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Acid–Base Imbalance in Pseudohypoaldosteronism Type 1 in Comparison With Type IV Renal Tubular Acidosis

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Abstract

Context: Pseudohypoaldosteronism type 1 (PHA1) has been treated as a genetic variant of type IV renal tubular acidosis (RTA), leading to the conception that PHA1 develops hyperchloremic acidosis with a normal anion gap (AG).

Objective: To delineate the acid–base imbalance in PHA1A (dominant type) and PHA1B (recessive type).

Methods: We conducted the following: (1) a retrospective chart review of our patient with PHA1B, and (2) a literature search of PHA1 cases focusing on acid–base balance. The main outcome measures were the incidence and nature of acidosis, including chloride levels and AG.

Results: In our patient with PHA1B, 7 salt-wasting episodes were analyzed. Acidosis was ascertained each time, and it was accompanied by hypochloremia except in 1 episode. AG was elevated in 5 episodes, while hyperlacticaemia was present in 3. In the literature, 41 cases of PHA1A and 65 cases of PHA1B have been identified. During salt-wasting crises, acidosis developed in 85% of PHA1A cases and 87% of PHA1B cases. Hypochloremia was present in 69% of PHA1A cases with available data (n = 13) and 54% of eligible PHA1B cases (n = 13), with mean chloride levels of 96 mEq/L and 95 mEq/L, respectively. Increased AG was less frequently reported (14% in PHA1A and 44% in PHA1B).

Conclusions: Patients with PHA1 frequently presented with metabolic acidosis. However, hyperchloremia may not be a universal finding, whereas hypochloremia and increased AG may occur in a substantial proportion of the patients.

Key Words: acidosis, anion gap, hyperkalemic RTA, hypochloremia, hyporeninemic hypoaldosteronism

Abbreviations: AG, anion gap; CKD, chronic kidney disease; ENaC, epithelial sodium channel; HH, hyporeninemic hypoaldosteronism; PHA1, pseudohypoaldosteronism type 1; RTA, renal tubular acidosis; volt-dRTA, voltage-dependent distal RTA.

Pseudohypoaldosteronism type 1 (PHA1) is a heritable disorder caused by impaired aldosterone action in the aldosterone-sensitive distal nephron spanning from the distal convoluted tubule to the collecting duct [1-3]. Renal salt-wasting, accompanied by volume depletion and hyperkalemia, is a hallmark of PHA1. Classification based on a molecular basis has been established [4, 5], namely, autosomal dominant PHA1 (PHA1A, alternatively called *renal form*) and autosomal recessive PHA1 (PHA1B, *generalized form*). In PHA1A, which is caused by a heterozygous loss-of-function mutation in *NR3C2*, which encodes the mineralocorticoid receptor, aldosterone unresponsiveness is confined to the distal nephron. Salt-wasting in PHA1A is usually mild, and life-long therapeutic salt supplementation is not essential [1-3]. In contrast, PHA1B is caused by homozygous or compound heterozygous mutations in 1 of the 3 genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*) encoding each subunit that constitutes the epithelial sodium channel (ENaC). ENaC is expressed mainly in the principal cells in the collecting duct, and is upregulated by aldosterone [6]. In PHA1B, extrarenal tissues, such as the exocrine glands and respiratory tract epithelium, also show

aldosterone unresponsiveness. Life-threatening salt-wasting crisis may occur during the neonatal period. In addition, patients with PHA1B usually experience repetitive salt-wasting episodes despite high-dose salt supplementation [1-3].

Type IV renal tubular acidosis (RTA), alternatively referred to as the hyperkalemic form of RTA, is a form of acid–base imbalance that often develops in adults with mild to moderate chronic kidney disease (CKD) [7-11]. The prototype of type IV RTA is hyperkalemia, hyperchloremia, and metabolic acidosis with a normal anion gap (AG). Whereas type IV RTA is usually found in adults with underlying diseases such as diabetes, PHA1 has been treated as a pediatric counterpart of type IV RTA and has been described as an example of the genetic version of this entity. The literature often states that PHA1 shows type IV RTA and is accompanied by hyperchloremic metabolic acidosis with a normal AG [7, 8, 11-16].

