Original Research

PSYCHIATRY

Identification of risk factors associated with hyponatremia in psychiatric patients: a case-control study

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Abstract

Background and aims. Prompt recognition and optimal management of hyponatremia helps the physician devise a better treatment plan to prevent future complications in patients. Hence this study aims to identify the risk factors associated with hyponatremia in psychiatric patients.

Methods. A case-control study was conducted among psychiatric inpatients in a tertiary care teaching hospital. Patients admitted from January 2013 to December 2017 were identified using ICD-10 code F01-F99. Patients with serum sodium levels < 135 mmol/L were considered to have hyponatremia and between 135-145 mmol/L as controls. Factors associated with hyponatremia were identified by multiple logistic regression, and the odds ratio (OR) was calculated.

Results. Based on the inclusion and exclusion criteria, 264 cases of hyponatremia and 253 matching controls were included in the study. The mean age of patients with hyponatremia was 56.4 ± 16.8 years compared to 39.6 ± 13.9 years in controls, and 65.7% of them were males. Seizure disorder (OR = 3.14, p = 0.047), bipolar disorder (OR = 6.03, p = 0.001), depression (OR = 4.78, p = 0.0005), use of quetiapine (OR = 2.11, p = 0.007) and insulin (OR = 3.53, p = 0.038) were independent risk factors associated with development of hyponatremia.

Conclusions. The chances of developing hyponatremia are increased in psychiatric patients with a seizure disorder, bipolar disorder, depression and using quetiapine or insulin. And they should be monitored carefully.

Keywords: hyponatremia, risk factors, psychiatric illness, quetiapine, insulin

Introduction

Hyponatremia is defined as serum sodium concentration of less than 135 mmol/L [1]. It is the most prevalent electrolyte imbalance encountered in hospitalized patients in both general and psychiatric wards. Hyponatremia is a prevalent and potentially dangerous condition in psychiatric patients and accounts for 10.5% of the cases [2]. Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical signs may mimic psychopathological symptoms of the underlying condition. Well recognized risk factors for hyponatremia include extreme old age, over 80 years, low body weight, female gender, history of hyponatremia/ low baseline sodium concentration, longer psychiatric illness duration, and co-therapy with drugs known to be associated with causing hyponatremia [1,3]. Many elderly people are especially vulnerable to hyponatremia as they will be on diuretics. Loss of kidney function, polypharmacy, dementia, and other advanced-age disorders can increase the severity of hyponatremia [4]. Also, the conditions

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that increase water intake, such as delusional states, obsessive-compulsive behavior, and dry mouth associated with the anticholinergic side effects of many psychiatric medicines, are potential risk factors for the development of hyponatremia in psychiatric patients. As a result of their excessive drinking, hospitalized patients with alcoholism or an eating disorder drink more water to generate a false sense of fullness, resulting in dilutional hyponatremia [5]. De Leon found that 11% of 61 patients admitted to a state mental hospital's long-term care unit and 13% of a subgroup of 32 patients with schizophrenia had a history of hyponatremia [5]. Hyponatremia can lead to severe complications, such as cerebral edema, brain disease, herniation of the brain, cardiopulmonary arrest, seizure, coma and even death [6].

In previously published studies, renal diseases were confirmed to be the strongest risk factor associated with hyponatremia in psychiatric patients. Hence in this study, renal diseases were excluded. This may help identify other factors contributing to hyponatremia. Early recognition and optimal management of hyponatremia in hospitalized patients may help reduce in-hospital mortality and severity allowing less-intensive hospital care, thereby decreasing the duration of hospitalization and associated costs. Early recognition of the condition will also help the physician establish a relationship between the severity of hyponatremia and comorbid conditions/drugs and hence devise a better plan for preventing hyponatremia and related complications [7].

Therefore, it is crucial to identify and manage hyponatremia before it interferes with the treatment of the main psychiatric illness. This study emphasizes the identification of risk factors (comorbid illness and current drug therapy) associated with hyponatremia in psychiatric patients rather than focusing on a single risk factor or mental disorder, giving the physician a better insight on the prediction, and prioritizing of management of hyponatremia.

Methods

Study design

A case-control study was performed in psychiatric inpatients in a tertiary care hospital from January 2013 to December 2017, of which 264 deemed cases of hyponatremia were confirmed based on recorded serum sodium levels (< 135 mmol/L); 253 patients without hyponatremia (135-145 mmol/L) were considered as controls. Initially 400 cases of hyponatremia were selected from the medical records files, from that 136 cases were excluded based on the exclusion criteria.The total number of hyponatremia cases included in the study was 264. Ethical approval was obtained from the Institutional Ethics Committee. Figure 1 shows the study design and patient selection process.

