Research Article

Cognitive functioning in Wernicke's encephalopathy following chronic alcoholism

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ABSTRACT

Background: Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome caused by a deficiency of thiamine (Vitamin B1) in chronic alcoholics. In chronic alcoholics, there is always deficiency of thiamine because of an inadequate supply of thiamine and neurotoxic effect of alcohol. The thiamine deficiency in the neuronal cells of the brain usually results in cognitive dysfunctions in chronic alcoholics. **Objectives:** To assess the memory functioning, intelligence, spatial ability, and visuomotor coordination in patients with WE following chronic alcoholism. **Materials and Methods:** This study was conducted in the Deaddiction Centre of Mental Health Institute (COE), S.C.B. Medical College and in another Deaddiction Centre of Cuttack. A total number of 34 cases, among 70 cases of chronic alcoholics, had symptoms of WE (global confusion, unsteady gait, and ophthalmologic signs) during admission and were finally selected for the study. The study was conducted from July 2014 to 2016. PGI-battery of brain dysfunction was administered to assess cognitive functioning of these patients, after 1-2 months of the admission in the Deaddiction Centre. **Results:** Findings suggested dysfunctions in attention-concentration, recent memory, mental balance, immediate recall, delayed recall, visual retention, recognition, abstract reasoning, planning, visual acuity, depth perception, and visuomotor coordination domains of neurocognitive functioning. **Conclusion:** It is highly essential to take into account the cognitive dimensions of chronic alcoholics before preparing their treatment plan in the long-term management while the patients are in the rehabilitation phase or in the domiciliary treatment and palliate their difficulties in activities of daily living.

KEY WORDS: Wernicke's Encephalopathy; Vitamin B1 (Thiamine); Cognitive Dysfunction; Memory

INTRODUCTION

Chronic abuse of alcohol leads to the development of variety of mental and physical health morbidities over the years. All the organs of the body are affected by the overuse of alcohol including the basic cognitive functioning of the brain. Wernicke's encephalopathy (WE) is a neuropsychological dysfunction affecting the cognitive dimension of the brain after long-term abuse of alcohol due to deficiency of thiamine (Vitamin B_1). Lifetime prevalence of WE following chronic alcoholism in the developed world is around 1% (0.4-2.8%) according to various studies.[1] The prevalence rate of WE as estimated from postmortem studies is 1% to 2% of the general population and in chronic alcoholics, it is around 10%.[2,3] The prevalence of WE varies throughout the world in different countries in different studies, which were 0.2-2% in the USA, 1.7-2.8% in Australia, and 0.5% in the UK.[2,3] Among the patients of WE, there is a history of chronic alcoholism in 77-90% of cases, and most of the patients have a clear history of malnutrition.[4,5] Again in neuropathologic studies of chronic alcoholics, WE is found in 8.9-12.9% of patients.[6,7]

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WE was described in 1881 by a German physician Karl Wernicke (1848-1905) as an acute illness affecting the persons with chronic alcoholism.[8] The early symptoms of WE are acute global confessional state, ataxic or unsteady gait, impairment of consciousness, paresis of ocular muscles, and nystagmus.

The cardinal features of WE are: (a) Disorders of mental state or confusion, (b) oculomotor abnormalities, and (c) stance and gait ataxia. Usually, on examination, only one or two of the cardinal features of WE are found, and all three symptoms are found only in one-third of patients. The most common feature is global confusional state, lethargy and apathy often without prominent agitation. Attention-concentration and memory are generally impaired in most of the cases and in severe cases delirium tremens, stupor and coma are present. Similarly, the gait ataxia is found in majority of patients which varies from mild imbalance and unsteadiness with difficulty in tandem (heel to toe), walking to wide based shuffling or ataxic gait. Polyneuropathy is seen among (60-82%) of patients affecting both the extremities (25%) or affecting the lower extremity (57%).[9] In chronic alcoholics, the polyneuropathy is generally seen early or shortly before the patients presenting with WE symptomatology adding to neurological complication of the disease.

