

RESEARCH

Prevalence of adrenal insufficiency among patients with euvolemic hyponatremia

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Abstract

Background: The diagnosis of syndrome of inappropriate anti-diuresis requires the exclusion of secondary adrenal insufficiency (AI) among patients with euvolemic hyponatremia (EuVHNa). Studies have suggested that about 2.7–3.8% of unselected patients presenting to the emergency room with EuVHNa have undiagnosed AI and it is as high as 15% among patients admitted to specialized units for evaluation of hyponatremia.

Objective: To study the prevalence of AI among in-patients with EuVHNa in a general medical ward setting.

Methods: This was a prospective, single-center observational study conducted among general medical in-patients with EuVHNa, defined as patients with a serum sodium <135 mmol/L, clinical euvolemia and urine spot sodium >30 mmol/L. Additionally, patients with recent vomiting, current renal failure, diuretic use and those with uncontrolled hyperglycemia were excluded. Adrenal functions were assessed by a modified adrenocorticotrophic hormone (ACTH) stimulation test called the Acton Prolongatum™ stimulation test (APST). A cut-off cortisol value of <18 mg/dL after 60 min of ACTH injection was used to diagnose AI.

Results: One hundred forty-one patients were included and underwent an APST. APST suggested 20/141 (14.2%) had undiagnosed AI. The commonest cause of AI (9/20) was secondary AI because of the use of steroids including inhaled steroids and indigenous medicines contaminated with steroids. In 5 (3.5%) patients hypopituitarism was newly diagnosed. Despite primary AI (PAI) not commonly presenting as EuVHNa, 2/20 patients had PAI.

Conclusions: AI is much commoner in our country, among in-patients with EuVHNa primarily driven by exogenous steroid use and undiagnosed hypopituitarism.

Key Words

- ▶ hyponatremia
- ▶ euvolemic hyponatremia
- ▶ adrenal insufficiency
- ▶ secondary adrenal insufficiency
- ▶ hypopituitarism

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Introduction

Two percent of community-dwelling adults in America have hyponatremia. These rates are more than double among adults over the age of 71 years (1). In hospitalized patients, the prevalence of hyponatremia is between 15 and 20% and it remains the commonest electrolyte disturbance seen among them (2). Hyponatremia leads

to increases in morbidity, length of hospitalization and mortality among those admitted in hospital (3, 4, 5).

A large majority of in-patients with hyponatremia have osmotically inappropriate anti-diuretic hormone (ADH) secretion (6). This makes the use of direct measurements of ADH or co-secreted proteins like co-peptin or other

indirect markers like urine osmolality and solute-free water clearance not of much clinical value in management of in-patient hyponatremia except in rare cases of primary polydipsia or inappropriate in hospital fluid management (7).

Currently, clinicians still use the diagnostic scheme first proposed by Schrier and colleagues almost 30 years back for classifying hyponatremia based on volume status (8). Despite decrease (in hyponatremia with dehydration), near-normal (euvolemic hyponatremia) or increase (edematous hyponatremia) in total body sodium among patients with hyponatremia, all three conditions are associated with a relative excess of water (6). This selective water retention in all three conditions is mediated by osmotically inappropriate release of ADH from the posterior pituitary. This is one reason why hyponatremia should be essentially considered a hormonal disorder of water metabolism and should involve active involvement of endocrine specialists.

Most hospitalized patients with hyponatremia do not get appropriately investigated even in tertiary care hospitals around the world (9, 10, 11, 12). There is some evidence that this lack of proper investigations maybe contributing to the mortality that is seen with severe hyponatremia (13). A retrospective study from the United Kingdom suggested that patients who were reviewed by the endocrinology service in the hospital were 16 times more likely to have a more complete laboratory workup than those not referred to endocrinology services (14).

The syndrome of inappropriate anti-diuresis (SIAD) is the principal cause of euvolemic hyponatremia (EuVHNa). Although SIAD has a specific diagnostic criteria, it remains a diagnosis of exclusion and needs the absence of secondary adrenal insufficiency (AI) and hypothyroidism as an essential criterion for the diagnosis. Evaluation of the hypothalamic-pituitary-adrenal (HPA) axis is, however, missed in over two-thirds of the patients labeled as having SIAD (14).

