Chapter

Diagnosis of Hypoaldosteronism in Infancy

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Abstract

Hypoaldosteronism is associated with either insufficient aldosterone production or lack of responsiveness to aldosterone and can be isolated or in the context of primary adrenal failure. The severity of clinical manifestations is inversely correlated to age, with the neonatal period being the most vulnerable time for a patient to present with mineralocorticoid insufficiency. Salt-wasting forms of congenital adrenal hyperplasia (CAH), adrenal hypoplasia congenita (AHC), aldosterone synthase deficiency (ASD) and pseudohypoaldosteronism (PHA) are all causes of hypoaldosteronism in infancy. Affected infants present with salt wasting, failure to thrive and potentially fatal hyperkalemia and shock. A blood sample for the essential hormonal investigations should be collected before any steroid treatment is given, in order to confirm aldosterone insufficiency and to determine the underlying cause. Renal ultrasonography and urine culture are also useful for exclusion of secondary causes of aldosterone resistance. Initial management requires treatment of electrolyte imbalances and restoration of intravascular fluid volume. In case of a salt-wasting crisis, affected infants are usually treated initially with both hydrocortisone and fludrocortisone, pending the results of investigations. Interpretation of the hormonal profile will guide further therapy and molecular analysis of candidate genes.

Keywords: hypoaldosteronism, salt-wasting crisis, hyponatremia, hyperkalemia, pseudohypoaldosteronism

1. Introduction

Aldosterone, the most important mineralocorticoid, regulates electrolyte balance and intravascular volume by controlling renal sodium reabsorption and potassium excretion. Hypoaldosteronism is a rare, but potentially severe condition, associated with hyponatremia, hyperkalemia, metabolic acidosis and volume depletion. Given the higher mineralocorticoid demand during the critical neonatal period, the clinical presentation of aldosterone insufficiency in this age group can be dramatic [1–3].

2. The renin-angiotensin-aldosterone system in infancy

Regulation of fetal salt and water balance is handled by the placenta, so newborns with aldosterone defects have a normal electrolyte profile at birth.

Postnatally, healthy term neonates display a state of functional hypoaldosteronism (lower sodium and higher potassium concentrations), that contrasts with markedly increased aldosterone and renin secretion rates [2–5]. Indeed, it has been reported, that neonates have a mean plasma aldosterone level of 80 ng/dl versus 16.6 ng/dl for adults. Similarly, plasma renin activity (PRA) is severalfold higher in the first 3 months of life, than the levels reported later in adult life (450 and 25 ng liter^{-1} min^{-1} respectively) [6]. Concurrent partial aldosterone resistance is attributed to the low mineralocorticoid receptor (MR) expression and the weak 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) activity of the neonatal kidney. Aldosterone unresponsiveness may, at least in part, account for the extracellular fluid compartment contraction and weight loss during the first days of life [7–9].

3. Clinical presentation of hypoaldosteronism

Biochemically, hypoaldosteronism is characterized by hyponatremia, hyperkalemia, prerenal azotemia and non-anion gap metabolic acidosis (hyperkalemic or type 4 renal tubular acidosis). The severity of clinical manifestations is inversely correlated to age, due to changes in adrenal and renal physiology [10, 11].

The critical neonatal period is clearly the most vulnerable time for an affected person to present with hypoaldosteronism [3]. Babies with mineralocorticoid insufficiency start to lose whole body sodium and water from day 1 in their urine. Overt electrolyte disturbances usually develop after the 4th day of life in infants with salt-wasting 21-hydroxylase deficiency, but a very early onset of symptoms may be seen in cases of severe systemic PHA. Affected infants eventually present with dehydration, vomiting and failure to thrive, while urine output remains excessively high for the degree of dehydration [6, 10]. Early warning signs, such as failure to reach birth weight by two weeks of age or excessive weight loss (greater than 10–12%) during the first days of life, should always prompt a careful assessment of hydration status, kidney function and electrolyte profile [7].

Clinical manifestations associated with hyponatremia are primarily neurologic, due to osmotic water shift intracellularly, parenchymal edema and brain ischemia. Frequent symptoms include vomiting, poor feeding and lethargy or irritability. Pronounced symptoms, such as seizures, are encountered rarely due to the insidious onset (>48 h) of hyponatremia. Open sutures and fontanelles in neonates, also act as a protective mechanism preventing intracranial hypertension [12, 13]. Yet infants with hypoaldosteronism are at risk of acute deterioration and might present in circulatory collapse with lethargy, tachycardia, hyperpnea, prolonged capillary refill, and cool and mottled extremities. Hypotension, a very late dehydration sign, occurs when all compensatory mechanisms to maintain organ perfusion have failed [14]. Hyperkalemia is clinically manifested by muscular weakness and cardiac disturbances (bradycardia, ventricular fibrillation, hypotension or cardiac arrest). Electrocardiogram (ECG) signs of hyperkalemia include repolarization abnormalities, peaked T-waves, QRS widening and depression of ST-segment. Arrhythmias may appear at any time and can lead to sudden death [15, 16].

Hypoaldosteronism has a much milder course in older children and adults, as aldosterone requirements normally decrease with age. Children with aldosterone insufficiency may present with subtle symptoms, such as postural hypotension and salt craving or even with asymptomatic growth failure. Autonomous addition of salt in the diet can delay or mask the presentation, until a simple viral gastroenteritis or a hot day associated with excessive sweating triggers the cascade of clinical manifestations [10, 11].

Reversible growth impairment is a well-known feature of several conditions accompanied by acidosis or electrolyte derangement (e.g., Bartter's syndrome or renal tubular acidosis) [6]. Accordingly, children with aldosterone insufficiency may present with linear growth deceleration due to chronic hyponatremia and acidosis. Sodium is an important growth factor, stimulating cell proliferation, protein synthesis and increasing cell mass. The mechanism whereby Na^+ promotes growth is through alkalinization of the cell interior, via a sodium-dependent Na^+/H^+-antiporter. Sodium depletion and acidosis lead to decreased antiporter system's activity and despite adequate macronutrient intake, children fail to thrive [17, 18].

