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Original Article

Yield of workup for patients with idiopathic presentation of the syndrome of inappropriate antidiuretic hormone secretion

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ABSTRACT

Purpose: To determine the proportion of patients for whom the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the presenting symptom of an underlying disorder, to describe the yield of different diagnostic modalities for patients with SIADH and an unknown etiology, and to define patients for whom such a workup is indicated.

Methods: A single center retrospective study including all patients diagnosed with SIADH without an apparent etiology in a large community hospital and tertiary center between 1.1.07 and 1.1.13. Two physicians reviewed every patient's medical file for predetermined relevant clinical data.

Results: Eleven of the 99 patients without an apparent etiology for SIADH at presentation were found to have an underlying cause on workup. Yield of performed workup was low, with a pathology demonstrated on 0%–30.8% of tests according to the different modalities used. Patients with presumed idiopathic SIADH at presentation who were later found to have a specific etiology were younger than patients with true idiopathic SIADH, had a significantly shorter duration of hyponatremia prior to SIADH diagnosis, had higher urine osmolality and a clinical presentation suggestive of an undiagnosed disorder.

Conclusions: Our findings support a clinically-based approach to patients with idiopathic SIADH, rather than an extensive routine workup for all patients.

1. Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) was described more than 50 years ago by Schwartz and Bartter, whose observations and diagnostic criteria remain essentially unchanged [1–4]. SIADH accounts for approximately one third of all cases of hyponatremia and is the most common cause of hyponatremia in euovolemic patients [2–4]. SIADH is caused either by secretion of ADH from the posterior pituitary in response to non-osmotic stimuli or to ectopic paraneoplastic secretion [5,6].

Numerous common medical conditions can cause SIADH, including malignant diseases, pulmonary disorders including infections, central nervous system disorders, various medications and severe pain or nausea, common in postoperative patients [2–4]. Despite SIADH being a common, clinically significant disorder, published data regarding distribution of etiologies is scarce. However, according to the available data, idiopathic SIADH is a common entity. In a recent study describing the distribution of SIADH etiologies in a general hospital during a ten year period, Hsu et al. reported that 172 of 439 (39.2%) of the patients had no identified etiology [7]. In an analysis of patients diagnosed with SIADH from our hospital during a six year period (2007–2012), we found 88 of 555 (15.9%) of the patients to have idiopathic SIADH [8]. Our data differs from that of Hsu et al., probably due to the different patient populations studied. Idiopathic SIADH was found to be even more common in cohorts of elderly patients, representing 60% of SIADH cases in a report by Hirshberg and Ben-Yehuda [9]. Thus, idiopathic SIADH is common in clinical practice, perhaps being more common than SIADH caused by a specific etiology in some patient populations.

SIADH might be the first manifestation of an occult disorder. There are numerous case reports describing patients presenting with symptomatic hyponatremia who are diagnosed with an SIADH-associated etiology following workup ([10–13], to cite several recent cases). However, the proportion of patients for whom SIADH is the presenting symptom of an underlying disorder is unknown. Furthermore, the yield of different modalities used to pursue a specific etiology and

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thus to differentiate between patients with an occult disorder compared to true idiopathic SIADH is unknown. Finally, it is unknown whether patients with underlying disorders differ from patients with idiopathic SIADH, and can be identified using clinical data available on presentation. We therefore conducted a single center retrospective study to address these issues.

2. Methods

The study was approved by the hospital's Institutional Review Board. The study population included all adult patients older than 18 and hospitalized between 1.1.2007 and 1.1.2013 in Beilinson Hospital, Rabin Medical Center, Israel (a large community hospital and a university affiliated tertiary center) who had hyponatremia (serum sodium ≤ 134 mEq/L) and concomitant urine osmolality ≥100 mOsm/kg and urine sodium concentration ≥30 mEq/L. Patients with glomerular filtration rate (GFR) ≤60 mL/min according to the CKD-EPI formula were excluded [14]. Every patient's medical file was reviewed by at least two physicians (D.S. C.L., A.K. or S.Z.). In case of disagreement between the physicians reviewing the patients' charts a third physician made the final decision (D.S.). Patients with diuretic usage (including thiazides, loop diuretics, aldosterone antagonists or any other diuretic), hypervolemia or hypovolemia, hypothyroidism or adrenal insufficiency, based on documented history and clinical examination were excluded. As serum osmolality is not routinely performed in our hospital, patients with hypertriglyceridemia (triglycerides ≥ 500 mg/dL) and any paraproteinemia (globulin ≥ 3.5 g/dL or monoclonal gammopathy) were excluded as well. Patients with hyperglycemia were included if sodium concentration was ≤134 after adding a correction factor of 2.4 meq/L for every 100 mg/dL increase in plasma glucose concentration [15]. We included only patients with presumed SIADH without an obvious etiology after an initial baseline evaluation which included only medical history, physical examination, blood count, chemistry, thyroid and adrenal function testing and chest X-ray (CXR). These patients were defined as having idiopathic SIADH. Further workup for SIADH, including imaging studies such as head, chest or abdominal computerized tomography (CT) were documented for these patients.

