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Hyponatremia secondary to severe atopic dermatitis in early infancy

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Abstract

Background

Infants with atopic dermatitis who developed hyponatremia and hyperkalemia with raised aldosterone level have been repeatedly described in Japanese domestic literatures. However, similar reports from other countries are scarce.

Methods

Including our experiences, we collected reports of atopic dermatitis complicated with hyponatremia (≤ 130 mEq/L), written either in English or in Japanese, to delineate the characteristics and to elucidate the pathophysiology of this condition.

Results

Totally 36 patients were collected, of whom 35 were Japanese. All patients were infants younger than 9 months. Mean height SDS at presentation was -2.1 ± 1.4 ($n=25$), with mean body mass index 14.1 ± 1.7 ($n=28$). Mean sodium level was 120.7 ± 6.1 mEq/L. While 28 patients had hyperkalemia, 7 patients showed normokalemia. Elevated aldosterone level was documented in 15 patients. Nutrition mainly with breastfeeding (97%), parental refusal of steroid ointment (77%), and the association of hypoalbuminemia (73%) were frequent findings. Diminished urinary sodium level was verified in all 12 patients tested, indicating that sodium loss from the skin exudates, with limited supply of sodium from breast-milk, is the primary cause of hyponatremia. Hyperkalemia seems to result from decreased delivery of sodium to the distal nephron and from the mechanism of so-called 'aldosterone paradox' that inhibits potassium secretion. In addition, physiological aldosterone insensitivity during infancy, low muscle volume, and impaired Na^+, K^+ -ATPase function due to protein deficiency seems to exaggerate the hyperkalemia.

Conclusions

Hyponatremia secondary to severe atopic dermatitis is age-dependent manifestation, elicited by inappropriate treatment which leads to sodium loss from the damaged skin and resultant hyperkalemia via multifaceted mechanisms.

In Japanese medical literature, there are cumulative case reports of infants with severe atopic dermatitis (AD) who developed hyponatremia, often with hyperkalemia, in the face of raised aldosterone level.¹⁻³ Similar reports from other countries, however, are very scarce.⁴ Although a precise mechanism of hyponatremia in severe infantile AD has not been clarified, high sodium level in skin exudates was once demonstrated,¹ suggesting that sodium loss from the damaged skin may be responsible. This pathophysiology is reminiscent of a rare variant of pseudohypoaldosteronism (PHA), which derives from mutations in *CA12* encoding carbonic anhydrase 12.^{5,6} Apart from classic PHA with aldosterone unresponsiveness in the distal nephron, which is caused by mutations either in epithelial sodium channel (ENaC- α , - β , and - γ) genes or in aldosterone receptor gene (*NR3C2*).⁷⁻⁹, the variant PHA is characterized by sodium loss exclusively from sweat gland.

The purpose of this study is to delineate the clinical and laboratory characteristics of hyponatremia secondary to AD by extensive literature search including domestic case reports. In addition, utilizing the obtained knowledge from the case series, we tried to elucidate the pathophysiology of this condition.

Presentation of our patients

For each patient described below, an informed consent form to permit publication was obtained from the parents.

Patient 1

This female patient was born via uneventful delivery at 40 weeks with birth weight 3,010 g. She is an only child of healthy Japanese parents. Eczema developed 2 weeks of age. The diagnosis of AD was made by a local pediatrician, who instructed deprivation of egg, cow milk, wheat, soy, and rice from the diet of her mother. However, steroid ointment therapy was refused by her parents. She had been exclusively breastfed.

At an evening of her 4 months of age, the patient was noticed to be inactive. Because peripheral coldness and poor feeding developed at the night, she was brought to a nearby emergency department. During triage, cyanosis, respiratory distress, and bradycardia of 20/min. was noticed, and then cardiopulmonary resuscitation was initiated followed by bolus saline ingestion. Laboratory test disclosed hyponatremia (126 mEq/L), hyperkalemia (10.2 mEq/L), low albumin level of 1.9 g/dL, and impaired renal function (BUN 57 mg/dL, and creatinine 1.5 mg/dL). Blood gas analysis indicated metabolic acidosis; pH 7.193, pCO₂ 26.0 mmHg, HCO₃⁻ 11.7 mmol/L, base excess (BE) -17.0 mmol/L.

For further management, she was transferred to our intensive care unit. On admission, 3 hr after collapse, her height was 58.0 cm (-2.1 SD) and her weight was 4,860 g, revealing 9.8% weight loss from 1 month earlier (5,390 g). Despite catecholamine infusion, she remained to be hypotensive, which precluded critical urine sample collection. Atopic skin lesion was present throughout her scalp, face, trunk, and extremities, with yellowish exudation and desquamation. Because methicillin-sensitive *Staphylococcus aureus* and *Streptococcus agalactiae* grew in blood specimen, parenteral antibiotic therapy was initiated. With topical steroid therapy, gradual improvement of

skin lesion was achieved. Fluid replacement with catecholamine infusion promptly corrected serum sodium level (s-Na), which increased to 139 mEq/L 6 hr after admission. For hyperkalemia, calcium glucuronate and insulin was used, resulting in normalization of serum potassium level (s-K) to 4.5 mEq/L within 9 hr after admission. Metabolic acidosis subsided within 24 hr. Transient pleural effusion and ascites developed with further decline of serum albumin level to 1.1 g/dL. Following infusion of plasma preparation, serum albumin normalized on 7 days after admission. Her renal function recovered completely, and morphological evaluation of her urinary tract and kidneys revealed no abnormality. Following two-day therapeutic mild hypothermia and four-day mechanical ventilation, she showed excellent recovery.