4. Diagnostic workup

Hypoaldosteronism should be considered in any infant with persistent hyperkalemia and hyponatremia if there is no apparent cause, such as renal failure or prematurity. A diagnostic algorithm for infants presenting with salt-wasting and hyperkalemia (suspected mineralocorticoid defect) is presented in **Figure 1** [8, 16].

Renal function must be evaluated carefully, since renal excretion of potassium is directly dependent upon glomerular filtration rate (GFR). Renal adaptive mechanisms allow the kidneys to maintain potassium homeostasis until the GFR decreases to less than 15 ml/min/1.73 m^2 [16, 19].

Hyperkalemia and hyponatremia are well-recognized complications of prematurity. Hyperkalemia may be observed, even in the absence of oliguria, in very low birth weight preterm infants weighing less than 1,000 g. The serum potassium concentration may be as high as 9.0 mEq/1 and be accompanied by significant ECG irregularities [15]. Plasma potassium concentration decreases gradually from 6.5 ± 0.5 mEq/1 at 30— 32 weeks to 5.1 ± 0.2 mEq/1 at 39–41 weeks. Premature infants of <36 weeks gestational age (GA) are also unable to conserve sodium. The more immature the infant, the greater the risk and the degree of hyponatremia [20]. Urinary sodium excretion is 3.1 ± 0.5 mEq/kg/day (mean ± SE) in the newborn of 30–32 weeks gestational age and 1.2 ± 0.4 mEq/kg/day at 36—38 weeks gestational age [21].

The clinical scenario of a dehydrated infant with salt wasting and hyperkalemia represents a medical emergency implying inadequate mineralocorticoid action or complete adrenal insufficiency (both glucocorticoid and mineralocorticoid deficiency). The most common diagnosis in neonates is CAH due to 21-hydroxylase deficiency. Other conditions to be considered in infancy are the rare salt-wasting forms of CAH adrenal hypoplasia congenita, aldosterone synthase deficiency, PHA and drug effects [7, 22, 23].

Considerable overlap exists in the clinical and biochemical presentation of most of the above-mentioned endocrine diseases and only a few clinical signs can help clinicians to differentiate between them [23, 24]. A careful examination of the external genitalia is indicated in all infants with hyponatremia and hyperkalemia and might reveal valuable information towards the appropriate diagnosis [25]. 46, XX infants with 21-hydroxylase deficiency exhibit variable extent of virilization due to excessive androgen production. On the contrary, signs of undervirilization such as hypospadias are noted in 46,XY infants with 3β-hydroxysteroid dehydrogenase deficiency due to decreased androgen production. Infant boys with 21-hydroxylase deficiency have normal external genitalia or subtle penile enlargement that can be easily overlooked [25–29]. Impaired cortisol secretion is suggested clinically by low glucose levels and vascular tone insufficiency (hypotension) that is unresponsive to initial resuscitation. Last, although not always clinically obvious, increased pigmentation is a distinguishing

