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Corelation of Hepatic Enzymes and Serum Electrolytes in Patients with Alcohol withdrawal Delirium Tremens

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Abstract
Background: *Delirium Tremens (DTs) is an emergency situation with high mortality rate ranges from 5-15 % due to respiratory failure and cardiac arrhythmias despite in an era of intensive care and advanced pharmacotherapy.*
Aims and objectives-,
1. *To estimate and co relate the level of serum ions (Na^+, k^+,Mg^{2+},Cl-) and hepatic enzymes (ALT, AST, GGT) in alcohol withdrawal patients with and without delirium tremens.*

Methods: *A prospective cross sectional study was conducted for a period of one year from July 2013 to July 2014 at department of psychiatry, Assam medical College Hospital. 50cases of with Delirium tremens (F 10.4) and 50 cases alcohol withdrawal without DT (F10.3) were studied from the same socio-cultural background after ethical clearance from institutional review board . Diagnosis of alcohol withdrawal (F10.3) and DT (F10.4)were confirmed both clinically, using ICD-10 and patients were evaluated using Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) . Clinical and investigation details were studied with the help of advanced clinical biochemistry Laboratory, Assam medical college and hospital.*

Results: *A positive correlation observed between Serum potassium with Hepatic enzyme ALT in patients with delirium tremens.*

Conclusion: *Patients with Delirium tremens have deranged levels of hepatic enzymes and serum ions and a positive correlation found between serum k+ and ALT level.*

Keywords: *Corelation, hepatic enzymes. serum ions, Mortality of delirium tremens*

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I. Introduction

There are many dilemmas and controversies with respect to the prevalence, aetiology, pathogenesis, evaluation and management of delirium tremens (DT). According to national household survey(NHS) 2004, the prevalence of alcohol in India is 21.4%, regional variation of alcohol abuse is seen highest in north east belt of India.[1] Delirium tremens' is manifested by global confusion, agitation, disorientation, hallucination, hyperthermia, hypertension and sympathetic overdrive which can progress to cardiovascular collapse. Symptoms can appear 48-72 hours after alcohol cessation and has its highest intensity on the 4th or 5th day, characteristically worse at night [2].

Among patients with alcohol dependence treated in psychiatric hospitals, the annual prevalence of delirium was 4.9–7.4%, while in alcohol treatment settings it is 5–15%.[1]. It has always been an enigma as to what makes certain individuals vulnerable to a severe withdrawal state as compared to others. Research till date has implicated clinical, laboratory and alcohol use related variable hepatic enzyme level, altered serum ion as the offending factors.

There is dearth of study on factors such as, levels of serum electrolyte and hepatic enzymes in alcohol withdrawal patients as well as delirium tremens in North East India yet where regional variation of alcohol abuse is seen. Moreover it has been observed that many patients admitted with alcohol withdrawal in de addiction ward develop delirium tremens despite the cover up of conservative medication. Understanding the various factors associated with DT will be useful in predicting the occurrence of severe withdrawal state in the treatment of alcohol related disorders

With long-term alcohol consumption, in an attempt to maintain homeostasis, receptors in the brain undergo adaptive changes. When a person stops a prolonged drinking session, the adaptations that developed to

offset alcohol's initial inhibitory actions are unopposed, resulting in a rebound hyper-excitability or withdrawal syndrome [2] .