Inclusion criteria

Cases: All psychiatric patients with serum sodium levels of less than 135 mEq/L.

Controls: All psychiatric patients with serum sodium levels between 135-145 mEq/L.

Exclusion criteria

Psychiatric patients in whom serum sodium levels were not checked.

Patients with renal disease: Acute renal failure or chronic renal failure.

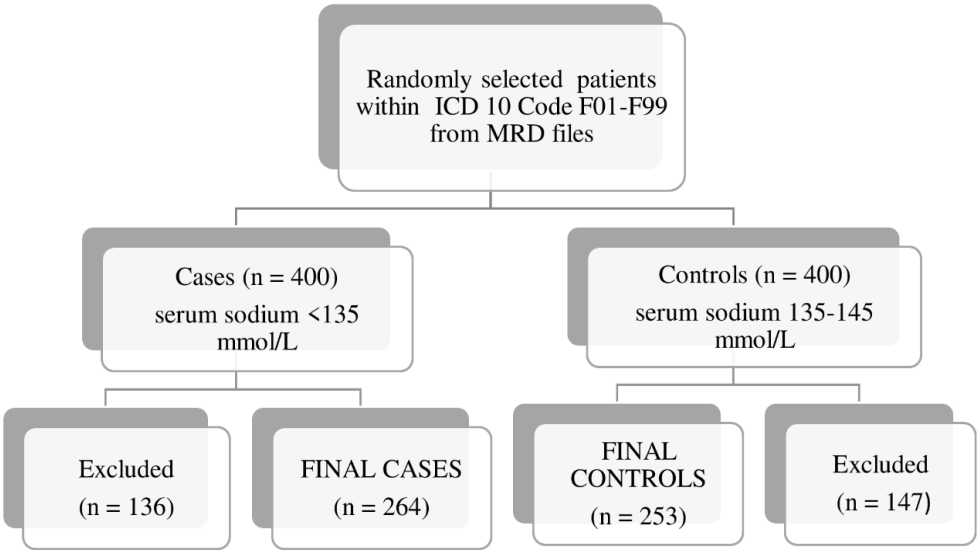

Figure 1. Flowchart depicting the selection procedure of the study participants.

Patient identification and collection of data

Psychiatric patients were identified from the medical records department (MRD) using ICD 10 code F01-F99 belonging to class mental, behavioral and neurodevelopmental disorders who were admitted to a tertiary care teaching hospital from January 2013 to December 2017 for laboratory evidence of hyponatremia. Patients whose serum sodium values were between 135 mmol/L to 145 mmol/L during hospital stay were selected as controls. From each selected patient file, demographic information and clinical data, basic laboratory tests, social history, family history, duration of psychiatric illness, comorbidities and drugs prescribed were collected and entered in the case record forms (CRF).

Statistical analysis

Continuous data was expressed as mean ± SD. Nominal data was described and presented in frequency and percentage. Chi square test was used to identify the association of categorical variables with hyponatremia. Unpaired t-test was used to compare the statistical significance of continuous variables between cases and controls. Multiple logistic regression was used to identify the factors associated with hyponatremia and calculation of odds ratio (OR). Initially independent variables for logistic regression were selected based on previous empirical investigations, clinical considerations, and univariate statistical analyses. In the final regression analysis only the variables showing statistical significance in univariate analysis with an adequate number of events (10 to 20 events per covariate) per independent variable were selected to avoid an overfit model. A p value of < 0.05 was considered statistically significant. Data entry and statistical analysis were done using IBM SPSS software version 20.0 (IBM Corp. Armonk, NY).

Results

Demographic and other characteristics

The demographic and other characteristics of the study population are described in table I. The mean age of the hyponatremia population was 56.4 ± 16.8 years when compared to 39.6 ± 13.9 years in controls and there was a statistically significant ($p = 0.001$) difference in mean age between cases and control. The majority of the patients who were of > 60 years of age accounted for the maximum number of cases (n = 120, 81.6%). The study population comprised of a higher population of males (n = 340, 65.7%) compared to females. Hyponatremia was found to be predominant in males (n = 180, 52.9%) than females (n = 84, 47.5%).