In 2001, The Royal College of Physicians published guidelines on the diagnosis and treatment of WE (A presumptive diagnosis of WE).[10] Important additions to those are recommendations by Thomson and Marshall on the treatment of patients at risk of developing WE in community.[11] On the basis of this criteria, diagnosis of a presumed WE among alcoholics requires patients having a history or signs of chronic alcohol misuse and any of the following symptoms: Acute confusion (not due to intoxication), delirium tremens, memory disturbances, decreased conscious level, ophthalmoplegia or nystagmus, ataxia (not due to intoxication), or unexplained hypothermia with hypertension should be presumed to have WE.

In chronic alcoholics, there are multiple reasons of thiamine deficiency which are: Nutritional deficiency with a coexisting decrease in thiamine intake, repeated diarrhea, and vomiting.[12] Again in addition, human liver stores a larger part of thiamine which is supplied to the body and in chronic alcoholics, because of liver dysfunction it's capacity of storing thiamine is reduced. The additional load of requirement of thiamine is increased after increase of the metabolic rate of the body which happens in situations such as alcohol withdrawal, delirium tremens, and infections in chronic alcoholics.[13] Due to decreased utilization of thiamine [lower fraction of thiamine in its active form as thiamine diphosphate, the formation of active thiamine-requiring enzyme such as transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase is inhibited in chronic alcoholics which are the key enzymes in the glucose and amino acid metabolism. In addition to that, in chronic alcoholics, there occurs up-regulation of N-methyl-D-aspartate (NMDA) receptor that appears to increase the neurological damage in thiamine deficiency through NMDA receptor-mediated excitotoxicity.[14,15]

The characteristics of cognitive impairment in WE are: Deficit in attention and concentration, visuospatial ability, verbal fluency, planning and organization and shift of set, and error utilization.[16] Chronic alcoholics show impairment is several cognitive domains including memory, abstract ability, motor efficiency, visuospatial integration, and learning[17] In chronic alcoholism, which is associated with impairments in information processing, attention and concentration, memory, and concept formation that lead to progressive difficulty in activities of daily living (ADL) and ultimately leading to disruption of quality of life (QOL). Chronic alcoholics having a history of prolonged period of drinking have greater deficits in abstract abilities and conceptual shifting independent of age.[18] Through the cognitive deficit improve over the passage of time, the performance of alcoholics does not attend the baseline level ultimately impair of attention, memory, and planning lead to a reduction in information processing ADL and QOL.[19]

Computed tomography (CT) scan and magnetic resonance imaging findings of the patients in different stages of WE always added to clinical examination and neuropsychological assessment always hold the key for early diagnosis, therapeutic intervention, and ultimately management of the patients.[20]

Hence, this study was planned with the objective to assess the memory functioning, intelligence, spatial ability, and visuomotor coordination in patients with WE following chronic alcoholism.

MATERIALS METHODS

Type of Research Design

The study was a cross-sectional descriptive study design.

Procedure

This study was conducted in the Deaddiction Centre of Mental Health Institute (COE), S.C.B. Medical College, Cuttack, and in another Deaddiction Centre of Cuttack, Odisha, India. A total number of 70 cases of chronic alcoholics were recruited for the study. Among these patients who had symptoms of WE (global confusion, unsteady gait, and ophthalmologic signs) during admission were finally selected for the study. The study was conducted from July 2014 to 2016. The information was collected from the patients as well as from the caregivers. Those who had interested in taking part in this study were included. Through the semi-structured interview, all information were recorded in a scientifically designed structured performa,

i.e., sociodemographic data sheet. PGI-battery of brain dysfunction (PGIBBD) was administered to these patients after 1-2 months of the admission in the Deaddiction Centre when the patient became communicative and physically stable for administration of test materials. The consent was taken from the patients and the caregivers to take part in the study.

