Relevance of uric acid levels in hyponatremia management

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Abstract

Introduction: Hyponatremia is a common electrolyte disorder seen in routine clinical practice with diverse etiologies and manifestations. Patient's volume status assessment and to know the type of hyponatremia is of key value in the management of hyponatremia. This study is aimed to determine the frequency of hypouricemia and hyper uricemia in euvolemic and volume depleted patients of hyponatremia.

Aim: To determine the frequency of euvolemia and hypovolemia in patients of hyponatremia and to compare the frequency of hpouricemia and hyperuricemia in euvolemic and volume depleted patients of hyponatremia.

Study Design: This was a descriptive case series study.

Study Setting: This study was conducted in Emergency department of Shifa International Hospital, Islamabad from February, 2014 to August, 2014.

Subjects and Method: 156 hyponatremic patients, 18 years and above from both genders were included in the study. Volume status of the patients assessed and patients were divided into euvolemic and hypovolemic groups. Serum uric acid of all the patients was checked. A standard Performa was used to collect the data and SPSS 16 version was to analyze the data.

Results: Mean age was 55.22 years with a range of 19 to 90 years. 54.5% were male and 45.5 % were females. In the study 97.2% hypovolemic patients showed hyperuricemia and among euvolemic patients 92.9% had uric acid less the 6 mg/dl. Fisher's Exact Test showed derived p-value of .000 showing a significant relation of hypo and hyper uricemia with euvolemic and volume depleted patients of hyponatremia.

Conclusion: Hyponatremia is a common disorder with diverse etiologies and clinical manifestations. Apart from a good clinical evaluation serum uric acid is very helpful in discriminating two subsets of hyponatemia one with euvolemia and other with volume depleted state. Clinicians need to be aware of this diagnostic role of serum uric acid in hyponatremia.

Keywords: Hyponatremia, Hypouricemia, Hyperuricemia, Euvolemia, Hypovolemia.

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HIGHLIGHTS

Hyponatremia which means low serum sodium is defined as serum sodium concentration less than 135 mmol/l once trans locational and pseudo hyponatremia are ruled out1. It is the most common electrolyte disorder encountered by the physicians2. Mild hyponatremia (serum sodium <135 mEq/L) has been reported to occur in 15% to 22% of hospitalized and 7% of outdoor patients. Moderate hyponatremia (serum sodium <130 mEq/L) occurs in 1% to 7% of hospitalized patients. It is very much important to diagnose hyponatremia early because of potential serious consequences and also as it may be a marker of underlying disorder3.

The clinical manifestations of hyponatremia are diverse and range from no symptoms to seizures and obtundation. Occasionally cerebral edema caused by hyponatremia may be severe enough to cause tentorial herniation and death of the patient due to raised ICP. This is the reason that hyponatremia is a clinical emergency. Pathophysiology of hyponatremia is complex and causes are many including syndrome of inappropriate ADH secretion (SIADH), which

is the most common cause hyponatremia2. Apart from other causes certain drugs are known to lead to hyponatremia. In the drugs list thiazide diuretics are very important because of their common clinical use and association with hyponatremia2,4. Hyponatremia can be classified in different ways one of which is volume based which stratifies patients according to volume status i, e hypovolemic, euvolemic, and hypervolemic 5,6.

Renal handling of serum uric acid is altered according to the etiology involved in the pathogenesis of hyponatremia. Serum uric acid concentration has been noted as an index of differentiation in different types of hyponatremia4.It has been reported in different studies that value of serum uric acid remains low in syndrome of inappropriate ADH secretion(SIADH) and SIADH like states and tends to be on higher side in volume depleted conditions. In one study 35% patients with clinical euvolemia showed hypouricemia where as 65% having picture of volume depletion noted to have uric acid levels on higher side4. Routine laboratory tests like urinary sodium and its fractional excretion become less reliable in many hyponatremic patients as some of them use diuretics2. Here some alternative tests like serum uric acid can be helpful in formulating diagnosis and in knowing the volume status of the patients2,4,5. Hypourecemia in the setting of clinical euvolemia in hyponatremic patients is suggestive of SIADH, and if fractional excretion of uric acid is combined with urinary sodium the diagnostic accuracy becomes very high 3,7.

Diagnostic utility of serum uric acid in the setting of hyponatremia has been proven in different studies but it has not been verified in large series of patients4.Some studies done in past do not support diagnostic significance of serum uric acid in hyponatremia6. Also there is lack of local data to support the relation between these two variables. Serum Uric acid is a cost-effective, widely available, easy to perform and has less reporting time. In our study we want to check the serum uric acid levels as an additional tool to asses' volume status of the hyponatremic patients. Accurate assessment of volume status is of key value in the management of hyponatremia.

AIM OF THE STUDY

To determine the frequency of euvolemia and hypovolemia in patients of hyponatremia and to compare the frequency of hpouricemia and hyperuricemia in euvolemic and volume depleted patients of hyponatremia.

MATERIAL AND METHODS

Study design

This was a descriptive case series study.