Prevalence of alcoholism was statistically significant (< 0.005) among cases (n = 92, 65.2%) compared to control (n = 49, 34.8%).

Comorbidities/ psychiatric illness in the study population

The frequency of comorbidities of the study population is described in Table II**.** The syndrome of inappropriate antidiuretic hormone secretion (SIADH) (90%) was the most common comorbidity with the highest incidence of hyponatremia followed by pneumonia (88.8%), gastrointestinal diseases (83.6%), cardiovascular accident (CVA) (83.3%), chronic obstructive pulmonary disease (COPD) (83.3%) and pulmonary tuberculosis (PTB) (83.3%).

Figure 2 depicts the percentage distribution of psychiatric illness in the study population. Dementia (95%) accounted for a maximum number of cases followed by bipolar disorder, depression, alcohol dependence syndrome (ADS) and delirium.

Table I. Demographic and biochemical characteristics of study population.

Parameter	Total (n = 517)	Cases (n = 264)	Control (n = 253)	P value
Age (mean ± SD)	48.19 ± 17.62	56.4 ± 16.78	39.58 ± 13.99	0.001
Age Category • < 60, n (%) • > = 60, n (%)	 370 (71.5%) 147 (28.4%)	 144 (38.9%) 120 (81.6%)	 226 (61.1%) 27 (18.3%)	
Gender, n (%) • Males, n (%) • Females, n (%)	 340 (65.7%) 177 (34.2%)	 180 (52.9%) 84 (47.5%)	 160 (47.1%) 93 (52.5%)	
Smoking, n (%)	61 (11.7%)	30 (49.2%)	31 (50.8%)	0.754
Alcoholism, n (%)	141 (27.2%)	92 (65.2%)	49 (34.8%)	0.005
Serum Sodium (mean ± SD)	132.44 ± 8.22	125.85 ± 6.23	139.32 ± 2.28	
Hyponatremia category, n (%) • Mild • Moderate • Severe	 66 (25.1%) 119 (45.2%) 78 (29.7%)			

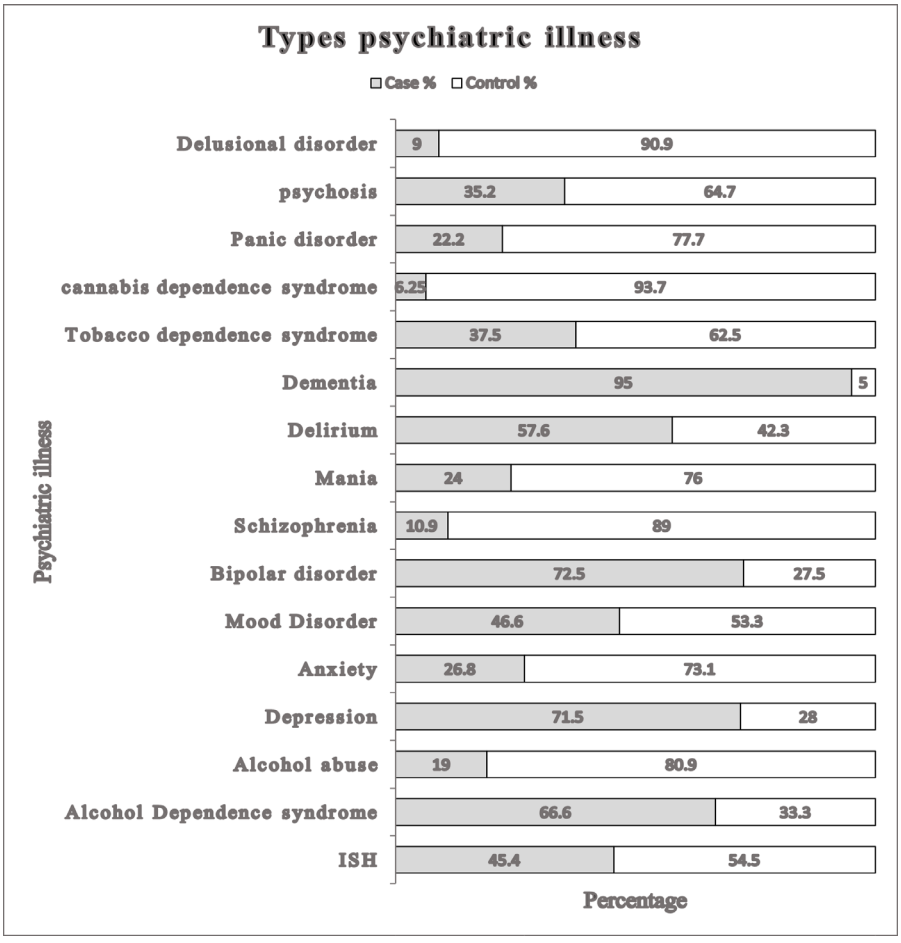

Figure 2. Percentage distribution of psychiatric illness in the study population.