However, these statements do not seem to be based on firm evidence. We could not find any prior studies focusing on the acid–base balance in PHA1, which might clearly demonstrate the association between PHA1 and type IV RTA. In addition, considering that PHA1 is a salt-wasting disorder, the

development of hypochloremia, and not hyperchloremia, seems natural.

In this study, we retrospectively reviewed the acid–base status of our patient with PHA1B, focusing on chloride levels and AG during the salt-wasting crisis. In addition, we searched the medical literature and included case reports of both types of PHA1. Therefore, the purpose of this study was to delineate the acid–base imbalance observed in PHA1A and PHA1B, with consideration regarding the pathophysiology of acidosis found in these disorders.

Materials and Methods

The case of a Japanese male patient with PHA1B has been previously described [17, 18]. In brief, the patient collapsed at 7 days of age with marked hyponatremia (116 mEq/L), hypochloremia (84 mEq/L), hyperkalemia (8.6 mEq/L), and metabolic acidosis (HCO_3^- 14.7 mmol/L). Molecular investigations revealed compound heterozygous mutations in *SCNN1G* (c.1627delG and c.1570-1G>A). Similar to other patients with PHA1B, this patient experienced repetitive salt-wasting crises during childhood. We rechecked the patient's medical records at the time of hospitalization and obtained laboratory data to evaluate the degree and nature of the acid–base imbalance.

A literature search was conducted using PubMed and Google Scholar between May and August 2022 with the single query *pseudohypoaldosteronism*. Only studies written in English and those that included clinical information on the cases were selected. Included in the study were the pediatric PHA1A cases with documented heterozygous *NR3C2* mutations and the PHA1B cases in whom mutations in either of *SCNN1A*, *SCNN1B*, or *SCNN1G* were ascertained in themselves or their relatives. Since the mid-1980s, the laboratory methodology for chloride measurement has changed, from the colorimetric method to the use of ion-selective electrodes, and chloride levels obtained by the latter can be substantially higher than those by the former [19]. Therefore, to eliminate this bias as much as possible, studies published before 2008 were omitted with a sufficiently safe margin. In addition, we have added data from our patient with PHA1A. In every case, only the laboratory data which were verified to be obtained prior to fluid infusion and drug administration were used for the analysis.

In this study, normal chloride levels were defined as 98 to 106 mEq/L [20]. However, a precise definition of acidosis or acidemia is lacking; we found definitions of childhood metabolic acidosis as a pH < 7.35, HCO_3^- level < 22 mEq/L, or base excess ≤ 5 mmol/L [11, 21]. In our study, in an attempt to determine the prevalence of overt acidosis, the definition of acidosis was arbitrarily set as either a pH < 7.30 or HCO_3^- < 20 mEq/L. AG was calculated using the following equation:

$$AG = [Na^+] - [Cl^-] - [HCO_3^-] \tag{1}$$

$$AG = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-] \tag{2}$$

In PHA1, where sodium $[Na^+]$ decreases and potassium $[K^+]$ increases, we considered Formula 2 to be more suitable because the contribution of $[K^+]$ should not be ignored. Accordingly, throughout the study, increased AG was defined as a Formula 2-derived AG > 20.8 mEq/L, which corresponds to +2 SD of the data obtained from 29 490 adult patients with normal renal function and electrolyte levels [22].

Statistical Analysis

Each value was presented as mean ± SD. The Student *t* test was used according to the parametric nature of the data to compare the laboratory data between PHA1A and PHA1B, including electrolyte levels, HCO_3^-, pH, and AG. The Mann–Whitney *U*-test was applied to compare the age distribution in PHA1A and PHA1B cases. The proportion of neonates in both categories was compared using Yates's χ^2 test. The ratio of acidosis and increased AG was compared using the Fisher exact test. The correlation between the sodium and chloride levels in the collected PHA1 cases was verified using the Pearson product-moment correlation coefficient. Statistical analyses were performed using International Business Machine (IBM) Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY, USA). A *P* value < 0.05 was considered statistically significant.

Results

From the records of the patient with PHA1B who had been cared for at our hospital, after eliminating episodes with insufficient data records, 7 salt-wasting crises that required hospitalization were included in the analysis. In this patient, these crises occurred between the ages of 3 and 15 years. All laboratory data were verified to be obtained prior to fluid infusion and drug administration. As shown in Table 1, acidosis was present in every episode according to our definition. Chloride levels ranged between 77 and 98 mEq/L, and hypochloremia was ascertained in all but one episode. Among these episodes, 5 were accompanied by increased AG, whereas the remaining 2 showed normal AG. While hyperlacticemia was documented in 3 of the 4 episodes, the urinary ketone bodies were either negative or slightly positive in most cases.