Alcoholics are already at higher risk of developing electrolyte disturbance due to vomiting, diarrhoea and malnutrition whilst drinking. **Serum Electrolytes** variation during alcohol withdrawal is still poorly understood. Homeostasis of **Serum Sodium [**Normal serum Na^+ = 135-155 meq/l] is maintained by antidiuretic hormone, aldosterone, atrial natriuretic peptide and renal hemodynamic factors . In compromised hepatic state, arterial pressure decreases, which leads to an increase in (ADH),catecholamine, aldosterone, and renin-angiotensin system causing sodium and water retention [3]. Hyponatremia occurs from a reduction in filtered sodium, an increase in sodium reabsorption in the proximal tubule, and a reduction in free water clearance [4].**Serum Potassium** [Normal reference value--3.5-5.5 meq/l] mostly as intracellular ion is important in determining the cellular membrane potential as small changes in the extracellular potassium level can have profound effects on the function of the cardiovascular as well as neuromuscular systems.. Hypokalemia can exacerbate hepatic encephalopathy by increasing renal ammonia genesis and systemic ammonia levels. Acid-base and potassium disorders occur frequently in the setting of liver disease[5]. A number of factors contribute to acid-base imbalance in liver disease[6] .1) impaired gluconeogenesis leads to metabolic acidosis, 2)abnormalities in the efficiency of the urea cycle can cause a reduction in bicarbonate use, and 3) a reduction in protein synthesis and primarily albumin in the setting of liver disease all contribute to changes in acid-base balance. Hyperventilation is an almost universal finding with advanced liver disease, leading to chronic respiratory alkalosis [5]. Anion gap represents the unmeasured anions in plasma and serves the first step to identify whether the acid base disorder,acidosis is due to retention of H^+, Cl^- or to another acid. The normal anion gap is measured by[7],

$$\text{ANION GAP} = [Na^+ + K^+] - [Cl^- + HCO3^-].$$

Alcohol acting as agonist on the GABA-A receptor complex, amplified chloride ion(Cl-) influx to a greater degree or more frequently. In the Alcohol Withdrawal State, sudden cessation of alcohol leads to altered function of GABA receptor complex**, leads to decrease chloride (cl-) ion influx and hyper excitability**.[8]
Magnesium ion(Mg^{++}) keeps the excitory N-methyl-D-aspartate (NMDA) ion channel complex in resting state, not allowing the channel to open by preventing to bind both Glutamate and Glycine in their respective sites. In alcohol withdrawal state these(NMDA) receptors are up-regulated, contributing to the delirium and neurotoxicity is noticed[8,9].

Different HEPATIC ENZYME represents as a marker for different pathological status of Hepatic function .Elevated Aspartate amino transferase (AST) are observed in parenchymal liver injury. [Normal AST--15-37 IU/l]. Alanine transaminase (ALT) is elevated in hepatic inflammation, either due to injury or disease process[Normal ALT—30-65 IU/l]. High levels of Gamma glutamyl transpeptidase/transferase (GGT) indicates cholestatic damage or alcohol toxicity [Normal value of GGT—8-85 IU/l].A rise in AST and ALT could indicate alcoholic hepatitis or cirrhosis of the liver.

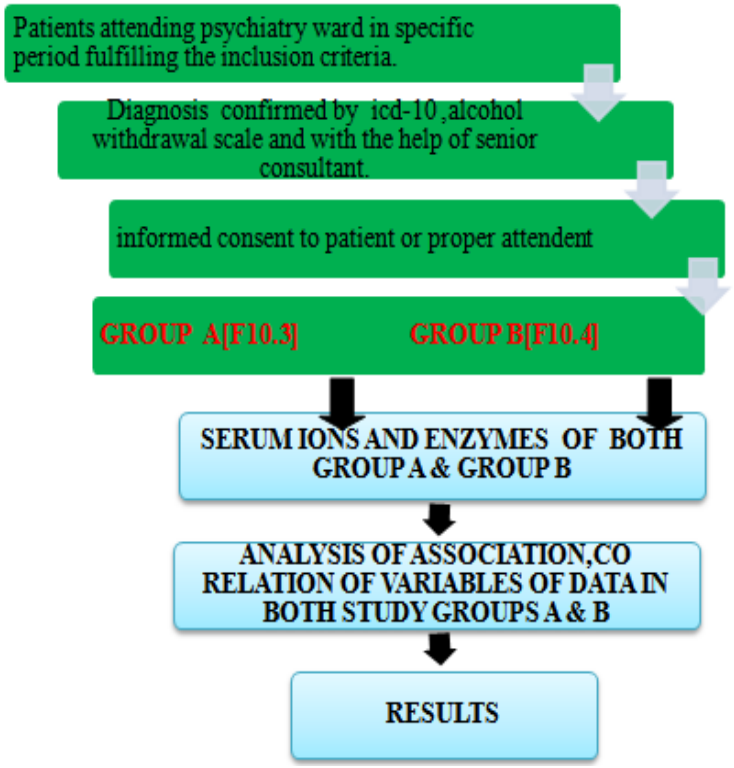
1.1) Aims and objectives---
To estimate the Level and study the correlation of Serum ions Na^+,k^+,Mg^{2+},Cl- with Hepatic enzymes AST,ALT,GGT in alcohol withdrawal with and without delirium tremens

