Frontal lobe executive dysfunction and cerebral perfusion study in alcohol dependence syndrome

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Background: Long-term alcohol use leading to frontal lobe impairment has been a cause of concern for many decades. However, there are very few studies from India of evaluation of frontal lobe executive dysfunction among alcoholics. Hence, this study was undertaken to evaluate the frontal executive dysfunction using Wisconsin Card Sorting Test (WCST) and perfusion deficits by Single-Photon Emission Computerized Tomography (SPECT) among alcohol-dependent patients. Aim: The aim of this study is to evaluate the frontal executive dysfunction using WCST and frontal lobe perfusion deficits by SPECT among alcohol-dependent patients. Materials and Methods: This was a cross-sectional study involving 20 alcohol dependence syndrome patients in a tertiary care center. After ethical clearance and informed consent, all were evaluated using WCST and SPECT. Results: About 45% patients had impairment on WCST, and it was related to the duration of drinking. About 55% showed reduced frontal lobe perfusion on SPECT scan and they had a long duration of drinking compared to controls. Among the patients showing impairment on WCST subscores, more than 50% had reduced frontal lobe perfusion on SPECT. Conclusion: This study not only confirmed the executive function impairment and frontal lobe perfusion deficits in alcohol-dependent patients but also showed a concomitant presence of both in patients with chronic alcohol abuse.

Keywords: Alcohol dependence syndrome, executive dysfunction, frontal lobe perfusion

Alcohol dependence syndrome is a major public health problem, and it impacts the social, psychological, medical, economic, and religious spheres of our existence.[1]

Alcohol can induce a wide spectrum of effects on the central nervous system. These effects can be recognized at the neurophysiological, morphological, and neuropsychological levels. Chronic use of alcohol has been consistently associated with cognitive impairments.[2] Neuropsychological studies in long-term alcoholics have highlighted frontal (executive) function impairments including domains of planning, abstraction, attention, shifting of attention, mental flexibility, and concept generation.[3]

Wisconsin Card Sorting Test (WCST) is a measure of prefrontal cortical function (executive function, abstract conceptual skills, concept formation, cognitive flexibility, and working memory), and previous studies using the WCST have demonstrated an impairment in alcohol-dependent patients.[2] Persistent alcohol use leads to significant reduction in regional cerebral blood flow, predominantly in frontal lobes.[4] Functional neuroimaging studies using Single-Photon Emission Computed Tomography (SPECT) have revealed reduced cerebral perfusion in frontal regions in chronic alcoholics.[3]

Results of in vivo magnetic resonance imaging and postmortem neuropathological studies of uncomplicated alcoholics indicate that the most apparent cortical abnormalities occur in the frontal lobes, with concurrent thinning of the corpus callosum and concomitant compromise of pontocerebellar and cerebellothalamocortical systems.[5] Compromise

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of components in the circuitry of this extensive reward and oversight system may adversely influence the remote regions within that circuit, resulting in characteristic alcoholism-related cognitive and motor deficits. However, even when one component may be compromised, another component may be invoked as a compensatory processing adjunct in situations where alcoholics are faced with difficult cognitive challenges.\[^{6,7}\]

Recent neuroimaging studies of the human frontal lobes have suggested that they are organized hierarchically in a rostrocaudal direction. As such, cognitive control is supported in progressively caudal regions during concrete action decisions, whereas rostral regions control more abstract decisions and actions.\[^{8}\] Through the multiple innervations of its different centers, preserved prefrontal brain circuitry is essential for functions such as memory consolidation and recall, spatial and contextual sensory processing, integration of stimulus-reward associations, decision-making, and determination of mood.\[^{9-11}\] Executive functions and appreciation of nonemotional environmental stimuli are thought to be under control of the lateral prefrontal brain system,\[^{12}\] with connections that include parietal cortex, the ventral striatum, and the hippocampus and their interconnected fiber pathways.\[^{13,14}\] Response inhibition, emotional expression, and memory for social cues are controlled by a ventral/orbital frontal circuit, with strong amygdala influence.\[^{15,16}\] The medial prefrontal cortex (PFC), essential for inhibitory control and error-monitoring, has a role in emotions as well, specializing in the expression of emotions through pathways to autonomic structures.\[^{13,17,18}\]