Through a literature search, we collected 85 reports written in English describing the clinical course of patients with PHA1, along with sufficient laboratory data (the bibliography will be provided upon request to the corresponding author). After excluding cases that did not meet the inclusion criteria and adding 1 patient with PHA1A who presented at our hospital, we included 41 cases of PHA1A and 65 cases of PHA1B for subsequent analyses.

Table 2 shows the results of the literature search. The PHA1B cases were younger than the PHA1A cases (*P* < 0.01) at presentation, and the proportion of neonates was higher in the former (*P* < 0.01). Patients with PHA1B showed a more profound degree of hyponatremia and hyperkalemia than those with PHA1A (*P* < 0.01). Chloride levels were often omitted in the reports and included in less than one-third of the cases: 13 in PHA1A (32%) and 13 in PHA1B (20%). Nevertheless, the mean chloride levels—96 mEq/L in PHA1A cases and 95 mEq/L in PHA1B cases—were well below the normal range. While a substantial proportion of cases (PHA1A [9/13] and PHA1B [7/13]) were reported to be hypochloremic, none of the cases showed hyperchloremia.

Information on acid–base balance was also infrequently reported and was available for 13 patients with PHA1A (32%) and 30 with PHA1B (46%). In addition, patients for whom AG was calculable were limited, including 7 with PHA1A and 9 with PHA1B. However, analyses of these cases revealed that metabolic acidosis was frequently present (85% in PHA1A and 87% in PHA1B with no significant difference [ns]), with more severe acidosis found in PHA1B (*P* < 0.01). However, increased AG was observed less frequently, with

Table 1. Detailed data on the acid–base imbalance in a patient with pseudohypoaldosteronism type 1B recorded during severe salt-wasting episodes

Age (years)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	pH	Base excess (mmol/L)	Anion gap (mEq/L)		Lactate (mg/dL)	Urinary ketone
							Formula 1	Formula 2		
3	123	8.5	88	10.8	7.446	−12.4	24.2	32.7	ND	(±)
3	131	5.8	98	16.8	7.230	−10	16.2	22.0	ND	(−)
5	127	6.4	97	18.2	7.375	−5.5	11.8	18.2	ND	(−)
7	123	6.5	95	19.8	7.434	−3.3	8.2	14.7	18.7	(±)
8	131	6.8	95	11.4	7.270	−13.7	24.6	31.4	42.0	(2+)
9	116	7.5	77	14.0	7.299	−10.7	25.0	32.5	27.1	(±)
15	123	8.8	80	11.9	7.299	−12.1	31.1	39.9	46.6	ND

Underlined values in the chloride column indicate hypochloremia, that is, < 98 mEq/L.
The shaded cell indicates either a lower pH and HCO_3^-, judged as acidosis, or an increased anion gap. Abbreviation: ND, not determined.

an incidence of 14% in PHA1A cases and 44% in PHA1B cases (ns). Lactic acid levels have seldom been mentioned in the reports.

Figure 1 shows the significant positive correlation between sodium and chloride levels in 26 PHA1 cases where both electrolyte levels were simultaneously determined. The significance of the correlation was still found when PHA1A (n = 13) and PHA1B (n = 13) were analyzed separately.

Discussion

In this study, we attempted to delineate how the acid–base balance was disturbed in PHA1A and PHA1B. This study was motivated by the discrepancy between the repetitive description in the literature connecting PHA1 and type IV RTA [7, 8, 11-16] and the absence of detailed studies on the acid–base imbalance in PHA1. In fact, even the frequency and degree of acidosis in PHA1 have not been thoroughly investigated. We wondered if the previously believed concept that PHA1 shows type IV RTA arose solely from the theoretical logic that an impaired aldosterone effect must induce type IV RTA. However, aldosterone deficiency is not a sufficient condition for the development of acidosis, as we will discuss later. In addition, it seems strange how AG should be calculated in PHA1 has never been discussed so far, considering the grossly abnormal sodium and potassium levels in PHA1. In this study, an equation that includes the potassium level (Formula 2) was employed because we believe that the contribution of [K+] should not be ignored in hyperkalemic situations.

