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Original Research Article

A Cross Sectional Study on Correlation of Serum C-Reactive Protein Level with Cognitive Deficits in Patients with Schizophrenia

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Abstract

Background: Serum levels of C-reactive protein (CRP) were thought to be altered in schizophrenia, the association between autoimmunity, chronic inflammation, and psychosis is not new. Hence this study was planned to confirm the association between CRP level and cognitive performance and to determine whether CRP was a new biological indicator with the potential clinical applications in Schizoprenia patients.

Methods: This study was done as a Cross sectional study, in 60 cases of schizophrenia for period of one year done after obtaining ethical clearance, from the Institutional Ethics Committee, Government Mohan Kumaramangalam Medical College, Salem. The neurocognitive assessment tools used in this study are: a). Attention – digit span. b) Verbal memory – Rey auditory verbal learning test. C) Visual memory – Rey Osterrieth complex figure test d) Verbal fluency – COWAT – controlled oral word association test. For executive functions – Stroop colour test, Trail Making Test, were used. Assesment of CRP done by Nephelometry.

Results: There were significant differences in the cognitive subdomain analyses among the two groups based on CRP level. Serum CRP levels were found positively correlated with neurocognitive assessment tools.

Conclusion: This study supports the Neuroinflammatory theory of schizophrenia as evidenced by the rise in serum C - reactive protein values in the course of illness and there exists a positive correlation between serum C - reactive protein level and Cognitive deficits. Serial measurements of serum C - reactive protein and cognitive deficits are to be assessed, to know their fate longitudinally, over the period of time.

Keywords: schizophrenia, C-reactive protein, cognitive deficit.

Introduction

Schizophrenia is a major mental illness. It comprises a group of disorders with heterogeneous etiologies and also with different clinical presentations, treatment response and courses of illness. Signs and symptoms are variable which include changes in perception, emotion, cognition, thinking, and behaviour. The expression of these manifestations varies across patients

and over time, but the effect of the illness is always severe and is usually long-lasting. The disorder usually begins before age 25 years, persists throughout life, and affects persons of all social classes. Both patients and their families often suffer from poor care and social ostracism because of widespread ignorance about the disorder.

Patients with schizophrenia typically exhibit subtle cognitive dysfunction. There is a possibility that every person who has schizophrenia has some or other cognitive dysfunction. The study conducted by Taylor, M. A., & Abrams [1] concluded that Schizophrenic patients have cognitive impairment when compared to normal controls on all measures and showed bilateral impairment that was comparatively worse in the dominant frontotemporal regions. They found these differences were not a function of age, sex, handedness, or drug administration.

Cognitive dysfunctions are strongly related to the functional outcome of the illness. For this reason, they have clinical value as prognostic variables and also for treatment planning. Neurocognitive deficits have been shown to be associated with impairment in functional outcomes such as difficulty in instrumental and problem-solving skills, the inability to maintain successful employment, difficulty with community functioning and reduced success in psychosocial rehabilitation programmes.

The association between autoimmunity, chronic inflammation, and psychosis is not new. German neuropsychiatrist Hermann Lehmann-Facius first postulated this Inflammatory theory in 1937, which was further expanded by P.R.J. Burch in the early 1960s. Recently, scientists have expanded this theory, prompted by repeated findings of elevated inflammatory markers in patients with schizophrenia [2]. Elevated serum levels of nonspecific proinflammatory markers such as C-reactive protein and prostaglandin E2 have been noted across multiple studies, in addition to the elevated inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) [1]. Interlukin -6 is a cytokine which induces synthesis of acute phase proteins which includes C-reactive protein, serum amyloid A, and fibrinogen.

C - reactive protein and Cognitive impairment in Schizophrenia

C-reactive protein (CRP) is an annular, pentameric protein. It is found in blood plasma. It is a member of the pentraxin family of proteins and its level rises in response to inflammation [39]. It is an acute-phase protein of hepatic origin that increases following Interleukin -6 secretions by macrophages and T cells. The physiological role of CRP is to bind to Lys phosphatidylcholine expressed on the surface of dead or dying cells in order to activate the complement system via C1q. CRP is synthesized by the liver [3] in response to factors released by macrophages and adipocytes. Normal value is between 2 - 6 mg / dL. Immune system disorder is also contributing factor in the etiology of schizophrenia. Study conducted by Yolken and Torrey [4] supports the fact that inflammatory and infectious processes are potential contributing factor in the etiology and pathogenesis of schizophrenia.

