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Review article

Pathophysiologic approach in genetic hypokalemia: An update

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ABSTRACT

The pathophysiology of genetic hypokalemia is close to that of non-genetic hypokalemia. New molecular pathways physiologically involved in renal and extrarenal potassium homeostasis have been highlighted. A physiological approach to diagnosis is illustrated here, with 6 cases. Mechanisms generating and sustaining of hypokalemia are discussed. After excluding acute shift of extracellular potassium to the intracellular compartment, related to hypokalemic periodic paralysis, inappropriate kaliuresis (> 40 mmol/24 h) concomitant to hypokalemia indicates renal potassium wasting. Clinical analysis distinguishes hypertension-associated hypokalemia, due to hypermineralocorticism or related disorders. Genetic hypertensive hypokalemia is rare. It includes familial hyperaldosteronism, Liddle syndrome, apparent mineralocorticoid excess,11beta hydroxylase deficiency and Geller syndrome. In case of normo- or hypo-tensive hypokalemia, two etiologies are to be considered: chloride depletion or salt-wasting tubulopathy. Diarrhea chlorea is a rare disease responsible for intestinal chloride depletion. Due to the severity of hypokalemic metabolic alkalosis, this disease can be misdiagnosed as pseudo-Bartter syndrome. Gitelman syndrome is the most frequent cause of genetic hypokalemia. It typically associates renal sodium and potassium wasting, hypomagnesemia, conserved chloride excretion (> 40 mmol/24 h), and low-range calcium excretion (urinary Ca/creatinine ratio < 0.20 mmol/mmol). Systematic analysis of hydroelectrolytic disorder and dynamic hormonal investigation optimizes indications for and orientation of genotyping of hereditary salt-losing tubulopathy.

1. Introduction

1.1. Potassium homeostasis

Plasma potassium is normally maintained within narrow limits (typically, 3.5 to 5.0 mmol/L) by several regulating mechanisms (for a review, [1]) that protect the organism from life-threatening increases in plasma potassium. Total extracellular potassium is about 60 to 80 mmol (20 to 25 mmol in plasma); thus, a meal can provide an extracellular volume equivalent to the prior extracellular potassium content, and could be expected to increase the extracellular potassium concentration 2-fold (Fig. 1). This is, however, prevented by early extracellular potassium shift toward the intracellular compartment (regulation of internal balance) and slower renal excretion of potassium intake (regulation of external balance). Although renal excretion of absorbed potassium is essential for the long-term regulation of serum potassium, it is not sufficient to maintain a constant serum potassium level after acute potassium intake [2]. It has been shown experimentally that approximately half of the potassium load is eliminated in the urine within 4–6 hours of acute intake. The small rise in serum potassium despite retention of the other half of the potassium load attests to a significant transfer of retained potassium to the intracellular compartment. This mechanism can be altered by inhibiting secretion of insulin or aldosterone or by blocking the β-adrenergic system, demonstrating the preponderant role of these hormonal systems in tolerance of acute potassium load [3–5]. Renal excretion of potassium load is a biphasic adaptation, with early "predictive" and slower secondary increases in potassium excretion. The predictive or "feed-forward" adaptation occurs before any increase in systemic plasma potassium level [2]. Due to these combined regulations, variations in plasma potassium level during the course of the day are commonly no greater than 10% [2].

Urinary potassium excretion is the result of two successive events: first, glomerular filtration, which determines the potassium load delivered to the renal tubules (approximately 4 mmol/L × 180 glomerular filtrate per 24 h: i.e., 720 mmol/24 h); and second, net renal tubular reabsorption (the sum of reabsorption and secretion). All segments of the nephron contribute to reabsorption of potassium, and more than 90% of this reabsorption is localized in the segments upstream of the distal tubules. It is generally agreed that only adaptation of potassium movement in the distal convoluted

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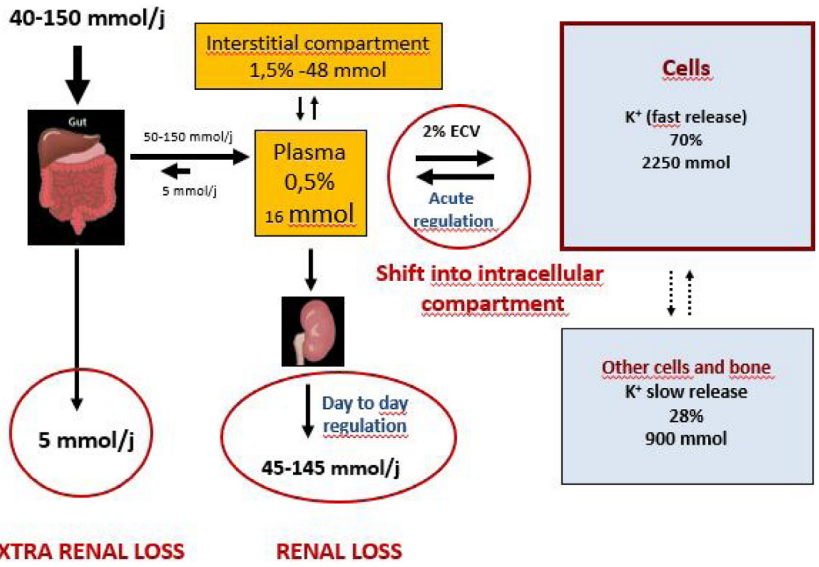

Fig. 1. Body potassium is very unequally distributed between extracellular and intracellular volumes, which contain respectively about 65 mmol and > 3000 mmol potassium. After a meal, about 50% of the potassium load shifts into the intracellular compartment, preventing onset of life-threatening hyperkalemia before the kidney has excreted the potassium intake. The pathophysiology of hypokalemia, and especially of genetic hypokalemia, may implicate abnormalities in either acute potassium shift into cells, or extra-renal or renal potassium wasting.

tubules and the collecting duct determine the fine regulation of serum potassium [5,6]. Physiologically, the distal part of the distal convoluted tubules and the collecting duct are the sites of net of potassium secretion. It is ensured by the principal cells, which express two major channels at their luminal side: the epithelial sodium channel (ENaC), sensitive to amiloride, enabling electrogenic transcellular reabsorption of sodium, and the renal outer medullary potassium channel (ROMK), enabling secretion of potassium into the tubular fluid [7]. Due to the reabsorption of water in the cortical and medullary collecting duct, which concentrates the secreted potassium, the rise in urinary concentration of potassium could favor back-diffusion of potassium toward the medullary interstitium. These phenomena are limited by the high concentration of interstitial potassium (> 30 mmol/L), generated by the mechanism of recycling and counter-current concentration of electrolytes [8].

The pathophysiology of hypokalemia and especially genetic hypokalemia may be related to abnormalities in either extra-renal or renal potassium homeostasis.