Sample Design

Purposive sampling method was used for selecting the patients for the study. A total of 70 chronic alcoholic patients were taken for the study. Out of 70 patients, only 34 patients were fulfilled the criteria of WE on whom PGIBBD was administered to assess their cognitive functioning.

Inclusion Criteria

i) Patients who are diagnosed as alcohol dependence according to the research criteria of ICD-10.[21]
ii) Those who fulfilled criteria of presumptive diagnosis of WE.[10]
iii) Those who are in between age range of 20 and 55 years.
iv) Patients with duration of alcohol intake are at least 10-30 years are included.
v) Abstinence from alcohol for at least 4 weeks.
vi) Not taking any psychotropic drug for at least 2 weeks.
vii) Negative history of head injury, clinically apparent medical/neurological problems, previous history of psychiatric illness including dementia, mental retardation, and any other drug abuse.

Tools Used

i. A semi-structured performa especially designed for the study purpose was used for collecting data from patients and caregivers containing sociodemographic details of the patient, duration of alcohol consumption, age of onset, frequency of taking alcohol, period of abstinence of alcohol, family history of mental illness, etc.
ii. PGI-BBD: This test has been developed by Pershad and Verma to assess neurocognitive functions. PGIBBD consists of five subtests, i.e. Memory Scale, Bhatia's Battery of Performance Intelligence Scale, Verbal Adult Intelligence Scale, Nahor-Benson test, and Bender-Gestalt test.[22]

Statistical Analysis

Categorical variables were analyzed using frequency and percentages. Continuous variables were analyzed by mean and standard deviation. Data analysis was performed by SPSS, Version 11.0 (SPSS Inc. Illinois, USA).

Ethical Clearance

Institutional Ethics Committee clearance was obtained before the commencement of the study.

RESULTS

All the patients are male and belonging to Hindu religion (n = 34). Mean age of these patients is 43.64 ± 6.62 years. Mean duration of alcohol intake is 18.85 ± 6.38 years. Mean duration of onset of psychiatric symptoms in these patients is 25.85 ± 5.24 months. Majority of people are married (91%), educated up to primary level (29%), and hailing from rural domicile (44%). All the patients are earning their living hood by their own except one patient. Family history of any psychiatric illness is found in the case of 44% of patients. CT scan abnormalities were found in 32% of patients. (Table 1) Among the three cardinal features of WE, most of the patients were presented with global confusion and ataxic or unsteady gait during the time of admission (Table 2).

Table 1: Sociodemographic profile of Wernicke's encephalopathy patients (n=34)

Variables	*n* (%)
Education	
Primary	10 (29.41)
Secondary	6 (17.65)
Higher secondary	9 (26.47)
Intermediate	4 (11.76)
Graduation and above	5 (14.71)
Marital status	
Married	31 (91.18)
Unmarried	3 (8.82)
SES	
Lower	8 (23.53)
Upper lower	10 (29.41)
Lower middle	10 (29.41)
Upper middle	5 (14.71)
Upper	1 (2.94)
Domicile	
Rural	15 (44.12)
Semi-urban	6 (17.65)
Urban	23 (67.65)
Family history of psychiatric illness	
Yes	14 (41.18)
No	20 (58.82)
CT scan abnormalities	
Yes	11 (32.35)
No	23 (67.65)
Liver dysfunction	
Acute alcoholic hepatitis	2 (5.88)
Fatty liver	12 (35.29)
Cirrhosis of liver	14 (41.18)
No dysfunction	6 (17.65)

SES: Supplemental educational services, CT: Computed tomography

In memory subtest of PGIBBD, recent memory, mental balance, attention-concentration, immediate recall, retention for dissimilar pairs, visual retention, and recognition were found to be disturbed in most of the patients (Table 3). Findings also suggest disturbances in general information, performance intelligence (abstract reasoning and practical ability to deal with the environment), visual acuity, depth perception, and visuomotor coordination were observed in these patients (Tables 4 and 5).

