Water Balance and ‘Salt Wasting’ in the First Year of Life: The Role of Aldosterone-Signaling Defects

Carla Bizzarri^a Stefania Pedicelli^a Marco Cappa^a Stefano Cianfarani^{b, c}

^aUnit of Endocrinology and Diabetes, ‘Bambino Gesù’ Children’s Hospital, and ^bMolecular Endocrinology Unit, ‘Bambino Gesù’ Children’s Hospital-Tor Vergata University, Rome, Italy; ^cDepartment of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden

Key Words

Newborn and infant · Salt wasting · Sodium disturbances · Aldosterone · Pseudohypoaldosteronism

Abstract

In newborns and infants, dehydration and salt wasting represent a relatively common cause of admission to hospital and may result in life-threatening complications. Kidneys are responsible for electrolyte homeostasis, but neonatal kidneys show low glomerular filtration rate and immaturity of the distal nephron, leading to reduced ability to concentrate urine. High extrarenal fluid losses often contribute to the increased occurrence of electrolyte disorders. Aldosterone is essential for sodium retention in the kidney, salivary glands, sweat glands and colon. A partial and transient aldosterone resistance is present in newborns and infants, thus reducing the capability of maintaining sodium balance in specific pathological conditions. The present review examines the mechanisms making infants more susceptible to salt wasting. Peculiar aspects of renal physiology in the first year of life and management of electrolyte disorders (i.e. sodium and potassium) are considered. Finally, inherited disorders associated with neonatal salt wasting are examined in detail.

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Introduction

Water and electrolyte requirements are very high in early postnatal life and decrease with age until adulthood. Studies on water and electrolyte metabolism in newborns and infants are limited. During the first months of life, kidneys show tubular immaturity leading to impaired sodium and water reabsorption. This may predispose to failure to thrive and dehydration under pathological circumstances [1]. The alteration of sodium reabsorption during the perinatal period has been related to a partial and transient renal resistance to aldosterone [1].

The initial paragraphs of this review analyze peculiar characteristics of water and electrolyte homeostasis and functional aspects of the renin-angiotensin-aldosterone system in the first year of life. The following paragraphs focus on the clinical presentation of salt wasting and the different forms of aldosterone resistance in infants. Finally, the key points of emergency management and long-term follow-up of infants affected by these defects are discussed.

Water and Electrolyte Homeostasis in the Neonate

Body water progressively decreases from intrauterine life to adulthood. Water represents about 90% of body weight in a 24-week-old fetus, 70% in a term infant and 60% in an adult [2–4]. During the third trimester of gestation, body water content decreases along with the relative increase of fat mass. Water turnover is elevated in neonates and decreases with increasing age and concurrent reduction of metabolic rate and growth velocity [2–4]. Water turnover, like energy turnover, is related to lean body mass (LBM), but has no close relationship with body fat mass. Infants with very low birth weight have a lower fat mass and a relatively higher LBM and body water than infants with normal birth weight, consequently showing an elevated water turnover. Body water is divided into 2 compartments: intracellular fluid (ICF) and extracellular fluid (ECF) [5].

Potassium is the major ion of ICF, and its intracellular concentration depends on the $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity, which is impaired in case of an insufficient supply of oxygen and energy [6–9]. The normal range of plasma potassium in neonates is 4.0–6.5 mmol/l [6–8]. Potassium is able to shift between ICF and ECF in response to several factors, including alterations of acid-base balance. Acidosis leads to a shift of potassium out of the cells, while alkalosis determines its return into the cells. The potassium pool is positively correlated with LBM and 10% of the potassium body pool is not exchangeable (bone, connective tissue, cartilage) [6–9].

ECF is subdivided into intravascular and extravascular components, as well as a ‘third space’ consisting of free fluid in body compartments under physiological (urine in the bladder, cerebral spinal fluid) and pathological conditions (ascites, pleural effusion). The major ion in ECF is sodium. Sodium modulates the maintenance of the intravascular and interstitial volumes. Sodium excretion occurs primarily through urine, but also through sweat and feces. The total volume of intracellular water increases, whereas extracellular water decreases in parallel with the augmentation in the number and size of cells during body growth. Blood volume in neonates is 85–100 ml/kg body weight, in comparison with 60–70 ml/kg body weight in adolescents [10]. In the assessment of fluid balance in infancy, metabolic water production may be a key element due to the high metabolic rates of infants. Endogenous water production is about 0.6 ml per gram of carbohydrates, 1.0 ml per gram of fat, and 0.4 ml per gram of protein oxidized [11].