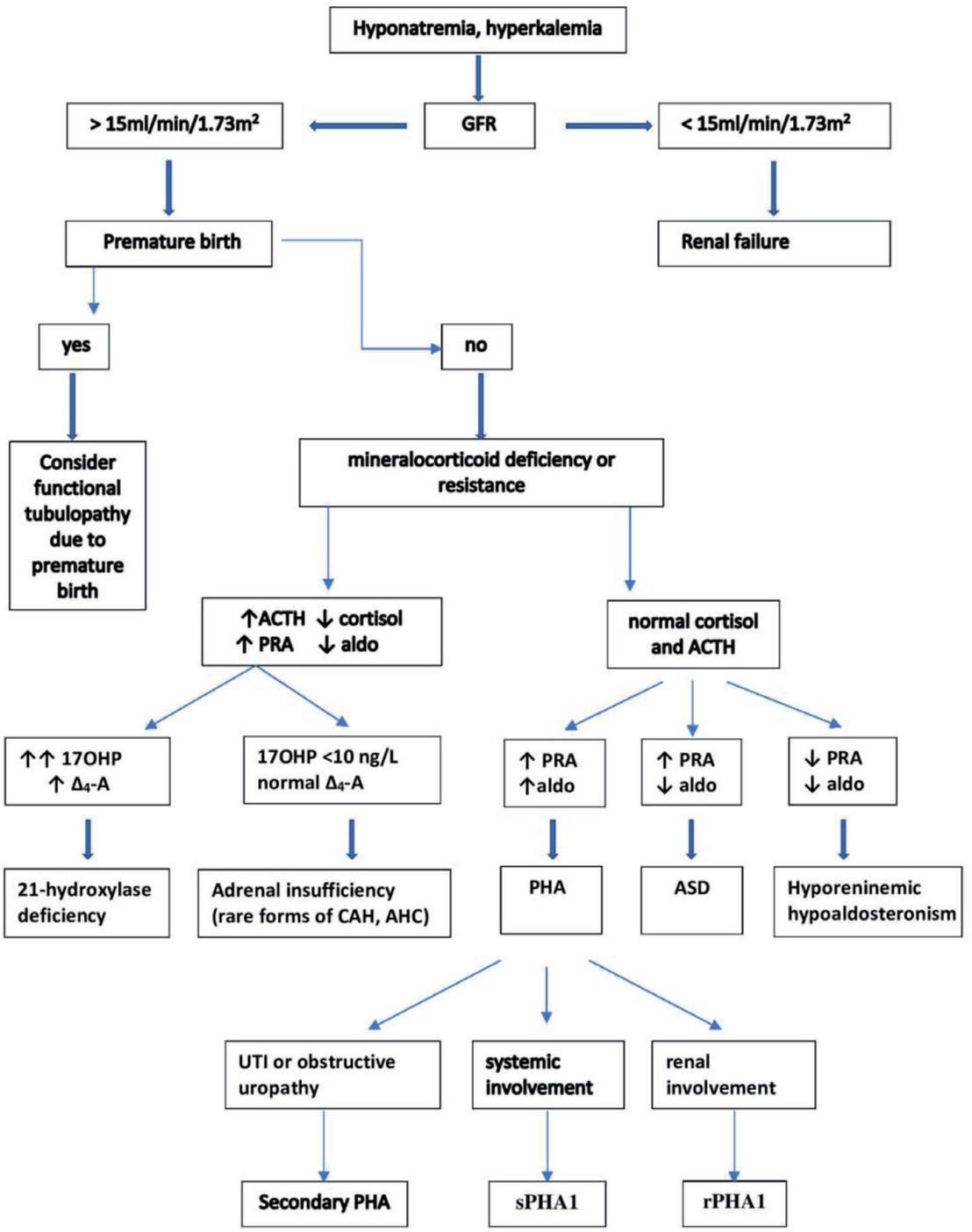

Figure 1.
Diagnostic approach to infants presenting with hyponatremia, hyperkalemia from references [8, 16] (GFR: glomerular filtration rate, PRA: plasma renin activity, 17OHP: 17-hydroxyprogesterone, Δ_4-A: Δ_4-androstenedione, Aldo: aldosterone, CAH: congenital adrenal hyperplasia, AHC: adrenal hypoplasia congenita, PHA: pseudohypoaldosteronism, sPHA: systemic PHA, rPHA: renal PHA, ASD: aldosterone synthase deficiency, UTI: urinary tract infection).

feature of primary adrenal insufficiency (PAI) associated with high levels of melanocyte-stimulating hormone (MSH), a ligand derived from pro-opiomelanocortin that causes hyperpigmentation of melanin-containing skin cells [6, 28].

The following investigations are suggested as a first - line diagnostic workup in infants with apparent mineralocorticoid deficiency:

- A critical sample for ACTH determination, cortisol, 17-hydroprogesterone (17- OHP), Δ_4 - androstenedione, aldosterone levels and renin level or PRA should be drawn before administration of hydrocortisone.

- A urine collection by suprapubic aspiration or catheterization for microscopic analysis, urine culture and urine electrolytes measurement.

- Abdominal ultrasonography [7, 10].

Hypoaldosteronism may be challenging to diagnose promptly, because aldosterone and renin assays are generally sent to a reference laboratory and results are usually delayed. Thus, urinary electrolyte assessment and abdominal ultrasonography are useful adjuncts in a clinical setting [12, 30].

4.1 Urine electrolytes

Urine sodium is expected to be low (usually <25) in hyponatremia, when the renal response is intact. A urine sodium concentration greater than 25 mEq/L demonstrates inappropriately high sodium excretion in the hyponatremic infant, suggesting aldosterone deficiency or resistance. Nevertheless, we should keep in mind that urinary sodium losses may not be excessive if the infant is salt depleted [12, 30, 31].

In addition to measuring urinary sodium, it is useful to estimate potassium excretion. The preferred method to estimate potassium excretion by the distal tubule is the transtubular potassium (K) concentration gradient (TTKG):

$$\text{TTKG} = \left(\text{Blood Osmolality} * \text{Urine K}\right) / \left(\text{Blood K} * \text{Urine Osmolality}\right)$$

TTKG is expected to be high (>10) during hyperkalemia, as a result of appropriate aldosterone activity. TTKG values of less than six indicate impaired aldosterone action in the distal nephron as the cause of the hyperkalemia [31, 32]. Calculating TTKG before and after fludrocortisone administration is also useful in distinguishing patients who have mineralocorticoid deficiency versus resistance. An increase in TTKG values is observed after administering fludrocortisone in aldosterone-deficient states, but no change is seen in the case of aldosterone resistance [16].

4.2 Abdominal ultrasonography

Abdominal ultrasonography is a rapid, sensitive and non-invasive test that can provide valuable diagnostic information. The diagnosis of CAH is supported when a combination of 2 or more of the three following abnormalities are evident in adrenal sonography: (a) increased size (limb width > 4 mm), (b) lobulated or cerebriform surface and c) abnormal echogenicity. Adrenal imaging can also detect physical causes of adrenal insufficiency such as hemorrhage [33, 34].

Pelvic ultrasonography is indicated to evaluate internal genitourinary anatomy in infants with a suspected defect in steroidogenesis. Ultrasonography might reveal the presence of Müllerian structures in severely virilized infants with 21-hydroxylase deficiency carrying a 46,XX karyotype [35]. Accordingly, the lack of Müllerian structures in an infant with a salt-wasting crisis and female appearing external genitalia is found in 46,XY infants with classic congenital lipoid adrenal hyperplasia (CLAH) [36].

Urine culture and renal ultrasonography may allow early recognition of secondary PHA in infants with salt-wasting by detecting renal malformations and urinary tract infection (UTI). Further imaging with voiding cystourethrography (VCUG) and 99mTc-mercaptoacetyltriglycine (MAG3) scintigraphy may demonstrate vesicoureteral reflux (VUR) or obstruction [37].

4.3 Adrenal function tests

Evaluating apparent mineralocorticoid deficiency and eliciting the correct diagnosis requires a careful interpretation of adrenal function tests. Hypoaldosteronism can be isolated or in the context of PAI and concurrent cortisol production failure [38]. Serum cortisol level is expected to be elevated in the hypovolemic, acidotic patient with a functioning adrenal gland [39]. Diagnosis of PAI is suggested by an elevated plasma corticotropin (ACTH) concentration (frequently >100 pg/mL) in the presence of a low serum cortisol concentration (usually <10 mg/dL) [40]. Samples in young infants may be obtained at random, because diurnal secretion of ACTH and cortisol is not yet established, while by 6 months of age and beyond samples should be collected close to 8 AM [41]. In the setting of diagnostic uncertainty, confirmation of the diagnosis is established by an ACTH-stimulation test (250 μg for children >2 years, 15 μg/kg for infants and 125 μg for children <2 years, intravenously). A subnormal peak cortisol level (<18 μg/dL) 30 or 60 minutes after ACTH administration is diagnostic of PAI [28, 29].

