Clinical, pathophysiological and genetic aspects of inherited tubular disorders in childhood

ABSTRACT

In this review, we described the tubular function of each nephron segment followed by the most important changes that may occur in the transporters expressed therein. Thus, knowledge of the changes in renal tubular function allows the understanding and recognition of renal tubular diseases that can cause stillbirth or death in newborns or in childhood. Moreover, children with tubular disorders may progress to chronic renal disease at an early stage of life and they may also show disturbances of growth and development associate or not with neurological dysfunction. Therefore, we used the keyword "inherited tubular disorders" to select the children studies that have been published in the PubMed database since 2006. We hope that this review may help physicians to perform an early diagnosis in patients with tubular disorders allowing a specialized treatment and an improvement in their prognosis and quality of life.

Keywords: acidosis, renal tubular; Bartter syndrome; electrolytes; Fanconi syndrome; Gitelman syndrome; sodium-potassium-exchanging ATPase.

INTRODUCTION

Water and electrolyte homeostasis and acid-base balance are regulated by the kidneys and play a vital role in bodily functions. To play such role, the cells in the renal tubules require separate ion channels, carriers, exchangers, cotransporters, and pumps to transport water and different solutes.1 Thus, genetic defects in any of these transport systems may result in a wide range of nephropathies.2-5

Inherited tubulopathies are usually severe and may either cause the death of the fetus, neonate, or child affected by it or lead to the early onset of end-stage renal disease. Additionally, children diagnosed with inherited tubulopathy may also have growth disorders and delayed development associated or not with neurological impairment. Diagnosis is frequently delayed by nonspecific and often silent clinical symptoms. Therefore, knowledge of renal physiology, the molecular bases of tubular transport, and the possible pathophysiological alterations is required to clinically understand and recognize individuals with these diseases. In recent decades the developments in molecular biology and genetics have provided the tools to investigate the presence of inherited tubulopathies, thus improving the diagnosis, treatment, and prognosis of the affected children.2-5

This paper presents a brief account of the physiological mechanisms involved in tubular transport in each segment of the nephron along with a description of the main pediatric inherited tubulopathies in terms of the following factors: a) pathophysiological alterations; b) clinical manifestations, and c) recent genetic findings. The nomenclature developed by Kelly & Landman was used to describe the segments of the nephron.6
Proximal convoluted tubule

The proximal convoluted tubule is highly capable of reabsorbing mostly filtered solutes connected to sodium reabsorption. Approximately two thirds of the filtered Na⁺ is reabsorbed in this segment of the nephron mainly via the paracellular pathway. However, active transcellular sodium transport mediated by Na⁺-K⁺-ATPase expressed in the basolateral membrane also occurs in the cells of the proximal tubule. The energy generated by Na⁺-K⁺-ATPase activity is transferred to glucose, amino acid, phosphate and other transporters of the luminal membrane (Figure 1).

Approximately 80% of the bicarbonate is reabsorbed in the beginning of the proximal tubule, in a multiple-step process. Initially, filtered HCO₃⁻ binds to H⁺ secreted by the Na⁺-H⁺ transporter, NHE3, expressed in the apical membrane. This reaction produces carbonic acid (H₂CO₃), which is then converted to CO₂ and H₂O in the presence of carbonic anhydrase isoform IV in the luminal membrane of these cells. Then CO₂ penetrates the cell by diffusion or is transported by aquaporin 1 to once again produce carbonic acid from a reaction between CO₂ and water. Carbonic acid is then catalyzed by carbonic anhydrase isoform II in the intracellular medium to produce H⁺ and HCO₃⁻. The anion is transferred to the cell interstices by the Na⁺/HCO₃⁻ transporter, NBC-1, expressed in the basolateral membrane, and H⁺ is secreted into the lumen of the tubule with the aid of transporter NHE3 (Figure 1).

Proximal tubular cells can generate extra bicarbonate through glutamine deamination into glutamate and thus form alpha-ketoglutarate. This metabolic process produces bicarbonate and ammonia. Bicarbonate is transported to the peritubular capillaries and ammonia to the lumen of the collecting duct to form the ammonium ion (NH₄⁺) after binding to H⁺.

Isotonic reabsorption of sodium and water in the proximal tubule increases the concentration of chloride and calcium in the tubular lumen, thus facilitating the secondary passive reabsorption of these ions. Approximately 60% of the filtered calcium is reabsorbed in the proximal tubule.

About 30% of the filtered magnesium is reabsorbed in the proximal tubule, preferentially via the paracellular pathway.