An adaptation process early after birth affects water and electrolyte metabolism as a result of the discontinu-

ation of placental exchange and the onset of significant insensible water loss and thermoregulation. Postnatal adaptation involves renal regulation of fluids and electrolytes, concurrently with the beginning of the oral intake of fluids and other nutrients.

The time course of neonatal adaptation may be divided into 3 phases:

- Phase I: The immediate postnatal phase is characterized by oliguria [12], followed by a diuretic phase leading to ECF contraction with a net loss of sodium and water (lasting about 7 days). These changes are related to the elevated natriuresis already ongoing during fetal life [13] and to the remarkable evaporative water loss via the immature skin. Phase I usually ends when maximum weight loss has occurred. The generally accepted water loss is up to 10% of birth weight.
- Phase II: Beyond the first week of life, a positive sodium balance is necessary for growth. Insensible water losses decrease along with the increasing keratinization of the skin, and a progressive fall in urine volume with low sodium excretion occurs.
- Phase III: Stable growth is characterized by continuous weight gain with a positive net balance of water and sodium.

Renal glomerular surface and filtration rate (GFR) are smaller in neonates than in older infants and adults [14–20]. In term infants, GFR increases significantly during the first week of life [15] and continues to rise over the first 2 years of life [18]. Immaturity of the distal nephron with an anatomically shortened Henle loop leads to a reduced ability to concentrate urine. Maximum urinary osmolarity is up to 550 mOsm/l in preterm infants and 700 mOsm/l in term infants, compared to 1,200 mOsm/l in adults [18–19]. Although hormonal factors, i.e. renin-angiotensin-aldosterone system, and arginine-vasopressin are mature early in gestation, their effects are limited by renal immaturity [20]. Neonates are at risk for volume depletion when solutions containing a high solute load are administered, because the high renal solute load cannot be eliminated in a small urine volume due to the inability to produce concentrated urine [18]. A lower plasma oncotic pressure and a higher permeability of the capillary wall enhance the shift of water from the intravascular to the interstitial compartment, with an increased risk of edema especially under pathologic conditions, such as sepsis. During the first week of life, preterm babies require more fluids than those recommended for term infants, because of their higher insensible water losses. Evaporation of water from upper airways accounts for approximately one third of net insensible water losses

Fig. 1. The renin-angiotensin-aldosterone system.

[20–22], reaching 0.8–0.9 ml/kg/h in preterm and 0.5 ml/kg/h in term neonates. Additional losses may occur under pathological conditions, e.g. bowel obstruction, ileostomy, pleural effusion, peritoneal drainage and external cerebrospinal fluid drainage. In these conditions, the electrolyte content of lost fluids cannot be predicted precisely [23]. Moreover, extra needs for body mass accretion require an adequate supply of electrolytes. The normal growth rate results in a net storage of about 1.0–1.5 mmol/kg/day of sodium in infants, 2.7 mmol/kg/day in older children [24]. Restricted water and sodium intakes impair postnatal weight gain, but significantly reduce the risk of patent ductus arteriosus and necrotizing enterocolitis in otherwise healthy preterm infants [20, 23, 25, 26].

The Renin-Angiotensin-Aldosterone System

Published data about the peculiarities of the renin-angiotensin-aldosterone system during the first year of life are scarce. Weldon et al. [27] reported that the aldoste-

rone secretion rate of newborns and infants was similar to that of older children and adults (mean: 81 µg/24 h ranging from 25 to 162 µg/24 h). Therefore, the aldosterone secretion rate corrected for body surface area was much higher in infancy than later in life. Kowarski et al. [28] reported mean aldosterone levels in adults of 16.6 ± 11.9 ng/dl, not significantly different from the mean levels of children >1 year of age (24.9 ± 17.6 ng/dl). On the contrary, the mean aldosterone levels in infants <1 year were found to be 79.9 ± 47.9 ng/dl, which were significantly higher than those of older children and adults. Van Acker et al. [29] demonstrated that, despite a marked overlap between values in the different age groups, a net decrease of the mean values of plasma renin activity and plasma aldosterone was observed with increasing age. Urinary excretion rate of aldosterone, expressed as µg/kg body weight/24 h, also decreased with age.