1. In case of hypocortisolism the first step is to evaluate 17-OHP level, because 21-hydroxylase deficiency is the most common cause of PAI in neonates and young infants. Most affected infants have concentrations greater than 35 ng/L and all have concentrations greater than 10 ng/L. If 17-OHP levels are normal, other adrenal insufficiency causes need to be considered. Once 21-hydroxylase deficiency has been ruled out, the most frequent cause of adrenal insufficiency in male neonates are the DAX-1 mutations. Other causes include rare non-virilizing forms of salt-wasting CAH and neonatal adrenal hemorrhage. Adrenal hemorrhage should be suspected in the newborn presenting with adrenal insufficiency and hypovolemic shock in the first week of life and diagnosis is confirmed by abdominal sonography [34]. Screening for possible autoimmune adrenalitis with adrenal autoantibodies and for X-linked adrenoleukodystrophy (ALD) with very long-chain fatty acids (VLCFA) is indicated in infants presenting at an age older than 6 months [10, 42].

2. Normal cortisol, ACTH and 17-OHP levels are consistent with isolated hypoaldosteronism without parallel cortisol deficiency. The next step is to evaluate the renin and aldosterone levels. Elevated PRA and low aldosterone values, particularly an elevated PRA ratio to aldosterone are markers of primary (hyperreninemic) hypoaldosteronism [26]. Low aldosterone and renin concentrations are consistent with hyporeninemic hypoaldosteronism, a diagnosis that is rarely seen in infants. Last, the diagnosis of PHA is established when high aldosterone and renin concentrations are evident in the face of salt wasting and hyperkalemia. In such cases, a renal etiology should be sought as a cause of secondary PHA. Urine culture and renal ultrasonography should be performed in any infant with electrolyte disturbances to exclude infection and obstructive uropathy, even in the absence of fever or other symptoms and signs of pyelonephritis [43].

Antenatal Bartter syndrome should be included in the differential diagnosis of a neonate presenting with hyperkalemia, hyponatremia and hyperreninemic hyperaldosteronism. In general, Bartter syndrome is a group of inherited tubular disorders, characterized renal salt wasting, hypokalemia, metabolic alkalosis and normotensive hyperreninemic hyperaldosteronism. Interestingly, the initial clinical presentation of type II antenatal Bartter syndrome is an important mimic of type 1 PHA. Transient neonatal hyperkalemia, occasionally severe, is observed within the

first three weeks of life in the majority of patients, obscuring the initial diagnosis, until the infant becomes hypokalemic. A mean peak plasma potassium level of 9.0 mmol/L (range 6,3–10,5 mmol/L) was documented in 12 neonates with type II antenatal Bartter syndrome and ventricular tachycardia has complicated the clinical course in one of them [44, 45].

5. Treatment

Biochemical confirmation should not delay treatment initiation in acutely sick infants. Infants with a severe salt-wasting present in near-shock to shock and require immediate fluid resuscitation and correction of electrolyte abnormalities. Physicians should keep in mind that a blood sample for the essential hormonal investigations should be collected before any steroid treatment is given to confirm aldosterone insufficiency and to determine the underlying cause. [7, 14, 46]

Hyponatremia is usually long-standing and should be corrected slowly to prevent central pontine myelinolysis [47]. Resolution of hyperkalemia usually occurs rapidly with stress doses of hydrocortisone, due to mineralocorticoid effect. Still, when T-wave elevation is evident on electrocardiogram (ECG), 10% calcium gluconate can be used to stabilize membrane potential. Other specific treatments for hyperkalemia include nebulized salbutamol and intravenous insulin infusion at 1 U of insulin in 5 g dextrose to promote intracellular potassium shifting and kayexalate cation exchange resins to help rid the potassium burden. As a last resort, dialysis can correct hyperkalemia, if T-wave elevation is unrelieved by medical means [10, 16, 47].

Infants with life-threatening salt-wasting crisis are initially treated with parenteral hydrocortisone at stress doses (50–100 mg/m^2 per day divided q 8 h) pending steroid hormone analysis [48]. This approach is not unreasonable given that CAH is a potentially lethal condition if treatment is delayed. Stress doses of hydrocortisone also have adequate mineralocorticoid activity, as 20 mg of intravenous hydrocortisone is equivalent to 100 μg fludrocortisone [10]. Once the infant is stabilized, he or she may be transitioned to oral hydrocortisone and fludrocortisone acetate at doses 30 mg/m^2 per day divided q 8 h and 50 to 100 μg/24 h respectively [49].

Identification of the etiology is crucial to avoid inappropriate prolonged steroid treatment, in case of mineralocorticoid resistance or isolated hypoaldosteronism. Appropriate therapy varies according to the etiology and treatment should be adjusted when the results are available [50].

a. In case of hypocortisolism glucocorticoid replacement therapy is continued according to established guidelines [7]. Maintenance therapy in infants with CAH includes hydrocortisone 12–15 mg/m^2/d and oral fludrocortisone acetate (0.05 to 0.2 mg/24 h). The requirement for sodium in normally growing infants is ~1 mmol/kg per day, the amount provided by human milk. However, in infants with salt-wasting, this amount is insufficient and sodium chloride supplements are recommended at a dose of 1–2 g/d [51].

b. If appropriate cortisol levels are obtained, PAI is excluded and hydrocortisone can be discontinued. Serum aldosterone will further differentiate isolated hypoaldosteronism from PHA. In cases of isolated aldosterone deficiency therapy includes 9a-fludrocortisone and salt supplementation. However, infants with mineralocorticoid resistance will not respond to fludrocortisone treatment. Management of these cases is symptomatic with sodium repletion, ion - exchange resins and treatment of the precipitating cause (e.g. antibiotics for a urinary tract infection) [24].

6. Causes of hypoaldosteronism

Hypoaldosteronism is classified in three large categories, according to their pathophysiology; deficient production by the adrenal glands, aldosterone unresponsiveness and defective stimulation of aldosterone secretion by renin (**Table 1**) [52].

The most common cause of aldosterone deficiency in the first weeks of life, is CAH due to 21-hydroxylase deficiency [38]. However, this diagnosis becomes less likely outside the neonatal period, by which time most cases have been diagnosed, either based on newborn screening or a salt-losing crisis. In boys, once CAH has been ruled out, the most common cause of hypoaldosteronism in early infancy (birth to 2 months) are the DAX-1 mutations, causing AHC. Other defects in aldosterone biosynthesis include ASD, 3β-hydroxysteroid dehydrogenase deficiency, cholesterol side-chain cleavage enzyme deficiency and congenital lipoid hyperplasia due to deficiency of the steroidogenic acute regulatory (StAR) protein. PHA which results from diminished renal tubule responsiveness to aldosterone is another important cause of salt wasting in infancy [6]. Hyporeninemic hypoaldosteronism results in the same metabolic derangements, although this most often presents in adult populations. While rare in infants, the administration of nephrotoxic medications (e.g., ACE inhibitors, nonsteroidal anti-inflammatory drugs) should also be considered [30].