Approximately 85% of the filtered phosphate (Pi) is reabsorbed in the proximal tubule. Renal reabsorption is mediated by the SLC34 family of sodium-dependent phosphate transporters, which includes SLC34A1 (NaPi-IIa) and SLC34A3 (NaPi-IIc). The regulation of the renal transport of Pi is known to be affected by PTH, phosphorus intake, vitamin D, and hormonal factors or hormone-like peptides known as phosphatonin such as fibroblast growth factor 23 (FGF23), which inhibit the renal reabsorption of phosphate.

Main conditions affecting the proximal tubule

Proximal renal tubular acidosis

Proximal renal tubular acidosis (pRTA), or type 2 renal tubular acidosis (RTA), is caused by defective reabsorption of bicarbonate in the proximal tubule. This tubulopathy is characterized by hyperchloremic metabolic acidosis with a normal anion gap, growth failure, anorexia, polyuria, and constipation.

The autosomal recessive form of the disease results in ocular involvement, short stature, dental enamel defects, and intellectual deficit. It is caused by mutations in the SLC4A4 gene of the SLC4 family of genes encoding the Na⁺/HCO₃⁻ transporter, NBC1, expressed in the basolateral membrane of the proximal tubular cells.

The dominant form of the disease was considered in a family with children suffering from delayed growth and hyperchloremic metabolic acidosis, but normal renal function and urinary acidification. It is caused by mutations in the SLC4A4 gene of the SLC4 family of genes encoding the Na⁺/HCO₃⁻ transporter, NBC1, expressed in the basolateral membrane of the proximal tubular cells.

The dominant form of the disease was considered in a family with children suffering from delayed growth and hyperchloremic metabolic acidosis, but normal renal function and urinary acidification. A study with mice selected gene SLC9A3, which encodes NHE3, as a likely candidate. However, the most common form of type 2 RTA in children occurs secondarily to Fanconi syndrome.

Fanconi syndrome

Fanconi syndrome is a complex proximal tubule reabsorption disorder, with renal...
Figure 1. Proximal convoluted tubule cell showing enzyme Na⁺-K⁺-ATPase in the basement membrane, whose activity generates the electrochemical gradient needed by the sodium transporters expressed in the luminal membrane: Na⁺-glucose, Na⁺-amino acids, Na⁺-phosphate. Note the expression of the Na⁺-H⁺ transporter (NHE3) responsible for the secretion of H⁺ associated with Na⁺ reabsorption and bicarbonate thanks to brush border (type IV) and intracellular (type II) carbonic anhydrase isoforms and Na⁺-bicarbonate (NCB1) transporter in the basement membrane.

Tubular acidosis listed as only one of the multiple transport alterations occurring in this segment of the nephron. Patients diagnosed with Fanconi syndrome have aminoaciduria, phosphaturia, glucosuria, proteinuria, polyuria, and hyperchloremic metabolic acidosis. Due to multiple proximal tubule transporter disorders, patients may also present with cystinosis, tyrosinemia, galactosemia, and Lowe syndrome, in a heterogeneous array of diseases whose genes have been mapped against many chromosomal regions.¹⁵,¹⁶

Cystinosis

Cystinosis is a condition caused by a defect in the transport of cystine through the lysosomal membrane, which results in a dysfunction of protein cystinosin originated from mutations on gene CTNS in chromosome 17p13. Cystinosin inactivity leads to the accumulation of cystine and the formation of intralysosomal cystine crystals. Three clinical variants have been described: infantile nephropathic cystinosis, juvenile nephropathic cystinosis, and adult cystinosis. Fanconi syndrome is the renal manifestation of nephropathic cystinosis. Patients develop end-stage renal disease by the end of the first decade of life, unless they have been treated with cystine-depleting agents since the early stages of their lives. A recent study reported improvements in the condition of patients with renal failure after the administration of oral N-acetylcysteine (NAC). The authors attributed the improvement to the decrease in oxidative stress produced by NAC.¹⁷
Children diagnosed with cystinosis also suffer from hypothyroidism and photophobia secondary to ocular involvement. Individuals with increased intra-leukocyte cystine levels are diagnosed with cystinosis. Genetic tests may be used to confirm the diagnosis and aid in patient genetic counseling. 18,20

**LOWE SYNDROME**

The diagnostic triad for oculocerebrorenal syndrome (OCRS), or Lowe syndrome, includes ocular anomalies, neurologic deficits, and renal Fanconi syndrome with progressive evolution to end-stage renal disease. The disease is caused by variations in the DNA of gene OCRL1 in chromosome Xq26.1 encoding protein phosphatidylinositol 5-phosphate (PtdIns5P). PtdIns5P is located in the Golgi apparatus and endosomes, and regulates intracellular processes. 21,22

**DENT DISEASE**

Dent disease mutates the chloride channel CLC-5 expressed in proximal tubule cells and results in impaired reabsorption of protein by endocytosis from the ultrafiltrate. Clinical manifestations include: a) low-molecular weight proteinuria; b) hypercalciuria; c) renal lithiasis; d) nephrocalcinosis; and e) progressive renal failure. Dent disease may also be associated with Fanconi syndrome and is often complicated by rickets and osteomalacia. These signs are generally found in male patients and may be present since early childhood.