Patient 2

A Japanese boy developed eczema with face-dominant involvement at 2 months of age. Despite non-steroidal ointment therapy directed by a local pediatrician, skin lesion spread to his trunk and extremities. He had been exclusively breastfed. At 5 months, he was referred to our hospital due to weight loss of 1 kg during a recent month. He was an alert, but small and emaciated boy, with his height 64.1 cm (-0.9 SD) and body mass index (BMI) 12.5. Generalized skin lesion of red eruption, desquamation, and serous skin discharge was noted (Fig. 1). Laboratory data revealed hyponatremia (s-Na 124 mEq/L) and hyperkalemia (s-K 5.9 mEq/L). Notably, elevated levels of both aldosterone (30,400 pg/mL) and arginine vasopressin (AVP, 60.8 pg/mL) were obtained. Pertinent skin care with steroid ointment improved his condition, with elevation of s-Na to 130 mEq/L 13 days later.

Method

To delineate the clinical and laboratory profiles of hyponatremia secondary to severe AD, extensive literature search was attempted as follows. English literature was reviewed on PubMed using search expression 'atopic dermatitis AND (hyperkalemia OR hyponatremia OR electrolyte imbalance OR pseudohypoaldosteronism)'. Domestic literature was also retrieved in the same manner using ICHUSHI, a database developed by Japan Medical Abstracts Society (<https://www.jamas.or.jp/about/english.html>).

Inclusion criteria was pediatric patients with AD judged as severe in nature by each author, who presented hyponatremia ($s\text{-Na} \leq 130 \text{ mEq/L}$), regardless $s\text{-K}$ level. Clinical features and laboratory data were collected for each patient who met the criteria.

Reference ranges for $s\text{-Na}$, $s\text{-K}$, albumin, hemoglobin, and platelet were adopted from published standards of Japanese children as shown in Supplementary Table 1.

Age distribution of AD patients with hyponatremia was compared to that of AD patients with hypoalbuminemia. Patient reports of AD with hypoalbuminemia were searched on PubMed and ICHUSHI using search expression 'atopic dermatitis AND (hypoalbuminemia OR hypoproteinemia)'. Inclusion criteria were children with severe AD with normal $s\text{-Na}$ ($\geq 135 \text{ mEq/L}$) and with hypoalbuminemia. Those who were placed on extreme food restriction with severe malnutrition were excluded. Isolated hypo-gammaglobulinemia, namely those with normal albumin level, was also excluded.

To compare the clinical properties and the laboratory data between the patients with profound hyponatremia ($\text{s-Na} \leq 120 \text{ mEq/L}$) and those with mild hyponatremia (s-Na between 121 to 130 mEq/L), Student's t test, Mann-Whitney U -test, or Fisher's probability test was used according to the parametric/non-parametric nature of the data. Parametric data included the age at presentation, height SD score (SDS), and s-K, while BMI and albumin level were treated as non-parametric data. Correlation between s-K and BE or HCO_3^- was evaluated by Pearson product-moment correlation coefficient. Statistical analysis was carried out by the IBM SPSS Statistics version 24 (IBM Corporation, New York, NY, USA). A P -value less than 0.05 was considered to be significant.

Results

36 children with severe AD who developed hyponatremia ($\leq 130 \text{ mEq/L}$), including above-described patients, were collected from two English literature^{1,4} and 25 literature written in Japanese.^{2,3} 35 patients were Japanese ancestry. The distribution of the reported year with sex distribution is depicted in Supplementary Figure 1. Since the mid-1990s, reports of hyponatremia secondary to severe AD have been constantly appeared, with male predominance of 72%.

As shown in Fig. 2, patients' age at presentation of hyponatremia distributed within quite narrow range. All the patients developed hyponatremia before 9 months of age, and 94% of them presented before 7 months. For comparison, age distribution of severe AD

with hypoalbuminemia who lacked hyponatremia was also shown in Fig. 2, demonstrating wider age distribution from 3 to 25 months.

