

Mineralocorticoid responsive hyponatremia of the elderly

A systematic review

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Abstract

Background: Mineralocorticoid responsive hyponatremia of the elderly (MRHE) is an emerging concept of hyponatremia in aged people. Diagnosis of MRHE requires exclusion of syndrome of inappropriate antidiuresis and adrenal dysfunction. Thus we aimed to evaluate the characteristics of all patients with suspected MRHE available for a review.

Methods: We conducted a systematic review using MEDLINE and Google scholar. We included published case reports of adult patients diagnosed as MRHE, written by English and Japanese language. Serum and urine electrolytes as well as the levels of antidiuretic hormone (ADH), cortisol, plasma renin activity (PRA), and aldosterone were analyzed.

Results: A total of 27 MRHE patients were identified in 9 reports. In these patients, average age was 79 years, median serum sodium was 117 mEq/L. The median levels of ADH, cortisol, PRA, and aldosterone were 0.9 pg/mL, 18.7 μg/dL, 0.37 ng/mL/h, and 39.6 pg/mL, respectively. Water restriction test was conducted in 7 patients. Random sample cortisol measurements did not exceed satisfactory levels to rule out adrenal dysfunction in four cases. No cases underwent low-dose adrenocorticotropic hormone stimulation test. Only 27 patients from 9 case reports in Japanese were eligible for inclusion in our study.

Conclusion: All published cases of MRHE as a cause of hyponatremia are described for the first time. In these cases, latent adrenal sufficiency might have been hidden and should have been excluded.

Abbreviations: ACTH = adrenocorticotropic hormone, ADH = antidiuretic hormone, FENa = fractional excretion of sodium, MRHE = Mineralocorticoid responsive hyponatremia of the elderly, PRA = plasma renin activity, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RAS = renin-angiotensin-aldosterone system, SIAD = syndrome of inappropriate antidiuresis.

Keywords: adrenal insufficiency, hyponatremia, mineralocorticoid responsive hyponatremia of the elderly, syndrome of inappropriate antidiuresis

1. Introduction

Hyponatremia, defined as a serum sodium concentration <135 mEq/L, is the most common electrolyte imbalance and can lead to serious consequences in clinical practice.^[1] Mild hyponatremia is reported to occur in approximately 30% among hospitalized patients. Moderate to severe hyponatremia, which is defined as a serum sodium concentration <129 mEq/L, is

estimated to be recognized about 7% among those in hospitalization.^[2–4]

Mineralocorticoid responsive hyponatremia of the elderly (MRHE) was first described by Ishikawa et al in 1987, as an important differential diagnosis of syndrome of inappropriate antidiuresis (SIAD) among elderly patients with hyponatremia.^[5,6] MRHE is considered as mildly hypovolemic hyponatremia caused by a renal sodium loss. Age-related decreased sodium reabsorption at proximal renal tubules and hyporesponsiveness of renin-angiotensin-aldosterone system (RAS) may cause constantly increased urinary sodium excretion. Decreased sodium retention leads to volume depletion. Plasma antidiuretic hormone (ADH) level is elevated because of such hypovolemia. Table 1 shows the differences between SIAD and MRHE.^[7] Recommended treatment of MRHE is not water restriction, which may worsen hyponatremia, but administration of mineralocorticoid such as fludrocortisone acetate.

However, patients with MRHE have been reported only by Japanese investigators and some case reports were published by them in Japanese language journals. There have been no systematic reviews conducted for this entity. Definite diagnostic criteria of MRHE have yet been unclear. Important differential diagnoses might have been excluded in some cases. Therefore, our objective was to conduct first ever systematic review on all published cases of MRHE to determine its characteristics, possibility of including other causes for hyponatremia and finally to define its diagnostic criteria.