1.2) Study Design: The study was a cross sectional study
The study was carried out in the department of psychiatry, Assam Medical College and Hospital, Dibrugarh, Assam after the ethical approval from the institutional review board and a written consent was obtained from every participant or their proper attendants. The study duration was of one year from August 2013 to July 2014.
Sample: They were taken serially from patients that were admitted during the one year period in psychiatry dept drug deaddiction center, Assam medical college, in drug naive state , who fulfilled the inclusion criteria. Those patients who were diagnosed as cases of **Alcohol Withdrawal** but not in delirium tremens **[Non DT (F10.3)]** forms group A and number of total cases was 50 in this group. **GROUP B** is composed of ALCOHOL withdrawal patients **with Delirium Tremens [DT Group** (**F10.4**)] and composed of 50 cases.
Inclusion criteria-- Patients of age group between 18-65 years, of both sexes giving written informed consent[or consent by proper attendant] for the study , diagnosed cases of alcohol withdrawal by ICD-10 and **confirmed by senior consultant psychiatrist.**

Exclusion criteria--Adults with History of functional psychiatric disorder, Other substance abuse except nicotine, Chronic debilitating illness, Delirium due to other causes**,** Head injury in past**,** Jaundice due to other known causes(viral, obstructive jaundice)**,**Benign or malignant brain tumor, Neurosurgical interventions in the past were excluded from the study
Assesment Tools-1)Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar)[10] 2)ICD-10 was used to diagnose alcohol withdrawal including delirium tremens[11].

2) Procedure:

All patients in the age group 18-65 years fulfilling the inclusion criteria were included for the study. For estimation of Serum ion(Na^+, k^+, Mg^{2+}, Cl)and hepatic enzymes(ALT, AST , GGT) 5 ml blood was collected from intravenous route in drug naive status on the first day of admission and estimation was done at advanced clinical biochemistry laboratory, dept of biochemistry. The alcohol withdrawal patients developing **Delirium tremens (F10.4)** formed one study group . Another group was selected with age and sex matched Alcohol withdrawal population, which are not with delirium tremens (**F10.3**).



Schematic diagram of the study procedure.

II. Methods For Biochemical Parameters

Estimation Of Serum Na+,K+,Cl----ion electrode Selective (IES) [12] technology

Estimation Of Serum Mg++ ---Calamagite method[13]

Estimation of ALT,AST and GGTP---In vitro diagnostic test for quantitive determination [14]

Comparison and analysis of the observed was done between group A (F10.3) and group B(F10.4) by using Statistical Package for the Social Sciences (SPSS-20).

III. Results

Subject Characteristics: At the end of one year data was studied from a group of 50 subjects with a diagnosis of alcohol withdrawal delirium tremens (F10.4) and another group of 50 subjects who were alcohol withdrawal not in delirium tremens (F10.3). It is evident from the age distribution data, that both the delirium and non delirium alcohol withdrawal groups are mostly middle aged person. The DT group has a mean age of 42.36 years with a standard deviation of 8.55 years and the non DT group also has mean age of 41.72 years with a standard deviation of 7.71 years. Males comprised mostly in of both the groups than females .

Estimation of Serum electrolytes level in both delirium (groupF10.4) and non delirium group(group F10.3)

Serum Na^+, k^+, Mg^{2+},and Cl^- was estimated on the first day of admission in drug naive state. **In the** delirium tremens blood samples, the mean values of different parameters are observed as; serum sodium (136.08 ± 5.669), serum potassium (3.17±0.611), serum magnesium (2.239 ± 0.314) and serum anion chloride (99.582 ±7.75). Serum level of hepatic enzymes ALT , AST and GGT was also estimated on the first day of admission from diagnosed alcohol withdrawal patients with DT at advanced clinical biochemistry laboratory, dept of biochemistry. Hepatic enzymes level dearranged and mean values of hepatic enzymes gama glutamyl transpeptidase(GGTP),alanine transaminase(ALT), aspartate trnsaminase (AST) were observed 847.71±718.75,

88.28±65.69, 198.74±159.75 respectively.