2. Renal adaptation to potassium depletion

Several regulatory mechanisms account for the adaptation of urinary potassium excretion to reduced potassium intake. Notably, the kidney's capacity to adapt to reduction in potassium intake is not as powerful as its capacity to adapt to reduction in sodium intake by excreting less than 10 mmol of sodium per 24 hours. A gradual decrease in potassium intake in humans leads to hypokalemia (kalemia < 3.6 mmol) when potassium intake is between 20 and 40 mM/24 h, depending on the individual. Thus, kaliuresis ≤ 20 mmol/24 h definitely corresponds to extrarenal hypokalemia, and kaliuresis > 40 mmol/24 h corresponds to renal hypokalemia, leaving an interval of uncertainty when kaliuresis ranges between 20 and 40 mmol/24 h.

As stated above, renal potassium wasting occurs in the distal nephron. Regulation at this site is challenging, because it is the site of fine-tuned renal regulation of water, salt, potassium and acid-alkali balance, and each regulation needs to be independent from the others. In other words, adaptation to specific loads of water, potassium, salt or acids needs to be achieved without affecting other balances. This is enabled by specific transporters for water and solutes (Na and K channels, aquaporin 2, proton and bicarbonate transporters) that are regulated by separate hormones and by counter-regulatory processes.

For example, distal secretion of potassium can be stimulated by an increase in fluid or sodium delivery as well as by aldosterone and vasopressin. Isolated increases in salt intake increase sodium delivery but decrease aldosterone secretion (due to increased blood volume), so that potassium secretion remains stable. Similarly, isolated increases in water intake increase water delivery but decrease vasopressin, so that potassium secretion again remains stable [9].

Complementary mechanisms are involved in adaptation to hypokalemia when extrarenal potassium wasting occurs. Firstly, hypokalemia inhibits aldosterone secretion [9]. In hypertensive renal hypokalemia, the increase in distal secretion of potassium is due to increased mineralocorticoid activity (associated with usual sodium diet). Plasma potassium level becomes highly dependent on salt intake [9]. A normal (uninhibited) circulating aldosterone concentration, however, does not fully ensure renal adaptation to reduced potassium intake, suggesting aldosterone-independent mechanisms of adaptation to potassium depletion. Firstly, potassium depletion and aldosterone conversely regulate renal outer medullary potassium channel (ROMK) expression. Experimentally, cortical ROMK expression was upregulated by aldosterone, whereas medullary ROMK was downregulated by potassium depletion [10]. Secondly, potassium depletion stimulates the distal Na-Cl cotransporter via phosphorylation and inactivation of the Kelch-like 3 ubiquitin ligase [11,12]. The resulting increase in sodium reabsorption in the distal convoluted tubules reduces sodium delivery to the collecting duct, which in turn reduces distal secretion of potassium. Finally, potassium depletion induces expression of the collecting duct of an H^+/K^+ ATPase pump in the intercalated cells, responsible for net reabsorption of potassium [13]. In most cases, the mechanisms of renal hypokalemia onset are associated with adaptation defects. Hypertensive hypokalemia results from insufficient inhibition of aldosterone, by hypokalemia in primary aldosteronism or by diseases associated with apparent mineralocorticoid excess. The monogenic forms of hypertension, including hypokalemic forms, were recently reviewed [14]. Normo- or hypo-tensive renal hypokalemia mostly results from increased

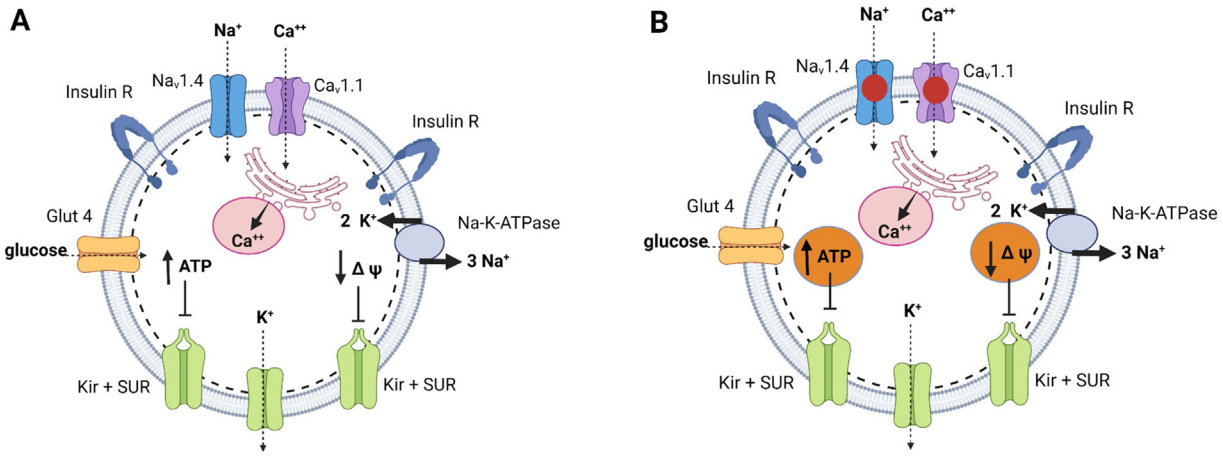

Fig. 2. Pathophysiologic hypothesis for hypokalemic periodic paralysis. A: In physiological settings, the resting potential of the cell membrane mainly depends on the activities of Na-K-ATPase and the inward rectifier K+ channel (Kir). The latter becomes voltage- and ATP-sensitive when associated with the sulfonylurea receptor (SUR). The depolarization wave activates sodium and then calcium voltage-gated muscle channels, leading to increased intracellular calcium and, in turn, muscle contraction. B: Hypokalemic periodic paralysis is mainly associated with mutations in skeletal muscle sodium (Nav1.4) and calcium (Cav1.1) channels (in 15% and 70% of cases, respectively). Mutated channels cause an anomalous leakage current, which is active at resting potential and produces susceptibility to paradoxical depolarization, leading to flaccid paralysis. After a high-carbohydrate meal, glucose enters through GLUT4, which is highly expressed in type II muscle fibers. Intracellular glycolysis increases the ATP/ADP ratio, which inhibits Kir activity and in turn depolarizes the plasma membrane. During exercise, Na-K-ATPase is stimulated by the high concentration of extracellular potassium. On cessation of exercise, Na-K-ATPase remains high, responsible for transient hypokalemia that favors paradoxical depolarization, which can trigger paralytic attacks.

salt delivery to the distal tubules without appropriate decrease in plasma aldosterone concentration.

3. Extrarenal genetic hypokalemia

3.1. Case report 1. Hypokalemic periodic paralysis

> A 31-year-old man old was referred for history of flaccid paralysis, accompanied by profound hypokalemia (2.2 mmol/L). He reported that, the day before, he had consumed a boxful of candies while watching a soccer game on TV. He was transferred to the emergency unit, and infused with potassium. Hypokalemia was corrected and the patient was discharged the day after. He had experienced such transient paralysis once in the past, 1 hour after riding a jet ski, but plasma potassium was not measured at that time and the paralysis resolved within a few hours. At consultation, the patient had normal clinical examination and blood analysis, including ionogram; renin and aldosterone concentrations were within the normal range.

