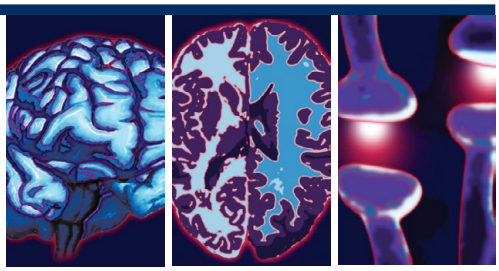
Research



Whole Blood Thiamine Levels and its Relationship with Severity of Alcohol Withdrawal and Neurological Soft Signs in Patients with Alcohol Use Disorder

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Abstract

Objective: Thiamine deficiency has often been reported in patient with alcohol use disorder and its role in alcohol withdrawal is unclear. This study was conducted to find out levels of whole blood thiamine in patients with alcohol use disorder and its relationship with demographic variables, severity of alcohol withdrawal symptoms and neurological soft signs.

Methods: A total of 60 consecutive male patients with alcohol use disorder were recruited and assessed with Sociodemographic and clinical data sheet, Clinical Institute Withdrawal Assessment for Alcohol Scale and Extended Standard Neurological Assessment Instrument. High Performance Liquid Chromatography was used for assessing levels of whole blood thiamine level. Mean whole blood thiamine level was 8.7 (SD ± 12.9) µg/l. Seventy percent of patients developed withdrawal symptoms, while more than half of the patients had neurological soft signs. In multiple regression analysis seven predictors explained 31.6 % of the variance (R^2 = .316, F = 3.430, p < 005) of whole blood thiamine levels. The two predictors that statistically significantly predicted the value of whole blood thiamine level were duration of the current episode of alcohol intake (Beta= - .357, t= - 2.889, p< .001) and quantity of daily alcohol intake (Beta = - .259, t =- 2.122, p < .05). Score of neurological soft sign and withdrawal score did not predict significantly the whole blood thiamine level.

Conclusions: Based the finding of this study, it may be concluded that low levels of whole blood thiamine is common in patient with alcohol use disorder and positively associated with quantity & duration of alcohol intake. Severity of alcohol withdrawal and soft neurological signs are not associated with whole blood thiamine levels.

Keywords: Thiamine; Alcohol withdrawal; Neurological soft signs; Alcohol use disorder

Introduction

Thiamine (Th) is a water soluble vitamin, stored as thiamine diphosphate /pyrophosphate [1]. In patient with Alcohol Use Disorder (AUD) decrease in dietary intake and malabsorption are often the cause of Thiamine Deficiency (TD) [2-4]. Th plays a vital role as coenzyme, in glycolysis and the citric acid cycle.These metabolic cycles maintain the level of the neurotransmitters such as glutamate, gamma amino butyric acid and aspartate in the brain, which believed to mediate the Alcohol Withdrawal Symptoms (AWS) in patients with AUD[5]. However the role of Th in the pathogenesis of AWS is unclear. Some studies did not find differences in erythrocyte transketolase activity between patients with

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severe AWS and control while other had conflicting reports[6-10].

The most severe complication of TD is Wernicke's Encephalopathy (WE) characterised by a triad of ocular abnormalities, ataxia, and a global confusional state[11]. However, in most cases of WE the classic triad is not observed[11,12]. Thomson et al. reported that only about 10% of patients present with the classical triad of signs, and we might be failing to detect neurological deficits or mild form of disease in up to 90% of patients[4]. This finding was also supported by post-mortem and other studies[13,14]. The TD leads to atrophy of different part of the brain, which may present as Neurological Soft Signs (NSS)[11]. Up to ninety percent of neurological deficits caused by TD may persist for months in milder form, even after the treatment with Thiamine[11,15]. NSS may be missed as they are not apparent on conventional neurological examination[16].There is no published report that examined the milder form of neurological signs in relation to the whole blood thiamine level in patients with AUD. Hence this study was conducted to find out the relationship of severity of AWS and NSS with Whole Blood Thiamine Levels (WBTL). We have hypothesized that clinical variables, AWS and NSS can predict the value of the WBTL.

Accurate estimation of the blood Th levels is challenging. Blood pyruvate concentration, erythrocyte transketolase activity and thiamine pyrophosphate effect are not specific and influenced by the factors other than TD[17-20]. Thus, in this study, direct high performance liquid chromatographic method was used to measure the principal physiological form of Th, thiamine pyrophosphate in erythrocytes, a tissue that has been shown to be a good indicator of body Th store[21,22].