Table 2: Symptomatology of Wernicke's encephalopathy shown by the patients (*n*=34)

Symptoms	*n* (%)
Global confusion	32 (94.12)
Ataxic or unsteady gait	28 (82.35)
Optic nerve palsy or nystagmus	5 (14.71)

Table 3: Memory scale findings (*n*=34)

Variables	*n* (%)		
	Great deviation	Slight deviation	No deviation
Remote memory	7 (20.59)	6 (17.65)	21 (61.76)
Recent memory	8 (23.53)	17 (50.00)	9 (26.47)
Mental balance	16 (47.06)	13 (38.24)	5 (14.71)
Attention-concentration	10 (29.41)	22 (64.71)	2 (5.88)
Delayed recall	6 (17.65)	11 (32.35)	17 (50.00)
Immediate recall	9 (26.47)	20 (58.82)	5 (14.71)
Retention for similar pairs	3 (8.82)	8 (23.53)	23 (67.65)
Retention for dissimilar pairs	17 (50.00)	14 (41.18)	3 (8.82)
Visual retention	13 (38.24)	13 (38.24)	8 (23.53)
Recognition	11 (32.35)	15 (44.12)	8 (23.53)

Table 4: Verbal adult intelligence scale findings (*n*=34)

Variables	*n* (%)		
	Great deviation	Slight deviation	No deviation
Information	3 (8.82)	19 (55.88)	12 (35.29)
Digit span	3 (8.82)	20 (58.82)	11 (32.35)
Arithmetic	6 (17.65)	10 (29.41)	18 (52.94)
Comprehension	1 (2.94)	12 (35.29)	21 (61.76)

Table 5: Findings of performance intelligence test, Nahor-Benson test and Bender-Gestalt test (*n*=34)

Tests	*n* (%)		
	Great deviation	Slight deviation	No deviation
Performance intelligence test	6 (17.65)	14 (41.18)	14 (41.18)
Nahor-Benson test	10 (29.41)	17 (50.00)	7 (20.59)
Bender-Gestalt test	6 (17.65)	15 (44.12)	13 (38.24)

DISCUSSION

In chronic alcoholics, there is always risk of developing WE, the reasons for which are discussed after evaluating the results of this study. WE is an acute neuropsychiatric syndrome found in chronic alcoholics, characterized by mental status changes, unsteadiness of stance and gait, nystagmus, and ophthalmoplegia - although this triad is seen in only 16% of patients,[23] which is the result and effect of deficiency of thiamine whose biologically active form thiamine pyrophosphate (TPP) is an essential coenzyme in several biochemical pathways in the brain. In our study, the global confusion was observed in 94% of cases with gait disturbances in 82% of cases. However, the ophthalmologic finding was found only in 21% of cases. The triad symptoms of WE were observed in around 9% of patients in our study.

The age of incidence varies from 30 to 55 years with the highest incidence in the 4th decade of life. Chronic alcohol use was frequently associated with inadequate dietary intake over a period of years with alcohol misuse.[24] Out of 34 cases, 12 cases had fatty liver, 14 cases had cirrhosis, and 2 cases had acute alcoholic hepatitis which indicates patients may have had a chronic form of the disease due to subclinical encephalopathy in which normal signs were absent. Harper et al. studied 51 cases of WE in Australia and observed the highest incidence in the 5th decade with around 70% of cases having liver dysfunction.[25]

The structural abnormality as observed by findings of CT scan of the brain in 32% of patients in this study which is consistent with other studies. CT identified low-density signal abnormalities in paraventricular region and volume deficits in the cerebral cortex and frontal lobe. The most frequently affected regions were thalamus and periventricular region, the regions of the brain which are proposed to be more sensitive to thiamine deficiency due to their high rate of thiamine-related glucose and oxidative metabolism. Another important finding in CT was cortical thinning and sulcal widening.[20,26,27]