Clinical profiles in 36 patients are presented in Supplementary Table 2 and are summarized in Table 1. Most frequent chief complaint was failure to thrive and/or weight loss. Although diarrhea was chief complaint in 6 patients, the presence of diarrhea was documented in total of 10 patients, including one patient with intractable diarrhea. Most of the patients were exclusively or mostly breastfed. Usage of steroid ointment was ascertained in only one patient, whereas steroid ointment was not provided in 29 patients, including 23 patients with parental refusal for steroid use. The patients had reduced height SDS with low BMI. As for skin conditions, either significant amount of exudates or wet skin was clearly documented in 33 patients, while active dermal infection demanding parenteral antibiotic therapy was present in 2 patients.

Table 2 summarizes the laboratory findings of the patients, the details of which are shown in Supplementary Table 2. About one third of the patients (n=13) suffered from profound hyponatremia of $s\text{-Na} \leq 120$ mEq/L. Serum potassium level was available in 35 patients, with 7 patients of normokalemia and 28 of hyperkalemia. Data of acid-base balance were available in limited number of the patients, showing that 6 out of 10 patients presented with metabolic acidosis, with mild degree in most patients. Significant correlation was observed between BE and s-K (Fig. 3), as well as between HCO_3^- and s-K ($R^2=0.608$, $p<0.05$). Information about urinary sodium excretion and circulating aldosterone concentration was also limited. Nevertheless, all 12 patients with documented urinary sodium level showed that below 20 mEq/L, whereas all 15 patients with available aldosterone level were hyperaldosteronemic. In addition, plasma renin activity (PRA) was above 20 ng/mL/h in all 10 patients measured. Remarkably, 19 out of 26 patients (73%) with documented serum albumin level showed hypoalbuminemia.

Renal function was normal in 21 patients, whereas elevated creatinine and BUN was documented in 5 patients, including our Patient 1. Thrombocytosis was documented in 10 out of 27 patients.

Normalization of hyponatremia and hyperkalemia could be obtained usually in a week with peripheral transfusion coupled with pertinent skin management. Specific potassium-lowering therapy such as calcium gluconate, glucose-insulin, or ion-exchange resin was utilized in 4 patients, while peritoneal dialysis was never performed. Complications during treatment included cerebral infarction in one patient, and subdural hematoma in another. Brain atrophy by imaging study was ascertained in 5 patients at first presentation. Long-term intellectual sequelae were seldom reported. One patient, however, achieved normal development at 20 months of age, whereas developmental level around 10 months of age was documented in another patient at 20 months of age.

Then we categorized the patients according to the degree of hyponatremia, namely, those with $s\text{-Na} \leq 120$ mEq/L and those with $s\text{-Na}$ between 121 to 130 mEq/L. There observed no significant difference between the groups regarding age, use of steroid, nutrition method, height SDS, BMI, $s\text{-K}$, and albumin levels (Table 3).

Discussion

Collected patients of hyponatremia secondary to severe AD shared substantially uniform clinical characteristics. The prototype is infants between 4-7 months of age who had been breastfed, who had not undergone steroid therapy, often due to parental refusal, and who had short stature with low BMI at presentation. They also showed the similar

laboratory findings: hyponatremia with low urinary sodium concentration, hyperkalemia, raised aldosterone and PRA levels, with acid-base balance from normal state to metabolic acidosis. Because the findings indicative of renal insufficiency was documented in only 5 out of 26 patients, hyperkalemia seemed not to be caused by reduced renal flow in most of the patients. Linear correlations between s-K and both BE and HCO_3^- indicate that metabolic acidosis can be substantially elucidated by hyperkalemia and resultant reduced reabsorption of ammonium at thick ascending limb of Henle, caused by competence with increased potassium reabsorption.¹⁰⁻¹²

The primary cause for hyponatremia seems sodium loss with the exudates from the damaged skin, considering low urinary sodium level. Although the direct evidence of this assumption is scarce, high sodium level in skin exudates, 173 mEq/L, was demonstrated in one study.¹ In addition, the presence of skin exudates was clearly stated in 33 patients. Moreover, the cause of hypoalbuminemia, another serious complication in severe AD, has also been considered to be the loss of serum proteins from the exudates.¹³⁻¹⁵ Meanwhile, 97% of the patients were reported to be exclusively or mostly breastfed, suggesting lower sodium concentration in breast milk compared to formula milk is also responsible for sodium deficiency. Because 10 patients suffered from diarrhea, sodium loss from gastrointestinal tract may be involved. However, any information of sodium level in diarrheal stool could not be obtained.

In general, aldosterone secretion from adrenal gland is stimulated either by angiotensin II following extracellular volume depletion or by potassium loading usually from diet.^{11,16,17} Because hyperaldosteronism in our patients was associated with elevated PRA, a primary stimulus for aldosterone is supposed to be volume depletion due to sodium loss. Extraordinary high AVP level in Patient 2 also supports the presence of volume depletion.¹⁸ Anyhow, increased aldosterone secretion will enhance sodium

reabsorption and potassium excretion at distal nephron via a variety of mechanisms, including 1) increment of activity and density of both Na^+Cl^- cotransporter (NCC) in distal convoluted tubule and ENaC from connecting tubule to collecting duct and, 2) stimulation of Na^+, K^+ -ATPase on basolateral membrane, and 3) activation of renal outer medullary potassium channel (ROMK) function.^{11,16} Therefore, electrolyte aberrations, especially hyperkalemia, found in the AD patients despite raised aldosterone level seems to be contradictory.