Material and Methods

This hospital based study was conducted at the Centre for Addiction Psychiatry, Central Institute of Psychiatry, Ranchi, India. The inclusion criteria were male aged 18 - 55 years, a diagnosis of moderate to severe AUD as per Diagnostic and Statistical Manual of Mental Disorders, 5th edition, last drink ≥ 12 hours before the assessment and stay of two weeks as an inpatient [23]. Patients were excluded if they have received any pharmacological treatment for AUD within the past one month or receiving any psychotropic medications, as it can influence the severity and course of AWS. For the same reason patients with a history of other psychoactive substance dependence (except nicotine dependence), co-morbid psychiatric or chronic physical disorder, significant head injury, epilepsy or neurological disease were also excluded. Out of seventy six consecutive admitted patients with AUD, sixty consented to participate in this study. Before receiving any treatment, patients were assessed with Sociodemographic and clinical data sheet design for this study and Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar)[24]. A detailed physical examination was done and blood samples were collected in an Ethylene Diamine Tetra Acetate (EDTA) anticoagulated vial. Except for Th estimation, all other blood examinations were done on the same day. Then treatment was started as per treating psychiatrist including standard detoxification with Tab Lorazepam, Injection thiamine 100 mg intravenous daily for a week, followed by tablet thiamine 100 mg twice daily for the next week. Blood sample for analysis of WBTL was stored in a closed vial at -20°C, protected from light and was analyzed later in a High Performance Liquid Chromatography (Breez company, Germany) using a fluorescence detector-EX 367 nm, EM 435nm. Data were obtained through inbuilt breeze computer software that calculates the area and height obtained in the chromatogram. To avoid confusion between withdrawal symptoms and NSS, the Extended Standard Neurological Assessment Instrument (ESNAI) was performed after two weeks of abstinence during inpatient treatment [25].

Data were analyzed using SPSS 16.0. Descriptive statistics were used to express demographic and clinical variables. Multiple regression analysis was done (using enter method) to know if clinical variable, withdrawal score (score on CIWA-Ar) and NSS score (score on ESNAI) can predict the value of the WBTL. The significance level of results was set at $P < 0.05$.

Results

In this study, the majority of the patients were educated Hindu with a family history of AUD **(Table 1)**. The mean amount of alcohol intake was 52.5 (SD ± 31.9) units per day; while mean whole blood thiamine level was 8.7 (SD ± 12.9) µg/l. Mean duration of the current episode of alcohol intake was 2.6 (SD ± 2.0) years. AWS score and NSS score had a

mean of 3.5 (SD ± 2.0) & 24.6 (SD ± 7.5) respectively **(Table 2)**.The common AWS were tremor (95%), anxiety (92%), nausea-vomiting (77%), agitation (58%), paroxysmal sweating (50%) and headache (45%) **(Table 3)**. Common NSS were tremor (70%), right-left confusion (oneself) (51%), dysdiadochokinesia (28%) and graphesthesia (21%) **(Table 4)**.

In multiple regression analysis, seven predictors explained 31.6 % of the variance (R^2 = .316, F = 3.430, p < 005) of Th levels, out of which two predictors, duration of current episode (Beta = -.357, t = -2.889, p < .001) and quantity of daily alcohol intake (Beta = - .259, t = - 2.122, p < .05) had statistically significantly predicted the value of WBTL **(Table 5)**.

Discussion

■ Sociodemographic and Clinical Features

Demographic and clinical characteristics observed in this study were similar to other studies conducted in India among patients with AUD, and Indian socio-cultural background have been attributed for such observation [26,27]. Mean of WBTL was 8.7 (SD ± 12.9) µgm/l; lower than the normal reference range (18-100 µg/l). In patient with AUD regular intake of alcohol impairs Th absorption, transport and utilization[28,29]. Poor dietary intake and any attempt to compensate energy requirement with high caloric carbohydrate diet further reduces Th level. Lower mean level of thiamine indicates that study population were predisposed to develop the ramification of TD. Thiamine is required as a cofactor for the enzymes transketolase, Pyruvate Dehydrogenase (PDH) and Alpha-Ketoglutarate Dehydrogenase (α-KGDH). In pentose phosphate pathway, glucose-6-phosphate (a molecule derived from the sugar glucose) is modified by transketolase to ribose-5-phosphate and a molecule called reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH). Ribose-5-phosphate is needed for the synthesis of nucleic acids and complex sugar molecules, while NADPH needed for synthesis of steroids, fatty acids, amino acids, certain neurotransmitters and glutathione. PDH and α-KGDH participates in glycolysis and the citric acid cycle that are responsible for the generation of Adenosine Triphosphate (ATP), which provides energy for numerous cellular processes and reactions; and reduced ATP synthesis contribute to cell damage and even cell death [30].

