Working memory deficit in stable patients of schizophrenia and it's correlation with biochemical markers: A cross sectional study at tertiary care hospital in north India

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Abstract-
Background:
Little stress was paid on the status of cognition in stable or remission state in recent past. Deficiency of micronutrients such as vitamin B12, folate and calcium are often under recognized condition causing cognitive symptoms. Association of these biochemical parameters with working memory impairment in unknown which emphasize the management plan for cognitive domain.
Aim:
We investigated working memory deficit and its correlation with serum vitamin B12, serum folate and serum calcium in stable schizophrenic patients.
Methods:
Thirty-five schizophrenic patients stable on treatment after assessing with PANSS scale as per ICD 10 criteria and thirty-five controls were recruited free of neurological comorbidities. Working memory questionnaire was applied in Hindi language for assessment of working memory deficit.
Results:
Significantly high scores of total working memory (U= 58.5, p= 0.00), storage domain (U= 58.0, p= 0.00), attention domain (U= 85.5, p= 0.00) and executive domain (U= 92.0, p= 0.00) were obtained in schizophrenia group than control suggesting working memory deficit in stable schizophrenic patients. Mean serum vitamin B12 and folate level were significantly higher in control than schizophrenics.
Significantly negative correlation of serum vitamin B12 with total working memory scores, storage domain, attention domain and executive domain and serum folate with only executive domain were detected. Correlation of serum calcium was found insignificant.
Conclusion:
Schizophrenic subjects still had significant daily routine problems due to working memory deficit even after treatment. Serum vitamin B12 and folate negatively correlated with working memory deficits and executive dysfunction respectively.

***Keywords*: Working-memory, storage, attention, executive, folate, vitaminB12**

Introduction

Cognitive dysfunction has drawn interests as a distinctive phenotype across psychotic disorders. Schizophrenia is a clear example of those conditions in which disrupted memory system present challenges for patients beyond the typical symptoms. Working memory is an important domain of cognitive system with a limited capacity that can hold information temporarily.[1,2] Schizophrenia has been thought to be a most puzzling disorder of the brain, in which psychotic symptoms are associated with variable cognitive dysfunction.[3] Data reported high prevalence of working memory impairment ranging from 65-90 % depending on stage of disease, duration of illness, severity of symptoms and medication profile.[4,5] Previous reports suggested greatest severity of cognitive impairment in the domains of storage, attention, executive function and processing speed.[6]

Previous work regarding cognitive decline in schizophrenia have been performed and various associated factors were analysed. A multicentred study comparing working memory impairment in recent-onset and chronic schizophrenia noticed that deficits progress beyond normal aging, emphasizing association of problem solving and episodic memory deficits with greater length of illness.[7] However, another study done earlier showed no difference of visual-verbal working memory task between first-episode psychosis and chronic schizophrenia.[8] Deficits are also present to an

extent in some patients with schizophrenia prior to the onset of symptoms as a premorbid cognitive impairment that worsen throughout the development and stabilize in psychotic episode.[9] Severe working memory impairment were found in schizophrenic patients having poorly adjusted premorbid personality than who were stable and well adjusted.[10] In recent past little stress was paid about the status of cognition in stable or remission state. In our work, we aim to assess the daily routine problems associated with working memory deficits in stable patients of schizophrenia.

Deficiency of micronutrients such as vitamin B12, folate and calcium are often under recognized condition causing cognitive and psychiatric symptoms [11,12] and these micronutrients were also found to be altered in psychiatric disorders.[13,14] Levels of serum folate was found to be deficient in schizophrenic patients compared to controls.[14,15,16] One study has demonstrated reduced serum levels of both folate and cobalamin among schizophrenic patients.[13] However data are limited pointing these altered biochemical parameters have impact on cognitive functions knowing the most of the neuropsychiatric disorders themselves cause cognitive impairment like Alzheimer's disease. Chen X demonstrated negative correlations of serum folate with negative symptoms and positive correlation with cognitive function scores in first episode schizophrenic patients.[17] Results of a follow up study depicted significant improvement in memory and processing speed in the folic acid group than in the placebo group with three-year treatment with a folic acid (800 μg/day) in subjects with relatively low folate levels.[18] The implication of calcium homeostasis was emphasized in psychosis.[19] Although findings were inconsistent with little evidence, high serum calcium levels are associated with faster decline in cognitive function in elderly in the general population.[20] Tilvis RS et al emphasized the altered calcium metabolism as a preventable and remediable risk conditions of cognitive decline.[21]

In our study we tried to understand the correlation of working memory deficits in stable schizophrenic patients with biochemical parameters consisting serum vitamin B12, serum folate and serum calcium level considering the previous work with inconsistent findings.