Recently a special attention has been paid to C- Reactive Protein (CRP) [5] CRP is a main indicator showing inflammation or infection in the blood and body. Meta-analysis by Brian J Miller concluded the elevated levels of CRP in schizophrenia patient when compared to healthy controls. Elevated levels of CRP have been associated with more severe psychiatric symptoms and also has been associated with cognitive impairment [6] Recent studies revealed the causal association of serum CRP in the

schizophrenia patients. The study conducted by Faith Dickerson and Cassie Stallings [7] has concluded that C - reactive protein is associated with the severity of cognitive impairment. Our hypothesis is there is definitely a relation between c reactive protein levels and cognitive deficit in schizophrenia patients, based on this aims and objectives of our study is to assess the correlation between overall cognitive deficit, impairment in specific cognitive domain and Serum C- Reactive protein level in patients with schizophrenia. Also to correlate the chronicity of Schizophrenia with serum C-reactive protein level.

Materials and Methods

This study was done as a Cross-sectional study, in 60 cases of schizophrenia for period of one year from December 2020 to November 2021, done after obtaining ethical clearance, from the Institutional Ethics Committee, Government Mohan Kumaramangalam Medical College, Salem. Sample was collected as convenient sampling during the time period and all patients eligible as per inclusion criteria were included in the study. An informed consent was obtained from all the participants. Patients in age group 19-45 years, with minimum education up to 8th std those willing to participate with a diagnosis of schizophrenia and on treatment for the same were included in the study. While Aggressive and Un co-operative patients, Patients with severe catatonic symptoms, history of substance use disorders, with past history of ECT treatment, with Chronic physical inflammatory conditions which likely to increase serum CRP level and those who were not willing to participate were excluded.

A Semi-structured proforma to collect the information regarding basic socio demographic information (marital status, domicile, education and socio economic status) and duration of illness. The neurocognitive assessment tools used in this study are: a). Attention – digit span.b) Verbal memory – Rey auditory verbal learning test. C) Visual memory – Rey Osterrieth complex figure test d) Verbal fluency – COWAT – controlled oral word association test. For executive functions – Stroop colour test, Trail Making Test, were used. Assessment of CRP done by Nephelometry.

Statistical Methods

Collected data were analysed by using an appropriate statistical package (SPSS). The statistical methods used are, for descriptive statistics - Chi-square test to analyse categorical variables, independent sample t-test to asses mean and standard deviation values, and Correlation tests. As it was a cross-sectional study, the issue of loss to follow was not met.

Results

A study of 60 patients with Schizophrenia has revealed the following findings. The whole study population is divided into two groups - Group 1 and Group 2 based on the median serum CRP value.

The demographic characteristics and clinical correlates are shown below with appropriate pictorial representations. The majority of them were males (n=40). The mean age of the participants is 29.85 with a standard deviation of 6.436 (N=60). The majority of them (83.3%) reside in rural areas while only 16.7% come from urban areas. The majority of them (61.7%) were unmarried.

The following table details the education of the respondents. A majority (81.7%) of them had studied up to 8th to 12th standard. 85% of them come from lower socioeconomic status. The mean duration of illness among the study participants is 4.83 years (N=60).

Serum C - reactive protein:

The mean level of serum C-reactive protein is 14.44 (N=60). The median value of serum

CRP level was found to be 14.66. Patients were grouped based on this level. The age of the participants shown significance.

The overall participants has been divided into three groups based on their age. (<25 years. 25 - 45 years and > 45 years). Age of the patient has shown a significant increase in serum CRP level. The p value is 0.039. The educational qualification and duration of illness has also shown a significance between the two groups. The p- value is <0.5.

Cognitive function tests

The results depict the comparison between two groups along with Independent T-test values. The results are significant and are better with lower Serum CRP.