Current medications in the study population

The data about current medications is described in table II. The descriptive analysis of current medications suggested maximum use of insulin among the cases, i.e. 81.4%, followed by metoprolol (73.6%), levetiracetam (73.6%) and quetiapine (66.6%) as compared to controls.

Identification of risk factors for hyponatremia by multiple logistic regression

The results of multiple logistic regression along with the OR, 95% CI, and *p*-value are presented in Table III**.**

All the factors identified in the univariate analysis showed statistically significant association with hyponatremia when analyzed with other factors in the multivariate analysis except age and alcohol use due to the presence of confounding factors.

Association between comorbidities, psychiatric illness, and risk of hyponatremia

Seizure disorder was to be the strongest independent risk factor for the development of hyponatremia (OR = 3.14; 1.01- 6.66, p = 0.047).

Patients with bipolar disorder (OR = 6.03; 2.16-16.81, p = 0.001) showed a higher magnitude of the associated OR making it one of the leading independent risk factors causing hyponatremia. Next in the list was depression (OR = 4.78; 2.16-10.61, p = 0.0005). Anxiety was found to reduce the incidence of hyponatremia with an OR of 0.27.

Current medications prescribed and risk of hyponatremia

The multi-variate analysis showed that use of quetiapine (OR = 2.11; 1.22-3.65, p = 0.007) and insulin (OR = 3.53; 1.07-11.66, p = 0.038) are strong risk factors for the development of hyponatremia among psychiatric patients. Whereas use of risperidone (OR = 0.43, p = 0.0056), olanzapine (OR = 0.35, p = 0.004), clonazepam (OR = 0.24, p = 0.005), and zolpidem (OR = 0.42, p = 0.013) were found to reduce the incidence of hyponatremia.

Table II. Co-morbidities and current drugs in the study population.

Co-morbidity	Total (n = 517)	Cases (n = 264)	Control (n = 253)
CNS			
• Seizure disorder	33 (6.3)	27 (81.8%)	6 (18.1%)
• CVA	12 (2.3%)	10 (83.3%)	2 (16.6%)
CVS			
• Hypertension	103 (19.9)	66 (64%)	37 (35.9%)
Endocrine			
• Diabetes mellitus	83 (16%)	54 (65%)	29 (34.9%)
• SIADH	11 (2.1%)	10 (90%)	1 (9.09%)
Hepatic			
• Cirrhosis	16 (3%)	13 (81.2%)	3 (18.7%)
• ALD	18 (3.4%)	11 (61.1%)	7 (38.8%)
Orthopedic*	22 (4.2%)	12 (54.5%)	10 (45.4%)
Pulmonary			
• Pneumonia	18 (3.4%)	16 (88.8%)	2 (11.1%)
• COPD	12 (2.3%)	10 (83.3%)	2 (16.6%)
• PTB	18 (3.4%)	15 (83.3%)	3 (16.6%)
Gastrointestinal	49 (9.4%)	41 (83.6%)	8 (16.3%)
Current Medications			
Quetiapine	120 (23.2%)	80 (66.6%)	40 (33.3%)
Risperidone	50 (9.6%)	12 (24%)	38 (76%)
Aripiprazole	47 (9%)	16 (34%)	31 (65.9%)
Lithium	30 (5.8%)	6 (20%)	24 (80%)
Haloperidol	83 (16%)	47 (56.6%)	36 (43.3)
Chlorpromazine	21 (4%)	6 (28.5%)	15 (71.4%)
Olanzapine	89 (17.2%)	20 (22.4%)	69 (77.5%)
Sertraline	22 (4.2%)	8 (36.3%)	14 (63.6%)
Escitalopram	41 (7.9%)	18 (43.9%)	23 (56%)
Trazodone	20 (3.8%)	9 (45%)	11 (55%)
Duloxetine	14 (2.7%)	5 (35.7%)	9 (64.2%)
Amitriptyline	18 (3.4%)	8 (44.4%)	10 (55.5%)
Carbamazepine	22 (4.2%)	9 (40.9%)	13 (59%)
Divalproex	14 (2.7%)	6 (42.8%)	8 (57.1%)
Clonazepam	90 (17.4%)	26 (28.8%)	34 (37.7%)
Levetiracetam	38 (7.3%)	28 (73.6%)	10 (26.3%)
Lorazepam	195 (37.7%)	79 (40.5%)	116 (59.4%)
Valproic acid	32 (6.1%)	11 (34.3%)	21 (65.6%)
Levothyroxine	31 (5.9%)	5 (16.1%)	26 (83.8%)
Telmisartan	13 (2.5%)	7 (53.8%)	6 (46.1%)
Metoprolol	19 (3.6%)	14 (73.6%)	5 (26.3%)
Propranolol	18 (3.4%)	7 (38.8%)	11 (61.1%)
Amlodipine	68 (13.1%)	41 (60.2%)	27 (39.7%)
Metformin	46 (8.8%)	22 (47.8%)	24 (52.1%)
Insulin	27 (5.2%)	22 (81.4%)	5 (8.5%)
Atorvastatin	25 (4.8%)	16 (64%)	9 (36%)
Acamprosate	23 (4.4%)	12 (52.1%)	11 (47.8%)
Zolpidem	79 (15.2%)	27 (34.1%)	52 (65.8%)
Trihexyphenidyl	82 (15.8%)	21 (25.6%)	61 (74.3%)