Mutations on gene CLCN5 in chromosome Xq25 characterize Dent disease type 1, while Dent disease type 2 is characterized by mutations on gene OCRL1 in chromosome Xp11.22,23,24

**HYPOPHOSPHATEMIC RICKETS**

Hereditary hypophosphatemic rickets includes a group of diseases characterized by urinary loss of phosphate, inadequate serum levels of 1,25-dihydroxyvitamin D3, delayed growth, rickets, and osteomalacia. 25 Its most common form is X-linked hypophosphatemic rickets. This disease is caused by mutations on gene PHEX in chromosome Xp22.1-22.2. 25,26 Gene PHEX regulates the expression of FGF23 as part of a hormonal axis between bone tissue and the kidneys and controls the systemic homeostasis of phosphate. The mutation on gene PHEX results in reduced degradation and/or increased biosynthesis of FGF23.27

The incidence of autosomal hypophosphatemic rickets is much lower and includes the dominant form of the disease, accompanied by mutations to the FGF23 gene. Recessive hypophosphatemic rickets features mutations to the dentin matrix protein 1 (DMP1) gene and mutations to the ectonucleotide pyrophosphatase/phosphodiesterase-1 gene. 14

Klotho coreceptors have been recently associated with adequate FGF23 signaling. A translocation in the FGF23 gene has been found to increase Klotho levels and cause hypophosphatemic rickets with hyperparathyroidism. 14

Table 1 shows the recently identified genetic alterations associated with hypophosphatemic rickets. 13

**DISTAL STRAIGHT TUBULE (THICK ASCENDING LIMB OF THE LOOP OF HENLE)**

The Na⁺-K⁺-2Cl cotransporter (NKCC2) is encoded by gene SLC12A1. NKCC2 is expressed in the luminal side of the cells the distal straight tubule and transports sodium and chloride in this segment of the nephron. Na⁺, K⁺-ATPase expressed in the basement membrane of these cells actively transports sodium to outside the cell while chloride leaves the cell through specific chloride channels referred to as CLC-Ka and CLC-Kb. Genes CLCNKA and CLCNKB encode each respective channel. Both chloride channels rely on an accessory protein, beta subunit Barttin, BSDN. 28,29 The intracellular transportation of potassium is also due to NKCC2 activity. But potassium returns to the tubular lumen through ion channel Kir 1.1 (ROMK) encoded by gene
Hereditary tubulopathy in children

**Table 1** INHERITED HYPOPHOSPHATEMIAS - MUTATED PROTEINS AND CLINICAL PARAMETERS

<table>
<thead>
<tr>
<th>Protein</th>
<th>Disease</th>
<th>Serum Ca++</th>
<th>1,25(OH)D</th>
<th>FGF23</th>
<th>PTH</th>
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<tbody>
<tr>
<td>PHEX</td>
<td>X-linked hypophosphatemic rickets</td>
<td>Normal</td>
<td>Low/Normal</td>
<td>High/Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>DMP1</td>
<td>Autosomal recessive hypophosphatemic rickets</td>
<td>Normal</td>
<td>Normal</td>
<td>High/Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FGF23</td>
<td>Autosomal dominant hypophosphatemic rickets</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>NHERF1</td>
<td>Hypophosphatemic nephrolithiasis/osteoporosis-2</td>
<td>Normal</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>KLOTO</td>
<td>Hypophosphatemic rickets with hyperparathyroidism</td>
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<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
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<td>High</td>
<td>Not determined</td>
<td>Not determined</td>
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<tr>
<td>SLC34A3</td>
<td>Hypophosphatemic rickets with hypercalciuria</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>


KCNJ1. The recirculation of potassium is needed so that there is enough substrate for the Na⁺-K⁺-2Cl⁻ cotransporter to function properly (Figure 2).¹²,²⁸

Sodium and chloride reabsorption and potassium recirculation generate a lumen-positive transepithelial potential difference in the thick ascending limb of the loop of Henle, which favors passive paracellular calcium and magnesium reabsorption through proteins claudin-16 and claudin-19 present in the cell junctions of the distal straight tubule (Figure 2).¹²,³⁰