Clear estimates of the contribution of secondary AI to EuVHNa are hard to come by. We could locate only one previous study that prospectively evaluated the HPA axis in-patients with EuVHNa. In a large single-center study done from Beaumont Hospital in Ireland, unsuspected AI was noted in 3.8% of patients and was identified as SIAD. A little less than half of them (1.5%) had undiagnosed pituitary disease (15).

Secondary AI among patients with EuVHNa is likely to be higher in India because of two reasons. The first reason being the significant number of patients prescribed inappropriate unlabeled glucocorticoids either as part

of local remedies or as injectables by unqualified medical practitioners (16). The second reason being an increased prevalence of undiagnosed hypopituitarism among older menopausal women due to post-partum pituitary necrosis (Sheehan's syndrome) reflecting poor obstetric care received decades earlier (17).

With this background, we planned this study to prospectively ascertain the prevalence of AI among in-patients admitted to medical wards with EuVHNa.

Materials and methods

Study design and study location

This was a prospective observational study conducted in the Department of Medicine at Christian Medical College and Hospital in the North Indian city of Ludhiana from 15 December 2017 to 14 December 2018. The hospital is a tertiary care teaching hospital with a total of 720 beds which includes 120 beds for general medicine.

Patient selection

All adult patients admitted into the general medical wards consisting of 120 beds over a period of 1 year between 15 December 2017 and 14 December 2018 were evaluated for hyponatremia (serum sodium <135 mmol/L). Among them, patients with EuVHNa who met the inclusion criteria and provided consent were further evaluated with the determination of thyroid functions tests and an Acton Prolongatum® (adrenocorticotrophic hormone(1-34) (ACTH(1-34)) stimulation test (APST).

Inclusion and exclusion criteria

Adult patients (≥ 18 years) with EuVHNa who provided consent were included. Patients were considered to have EuVHNa if they met the following three criteria: (i) Serum sodium levels <135 mmol/L; (ii) No clinical evidence of dehydration (sunken eyes, loss of skin turgor, dry oral mucosa and hypotension) or evidence of fluid excess (pre-sacral or pedal edema or ascites) and (iii) Urine spot sodium values >30 mmol/L.

Some causes of hyponatremia could potentially have urine spot sodium levels >30 mmol/L despite not being euvolemic. These were excluded as far as possible. Exclusion criteria included patients with >4 episodes of vomiting over the past 24 h prior to assessment, patients on diuretics within the past 72 h and patients with renal failure

(eGFR <30 mL/min/1.7 m²). Unwell patients requiring transfer or transferred in from high dependency unit or intensive care unit were also excluded. All patients were evaluated for inclusion by a single researcher (first author). Additionally, patients with possible pseudohyponatremia defined as serum triglyceride levels >500 mg/dL (5.65 mmol/L) or total protein levels >10 mg/dL (100 g/L) were excluded. Patients receiving mannitol infusions were excluded. Other exclusion criteria included patients with blood glucose values >400 mg/dL (22.2 mmol/L), those who received oral or i.v. steroids within the last 6 months from screening, those with established AI and those who previously have had allergic reaction to Acton Prolongatum™ or Synacthen™.

Ethical approval and registration of study protocol

The study protocol was approved by the Institutional Ethics Committee of Christian Medical College and Hospital prior to any study related activities. The protocol was registered with the Baba Farid University of Health Sciences (<http://www.bfuhs.ac.in/examination/PlanOfThesis/Topic20172020.pdf>) prospectively as part of Doctor of Medicine (MD) thesis in general medicine for the first author and the principal investigator of the study under supervision of the other two authors. All patients only underwent study procedures once they provided an informed consent in a language comfortable to them (English, Hindi and Punjabi). Consent from a legally acceptable representative was sought if the subject was unable to provide consent.

Biochemical methods

Quantitative estimation of sodium in serum was performed using indirect ion selective electrodes (ISE). The samples received for serum sodium estimation were centrifuged immediately to separate the serum. Grossly lipemic serum was rejected. The measuring range for serum sodium using indirect ISE was 80–180 mmol/L. Precision and repeatability were checked daily by running quality control samples in both low to normal and high ranges of sodium. For repeatability testing, the coefficient of variation (CV) % for low to normal and high levels was 0.3 and 0.2%, respectively. For precision testing, the CV% for low to normal and high sodium levels was 1.1 and 0.4 mmol/L, respectively.