We tried to elucidate the above enigma as follows. At first, the quite narrow distribution of age at presentation (Fig. 2) indicates that physiological aldosterone unresponsiveness during early infancy^{19,20} must be involved. This unresponsiveness is reflected by high aldosterone levels in normal infants,²¹ and is elucidated by paucity of plasma membrane potassium channels like ROMK. Comparison with wider age distribution found in hypoalbuminemia (Fig. 2) supports the notion that the patient's age is critical for the development of hyponatremia.

Second, as mentioned by some authors,¹⁻³ decreased delivery of sodium to the distal nephrons will inhibit aldosterone function to promote potassium excretion there. Decreased sodium entering into tubular epithelial cells through NCC and ENaC will fail to generate a lumen negative voltage, which will in turn result in disturbed potassium secretion through ROMK. This hypothesis was suggested as a mechanism for a variant of PHA with sodium loss exclusively from sweat gland, as early as 1976.²²

Thirdly, although speculative, malnutrition of the patients, often accompanied by hypoalbuminemia, may impair the activity of energy-requiring Na^+, K^+ -ATPase of the tubule epithelial cells, which is a main driving force to generate lumen negative voltage.²³

Fourth, so-called aldosterone paradox will take part in for limited potassium secretion from ROMK.^{11,16,24} This paradox refers to the situation where sodium retention will occur under the volume depletion state without increment of potassium secretion, whereas potassium excretion will increase in response to potassium load without affecting sodium reabsorption. This paradox is partly reconciled by the knowledge suggesting with-no-lysine kinase 4 (WNK4) as the molecular switch of aldosterone's function in the distal nephron.^{16,25} Briefly, in hypovolemia, concomitant increase of aldosterone and angiotensin II will force WNK4 to stimulate sodium reabsorption via ENaC and NCC and inhibit potassium excretion via ROMK, whereas, in hyperkalemia, ROMK function will not be impaired because of the absence of high angiotensin II level. Thus, in the case of severe AD with volume depletion, potassium excretion via ROMK will be impaired.

Finally, insufficient buffering mechanisms of extracellular potassium may be responsible. Because muscle is the primary site of insulin-dependent potassium transition from extra- to intra-cellular spaces,¹¹ scanty muscle volume in infants, especially in the small and emaciated AD patients, will promote hyperkalemia. In addition, impaired Na⁺,K⁺-ATPase activity, which is also required for potassium uptake,¹¹ may also be responsible.

Taken together, all the above laboratory findings, namely, hyponatremia, hyperkalemia, metabolic acidosis, and increased renin-angiotensin-aldosterone activity, seem to be elicited primarily by sodium loss from the skin. This situation must be identical to that in a variant of PHA with *CA 12* mutations.^{5,6,22} Summarized in Fig. 4 is the proposed pathophysiology of hyponatremia secondary to severe AD in early infancy.

Although hyponatremia and hyperkalemia improved promptly following pertinent intervention mainly composed of skin management and transfusion in all the patients ascertained, electrolyte aberrations can elicit serious complications. Indeed, a pre-shock state in our Patient 1 seemed to be the severest acute manifestation. In addition, one patient was reported to have developed cerebral infarction during the recovering phase. The association of hypoalbuminemia, which was found in 73% of the patients, as well as thrombocytosis, found in 37%, may further increase the risk of complications. Because of the retrospective nature of this study, long term prognosis regarding intellectual status is unknown. However, hyponatremia will induce the expansion of cerebral neurons, which may lead to low intelligence in later life.

Degree of hyponatremia did not yield to any significant differences in height deficit, BMI, albumin level, and s-K level. This fact means that even in the patients with mild hyponatremia, profound hyperkalemia may occur. Although speculative, serum sodium level may fluctuate widely from day to day according to the skin condition, feeding volume, and the severity of diarrhea. Therefore, it may be the case that serum sodium level alone cannot be used as an indicator of the disease severity.

There remain two unanswered issues. First, male predominance of 72% is a remarkable finding in our series. It is of interest that, hypoproteinemia in AD also showed male predominance of 73.3%¹⁴ and 92.3%.¹⁵ Next, we have no plausible explanation for the paucity of the identical reports from other countries. Steroid phobia, still prevalent in Japanese population, must be responsible partly.²⁶ In addition, because a case series of 26 patients with hypoproteinemia in AD, recently reported from South Korea,¹⁵ included 10 patients of hyponatremia and 12 of hyperkalemia, hyponatremia secondary to severe AD may be under-reported.

Conclusion

We assume that hyponatremia secondary to severe AD in early infancy should be regarded as a distinct disease entity. Avoidance of this serious condition by pertinent care and education for caregivers in infantile AD is of vital importance.