At birth, human kidneys display tubular immaturity leading to sodium wasting and impaired ability to reabsorb water. The achievement of a balance between the life-threatening risk of dehydration and the morbidity as-

Fig. 2. Aldosterone-dependent regulation of volume and electrolyte balance in the distal nephron.

sociated with excessive sodium and water supplementation in conditions such as bronchopulmonary dysplasia, patent ductus arteriosus and necrotizing enterocolitis, is challenging for neonatologists [26]. Sodium homeostasis is mainly controlled by the renin-angiotensin-aldosterone system [30, 31]. Renin is released by the juxtaglomerular apparatus in response to hypotension or hyperkalemia. Renin cleaves the angiotensinogen synthesized by the liver to produce angiotensin I. Angiotensin I is rapidly cleaved by angiotensin-converting enzyme in the lung and other tissues to form angiotensin II. Angiotensinase cleaves the NH₂-terminal Asp residue from angiotensin II and produces angiotensin III. Angiotensin II and III stimulate aldosterone secretion and vasoconstriction (fig. 1). The angiotensins are inactivated within minutes by tissue and plasma peptidase. Circulating renin levels are the rate-limiting factor of this process. Moreover, hyponatremia and hyperkalemia have a direct stimulating effect on aldosterone secretion. Aldosterone is a mineralocorticoid hormone responsible for the regulation of sodium absorption and potassium excretion in the kidney, salivary glands, sweat glands and colon. It is secreted by the zona glomerulosa of the adrenals. Aldosterone crosses the epithelial cell membrane and binds to the mineralocorticoid receptor (MR), a ligand-dependent transcription factor. The complex is then translocated into the cell nucleus. Most aldosterone effects are mediated by MR; moreover, aldosterone directly stimulates protein kinases and signaling cascades acting independently on molecular targets of the cell membrane and

modulating MR-mediated transcriptional action of aldosterone [32]. Short-term effects of aldosterone binding to MR result from the activation of preexisting transport proteins, whereas long-term effects depend on the actions of the receptor-hormone complex in the nucleus, where it interacts with the promoters of target genes, either by inducing or repressing genes whose products are involved in transepithelial sodium transport [32–34]. The bound aldosterone-MR complex results in an increased expression of the epithelial sodium channel (ENaC) and an augmented activity of the renal outer medullary potassium (ROMK) channel in the luminal membrane and Na⁺-K⁺-ATPase in the basolateral membrane. ENaC consists of 3 genetically unique subunits assembled as α , β and γ (encoded by the genes *SCNN1A*, *SCNN1B* and *SCNN1G*, respectively). Each subunit has two transmembrane segments, an extracellular loop and an intracellular N- and C-terminus region. In the principal cells of the distal nephron, sodium is reabsorbed by ENaC and its uptake is facilitated by the action of the basolateral Na⁺-K⁺-ATPase pump, which creates the electrochemical gradient promoting sodium movement into the cells and also provides a basolateral exit for sodium in exchange for potassium. Electrical balance for sodium uptake can be provided by potassium secretion through the luminal potassium channel ROMK or by proton secretion from neighboring intercalated cells via the H⁺-K⁺-ATPase [35] (fig. 2).

In previous decades, MR expression was considered restricted to the polarized tight epithelia, where MR is involved in aldosterone-dependent transepithelial sodium

transport. These MR expression sites include distal convoluted tubules and cortical collecting ducts of the kidney, distal colon, airway epithelia of the lung and the salivary and sweat glands [35]. Recently, MR expression has been demonstrated in eyes, placenta, uterus, testis and keratinocytes. Unexpectedly, MR expression has also been detected in nonepithelial tissues such as heart, large vessels, hippocampus, hypothalamus, leukocytes, macrophages, pancreas and adipose tissue [35].