Quantitative determination of serum cortisol was performed using Elecsys Cortisol II kit on Cobas e411/601 fully automated analyzer from Roche™. The Elecsys

Cortisol II assay makes use of a competition test principle using a MAB which is specifically directed against cortisol. Endogenous cortisol which has been liberated from binding proteins with danazol competes with exogenous cortisol derivative in the test which has been labeled with ruthenium complex for the binding sites on the biotinylated antibody. Measuring range of the test was 0.054–63.4 µg/dL (1.5–1750 nmol/L). Values below the limit of detection were reported as <0.054 µg/dL (<1.5 nmol/L) and values above the measuring range >63.4 µg/dL or up to 634 µg/dL (17,500 nmol/L) after 10-fold dilution of samples.

The values of free T₄ (FT₄) and TSH in human serum were determined using the electrochemiluminescence immunoassay on Cobas e411/601 immunoassay analyzer. These tests were performed on undiluted serum samples collected in standard sampling tubes without additives. For FT₄ estimation, the measuring range was 0.3–100 pmol/L and for TSH the measuring range was 0.005–100 mIU/L. The analytical sensitivity and total precision values for FT₄ were 0.30 pmol/L and 2.7% and for TSH assays, they were 0.005 mIU/L and 2.2%, respectively. In adult patients, the normal reference range for FT₄ was 12–22 pmol/L and for TSH it was 0.270–4.20 mIU/L.

Acton Prolongatum™ (ACTH(1–34)) stimulation test

A guideline from the Endocrine Society recommends the use of a standard (250 µg) dose of cosyntropin (tetracosactide hexacetate) as the stimulus of choice to perform stimulation testing of the HPA axis (18, 19). Synacthen™ (brand of cosyntropin) has not been officially marketed in India for over a decade. The drug is currently available from select importers of the drug at high costs with poor reliability of supplies. In 2013, Gundurthi and colleagues first suggested using the porcine sequence ACTH(1–34) easily available in India from Ferring Pharmaceuticals as a treatment of infantile spasms. The product is marketed in India with the brand name of Acton Prolongatum™ and is available as 60 IU/mL multidose vial of 5 mL each. They used 25 IU of this preparation intramuscularly and for the first time established its effectiveness as an adequate stimulus to check the HPA axis. The post-injection sample was drawn at 60 min. This test is also referred to as the APST (20).

We followed a similar protocol for the APST in our study. Subjects had a basal sample drawn following which 25 IU (~0.4 mL) of Acton Prolongatum® was drawn using an insulin syringe (~16 units with a 40 IU/mL syringe which is commonly available in India). This was administered over

the deltoid region as an i.m. injection. The post-injection sample was drawn at 60 min.

Standard cut-offs were used to define AI at 60 min post-APST. Patients with 60 min post-APST values less than 18 µg/dL (500 nmol/L) were considered to have AI as with the standard cut-offs for short Synacthen test (SST) (18). Patients with suboptimal cortisol responses were immediately treated with i.v. hydrocortisone after discussion with treating consultant. All APST tests were done in the ward during hospitalization. Further evaluations for patients with AI were performed by the treating medicine team, and the endocrinology team was only involved when specifically consulted and repeat testing was done in an outpatient setting if indicated to decide on long-term steroid replacements.

Recently, two further papers from India have suggested a good agreement between the standard SST and APST and highlighted the significant cost savings (21, 22).

Sample size calculations and statistical methods used

Using the prevalence of EuVHNa of 50.7% among patients admitted with hyponatremia to a similar tertiary hospital in India, we calculated the sample size of at least 140 patients using the formula $n = Z\alpha^2 \times P \times (1 - P)/d^2$ where $Z\alpha^2 = 1.96$, the standard normal deviate and $P = 50.7\%$ and $d = 8\%$ as allowable error (23).

All obtained data were entered in MS Excel sheet and summarized using distribution and descriptive statistics. Chi-square test was used to find association between

categorical variables and Fisher's exact test was used to find the significant difference of continuous variables.