The calcium-sensing receptor (CaSR) is also expressed in the basement membrane of the cells in the thick ascending limb of the loop of Henle. CaSR regulates PTH secretion in the parathyroid cells and the renal absorption of calcium in response to elevated calcium plasma levels. In this situation, CaSR is activated due to high levels of calcium in the vasa recta resulting from the triggering of cell signaling pathways to inhibit the Na⁺-K⁺-2Cl⁻ cotransporter or the luminal K⁺ channel. Then tubular lumen is altered and the paracellular reabsorption of Ca⁺⁺, Mg⁺⁺, and K⁺ is inhibited (Figure 2).¹²,²²,³¹

**Main conditions affecting the distal straight tubule (thick ascending limb of the loop of Henle)**

**Bartter syndrome**

NaCl transport in the distal straight tubule requires the presence and activity of at least five genes related to transporter function: a) NKCC2, which uses the electrochemical gradient generated by Na⁺-K⁺-ATPase activity in the reabsorption of sodium, chloride, and potassium in the lumen; b) ROMK channels, which allow potassium to migrate to the face of the lumen thus increasing the availability of a substrate for NKCC2 to function; c) Na⁺-K⁺-ATPase, which drives the movement of ions; d) CLC-Kb and CLC-Ka, which require the Barttin subunit to transport chloride through the basement membrane. Mutations on genes SLC12A1, ROMK1, CLCNKB, and BSDN (Barttin) are the respective causes for Bartter syndrome types I, II, III, and IV, a group of autosomal recessive disorders.³²-³⁵

The clinical signs observed in individuals diagnosed with Bartter syndrome include hypokalemia, hyperreninemia, hyperplasia of the juxtaglomerular apparatus, metabolic alkalosis, low or normal blood pressure, and increased urinary loss of Na⁺ and K⁺.³²,³³

Gene SLC12A1 encoding transporter NKCC2 is mutated in patients with type-1 Bartter syndrome. The main clinical manifestations are polyuria and dehydration within the first weeks of birth, which requires the prescription of volume replacement therapy. Neonates may also present hypokalemia, metabolic acidosis, and elevated plasma renin levels. At later stages, nephrocalcinosis may be diagnosed through renal ultrasound tests.³⁸,³²-³⁵
Figure 2. Cell of the distal straight tubule or thick ascending limb of the loop of Henle; enzyme Na⁺-K⁺-ATPase is expressed in the basement membrane, and its activity generates the electrochemical gradient needed by the Na⁺-K⁺-2Cl⁻ (NKCC2) cotransporter in the luminal membrane. The luminal K⁺ channel (ROMK) is needed in K⁺ recirculation and promotes increased NKCC2 efficiency. The lumen of the tubule is positively charged due to the passive transport of Cl⁻ by CIC-Kα and CIC-Kβ expressed in the basement membrane and the recirculation of K⁺. Thus, cations (Ca²⁺ and Mg²⁺) are reabsorbed with the aid of paracellular junction proteins called claudins. The calcium-sensing receptor (CaSR) is also present in the basement membrane to inhibit NKCC2 luminal activity in hypercalcemia, leading to increased urine output and urinary excretion of ions.

Patients with type-II Bartter syndrome may have hyperkalemia within the first days of birth caused by ROMK channel and potassium excretion impairment. Other potassium channels may compensate for the impairment at a later stage and patients may become hypokalemic.²⁸,³²-³⁵

Individuals with type-III Bartter syndrome may have milder clinical signs and overlapping symptoms of Bartter and Gitelman syndromes. After an uneventful neonatal life, patients usually experience growth failure. Renal sodium loss progresses slowly and unaccompanied by evident polyuria, thus delaying the diagnosis of the condition. Few patients develop medullary nephrocalcinosis. Clinical signs stem from a defect on CLC-Kβ, also expressed in the distal convoluted tubule. In the revised nomenclature, type-III Bartter syndrome is a disorder of the distal convoluted tubule.²⁸,³²-³⁵

Type-IV Bartter syndrome is a more severe, and fortunately less common, form of the disease caused by a defect in the Barttin subunit. Prenatal manifestations include polyhydramnios, a contributing factor to extreme preterm birth. Neonates develop polyuria and are at higher risk for hypotension and hypovolemic shock. Patients have progressive chronic kidney disease, although usually without nephrocalcinosis.²⁸,²⁹,³²-³⁵
**AUTOSOMAL DOMINANT HYPOCALCEMIA WITH HYPERCALCIURIA (ADHH) AND TYPE-V BARTTER SYNDROME**

As described above, CaSR indirectly controls the reabsorption of divalent cations by indirectly controlling the formation of positive voltage in the lumen of the distal straight tubule. Higher plasma concentration of Ca$^{2+}$ activate CaSR, thus inhibiting the activity of the Na$^+$$-$K$^+$-$2Cl$^-$/cotransporter and preventing the opening of the ROMK channels, thus making it impossible for the voltage in the lumen to become positive. In a context of mutation and CaSR functional gain, patients develop hypocalcemia due to hypercalciuria with PTH suppression and Bartter-like syndrome. In such clinical setting, the genetic defect is found in chromosome 3q21.1.