(* - fractures, spondylitis, herniated disc)

(CVA - cardiovascular accident, SIADH - syndrome of inappropriate antidiuretic hormone secretion, COPD - chronic obstructive pulmonary disease, ALD – alcoholic liver disease, PTB - pulmonary tuberculosis)

Table III. Multivariate analysis of risk factors for hyponatremia.

Factors	OR	95 % CI	P value
Comorbidities			
Depression	4.787	2.16 – 10.61	0.0005
Bipolar disorder	6.028	2.16 – 16.81	0.001
Seizure disorder	3.135	1.01 – 6.66	0.047
Current Medications			
Quetiapine	2.114	1.22 – 3.65	0.007
Insulin	3.534	1.07 – 11.66	0.038
Risperidone	0.425	0.18-1.00	0.0056
Olanzapine	0.352	0.17-0.72	0.004
Clonazepam	0.24	0.12-0.48	0.005
Zolpidem	0.421	0.21-0.83	0.013

Discussion

Hyponatremia is a prevalent and potentially dangerous condition in psychiatric patients and accounts for 15% of the cases. Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical signs may mimic psychopathological symptoms of the underlying condition [4]. With the progressive loss of kidney function, derangements in electrolytes and acid-base inevitably occur and contribute to poor patient outcomes [8]. Sodium is generally retained but may appear normal, or hyponatremic, because of dilution from fluid retention [9]. Hence in this study, patients with renal diseases were excluded to avoid confounding which gives us an edge to find more risk factors other than the well-established ones.

The study population comprised of a higher population of males (65.7%) which was similar to a study conducted by Joshi HM et al where hyponatremia was significantly more common in male psychiatric inpatients ($p<0.04$) [4]. There was a statistically significant difference in the mean age of patients in cases and controls. It was found that patients with age > 60 years comprised most of the cases. The elderly population has a higher risk of bone fractures, impaired attention and falls due to asymptomatic hyponatremia which can be dangerous. Thus, to reduce morbidity and mortality, the correction of hyponatremia is of utmost importance [10]. The mean age of the hyponatremia population in our study was 56.4 ± 16.8 years. Three of the four hyponatremia cases in the case series were over 50 years old, indicated a link between age and hyponatremia. These findings are consistent with recent research, which show that age is one of the most important predictors of hyponatremia, which could be attributable to a variety of factors [4]. However, another study showed that age also seems to be strongly confounded by drugs and comorbidities which usually are present in the older age and might be responsible for the hyponatremia [11].

The majority of the patients with hyponatremia had a medical history of alcoholism. Serum creatinine, serum potassium, and BUN were found to be moderately high in the cases but not to the extent to cause uremia or hyperkalemia.