Hypokalemic periodic paralysis type 1 (OMIM 170400) is a rare disease (prevalence 1/100,000). It is characterized by focal or generalized skeletal muscle flaccid paralysis episodes, lasting between hours and days, and associated with concomitant acute hypokalemia (<2.5 mEq/L) [4,15–17]. This disease has dominant inheritance, but shows markedly lower penetrance in females, whereas penetrance is 100% in males. The first attack usually occurs in the first or second decade of life, but frequency is variable, from once a lifetime to several per week, and is highest between the ages of 15 and 35 years, subsequently decreasing with age. In the fourth or fifth decade of life, a number of patients develop permanent muscle weakness, due to vacuolar myopathy. Attacks of muscle weakness usually involve all four limbs but spare the face.

For more information, we recommend the video posted by a young physician suffering from the disease who recorded a self-video during an attack[1]. Attacks are frequently triggered (as in the present case) by carbohydrate load or by rest after exercise (but not during exercise). Other triggering factors include emotion, stress, cold exposure and alcohol consumption. Administration of potassium during the attack improves symptoms and shortens their duration. Preventive measures include avoiding the main trigger factors (carbohydrate-rich meals and strenuous exercise). Acetazolamide as well as potassium salts are useful in preventing attacks, and oral administration of concentrated potassium solution reduces its severity and duration [15,16]. The hallmark of the disease is sarcolemma depolarization, induced by hypokalemia (2.5 to 3.5 mEq/L) during the attacks. This hypokalemia-induced depolarization is in contrast to the prediction, based on Nernst's equation that membrane potential hyperpolarizes during hypokalemia, and is therefore termed "paradoxical". Paradoxical depolarization is central to the pathogenesis of hypokalemic periodic paralysis, as it inactivates the voltage-gated Na channels in skeletal muscle, causing muscle non-excitability and paralysis [17]. Hypokalemic periodic paralysis is, in 70% of cases, associated with mutations in the *CACNA1S* gene encoding the alpha-1 subunit of the calcium L-type voltage-gated channel (Cav1.1). About 15% of cases are related to mutations in the *SSN4A* gene encoding for subunit 4 of the sodium voltage-gated channel (Nav1.4). About 10-15% of familial cases of hypokalemic periodic paralysis are unmapped. Mutated muscle channels cause an anomalous leakage current, which is active at the resting potential and is liable to induce paradoxical depolarization [15–17] (Fig. 2). Acquired hypokalemic paralysis is reported in patients with metabolic acidosis or thyrotoxicosis, regardless of etiology. Typically, paralytic attacks in thyroid toxicosis cease when hyperthyroidism is controlled, and recur if hyperthyroidism returns. Evidence indicates that thyrotoxic periodic paralysis results from a combination of genetic predisposition, thyrotoxicosis and environmental factors (such as high-carbohydrate diet) [18,19].

[1] (https://www.youtube.com/watch?v=tbP9VhaREO0).

3.2. Case report 2. Familial hyperaldosteronism

A 41-year-old man and his 16-year-old son old were referred in 1964 for hypertension. The father had been hypertensive since the age of 19. Reserpine treatment was ineffective and treatment by chlorthalidone led to profound hypokalemia (2.0 mmol/L). His son was found to be hypertensive at 13 years of age. In both, renin activity was depressed, with plasma aldosterone elevation. At admission, the father's and son's blood pressure was 190/110 mmHg and 180/120 mmHg, respectively. Both had low plasma potassium (2.5–3.1 mmol/L for the father, 3.2–3.8 mmol/L for the son). Fine steroid phenotyping revealed no baseline or circadian corticosteroid abnormalities in response to ACTH or dexamethasone. Unexpectedly, all abnormalities in both father and son were relieved by dexamethasone 2 mg daily, recurred following cessation of treatment and were again relieved by a second course of treatment. Both hypertension and hypokalemia were sensitive to aldosterone antagonists, but the patients were treated with dexamethasone after discharge.

This is a short summary of the first case report of what was known as glucocorticoid-remediable aldosteronism (GRA), now referred to as familial aldosteronism type 1 [20].

In the last decade, the discovery of genetic abnormalities responsible for sporadic and familial forms of primary aldosteronism has shed light on the pathogenesis of this disorder.

Familial hyperaldosteronism type 1 (FH1, OMIM 103900) generally presents with severe hypertension in childhood or young adulthood, with autosomal dominant inheritance. The final three steps of aldosterone synthesis, 11 beta- and 18-hydroxylation and 18-oxidation, are mediated by CYP11B2, a cytochrome P450 in the zona glomerulosa of the adrenal cortex. A related isozyme in the zona fasciculata, CYP11B1, is required for cortisol synthesis; this isozyme, which is normally expressed at much higher levels than CYP11B2, only has 11 β-hydroxylase activity. In humans, the *CYP11B1* and *CYP11B2* genes encoding respectively for 11 β-hydroxylase and for aldosterone synthase have very strong sequence homology and are close together, at about 50 kb. In FH1, CYP11B2 activity is under the control of ACTH (which normally regulates CYP11B1), resulting in ACTH-sensitive hyperaldosteronism [21,22]. The disease is caused by unequal crossover of the *CYP11B1* and *CYP11B2* genes, resulting in a hybrid gene that combines the initial part of *CYP11B1*and the 3′ sequence of *CYP11B2*[21]. This duplication-fusion gives a chimeric gene coding for aldosterone synthase but under the control of ACTH (Fig. 3A). Accordingly, cell culture experiments demonstrated that hybrid gene expression was stimulated by ACTH, leading to increased CYP11B2 activity and production of aldosterone. Moreover, analysis of an adrenal tumor in an affected patient showed that the hybrid *CYP11B1/CYP11B2* gene was expressed at higher levels than either CYP11B1 or CYP11B2 in the adrenal cortex. Both *CYP11B1* and the hybrid gene were expressed in all three zones of the cortex (Fig. 3A) [21]. Exposure of cortisol to abnormal CYP11B2 activity in the zona fasciculate leads to increased production of 18-hydroxycortisol and 18-oxocortisol, excreted in large amounts, far above those observed in adrenal adenoma.

To date, other genetic forms of primary aldosteronism have implicated germline or somatic mutations in channels involved in cell signaling in adrenal aldosterone-productive cells [22,23]. In these cells, angiotensin II physiologically stimulates aldosterone synthesis by inducing depolarization of the membrane that activates voltage-gated Ca^{2+} channels, resulting in intracellular Ca^{2+} elevation. The calcium signal promotes transcription of aldosterone synthase (CYP11B2), resulting in production of aldosterone (Fig. 3B). Mutations in *KCNJ*5, encoding the potassium channel (somatic or germline in FH-3), in *ATP1A1*, encoding the Na-K-ATPase subunit (somatic), and in *CLCN2*, encoding the voltage-gated Ca channel (somatic or germline in FH-2), lead to cell membrane depolarization, calcium signaling and overproduction of aldosterone. Other mutations more directly affect intracellular calcium concentration: activating mutations in the *CACNA1H* gene, encoding voltage-gated calcium channels in FH-4, directly cause an increase in Ca^{2+} conductance, while mutations in *ATP2B3*, encoding Ca^{2+} ATPase, reduce Ca^{2+} export from the cell. Activated calcium signaling results in overproduction of aldosterone (Fig. 3C) [22,23].