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Table 1**Comparison between SIAD and MRHE.**

	SIAD	MRHE
Physical findings of dehydration such as dry tongue or skin	—	Present
Increased urinary sodium excretion	+	+++
Hypertonic urine	Present	Present
Adrenal function	Normal	Normal
Total body water	Increased	Decreased
Plasma renin activity	Inhibited	Low
Plasma aldosterone	Inhibited	Low
Plasma arginine vasopressin	Augmented	Augmented

ACTH = adrenocorticotropic hormone, MRHE = mineralocorticoid responsive hyponatremia of the elderly, SIAD = syndrome of inappropriate antidiuresis.

2. Methods

We performed a methodical search of the MRHE medical literature until September 2016, using the online database MEDLINE and Google Scholar. Initial search criteria phrase was “mineralocorticoid responsive hyponatremia of the elderly”; the search was not limited to any language. Citations from published articles were hand-reviewed.

Studies were included in this review if these were conducted within adult patients (≥ 18 years' old) by the way of case reports, who was diagnosed with MRHE. Publications were excluded if they were randomized controlled trials and review article only about etiology of hyponatremia.

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement checklist was used to assure accurate collection of variables.^[8] For this review, we collected and analyzed the levels of serum and urine sodium, potassium, chloride, ADH, cortisol, plasma renin activity, and aldosterone to find out the pathophysiology and diagnostic reassessment of MRHE. Ethics approval was waived, as this study was exclusively performed with the published data.

3. Results

3.1. Study selection and patient inclusion

A total of 912 articles were initially identified through electronic database search. The initial hand review by the authors eliminated 903 articles, in which 902 articles did not mainly discuss MRHE, one duplicate data with the other (Fig. 1).

Table 2 summarizes characteristics and laboratory data on admission in the included reports. Thus, 27 patients in 9 case reports of 912 publications remained in our review. Five of the 9 articles were published in Japanese language journals.^[7,9–12] Two of the 9 articles were the abstracts of conference presentations.^[12,13] One of these 2 articles was case series of 12 patients suspected MRHE.^[13] These 9 studies were published during the 27-year period (1987–2014) and were conducted in elderly patients aged 64 to 91 years. The mean age was 79 years and women were 73%.

3.2. Diagnosis of mineralocorticoid responsive hyponatremia of the elderly

No case reports proposed a definite diagnostic criterion. The descriptions of MRHE in all reports were basically based on “hypovolemic hyponatremia with fulfilled criteria for the syndrome of inappropriate antidiuresis (SIAD)”.

In all patients reviewed, median serum sodium was 117 mEq/L. Twenty-six patients showed physical findings of mild dehydra-

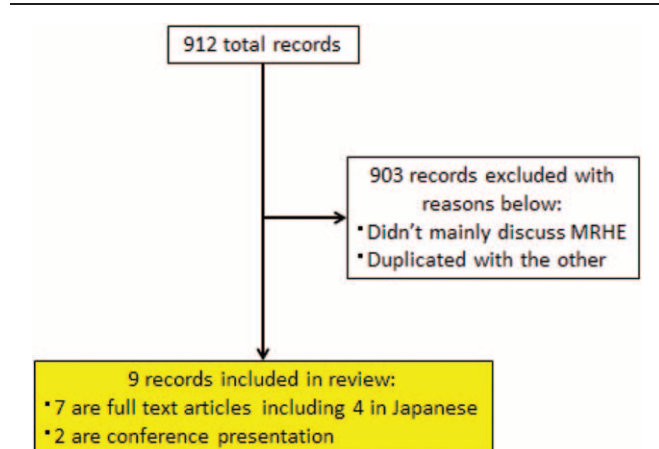


Figure 1. PRISMA flow chart demonstrating study identification and selection process.