The effect of thiamine depletion which is always cumulative adds with structural damage of the different parts of brain structures. Although there were no structural abnormalities observed in CT scan (68%), but in 74% of cases, recent memory dysfunction was the most characteristic finding causing dysfunction in ADL and QOL than the structural abnormalities. The neuroimaging study findings in frontal lobe, thalamus, and other areas of cerebral cortex are vital for memory functioning and executive function which is evident from neuropsychological tests and interruption of these circuits and interconnecting regions are responsible for cognitive dysfunction in WE.[20,27]

In this study, it was observed that different components of memory were affected in majority of patients, which is also

evident in other studies.[28,29,30] The components which are found to be impaired are recent memory, mental balance, attention-concentration, immediate recall, retention for dissimilar pairs, visual retention, and recognition. Abstract reasoning, problem-solving, planning, organizing, and general information (components of intelligence) were found to be affected in these patients in our study. This finding is consistent with studies conducted by Weiss et al.[31] The dysfunctions in these areas implicated the involvement of frontal lobe, affecting the skillful ADL and QOL. As a result of this, there's limited learning capacity, impairment of encoding and recollection process.

Visual acuity, depth perception, and visuomotor coordination were found to be affected in these patients. This finding is consistent with findings of Oscar-Berman and Marinkovic,[32] and Ratti et al.,[33] where they found impaired performance in visuospatial processing and visuoconstructional tasks.

Hence, the neuropsychological functioning deficits observed in these patients, affect the several areas of cognitive domain both in verbal and visual modalities which constitute an important component of global damage in WE.

CONCLUSION

It is highly essential to take into account the cognitive dimensions of chronic alcoholics before preparing their treatment plan in the long-term management while the patients are in the rehabilitation phase or in the domiciliary treatment and palliate their difficulties in ADL. After long years of research, dysfunctions in memory, intelligence, executive function, depth perception, and visuomotor coordination are well-established parameters which should be given paramount importance in the management of these patients. The structural brain damage which is observed in the CT scan is not a predominant finding; rather cognitive domain should be assessed in each and every case of chronic alcoholics. Finally, the clinical history, clinical examination findings, neuropsychological testings, blood chemistry and neuroimaging studies combined together determine the diagnosis and management. Hence, the impact of these impairments on the modalities and efficacy of management of WE should be the focused area of research for future decade. After observation of all these entities of cognition in clinical management, the cognitive remediation strategies should be one of the most promising interventions for patients of WE while doing follow-ups and rehabilitation of these patients.