Disclosure

The authors declare no conflict of interest.

Author contributions

M.A. designed the study; M.A., T.T., and C.I collected and analyzed data; M.A., T.T., and C.I. wrote the manuscript; M.A. performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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Figure Legends

Fig. 1: Photograph of the Patient 2 on admission.

Fig. 2: Distribution of the age at presentation in 36 patients of hyponatremia secondary to severe atopic dermatitis (open bars). For comparison, indicated by filled bars are the patients of severe atopic dermatitis with hypoalbuminemia and with normal sodium level.

Fig. 3: Correlation between serum potassium level and base excess in 10 patients, in whom both data were available.

Fig. 4: Proposed mechanism that will elucidate the hyponatremia and hyperkalemia secondary to severe atopic dermatitis in early infancy.

AGII: angiotensin II

ROMK: renal outer medullary potassium channel

WNK4: with-no-lysine kinase 4

Supplementary Fig. 1: Distribution of the reported year of hyponatremia secondary to severe atopic dermatitis in early infancy, coupled with sex distribution.

Table 1: Clinical characteristics of 36 patients of hyponatremia secondary to severe atopic dermatitis

sex (n=36)	onset of eczema (n=31)	age at hyponatremia (n=36)	chief complaint (n=31, multiple answer)	usage of steroid ointment (n=30)	nutrition (n=30)	*height SD score (n=25)	*body mass index (kg/m ² , n=28)
boy: 26	≤1m: 18	4m: 6	#FTT/weight loss: 19	yes: 1	exclusively	-2.1 ± 1.4	14.1 ± 1.7
girl: 10	2m: 9	5m: 14	developmental delay: 8	no: 29	breastfed: 27	(-5.3 - 1.1)	(10.1 - 17.0)
	3m: 3	6m: 7	vomit: 7	[including 23 by parental refusal]	mostly breastfed: 2	[including 13	[including 17
	4m: 1	7m: 7	inactivity/lethargy: 7		mixed	patients ≤	patients < 3 rd
		9m: 2	diarrhea: 6		nutrition: 1	-2SD]	%ile]
			poor feeding: 4				

In each parenthesis, number of available data is presented.

*For height SD score and body mass index, mean ± SD with range (in parenthesis) is provided.

FTT, failure to thrive

Table 2: Laboratory findings of 36 patients of hyponatremia secondary to severe atopic dermatitis

*s-Na	*s-K	HCO ₃ ⁻	base excess	u-Na	aldosterone	+PRA	*albumi	*hemoglobi	*platelet
(n=36)	(n=35)	(n=9)	(n=10)	(n=12)	(n=15)	(n=10)	n	n	(n=27)
[mEq/L]	[mEq/L]		[mEq/L]	[mEq/L]	[pg/mL]	[ng/mL/h]	(n=26)	(n=26)	[10 ⁴ /μL]
							[g/dL]	[g/dL]	
120.7±6.1	6.6±1.2	9.1 – 32.8	-17.0 - +6.8	0-10: #10 11-16: 2	1,500-104,000	>20: 10 (max. 570)	2.6±0.8 (1.1-4.1)	12.6±1.8 (9.0-16.4)	73.3±34.0 (11.9-190.5)
≤110: 3	hyperkalemia: 28	acidosis: 6			elevated: 15		low: 19	low: 2	low: 1
≤120: 13	normokalemia: 7	normal: 3			normal: 0		normal: 7	normal: 19	normal: 16
≤130: 36		alkalosis: 1					high: 0	high: 5	high: 10

In each parenthesis, number of available data is presented.

*For serum sodium, serum potassium, albumin, hemoglobin, and platelet, mean±SD with range (in parenthesis) is provided.