6.1 Deficient aldosterone production by the adrenal glands: hyperreninemic hypoaldosteronism

Where the primary defect is in aldosterone synthesis or release, the serum aldosterone concentration is low with a compensatory increase in PRA. Genetic defects in aldosterone biosynthesis, adrenal destruction and adrenal dysgenesis are the most common reported causes of hyperreninemic hypoaldosteronism [29, 53, 54].

A. Defective production by the adrenal glands: Hyperreninemic hypoaldosteronism (↓ aldosterone - ↑ renin)		
Combined with cortisol insufficiency		Isolated hypoaldosteronism
Genetic disorders	Salt-wasting forms of CAH Adrenal hypoplasia congenita	Aldosterone synthase deficiency
Metabolic disorders	Adrenoleukodystrophy/ Adrenomyeloneuropathy Wolman's disease	
Acquired disorders	Autoimmune adrenalitis Infections Intra-adrenal hemorrhage	Drugs: Heparin, ACE inhibitors, ARBs
B. Aldosterone resistance: Pseudohypoaldosteronism (↑ aldosterone - ↑ renin)		
Primary, due to an inherited receptor defect Secondary (UTI, urinary malformation, drugs)		
C. Defective stimulation by renin: Hyporeninemic hypoaldosteronism (↓ aldosterone - ↓ renin)		
In children with lupus nephritis, post-infectious glomerulonephritis or mild-to-moderate chronic renal insufficiency Drugs: NSAIDs, COX-2 inhibitors, beta-blockers		

Table 1.
Causes of Hypoaldosteronism (CAH: congenital adrenal hyperplasia, ACE: angiotensin-converting enzyme, ARBs: angiotensin II receptor blockers, UTI: urinary tract infection, NSAIDs: nonsteroidal anti-inflammatory drugs, COX-2: cyclooxygenase-2).

6.1.1 Salt-wasting forms of congenital adrenal hyperplasia

CAH is a group of autosomal recessive disorders characterized by cortisol insufficiency due to mutations affecting any of the steroidogenic enzymes required for cortisol synthesis [51]. About 95% of CAH is caused by 21-hydroxylase deficiency, with the aldosterone-deficient form of the disease occurring in approximately 1:20.000 births. Similarly, deficiencies of 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2), steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme (P450scc) inhibit both cortisol and aldosterone synthesis resulting in adrenal insufficiency with salt loss. Ambiguity of the genitalia in seen in 46,XX with 21OHD and 46,XY with 3βHSD2 deficiency. Paradoxically, 46,XX individuals born with severe 3βHSD2 deficiency can virilize slightly in utero, due to extra-adrenal 3βHSD1 activity. Infants with lipoid CAH (StAR deficiency) have 46,XY sex reversal and normal-appearing female genitalia secondary to a severe defect in Leydig cell steroidogenesis [1, 55]. A detailed review of this topic is beyond the scope of this chapter.

6.1.2 Aldosterone synthase deficiency

ASD is a rare case of hyperreninemic hypoaldosteronism inherited in an autosomal recessive pattern and caused by mutations in the CYP11B2 gene encoding the enzyme aldosterone synthase [10, 56]. The CYP11B2 gene is located on chromosome 8q22p, band q24.3, approximately 40 kb away from the 93% - identical CYP11B1 gene encoding the 11 β-hydroxylase enzyme [57]. Aldosterone synthase catalyzes the three final steps of aldosterone biosynthesis: first the 11-hydroxylation of deoxycorticosterone (DOC) to corticosterone (compound B), then the hydroxylation at position 18 to 18-hydroxycorticosterone (18OHB) and lastly the oxidation at position 18 to aldosterone. According to the relative levels of aldosterone and its precursors, ASD has been subdivided into type 1 and type 2. It is important to note that 11-hydroxylation of DOC is not impaired in either type of ASD because it is also catalyzed by the CYP11B1 isoenzyme, resulting in accumulation of both compound B and DOC [48, 58, 59].

Type 1 ASD, previously known as corticosterone methyloxidase I (CMO I) deficiency is typically characterized by total suppression of aldosterone synthase activity, resulting in impairment of both 18- hydroxylation and 18-oxidation. Thus, patients with ASD 1 have low to normal levels of 18OHB and very low to undetectable levels of aldosterone [58].

Type 2 ASD (CMO II deficiency) results from mutations in CYP11B2 gene that selectively affect the 18-methyl oxidase activity while preserving the 18- hydroxylation of corticosterone, resulting in excessive levels of 18OHB and low to normal levels of aldosterone. Determination of 18OHB-to-aldosterone ratio enables recognition of the site of the enzyme block [10, 19, 60, 61]. Type II ASD is characterized by a markedly (often 100-fold) elevated ratio in either urine or serum [62].

Despite their different biochemical profile, type 1 and type 2 ASD would be better considered a continuous spectrum of the same disease. 18-OHB exhibits minimal biological affinity for the MR and there is considerable overlap between the clinical, hormonal and genotypic features of the two types of the disease [6, 48]. The condition has manifestations ranging from life-threatening salt-wasting crisis in neonates to asymptomatic impairment of statural growth in children. The most common age of onset of major clinical salt wasting is between 1 week and three months of age [6, 58, 60]. Notably, impairment of linear growth may be the sole or the predominant feature in older children [6]. Although fatalities have occasionally occurred, the morbidity of ASD is usually not as severe as that of the salt-wasting forms of CAH, reflecting normal DOC, corticosterone and cortisol synthesis. Moreover, family studies have identified biochemically affected but asymptomatic adults with abnormal ratios of 18-oxygenated steroids [6, 62].