REFERENCES

1. Victor M, Adams R, Collins G, editors. The Wernicke-korsakoff 1. The Wernicke-korsakoff Syndrome and Related Disorders Due to Alcoholism and Malnutrition. 2nd ed. Fíladelfíu: F.A. Davis Company; 1989.
2. Sechi G, Serra A. Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007;6(5):442-55.
3. Galvin R, Bråthen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA; EFNS. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. 2010;17(12):1408-18.
4. Lindboe CF, Løberg EM. Wernicke's encephalopathy in non-alcoholics. An autopsy study. J Neurol Sci. 1989;90(2):125-9.
5. Harper C. The incidence of Wernicke's encephalopathy in Australia - A neuropathological study of 131 cases. J Neurol Neurosurg Psychiatry. 1983;46(7):593-8.
6. Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics. A neuropathological study with clinical correlations. J Neurol Sci. 1982;56(2-3):233-48.
7. Lindboe CF, Løberg EM. The frequency of brain lesions in alcoholics. Comparison between the 5-year periods 1975-1979 and 1983-1987. J Neurol Sci. 1988;88(1-3):107-13.
8. Wernicke C. Die acute, hämorrhagische polioencephalitis superior. In: Lehrbuch der Gehirnkrankheiten fur Aerzteund Studirende. Vol. 2. Berlin, Kassel: Theodor Fischer; 1881. p. 229-42.
9. Groen RH, Hoff HC. Wernicke's disease. A catamnestic study of 50 patients. Eur Neurol. 1977;15(2):109-15.
10. Thomson AD, Cook CC, Touquet R, Henry JA; Royal College of Physicians, London. The Royal College of Physicians report on alcohol: Guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. Alcohol Alcohol. 2002;37(6):513-21.
11. Thomson AD, Marshall EJ. The treatment of patients at risk of developing Wernicke's encephalopathy in the community. Alcohol Alcohol. 2006;41(2):159-67.
12. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. Alcohol Alcohol Suppl. 2000;35(1):2-7.
13. Butterworth RF. Thiamin. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern Nutrition in Health and Disease. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 426-33.
14. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. Curr Mol Med. 2001;1(2):197-207.
15. Dodd PR, Beckmann AM, Davidson MS, Wilce PA. Glutamate-mediated transmission, alcohol, and alcoholism. Neurochem Int. 2000;37(5-6):509-33.
16. Gurling HM, Curtis D, Murray RM. Psychological deficit from excessive alcohol consumption: Evidence from a co-twin control study. Br J Addict. 1991;86(2):151-5.
17. Goldman MS. Cognitive impairment in chronic alcoholics. Some cause for optimism. Am Psychol. 1983;38(10):1045-54.
18. Parker ES, Alkana RL, Birnbaum IM, Hartley JT, Noble EP. Alcohol and the disruption of cognitive processes. Arch Gen Psychiatry. 1974;31(6):824-8.
19. Clarke J, Haughton H. A study of intellectual impairment and recovery rates in heavy drinkers in Ireland. Br J Psychiatry. 1975;126:178-84.
20. Jung YC, Chanraud S, Sullivan EV. Neuroimaging of Wernicke's encephalopathy and Korsakoff's syndrome. Neuropsychol Rev. 2012;22(2):170-80.
21. World Health Organization. The International Classification of Diseases and Related Health Problems. 10th Revision (ICD-10) Classification of Mental and Behavioral Disorders: Diagnostic

Criteria for Research. Geneva: WHO; 1992.
22. Pershad D, Verma SK. A Handbook of PGI Battery of Brain Dysfunction (PGI-BBD). 2nd ed. Agra: National Psychological Corporation Publishers; 2009.
23. Victor M. The wernicke-korsakoff syndrome. In: Vinken PJ, Bruyn GW, editors. Handbook of Clinical Neurology. Vol. 28. Part II. Amsterdam: North-Holland Publishing Company; 1976. p. 243-70.
24. Harper C, Fornes P, Duyckaerts C, Lecomte D, Hauw JJ. An international perspective on the prevalence of the Wernicke-Korsakoff syndrome. Metab Brain Dis. 1995;10(1):17-24.
25. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatry. 1986;49(4):341-5.
26. Matsui T, Sakurai H, Toyama T, Yoshimura A, Matsushita S, Higuchi S. Clinical application of neuroimaging to alcohol-related dementia. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2012;47(3):125-34.
27. Sullivan EV, Pfefferbaum A. Neuroimaging of the Wernicke-Korsakoff syndrome. Alcohol Alcohol. 2009;44(2):155-65.
28. Bernardin F, Maheut-Bosser A, Paille F. Cognitive impairments in alcohol-dependent subjects. Front Psychiatry. 2014;5:78.
29. Pitel AL, Eustache F, Beaunieux H. Component processes of memory in alcoholism: Pattern of compromise and neural substrates. Handb Clin Neurol. 2014;125:211-25.
30. Behura SS, Swain SP. Neuropsychological functioning in Wernicke's encephalopathy. Ind Psychiatry J. 2015;24(1):99-103.
31. Weiss E, Singewald EM, Ruepp B, Marksteiner J. Alcohol induced cognitive deficits. Wien Med Wochenschr. 2014;164(1-2):9-14.
32. Oscar-Berman M, Marinkovic K. Alcohol: Effects on neurobehavioral functions and the brain. Neuropsychol Rev. 2007;17:239-57.
33. Ratti MT, Bo P, Giardini A, Soragna D. Chronic alcoholism and the frontal lobe: Which executive functions are imparied? Acta Neurol Scand. 2002;105(4):276-81.

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