Table 1: Cognitive Function Tests

	Group 1 (S.CRP<14.66) Mean	Group 2 (S.CRP>14.66) Mean	T-Test	p-value
Rey Osterrieth Complex figure				
Copy	18.17	14.20	4.797	<0.005
Immediate Recall	16.40	15.73	0.724	>0.05
Delayed Recall	12.73	11.00	2.525	>0.05
Trail test				
Trail A	64.97 secs	102.333 secs	-5.242	<0.005
Trail B	95.90 secs	160.40 secs	-6.904	<0.005
Stroop test				
I	44.40	40.47	2.418	<0.05
II	35.40	31.27	1.971	<0.05
III	13.07	11.63	1.485	>0.05
Digit Span				
Forward	9.53	8.20	2.725	<0.05
Backward	5.80	4.97	2.110	<0.005
COWAT	11.30	9.73	3.007	<0.005
AVLT (Average)	8.58	7.4	5.026	<0.005

Rey Osterreith Complex figure test (ROCF)

In ROCF test, there is a significant p value in the Copy. The p value is found to be less than 0.005. But, the p value is insignificant in the Immediate recall and Delayed recall methods which is found to be more than 0.05. In this test, the group 1 participants were able to score a better mean of 18.17 when compared to group 2 who were able to score only 14.20 as a mean score. This result is showing that patients with a low serum CRP are able to copy the figure in better manner when compared to those having a raised serum CRP values. Even though the p value is insignificant in case of Immediate recall and Delayed recall, the mean scores obtained by the group 1 is more when compared to group 2, which once again confirming the finding that there is better performance in patients having low serum CRP.

Trail Making Test (Trail A, Trail B)

In both Trail A and B, the two groups were compared on the basis of time taken to complete the trail making test. The p value is found to be significant in both the tests and is found to be less than 0.005. The mean time taken to complete Trail A test is found to be 64.97 seconds for group 1 patients with a serum CRP value less than 14.66. But, the group 2 patients with a serum CRP level more

than 14.66 has taken a mean duration of 102.33 seconds to complete the Trail A test. This has shown a considerable effect of raised serum CRP value in this test. The mean time taken for the completion of Trail B test by group 1 patients is found to be 95.90 seconds (Figure 8) when compared to the group 2 patients with a mean serum CRP value of more than 14.66 who were able to complete the Trail B test only with a mean duration of 160.40 seconds.

Stroop Test

In Stroop 1 test, the group 1 patients were able to score a mean value of 44.40 when compared to the group 2 with raised serum CRP level who were able to score a mean value of 40.47 which is less when compared to those having a serum CRP value less than 14.66. The p value is found to be less than 0.05 and is significant. In Stroop 2 test, the group 1 patients were able to score a mean value of 35.40 when compared to the group 2 patients who were able to make up only 31.27 as a mean value, which is less when compared to the group 1 patients. The p value is found to be less than 0.05 which is significant. In Stroop 3 test, there is only a minimal difference in between the two groups. The group 1 patients scored a mean value of 13.07 when compared to group 2 patients who scored 11.63 as a mean. The p value is found to be greater than 0.05 and is insignificant.

Digit span

In Forward Digit span (DF) task , group 1 patients with a serum CRP level less than median vale were able to score a mean vale of 9.53 which is better when compared to the group 2 with a mean score of only 8.20. The p value is found to be less than 0.05 which is significant. In Backward Digit span (DB) Task, there exists a significant difference with a significant p value of less than 0.005. The group 1 patients were able to score a mean value of 5.80 which is a better score when compared to the group 2 who were able to score a mean vale of 4.97.

Controlled Oral Word Association Test (COWAT)

COWAT shown a significant difference between the two groups. Group 1 were able to score a mean value of 11.30 which is a better score when compared to the Group 2 mean value of 9.73. The p value is found to be less than 0.005 which is significant.

Auditory Verbal Learning Test (AVLT)

The results depict the comparison between two groups along with Independent T-test values. The results are significant and are better with lower Serum CRP. AVLT consists of five trials. In Trial 1, the group 1 were able to score a mean value of 8.77 which is better when compared to the group 2 who were able to score a mean value of only 6.87. The p value is less than 0.005 which is significant. In Trial 2, the group 1 were able to score a mean value of 8.23 which is better when compared to the group 2 who were able to score a mean value of only 7.20. The p value is less than 0.005 which is significant. In Trial 3, the group 1 were able to score a mean value of 8.67 which is better when compared to the group 2 who were able to score a mean value of only 7.47. The p value is less than 0.005 which is significant.

