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DIAGNOSTIC IMPORTANCE OF THYROID PROFILE AND SERUM CORTISOL IN PATIENTS WITH HYPONATRAEMIA

Biochemistry

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ABSTRACT

Background: Euvolemic hyponatremia is associated with syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism and adrenal insufficiency , which are often overlooked in clinical diagnosis.

Aim: Evaluation of proportion of thyroid and adrenal derangement in patients with hyponatremia and correlate this with Severity of Hyponatremia and Plasma osmolarity.

Material and Method: A Hospital based cross sectional study was conducted with 60 clinically diagnosed euvolemic hyponatremia patients without co-morbidities .Thyroid profile and cortisol levels were estimated .

Results: A significant difference in the osmolarity and sodium levels was found in cases as compared to control. Nineteen patients had thyroid derangement (17/19 cases having hypothyroidism) frequently seen in severe grade hyponatremia . Cortisol level was found low (<28ng/ml) in 24 /60 patients predominantly in Moderate hyponatremia (08/29). There was a negative association between sodium and parameters like TSH, Cortisol, uric acid and a positive association with total protein.

Conclusion: Patients with euvolemic hyponatremia should be thoroughly investigated for adrenal and thyroid hormone status to reach to an etiological diagnosis.

KEYWORDS

Hyponatremia , Euvolemia , Osmolarity,Hypothyroidism, Adrenal function

INTRODUCTION:

Hyponatraemia is the most common electrolyte imbalance accounting for 22% of hospitalized patients [1].Symptomatology develops with the degree of severity as well as with the rapidity of development of hyponatremia, Acute Hyponatremia (developing <48hrs or less)are associated with severe degree , whereas Chronic Hyponatremia (developing >48hrs) experience Milder degree of cerebral edema [2]. Mostly hyponatremia patients are diagnosed on the basis of clinical as well as laboratory findings and are treated symptomatically to restore fluid and electrolyte balance , where the underlying cause left undiagnosed. Hyponatremia still remains incompletely understood and often challenges the clinician ,as the current diagnostic evaluation did not direct towards the pathogenesis and etiological causes.

Hyponatremia being multifactorial [Figure-1] , based on osmolarity is divided into isotonic , hypotonic and hypertonic, hypotonic being the commonest one. Based on the total body fluid volume , it can be hypovolemic with excess Gastrointestinal and renal loss , Hypervolemic with Congestive cardiac failure and Nephrotic syndrome i.e. conditions usually considered while diagnosing and treating hyponatremia cases or it can be Euvolemic hyponatremia with underlying causes like Syndrome of Inappropriate ADH secretion (SIADH), Secondary Adrenal Insufficiency and Hypothyroidism [3]. These conditions are often overlooked as the investigations like thyroid profiling, cortisol estimation, urinary sodium and urine osmolality are not routinely advised.

Most guidelines suggest hypothyroidism to be one of the causes of hyponatremia[4,5]. Hyponatremia appears in 45% of hypothyroid patients with raised serum creatinine and 21% of cases with normal creatinine levels[6]. There are three large studies showing weak association between the presence of hypothyroidism and hyponatremia[7-9]. One recent study evaluated hypothyroididsm and hypoadrenalism as two common endocrine etiological factors in hyponatremia patients with insignificant findings[10].Although there is evidence to suggest that short-term uncomplicated hypothyroidism can result in a reduction in glomerular filtration rate (GFR), the data supporting the development of hyponatraemia in this setting is limited and conflicting. On the contrary the prevalence of thyroid derangement and Adrenal disorder in hyponatremia patients is not studied elaborately. So, The current study was carried out with an objective to find out the proportion of thyroid and adrenal derangement in patients with hyponatremia and an attempt was made to correlate this with Severity of Hyponatremia and Plasma osmolarity.

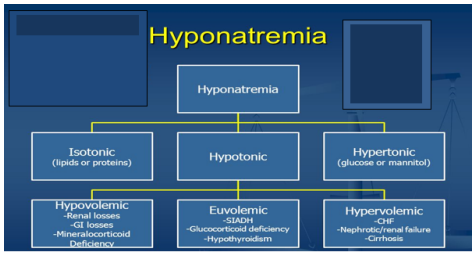

Figure-1 Multifactorial origin of Hyponatremia

MATERIAL AND METHOD:

This was a Hospital based cross sectional study conducted in the department of Biochemistry, AIIMS, Bhubaneswar during July 2017 to Feb 2018. Sixty clinically diagnosed euvolumic hyponatremia patients within the age group of 20-60 years of both sexes, from the Department of General Medicine , AIIMS, Bhubaneswar were included in this study. Sixty apparently healthy individuals were enrolled as control group. Ethical approval for the study was obtained from Institutional Ethics Committee. Informed written consent was taken from the patients before taking part in this study.

Hyponatremia patients with co-morbidities like Diabetes Mellitus, congestive Cardiac failure, Nephrotic Syndrome, severe diarrhea with vomiting as well as patients with Thiazide diuretics were excluded from the study.