3.3. Case report 3. Liddle syndrome

A 14-year-old boy was referred for evaluation of hypertension (blood pressure, 186–226/114–130 mmHg) and hypokalemia (2.31 mEq/L). Plasma renin activity and urinary aldosterone were respectively a third and a half of the lower limit of normal. The patient had severe growth retardation (−3 SD). Previous administration of spironolactone, triamterene and prednisone failed to lower blood pressure. Familial investigation identified 6 out of 30 relatives with severe hypertension and depressed plasma renin activity and hypokalemia (2.32–2.78 mmol/L). Both hypertension and hypokalemia resolved with 10 mg amiloride. Genetic investigation demonstrated a missense mutation (P614L) in the gene encoding the ß ENaC subunit, indicating Liddle syndrome. This is a summary of a case reported by Gao et al. [24].

Liddle syndrome (OMIM #177200) is an autosomal dominant disorder characterized by early-onset hypertension associated with hypokalemia, metabolic alkalosis, low plasma renin activity (PRA) and low aldosterone. The degree of phenotypic expression may vary even within a given family [25]. The syndrome was first described by Liddle et al. in 1963, in a 3-generation family presenting hypertension associated with hypokalemic alkalosis. The hypertension was due not to hyperaldosteronism but to a renal tubule peculiarity [25]. Thirty years later, in 1994, in the affected members of the kindred originally described by Liddle, Shimkets et al. identified a premature stop codon (R564X) in a subunit of the renal epithelial sodium channel (ENaC) [26]. ENaC is composed of 3 homologous subunits, α, β and γ, encoded by the *SCNN1A*, *SCNN1B* and *SCNN1G* genes, respectively. Liddle syndrome can be caused by missense mutations in the PY motif of the α, β or γ subunit (subtypes 1 to 3). Truncation of the C-terminal domain does not affect single-channel conductance or open-state probability, suggesting that the increase in ENaC function is related to an increase in apical cell-surface expression in the channel. Truncation of the C-terminal domain of a subunit leads to the loss of its PY motif, which disrupts binding to the ubiquitin ligase Nedd4-2 [26,27]. The lesser degradation pf proteasomes leads to accumulation of active channels at the cell surface [26]. The resulting increase in Na reabsorption in the distal tubules explains the elevated blood volume and blood pressure and low renin and aldosterone concentrations [26]. This mechanism also explains the high sensitivity to amiloride of this particular form of hypertension [24,25].

3.4. Case report 4. Apparent mineralocorticoid excess

The mineralocorticoid receptor (MR) itself does not discriminate between aldosterone and cortisol; mineralocorticoid specificity is conferred by the cytoplasmic 11β-hydroxysteroid dehydrogenase type 2 enzyme (11 β HD2), which rapidly converts cortisol

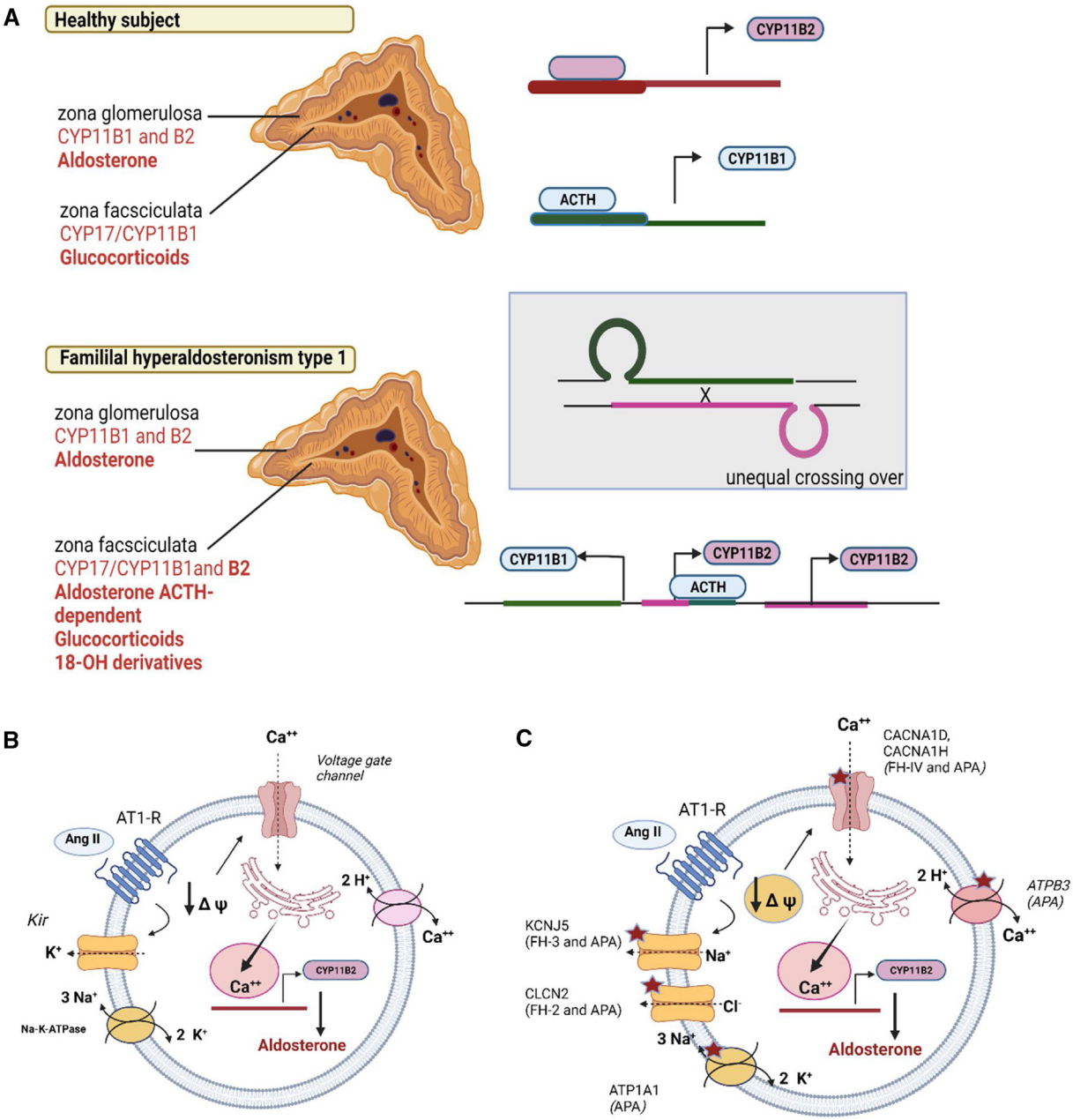

Fig. 3. Pathophysiology of genetic hyperaldosteronism. In healthy subjects, aldosterone is synthesized in the zona glomerulosa, which expresses CYP11B2 under the control of angiotensin II. The zona fasciculata expresses CYP17 and CYP11B1, mandatory for synthesis of cortisol, but CYP11B2 is lacking for 18-hydroxylation. A. In familial aldosteronism type 1 (FH1), an unequal crossover of *CYP11B1* and *CYP11B2* genes results in a hybrid gene producing aldosterone synthase under the control of ACTH. B. In adrenal cells, Ang II binding to AT1R leads physiologically to adrenal cell membrane depolarization, opening voltage-gated calcium channels and activating calcium signaling, the main trigger for aldosterone biosynthesis. C. Mutations in various channels and pumps have been reported in FH (germline mutations) and aldosterone-producing adenoma (APA: somatic mutations). Mutations in genes encoding the a1 Na-K-ATPase subunit (*ATP1A1*), a chloride or a potassium channel (CLCN2, *KCNJ5*), lead to sustained activation of voltage-gated Ca channels. Mutations in the gene coding for the calcium voltage-gated channel (*CACNA1D)* or αCa-ATPase pump (*ATPB3)* are more directly responsible for accumulation of calcium in cells.