MATERIAL AND METHODS

Participants

All procedures were approved by the research review board and ethical committee of the institution. An informed written consent was obtained from the patients and informants prior to participation. Patients were recruited as outpatient and inpatient in department of Psychiatry, SMS Hospital, Jaipur and control participants were taken from general population voluntarily via advertisements. The final sample included 35 patients of schizophrenia and 35 healthy controls.

Inclusion criteria were: Patients diagnosed with schizophrenia as per ICD 10 criteria, stable on treatment; Healthy control without history of any psychiatric, medical or surgical illness; Age 18 years and above; Either sex and Participants and attendants to give informed consent. Exclusion criteria were: Disorder of intelligence or language making the interview difficult; History of significant substance abuse in last 3 months excluding nicotine; History of medical, neurological or any other illness simulating or affecting the psychiatric illness; History of micronutrient intake (vitamin B12, folate, calcium) or other medication affecting serum level of above-mentioned parameters within last 6 months; History of Electroconvulsive therapy within last 6 months. Blood samples for serum vitamin B12, serum folate and serum calcium were sent. Working memory was assessed by "The working memory questionnaire" by Claire Vallat-Azouvi et al 2012[22] after permission.

Instruments

1. The working memory questionnaire

Self-administered working memory questionnaire, originally designed by Claire Vallat-Azouvi et al 2012, was used in Hindi language for assessment of working memory deficit in this study. Each question was rated on a five-point Likert-type scale, ranging from 0 (no problem at all) to 4 (very severe problem in everyday life). The questionnaire included questions addressing short term storage, attention and executive domain of working memory. Three sub-scores were computed, for each of the three domain (maximum score 40 for each domain), as well as a total score (out of 120). Higher scores corresponded to more difficulties/complaints.

After permission from original author, questionnaire was administered onto pilot subjects at department of psychiatry, SMS Medical College, Jaipur after informed written consent who were able to read, write and understand in both English and Hindi language. Based on Hindi translation, back to English translation, cross cultural modification retaining the contextual meaning, a final version was prepared. Validation was done at department of psychiatry, tertiary care centre. Correlation for paired sample were 0.980 (p value 0.00). Cronbach alpha coefficient for internal consistency was 0.90 and 0.88 respectively for English and Hindi version.

2. The positive and negative syndrome scale for schizophrenia (PANSS) was applied to assess the severity. Only those patients were included who scored less than 60 (stable on treatment).

Statistical analysis

Appropriate non parametric statistics were applied after exploring the data for normality distribution using computer software SPSS version 26. Comparison was done with Mann-Whitney U test and Kruskal Wallis test for continuous variables and Chi-square test for categorical variables. Spearman's correlation was applied to correlate two continuous variables.

RESULTS

Sociodemographic profile

A total of 70 participants (35 each of schizophrenic and healthy control) were evaluated. 68.6% were male and 31.4% were female in schizophrenia group; 51.4% belonged to rural while 48.6% belonged to urban background in schizophrenia. Sociodemographic profile has been shown in table 1.

Working memory scores and biochemical profile

Significantly high scores of total working memory (U= 58.5, p= 0.00), storage domain (U= 58.0, p= 0.00), attention domain (U= 85.5, p= 0.00) and executive domain (U= 92.0, p= 0.00) were resulted in schizophrenia group than in healthy control (table 2).

The mean serum vitamin B12 and folate level are depicted in table 3. Mean serum vitamin B12 (U= 1046.0, p= 0.00) and folate level (U= 827.50, p= 0.01) was significantly higher in healthy control than schizophrenics. No significant difference of the mean serum calcium level (U= 655.5, p= 0.61) was found as shown in table 3.