Table 1: Demographic Characteristics

Variables		n = 60
Age	< 30 (Years)	14 (23%)
	> 30	46 (77%)
Marital status	Unmarried	8(13%)
	Married	52 (87%)
Education	Uneducated	3(5%)
	Primary	6 (10%)
	Middle	5(8%)
	High School	28(47%)
	Graduate	18(30%)
Religion	Hindu	35(58%)
	Muslim	3(5%)
	Christian	22 (37%)
Occupation	Unemployed	15 (25%)
	Employed	45(75%)
Family history of mental illness	Present	32(53%)
	Absent	28 (47%)

Table 2: Clinical Characteristics

Variables	Mean ± SD
Age at onset (years)	25.2 ± 8.1
Total duration (years)	11.6 ± 6.8
Duration of current episode alcohol intake (years)	2.6 ± 2.0
Quantity of alcohol intake per day (Unit)	52.5 ± 31.9
Total score on withdrawal (no)	65.0 ± 42.3
Total no of neurological sign (no)	3.5 ± 2.0
Hemoglobin (gm/dl)	12.8 ± 1.5
Total Bilirubine (mg/dl)	1.3 ± . 6
Whole blood thiamine (µg/l)	8.7 ± 12.9
SGOT (U/ml)	106.9 ± 82.3
SGPT (U/ml)	71.2 ± 46.0
Sodium (mmol/l)	139.8 ± 6.7
Potassium (mmol/l)	3.9 ± . 5

Table 3: Frequency of alcohol withdrawal

Variables	n=60 (%)
Nausea and vomiting	46 (77%)
Tremor	57 (95%)
Paroxysmal sweat	30 (50%)
Anxiety	55 (92%)
Agitation	35 (58%)
Tactile disturbance	12 (20%)
Auditory hallucination	9 (15%)
Visual disturbance	8 (13%)
Headache	27 (45%)
Impaired orientation	15 (25%)

More than 90% of patients experienced AWS, and most common was tremor followed by anxiety. In India, patients with AUD usually seek medical help, when they suffer from severe symptoms or associated physical / psychosocial adversity. Since this study was conducted among inpatients and a selection criterion

Table 4: Frequency of soft neurological signs

Signs	n (%)	Signs	n (%)
Gaze impersistence	2 (3.3)	Tapping rhythms	2 (3.3)
Gaze nystagmus	2 (3.3)	Right left confusion (oneself)	31 (51.7)
Stereognosis	5 (8.3)	Intension tremor	23 (38.3)
Finger/thumb opposition	8 (13.3)	Postural tremor	42 (70.0)
Graphesthesia	13 (21.7)	Resting tremor	31 (51.7)
Blunt/sharp discrimination	7 (11.7)	Gait deviation	14 (23.3)
Dysdiadochokinesia	17 (28.3)	Whole body clumpsiness	7 (11.7)
Two object test	2 (3.3)	Unilateral sensory loss (central)	1 (1.7)
Complex motor acts	3 (5.0)	Unilateral coagwheel rigidity	1 (1.7)

Table 5: Predictors of whole blood thiamine levels

Model	Predictors	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	56.619	37.294		1.518	.135
	Age	- .307	.632	- .184	- .486	.629
	Age at onset	.086	.612	.054	.140	.889
	Duration of current episode	- 2.215	.767	- .357	- 2.889	.006
	Total Withdrawal Score	.118	.575	.062	.205	.838
	Quantity of alcohol intake	- .004	.002	- .259	- 2.122	.039
	Score on SNA	- .500	.795	- .081	- .629	.532
	Withdrawal score on CIWA	- .500	.377	- .179	- 1.327	.190

Dependent Variable: whole blood thiamine
$R^2 = .316, F = 3.430, p < 005$

was moderate to severe AUD, they were more likely to experience withdrawal symptoms. Chronic alcohol use results in neroadaptation characterised by up-regulation of NMDA, Ca channels, Dopaminergic and Noradrenergic system; and down regulation GABA. Withdrawal symptom that starts after the cessation of alcohol intake is due to relative hyperactivity of NMDA receptors and hypoactivity in the GABA, overstimulation of noradrenergic neurons and loss of noradrenergic autoinhibition, neuroexcitation due to an increased calcium flux and a reduced chloride shift in CNS neurons and transisent hyperthyroid state that potentiate noradrenergic hyperactivity [27] .