Results

During the study period, 4007 patients were admitted to the medical wards. Seven hundred eighty-three patients had biochemical hyponatremia at admission or on biochemistry done within 24 h of admission. One hundred forty-one patients with EuVHNa met the inclusion and exclusion criteria and were consented for the study. All of them underwent an APST. Based on the previously determined cut-off of patients with post-APST (60 min) values of <18 µg/dL (500 nmol/L), 20/141 (14.2%) patients had AI.

Baseline data among those who had AI and among those who did not have AI are given in Table 1.

More clinical details of the 20 patients diagnosed with AI including possible etiologies are given in Table 2. Undocumented steroid use or unscrupulous addition of steroids to indigenous medications was the cause for secondary AI in 5/20 (25 or 3.5% among all patients with EuVHNa) patients. The other causes included undiagnosed hypopituitarism 5/20 (25 or 3.5% among all patient with EuVHNa) which included three patients with post-partum pituitary necrosis (Sheehan's syndrome) and two patients with possible lymphocytic hypophysitis. We were surprised to note that the use of high-dose-inhaled steroids caused significant suppression of the HPA axis to cause significant hyponatremia in 4/20 patients (20 or 2.8%

Table 1 Baseline characteristics among patients with AI and among those without AI.

	Patients with AI (n = 20)	Patients without AI (n = 121)	P-value
Age in years (mean ± s.d.)	55 ± 12.02	58.31 ± 15.57	0.37
Male gender (%)	55	50.4	0.42
Weight in kg (mean ± s.d.)	64.2 ± 8.45	64.95 ± 13.35	0.81
eGFR in mL/min/1.73 m ² (mean ± s.d.)	116.76 ± 74.88	102.46 ± 44.79	0.24
Serum sodium in mmol/L (mean ± s.d.)	126.05 ± 5.86	125.13 ± 7.67	0.61
Biochemical severity			
1. Mild (%)	6 (30.0)	38 (31.4)	0.89
2. Moderate (%)	7 (35.0)	47 (38.8)	
3. Profound (%)	7 (35.0)	36 (29.8)	
TSH levels in mIU/L (mean ± s.d.)	8.69 ± 21.09	3.31 ± 4.55	0.01
Free T ₄ in pmol/L (mean ± s.d.)	17.54 ± 9.65	17.42 ± 5.71	0.94
Basal cortisol values in µg/dL (mean ± s.d.)	5.58 ± 3.80	15.78 ± 8.70	0.00
Post-APST – 60 min cortisol in µg/dL (mean ± s.d.)	13.04 ± 3.20	28.32 ± 10.74	0.00

Mild hyponatremia (serum sodium between 130 and 134 mmol/L), moderate (serum sodium between 125 and 129 mmol/L) and profound (serum sodium <125 mmol/L).

APST, Acton Prolongatum™ stimulation test; AI, adrenal insufficiency; eGFR, estimated glomerular filtration rate by modification in diet in renal disease formula; TSH, thyroid-stimulating hormone.

Table 2 Clinical Details of the patients ($n = 20$) who had AI among those with euvolemic hyponatremia.