Table 1: among various age groups, level of serum ions Na+ ,K+, Mg++ , Cl- and hepatic enzymes ALT, AST, GGTP in DT CASE(F10.4)group.

AGE GROUP (years) (cases)	Serum Na+ (meq/dl)		Serum K+ (meq/dl)		Serum Mg+ (meq/dl)		Serum Cl- (meq/dl)		ALT (IU/dl)		AST (IU/dl)		GGT (IU/dl)	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
18-29 (n =2)	140.9	1.27	2.61	.68	2	.14	96	7.07	96.5	23.33	157	65.05	736	800.4
30-41 (n=21)	137.02	3.39	3.37	.58	2.27	.29	100.4	5.73	101.5	57.43	225.1	195.1	1052.2	956.9
42-53 (n=23)	137.11	5.34	3.04	.57	2.19	.25	99.83	7.7	80.96	39.23	192.3	131.46	749.68	418.14

In the non delirium alcohol withdrawal group , the mean value of serum sodium is 138.42 ± 3.5,.The mean value of serum potasium is 3.41± 0.52. The mean serum magnesium in the non delirium group is 2.43± 0.45. For serum anion chloride, the observed mean value is 101.55 ±4.87.

Table–2: Among various age groups, level of serum Na^+,K^+,Mg^{2+} and Cl- and hepatic enzymes ALT, AST, GGTP in non DT CASES(F10.3)

AGE GROUP(years) (cases)	Serum Na+ (meq/dl)		Serum K+ (meq/dl)		Serum Mg++ (meq/dl)		SERUM Cl- (meq/DL)		ALT (IU/dl)		AST (IU/dl)		GGT (IU/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	MEAN	SD	MEAN	SD	MEAN	SD
18-29 (n=3)	134.16	4.45	3.51	.02	2.03	.05	95.5	6.8	81.66	7.57	127.66	27.59	484.6	411.6
30-41 (n=18)	140.24	2.54	3.38	.44	2.5	.31	103.7	3.9	118.9	71.8	153.33	71.7	552.8	309.8
42-53 (n=25)	137.8	3.65	3.49	.58	2.37	.44	100.9	4.74	93.6	59.8	129.4	75.79	415.2	319.4
54-65 (n=4)	136.9	2.5	2.9	.457	2.8	.914	100.3	4	112.4	33.07	185.77	126.52	818.7	165

The dearrangement of hepatic enzymes is also noted in the non delirium (F10.3) group. Mean values of GGTP, ALT, AST are observed as 501.2± 323.82, 103.54± 61.52, 142.44± 76.84 respectively.

Correlation of hepatic enzymes and serum ion level in F10.4 and F10.3group

The correlation factor is studied between the enzyme level and the serum ions level to rule out any positive or negative correlation in both delirium (F10.4) and non delirium (F10.3) group.

Table–3: co relation of hepatic enzyme alanine transaminase (ALT) with serum electrolytes in Group A (F 10.3)

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
ALT (93.6±59.8)	MEAN	138.42	3.41	2.43	101.55
	SD	3.559	.5206	.4572	4.87
Co relation r		+0.025	+0.084	+0.028	+0.160

***r value significant>±0.5**

In the non delirium group (F10.3) The relation between hepatic enzyme ALT with serum ions Na^+, K^+, Mg^{2+} is studied and there is no correlation observed between ALT level and serum ions with correlation factor 0.025, 0.084, 0.028 respectively(tab-3). However, In the delirium group (F10.4) , there is a **strong positive relationship between serum K+ and ALT** with r value +0.902. No relationship of ALT with other parameter serum Cl- ,Mg , Na^+ is noticed in this group(tab-4).