In the patient with PHA1B who had been cared for at our hospital, scrutiny of acid–base status was feasible in 7 salt-wasting crises. In every episode, the patient exhibited apparent metabolic acidosis. Most of them were not hyperchloremic acidosis but were definite hypochloremic acidosis. In addition, AG levels tended to be elevated and were frequently accompanied by hyperlacticemia. We speculate that the increased AG was induced by hyperlacticemia resulting from tissue hypoperfusion due to severe hypovolemia. The contribution of ketosis was trivial. Therefore, the acid–base imbalance in this patient was distinct from the prototype of type IV RTA, namely hyperchloremic acidosis with normal AG.

During the literature search, it was disappointing that information on the acid–base status was less frequently available. However, according to our definition, among the eligible cases,

the prevalence of acidosis was higher than 85% in both PHA1A and PHA1B cases. The degree of acidosis was more severe in PHA1B than in PHA1A cases, which seems to be consistent with the severity of salt-wasting indicated by the differences in sodium and potassium levels. Therefore, considering that our criteria for acidosis were set rather strictly to exclude mild acidosis, it can be inferred that PHA1, especially PHA1B, is truly accompanied by metabolic acidosis when a salt-wasting crisis occurs.

Chloride levels reported in the literature were consistent with those found in our patient with PHA1B. While we could not find reports of any patients with PHA1 who showed hyperchloremia, more than half of the cases were reported to be hypochloremic. In addition, the positive correlation between sodium and chloride levels among the reported cases (Fig. 1) supports the notion that hypochloremia is not an exception under salt-wasting conditions. Moreover, in a recent report comprising 22 patients with PHA1B from 13 unrelated families [23], the median lowest chloride level was 88 mEq/L (range, 81-108 mEq/L). Collectively, the existing data do not support the concept that hyperchloremia is a universal finding at acidosis in patients with PHA1 during salt-wasting crises and suggest that hypochloremia may be seen at a certain rate. Studies with a larger number of patients are needed to reveal the true chloride behavior in PHA1.

However, the results of AG found in the literature were inconsistent with the elevated AG observed in our patient with PHA1B. AG levels were normal in most PHA1A cases. Although AG was elevated in 44% of the PHA1B cases, there was no significant difference in AG levels between PHA1A and PHA1B. We cannot precisely elucidate this discrepancy regarding the AG status between our patient and the cases found in the literature. Because the number of cases in which AG was calculable was small, future studies focusing on AG and lactic acid levels are warranted.

In the following part of this discussion, we argue that pathophysiological differences exist between typical type IV RTA in adults and PHA1 (Fig. 2).

The acquired forms of type IV RTA in adults are divided into 2 categories: voltage-dependent distal RTA (volt-dRTA) and hyporeninemic hypoaldosteronism (HH) [7].

Volt-dRTA is typically observed in adults with obstructive uropathy [7, 24], sickle cell anemia accompanied by CKD [7, 25], or those who undergo kidney transplantation [26].

Table 2. Detailed data on the acid–base imbalance in pseudohypoaldosteronism (PHA) types 1A and 1B obtained through the literature search

	Age (days)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)[a]		Bicarbonate (mEq/L)	PH	Acidosis ratio[b]	Anion gap (mEq/L)[c]	Increased anion gap[d]
PHA1A (n=41)	28 [1-315] (n=41)	126±5.1 [113-136] (n=41)	6.7±1.3 [4.9-10.5] (n=39)	96±3.8 [91-104] (n=13)	Low: 9 Norm: 4 High: 0	17.0±2.5 [13.0-21.6] (n=12)	7.31±0.1 [7.16-7.44] (n=9)	85% (11/13)	16.0±5.0 [6.7-21.5] (n=7)	14% (1/7)
PHA1B (n=65)	**9 [1-225] (n=64)	**121±7.8 [105-136] (n=65)	***9.4±1.6 [5.1-13] (n=64)	ns 95±7.4 [83-104] (n=13)	Low: 7 Norm: 6 High: 0	**14.1±4.3 [8.2-22.6] (n=23)	**7.20±0.1 [6.70-7.41] (n=24)	ns 87% (26/30)	ns 18.9±7.50 [8.4-27.6] (n=9)	ns 44% (4/9)

In each cell, the mean ± SD is provided, with the distribution range in brackets. Regarding age, the median value is shown instead of the mean and SD.