tion such as dry tongue or skin.^[5,7,9–14] Thirteen patients showed normal to relatively increased urinary sodium excretion.^[5,7,9–12] Fractional excretion of sodium was recorded in 2 patients, but they were prescribed diuretics.^[9] Serum ADH levels were over the detectable concentration in 26 patients despite hyponatremia and its median is 0.9 pg/mL.^[5,7,9–13,15] Water restriction test was performed among 7 patients in 5 reports to differentiate them from SIAD.^[5,7,12,14,15] Hyponatremia in these 7 cases was exacerbated by the test. No thyroid function abnormality was noted. Recent use of diuretics was identified in 3 patients.^[9,11]

The median of plasma cortisol level, plasma renin activity, and plasma aldosterone concentration was 18.7 $\mu\text{g/dL}$, 0.37 ng/mL/hr, and 39.6 pg/mL respectively, which was relatively lower level. Three patients reported from Takeshita and Tamura also had lower plasma aldosterone concentration despite recent diuretic use, which suggest adrenal insufficiency or MRHE.^[9,11] Only 3 patients from Ishikawa underwent adrenocorticotropic hormone (ACTH) stimulation test. One patient in these 3 was measured and showed lower level of cortisol, that is, 9.0 $\mu\text{g/dL}$.^[5] In other cases, random sample levels of serum cortisol were measured and these values were from 13.2 to 36.2 $\mu\text{g/dL}$. These values were considered by the authors of the case reports as adequate responses of adrenal functions to rule out adrenal dysfunction. However, random cortisol level was ≤ 15.2 $\mu\text{g/dL}$ in at least 4 cases, suggesting the possibility of adrenal insufficiency.^[5,7,9,10] Low-dose ACTH stimulation test was not employed to rule out relative adrenal dysfunction. Fludrocortisone acetate 0.02 to 0.4 mg/day was administered in 20 cases and hyponatremia improved in 2 weeks. No patients died over the courses in the case descriptions.

4. Discussion

We performed the first systematic review on all published case reports of MRHE, including cases published in Japanese language journals. MRHE is an emerging disease concept as an important differential diagnosis of SIAD and it was first described by Ishikawa, a Japanese researcher. Cases of MRHE have been reported exclusively from Japan and thus our review also included Japanese language journals.

MRHE is considered to occur in elderly patients and is characterized by hypovolemic hyponatremia. All cases of our

Table 2

Characteristics and laboratory data on admission in patients who were considered to have MRHE.

Author	Ishikawa [5]	Ishikawa [7]	Ishikawa [13]	Yano [15]	Yano [14]	Takeshita [9]	Nakamura [10]	Tamura [11]	Morio [12]
Age	70	71	86	80	83	78	79	80	71
Sex	Man	Woman	Man	Woman	Woman	Woman	Man	Woman	Woman
Dehydration findings	Present	Present	Present	Absent	Present	Present	Present	Present	Present
Blood urea nitrogen, mg/dL	8	15	10	11	11	13	13	13	8.4
Serum creatinine, mg/dL	0.6	0.3	0.7	0.5	0.6	0.5	0.52	0.46	0.27
Serum sodium, mEq/L	127	135	117	119	121	113	120	107	111
Serum chloride, mEq/L	91	100	87	88	88	77	79	70	79
Serum potassium, mEq/L	4.2	2.7	3.1	4.6	2.7	2.4	2.4	3.4	3.6
Serum osmolality, mOsm	259	261	270	247	247	215	264	219	224
Urine sodium, mEq/L	324	240	225	247	129	33	43	72	60
Urine sodium, mEq/day	460	651	723	333	469	506	494	249	249
Plasma antidiuretic hormone, pg/mL	6.8	3.9	4.2	0.4	4.3	45.9	1.8	4.6	1.9
Plasma cortisol, µg/dL	22.8	9	13.2	22.7	16.4	14.7	36.2	20.1	26.5
Plasma renin activity, ng/mL/h	0.34	0.5	0.1	0.4	7.6	7.6	0.2	0.8	1
Plasma aldosterone, pg/mL	55	28	15	54	7.6	7.6	10	20.3	75
Water restriction test	Done	Done	Done	Done	Present	Present	Present	Present	Done
Recent diuretics use	Done	Done	Done	Done	Done	Done	Done	Done	Done
Rapid ACTH test	Done	Done	Done	Done	Done	Done	Done	Done	Done
Treatment of fludrocortisone	Done	Done	Done	Done	Done	Done	Done	Done	Done

ACTH = adrenocorticotropic hormone, MRHE = mineralocorticoid responsive hyponatremia of the elderly.