After overnight fasting, 5 ml of Venous blood samples were collected from all the patients . Fasting Blood Sugar, Serum Urea ,Uric acid and Creatinine estimation were done in fully automated Chemistry Analyzer using system compatible reagent packs. Thyroid profile i.e. Free T3 (FT3), Free T4(FT4) and TSH levels were done by Immunoassay System. Serum Sodium and Potassium concentration were estimated and Plasma Osmolarity was calculated by using the formula

Plasma Osmolarity = 2[Na+](mEq/L) + [Glucose]/18+Blood urea nitrogen/2.8

- Patients data were divided into 3 groups

Serum Sodium level of 135-145 m moles /L was treated as normal

- Mild Hyponatraemia 130 - 135 mEq/L
- Moderate Hyponatraemia 125 - 129 mEq/L

- Severe Hyponatraemia <125 mEq/L.
- Patients were further classified into Euosmolar, hypoosmolar and hyperosmolar
- Plasma osmolarity between 285-295 mmoles/L – Euosmolar
- >295 mmoles/L - Hyperosmolar
- <285mmoles/L – Hypoosmolar

Statistical analysis was carried by SPSS software. Student t test was performed to compare parameters between the cases and the control group . Analysis of thyroid parameters and cortisol in three sub groups of hyponatremia subjects (divided based on severity and the osmolarity) was done using one way ANOVA. Correlation analysis was done using Pearson correlation coefficient. The p-value of <0.05 was considered as statistically significant.

RESULTS :

General characteristics of the study population (Table -1) showed a significant difference in the osmolarity and sodium levels in the cases as compared to control. The other parameters were more or less same in both the study groups.

Table-1: Clinicodemographic profile of the study Participants

Sl No.	Parameters	Control	cases
1	Sodium(mEq/L)	141.25±4.94	**127.20±3.82
2	Potassium(mEq/L)	4.16±0.51	4.09±0.85
3	Chloride(mEq/L)	102.96±4.51	96.16±4.51
4	Calcium	8.56±0.95	8.21±1.06
5	Phosphate	4.09±0.83	3.74±1.38
6	FT3	2.66±0.40	2.35±0.38
7	FT4	1.58±0.27	1.04±0.28
8	TSH	3.75±1.05	6.14±1.43
9	Cortisol	13.72±3.52	31.08±13.06
10	Fasting Blood sugar(mg/dl)	87.07±8.29	103.67±28.96
11	Urea(mg/dl)	33.54±8.09	36.51±4.61
12	Creatinine (mg/dl)	0.99±0.17	1.15±0.95
13	Uric acid(mg/dl)	5.71±1.27	5.45±2.00
14	Triglyceride(mg/dl)	110.82±20.68	133.58±25.29
15	Total protein(mg/dl)	7.25±0.68	8.30±1.39
16	Blood Urea Nitrogen	18.64±3.23	21.73±13.82
17	Osmolarity	282.32±9.01	**269.29±9.17

** Indicates p<0.05 as compared to control - Highly significant

The proportion of thyroid derangement was analyzed in hyponatremia patients (Table -2) and out of 60 cases only 19 patients had thyroid derangement with 17/19 cases with hypothyroidism. Most of the patients (08/17) had severe hyponatremia and the proportion is less in mild hyponatremia.

Table-2: Proportion of Thyroid derangement in Hyponatremia Patients

	Hypothyroidism	Hyperthyroididsm	Total Thyroid derangement
Mild Hyponatremia	02	00	02
Moderate Hyponatremia	07	01	08
Severe Hyponatremia	08	01	09
Total	17	02	19

The alteration in serum cortisol levels was found in 24 /60 patients (Table -3) . Cortisol level was low (<28ng/ml) in 17/60 cases suggesting a condition of hypoadrenalism . The fall in cortisol level was more predominant in Moderate hyponatremia(08/29) as well as in severe hyponatremia (07/29) as compared to mild hyponatremia cases.

Table-3: Proportion of Cortisol alteration in Hyponatremia cases

	>28 ng/ml	<28ng/ml	Total Cortisol derangement
Mild Hyponatremia	02	02	04
Moderate Hyponatremia	05	08	13
Severe Hyponatremia	00	07	07
Total	07	17	24

Evaluation of thyroid profile and serum cortisol levels (Table-4) showed significant increase($p<0.05$) in the TSH value in patients with severe hyponatremia as compared to mild hyponatremia ,whereas the fall in Cortisol levels was not statistically significant.

Table-4: Thyroid Profile and Cortisol levels , based on severity of Hyponatremia

	FT3	FT4	TSH	Cortisol
Mild hyponatremia	2.44±0.34	1.06±0.20	3.90±1.06	33.22±15.08
Moderate Hyponatremia	2.27±0.33	0.98±0.22	5.22±1.31	29.94±12.15
Severe Hyponatremia	2.44±0.54	1.16±0.45	**8.48±3.15	28.74±14.24

** Indicates p<0.05 as compared to mild - Highly significant

When the thyroid parameters and the cortisol level were analyzed based on the plasma osmolarity (Table -5), it was found that the increase in the TSH level(7.13±1.64) was more significant ($p<0.05$) in hypoosmolar hyponatremia patients as compared to euosmolar TSH levels (2.75±2.42). There was no significant difference in the serum cortisol levels among hypoosmolar and euosmolar hyponatremia cases.