Study setting

This study was conducted in Emergency department of Shifa International Hospital, Islamabad from February, 2019 to August, 2019.

Sampling technique

Consecutive non-probability sampling technique was used in this study.

Inclusion criteria

A total of 156 patients included in this study. All patients with serum sodium of equal to or less than 130 mEq/l irrespective of the cause, duration or comorbid, 18 years and above from both genders were included in the study.

Exclusion criteria

Patients taking uricosuric agents and other uric acid lowering medicines like allopurinol were excluded from the study. Also those on chemotherapy and hypervolemic patients (Having edema, raised JVP) were not eligible for the study.

Data collection procedure

A total of 156 patients included in this study. All patients with hyponatremia as defined in operational definition were included in the study. Informed consent was taken. Demographic data like age and gender was collected. Detailed history was taken and clinical examination was performed and volume status of the patients was assessed and all patients were categorized into euvolemic and hypovolemic groups. Blood samples were drawn from all the patients and sent to

Laboratory for serum sodium and serum uric acid levels. Uric acid analysis was performed by enzymatic Uri case method on Abbot ARCHITECT c System and was represented as mg/dl. Serum sodium was performed by Ion-selective electrode diluted method on Abbot ARCHITECT c System ICT (Integrated Chip Technology) and represented as mEq/l. Both were reported and verified by the pathologist. A standard Performa was used to collect and enter the data.

Data analysis

Data was entered on SPSS 16 version. Descriptive analysis had been done for numerical variables like age and serum sodium and uric acid was presented as mean, and standard deviation. Whereas, frequencies/percentages were calculated for

categorical variables such as gender, hypovolemia, euvolemia, hypouricemia and hyperuricemia. Fisher, s Exact Test was used for comparison between two groups. P value < 0.05 was significant.

RESULTS

A total of 156 patients were included in this study. Mean age of the patients included in the study was 55.22 years. The range of the age was 19 to 90 years.

Table 1: Age of the patients (years)

N	Minimum	Maximum	Mean	Std. Deviation
156	19	90	55.22	16.057

Among the participants, 85 (54.5%) were males and 71 (45.5%) were females included in the study.

Table 2: Gender distribution of the patients

Gender	Frequency	Percentage
Male	85	54.5%
Female	71	45.5%
Total	156	100%

Frequency of hyperuricemia and hypouricemia

Among the patients, 76 (48.7%) had hyperuricemia while 80 (51.3%) were hypouricemic

Table 3: Uric acid level

Uric acid level	Frequency	Percentage
Hypouricemia	80	51.3%
Hyperuricemia	76	48.7%
Total	156	100%

Frequency of Euvolemia and Hypovolemia

Among the subjects, 84 (53.8%) were euvolemic whereas, 72 (46.3%) had hypovolemia as shown in the table IV.

Table 4: Volume status

Volume status	Frequency	Percentage
Hypovolumia	72	46.2%
Euvolumia	84	53.8%
Total	156	100%

Frequency of hyperuricemia and hypouricemia in relation to volume status

Among the hypovolemic patients 70(97.2%) demonstrated hyperuricemia while only 2 (2.8%) had hypouricemia. On the other hand from the participants who were euvolemic 78 (92.9%) exhibited hypouricemia and 6 (7.1%) showed hyperuricemia.

Table 5: Volume status and uric acid levels

Volume status	Hypouricemia	Hyperuricemia	Total
Hypovolumia	2	70	72
Hypervolumia	78	6	84
Total	80	76	156

Fisher's Exact Test showed p - value of 0.000 which reveals statically significant association of hpouricemia and hyperuricemia with euvolemic and volume depleted hyponatremia.

Table 6: Fisher's Exact Test

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.259E2[a]	1	.000		
Continuity Correction[b]	122.337	1	.000		
Likelihood Ratio	154.652	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases[b]	156				

DISCUSSION

Hyponatremia is a common clinical disorder encountered by the physicians in their routine practice. Timely and appropriate treatment of hyponatremia is very important especially if patient is symptomatic. From the management point of view knowing the volume status of the patient and establishing type of hyponatremia is of crucial value. The evaluation of a patient with low sodium begins with a detailed history and physical examination with a special focus on the volume status assessment. However, sometimes it is difficult to accurately comment on the fluid status of hyponatremic patients especially in euvolemic states like SIADH and in subjects with borderline fluid depletion. Although, clinical assessment is very important in volume status assessment. Some laboratory tests like urinary sodium and its fractional excretion provide a good guide in this regard. However, problem arises in those patients who use diuretics and thus having high

urinary sodium because of the natriuretic effect of the diuretics and this can mislead the clinicians. Here, some other diagnostic tests like serum uric acid provided an additional tool for volume status assessment and knowing the type of hyponatremia. Serum uric acid is therefore helpful in patient's management as accurate assessment of fluid status and knowing the type of hyponatremia is of key value in hyponatremia management.