In Trial 4, the group 1 were able to score a mean value of 8.53 which is better when compared to the group 2 who were able to score a mean value of only 7.73. The p value is less than 0.005 which is significant. In Trial 5, the group 1 were able to score a mean value of 8.70 which is better when compared to the group 2 who were able to score a mean value of only 7.70. The p value is less than 0.005 which is significant. On an average of the above five trials, the group 1 were able to score a mean value of 8.58 which is better when compared to the group 2 who were able

to score a mean value of only 7.40. The p value is less than 0.005 which is significant.

In List B, the group 1 were able to score a mean value of 8.23 which is better when compared to the group 2 who were able to score a mean value of only 7.20. The p value is less than 0.005 which is significant. In Immediate recall of list A, group 1 were able to score a mean value of 8.70 which is better when compared to the group 2 who were able to score a mean value of only 7.80. The p value is less than 0.05 which is significant.

In Delayed recall of list A, group 1 were able to score a mean value of 9.13 which is better when compared to the group 2 who were able to score a mean value of only

7.97. The p value is less than 0.05 which is significant. In Recognition hits, there is no significant difference between two groups. Group 1 patients scored a mean value of 26.13 when compared to the group 2 mean value of 25.77. The p value is more than 0.05 which is not a significant one.

In Omission, both the groups were able to perform almost in a similar manner. In Commission, Group 1 patients scored a mean value of 1.30 which is a better score when compared to the Group 2 patients who scored a mean value of 1.67. But, the p value is more than 0.05, which is not significant.

Correlation tests of cognitive function tests and Serum CRP

The results are significant and are better with lower Serum CRP. Rey copy shown a negative correlation of 0.453 which is significant at level of 0.01. Even though the p value of Immediate and Delayed recall is not significant, correlation tests shown a negative correlation in Immediate recall (-0.039) and also in the Delayed recall (-0.279) which is significant at the level of 0.05. Digit forward test has shown a negative correlation (- 0.364) which is significant at the level of 0.01. Digit backward also shown a negative correlation of 0.288 which is significant at the level of 0.05. Stroop 1, Stroop 2 and Stroop 3 shown a negative correlation with the values of 0.205, 0.273 and 0.271. These correlation values are significant at the level of 0.05.

Trail A and Trail B tests has shown a strong positive correlation with the values of 0.504 and 0.546 which are significant at the level of 0.01. COWAT shown a negative correlation of 0.243. AVLT in all the five trials and average score has shown a strong negative correlation with the findings of 0.578 (AVLT 1), 0.452 (AVLT 2), 0.573 (AVLT 3), 0.536 (AVLT 4), 0.547 (AVLT 5) and 0.547 (Average) which are significant at the level of 0.01 level.

List B, Immediate recall- A and Delayed recall- A has also shown a strong negative correlation with the finding of 0.540,0.417 and 0.384 respectively, which are significant at the level of 0.01. Recognition hits has shown a strong negative correlation of 0.398 which is significant at the level of 0.01. Omission has shown a positive correlation of 0.277 which is significant at the level of 0.05. Commission has shown strong positive correlation of 0.397 which is significant at the level of 0.01.

Discussion

Many studies already have shown the evidence for cognitive impairment in schizophrenia. It is a well observed fact that the cognitive impairment in schizophrenia is due to various etiopathology. Of all the causative factors behind the cognitive impairment in schizophrenia patients, the possible role of neuroinflammation is gaining importance in the recent studies.

The studies have analysed the neurocognitive function by using neurocognitive tests like Stroop colour test, Trail Making test, Digit forward and Digit backward tests. In this study, we have used the same tests to assess

the cognitive function. In Digit forward, our patients scored in a lower range. The maximum score in our study is 14 (Maximum score that can be obtained is 16) and the least score is 4. Majority of patients scored around only 8. In Digit backward also, our patients scored in a lower range. Maximum score in this study is 10 and minimum being 4 (Maximum score that can be obtained is 14).