**FAMILIAL HYPMAGNESEMA WITH HYPERCALCIURIA AND NEPHROCALCINOSIS (FHHNC)**

FHHNC is a rare autosomal recessive disease associated with kidney failure. Mutations in gene CLDN16 and chromosome 3q27 encoding protein claudin-16, also known as paracellin-1, have been linked to FHHNC. Individuals with these mutations have decreased ion permeability, which prevents the reabsorption of Mg$^{2+}$ in the distal straight tubule. Despite the concurrent impairment in Ca$^{2+}$ reabsorption, patients are able to maintain normal Ca$^{2+}$ serum levels, probably through alternative calcium recovery routes in the kidney and bowel. Individuals with mutations on gene CLDN19 have been reported to have a phenotype similar to the cases described above, in addition to severe ocular involvement.

**DISTAL CONVOLUTED TUBULE**

Solutes are reabsorbed in the distal convoluted tubules (DCT) via the transcellular pathway with the aid of Na$^+$$-$K$^+$-ATPase present in the basement membrane of the DCT cells. In this segment of the nephron, sodium chloride is transported to the intracellular medium through the thiazide-sensitive sodium chloride cotransporter (NCC) expressed in the apical membrane encoded by gene SLC12A3. Sodium chloride is thus reabsorbed, and sodium moves to the interstice with the aid of Na$^+$$-$K$^+$-ATPase, while chloride moves through specific chloride channels, CLC-Kb mainly (Figure 3). Magnesium is reabsorbed in the initial portion of the DCT through the TRPM6 expressed in the apical membrane of the DCT cells. In the final portion of this segment of the nephron and in the connecting tubule, TRPV5 allows calcium to be reabsorbed via the transcellular pathway (Figure 3). Main conditions affecting the distal convoluted tubule

**GITELMAN SYNDROME**

Individuals with Gitelman syndrome have hypokalemic metabolic alkalosis combined with hypomagnesemia and hypocalciuria. The clinical manifestations and biochemical markers for Gitelman syndrome may mimic the signs of type-3 Bartter syndrome. Symptoms may start during childhood and persist throughout adult life. Some individuals are asymptomatic, while others experience muscle weakness, cramps, severe neuromuscular symptoms, paresthesia, tetany or palsy correlated with hydroelectrolytic disorders.

The mutations found in most patients with Gitelman syndrome are located in gene SLC12A3.

**PSEUDOHYPOALDOSTERONISM TYPE II - GORDON’S SYNDROME**

Gordon’s syndrome is an autosomal dominant disease associated with increased NaCl renal reabsorption and impaired distal secretion of K$^+$ and H$^+$. The alterations inherent to the disease stem from mutations on the gene encoding WNK, a family of serine-threonine protein kinases. Some mutations remove the inhibitory effect WNK4 exerts over the NaCl cotransporter (NCC) in the distal convoluted tubule. Other mutations produce increases in the expression of WNK1. Once NCC is activated by WNK1, in such gene mutations the transport of Na$^+$ is upregulated.
Figure 3. Cells of the distal convoluted tubule showing the NaCl cotransporter (NCC) in the luminal membrane, activated after the expression of Na⁺K⁺-ATPase in the basement membrane. The cells in the initial portion of the distal convoluted tubule also express Mg²⁺ channel (TRPM6) on the luminal face. This channel is modulated by NCC efficiency and the transcellular movement of ions K⁺ and Cl⁻. TRPM6 channels are also modulated by the activation of the epithelial growth factor receptor (EGFR) expressed on the basement membrane. The mechanism by which Mg²⁺ leaves these cells is yet unknown. The cells at the end of the distal convoluted tubule and of the connecting tubule express Ca²⁺ channel (TRPV5) on the luminal face. TRPV5 is also modulated by NCC efficiency. Ca²⁺ leaves the cell with the aid of Ca²⁺-ATPase and Na⁺-Ca²⁺ cotransporter (NCX1) expressed on the basement membrane. These cells also have receptors to multiple hormones (HR), which regulate Ca²⁺ reabsorption - the cases of estrogen, PTH, and vitamin D.