	Age	Sex	Admitting symptoms	Primary diagnosis	Basal cortisol ^a	Post-APST cortisol ^b	Clinical suspicion ^b	Final cause of AI ^c	
1	PS	26	F	Fever/headache	Tuberculous meningitis	7.4	17.6	Not suspected	TB-related isolated SAI. Hyponatremia responded to steroids
2	JK	57	F	Nausea/vomiting	Acute gastritis	3.6	12.5	Not suspected	Hypopituitarism likely Sheehan's syndrome. Hyponatremia responded to steroids
3	GS	67	M	Cough/breathlessness	AE of COPD	3.77	3.57	Not suspected	SAI to inhaled steroids. Hyponatremia responded to steroids
4	KK	55	F	Fever/confusion	CAP	2.1	Not done	Suspected	Primary AI. Hyponatremia responded to steroids
5	PK	43	F	Fever/cough	CAP with AKI	6.25	10.45	Suspected	SAI due to undocumented oral steroid use. Hyponatremia responded to steroids
6	PS	63	F	Confusion/vomiting	Organophosphorus poisoning	3.32	11.3	Not suspected	Hypopituitarism likely Sheehan's syndrome. Hyponatremia responded to steroids
7	RK	62	M	Fever/cough	AE of COPD	5	17	Not suspected	SAI to inhaled steroids. Hyponatremia responded to steroids
8	SK	61	F	Syncopal/right-sided weakness	Left internal capsule bleed	12.4	15.4	Not suspected	Hypopituitarism likely Sheehan's syndrome. Hyponatremia responded to steroids
9	RS	55	M	Epistaxis	Hypertensive nasal bleed	3.4	13.8	Not suspected	SAI due to undocumented steroids. Hyponatremia responded to steroids
10	SK	48	F	Fever/cough	CAP	13.3	16.4	Not suspected	SAI due to indigenous medication-containing steroids. Hyponatremia responded to steroids
11	JK	54	M	Fever/headache	Scrub typhus/new diagnosis of Primary Hypothyroidism	8.8	15.3	Not suspected	Relative SAI likely because of untreated hypothyroidism. Hyponatremia responded to steroids
12	ML	50	M	Cough/breathlessness	AE of COPD	2.9	9.9	Not suspected	SAI to inhaled steroids. Hyponatremia responded to steroids
13	IK	65	M	Cough/breathlessness	AE of COPD	6	10.1	Suspected	SAI to inhaled steroids. Hyponatremia responded to steroids
14	SE	65	F	Fever/headache	Urosepsis/rheumatoid arthritis	8.22	11.8	Not suspected	SAI due to indigenous medication-containing steroids. Hyponatremia responded to steroids
15	JS	50	M	Altered sensorium	ALD/vitiligo	2.4	12.8	Not suspected	Hypopituitarism possible Lymphocytic hypophysitis. Hyponatremia responded to steroids
26	SS	60	M	Seizure	Alcohol withdrawal seizures/ALD	5.5	12.9	Not suspected	Etiology unclear/low albumin and malnutrition. Hyponatremia did not respond to steroids
17	VK	59	M	Vomiting	T2DM/acute gastritis	5	12.8	Suspected	Primary AI. Hyponatremia responded to steroids
18	JS	63	M	Vertigo/headache	Right posterior circulation stroke	0.6	13.4	Not suspected	SAI due to indigenous medication-containing steroids. Hyponatremia responded to steroids
19	CS	26	F	Fever	Systemic lupus erythematosus	2.7	13.7	Not suspected	Hypopituitarism etiology unclear. Hyponatremia responded to steroids
20	HS	75	M	Fall	Acute inflammatory demyelinating polyneuropathy	8.33	17.7	Not suspected	AI etiology unclear. However, result was borderline. Hyponatremia however responded to steroids

^aµg/dL; ^b If adrenal disease was suspected by treating physician prior to enrollment into study; ^cEtiology of AI as per endocrinology assessment.

AE, acute exacerbation; AI, adrenal insufficiency; AKI, acute kidney injury; ALD, alcoholic liver disease; CAP, community-acquired pneumonia; SAI, secondary adrenal insufficiency; T2DM, type 2 diabetes mellitus.

among all patients with EuVHNa). Primary AI (PAI) though does not cause of EuVHNa and is generally accompanied by some degree of dehydration was included among the study subjects as most likely these patients did not have clinically appreciable dehydration and had high urine spot sodium due to aldosterone deficiency and hence met the inclusion criteria for the study. PAI was seen in 2/20 (10 or 1.4% among all patients with EuVHNa) patients. More details are given in Fig. 1. In two patients, the etiology was unclear after work up and in retrospect at least one patient might have been erroneously labeled as having AI due to our protocol of assessment of total cortisol levels and lack of pre-specified modification of 60 min post-APST cut-off for AI among patients with low albumin levels. One patient had isolated SAI with tuberculous meningitis which has been previously well documented in the literature (24), and in one patient it is likely that a new diagnosis of significant untreated primary hypothyroidism led to a temporary relative AI that warranted short-term steroid replacements.