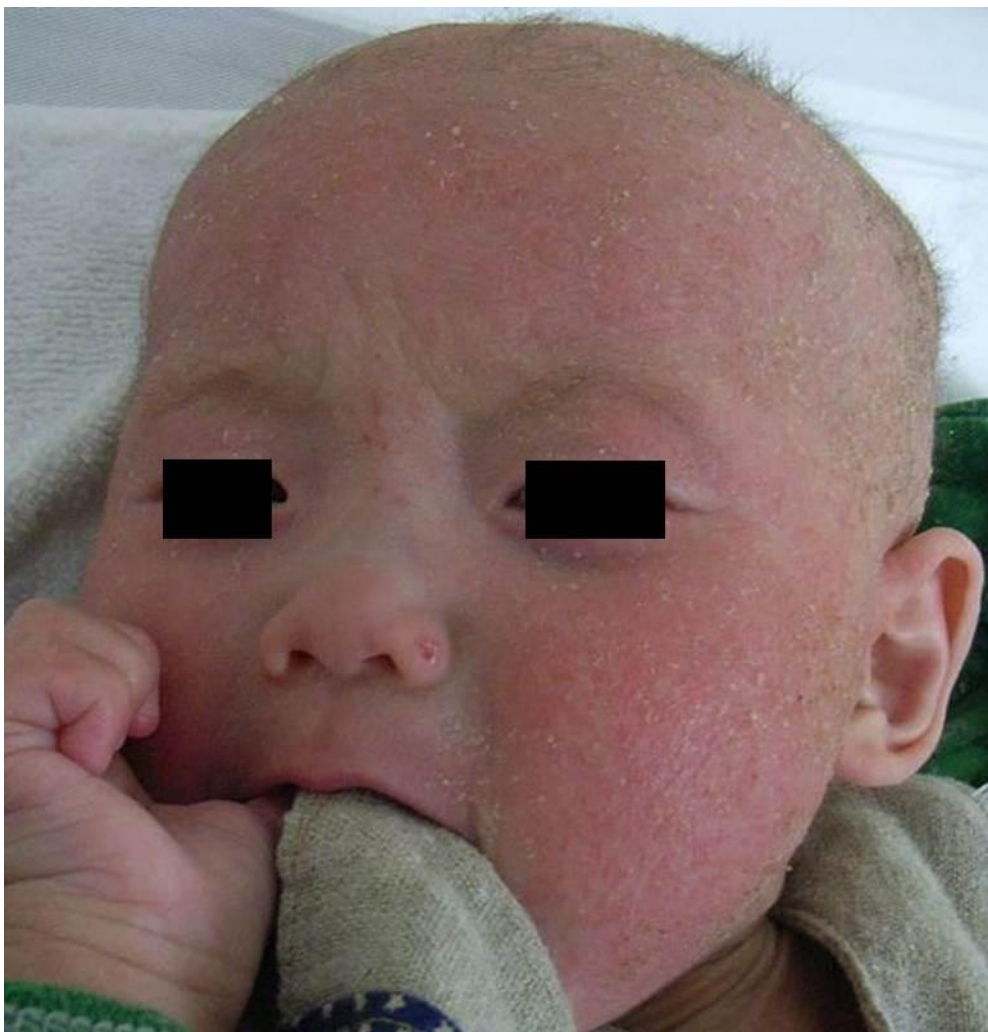
+PRA, plasma renin activity

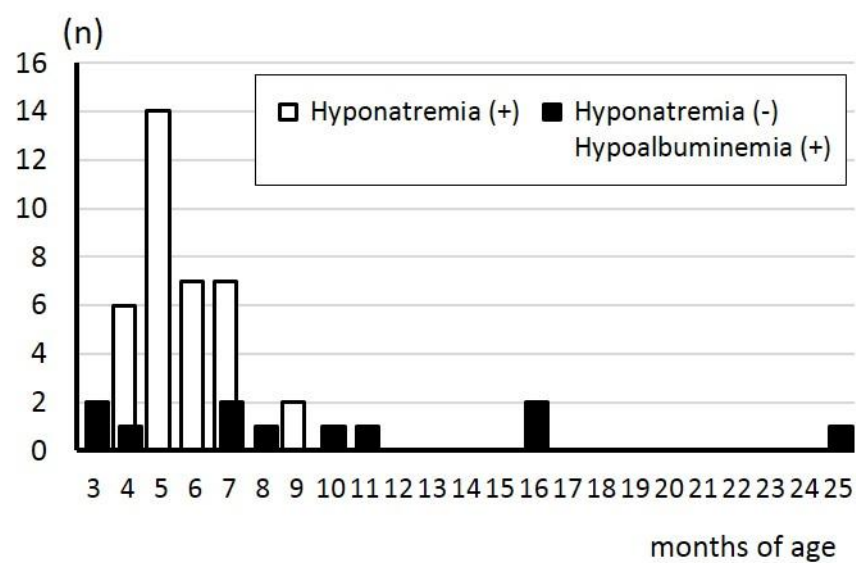
including one patient with low fractional excretion of sodium (FE_{Na}) of 0.02%

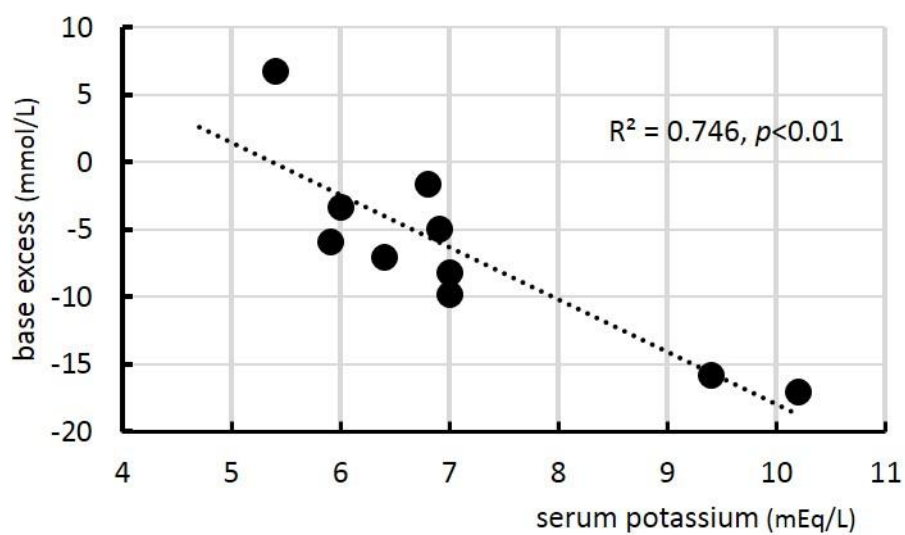
Table 3: Comparison of the patients with profound hyponatremia (s-Na $\leq$ 120 mEq/L) designated as ‘severe’ group, to those with s-Na >120 mEq/L designated as ‘mild’ group