Martinerie et al. [36] conducted a prospective study in 48 healthy full-term newborns and their mothers. Aldosterone, renin and electrolyte concentrations were evaluated in both umbilical cord blood and maternal plasma. Urinary aldosterone and sodium concentrations were also determined within 24 h after birth. Plasma potassium concentrations were found significantly higher in newborns than in their respective mothers, whereas neonatal and maternal plasma sodium concentrations were closely related. Aldosterone and renin levels in newborns significantly differed from maternal concentrations. Overall, this study indicates that maternal and fetal ionic balances are uncoupled. Neonatal partial aldosterone resistance was suggested by the high urinary sodium loss in presence of hyperactivity of the renin-angiotensin-aldosterone system. Although aldosterone has been previously shown to cross the placental barrier, the highest aldosterone levels detected in the cord blood originate from *de novo* synthesis by fetal adrenal gland [37]. It remains to be elucidated whether renal resistance to aldosterone corresponds to a protective mechanism of the kidney against high aldosterone levels required elsewhere for activation of genomic or nongenomic pathways, or whether the absence of an active renal mineralocorticoid pathway is necessary in the first days of life for adaptation to a nonaquatic environment. The weight loss related to ECF loss during the first week of life is the result of this tubular insensitivity [38].

Neonatal aldosterone resistance has been associated with a weak or undetectable renal MR expression at birth. MR mRNA is transiently expressed between 15 and 24 weeks of gestation, but it is undetectable in late gestational and neonatal kidney [39]. This cyclic MR expression is closely correlated with the behavior of 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) and ENaC α subunit. Aldosterone and cortisol are both able to bind MR with the same affinity. Mineralocorticoid selectivity is therefore essential to prevent permanent MR occupancy by cortisol, since cortisol plasma levels are 100- to 1,000-fold higher than aldosterone levels. This selectivity is ensured in epithelial target tissues by the 11 β HSD2 enzyme that inactivates cortisol into cortisone [40]. Placental

11 β HSD2 activity is very high prenatally, in order to protect the fetus from excessive maternal glucocorticoids; on the contrary, renal 11 β HSD2 activity is extremely low at birth [34]. Therefore, neonatal kidney shows a time window characterized by virtually absent mineralocorticoid signaling and activation of glucocorticoid signaling pathways, which could be finalized to favor renal maturation. A multicenter observational study involving both preterm and term newborn infants was conducted to analyze whether the aldosterone signaling defect is also present in preterm neonates and to what extent it contributes to sodium wasting [41]. Plasma aldosterone was measured in umbilical cord blood. Urinary aldosterone was assessed at birth, day 3, month 1, and month 3 after birth. The levels of urinary aldosterone at birth increased progressively with gestational age, concurrently with the levels of plasma aldosterone. The aldosterone/renin ratio significantly increased with gestational age, suggesting a defect of aldosterone secretion in preterm infants. At birth, urinary aldosterone concentrations and urinary Na/K ratio were not correlated in term neonates, thus indicating renal resistance to aldosterone. Renal resistance to aldosterone was also observed in moderate and late preterm neonates, but not in very preterm neonates. Between birth and 1 month, very preterm neonates became resistant to aldosterone, other preterm infants remained resistant to aldosterone, while renal sensitivity to aldosterone progressively improved in term infants. These findings are consistent with the transient renal MR expression during fetal life and the reduced expression of renal MR at the time of the physiological term of gestation [37].

Salt Wasting in Newborns and Infants

Sodium is the main determinant of serum osmolality, and changes in its serum concentration can result in fluid shifts between intracellular and extracellular compartments. Water influx into the intracellular space swells cells, which can cause cerebral edema and neurologic injury. Newborns and infants with hyponatremia (serum sodium concentration <130 mEq/l) may present with neurologic symptoms such as vomiting, irritability, weakness, and seizures [1, 6]. Most cases of hyponatremia occur in hospitalized infants due to the administration of hypotonic fluids, but also in children with central nervous system disease, lung disease or postsurgery complications. In the outpatient setting, hyponatremia is uncommon, but can be related to excess ingestion of free water and hypotonic fluids, such as overdiluted infant formula

or plant milk, or to elevated salt losses with diarrhea (these conditions will not be discussed further in this review) [1, 6, 20, 25].

Severe hyponatremia associated with hyperkalemia, dehydration and metabolic acidosis is life-threatening in newborns and infants and represents the most typical presentation of genetic forms of congenital adrenal failure. The most common form is congenital adrenal hyperplasia due to 21-hydroxylase deficiency, but also X-linked adrenal hypoplasia congenita and aldosterone synthase deficiency (primary hypoaldosteronism) are usually associated with 'salt wasting crisis' in newborns or young infants [42]. This clinical picture is also the most common presentation of aldosterone resistance (or pseudohypoaldosteronism, PHA) (table 1) [43].