Table 3**Diagnostic criteria for SIAD criteria.**

Essential criteria

- Effective serum osmolality <275 mOsm/kg
- Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
- Clinical euvolesmia
- Urine sodium concentration >30 mEq/L with normal dietary salt and water intake
- Absence of adrenal, thyroid, pituitary or renal insufficiency
- No recent use of diuretic agent

Supplemental criteria

- Serum uric acid <4 mg/dL
- Serum urea <21.6 mg/dL
- Failure to correct hyponatremia after 0.9% saline infusion
- Fractional sodium excretion >0.5%
- Fraction urea excretion >55%
- Fraction uric acid excretion >12%
- Correction of hyponatremia thorough fluid restriction

review met several among the disease characteristics listed below: hyponatremia, clinical hypovolemia, decreased serum osmolality, increased urine osmolality, relatively increased urinary sodium excretion, relatively lower RAS, and detectable serum ADH.

Thus, for diagnosing patients with MRHE, following criteria can be proposed^[16]:

- (1) Age >60 years
- (2) Meet SIAD criteria (Table 3) with 2 items below.
 - Worsening hyponatremia via fluid restriction
 - Clinical hypovolemia
- (3) Correction of hyponatremia by the use of fludrocortisone acetate

In this review, we found that adrenal insufficiency, which is one of the most important differential diagnoses of euvolesmic hyponatremia, might have been misdiagnosed as MRHE in some cases. Although low serum levels of basal or post-ACTH stimulation test cortisol is recommended for the use to rule out this disease, few case reports in this review conducted this test. Adrenal insufficiency is possible, if basal cortisol is <3 to 4 µg/dL or post stimulation cortisol is <18 µg/dL.^[17]

Low-dose (1 µg) ACTH stimulation test may have higher sensitivity and similar specificity compared to high-dose (250 µg) ACTH stimulation test for diagnosis of secondary or relative adrenal insufficiency in adults. It is related to the fact that serum ACTH level of healthy person induced by 1 µg ACTH administration is 100 to 300 pg/mL, same as the upper limit of physiological concentration. However, serum ACTH level induced by 250 µg ACTH administration is 1000 to 60,000 pg/dL, higher over the physiological concentration.^[17–19]

Instead, several case reports of our review measured random cortisol levels, as a test simply conducted in clinical practice. One report evaluating the relation between random and post-ACTH stimulation cortisol level among acute noncritically ill general medical patients indicated that post ACTH stimulation cortisol level is >20 µg/dL, if random cortisol level is >15.2 µg/dL, indicating that adrenal insufficiency has been ruled out in such cases.^[20] For these reasons, the possibility of adrenal insufficiency might not have been ruled out in at least 4 cases in our current review.^[5,7,9,10] In addition, cases with recent use of diuretic agent and correction of hyponatremia without the use of fludrocortisone acetate might need to be excluded.

4.1. Limitation

Our review has several limitations. We found only 27 patients from 9 case reports eligible for inclusion in our study. Patients were only Japanese and thus the results might not be generalizable to patients with other ethnicities. Some case reports provided little laboratory data, which could have led to biased results.

In conclusion, based on this first systematic review on patients with MRHE, only Japanese cases have been reported and some cases might have had latent adrenal insufficiency. The diagnostic criteria are proposed in current review. ACTH stimulation test should be conducted in cases with random level of serum cortisol of ≤15.2 µg/dL.

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