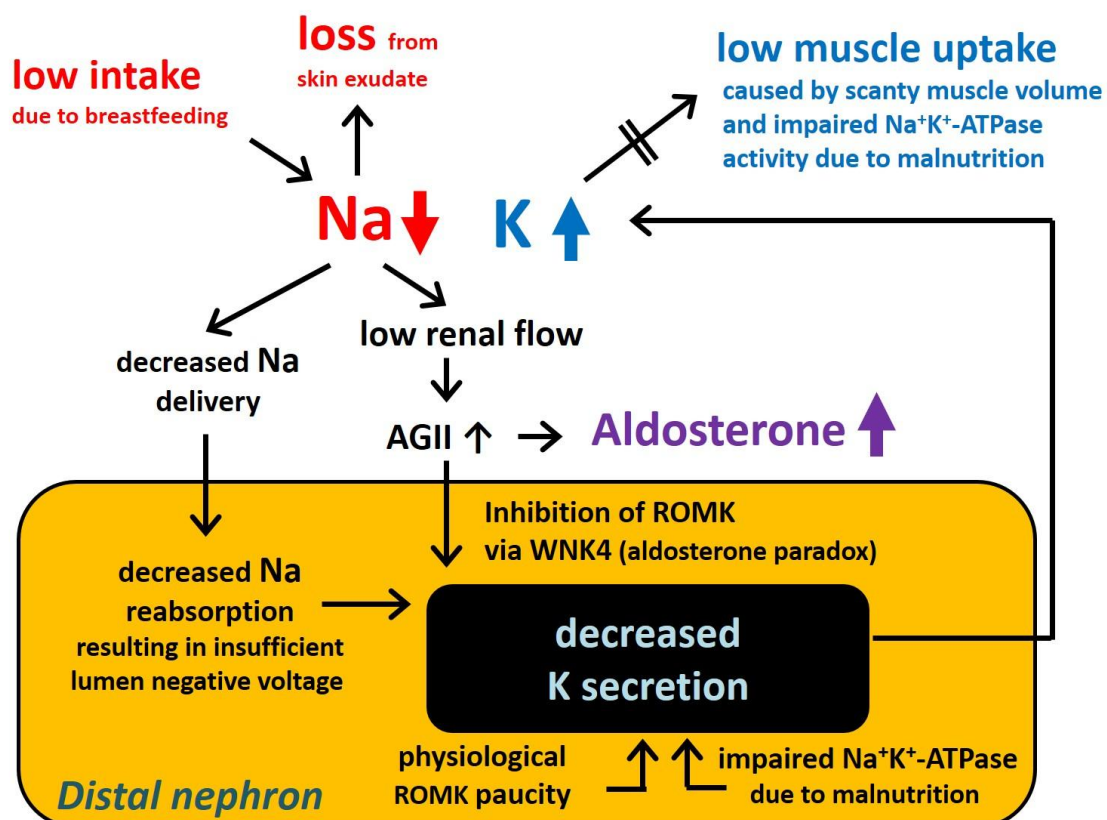
	*age at hyponatremia (month)	usage of steroid ointment	nutrition	*height SD score	*body mass index (kg/m ²)	*s-Na (mEq/L)	*s-K (mEq/L)	*albumin (g/dL)
mild (n=23)	5.4 $\pm$ 1.3 (4-9)	yes 1 no 18 unknown 4	exclusively/mostly breastfed: 17 mixed nutrition: 1 unknown: 5	-2.1 $\pm$ 1.6 (-5.3-+1.1) [n=17]	14.0 $\pm$ 1.4 (11.2-16.1) [n=19]	124.2 $\pm$ 2.8 (121-130) [n=23]	6.5 $\pm$ 1.4 (4.7-10.2) [n=22]	2.5 $\pm$ 0.7 (1.1-3.6) [n=16]
severe (n=13)	6.0 $\pm$ 1.3 (5-9)	yes 0 no 11 unknown 2	exclusively/mostly breastfed: 12 mixed nutrition: 0 unknown: 1	-2.0 $\pm$ 1.1 (-3.3-+0.2) [n=8]	14.4 $\pm$ 2.3 (10.1-17.0) [n=9]	114.5 $\pm$ 5.5 (101-119) [n=13]	6.6 $\pm$ 0.6 (5.4-7.7) [n=12]	2.9 $\pm$ 0.9 (1.7-4.1) [n=10]
P value	0.212	0.633	0.600	0.885	0.538		0.918	0.460

*For age at hyponatremia, height SD score, body mass index, serum sodium, serum potassium, and albumin, mean $\pm$ SD with range (in parenthesis) is provided.