ASD responds well to exogenous mineralocorticoid treatment. Infants will also require NaCl supplements for ongoing electrolyte management. Fludrocortisone doses do not need to be increased with age, since mineralocorticoid sensitivity increases throughout childhood [10, 63]. In the first months of life, fludrocortisone's recommended dosage is 0.05–0.3 mg/day. The dosage might be adjusted to about half of the initial dosage during the second year of life and a third or a quarter during the third year [64]. Mineralocorticoid replacement is typically continued throughout childhood, but is often gradually weaned by adolescence, as patients spontaneously ameliorate their salt-wasting syndrome. Normalization of serum electrolyte concentrations and suppression of PRA towards the normal age-adjusted range seem to represent reasonable objectives in children [6, 11, 63].

6.1.3 Familial hyperreninemic hypoaldosteronism unlinked to the aldosterone synthase (CYP11B2) gene

Isolated hyperreninemic hypoaldosteronism in infancy is usually caused by mutations in CYP11B2 gene. However, there have been several reports of infants with the same clinical picture, in whom no mutations of CYP11B2 were detected. An inherited form of hyperreninemic hypoaldosteronism, distinct from ASD, seems to be the cause and the affected gene(s) remain to be determined [57, 62].

6.1.4 Adrenal hypoplasia congenita

AHC is a rare inherited disorder of adrenal cortex development. It occurs in 2 distinct forms: The X-linked cytomegalic form and the autosomal recessive miniature adult form. In the X-linked or cytomegalic form, the adrenals do not differentiate beyond the fetal stage. They are characterized by an absence of the permanent zone and by abnormally large (cytomegalic) cells. The autosomal recessive or miniature adult form is characterized by small adrenal glands with normal architecture and normal adult zone structure [65–69].

X-linked AHC is caused by a defective NR0B1 (nuclear receptor subfamily 0, group B, member 1) gene [70]. About two thirds of boys with AHC have point mutations and the other one third has gene deletions [71]. The NR0B1 gene encodes the DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia, critical region on the X chromosome, gene 1) protein on the X-chromosome (Xp21) [69, 72, 73]. DAX-1 is an orphan nuclear receptor expressed in the adrenal cortex, testicular Leydig and Sertoli cells, ovarian theca and granulosa cells, pituitary gonadotropes and hypothalamus [70, 74]. Its actions are mediated by repression of another orphan nuclear receptor, steroidogenic factor 1 (SF-1) and together they regulate the embryological development and subsequent function of these tissues. The prevalence of NR0B1 mutations in the general population has been estimated as 1:70,000–1:600,000 [69, 70, 72–77].

The classic form of X-linked AHC is characterized by three main features: primary adrenal failure, hypogonadotropic hypogonadism (HHG) and infertility [10]. A family history of adrenal failure, unexpected death or HHG, in males in the maternal family is evident in almost 100% of affected individuals [77]. The gold standard for diagnosis of X-linked AHC is genetic testing, showing a deletion or mutation in the NR0B1 (DAX1) gene [69].

6.1.4.1 Primary adrenal failure in X-linked AHC

Classically, a bimodal presentation pattern is seen, with 60% of affected males presenting during the first eight weeks of life and 40% presenting between 1 to 10 years of age with primary adrenal failure or isolated mineralocorticoid

deficiency [76, 78]. The initial presentation of X-linked AHC is often a combination of mineral and glucocorticoid deficiency but, especially during the neonatal period, aldosterone deficiency may precede cortisol deficiency at onset [72]. An adult-onset form of X-linked AHC has also been described in 10 males and diagnosis was suspected observing the association of adrenal insufficiency and hypogonadotropic hypogonadism. Variability in the age of onset is evident even among patients of the same family, carrying the same mutation, indicating that epigenetic or environmental factors are also involved in the clinical course [67, 71, 72, 76, 77, 79].

Infants with PAI present with salt-wasting, failure to thrive, hyponatremia, hypoglycemia, and hyperpigmentation. Older individuals may present more insidiously with chronic adrenal insufficiency until a concomitant illness precipitates acute adrenal crisis [71, 73].

A cortisol value within the normal range does not necessarily exclude the diagnosis of AHC and in several cases, children with normal basal cortisol levels presented with clinical adrenal failure shortly after. Glucocorticoid function should be carefully assessed, possibly through a short Synachten test, with sometimes an increase of ACTH level indicating compensated primary adrenal failure [57, 72, 78].

6.1.4.2 Hypogonadotropic hypogonadism in X-linked AHC

X-linked AHC is associated with isolated hypogonadotropic hypogonadism that seems to be the result of both hypothalamic and pituitary dysfunction. The deficit in pituitary hormones is selective for gonadotropins as other hormones' production is normal. HHG usually becomes apparent in adolescence by absent or arrested pubertal development. Progression of puberty beyond Tanner III is extremely uncommon [65, 73, 76, 78, 80, 81].

Cryptorchidism may be present at birth, with at least 10% of infants having unilateral or more frequently bilateral undescended testes [76]. Against expectation, normal minipuberty of infancy with appropriately elevated gonadotropin and testosterone levels has been shown in 2 infants. The maternal uncles sharing the same DAX1 mutation with the infants, were affected by HHG [68, 82].

Other paradoxical features such as macrophallia or transient precocious sexual development have also been described in infancy and childhood, with several mechanisms proposed. Chronic excessive ACTH levels resulting from adrenal insufficiency may stimulate Leydig cells and lead to gonadotropin-independent precocious puberty in some boys with DAX1 gene mutations [70, 83, 84].

6.1.4.3 Complex Glycerol Kinase Deficiency

Males with confirmed X- linked AHC should be evaluated for clinical signs of other diseases mapped in Xp21 because deletions of the NR0B1 gene may also occur along with contiguous gene defects as part of Complex Glycerol Kinase Deficiency (CGKD) [65, 69, 85]. CGKD develops from partial deletion of the Xp21 chromosomal locus involving all or part of the gene for glycerol kinase deficiency (GKD) together with that for AHC and/or Duchenne muscular dystrophy (DMD). Much larger deletions including the ornithine transcarbamylase locus have also been described [86–88]. The syndrome can be both sporadic and familial, and the phenotype varies according to the extension of deleted DNA [89]. Patients with CGKD may show dysmorphic features including prominent eyebrows and forehead and depressed nasal root giving the face an hourglass appearance [86]. Mental impairment is also described, but specific causes have not been clearly defined. The terminal 3′ end of the DMD gene is essential for normal development of the brain and a gene mapped distal to the DMD locus is associated with a form of X-linked mental retardation [89].