Discussion

In our study of patients with hyponatremia admitted to general medical wards in Northern India, we found that 2.5% (20/783) patients had biochemical evidence of AI when selected patients with EuVHNa patients underwent a stimulation test to assess HPA axis. Among patients with EuVHNa, AI was seen in 14.2% (20/141) of patients. After exclusion of one patient with a transient relative AI due to untreated primary hypothyroidism and one patient with possible low post-APST cortisol due to low serum albumin, we still had 18/141 (12.7%) patients who had AI with EuVHNa. This is one of the highest prevalence of AI seen among published studies. The primary driver for the high prevalence appears to be exposure to exogenous steroids in non-traditional ways including contaminated indigenous medications, over the counter use of potent steroids and high potency inhaled steroids. We had by protocol excluded patients with any prescribed use of oral or parenteral steroids up to 6 months prior to enrolment. New diagnosis of hypopituitarism was seen in 3.5% of the cohort and was in part (60%) driven by undiagnosed long-standing post-partum pituitary necrosis that reflected poor obstetric care decades earlier in this part of the country.

In one of the largest prospective western hospital-based study from Ireland among patients labeled to have SIAD, Cuesta and colleagues found 3.8% of patients had undiagnosed SAI. Of the 22 patients they found had SAI, 13 of those were related to exogenous steroid usage and 9 (1.5%)

because of previously unrecognized hypopituitarism. However, among the 476 patients labeled with SIAD they used a 9-h cortisol value of >300 nmol/L (10.8 µg/dL) to exclude AI and only performed 40 SSTs among patients with lower values. Additionally, they performed another eight SSTs in-patients with 9-h cortisol value of >300 nmol/L because of a strong clinical suspicion of AI. Post-SST they used a similar cut-off of <500 nmol/L (18 µg/dL) as in our study to diagnose AI biochemically (15). Another retrospective study restricted to patients with moderate or profound hyponatremia (Serum sodium <130 mmol/L) found undiagnosed pituitary disease among 15% of 185 patients studied (25). Another prospective observational study involving a cohort of 298 patients with all cause profound hyponatremia (serum sodium <125 mmol/L) suggested that 1% of unselected patients with profound hyponatremia had AI and this worked out to 2.9% among the subgroup with EuVHNa (26). Two smaller retrospective studies determined AI in 2/59 (3.3%) and in 3/108 (2.7%) among patients with profound hyponatremia (27, 28).

Patients with secondary AI present with hyponatremia that is clinically very similar to hyponatremia seen with SIAD (29). Patients with hyponatremia because secondary AI meet all the criteria for SIAD. This is the primary reason SIAD should only be confirmed after assessment and establishment of a normal HPA axis. The primary mechanism of relative water retention leading to hyponatremia in secondary AI is excess ADH release due to a combination of stimulation of baroreceptors secondary to hypotension and the loss of steroid feedback suppression on ADH secretion (30). SIAD is generally treated by a combination of addressing the cause of SIAD and fluid restriction. However, patients with AI need glucocorticoid replacement therapy on an emergent basis and are likely to be harmed from fluid restriction. Our study suggested that the severity of hyponatremia was not indicative of the presence of AI and the presence of significant thyroid dysfunction should not limit the performance of ACTH stimulation testing.

The primary strengths of our study are first, the prospective use of ACTH stimulation test to assess the HPA axis among all patients with EuVHNa and suspected to have SIAD. We did not use a timed or random cortisol assessment to decide on the need for a stimulation test. This allowed us to perform the test at any time of the day upon recognition of EuVHNa, and subsequently, this led to early initiation of glucocorticoid replacement among patients with AI. Secondly, patients were recruited from general medical wards of our hospital and not from the patients in the endocrinology ward or from among