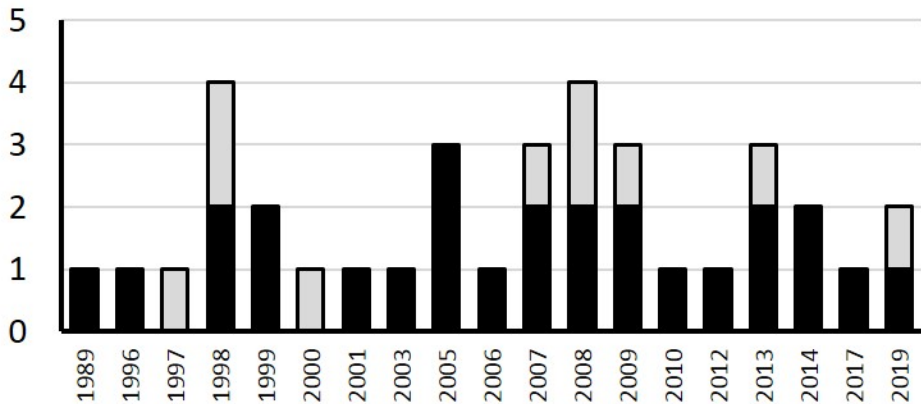






(n)

■ male □ female



Supplementary Table 1: Reference range of laboratory data used in this study

Age	s-potassium		total protein		albumin		aldosterone	hemoglobin		platelet	
	(mEq/L)		(g/dL)		(g/dL)		(pg/mL)	(g/dL)		(10 ⁴ /μL)	
	lower	upper	lower	upper	lower	upper	upper	lower	upper	lower	upper
	limit	limit	limit	limit	limit	limit	limit	limit	limit	limit	limit
>3m	4.1	5.6	5.1	6.8	3.1	4.6	679.3	9.5	13.7	25.0	82.0
>6m	4.0	5.4	5.3	7.2	3.2	4.8	366.3	10.0	14.2	22.0	76.0
>12m	3.6	5.1	5.7	7.5	3.4	4.7	293.2	*10.5/10.7	14.1	16.8	65.0
>24m	3.6	4.9	5.9	7.7	3.4	4.8	244.5	*10.7/10.9	14.2	18.0	62.0

* for boys/girls

Adopted from domestic literatures

23	m	6m	+	d	unk	eB		14.1	128	7.3			4,200		<10.0			190.5	
24	m	5m		d	-	eB	-3.0	12.8	119	6.8	23.3	-1.6	3,811.5	>83.0	9	1.7	13.4	77.9	(2009336742)
25	m	5m		d	-	unk	-1.8	12.8	122	7.0									(2010129120)
26	f	6m		d	-	unk	-1.7	16.0	123	8.16									
27	m	5m		d	unk	mx	-0.5	14.0	121	9.4	9.1	-15.8	6,007	>20	8	2.1	11.3	62.5	(2010125998)
28	m	9m			+	unk	-2.2	15.7	122	5.7						3.3	13.7	67.8	(2012226316)
29	f	4m	+	d	-	eB	-2.5	12.9	126	7.3				570		3.0	15.0	66.7	24129659
30	m	5m		d	-	eB	-3.3	13.7	115	7.0	14.5	-9.8	31,072		4	2.8	16.4	57.4	(2016214467)
31	m	7m	+	d	-	eB	-2.5	11.2	124	7.6						2.6	12.9	35.1	(2013245096)
32	m	7m		d	-	mB			107	6.0						2.2	12.5	11.9	(2015148836)
33	m	6m		d	-	eB	-3.9	14.0	122	5.8			104,000			3.1	12.4	73.5	(2015198463)
34	m	4m		d	-	eB	-5.3	16.0	124	6.7						1.9	14.5	87.1	(2018080703)
35	f	4m		d	-	eB	-2.1	14.4	126	10.2	11.7	-17				1.9	11.2	75.8	
36	m	5m		d	-	eB	-0.9	12.5	124	5.9	19.1	-5.9	30,400			3.2	12.8	75.7	our cases

BMI, body mass index; BE, base excess; PAC, plasma aldosterone concentration; PRA, plasma renin activity; Alb, albumin; Hb, hemoglobin; Plt, platelet
m, male; f, female; d, documented; unk, unknown; eB, exclusively breastfed; mx, mixed feeding; mB, mostly breastfed

* PMID is given for the references listed in PubMed, whereas UI (unique identifier) of ICHUSHI is shown in parentheses for other domestic literatures.