Aldosterone Resistance in Infants: Clinical Forms of PHA

PHA is characterized by renal tubular unresponsiveness to aldosterone and presents with hyponatremia, hyperkalemia and metabolic acidosis with elevated plasma aldosterone and renin concentrations [43]. Two different forms of primary PHA have been defined (PHA1 and PHA2). Clinical presentation of PHA1 usually occurs during infancy. It is characterized by failure to thrive, anorexia, nausea, vomiting, hypotension, hyperkalemia, hyponatremia and metabolic acidosis and associated with high aldosterone and renin levels. PHA1 is further categorized into two forms with different clinical severity: autosomal recessive PHA1 due to defects in the genes encoding for ENaC subunits and autosomal dominant PHA1 due to mutations of the MR gene [44–48]. Conversely, PHA2 or type 4 renal tubular acidosis (or Gordon's syndrome) is characterized by the kidney failure to appropriately secrete potassium, due to mutations in different genes encoding for sodium, potassium and chloride transporters and ROMK channel [49]. PHA2 is rarely symptomatic in neonates. Affected individuals show hyperkalemia, hyperchloremic acidosis and early-onset hypertension readily responsive to sodium restriction and thiazide diuretics. Plasma renin activity is variable, and plasma aldosterone is inappropriately low for the potassium level [50].

Autosomal Recessive PHA1

These patients have not only severe lifelong renal salt wasting, but also salt wasting from the other epithelial tissues with ENaC expression, such as lung, skin, colon, sweat and salivary glands. Patients experience recurrent

volume depletion, pulmonary infections, congestion, coughing and wheezing, cholelithiasis, skin infections and miliaria rubra. The initial presentation is usually a severe salt wasting crisis early after birth, but sometimes PHA1 has been diagnosed following the appearance of cutaneous signs [43, 51]. An abnormal accumulation of sebum in the eye due to a defect in the sodium channels has also been reported [51]. The clinical phenotype of autosomal recessive PHA1 may show a significant variability depending on the different mutations involved [52]. The pulmonary symptoms, which are clinically similar to those found in patients with cystic fibrosis, are due to poor absorption of liquids from airway surfaces and occur within weeks or months from birth [53]. It is noteworthy that neonatal respiratory distress has never been described in these patients, but they may experience recurrent lung infections caused by different pathogens such as *Pseudomonas*, *Pneumococcus*, *Staphylococcus aureus*, *Klebsiella* and *Serratia* [54].

Autosomal Dominant PHA1

Clinical expression of autosomal dominant PHA1 is confined to the kidney. Patients are generally diagnosed in infancy for mild renal salt wasting that attenuates in early childhood, though the onset can also occur in adulthood. Sometimes, this condition is unmasked by an intercurrent illness that impairs oral intake of fluids and salt or induces additional losses, such as viral gastroenteritis. Autosomal dominant PHA1 may also be incidentally diagnosed in asymptomatic adults with moderate elevation of renin and aldosterone, but normal blood pressure, normal or only slightly altered plasma electrolytes and inappropriately high urinary sodium excretion [44, 46–48]. Finally, in a few patients with clinically diagnosed PHA1 usually in the sporadic form, no molecular defects of MR or ENaC have been identified, thus suggesting a molecular heterogeneity [55].

Secondary (Transient) PHA

Secondary PHA is confined to the kidneys and has been described in infants and children with obstructive uropathy, pyelonephritis, tubulointerstitial nephritis and sickle cell nephropathy. It is the result of a transient aldosterone resistance related to the kidney infection in children with or without a predisposing renal malformation. Due to its frequent association with renal malformations, 80% of transient PHA cases have been described in male infants [56–59]. The risk of developing salt wasting seems to be age dependent, and it decreases progressively after 3 months of age; therefore, hyponatremia and hyperkale-

Table 1. Hyponatremia in newborns and infants: differential diagnosis [35, 42, 48]