into inactive metabolites and thus protects the MR from "illicit" occupation by cortisol. The importance of the enzyme becomes clear considering that the ratio of circulating aldosterone to cortisol is 1:100–1000. Apparent mineralocorticoid excess (AME, OMIM218030) is an autosomal recessive form of low-renin hypertension associated with low aldosterone, metabolic alkalosis, hypernatremia and hypokalemia [29,31]. The disorder is due to a congenital defect in 11-beta-hydroxysteroid dehydrogenase type 2 (HSD11B2) activity, resulting in decreased conversion of biologically active cortisol to inactive cortisone [31,32]; this defect allows cortisol to act as a ligand for the mineralocorticoid receptor, resulting in sodium retention and increased volume [32]. There is a favorable therapeutic response to spironolactone (Fig. 4).

In other inherited diseases, overstimulation of MR may be due either to accumulation of other mineralocorticoids than aldosterone or to abnormal MR specificity [14]. Patients with 11beta-hydroxylase deficiency present hypertension and hypokalemia. 11beta-hydroxylase is responsible for converting deoxycorticosterone to corticosterone in the zona glomerula and 11-deoxycortisol to cortisol in the zona fasciculata. In congenital adrenal hyperplasia, due to steroid 11beta-hydroxylase deficiency (OMIM 202010), aldosterone and cortisol are deficient, and

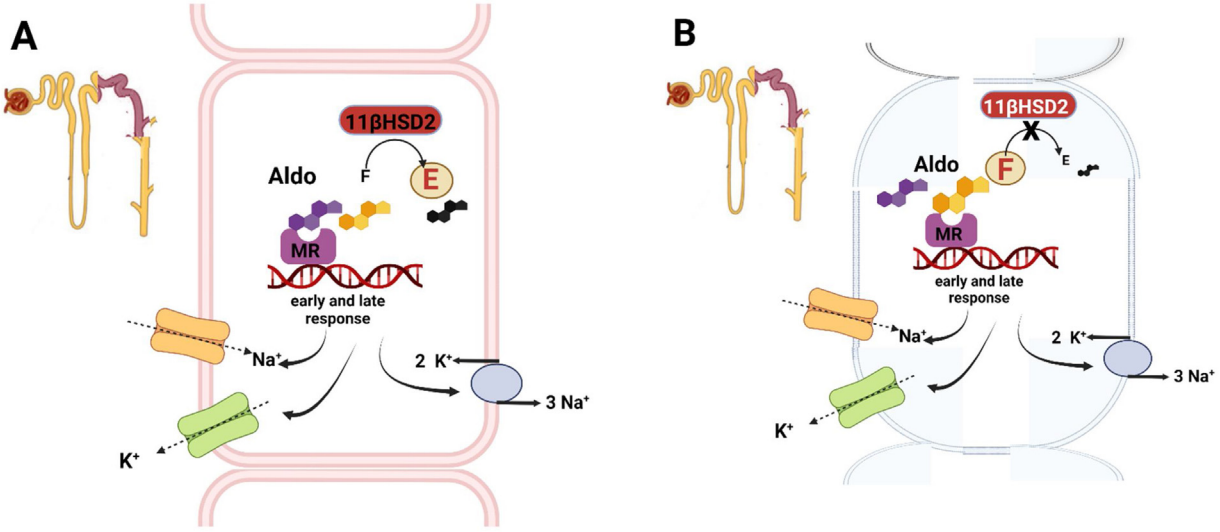

Fig. 4. Pathophysiology of apparent mineralocorticoid excess syndrome. A. In the mineralocorticoid-sensitive segment, 11β-hydroxysteroid dehydrogenase type 2 confers mineralocorticoid-specificity on aldosterone by converting cortisol into cortisone, which has little or no affinity for MR. B. A defect in this enzyme enables cortisol binding to the mineralocorticoid receptor. Because the concentration of cortisol is far higher than that of aldosterone, this results in severe apparent mineralocorticoid excess.

A 3-year-old girl was referred to the General Hospital, University of California School of Medicine, San Francisco, for history of hypertension (180/140 mm Hg) and hypokalemia (2.7 mEq/L) associated with cardiomegaly and left ventricular hypertrophy, all discovered within the first year of life. She had severe growth retardation (−3 SD). Previous administration of spironolactone, triamterene and prednisone failed to lower blood pressure. Under potassium supplementation, urinary aldosterone and morning plasma cortisol (4.9 µg/dL) levels were low. Plasma renin activity was depressed. Because of low 17-hydroxysteroid excretion, an ACTH test was performed, but 17-hydroxysteroid failed to increase. Under low sodium diet, weight decreased and blood pressure improved. Prolonged ACTH administration (40 units/day, for 5 days) under low sodium diet increased plasma cortisol to 32 µg/dL. Hypertension worsened concomitantly, and plasma potassium fell below 2.0 mmol/L despite no change in aldosterone excretion. In this case report, published in 1977, and very briefly summarized here, the authors suggested the presence of a mineralocorticoid other than aldosterone [28]. Two years later, in the same patient and another patient, Ulick et al. demonstrated a decreased rate of cortisone conversion [29]. This picture was referred to as "apparent mineralocorticoid excess". In 1995, Mune et al. identified 7 homozygous or compound heterozygous mutations in the *HSD11B2* gene in 9 patients from 8 families with apparent mineralocorticoid excess and hypertension. In-vitro functional expression studies showed that the mutant enzymes had low or undetectable enzyme activity as compared to controls [30].

androgens and mineralocorticoid precursors accumulate. Therefore, patients present hyperandrogenia, hypertension and hypokalemia [33]. In Geller syndrome (OMIM 605112), overstimulation of MR is due to a single S810L missense mutation in the gene encoding for the MR, which alters the hormonal binding domain specificity of the MR [34]. This results in constitutive MR activity and sensitivity to progesterone and other steroids lacking 21-hydroxyl groups. Thus, these steroids, which are normally MR antagonists, become potent MR agonists. MR L810 carriers display early-onset hypertension with low renin and aldosterone levels. Due to the 100-fold increase in progesterone during pregnancy, female carriers show aggravated hypertension during pregnancy and are at risk of precipitating delivery in the sixth or seventh month of gestation. Because spironolactone is a potent agonist of the mutated MR, it is contraindicated in MR L810 carriers [34].