The clinical manifestations of Gordon's syndrome include hyperkalemia, mild metabolic acidosis, suppressed plasma renin activity, and normal or elevated aldosterone levels. Lower levels of sodium in the collecting duct cells impair the generation of a potential difference and cause hyperkalemia and metabolic acidosis. The secretion of K⁺ and H⁺ is consequently decreased.

EAST/SeSAME SYNDROME

Two groups of researchers recently described a complex syndrome in which epilepsy, ataxia,
mental retardation, and sensorineural hearing loss occur in association with a salt wasting syndrome described by the acronym EAST. The disorders include the activation of the renin-angiotensin-aldosterone system, hypokalemic metabolic acidosis, and hypomagnesemia with hypocalciuria. Patient urine concentrating ability remains unaffected.28

The EAST/SeSAME syndrome is an autosomal recessive disease caused by mutations and loss of function of gene KCNJ10 encoding Kir 1.4, a potassium channel expressed in the basement membrane of the distal convoluted tubule. Kir 1.4 and Na⁺-K⁺-ATPase are thought to jointly aid in the local recirculation of potassium ions.35

**Hypomagnesemia with secondary hypocalcemia (HSH)**

Gene TRPM6 encoding the TRPM6 channel was identified as the culprit for HSH, an autosomal recessive disease.28,35

Clinical reports indicate hypomagnesemia is caused by reduced Mg²⁺ absorption in the bowel, and not necessarily by urinary loss of magnesium. Hypocalcemia is a secondary condition, given that patients benefit from the administration of Mg²⁺. Calcium homeostasis has been associated with Mg²⁺ blood levels.28,35

The clinical manifestations of HSH appear soon after birth in the form of spasms, tetany, and generalized seizures.28,35

**Isolated autosomal recessive hypomagnesemia**

This rare form of hypomagnesemia was initially described in two siblings with low Mg²⁺ blood levels caused by increased magnesium urinary excretion and normal Ca²⁺ blood levels. These individuals had seizures and psychomotor retardation. Genetic studies revealed a mutation in the epidermal growth factor (EGF) gene, which impaired the autocrine/paracrine secretion of EGF. EGF receptors regulate the insertion of the TRPM6 channels in the luminal membrane of the distal convoluted tubule. Therefore, the inhibition of the EGF receptors for lack of a substrate leads to magnesiuria secondary to diminished TRPM6 channel expression.28,35

**Isolated dominant hypomagnesemia**

Patients diagnosed with this type of hypomagnesemia experience renal losses of Mg²⁺ and hypocalciuria due to mutations in the structure of Na⁺-K⁺-ATPase. Na⁺-K⁺-ATPase has three described subunits: α, β, and γ; α and β are catalytic subunits and γ is a modulating subunit. Gene FXYD2 encodes subunit γ and G41R mutation causes changes in the affinity with Na⁺ and K⁺ and in the polarization of the apical membrane, which may decrease Mg²⁺ transport. However, the precise role of subunit γ in Mg²⁺ tubular transport regulation has not been entirely uncovered.28,35

**Collecting duct**

The collecting duct is characterized by the heterogeneity of its cells. This segment of the nephron contains principal cells and intercalated cells of types A, B, and non-A non-B.44

In the principal cells, sodium is reabsorbed separately from chloride via the transcellular pathway through the amiloride-sensitive epithelial sodium channel (ENaC). Sodium reabsorption is driven by the activity of Na⁺-K⁺-ATPase expressed in the basement membrane. Transcellular transport of sodium favors the secretion of a cation - potassium or hydrogen - as a consequence of the principle of electroneutrality. Principal cells also express ROMK channels in their apical membranes through which K⁺ is secreted.1,45

Urine acidification occurs in type-A intercalated cells due to the secretion of H⁺. The transport of this cation is made possible by the activity of H⁺-ATPase expressed in the face of the lumen of these cells and facilitated by the potential difference generated when the neighboring principal cells reabsorb sodium. H⁺ originates from the catalytic reaction between carbonic anhydrase II and carbonic acid. The latter is formed when CO₂ is hydrated.

Figure 4 shows that bicarbonate is regenerated in the type-A intercalated cells through CO₂ hydration followed by carbonic acid degradation. Bicarbonate is then transported to the bowel.
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**Figure 4.** Representation of three types of collecting duct cells: intercalated-A, principal, and intercalated-B cells. Intercalated-A cells express H+-ATPase on the luminal membrane and Cl-HCO₃ (AE1) transporter on the basement membrane. This arrangement favors the secretion of acids. The expression of enzyme H+-K+-ATPase on the luminal face helps conserve K⁺ in situations of potassium depletion. Intercalated-B cells express H+-ATPase on the basement membrane and Cl-HCO₃ transporter, called pendrin in these cells, on the luminal face. Thus, the individual can retain H⁺ and eliminate bicarbonate in situations of alkalemia. Principal cells express amiloride-sensitive epithelial sodium channel (ENaC) on the luminal face. Na⁺, K⁺-ATPase expression on the basement membrane generates an electrochemical gradient that allows the reabsorption of Na⁺ and the secretion of K⁺ by ROMK channels.