From multiple logistic regression, depression, bipolar disorder, seizure disorder, quetiapine, and insulin were found to be risk factors for the development of hyponatremia. Further, "apart from being commonly reported in patients with psychogenic polydipsia (due to development of SIADH in these patients following water intoxication), hyponatremia has also been reported in patients with schizophrenia, anorexia nervosa, psychotic depression, bipolar disorder, substance use disorders, mental retardation, and other neuropsychiatric conditions such as epilepsy" [3]. The average age of patients was 46 years in a systematic review of antipsychotic-induced hyponatremia that comprised case series, reports, and a few observational studies. Around 70% of the patients had a diagnosis of schizophrenia [12].

In patients with a seizure disorder, the concurrent usage of duloxetine and hydrochlorothiazide caused SIADH and sodium depletion respectively, which further resulted in life-threatening hyponatremic encephalopathy with seizures [13]. Literature reports that the use of various types of psychiatric medicines that are linked to SIADH increases the risk of hyponatremia [5]. The prevalence of SIADH has been estimated to be as high as 11% in acutely ill psychiatric patients [14]. A drug surveillance program reported that the highest incidence of hyponatremia was found in antiepileptic drug users when compared to all other psychotropic drugs [15].

Atypical antipsychotic therapy in older adults has been known to cause an increased risk of hospitalization due to hyponatremia within 30 days of commencement of therapy [16]. Quetiapine is an important risk factor for hyponatremia in psychiatric patients. Quetiapine has presented a positive re-challenge for causing hyponatremia in the elderly population [12]. Quetiapine has been associated with causing SIADH [17]. Atypical

antipsychotics such as aripiprazole, quetiapine, clozapine cause hyponatremia due to their serotonin-mediated effects on central 5-HT2 and 5-HT1c receptors which lead to the release of ADH. Moreover, serotonin resets the osmostat and thereby lowers the threshold for ADH secretion [18]. In a case series, one of the case received combination of trifluoperazine, haloperidol drugs along with quetiapine which was found to aggravate hyponatremia [4]. A case report by Reddy Mukku et al., found that elderly age, polydipsia, psychiatric illness, antihypertensive medicine (hydrochlorothiazide), and quetiapine are all factors that contribute to hyponatremia which was similar to our study findings [12].

Insulin stimulates the arginine-vasopressin-dependent expression of aquaporin-2 in the renal collecting duct, possibly augmenting the hydro-osmotic effect of vasopressin when circulating levels are increased in response to other influences. The latter effect may explain the reported association between insulin use and hospital-acquired hyponatremia in patients with diabetes [19].

In this study, incidence of hyponatremia was statistically less significant in patients who were on risperidone, olanzapine, clonazepam, and zolpidem. In a 15year follow-up study to explore hyponatremia in schizophrenic patients, approximately 6.7 percent of patients experienced hyponatremia, with an average age of 55 and one-third of them had no history of antipsychotic use prior to hyponatremia. Hyponatremia was linked to older age at diagnosis of schizophrenia, low socioeconomic status, physical illnesses, psychiatric hospitalizations, carbamazepine, and a background of atypical or typical antipsychotic usage in schizophrenia patients [20].

Clinical implications of the findings

If the identified factors are promptly noted and taken care well in advance, might reduce the chances of development of hyponatremia in psychiatric patients with those risk factors, So, chances of complications related to hyponatremia such as cerebral edema, brain disease, herniation of the brain, cardiopulmonary arrest, seizure, coma and even death will reduce. Also unnecessary hospitalization and treatment cost can be avoided. Moreover, it will also help to increase treatment compliance in patients with diabetes and psychiatric disorders.

Limitations

Being a case control study there may be bias in selection of cases. Study design may be inefficient to identify some rare exposure related risk factors. Also we were not able to calculate the incidence of hyponatremia and the absolute risk (relative risk). Usually case control studies are unable to detect very small relative risks (less than 1.5).

Conclusions

Hyponatremia was assessed to be attributable to comorbid conditions like seizure disorder, depression, bipolar disorder and currently prescribed drugs like quetiapine and insulin. Patients with these risk factors should be regularly monitored for serum sodium levels by medical professionals since when unattended or undiagnosed, hyponatremia can cause unnecessary delays in psychiatric treatment, at times even resulting in mortality. Thus, in case of the development of hyponatremia, the physician can immediately initiate precautionary measures like discontinuation of the responsible medications or excessive water intake. Prompt recognition, identification of risk factors and optimal management of hyponatremia in hospitalized patients would reduce in-hospital mortality, symptom severity, duration of stay and allow for less-intensive hospital care.

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