Collected data included demographics, clinical presentation, serum and urine sodium concentration, urine osmolality, blood urea and uric acid concentrations and the most likely SIADH etiology following workup during hospitalization according to the medical chart review. The use of hypertonic saline was documented. Median sodium concentration 1–3 months following SIADH diagnosis was calculated. Hyponatremia duration prior to SIADH diagnosis was calculated, defined as the time period for which more than two thirds of blood sodium concentration measurements were <135 mEq/L. Patients with hyponatremia onset of less than three months were defined as new onset hyponatremia. Number of prior hospitalizations due to hyponatremia was also noted for these patients. Follow-up time and survival as of 1.9.14 for all patients were calculated.

3. Statistical analysis

Chi-square and/or Fisher's exact test were used to compare categorical variables. Student's *t*-test was used to compare normally distributed continuous variables and Mann–Whitney *U* test was used for non-normally distributed groups.

Receiver operating characteristic (ROC) curve analysis was used to identify cut-off values for continuous variables that were significantly different between the groups.

Multivariate logistic regression analysis was used to identify variables associated with increased likelihoods of having a specific diagnosis identified.

4. Results

There were 1287 patients with serum sodium ≤134 mEq/L, urine osmolality ≥100 mOsm/kg, urine sodium ≥30 mEq/L and GFR ≥60 mL/min between 1.1.2007 and 1.1.2013 in our hospital. Of them, 732 patients who did not meet the criteria for SIADH were excluded. Of the remaining 555 patients, 456 had an apparent SIADH-associated etiology at presentation: 147 had medication-associated SIADH, 146 had cancer-associated SIADH, 66 had SIADH-associated with pulmonary infections, 39 with CNS disorders and 58 with pain or nausea. Thus, 99 patients with no obvious cause of hyponatremia on presentation were defined as having idiopathic SIADH, and were included in the final analysis (Fig. 1). An underlying disorder associated with euvolemic hyponatremia was diagnosed in 11 of them, while 88 patients had idiopathic SIADH after workup. Table 1 depicts the characteristics of patients with idiopathic SIADH at presentation: patients for whom a diagnosis was established after additional workup compared to those who remained idiopathic.

Clinical presentations of the 88 patients who were diagnosed with idiopathic SIADH after workup were as follows: 26 patients had weakness and non-specific symptoms, 14 had fever, 11 had altered mental status, 9 had shortness of breath, 8 were admitted after falling, 6 were admitted due to chest pain, 6 due to abdominal pain and 8 for other various conditions. Diagnoses at discharge were similarly unremarkable: 20 patients had complete resolution of symptoms, 28 had various infections, 16 were diagnosed with hyponatremia as the main cause of their symptoms, 11 had ischemia or arrhythmia, 5 were diagnosed with recurrent falls, 4 with anemia and 4 with other various conditions. Clinical presentations and final diagnoses of the 11 patients with SIADH who were diagnosed with an underlying disorder are depicted in Table 2.

4.1. Yield of evaluation

Most patients without an apparent etiology for presumed SIADH at presentation underwent at least one CT scan (Table 3). Yield of performed workup was low, with a pathology demonstrated on only 0%–30.8% of tests for the different modalities used (Table 3). Eleven patients, representing 11.1% of patients with no obvious etiology for SIADH on presentation were found to have a specific etiology for the hyponatremia after workup. Seven patients were diagnosed with various malignancies, two had chronic pulmonary infections and two had other SIADH-associated disorders (Table 2).

4.2. Patient characteristics associated with diagnosis of specific etiology

Patients who were found to have an underlying etiology to hyponatremia identified by workup differed from patients with idiopathic SIADH in several respects (Table 1). They were younger; 6/11 (54.5%) of patients with a specific diagnosis were 70 years of age or younger at SIADH diagnosis, compared to 7/88 (8%) of patients who had idiopathic SIADH (odds ratio (OR) 13.9, 95% confidence interval (CI) 3.4–34.2, $p < 0.001$). Patients with an underlying disorder were more likely to have new onset hyponatremia; 8/11 (72.7%) of patients with specific diagnosis had new onset hyponatremia, compared to 10/88 (11.4%) of patients with idiopathic SIADH (OR 20.8, 95% CI 4.7–91.5, $p < 0.001$). They also had a trend towards higher urine osmolality, while serum and urine sodium concentrations and serum uric acid were similar for both patient groups (Table 1).

By multivariate logistic regression analysis age of seventy or younger (OR 11.4, 95% CI 1.7–78.2, $p = 0.014$), new onset hyponatremia (OR 12.1, 95% CI 2.3–64.3, $p = 0.003$) and urine osmolality higher than 340 mOsm/kg (OR 7.1, 95% CI 1.1–44.4, $p = 0.037$) were all independent predictors for a specific etiology of hyponatremia, identified by the performed workup.