[Diagram showing the transport processes of H⁺, Na⁺, K⁺, Cl⁻, and HCO₃⁻ in the different types of collecting duct cells.]

through the Cl⁻–HCO₃ cotransporter expressed in the basement membrane of type-A intercalated cells (Figure 4). The H⁺ ions secreted in the tubular lumen combine with anions such as phosphate and ammonia (NH₃), resulting in the formation of ammonium (NH₄⁺). Ammonia is synthesized in the proximal tubule and transported to the renal medulla. Defective H⁺-
secretion reduces urine acidification and the excretion of ammonium. Type-A intercalated cells also express H+-K+-ATPase in their luminal membranes.\textsuperscript{1,9} Despite the numerous studies on the matter, there is no consensus in the literature over the role of H+-K+-ATPase in acid-base balance, only in potassium homeostasis.

Type-B intercalated cells are involved in the secretion of bicarbonate and play an important role in the regulation of the acid-base balance in contexts of alkalemia. Type-B intercalated cells express H+-ATPase in the basement membrane and chloride-bicarbonate exchange protein pendrin in the luminal membrane. Pendrin transports Cl\textsuperscript{-} into the intracellular medium and HCO\textsubscript{3}\textsuperscript{-} to the lumen of the tubule.\textsuperscript{1,44}

Non-A non-B intercalated cells express both H+-ATPase and pendrin in their apical membranes.\textsuperscript{44}

While the role of type-A and type-B intercalated cells has been established, the role of non-A non-B intercalated cells still requires some clarification.

**Main conditions affecting the collecting duct**

**Distal renal tubular acidosis**

Distal renal tubular acidosis, also known as type-1 RTA, is characterized by hyperchloremic metabolic acidosis arising from failure to secrete hydrogen ions in the collecting duct. Inherited type-1 RTA has two variants: a) autosomal dominant type-1 RTA with mild clinical manifestations and b) autosomal recessive type-1 RTA with severe symptoms during childhood, including hearing loss in some cases. Symptoms of early onset include polyuria, vomiting, dehydration, lower weight and height, hypokalemia, urinary pH above 6.0, hypercalcemia, hypocitraturia, and rickets.\textsuperscript{15,22} Hypercalcemia combined with a urinary pH above 6.0 favors the deposition of calcium in the kidneys and the establishment of nephrocalcinosis. Diagnosis is classically defined when higher urinary pH and systemic metabolic acidosis are identified. In some cases, patients with the disease may have normal blood pH and slightly increased urinary pH levels, making the diagnosis of the condition more challenging. In such circumstances, urine acidification tests with oral administration of ammonium chloride (NH\textsubscript{4}Cl) or furosemide combined with fludrocortisone are needed.\textsuperscript{46}

Mutations on gene AE1 (SLC4A1) have been associated with autosomal dominant type-1 RTA. The gene, located in chromosome 17q21-22, is a member of the anion exchanger family expressed in the basement membrane of type-A intercalated cells.\textsuperscript{8,47,48} Genome analysis has found two recessive genes associated with type-1 RTA: a) one in chromosome 2p13 encoding subunit B1 of H+/ATPase (ATP6V1B1) and b) another in the 7q33-34 locus encoding a specific renal proton pump subunit (ATP6V0A4).\textsuperscript{8}

**Liddle syndrome**

Individuals diagnosed with Liddle syndrome have severe hypertension, metabolic alkalosis, and hypokalemia, accompanied by low renin and aldosterone blood levels as a consequence of the mutations in the ENaC subunits.\textsuperscript{49} The ENaC is made up of subunits α, β, and γ. In the kidney, the ENaC allows Na\textsuperscript{+} to enter through the luminal membrane, while maintaining the homeostasis of the extracellular fluid and proper blood pressure levels.\textsuperscript{45} Mutations on genes SCNN1B and SCNN1G respectively affect subunits β and γ of the ENaC and cause Liddle syndrome. Patients diagnosed with the syndrome have significantly increased ENaC activity, which causes them to retain sodium and experience high blood pressure unrelated to renin or aldosterone levels. Additionally, increased sodium reabsorption stimulates potassium secretion and favors the onset of hypokalemia.\textsuperscript{49}