3.5. *Case report 5. Salt-wasting tubulopathy*

A 21-year-old man was referred for cramps and asthenia. Clinical examination showed no significant abnormality and normal blood pressure (123/88 mmHg, 73 bpm). Blood examination showed low serum potassium concentration (2.6 mmol/L) with inappropriate urinary potassium/creatinine ratio (> 2 mmol/mmol), and low magnesium concentration (0.40 mmol/L). Plasma renin concentration was 1.5-fold above the upper limit of normal, but aldosterone was in the normal range. The patient reported salt craving since childhood, and had history of growth retardation related to pubertal delay, with normal height on examination (173 cm). Genetic investigation confirmed the diagnosis of Gitelman syndrome, showing compound heterozygous mutation in *SLC12A3* gene encoding for the human thiazide-sensitive cotransporter (hTSC), also known as sodium chloride cotransporter (NCC). This is a personal (not previously reported) case report.

In salt-wasting tubulopathy, hypokalemia results from increased sodium delivery to the cortical collecting duct and secondary hyperaldosteronism. In Bartter/Gitelman syndromes, renal sodium and potassium wasting is associated with metabolic alkalosis and preserved chloride excretion. The syndromes involve inactivating mutations in transporters involved in transcellular reabsorption of sodium and chloride or their regulatory proteins (Fig. 5). Clinically, Bartter syndrome is classified in 2 subtypes: severe antenatal/neonatal Bartter syndrome, which develops during the fetal period with polyhydramnios and preterm delivery; and the relatively mild classic Bartter syndrome, which is usually revealed by failure to thrive during infancy [35]. Gitelman syndrome is 100-fold more frequent than Bartter syndrome (prevalence 1/10,000 vs. 1/1,000,000) and is usually diagnosed at school age, often on laboratory findings motivated by growth retardation, asthenia, cramps or concomitant disease. Salt craving since childhood is present in both diseases. In Bartter syndrome

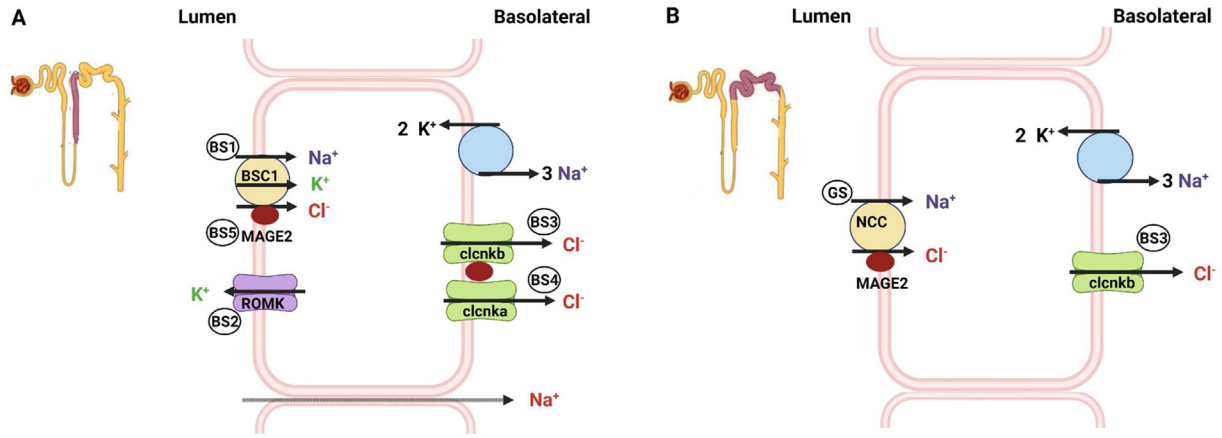

Fig. 5. Pathophysiology of Bartter and Gitelman syndromes. These syndromes involve inactivation mutations in transporters involved in transcellular reabsorption of sodium and chloride or their regulatory proteins (see text). Bartter syndrome (A) affects the thick ascending limb and Gitelman syndrome (B) affects the distal convoluted tubule. Bartter type 3 displays a broad range of phenotypes, from antenatal Bartter to Gitelman syndrome.

but not in Gitelman syndrome, urinary concentration is altered, resulting in polydramnios in antenatal forms and polyuria after birth. Hypomagnesemia is generally severe in Gitelman syndrome, but mild or absent in Bartter syndrome. Calcium excretion is low (calcium/creatinine ratio < 0.2 mmol/mmol) in Gitelman syndrome, but normal or elevated in Bartter syndrome [36]. Gitelman syndrome is mainly caused by inactivating variants in the *SLC12A3* gene that encodes NCC [37]. Bartter syndrome is a heterogeneous disease (for a review, see [38]). Antenatal Bartter syndrome may be related to alteration in sodium and chloride entry on the luminal side of thick ascending limb cells. In Bartter syndrome type 1 (OMIM 601678), this results from an inactivating mutation in the *SLC12A1* gene, coding for the Na-K-2Cl co-transporter NKCC2 [38]. In Bartter type 2 (OMIM 241200), luminal recycling of potassium is disrupted due to inactivation of *KCNJ1* coding for ROMK (OMIM 241200) [38]. Because ROMK is also expressed in the main cells of the collecting duct, this form is characterized by transient neonatal hyperkalemia preceding renal hypokalemia. Bartter syndrome can also be due to basolateral exit of chloride. Bartter syndrome type 3 (OMIM 607364) is due to an inactivating mutation in the *CLCNKB* gene coding for the ClC-Kb chloride channel, expressed in thick ascending limb cells and in the distal convoluted tubules. Bartter syndrome type 3 is usually diagnosed during infancy, due to failure to thrive. However, it displays a broad range of phenotypes, from antenatal Bartter syndrome to Gitelman syndrome, and this heterogeneity can even be observed within a single family [39]. Bartter syndrome type 3 is associated with severe alkalosis due to chloride depletion, likely due to CLC-kb's need for pendrin-dependent adaptation to chloride depletion [39]. ClC-Kb and CLC-ka, a homologue of CLC-kb also expressed at the basolateral membrane of thick ascending limb cells, share a common β subunit, named Barttin. An inactivating mutation of the *BSND* gene encoding this subunit leads to Bartter syndrome type 4a (602522), a severe antenatal Bartter syndrome associated with sensorineural hearing loss [40]. A similar phenotype was reported in patients with digenic mutations in both *CLCNKA* and *CLCNKB* genes, classified as Bartter syndrome type 4b (OMIM 613090) [41]. Bartter syndromes 1 to 4 are autosomal recessive diseases. In contrast, type 5 Bartter syndrome (OMIM 300971) shows a transient clinical picture from fetal to neonatal life, with an X-linked mode of inheritance. It is due to an inactivating mutation in the *MAGED2* gene [42]. *MAGED2* is located on the X chromosome and encodes for melanoma-associated antigen D2 (MAGE-D2). MAGE-D2 is expressed in the thick ascending limb of the loop of Henle and in the distal convoluted tubules in the developing and adult kidney, where it acts as a regulator of NKCC2 and NCCT expression. Onset of polyhydramnios Bartter syndrome 5 occurs several weeks earlier than in other forms of antenatal/neonatal Bartter syndrome, and may require serial amnioreduction. However, Bartter syndrome 5 improves after birth during the first 2 years of life [43].

