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. 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. Define 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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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. 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 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 were published in Japanese language journals. MRHE is an emerging disease concept as hypovolemic hyponatremia with fulminant increase in serum sodium concentration such as dry tongue or skin. Thirty-four patients showed normal to relatively increased urinary sodium excretion. Fractional excretion of sodium was recorded in 2 patients, but they were prescribed diuretics. Serum ADH levels were over the detectable concentration in 26 patients despite hyponatremia and its median is 0.9 pg/mL. Water restriction test was performed among 7 patients in 5 reports to differentiate them from SIAD. Hypo-
| Author | Age | Sex | Dehydration findings | Blood urea nitrogen, mg/dL | Serum creatinine, mg/dL | Serum sodium, mEq/L | Serum chloride, mEq/L | Serum potassium, mEq/L | Serum osmolality, mOsm | Urine sodium, mEq/L | Urine sodium, mEq/L/day | Urine osmolality, mOsm | Plasma antidiuretic hormone, pg/mL | Plasma renin activity, ng/mL/h | Plasma aldosterone, pg/mL | Water restriction test | Recent diuretics use | Rapid ACTH test | Treatment of fluid overload |
|--------|-----|-----|----------------------|---------------------------|------------------------|---------------------|---------------------|---------------------|----------------------|-----------------|------------------------|---------------------|--------------------------------|------------------------|----------------------------|------------------|-------------------------|----------------------|----------------------------|
| Ishikawa [5] | 70  | Man | Present              | 8                         | 0.6                    | 127                 | 91                  | 4.2                 | 259                  | 324              | 460                    | 6.8                 | 22.8                         | 0.34                   | 55                         | Done             | Done                    | Done                | Done                    |
| Ishikawa [7] | 71  | Woman | Present             | 15                        | 0.3                    | 135                 | 100                 | 2.7                 | 261                  | 240              | 651                    | 3.9                 | 9                          | 0.5                   | 28                         | Done             | Done                    | Done                | Done                    |
| Ishikawa [13] | 86  | Man | Absent               | 10                        | 0.7                    | 117                 | 100                 | 3.1                 | 270                  | 225              | 723                    | 4.2                 | 4.2                         | 0.1                   | 15                         | Done             | Done                    | Done                | Done                    |
| Yano [15] | 82  | Woman | Present             | 12                        | 0.36                   | 117                 | 87                  | 4.1                 | 249                  | 129              | 325                    | 0.9                 | 13.2                        | 0.3                   | 18                         | Done             | Done                    | Done                | Done                    |
| Yana [14] | 80  | Woman | Absent              | 11                        | 0.5                    | 115.6               | 88                  | 4.6                 | 247                  | 175              | 500                    | 2.9                 | 22.7                        | 0.4                   | 74                         | Present          | Present                  | Present             | Done                    |
| Takeshita [9] | 78  | Man | Present              | 11                         | 0.5                    | 119                 | 87                  | 4.6                 | 247                  | 125              | 500                    | 0.4                 | 22.7                        | 0.3                   | 74                         | Present          | Present                  | Present             | Done                    |
| Nakamura [8] | 64  | Woman | Present             | 13                        | 0.46                   | 129                 | 77                  | 2.7                 | 215                  | 30               | 474                    | 2.6                 | 16.4                         | 0.3                   | 76                         | Present          | Present                  | Present             | Done                    |
| Tamura [11] | 79  | Woman | Present             | 11                         | 0.59                   | 109                 | 70                  | 2.4                 | 221                  | 52               | 404                    | 0.9                 | 14.7                         | 0.2                   | 50                         | Present          | Present                  | Present             | Done                    |
| Morio [12] | 83  | Woman | Present             | 12                         | 0.52                   | 120                 | 79                  | 3.4                 | 251                  | 64               | 439                    | 4.6                 | 26.5                         | 1.9                   | 38                         | Present          | Present                  | Present             | Done                    |

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

Thus, for diagnosing patients with MRHE, following criteria can be proposed\[^{10}\].

1. Age >60 years
2. Meet SIAD criteria (Table 3) with 2 items below.
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 euvoletic 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 adrenal insufficiency, increased urine osmolality, relatively increased urinary sodium excretion, relatively lower RAS, and detectable serum ACTH.

Thus, for diagnosing patients with MRHE, following criteria can be proposed\[^{10}\].

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2. Meet SIAD criteria (Table 3) with 2 items below.
3. Correction of hyponatremia by the use of fludrocortisone acetate

| 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 euvoleticism               |
| 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 >5%         |
| Fraction uric acid excretion >12%   |
| Correction of hyponatremia thorough fluid restriction |

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