Together, these cortical-subcortical networks control the high-level cognitive and emotional processes important for learning reward-values and affective properties of stimuli, and they allow us to modulate our responses.\[^{11,19}\] Thus, this system is strongly involved in many biobehavioral functions impaired in alcoholics, and its breakdown and dysfunction are responsible for a variety of abnormalities, for example, impaired maintenance and monitoring of spatial and object information,\[^{20}\] disruption of decision-making,\[^{21-24}\] insensitivity to feedback or rewards,\[^{25,26}\] impairments in emotional control and behavioral inhibition,\[^{27}\] and initiating drug use or relapse after protracted abstinence.\[^{13,28}\]

The WCST is designed to assess the ability of reasoning and of shifting cognitive strategies and is generally considered a useful tool for detecting frontal lobe dysfunction and for assessing the integrity of executive functions. Functional neuroimaging studies have confirmed the involvement of the PFC in the performance of the WCST.\[^{29-32}\] Neuropsychological research in the past has revealed that alcoholics make more errors in the WCST compared to control participants,\[^{33,34}\] although not all studies showed more perseveration errors.\[^{33,35}\] Nowakowska et al. demonstrated that the longer the addiction period, the more perseveration errors were made by the examined persons and they also sorted fewer categories and presented with a lower index of answers, conformable with the logical concept on WCST. It may be evidence for enhancing disorders of executive functions in long-addicted persons.\[^{36}\]

Tutus et al. performed \[^{37}\^9\text{mTc}HMPAO\] brain SPECT on the day of admission in nonmedicated conditions and again after all the withdrawal symptoms had subsided in the patients.\[^{37}\] Results indicated that there were significantly reduced the left frontal and the right frontal, parietal, and temporal regional cerebral blood flow (rCBF) values in the patients during alcohol withdrawal compared to those of their remitted state, which were not different from those in the control group.

Kuruoglu et al. examined 40 patients with alcohol dependency, including 15 with antisocial personality disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders-III-R, and 10 age- and sex-matched healthy controls.\[^{38}\] The alcoholics were studied after termination of withdrawal symptoms, using the high-resolution SPECT, CT, and brainstem auditory evoked potentials. The authors found a significant reduction in rCBF measurements of the alcoholic patients. Interestingly, Gansler et al. examined the relationship between cerebral hypo-perfusion and residual deficits in the functioning of frontal brain systems in abstinent alcoholics long-term.\[^{39}\] CBF was observed through the use of SPECT perfusion images. Results showed a positive relationship between perfusion levels in the left inferior frontal brain region and years of sobriety. Consequent to long-term alcohol use, frontal lobe impairment has been a cause of concern for many decades. However, there are fewer studies done in India for frontal lobe evaluation of alcoholics. This study was to evaluate the frontal executive dysfunction using WCST and frontal lobe perfusion deficits by SPECT among alcohol-dependent patients.

### MATERIALS AND METHODS

The study was carried out in the deadc dichard ward of a tertiary care teaching hospital after taking ethics committee approval. All the consecutively admitted patients with a diagnosis of alcohol dependence syndrome during a period of 1-year of study were taken for the study. The diagnosis was made independently by two psychiatrists as per International Classification of Diseases 10\(^{th}\) Edition criteria. Institutional Ethical Committee clearance was obtained and informed written consent was taken from study participants. The patients meeting diagnostic
criteria for any other psychiatric disorder, the presence of any systemic illnesses affecting cerebral blood flow, or cognitive function were excluded from the study. Baseline demographic data of cases along with relevant investigations were entered in semi-structured proforma. The patients were evaluated after the withdrawal features if present were subsided.

The patients completed the 128-card computerized version of the WCST CV-4. Participants had to sort cards with a number of colored geometrical shapes. The sorting rule referred to either shape (triangle, star, cross, or circle), number (one, two, three, or four figures), or color (red, green, yellow, or blue). The correctness of the chosen sorting rule was indicated by a feedback stimulus. A given sorting rule was valid for a fixed number of stimuli (a series of 10 consecutive correct responses [CR]), after which it changed, without warning the participant. After the change, participants had to figure out which rule had to be followed for the subsequent series. The participants were instructed to wait for a negative feedback signal before applying a different sorting rule.

SPECT of the brain is a technique for obtaining tomographic images of the 3-dimensional distribution of a radiopharmaceutical, which reflects regional cerebral perfusion. Radioactive isotope used in the study was ⁹⁹ᵐTe⁰₄Technetium-ethyl cysteine dimer. All standard safety measures were taken. SPECT – GammaCamera (E-CAM, Siemens version 2000) was used for the study. The distribution of radioactivity in the cerebral and cerebellar regions, focal or global perfusion differences, and left-to-right and anterior-to-posterior asymmetry by SPECT scans were interpreted by Nuclear Medicine Specialist. Data were statistically analyzed with the suitable statistical method.