Table-5: Thyroid Profile and Cortisol levels in hyponatremia cases, based on Osmolariy

	FT3	FT4	TSH	Cortisol
Hypoosmolar	2.38±0.42	1.04±0.30	**7.13±1.64	30.98±13.45
Euosmolar	2.17±0.18	1.07±0.19	2.75±2.42	34.74±13.69
Hyperosmolar	2.37±0.40	0.91±0.21	٤,٢٥±1.74	25.20±4.57

**Indicates p<0.05 as compared to euosmolar - Highly significant

Correlation studies (Table-6) registered a negative association between the Sodium and TSH, Cortisol and uric acid which was not statistically significant. Total protein and sodium had a positive association (correlation co-efficient r = 0.05) .

Table -6: Correlation between Sodium and TSH,Cortisol,Uric acid, Total protein

	TSH	Cortisol	Uric acid	Total Protein
Sodium	-0.224	-0.048	-0.04	-0.05
P value	0.11	0.75	0.97	0.73

Table-7 showed a negative association between plasma osmolarity and TSH (r = -0.13) and Cortisol (r = - 0.08) which was not significant statistically.

Table -7: Correlation between Osmolarity and TSH, Cortisol levels

	TSH	Cortisol
Plasma Osmolarity	-0.13	-0.08
P value	0.35	0.55

DISCUSSION:

Hyponatremia is one of the frequently observed electrolyte derangements in critical care unit. Though hypovolemic and hypervolemic hyponatremia attribute to the majority of cases, the Euvolemic hyponatremia (having normal extracellular volume) is the least diagnosed condition. Syndrome of Inappropriate ADH secretion (SIADH) , hypothyroidiam , Secondary Adrenal Insufficiency and primary polydipsia are the common causes of Euvolemic hyponatremia and etiological diagnosis will help in proper decision making before starting the treatment modality[11].

In the present study hypothyroidism was the predominant hormonal derangement found in 17/19 patients. Reports based on earlier studies suggested that the pathogenesis of "hypothyroid hyponatremia" could be due to the inability to excrete a free water load secondary to either decrease in the delivery of water to the distal nephron [12,13] or an excess vasopressin secretion [14]. The thyroid parameters showed alteration in FT3 , FT4 and TSH out of which only TSH was significantly increased in severe hyponatremia patients in the present study suggesting a state of hypothyroidism associated in hyponatremia . These findings are in concurrence with the earlier studies [15,16].

Twenty four patients had cortisol alteration with 17 cases having less cortisol levels pointing towards hypocorticism. Earlier studies have suggested that hypocorticism in Primary adrenal insufficiency could

be associated with diminished secretion of aldosterone as well as hyperkalemia [17,18]. Hyponatremia in these cases could be due to inappropriate increase in vasopressin secretion/action due to cortisol deficiency [19] and inability to excrete free water. Cortisol deficiency results in increased hypothalamic secretion of corticotropin releasing hormone (CRH), an ADH secretagogue. Cortisol feeds back negatively on CRH and ACTH, an inhibitory effect that is removed with adrenal insufficiency. It has been documented that cortisol directly suppress ADH secretion. Thus, ADH levels increase when plasma cortisol levels are low [20]. In the present study, there was a steady fall in the cortisol levels with the severity of hyponatremia, however ,that was not significant.

The cortisol levels and thyroid profile when compared with plasma osmolarity, there was a significant increase in TSH levels in hypoosmolar group suggesting a hypothyroid state more prevalent in hypoosmolar hyponatremia. Similar findings were documented by earlier studies.[21,22]

The aetiological diagnosis of hyponatraemia is based on the analysis of calculated or measured plasma osmolality , as well as blood volume. Some endocrinopathies (glucocorticoid deficiency and hypothyroidism) are associated with euvolaemic, hypoosmolar hyponatraemia, which must be distinguished from SIADH [23]. The serum uric acid levels (<4 mg/dl) along with cortisol (normal values) and potassium (normal values) were used to provisionally diagnose the SIADH cases.

The correlation study showed a negative association between sodium and parameters like TSH, Cortisol, uric acid and a positive association with total protein, suggesting the fact that hypothyroidism(raised TSH) is more associated with hypoosmolar hyponatremia .

Limitations of the study :

Further evaluation with ACTH stimulation test should be conducted in cases with low cortisol to confirm primary or secondary adrenal insufficiency in hyponatremia cases. Urinary sodium and urinary osmolarity could be included for better evaluation of SIADH .

CONCLUSION:

Hypothyroidism and Hypocorticism are the important underlying disorders associated with euvolemic hyponatremia. Diagnosis of SIADH should only be made after thorough investigation of the adrenal and thyroid hormone status to reach to a etiological diagnosis .

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