TABLE–4: co relation of hepatic enzyme **alanine transaminase (ALT**) with serum electrolytes in **GROUP B (F10.4)**

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
ALT (80.96±39.23)	MEAN	136.08	3.17	2.239	99.582
	SD	5.669	.611	0.314	7.75
Co relation r		+0.218	**+0.902***	-0.113	+0.099

***r value significant>±0.5**

The hepatic enzyme AST has no corelation observed with serum K, Mg, Cl- in the non delirium group (F10.3) with r value -0.036,-0.099,-0.0307 respectively.(TAB-5)

Table–5: co relation of hepatic enzyme Aspartate Aminotransferase (Ast) With Serum Electrolytes In Group A(F 10.3)

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
AST (129.4±75.79)	MEAN	138.42	3.41	2.43	101.55
	SD	3.559	.5206	.4572	4.87
Co relation r		+0.049	-0.036	-0.099	-0.0307

***r value significant>±0.5**

In the delirium group (F10.4) also, correlation is not found between serum ion Na+, k+ ,Mg++, Cl- level with AST. The serum Na+ ,k+, Cl- has a tendency towards positive relationship with AST however serum Mg maintains a tendency of negative relationship with AST(tab-6).

TABLE–6: co relation of hepatic enzyme aspartate aminotransferase(ast) with serum electrolytes in Group b (f10.4)

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
AST (192.3±131.46)	MEAN	136.08	3.17	2.239	99.582
	SD	5.669	.611	0.314	7.75
Co relation r		+0.238	+0.047	-0.086	+.090

***r value significant>±0.5**

The GGTP has no correlation ship observed with serum parameters Na+, k+, Mg++, cl- in non delirium group (F10.3).The serum K+ has a tendency of negative correlation with GGTP where as serum Mg maintains a tendency of positive correlation(tab-7)

Table–7: Co Relation Of Hepatic Enzyme Gamma Glutamyl Transpeptidase (Ggt) With Serum Electrolytes In Group A (F10.3)

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
GGT (415.2±319.4)	MEAN	138.42	3.41	2.43	101.55
	SD	3.559	.5206	.4572	4.87
Co relation r		-0.0018	-0.123	+0.153	-0.0157

***r value significant>±0.5**

In the delirium group (F10.4),There is no correlation ship with GGTP and serum ion. The serum ions Na, Mg and Cl- maintains a tendency of positive relationship with GGTP whereas serum K+ maintains a tendency towards negative relationship(r=-0.029) with GGTP in delirium tremens group.(tab-8)

Table–8: Co Relation Of Hepatic Enzyme Gamma Glutamyl Transpeptidase(Ggt) With Serum Electrolytes In Group B(F10.4)

VARIABLES		Serum Na^+	Serum K^+	Serum Mg^{2+}	Serum Cl^-
GGT (749.68±418.14)	MEAN	136.08	3.17	2.239	99.582
	SD	5.669	.611	0.314	7.75
Co relation r		+.1235	-0.029	+0.0964	+0.1974

***r value significant>±0.5**

IV. Discussion

A sincere attempt is given to evaluate the factors and biochemical changes in delirium tremens in this study. Data related to 50 patients with delirium tremens and 50 age and sex matched alcohol withdrawal without delirium tremens (F10.3) were interpreted and evaluated with ICD 10 and CIWA scale, at the end of 1 year. The age of participants in both the group ranged between 18 to 65 years. The group (F10.3) consisted of 48 males

and 2 females. The study group (F10.4) consisted of 49 males and 1 females. The correlation of hepatic enzyme and serum ions are studied in both delirium and non delirium group to find out any predictive value for the occurrence of delirium tremens.

In the non delirium (F10.3) group hepatic enzyme AST has no correlation but a tendency of a positive correlation is observed(r= +.04) with serum Na+, the other serum ions (k+, Mg++, Cl-) has also no correlation, but they have a tendency of negatively correlation (r= -0.03, -0.09, -0.03) respectively with AST. Enzyme GGTP has also no correlation with serum ions. However with serum Mg++, a tendency to positive correlation (r= +0.15) is observed. ALT has a tendency but the correlation is not significant with correlation factor r=+0.02, +0.08, +0.02, +0.16 with Na+, K+, Mg++, Cl- respectively . In the delirium (F10.4) group serum AST has no correlation with serum ions, It has a tendency of positive correlation with correlation factor r= +0.23 with Na+ . Enzyme GGTP has a tendency of positive correlation factor r=+0.12,+0.09,+0.19 with Na+ ,Mg++,Cl- respectively. it is observed in delirium group that, ALT has **strong positive** correlation with K+ (r= +0.90) and with other ions ALT has no significant correlation. A tendency of a positive correlation is observed with Na+, and Cl- with r value+0.21,+0.09 respectively and with Mg++ the tendency is weakly negative(r= -0.11).