RESULTS

A total of 20 patients were enrolled in the study. The age range of the study group was 26–55 years with mean age of 38.9 years (standard deviation [SD]–8.18). The mean age of onset of alcohol use was 24.25 years (SD–8.36) and mean duration of years of drinking was 14.8 years (SD–6.7).

About 20% showed impairment in WCST correct response, 55% showed impairment in perseverative response and perseverative error, and 50% showed impairment in conceptual level response [Table 1]. In patients with WCST subscores showing mild-to-moderate and moderate impairment, the mean years of drinking were more than in patients with WCST subscores showing mild impairment or normal range of performance [Table 2]. About 55% showed reduced frontal lobe perfusion on SPECT Scan. The mean years of drinking were 11.5 years in cases with normal frontal lobe perfusion and 17.4 years in cases with reduced frontal lobe perfusion [Table 3]. Among patients showing impairment on WCST subscores, more than 50% had reduced frontal lobe perfusion on SPECT [Table 4].

DISCUSSION

On WCST, 45% of total cases showed impairment (T score ≤39) on one or more of the four parameters analyzed in this study. There was a noticeable difference among the scores of variables studied, i.e. CR, perseverative responses (PR), perseverative errors (PE), and conceptual level responses (CLR) as evident from Table 1.

For CR in WCST, 20% of the study sample showed impairment. For PR and PE, 55% of the study sample showed impairment on both. Similarly, for conceptual level responses, 50% of the study sample was in the impairment range.

This implies that frontal lobe executive function deficits as evident on WCST performance are prominent in Alcohol Dependence Syndrome. This is well supported by studies in the past.[23] Ratti et al. reported significant impairment in categories completed and total errors in WCST. However, in the percentage of PR, they did not find any difference between the alcoholics and the controls. Another study had reported that on Wisconsin Card Sorting Task, Korsakoff and non-Korsakoff alcoholics achieved fewer categories than controls but only Korsakoff alcoholics made PE.[33]

As seen in Table 2, the duration of the mean years of drinking was more in the patients with WCST subscores showing mild-to-moderate and moderate impairment, as compared to those with WCST subscores showing mild impairment or normal range of performance. This finding is in agreement with a previous study where it was demonstrated that the longer the addiction period, the more PEs were made by the examined persons and they also sorted fewer categories and presented with a lower index of answers, conformable with logical concept on WCST.[34]

This study revealed that in the study sample, 55% showed reduced frontal lobe perfusion on SPECT scan. The mean years of drinking were 17.4 years in cases with reduced frontal lobe perfusion as compared to 11.5 years in cases with normal frontal lobe perfusion [Table 3]. The relative perfusion deficits in our study sample were limited to the frontal regions of the brain.
Table 1: Wisconsin card sorting test response

| Range of performance (t scores) | WCST response |
|---------------------------------|---------------|
|                                 | Correct responses (n=20), n (%) | Perseverative responses (n=20), n (%) | Perseverative errors (n=20), n (%) | Conceptual level responses (n=20), n (%) |
| <25 (severe impairment)         | 1 (5)          | 3 (15)          | 3 (15)          | 4 (20)          |
| 25-39 (moderate impairment)     | 2 (5)          | 2 (10)          | 2 (10)          | 2 (10)          |
| 30-34 (mild-to-moderate impairment) | 1 (5)          | 1 (5)          | 2 (10)          | 2 (10)          |
| 35-39 (mild impairment)         | 1 (5)          | 5 (25)          | 4 (20)          | 2 (10)          |
| 40-44 (below average [normal])  | 1 (5)          | 2 (10)          | 2 (10)          | 3 (15)          |
| 45-54 (average [normal range])  | 2 (10)         | 2 (10)          | 2 (10)          | 5 (25)          |
| >55 (above average [normal])    | 13 (65)        | 5 (25)          | 5 (25)          | 2 (10)          |