$*P < 0.05$ compared with that of PHA1A, $**P < 0.01$ compared with that of PHA1A, ns no significant difference compared with that of PHA1A.

[a]In the right column of chloride, the numbers of hypochloremia (<98 mEq/L), normo-chloremia, and hyperchloremia (>106 mEq/L) are shown.

[b]Acidosis ratio: the prevalence of cases with pH <7.30 or HCO_3 <20 mEq/L.

[c]Anion gap is calculated using Formula 2 stated in the text, namely, anion gap = $[Na^+]+[K^+]-[Cl^-]-[HCO_3]$.

[d]Increased anion gap: ratio of cases with anion gap >20.8 mEq/L, estimated using Formula 2.
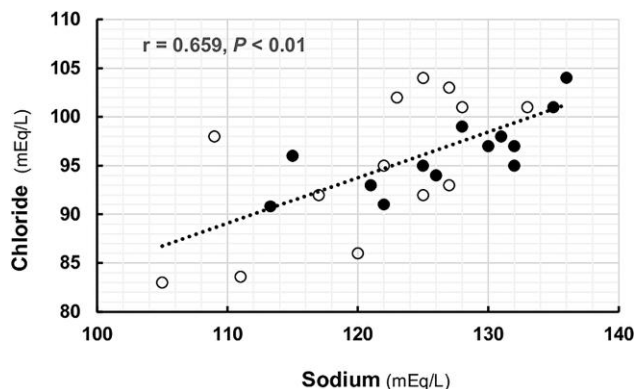

Figure 1. Scatter plot of sodium and chloride levels in the reported pseudohypoaldosteronism type 1 (PHA1) cases. Simultaneous measurements of sodium and chloride were available for 13 PHA type 1A (PHA1A, indicated by filled circles) and 13 PHA type 1B (PHA1B, open circles) cases. As depicted, a significant positive correlation was observed ($P < 0.01$). The correlation was also significant when evaluated separately for PHA1A and PHA1B (data not shown).

In volt-dRTA, impairment of Na^+ ion reabsorption in the collecting duct is believed to be the basic mechanism for developing type IV RTA [7]; impaired Na^+ reabsorption fails to establish a sufficient lumen-negative electric gradient (voltage) in the collecting duct, which normally facilitates the excretion of both K^+ ions and protons (H^+). In addition, hyperkalemia itself exacerbates acidosis through decreased ammonia (NH_3) production in the proximal tubules. Moreover, the inability to maintain a high NH_3 concentration in the medullary interstitium owing to CKD decreases the excretion of NH_3 to the collecting duct.

In contrast, HH develops in the situation of CKD due to conditions such as diabetic nephropathy, chronic interstitial nephritis, or methylmalonic acidemia [7, 27-29]. Confusingly, HH is sometimes referred to as type IV RTA in a narrow sense. As its name indicates, fundamental pathogenesis is believed to be impaired renin production in the juxtaglomerular apparatus, leading to inadequate aldosterone synthesis and release from the zona glomerulosa. The precise mechanism by which aldosterone deficiency causes acidosis under volume overload remains unclear. Putative mechanisms include an attenuated activity of both the apical H^+-ATPase and basolateral anion exchanger protein 1 (AE1) in a-intercalated cells and attenuated activity of pendrin (bicarbonate-chloride exchanger) located at the apical surface of b-intercalated cells. Moreover, just like as in volt-dRTA, decreased NH_3 production or excretion due to hyperkalemia and CKD may be responsible [7, 27, 28].