6.2 Defective aldosterone action: pseudohypoaldosteronism (PHA)

Syndromes characterized by apparent aldosterone deficiency, despite elevated aldosterone levels are classified as PHA. This may be either primary (PHA type 1 and 2) or secondary (PHA type 3) phenomenon. Primary PHA type 1 is subclassified into two genetically distinct syndromes, that differ in the involvement of aldosterone target organs and the severity of salt wasting: (1) the autosomal dominant (AD) or sporadic form (also called renal form) and (2) the autosomal recessive (AR) or generalized form. The biological characteristics of primary PHA1 and secondary PHA3 are dehydration accompanied by hyponatremia, hyperkalemia, and metabolic acidosis despite high aldosterone levels [27].

In contrast, type 2 PHA (Gordon syndrome or familial hyperkalemic hypertension) is a rare potassium retaining syndrome characterized by hyperkalemia, normal GFR, hypertension, metabolic acidosis, suppressed PRA and variable aldosterone levels. It is caused by mutations affecting WNK1 and WNK4 kinases, as well as Cullin3 (CUL3) and Kelch-like3 (KLHL3) proteins. Comparison between the different types of PHA is presented in **Table 2** [47, 91–93].

6.2.1 Multi-system PHA type 1

Multi-system PHA type 1 (sPHA) is characterized by multiple end-organ resistance to aldosterone and is inherited as an autosomal recessive trait [94]. It is caused by homozygous or compound heterozygous inactivating mutations in the genes encoding the alpha, beta and gamma subunits of the ENaC. Both genes encoding the β- (SNCC1B) and γ-subunits (SNCC1G) are located in 16p12, while the gene encoding the α-subunit (SNCC1A) is located in 12p13 [71, 91, 95–97].

PHA	**sPHA type** I	**rPHA type** I	**PHA type** II	**PHA type** III
inheritance	AR	AD	AD	not inherited
mutated protein	ENaC	MR	WNK1, WNK4, KLHL3, CUL3	none
patho-physiology	salt loss K^+ retention	salt loss K^+ retention	salt and K^+ retention	salt loss K^+ retention
age of onset	neonatal period	neonatal period early infancy	scholar, adolescence	neonatal period early infancy
blood pressure	hypotension	hypotension	hypertension	hypotension
electrolyte levels	hyponatremia, hyperkalemia	hyponatremia, hyperkalemia	hyperkalemia	hyponatremia, hyperkalemia
PRA	↑	↑	↓	↑
aldosterone	↑	↑	variable	↑
treatment	supplemental sodium, potassium binding resins	supplemental sodium	salt restriction, thiazides	treatment of underlying cause, supplemental sodium
duration	persistent	self-limited	persistent	transient
prognosis	poor	good	good	good

Table 2.
Comparison Between the Different Types of PHA from references [47, 90] (PHA: pseudohypoaldosteronism; AR: autosomal recessive; AD: autosomal dominant; MR: mineralocorticoid receptor; ENaC: epithelial sodium channel; WNK: with-no-lysine (K) kinase; CUL3: Cullin3 and KLHL3: Kelch-like3).

Since the ENaC is expressed in all aldosterone - dependent epithelial tissues (distal part of the nephron, distal colon, salivary ducts, sweat glands, respiratory airway, pulmonary alveoli and nasal mucosa), sPHA is associated with widespread systemic manifestations [91, 98]. The pattern of laboratory abnormalities is diagnostic and shows hyponatremia, hyperkalemia, metabolic acidosis, elevated PRA and aldosterone concentrations. The course of the disease is severe and lifelong treatment is required [92, 99].

In utero, uncontrolled saliuretic fetal polyuria due to mineralocorticoid resistance may lead to polyhydramnios. In the postnatal period, sPHA is characterized by failure to thrive, vomiting and severe dehydration. Affected infants may also have chronic diarrhea, excessive pulmonary secretions, cholelithiasis and recurrent skin rashes [99–101]. Other associated symptoms include chronic discharge of clear liquid from the nose and salt loss from the Meibomian glands of the eyelids [90, 93, 102].

Lower respiratory tract involvement associated with sPHA makes the disease an important mimic of cystic fibrosis. ENaC plays a major role in airway sodium absorption, airway liquid volume and composition [103]. First, the increased volume of intraluminal liquid results in airway narrowing. This is especially evident during infancy and early childhood, when the airway diameter is small. Besides, changes in the airways' ionic composition may compromise normal mucociliary function, predisposing to lower respiratory tract infections. However, children generally do not present after age 5 and do not typically develop *Pseudomonas aeruginosa* lung infections. These features differentiate children with sPHA from those with cystic fibrosis [94, 95, 103–105]. Infants with sPHA sustain recurrent episodes (3–6 per year) of chest congestion, coughing and tachypnea, often associated with fever, wheezing and crackles. It is noteworthy, that respiratory symptoms begin within weeks or months after birth and only two newborns with neonatal respiratory distress syndrome (RDS) and sPHA have been described. Both were premature, one born at 31 weeks of gestation and one born at 36 weeks. Older patients (more than five years of age) have less severe and less frequent respiratory symptoms [47, 90, 98].

Defective ENaC function is also responsible for the high sweat salt concentration of infants with sPHA, making the sweat test an excellent discriminant between the systemic and the renal type of the disease [92]. The high sodium concentration also causes chronic inflammatory changes around and within the sweat ducts resulting in recurrent skin rashes. Cutaneous manifestations of patients with sPHA1 mimic pustular miliaria rubra and are described as discrete erythematous pustules, that worsen during salt-depletion crises and clear spontaneously with stabilization. Interestingly, inflammatory pustules have not been noted in patients with cystic fibrosis. The reason for this is unknown, but may relate to higher sweat salt concentrations in sPHA. Typical sweat chloride concentrations in infants with sPHA range between 110 and 150 mmol/L. In comparison, sweat chloride concentrations higher than 75 mmol/L are reported in patients with cystic fibrosis [99, 102, 106].