More than half of the patients had NSS such as tremor, right left confusion and dysdiadochokinesia. This finding was consistent with other study that reported common NSS as blunt vs. sharp discrimination, dysdiadochokinesis & graphesthesia that were not apparent on conventional neurological examination [16].

Anatomical structures likely to be involved in TD associated soft-neurological sign are cerebellum, in pons, mammillary bodies, hippocampus, thalamus, cerebellum, and the frontal cortex. Microscopic pathology are characterised by neuronal loss, gliosis and vascular damage. At cellular level major pathophysiological mechanism implicated in pathogenesis of TD is excitotoxicity that occurs in area of focal vulnerability as a consequence of impairment in mitochondrial energy metabolism, sustained cell membrane depolarization and decreased uptake of glutamate by astrocytes due to the loss of excitatory amino acid transporters. Cerebellum is sensitive to thiamine deficiency and thought to be the initial target of alcohol-related damage. It is connected to the basal ganglia and thalamus to the frontal lobe through a pathway that mediates motor control, perceptual– motor tasks, executive functions, and learning and memory, all of which are impaired in person with alcohol use disorder [30]. Also, alcohol itself can alter the structure and function of brain in patient with AUD and is responsible for the development of neurological sign and symptoms [31, 32].

■ Predictors of whole blood thiamine levels

We observed that the amount of daily drinking and duration of the current episode of alcohol intake significantly predicted the value of WBTL in regression analysis with a negative beta coefficient. In other word value of WBTL decreased when there was an increase in the duration of the current episode of alcohol intake or quantity of alcohol intake per day. As mentioned earlier, regular alcohol intake interferes the absorption of Th from the gastrointestinal tract and lesser quantity is converted to active forms [2-4,8,22,29,33,34]. Regular intake of large amount alcohol may proportionately hamper Th absorption. Longer duration of regular intake may constantly hamper the amount of Th absorption. Impaired liver function that commonly accompanies AUD (as observed in this study) further aggravates the deficiency state [33].These findings also support the empirical use of routine Th use during detoxification.

In this study withdrawal score did not predict significantly the value of WBTL. However, there was negative beta coefficient observed during regression analysis. Though statistically non-significant inverse relationships were observed between WBTL and withdrawal score, Th did not emerge as a significant cause for severity of withdrawal symptoms, and this finding was consistent with the previous report [8,22]. It appeared that the observed withdrawal symptoms and thiamine level are consequences of alcohol use, and are independent of each other. Moderate

to severe AUD led to the lower thiamine level and more withdrawal symptoms and this trend might have emerged as inverse relationship. However, the severe TD may manifest as associated symptoms such as irritability, fatigability, muscle cramp, paresthesia, incoordination and altered sensorium along with alcohol withdrawal symptoms in severe withdrawal state [35].

The score of NSS did not predict significantly the value WBTL in this study, though a negative beta coefficient was observed. Since all patients received Th daily, it was likely that neurological signs associated with low Th levels improved at the end of two weeks when it was assessed. Other possibilities are that NSS is determined combined effect of thiamine and other factors, or like other psychiatric disorder such as mood disorder, anxiety disorder and psychotic disorder, NSS may also accompany AUD.

Based on the finding of this study it can be concluded that patient with AUD may have low levels of whole blood thiamine. Duration of the current episode and quantity of daily alcohol intake may predict WBTL in patient with AUD admitted in a tertiary care centre for de-addiction. These findings support the current recommended dose (100 mg IV/PO daily) for Th replacement. Though our hypothesis was largely untrue, the result should be interpreted with caution as the sample size was small, the study was conducted at a tertiary care centre by consecutive sampling, diet habit was not assessed, only male patients were included and there was no control group.

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