Correlation between working memory scores and biochemical parameters in schizophrenia were depicted in table 4. Significantly negative correlation of serum vitamin B12 was resulted with total working memory scores (rs= -0.67, p= 0.00), storage domain (rs= -0.68, p= 0.00), attention domain (rs= -0.69, p= 0.00) and executive domain (rs= -0.50, p= 0.00). Only executive domain score (rs= -0.40, p= 0.01) had significant correlation with serum folate. No significant correlation was found between serum calcium and working memory scores and its domains.

Discussion

The study comprises the demonstration of working memory deficits in schizophrenia and the correlation with biochemical markers. Significantly higher scores of total working memory and its domains suggest more daily routine difficulties associated with working memory deficits in schizophrenic subjects who were clinically stable after treatment.

Results of our study about working memory are in concordance with the previous studies. **Conklin HM et al 2000** resulted that schizophrenia patients had impairment on both the forward and backward digit span tasks, the measures of attention and working memory.[23] **Hintze B et al 2004** described longer reaction time in forced choice tasks and reduced immediate visuospatial memory span related to working memory.[24] Similar results were found by other studies.[25,26,27] A study conducted in 2002 observed deficits in spatial working memory suggesting general WM impairment. Executive function as assessed with the self-ordered pointing tasks was also impaired in the patients suffering from schizophrenia.[28] Another study performed in 2001 indicated that the deficit group performed significantly worse on the executive functioning factor sparing the verbal memory domain suggesting specific cognitive impairment in executive function and not the global.[29]

Regarding micronutrients, mean serum vitamin B12 and serum folate level were significantly higher in healthy control participants than schizophrenia group in our study. Results are in line with previous studies showing high cobalamin levels in healthy controls than schizophrenic subjects.[30,13] A recent study observed significantly higher prevalence of vitamin B12 deficiency in schizophrenia group than in the healthy control group (45.5% vs. 11.5%).[31] Prevalence of low vitamin B12 level were found in about 28.6% [32] and 39% [33] schizophrenic patients.

In contrast, few studies disagreed with our results and found significantly higher serum cobalamin level in schizophrenic patients than healthy controls. Statistically lower prevalence of cobalamin deficiency was observed in schizophrenic subjects (13.3%) than controls (23.3%).[14] A Mexican survey reported no difference of mean serum cobalamin levels in schizophrenic patients (409.75 ± 243.79) vs controls (407.71 ± 210.18).[15]

Comparing the results of serum folate with the previous studies, **Saedisomeolia A et al 2011** observed folate deficiency in 8.3% participants in schizophrenic group compared to controls where no folate deficiency was seen.[14] Similarly reduced folate levels were detected in other studies.[16,13, 31,33] Contrary to our findings, a cross sectional study did not find any difference in folic acid status among different psychiatric disorders versus healthy controls.[34]

In our work, mean serum calcium level did not differ significantly in schizophrenia v/s healthy control. Discussing the findings **Khan A et al 1990** revealed no significant differences in levels of serum calcium between schizophrenics versus non-schizophrenic groups.[35] **Alexander PE et al 1978** showed no significant difference in unmedicated schizophrenic patients compared with normal controls.[36]

Although there were rare studies in recent past describing the association of cognitive impairments with serum folate, serum cobalamin and calcium level however **Shereen M Abd EI Mawella et al 2018** showed negative correlation between negative symptoms and serum folate level and serum vitamin b12 level however results were insignificant.[33] **Roffman JL et al 2013** found that folate and cobalamin improved negative symptoms significantly compared to placebo.[37] No significant correlation of serum calcium was detected with neuropsychological composite, information processing speed and executive function in schizophrenic patients that shows concordance with our finding.[38]

Although there were growing evidence of working memory deficits in schizophrenia, however results were inconsistent considering the different procedural methods used to assess the working memory over the period of time. Out of those fewer have evaluated the impairment in stable patient. In our study we have used the questionnaire to assess problems associated with working memory impairment. Our study is one of the rarest studies which has explored the whole domains and aspects related to working memory in a single validated questionnaire on stable patients of schizophrenia. We have few limitations in the study. First the sample size is smaller and generalization onto community samples would be difficult. Samples on the basis of duration could not be distinguished, both the acute and long-term chronic patients have been recruited if they were stable clinically. Impact of medication on working memory functions and dietary pattern on serum levels of micronutrients have not been assessed. Despite that, the study has future implication in terms of treatment challenges regarding cognitive impairments in schizophrenia.