	Autosomal dominant PHA1	Autosomal recessive PHA1	PHA2	21-Hydroxylase CAH	X-linked AHC	Primary hypoaldosteronism
Clinical phenotype	Varying severity from asymptomatic to failure to thrive due to chronic dehydration	Severe dehydration, failure to thrive, pulmonary infections	Hypertension in young adults	Varying, dehydration and vomiting, $\pm$ ambiguous genitalia in females	Varying, dehydration and vomiting in male newborns (60%), onset during late childhood (40%)	Varying, dehydration and vomiting in newborns
Incidence per year	1:66,000	1:166,000	Unknown	1:5,000 – 1:15,000	1:70,000 males	Probably <1:1,000,000
Laboratory	Mild hyponatremia, hyperkalemia, metabolic acidosis (not always evident)	Hyponatremia, hyperkalemia, metabolic acidosis	Hyperkalemia, hyperchloremia, metabolic acidosis	Hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis	Hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis	Hyponatremia, hyperkalemia, metabolic acidosis
Hormones	Elevated renin and aldosterone may normalize after 3 years of age	Lifelong elevated renin and aldosterone	Decreased renin, normal aldosterone	Decreased cortisol, decreased aldosterone, high renin, high ACTH	Decreased cortisol, decreased aldosterone, high renin, high ACTH	Decreased aldosterone, high renin
Treatment	Salt supplementation in early childhood	Lifelong salt supplementation, potassium-binding resins	Low-dose thiazide diuretics	Corticosteroid and mineralocorticoid supplementation	Corticosteroid and mineralocorticoid supplementation	Mineralocorticoid supplementation
Patho-physiology	Mutations in MR gene	Mutations in ENaC genes	Not fully elucidated, failure of the kidney to appropriately secrete potassium	Dysfunction in production of glucocorticoids and mineralocorticoids	Dysfunction in production of glucocorticoids $\pm$ mineralocorticoids	Dysfunction in mineralocorticoids
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal dominant	Autosomal recessive	X-linked	Autosomal recessive, autosomal dominant with mixed penetrance
Genes	<i>NR3C2</i>	<i>SCNN1A</i> , <i>SCNN1B</i> , <i>SCNN1G</i>	<i>WNK1</i> , <i>WNK4</i> , <i>KLHL3</i> , <i>CUL3</i>	<i>CYP21A2</i>	<i>NR0B1</i>	<i>CYP11B2</i>
Chromosomal location	4q31.23	12p13.31, 16p12.2, 16p12.2	12p13.33, 17q21, 5q31.2, 2q36.2	6p21.3	Xp21.3	8q24.3
Gene products	Mineralocorticoid receptor	α , β , γ subunits of ENaC	Na-Cl and Na-K-Cl co-transporters, ROMK channel	Adrenal 21-hydroxylase enzyme	Nuclear hormone receptor DAX1	Adrenal 11/18- β -hydroxylase (aldosterone synthase)

AHC = X-linked adrenal hypoplasia congenita; CAH = congenital adrenal hyperplasia; DAX1 = dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1.

mia are extremely uncommon beyond this age [57]. The intrarenal expression of tumor necrosis factor, interleukin 1 and 6, transforming growth factor 1, angiotensin II, endothelin, thromboxane A2 and prostaglandins is increased in the course of urinary tract infections. These changes result in inhibition of aldosterone action through downregulation of its receptors, vasoconstriction and reduction of the GFR, increased natriuresis and decreased Na^+ - K^+ -ATPase activity [56]. The prognosis of secondary PHA is good, as this condition usually resolves with the

resolution of the infection. Kuhnle et al. [58] documented reduction of aldosterone receptors in two patients with transient PHA due to obstructive renal disease. Aldosterone receptors returned to normal in both patients when studied after the surgical correction of the obstruction. A secondary form of PHA has also been associated with medications causing aldosterone resistance, such as ENaC blockers (amiloride, triamterene, trimethoprim, pentamidine), MR blockers (spironolactone) or drugs producing multiple effects (cyclosporine) [56].

Fig. 3. First-line diagnostic workup in an infant presenting with salt wasting (dehydration hyponatremia and hyperkalemia). AHC = X-linked adrenal hypoplasia congenita; CAH = congenital adrenal hyperplasia.

Key Points of Therapy

Initial management of infants presenting with dehydration, hyponatremia and hyperkalemia requires correction of water losses and treatment of electrolyte imbalances. Glucocorticoid therapy is essential and lifesaving in adrenal insufficiency, while it is not effective in restoring salt and water balance in PHA1 (table 1). Nevertheless, the differential diagnosis between primary congenital adrenal insufficiency and PHA1 may be difficult in emergency settings, and sometimes hospitalized infants presenting with salt wasting and metabolic acidosis are immediately started on mineralocorticoid and glucocorticoid therapy to avoid life-threatening complications, before the correct diagnosis is established [51, 59–61]. Physicians involved in the management of these children should keep in mind that, whenever practicable, a blood sample for the essential hormonal investigations (fig. 3) should be collected before starting the steroid therapy.