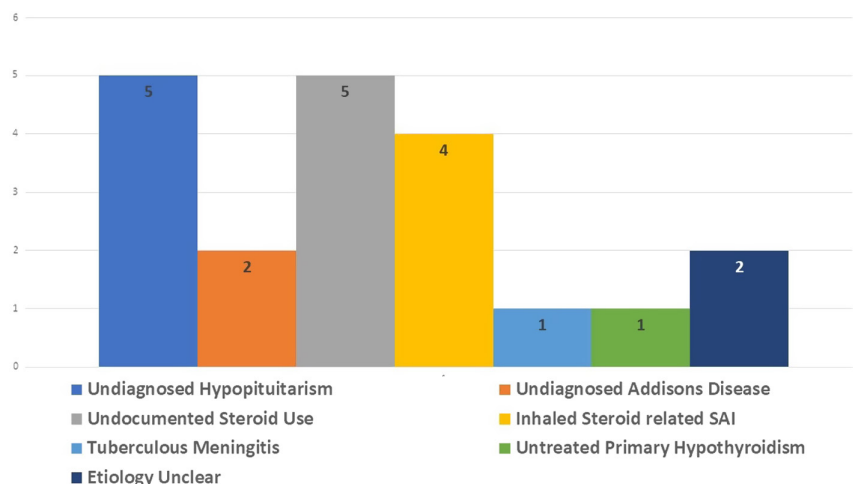


Figure 1

Bar graph detailing the various causes of adrenal insufficiency among the patients with euvolemic hyponatremia.

those referred to endocrine services reducing the bias related to endocrine referral of suspected pituitary and adrenal diseases. In only 4/20 patients, AI was clinically suspected by the treating physicians and would have led to cortisol assessments and initiation of glucocorticoid replacements.

At the time of the initiation of the study, we decided on APST rather than SST as the modality of choice for assessment of HPA axis. This was driven partly by the patchy availability of cosyntropin in the country and the cost differences between the two forms of ACTH. At that point, APST was not as well validated as it is currently and would have remained a major drawback of the study. However, over the last couple of years, publications of papers validating the use of APST have fortunately reduced some of the uncertainty related to this newer form of ACTH stimulation test (21, 22). Our second drawback was using the same cut-offs of <18 µg/dL (500 nmol/L) post-APST for patients with co-existing hypoalbuminemia. Since, the laboratory measures total cortisol levels and not free cortisol levels this would mean patients with low albumin and those with changes in cortisol binding globulin levels (e.g. those getting estrogen therapy) would have different total cortisol responses to APST. However, we feel this played a role in only one patient with AI in our study. Most patients with significant hypoalbuminemia would likely have edema and hence were excluded from our study. Our third drawback was using the prevalence of EuVHNa among unselected patients with hyponatremia as the basis of our sample size. We should have used the prevalence of AI among unselected patients with hyponatremia to determine the sample size. This was done primarily because the project was undertaken as a MD thesis and required to be completed in a time-bound fashion to allow the first author to complete his

course. The standard SST is an evaluation performed in an outpatient setting. In critically unwell patients and in patients with acute AI this is less reliable. However, we believe in-patients admitted in general medical wards this is an appropriate first screening test in patients suspected of having AI.

The other interesting finding noted in the study was the frequency of HPA axis suppression with the use of high potency inhaled steroids among patients with chronic obstructive airway disease. A recent retrospective review of SSTs was done in Birmingham; 166 SSTs were done in patients only prescribed inhaled steroids. Among these patients, 34 (20.5%) patients failed the test and it was noted that the suppression of HPA axis was dependent on the total dose of inhaled steroids (31). Even mild hyponatremia among patients with acute exacerbation of chronic obstructive airway disease (COPD) impacted prognosis and delayed hospital discharge (32). Our findings should encourage clinicians to order evaluation of the HPA axis among patients presenting with COPD and low sodium.

In conclusion, our findings suggest that all patients with EuVHNa should undergo assessment of the HPA axis either as a single random timed sample or as a stimulation test irrespective of the degree of hyponatremia. Among hospitalized patients with EuVHNa, ACTH stimulation testing can be done at any time and once the test is performed presumptive steroids can be started in patients with high index of suspicion and among the rest once the diagnosis of AI is established. In North India, the prevalence of AI among patients with hyponatremia is 2.5% and among selected patients with EuVHNa is likely between 12 and 14% and makes the undertaking of an APST in all patients with EuVHNa cost-effective and clinically appropriate.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Previous presentation

The paper was presented at the Annual Meeting of the Endocrine Society in 2020 and an abstract was published: Kumar A, Ghosh M, Jacob JJ. OR25-04 Over 14% of Inpatients with Euvolemic Hyponatremia Have Undiagnosed Adrenal Insufficiency. *J Endocr Soc.* 2020 4(Suppl 1) OR25-04. (<https://doi.org/10.1210/jendso/bvaa046.1039>).

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