Other tubulopathies are associated with renal wasting of sodium, potassium and/or magnesium. Severe cases of autosomal dominant hypocalcemia accompanied by hypokalemia, hypomagnesemia and metabolic alkalosis have been reported [44,45]. Patients affected with renal cysts and diabetes syndrome (OMIM 137920) can have hypokalemia and hypomagnesemia. The disease has autosomal dominant inheritance and is due to mutations in the *HNF1B* gene encoding transcriptional factor HNF1B [46]. Hypokalemia, metabolic alkalosis and hypomagnesemia are also present in SESAME/EAST syndrome (OMIM612780) and associated with seizures, sensorineural hearing loss, ataxia, mental retardation and electrolyte imbalance. It is caused by loss-of-function mutations in the *KCNJ10* gene encoding for the KCNJ10 inwardly-rectifying potassium channel. This channel is expressed on the basolateral side of distal renal tubules. It contributes to a cell-negative transmembrane potential and sustains the function of primary sodium/potassium ATPase by recycling potassium at the basolateral side of the cells. The extrarenal phenotype in this disease predominates, leading to early pediatric diagnosis [47].

3.6. Case report 6. Congenital extrarenal chloride depletion

A 34-year-old man was referred for diarrhea since birth. In early childhood he was hospitalized many times because of volume depletion and hypokalemia, and "congenital alkalosis with diarrhea" was diagnosed. Endoscopic and X-ray studies of the gastrointestinal tract were repeatedly normal. In adulthood, he suffered diarrhea with fecal incontinence, with 6 to 12 stools a day. Under regular diet, stool volume was 2.2 l/day, with a higher chloride concentration (139 mmol/L) than the sum of sodium and potassium concentrations (90 + 37 mmol/L). It was hypothesized that inhibition of chloride secretion might reduce the amount of chloride delivered to the intestine. High-dose omeprazole was given and almost fully inhibited gastric secretion of chloride acid, dramatically improving the patient's condition. The number of stools decreased to 2–4 per day, and fecal incontinence and hydro-electrolytic disorder resolved. This report, published in 1997, was the first to suggest efficacy for proton pump inhibitors in congenital chloride diarrhea [48].

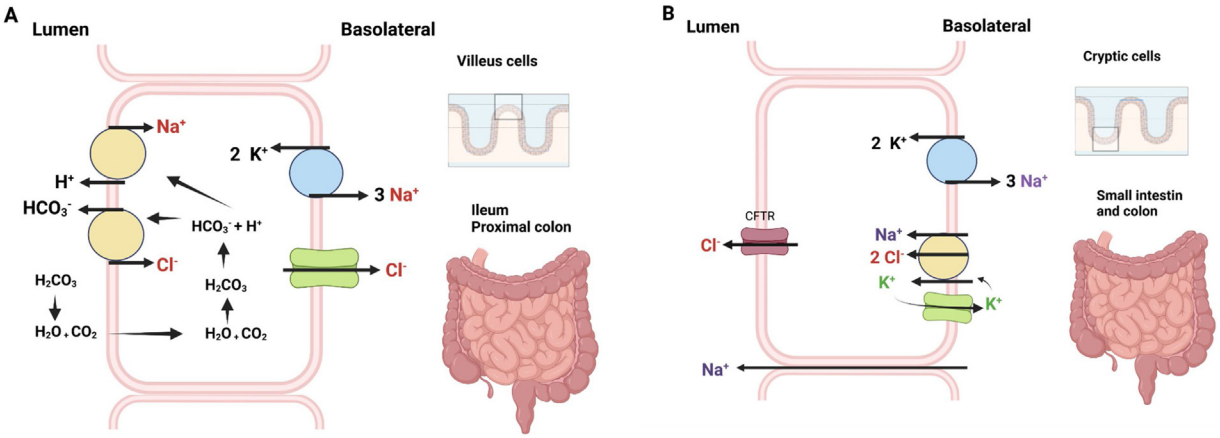

Fig. 6. Pathophysiology of congenital chloridorrhea. A: Congenital chloridorrhea is due to mutation in *SLC26A3* leading to loss of function of a Cl/HCO_3 exchanger (DRA). In villous intestinal cells, sodium and chloride absorption partly involves coupling of Na/H and Cl/HCO_3 exchangers. Loss of function in Cl/HCO_3 exchangers leads to intestinal chloride wasting and decreased bicarbonate secretion and hence to chloride-depleted metabolic alkalosis. B: In cryptic intestinal cells, transcellular chloride secretion involves basolateral chloride entry though an Na/K/Cl cotransporter that exits across the CFTR chloride channel. Transcellular chloride secretion is coupled to paracellular voltage-driven sodium secretion. In cystic fibrosis, overactivity of CFTR leads to increased chloride secretion in cryptic cells. These diseases can be misdiagnosed as Bartter syndrome if urinary chloride excretion is not measured.

Chloride-depletion hypokalemia involves extrarenal chloride wasting associated with bicarbonate gain. In this setting, the loss of potassium is not extrarenal but due to renal potassium wasting. The bicarbonate load is excreted by the kidney in association with cations, mainly sodium and potassium. This results in renal sodium and potassium wasting. In vomiting, the acute load of bicarbonate generated by gastric loss of chloride hydrogen results in severe metabolic alkalosis, secondary hyperaldosteronism, renal potassium wasting and low chloride excretion (< 20 mmol/L). In recent vomiting, metabolic acidosis remains, natriuresis drops, but adaptation to hypokalemia is impaired by secondary hyperaldosteronism and chloride depletion. Thus, potassium excretion remains > 20 mmol/24 h. Congenital chloride depletion is due not to increased gastric chloride hydrogen secretion but to either decreased intestinal chloride absorption or increased intestinal chloride secretion.