WCST: Wisconsin card sorting test

Table 2: Relationship between range of performance in Wisconsin card sorting test subscores and mean years of drinking

| WCST: Range of performance (t scores) | Mean years of drinking in years among WCST subscores |
|---------------------------------------|-----------------------------------------------------|
|                                       | Correct responses (n=20) | Perseverative responses (n=20) | Perseverative errors (n=20) | Conceptual level responses (n=20) |
| <25 (severe impairment)               | 28 (n=2)                | 9.7 (n=3)                     | 9.7 (n=3)                     | 9.5 (n=4)                             |
| 25-39 (moderate impairment)          | 24 (n=2)                | 17.5 (n=2)                    | 17.5 (n=2)                    | 22.5 (n=2)                             |
| 30-34 (mild-to-moderate impairment)  | 8 (n=1)                 | 28 (n=1)                      | 18.5 (n=2)                    | 21 (n=2)                               |
| 35-39 (mild impairment)              | 16 (n=1)                | 16 (n=5)                      | 17.7 (n=4)                    | 14 (n=2)                               |
| 40-44 (below average [normal])       | 5 (n=1)                 | 12 (n=2)                      | 12 (n=2)                      | 17 (n=3)                               |
| 45-54 (average [normal range])       | 15 (n=2)                | 21 (n=2)                      | 21 (n=2)                      | 15.8 (n=5)                             |
| >55 (above average [normal])         | 14 (n=13)               | 11.6 (n=5)                    | 14.2 (n=5)                    | 6.5 (n=2)                              |

In patients with WCST subscores showing mild-to-moderate and moderate impairment, the mean years of drinking were more than in patients with WCST subscores showing mild impairment or normal range of performance. WCST – Wisconsin card sorting test

Table 3: Relationship between Single-Photon Emission Computed Tomography findings and mean years of drinking

| SPECT findings                      | Number of cases (n=20), n (%) | Mean years of drinking (years) |
|-------------------------------------|-------------------------------|--------------------------------|
| Normal frontal lobe perfusion       | 9 (45)                        | 11.5                           |
| Reduced frontal lobe perfusion      | 11 (55)                       | 37.4                           |

SPECT – Single-photon emission computerized tomography

Table 4: Relationship between range of performance in Wisconsin card sorting test subscores and frontal lobe perfusion by single-photon emission computerized tomography

| WCST Subscores | Range of performance | Frontal lobe perfusion by SPECT |
|----------------|----------------------|---------------------------------|
|                |                      | Normal | Reduced |
| Correct responses | Normal (240) (n=16) | n=7    | n=9     |
| Perseverative responses | Normal (240) (n=9) | n=5    | n=4     |
| Perseverative errors | Normal (240) (n=9) | n=5    | n=4     |
| Conceptual level responses | Normal (240) (n=10) | n=5    | n=5     |

Among patients showing impairment on WCST subscores, >50% have reduced frontal lobe perfusion on SPECT. SPECT – Single-photon emission computerized tomography; WCST – Wisconsin card sorting test

One study had reported that 30 out of the 40 alcoholics showed hypoperfusion areas on the SPECT scan, and the rCBF ratio was especially reduced in frontal lobes.\(^{(3)}\) Another study of 40 patients with alcohol dependency after termination of withdrawal symptoms and found a significant reduction in regional cerebral blood flow (rCBF) measurements in frontal regions and in 67.5% of the patients, it was directly associated with the duration of alcohol consumption.\(^{(38)}\) However, Tutus et al. had noted that there were significantly reduced the left frontal and the right frontal, parietal and temporal rCBF values in the patients during alcohol withdrawal compared to those of their remitted state, which were not different from those in the control group.\(^{(37)}\)

As seen in Table 4, among patients showing impairment on WCST subscores, more than 50% have reduced frontal lobe perfusion on SPECT. There have been very few studies which have incorporated both frontal lobe executive functioning using WCST and frontal lobe perfusion deficits using SPECT and none of them have found any significant correlation between these two. Demir et al. found no correlation between the frontal lobe skill abnormalities detected by WCST and regional perfusion rates seen on SPECT, whereas Dupont et al. found an insignificant association between neuropsychological abnormalities and perfusion rates.\(^{(40,41)}\)
Although this study has much strength, few limitations are to be kept in mind while interpreting the results. The sample size is small, though most of the similar studies had small sample size only. This study involved male patients only since the inpatient facilities were not available for female patients due to administrative reasons. In addition, this was only a cross-sectional study and serial follow-up evaluations could have added knowledge about the rate of recovery following abstinence.

CONCLUSION

This study is among the fewer Indian studies to assess frontal lobe dysfunction in alcohol-dependent patients. It not only confirmed the executive function impairment and frontal lobe perfusion deficits in alcohol-dependent patients but also showed a concomitant presence of both in patients with chronic alcohol abuse. The findings of this study can be of great help for clinicians, patients, and their caregivers in planning suitable remedial, rehabilitative, and relapse prevention measures.

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Conflicts of interest

There are no conflicts of interest.

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