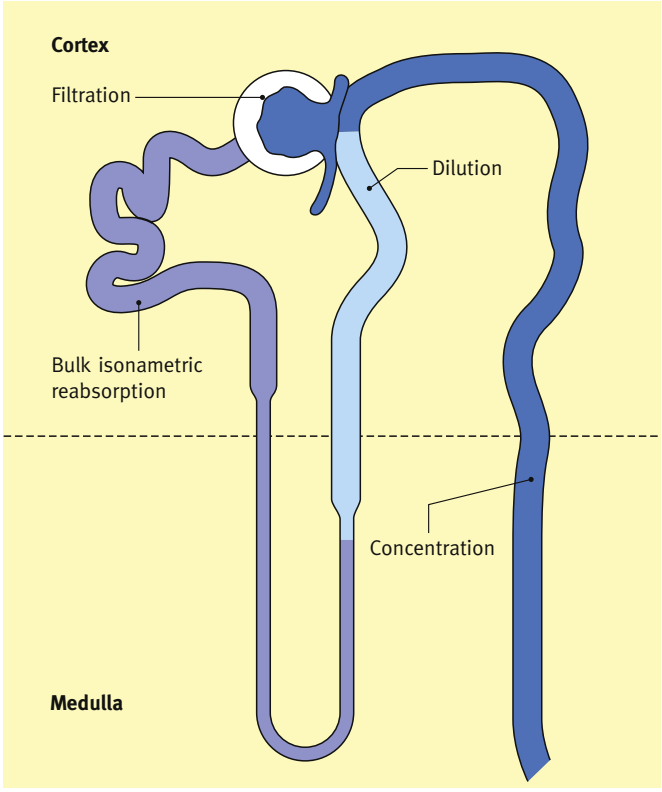

Figure 1 Simplified drawing of a nephron. Isonatremic reabsorption of tubular fluid takes place in the proximal tubule in the cortex. The thick ascending limb of the loop of Henle is a diluting segment in which sodium chloride is avidly recovered but water does not follow. All the distal nephron can be regarded as a functional whole. It is derived from the original ureteric bud. It is responsive to hormones that regulate volume osmolality and potassium concentrate. Note that the junction between the diluting and concentrating segments meets at the juxtaglomerular apparatus of the self-same nephron providing a point at which tubular performance regulates the rate of glomerular filtration. (From Forfar and Arneil — figure 16.1).

average body surface area 1.73 m^2) filter 180 litre of plasma each day. Since the average daily adult urine production is only 1.5 litre, it is clear that the reabsorptive properties of the tubule, for water at least, must be highly efficient. The fact that 180 litre of plasma are filtered each day also means that the extracellular fluid volume is turned over approximately 10 times daily, hence homeostatic mechanisms with regard to acid–base and electrolyte regulation need to be able to respond rapidly and precisely to avoid major perturbations in body chemistry.

In gross terms, the proximal tubule and loop of Henle are bulk resorbers of water and solute whilst the distal tubule has an important role in fine-tuning. The reabsorption may be across the tubular cells (transcellular) or passively across the tight junctions in between tubular cells (paracellular). It is the *polarity* of tubular cells that gives them their unique properties. Polarity means that the apical (that side of the cell adjacent to the tubular lumen) and basolateral (that side of the cell adjacent to peritubular capillaries) membranes have differing properties through expressing different channels or transporters. The polarity is maintained by the intercellular tight junctions. Most transport, both reabsorption and secretion, is linked directly or indirectly to sodium reabsorption. The sodium–potassium ATPase pump on the basolateral membrane actively pumps three sodium ions from the tubular cell into the peritubular space (where they are subsequently absorbed into peritubular capillaries) in exchange for two potassium ions, at the cost of one molecule of ATP. This active transporter thus generates a state of intracellular sodium depletion which favours entry of sodium from the tubular lumen down an electrochemical gradient. Sodium is reabsorbed through sodium channels or co-transporters which link the absorption of sodium to that of other molecules against their own electrochemical gradient. Sodium reabsorption in exchange for hydrogen ion secretion in the proximal tubule is an important example of this and is shown in Figure 2.

Renal regulation of potassium and acid base balance

Around 65% of filtered potassium is reabsorbed in the proximal tubule where it is closely linked to the reabsorption of sodium and water. Here sodium–potassium co-transporters reabsorb potassium in a similar way to the excretion of acid shown in Figure 2. A further 30% is reabsorbed in the thick ascending limb of the loop of Henle via a sodium co-transporter specific to the loop — the sodium–potassium–chloride co-transporter, NKCC2 (Figure 3). This co-transporter is the site of action of loop diuretics such as furosemide. In the loop there is further reabsorption of potassium via the paracellular route which proceeds down an electrochemical gradient.

The remaining 5–10% of filtered potassium is delivered to the distal tubule. In the cortical collecting tubule and duct, there is both potassium secretion (by principal cells) and potassium reabsorption (by intercalated cells) but the more significant process is secretion. Factors affecting potassium excretion include:

- Hyperkalaemia (favours increased potassium secretion through a greater osmotic load).
- Aldosterone secretion. Aldosterone combines with a cytosolic receptor to increase the number of open sodium

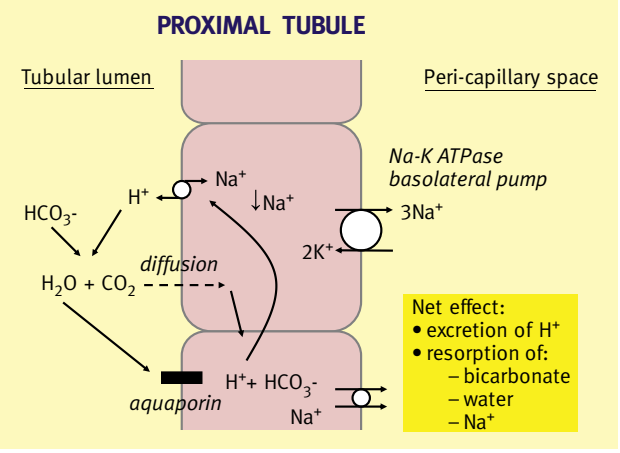

Figure 2 The driving force is the generation of a low intracellular sodium concentration which occurs due to the Na–K ATPase pump in the basolateral membrane pumping out three sodium ions in exchange for two potassium ions at the cost of one molecule of ATP.