**Pseudohypoaldosteronism type I (PHAI)**

Pseudohypoaldosteronism type 1 is a form of mineralocorticoid resistance characterized by salt wasting. Two inheritance patterns have been described: a) autosomal dominant, limited to the kidneys and caused by a mutation with loss of function of gene NR3C2, which results in decreased cytoplasmic mineralocorticoid receptor activity; and b) autosomal recessive, originated from mutations in the gene encoding...
the ENaC, which results in loss of function in the Na$^+$ transport in aldosterone target tissues. The clinical manifestations seen in patients diagnosed with PHA1 include neonatal renal sodium wasting, dehydration, life-threatening hypotension, hyperkalemia, metabolic acidosis, and growth failure.\textsuperscript{50-52}

**Congenital Hypoaldosteronism**

Congenital hypoaldosteronism is a rare inherited autosomal recessive disease correlated with gene CYP11B2 in chromosome 8q24.3. Gene CYP11B2 encodes aldosterone synthase (CYP11B2), an enzyme responsible for the synthesis of aldosterone in the adrenal cortex. When mutated, gene CYP11B2 blocks the synthesis of aldosterone. Consequently, patients with congenital hypoaldosteronism experience recurring episodes of hypovolemia with hyponatremia, hyperkalemia, and metabolic acidosis.\textsuperscript{53}

**Congenital Adrenal Hyperplasia**

Gene CYP11B1 is located adjacent to gene CYP11B2 in chromosome 8q22. Gene CYP11B1 encodes enzyme 11\(\beta\)-hydroxylase, which mediates the synthesis of cortisol. Mutations to this gene decrease the synthesis of cortisol, thus increasing the secretion of ACTH. Consequently, steroid precursors are overproduced, resulting in virilization of the female genitalia in neonates, precocious pseudopuberty, accelerated somatic growth, premature epiphyseal closure in individuals of both genders, and high blood pressure in approximately two thirds of the individuals carrying the mutation. The mutation on gene CYP11B1 is the second most common cause of congenital adrenal hyperplasia.\textsuperscript{54}

**Apparent Mineralocorticoid Excess**

Enzyme 11\(\beta\)-hydroxysteroid dehydrogenase type 2 (11\(\beta\)HSD2), expressed in the cytoplasm of the principal cells, acts on steroid degradation and prevents the activation of mineralocorticoid receptors by glucocorticoids. Mutations on gene HSD11B2 encoding the enzyme may cause a rare hypertensive syndrome, referred to as apparent mineralocorticoid excess, whose clinical manifestations include salt-dependent hypertension, hypokalemia, and metabolic alkalalemia.\textsuperscript{55} Numerous case reports of apparent mineralocorticoid excess published in the literature have linked the disease to injudicious use of medicinal herbs. *Glycyrrhiza glabra*, also known as licorice, inhibits 11\(\beta\)HSD2 and consequently stimulates constant mineralocorticoid receptor due to cortisol overproduction.\textsuperscript{55-57}

**Nephrogenic Diabetes Insipidus**

The kidneys of individuals with nephrogenic diabetes insipidus cannot concentrate urine in response to the antidiuretic hormone. Children with nephrogenic diabetes insipidus have polydipsia, polyuria, hyposthenuria, dehydration, hypernatremia, and growth failure. Approximately 90% of the individuals diagnosed with nephrogenic diabetes insipidus have the X-linked recessive form of the disease caused by mutations on gene AVPV2 in chromosome Xq28. Autosomal dominant and recessive nephrogenic diabetes insipidus has been associated with mutations on gene AQP2 in chromosome 12q13.\textsuperscript{58,59}

**Final Considerations**

Inherited tubulopathies can affect the growth and development of children and may be accompanied or not by neurological disorders. A significant share of the children diagnosed with inherited tubulopathies develops pediatric chronic kidney disease.

Physicians must pay particular attention to clinical manifestations of persistent vomiting, polyuria, recurring episodes of dehydration, growth disorders, delayed development, and neurological involvement in pediatric patients, so that these individuals can be promptly referred to specialized centers. Knowledge of associated genetic defects and tubular transport mechanism alterations also improve diagnostic accuracy. Inherited tubulopathies will soon leave the category of rare renal diseases to join the roster
of ailments with new and better treatments, thus improving the prognosis of the children affected by them.

Despite the growing knowledge around the gene mutations associated with renal diseases, genetic tests are available only at a few centers. In Brazil, genetic tests are performed at a handful of teaching hospitals, such as the Hospital of the Federal University of Paraná, and the Central Institute and the Children’s Institute of the Hospital of the University of São Paulo.

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