The guidelines for glucocorticoid replacement therapy in newborn infants with congenital adrenal insufficiency are well established and mainly derive from studies on patients with 21-hydroxylase congenital adrenal hyperplasia [62]. Treatment includes short half-life glucocorticoids to prevent adrenal crises along with minimizing the growth suppression associated with long-acting glucocorticoids. Whenever available, the use of hydrocortisone, which is identical with endogenous cortisol, should be recommended [63]. The current recommendations for mineralocorticoid replacement are based on expert opinions, suggesting an initial dose of 100–200 µg/day of 9- α -fludrocortisone, and a regular dose reassessment. The dose adjustments should be based on clinical and laboratory parameters, such as blood pressure, plasma sodium, potassium and renin levels [42, 64]. The higher mineralocorticoid demand during early infancy is explained by the renal immaturity, the limited sodium content of breast milk and the high sodium requirements for growth [36]. Mineralocorticoid replacement doses gradually decrease during infancy, with the progressive improvement in mineralocorticoid sensitivity.

The resolution of hyperkalemia in congenital adrenal insufficiency usually occurs progressively after starting mineralocorticoid therapy, and no specific potassium-lowering treatment is necessary. The most important, immediate treatment for PHA1 is volume expansion with intravenous infusion of saline solution. Potassium-reducing treatments are often not needed after volume expansion. Nevertheless, sometimes children with PHA1 may require specific treatments of hyperkalemia includ-

ing calcium carbonate for cardioprotection, β -agonists and insulin with glucose to drive potassium intracellularly, potassium-wasting diuretics and sodium polystyrene sulfonate (Kayexalate), orally or intrarectally [61]. Colonic necrosis has been described as a rare complication of therapy with sodium polystyrene sulfonate mixed with sorbitol, a cathartic added to avoid constipation and fecal impaction. Bowel movements of treated patients should be closely monitored [65]. In severe and life-threatening conditions, dialysis can be used to correct electrolyte abnormalities. Infants with PHA1 are fed with low-potassium formulas or formulas pretreated with potassium-binding agents, such as sodium polystyrene sulfonate. Potassium-binding agents work by binding potassium, allowing a low-potassium milk to be obtained by eliminating the precipitate. Each gram of sodium polystyrene sulfonate has the in vivo capacity of binding 1 mEq of potassium. In some patients, salt supplementation requires the positioning of a nasogastric or gastrostomy tube [66]. In order to overcome the underlying resistance to aldosterone and the resulting salt wasting and hyperkalemia, PHA1 patients require high-dose sodium chloride supplementation (5–15 mEq/kg daily). In case of concurrent severe metabolic acidosis, sodium bicarbonate (5–10 mEq/kg daily) should be added [46, 60, 61]. Patients with autosomal recessive PHA1 require dietary measures, salt supplementation and potassium-wasting agents throughout their lives. In these patients, extrarenal complications must also be addressed. In particular, subjects with significant lung infections may require treatment regimens similar to those affected by cystic fibrosis, including antimicrobial therapy and chest physiotherapy [54]. Patients with autosomal dominant PHA1 may require salt supplementation during the first 3 years of life and do not need potassium-binding agents [67]. A few alternative and less evidence-based treatments have been proposed for PHA1. Patients with autosomal dominant PHA1 are partially responsive to mineralocorticoid supplementation due to the presence of one wild-type allele encoding for MR [68]. Early studies reported treatment with indomethacin in refractory patients, as decreased prostaglandin activity results in improved sodium reabsorption in the proximal tubule. Indomethacin, however, is not routinely used due to its side effects, particularly the risk of gastrointestinal bleeding [69]. Carbenoxolone, an 11 β HSD2 inhibitor, was employed in autosomal dominant PHA1 and an improvement was observed. Carbenoxolone inhibits the conversion of cortisol to cortisone in the kidney, enhancing the effect of cortisol as a ligand for MR [68, 70].

Conclusion

Early diagnosis and treatment of salt wasting conditions in the first year of life represent a major challenge for neonatologists and pediatric endocrinologists. The knowledge of the different conditions is essential for establishing the appropriate care of these infants who are at major risk for life-threatening dehydration.

Disclosure Statement

The authors have no financial disclosure and no conflict of interest to declare.

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