There is no such type of literature found where correlation between serum ions and hepatic enzymes are revealed. Literature revels in one study done by Laso F J et al [15] found a close negative correlation (r= -0.751) between severity of alcohol withdrawal and serum K+ ion level. Brasiskiene et al [16] observed a negligible correlation among the concentrations of serum macro and microelements(K, Na, Mg, Ca, Sr, Cr, Mn, Fe, Cu, Zn, Cd, Ni, Co and Pb) and of liver enzymes (ALT, AST, ALP and GGT) in human blood plasma from non-infected patients, those infected with hepatitis C virus and from patients with viral C cirrhosis. Himmerich H et al [17] found a significant positive Spearman correlations between vitamin B12 and hepatic enzyme (GGT: $r_S = 0.58$; ALT: $r_S = 0.43$; AST: $r_S = 0.47$;) in their study of serum Vitamin B12 levels and markers for alcohol consumption in 80 male alcohol-dependent patients. Ibrahim A et al[18] observed that deranged liver functions, especially GGT, had the strongest correlations with obesity and insulin resistance in Saudi adults with restricted alcohol intake.

In our study, we got a positive strong correlation between serum potassium ion with ALT enzyme; it is a novel finding. Further investigations are needed to prove the impact of serum ions on the activity of liver enzymes and their relationship with the alcohol withdrawal serum. The possible explanation in this regard is that ALT is a marker of hepatic cell injury; in chronic inflammation of hepatic cell, gluconeogenesis is impaired, and leads to accumulation of lactic acid and decreased albumin production, which will progresses to metabolic acidosis that may lead to hyperkalemia. Further study in this field will determine about this correlation and the mechanism between these two factors, their implication in delirium tremens management.

V. Conclusion

The present study has shown that delirium tremens patient have a considerable amount of derangement in both hepatic enzyme and serum ions level than non delirium alcohol withdrawal group. There was very weakly correlation between hepatic enzymes and serum ions in both F10.4 and F10.3 group. But in delirium tremens group serum K+ had a positively strong correlation with hepatic enzyme ALT with correlation factor (r=+0.902).

Strengths Of The Study

The current study is for evaluation of biological parameters of cases who develop Delirium Tremens and parameters are compared with age and sex matched alcohol withdrawal non delirium group. Detailed clinical assessment was conducted and all the indicated laboratory investigations; ie for hepatic enzymes and serum ions were performed in advanced biochemical laboratory, Assam medical college.

Limitations

1)The study involved one-time assessment and lacked follow up. The reason for this was time constraint. 2)The sample size of the study was small.3)Cases included were those which were in drug de-addiction centre, psychiatry department which may have with less medical co morbidity. However, As alcohol is known to be associated with various medical conditions and higher morbidity and mortality, the case selection may have had an influence on the current findings.4)Cases included were those with habit of different types of alcohol; homemade, country made, Indian made foreign liquor etc where percentage of alcohol are variable and duration of alcohol taking habit were also variable.

Future Implications

This study, a holistic approach is emphasised towards alcoholism and alcohol withdrawal care. Apart from the physical sign symptoms, the derangement in serum level should be taken for better treatment of

alcohol withdrawal patients. Targeting and correcting the sources or dearranged serum anions and cations can prove to be a key factor in the treatment , survival as well as healthy quality of life for patients.
Further studies are needed to address the various deranged serum parameter as a predictor in patients with delirium tremens, as well as the correlation of hepatic enzymes with serum ions in alcohol withdrawal patient. In the management of DT by correcting the serum ions which correlated with deranged hepatic enzymes, to cut short delirium duration as delirium tremens is itself a dreaded complication in alcohol withdrawal patients, especially in the Indian context where very few studies have dealt in this area.

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Declaration of interest: None

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