Normalization of fluid and electrolyte balance in generalized PHA1 is particularly challenging. Patients are insensitive to mineralocorticoids and require high doses of sodium supplementation (between 20 and 50 mEq/kg/d), together with orally administered ion exchange resins and dietary potassium restriction. Although a slight amelioration is observed with ageing, treatment is mandatory throughout life [102, 107].

6.2.2 Renal PHA type 1

Renal PHA type 1 (rPHA) is an autosomal dominant (AD) disease caused by heterozygous mutations in the NR3C2 gene. The NR3C2 gene located on chromosome 4q31.1 is responsible for encoding the the distal renal tubule's mineralocorticoid

receptor [90, 91, 94]. More than 50 different mutations have been identified in this receptor, which lead to renal resistance to aldosterone [71]. The renal type of PHA represents the most frequent form of the disease with a prevalence of 1 per 80.000 newborns [102].

AD-PHA is restricted to the kidneys and clinical symptoms usually remit with age. Although less severe in its course, rPHA has been reported to be associated with high infant mortality rate. In fact, patients with rPHA resemble a striking phenotypic diversity, with a clinical spectrum ranging from asymptomatic to severe PHA. Characteristic of the autosomal dominant form is an affected, symptomatic index case, with family members who are biochemically affected but clinically asymptomatic. Sporadic cases due to de novo mutations have also been reported [90, 97, 108–110].

Patients mainly manifest in early infancy, between 0.5 and 6 months of age, with isolated renal resistance to aldosterone, leading to renal salt loss, hyponatremia, hyperkalemia, metabolic acidosis, failure to thrive and elevated plasma renin and aldosterone concentrations. The main clinical symptom is failure to thrive due to chronic dehydration. Hyperkalemia is generally mild, and metabolic acidosis is not always detectable [93].

In rPHA, 3–20 mEq/kg/daily dose of sodium is sufficient to compensate for the salt loss and is followed by a rapid clinical and biochemical improvement [105]. Potassium-binding resins are rarely needed. Although the primary defect persists for life, improvement usually occurs after the first years of life and sodium supplementation generally becomes unnecessary by 2–3 years of age. Amelioration of the phenotype is attributed to the renal tubule's maturation, autonomous addition of salt to the diet and chronic up-regulation of mineralocorticoid axis. Chronic salt depletion and resultant hyperreninemia possibly stimulates zona glomerulosa leading to the zone's hypertrophy and tertiary hyperaldosteronism. Thus, PRA decreases into normal range, while high plasma aldosterone levels persist into adulthood [90, 102, 105, 108].

6.2.3 Secondary PHA type 3

Secondary PHA in infancy is a transient condition characterized by lack of response to aldosterone in the distal tubule due to obstructive uropathy, VUR and/or UTI [111]. Any kind of urinary tract obstruction, including posterior urethral valves, ureterocele, ureteropelvic junction obstruction and ureterohydronephrosis may lead to PHA [106, 109].

The underlying pathogenesis for secondary aldosterone resistance has not been fully elucidated. Early infancy, however, seems to be the main contributing factor, as the prevalence rate of secondary PHA diminishes considerably after three months of age, with the majority of infants being less than seven months old [106, 110, 112].

Inflammation and production of cytokines is an additional factor contributing to aldosterone resistance. Circulating bacterial endotoxins can directly damage aldosterone receptors, as well as stimulate the intrarenal synthesis of cytokines like prostaglandins, leukotriens, endothelin, interleukin (IL)-1 and thromboxane. Similarily, parenchymal renal damage in case of obstructive uropathy increases the intrarenal expression of tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, transforming growth factor beta-1 (TGF-β1), angiotensin II, endothelin, thromboxane A2 and prostaglandins. These cytokines induce vasoconstriction, reduction of GFR, natriuresis and/or decreased Na^+-K^+-ATPase activity [90, 111].

Secondary PHA is typically an acute condition. Electrolyte imbalance usually resolves after 24–48 hours of intravenous fluid replacement and antibiotic therapy

in the case of UTI [113]. However, signs of pseudohypoaldosteronism have been reported to persist even after successful surgery in infants with congenital hydronephrosis, indicative of ongoing distal tubular dysfunction. The required time period for salt supplementation ranges from 3 to 13 months in reported cases, with the youngest infants requiring longer supplementation [25, 106]. If secondary PHA improves with treatment of UTI or obstructive uropathy, further genetic testing for primary PHA1 is not usually suggested [114]. Interestingly, a pathogenic mutation on NR3C2 has been recently identified in an infant with UTI-associated type IV renal tubular acidosis (RTA). Identification of MR or epithelial sodium channel (ENaC) gene polymorphisms in the presence of secondary PHA is suggestive of a possible overlap between primary and secondary type IV RTA [106, 115].

6.3 Defective stimulation by renin: hyporeninemic hypoaldosteronism

Hyporeninemic hypoaldosteronism results from insufficient stimulation of the adrenal gland due to a defect of renin secretion. The syndrome has been especially observed in adults with chronic renal insufficiency due to diabetic nephropathy and rarely in children with lupus nephritis or acute post-infectious glomerulonephritis [15, 116].

Only five infants with hyporeninemic hypoaldosteronism have been reported to date. An 8-month-old boy with chronic kidney disease (CKD) stage 3 caused by tubulointerstitial disease manifested hyperkalemia (potassium = 7.1 mEq/L) with normal GFR in the context of hyporeninemic hypoaldosteronism [117]. Hyporeninemic hypoaldosteronism has also been reported in a 3-month-old boy with severe psychomotor retardation and growth failure and a 5-month-old boy with severe mental retardation lactic acidosis and deafness [116]. Finally, the report of two male siblings, presenting with hyporeninemic hypoaldosteronism at the age of 12 and 2 months suggested a congenital primary defect [118].

7. Conclusions

Although rare, hypoaldosteronism is a potential cause of neonatal morbidity and mortality due to electrolyte disturbances and hypovolemia. Early diagnosis and treatment represent a major challenge for pediatricians, who should be aware of this condition either as isolated hypoaldosteronism or in the context of PAI. A deeper understanding of the etiology of hypoaldosteronism is crucial, to improve care of affected infants [1, 119].

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