The current study was carried out at Shifa international hospital, Islamabad, from 4th February, 2013 to 3rd August, 2013, for a period of 06 months. The aim was to determine the frequency of hypouricemia and hyperuricemia in euvolemic and volume depleted patients of hyponatremia. The results of the study will be discussed and compared with studies done in other parts of the world.

The mean age of the participants was 55.22 years with a range of 19 to 90 years. Among the patients 85 (54.5%) were males and 71 (45.5%) were females. The frequencies of hypouricemia and hyperuricemia in our study were 51.3% and 48.7% respectively. This is in comparison to a study done in Greece which shows this distribution as 35% hypouricemic and 65% hyperuricemic patients 4.Among the patients enrolled for the study 84 (53.8%) were euvolemic and 72 (46.2%) were hypovolemic.

In this study among the hypovolemic patients 70 (97.2%) showed uric acid ≥ 6mg/dl whereas, hypouricmia was seen only in 2 (2.8%) patients. On the hand in patients who were euvolemic 78 (92.9%) had serum uric acid ≤ 6mg/dl and only 6 (7.1%) demonstrated hyperuricemia. The p value calculated through Fisher's Exact Test (as number of subjects in one of the variables were only two) was found to be .000 (<.05).Our study therefore has produced the results of high uric acid levels in volume depleted patients and hypouricemia in euvolemic patients of hyponatremia.

Results of our study go with the much of the published data on this topic showing low uric acid levels in euvolemic hyponatremia and hyperuricemia in volume depleted hyponatremic conditions. One study which was conducted by Liamis G. and his colleagues in 2007 on Uric acid homeostasis in diuretic induced hyponatremia4.Total 40 patients were enrolled for the study. Results showed that hyponatremic patients with clinical euvolemia(n=14) were having serum uric acid less than 4 mg/dl whereas hyperuricemia(n=26) was seen in patients with volume depleted state. So it was concluded in the study that serum uric acid can discriminate between the two constructs of hyponatremia one with euvolemia and other with volume depletion.

Another study done by Paul M. and his colleagues again produced the same results of hypouricemia (6/6) in patients with SIADH and coexistence of hypouricemia and hyponatremia predicted SIADH reliably10. There have been other studies which demonstrate low uric acid levels associated with SIADH (70%) compared to salt depleted states (40%) 9.

A study done in USA by Imbriano and his colleagues in 2012 again reported the hypouricemia in SIADH patients although in this study the main focus was on the fractional excretion of urate. This study concluded that a normal fractional excretion of uric acid in a euvolemic patient is highly suggestive of reset osmotic and is superior to serum uric acid in this regard. There has been some data which do not support the discriminative role of serum uric acid in SIADH and other causes of hyponatremia. A French study done in 2010 including 55 patients all of them were hypouricemic. Study showed that hypouricemia does not performed well in diagnosis, 71% sensitive and 53% specific 6.

There is no published data from Pakistan on uric acid and its relation with hyponatremia so for. Limited studies which are available from this country are mainly focusing on etiology of hyponatremia or its frequency, for example a study done at Agha Khan university Hospital, Karachi mainly focusing on etiology of hyponatremia revealed that it is more prevalent in elderly people and gastrointestinal losses and drugs being the major cause of it. Role of uric acid in hyponatremia was not studied 8. In fact no published study on the role of uric acid in hyponatremia is available in Pakistan. Data from neighboring countries

like India is also lacking on uric acid homeostasis in hyponatremia. Although lot of studies from Iran covering different aspect of hyponatremia are available but none of them analyzed any role of uric acid in hyponatremia 11.

Similarly, serum uric acid levels may be used in the differential diagnosis of hyponatremia.12,13 It has been reported that patients with hypovolemia tend to exhibit increased serum uric acid levels (greater than 0.3 mmol/L).14 In contrast, in patients with SIADH, serum uric acid levels are actually depressed (less than 0.24 mmol/L).,17 This decrease in serum uric acid levels typically results from an increase in urate excretion (fractional excretion of urate greater than 10%). Hyperuricuria has been attributed to water retention and the resultant expansion of serum volume, which, in turn, leads to reduced sodium and urate reabsorption.15,16 However, it remains questionable whether volume expansion per se is a major determinant that causes a significant increase in urate excretion rates in humans.18 In fact, there is evidence that hypouricemia related to high urate clearance may also be encountered in some hypovolemic patients who exhibit cerebral salt-wasting syndrome19

CONCLUSION

Hyponatremia is a common disorder with diverse etiologies and clinical manifestations. Apart from a good clinical evaluation serum uric acid is very helpful in discriminating two subsets of hyponatemic states one with euvolemia and other with volume depleted state. Clinicians need to be aware of this diagnostic role of serum uric acid in hyponatremia.

LIMITATIONS

1. The sample size was small and it represented patients only from a single tertiary care hospital. A broader and more comprehensive study with patients from different other hospitals needs to be done.
2. Had the cause of hyponatremia in every participant was explored then it could have been a more informative study.
3. The treatment given to the patients and its outcome should have also been discussed in the study to make it a more comprehensive study.

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