In villous intestinal cells, sodium and chloride absorption partly involves coupling of Na/H and Cl/HCO_3 exchangers. Congenital chloridorrhea type 1 is an autosomal recessive disease characterized by lifelong watery diarrhea of prenatal onset (OMIM 214700). It is caused by mutation in member 3 of the solute carrier family 26 (*SLC26A3*), encoding for a luminal intestinal Cl/HCO_3 exchanger (Fig. 6A). Affected children have diarrhea with an extremely high stool chloride concentration (> 90 mmol/L), a direct consequence of absence of the apical membrane Cl/HCO_3 exchanger. Intestinal HCO_3 secretion is reduced, associated with chloride depletion, and patients are markedly alkalotic with secondary hyperreninemic hyperaldosteronism, so that the disease can be misdiagnosed as pseudo-Bartter syndrome [49]. The down-regulated in adenoma (DRA) gene also transports sulfate and other anions. DRA is distinct from the AE (anion exchanger) gene family that encodes the Cl/HCO_3 exchangers in erythrocytes and several other tissues. Thus, Cl/HCO3 exchange in renal tubules, erythrocytes and other cells is unaffected in individuals with congenital chloridorrhea, as are other intestinal transport processes. Oral intake of chloride, sodium and potassium must exceed fecal output. Proton pump inhibitors have been proposed as treatment (as in the present case) but were not constantly effective [48,50,51]. In contrast, butyrate and cholestiramine treatments reproducibly reduced diarrhea severity through stimulation of NHE2 and NHE3 Na/H exchangers (stimulation of reabsorption in villous cells) and inhibition of the basolateral Na-K Cl cotransporter in cryptic cells (inhibition of NaCl secretion in cryptic cells) [49].

Similar patterns of congenital chloridorrhea are observed in cystic fibrosis. The disease results from mutations in the *CFTR* gene (located on chromosome 7) that alter the function of its product, CFTR, an ATP-binding cassette. This protein functions as a low-conductance Cl-selective channel gated by cycles of ATP-binding. CFTR is expressed on the apical plasma membrane of many epithelial cells. In these cells, transcellular chloride secretion involves basolateral chloride entry though an Na-K-2Cl cotransporter and luminal exits across the CFTR chloride channel. Transcellular chloride secretion is coupled to paracellular voltage-driven sodium secretion. In cystic fibrosis, CFTR overactivity leads to increased chloride secretion by cryptic intestinal cells (Fig. 6B).

3.7. Case report 7. Congenital tubular acidosis

A 19-year-old woman was addressed for follow-up of nephrocalcinosis discovered at the age of 6.5 years, revealing tubular metabolic acidosis. Familial investigation found metabolic acidosis in her younger sister, mother and aunt. She displayed no extrarenal symptoms. She was asked to stop bicarbonate salt supplements the day before investigation. Blood examination showed metabolic acidosis (urinary pH 7.32, PCO_2 38 mmHg, HCO_3^- 19 mmol/L), inappropriate renal adaptation to acidosis (urinary pH 7.30, ammonium excretion 17 mmol/24 h and titratable acid 1 mmol/24 h). She had stage 2 renal failure (CKDepi 55 ml/min/1.75 m^2) with elevated calcium excretion (7 mmol/24 h) and secondary hyperaldosteronism (renin and aldosterone concentrations respectively 1.5 and 2-fold above the upper limit of normal). Urinary citrate excretion was almost fully abolished. Genetic investigation found missense mutation in the gene encoding for the kidney-specific Cl/HCO3- exchanger kAE1, expressed at the basolateral membrane of type-A intercalated cells of medullary collecting ducts. The mutation changes a well-conserved amino acid (R589C), leading to misrouting of the antiporter to the luminal membrane.

Maintenance and control of systemic acid–alkali balance by the kidney is achieved via 3 major processes: reabsorption of filtered bicarbonate, excretion of acid (mostly in the form of ammonium and titratable acidity), and de-novo synthesis of bicarbonate

to replenish bicarbonate lost in metabolism. The kidneys filter about 4500 mEq bicarbonate per day, which is usually entirely reabsorbed along the nephron. About 80% of filtered bicarbonate is reabsorbed in the proximal tubule. Metabolism consumes bicarbonate and produces acids that require buffering by bicarbonate. Urinary acidification involves all the mechanisms that allow distal secretion of protons and titration by buffers, in order to excrete acid load as titratable acids and ammonium ions. Renal tubular acidosis (RTA) occurs when the kidneys are unable to adequately reclaim filtered HCO_3^- or secrete sufficient hydrogen ions to maintain acid–alkali homeostasis. RTA is classified as proximal or distal, but a combination of the two can be observed, especially in children [52]. In proximal RTA, the primary defect is an inability to reabsorb bicarbonate in the proximal tubules. Excretion of acid in the distal tubule is normal, and the urine is normally acidic, with pH down to 5.5 during acidosis. Proximal RTA can be part of a Fanconi syndrome (not detailed here), or isolated tubular dysfunction, sometimes associated with extrarenal signs. Proximal autosomal RTA associated with ocular abnormalities and mental retardation is an autosomal recessive disease (OMIM 604278). In its complete form, it associates severe hyperchloremic acidosis, maximum tubular bicarbonate reabsorption about half normal, growth retardation, and mental retardation. Ocular signs include nystagmus, cataract, corneal opacity, glaucoma, and band keratopathy. It is due to mutation in the *SLC4A4* gene encoding for the Na-HCO3-cotransporter, expressed at the basolateral membrane of proximal tubular cells. Autosomal recessive proximal RTA associated with osteopetrosis has been attributed to an inactivating mutation in the CA2 gene encoding carbonic anhydrase II (OMIM 259730). Patients suffer fractures and severe mental retardation. Distal renal tubular acidosis (dRTA) involves inability of the distal tubule to generate a sufficiently large hydrogen ion gradient between blood and tubular fluid. Thus, excretion of ammonium ions and titratable acid is reduced, and urinary pH is usually above 5.3 despite overt acidosis.

dRTA may present as a familial disease transmitted in either autosomal dominant or recessive pattern (for review see [53]). Congenital dRTA results from a defect in distal proton secretion. In the α-intercalated cells of the distal nephron, luminal secretion of hydrogen ions is mediated by the H^+-ATPase pump. It is associated with basolateral efflux of bicarbonate across the membrane, mediated by kidney anion exchanger 1 (kAE1). Autosomal dominant renal tubular acidosis is related to a defect in basolateral kAE1, due to mutation in its *SLC4A1* gene. The most frequent mutations in *SLC4A1* occur at codon 589 (CGC), a "mutational hotspot" [54]. In heterozygous state, these mutations impair the folding of the AE1 protein, with dominant negative effects of the wild-type protein in the kidney. They do not affect chloride transport in erythrocytes. In its recessive form, AE1 activity is reduced or abolished in both erythrocytes and kidney. Destabilization of the red-cell membrane leads to hereditary spherocytosis.

Recessive dRTA more often implicates mutations in the *ATP6V1B1* and *ATP6N1B* genes encoding for vacuolar H-ATPase subunits ATP6B1 and ATP6V0A4, which abolish luminal secretion of protons in α-intercalated cells. dRTA has recessive transmission and is associated with progressive sensorineural hearing loss [55]. Finally, not all patients with recessive dRTA have mutations in these 3 genes, and further genetic heterogeneity is likely present. Not all cases of dRTA are associated with hypokalemia, especially when low voltage due to low sodium reabsorption in the principal cells of the cortical collecting duct is implicated. Pseudo-hypoaldosteronism due to mutations in the gene encoding the epithelial sodium channel in the mineralocorticoid receptor is responsible for hyperkalemic acidosis.

Ethical statement

The author declares that authorizations of patients have been provided about that short report of their medical histories.

Disclosure of interest

The author declares that he has no competing interest.

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