Conclusion

This study was performed highlighting the whole domains of working memory in stable patients of schizophrenia rather than acute and untreated patients having florid psychotic or negative symptoms where evaluation of cognitive functions might be biased. Study concluded that schizophrenic subjects who recovered with treatment still had significant daily routine problems due to working memory deficits. Serum vitamin B12 and folate level were significantly low. Our study is of those rare studies which identified relation of working memory deficit with biochemical parameters in stable patients. Vitamin B12 had negative correlation with working memory deficits while folate had negative correlation with executive dysfunction.

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Table 1. Sociodemographic variables in Schizophrenia and Healthy control

		S (N=35)	HC (N=35)
		Mean±SD	
(1)	Age (Years)	31.66±8.0	36.77±9.6
(2)	Duration of illness (Years)	4.32±3.69	-
		N(%)	
(3)	Gender		
Male		24(68.6)	20(57.1)
	Female	11(31.4)	15(42.9)
(4)	Education		
Illiterate		2(5.7)	1(2.9)
	Primary	1(2.9)	4(11.4)
	Middle	13(37.1)	7(20)
	High	13(37.1)	17(48.6)
	Graduate and above	6(17.1)	6(17.1)
(5)	Residence		
Rural		18(51.4)	15(42.9)
Urban		17(48.6)	20(57.1)
(6)	Religion		
Hindu		33(94.3)	29(82.9)
Muslim		2(5.7)	6(17.1)
(7)	Marital status		
Married		13(37.1)	26(74.3)
Unmarried		22(62.9)	9(25.7)
(8)	Socioeconomic status		
Lower		-	-
Upper-lower		5(14.3)	-
Lower-middle		24(68.6)	19(54.3)
Upper-middle		6(17.1)	13(45.7)
Upper		-	-

S= Schizophrenia, HC= Healthy control; N= number; SD= Standard deviation

Table 2. Comparison of working memory between schizophrenia and healthy control

		Mean(SD)		Mann-Whitney U	P value
		S(N=35)	HC (N=35)		
(1)	Total working memory score	54.46(21.9)	16.89(7.6)	58.50	< .001
(2)	Storage domain	18.46(8.1)	5.20(2.6)	58.0	< .001
(3)	Attention domain	19.63(8.0)	6.34(3.4)	85.50	< .001
(4)	Executive domain	16.11(7.6)	5.29(3.1)	92.00	< .001

Table 3. Comparison of biochemical profile between schizophrenia and healthy control

		Mean(SD)		Mann-Whitney U	P value
		S(N=35)	HC (N=35)		
(1)	Serum vitamin B12	376.9(137.9)	652.74(207.1)	1046.0	< .001
(2)	Serum folate	5.82(2.2)	6.91(1.4)	827.50	.01
(3)	Serum calcium	9.16(.7)	9.34(.9)	655.50	.61

Table 4. Correlation between working memory score and biochemical markers in schizophrenia

		rs	P value
(A)	Total working memory score		
(1)	Total WM score- Serum vitamin B12	- 0.67	< .001
(2)	Total WM score- Serum folate	-0.21	.22
(3)	Total WM score- Serum calcium	-0.01	.94
(B)	Storage domain		
(1)	Storage domain score-Serum vitamin B12	-0.5	< .001
(2)	Storage domain score-Serum folate	-0.17	.30
(3)	Storage domain score-Serum calcium	-0.12	.48
(C)	Attention domain		
(1)	Attention domain score-Serum vitamin B12	-0.69	< .001
(2)	Attention domain score-Serum folate	0.06	.71
(3)	Attention domain score-Serum calcium	-0.12	.48
(D)	Executive domain		
(1)	Executive domain score-Serum vitamin B12	-0.50	< .001
(2)	Executive domain score-Serum folate	-0.40	.01
(3)	Executive domain score-Serum calcium	0.22	.18

rs= correlation coefficient