Although the precise mechanism for the development of acidosis in PHA1 has never been elucidated, it must be different from the pathophysiology in volt-dRTA and HH (Fig. 2). First, because patients with PHA1 develop hyperkalemia periodically, in contrast to chronic hyperkalemia present in patients with both volt-dRTA and HH, decreased NH_3 production due to hyperkalemia may play only a minor role in PHA1. Second, because CKD, which is a prerequisite for developing volt-dRTA and HH, is absent in PHA1, impaired NH_3 excretion to the collecting duct may not be the case. Third, in a study of adrenalectomized patients with a normal renal function who were administered glucocorticoid and mineralocorticoid, transient discontinuation of mineralocorticoid
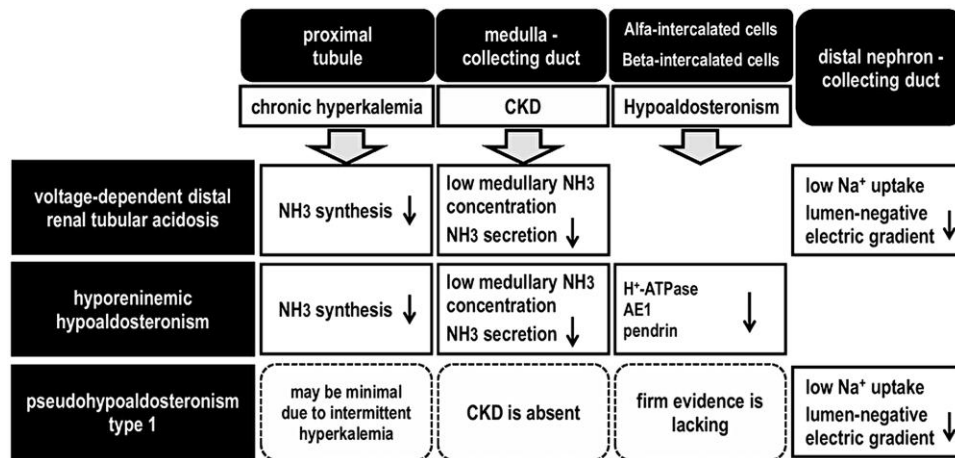
Figure 2. Suggested pathophysiology for acidosis in type IV renal tubular acidosis and pseudohypoaldosteronism type 1 (PHA1). In PHA1, decreased NH3 production induced by chronic hyperkalemia and decreased NH3 excretion accompanied by chronic kidney disease may not be involved. In addition, the direct effects of aldosterone on intercalated cells have not been verified and may be minimal or absent in humans. Abbreviations: AE1, anion exchanger protein 1; CKD, chronic kidney disease; NH3, ammonia.

decreased plasma HCO_3^- levels by only 1.1 mEq/L, suggesting that aldosterone plays only a permissive role in net acid excretion in patients with normal kidney function [30]. In addition, the direct positive effects of aldosterone on H^+-ATPase, anion exchanger protein 1, and pendrin described above have not been clearly proven in humans [31]. Surprisingly, 11β-hydroxysteroid dehydrogenase, which is indispensable for aldosterone to function fully via the mineralocorticoid receptor, was absent in rat α-intercalated cells [31, 32]. Furthermore, most mineralocorticoid receptors in α-intercalated cells have been found to be in an inactive, phosphorylated form [31, 33]. All the above findings suggest that the mechanism of metabolic acidosis in PHA1 differs from that in type IV RTA.

Thus, we assume that the most likely scenario is decreased lumen-negativity along the collecting duct, which results directly from impaired Na^+ reabsorption through ENaC. Diminished lumen-negativity also decreases paracellular chloride movement via claudin, which may be relevant to the hypochloremia observed in this study. Accordingly, PHA1 shares the pathophysiology of decreased lumen-negativity with volt-dRTA. However, because CKD is a prerequisite for acidosis development in volt-dRTA, it is questionable whether decreased lumen-negativity is sufficient for acidosis development in PHA1. Future studies are warranted to elucidate the origin of acidosis fully in patients with PHA1.

Our study had some limitations because of its retrospective study design. First, there were several cases of missing data in the included reports. Chloride, pH, and bicarbonate levels were often omitted. As a result, AG could be determined only for a limited number of cases. Next, the specific methods for electrolyte and bicarbonate determination were seldom mentioned in the reports and may be diverse. In particular, because the accuracy of measuring chloride levels has improved over time [19], the methodology should ideally be identical across different studies. Finally, although a prospective case accumulation is ideal, such studies may require considerable time and labor, considering the quite low incidence of PHA1. Accordingly, we assume that our retrospective study is still significant.

In conclusion, both PHA1A and PHA1B present metabolic acidosis at a substantial rate during salt-wasting crises.

Although PHA1 and type IV RTA share decreased lumen-negativity as common pathophysiology, acidosis in PHA1 is not always identical to that in type IV RTA. Hyperchloremia may not be a universal finding, whereas hypochloremia and increased AG may occur in a substantial proportion of patients.

Acknowledgments

Disclosures

Data Availability

Some datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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