In Trail making test- A, out of 60 patients in our study, 28 patients are able to complete the task in a duration of more than 78 seconds which is exceeding the normal time needed to finish the test. Also, in Trail making test-B, the normal average time being 75 seconds, majority of the participants in this study (54 out of 60) completed the task taking a time more than the average duration.

In all these neurocognitive assessment tests in this study, we also have a similar decline in the domains like working memory, Immediate and Declarative memory, Attention and visuospatial abilities, as concluded by the study done by Reichenberg and Harvey which is further favouring our study results. In the meta-analysis done by Aleman A [8] they revealed a stable and also a significant association between the schizophrenia and the short-term memory impairment.

We have similar results in this study indicating a significant correlation between the schizophrenia and the memory impairment that too in various domains. In the Auditory verbal learning test, significant proportion of patients in our study scored a lower value in all the trials except recognition component of Auditory verbal learning test.

In this study, we assessed the various cognitive domains using Digit span, Trail making test, stroop test, Rey Auditory verbal learning test. After the interpretation of neurocognitive test results, we found that majority of study population had deficits in most of the domains. In trail making test A, about 45 percent of participants are able to complete the task in a period of more than 78 seconds which indicates a deficiency in the processing speed and only one patient completed the task within the normal average time of 29 seconds. The remaining participants took more time than the average duration to complete the task. From this it can be deduced about 75 percent of our patients are having impairment in this particular domain. This percentage is similar to the quantitative study done by Heinrichs and Zakzanis [9]

In Auditory verbal learning test, except the recognition, in all the other trials the participants in this study have scored a lesser score. In this study, the mean duration of illness is 4.83 years, which is less when compared to the mean duration of illness(12.7 years) in the study conducted by Heinrichs and Zakzanis [9]. This indicates that the cognitive impairment can occur even with a lesser duration of illness. From all the above studies, it is evident that there is undoubtedly cognitive impairment in schizophrenia. The prevalence of cognitive impairment in schizophrenia in our study is comparable to the results of various studies already conducted in this particular aspect.

In the study conducted by Abayomi O. Akanji *et al*, they found that patients with schizophrenia were having an increased high sensitivity C-Reactive protein levels (hs-CRP). They evaluated 207 schizophrenia patients and 165 healthy controls. They found a significant raise in the hs - CRP of the schizophrenia patients when compared to the healthy controls. This study further reinforced the inflammatory basis of schizophrenia.

In this study, as explained earlier in the methodology, the whole study population have been divided into two groups (Group 1 and Group 2) based on the median value of serum C- Reactive protein value, for the

purpose of comparing the neurocognitive test results between the two groups. The study conducted by Nazila Diyanoosh [10] *et al* have revealed a positive and also a significant correlation between the cognitive impairment and the serum C - reactive protein level. They assessed the correlation between serum C - reactive protein and cognitive impairment in 75 schizophrenia patients within an age group of 18 to 65 years.

They found high serum C-reactive protein levels even up to 60.3 in their study. They have used Mini Mental Status Examination in their study to assess orientation, information registering, attention and calculation, verbal, movement, and design skills. The minimum cognitive deficit score was 6 and maximum was 30, showing a considerable cognitive deficit. They found that rise in serum C-Reactive protein concentration resulted in an increased deficit in cognitive performance.

In a cohort study conducted by Dickerson *et al* [11] they measured serum C-Reactive protein levels in 413 individuals with schizophrenia. The selected patients were in the age group of 13 to 65 years and with a mean duration of schizophrenia of 19.1 years. Participants were administered a brief cognitive test battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), 127 patients were found to have elevated CRP constituting to about 26.1 percent of the participants.

They found that the mean RBANS score of the CRP elevated group was lower than that of the CRP normal level group. They came to a conclusion that the cognitive impairment in CRP elevated schizophrenia patients likely to be related to an inflammatory process occurring within the vasculature of the central nervous system.

In this study, about 85 percent of participants are with elevated serum C - reactive protein. The mean duration of schizophrenia is also 4.83 years. This can be explained by the study conducted by Ohaeri *et al[4]* which revealed that serum CRP levels might rise even during the onset of psychotic symptoms at the initial stage of schizophrenia.

In the study conducted by Ewa Bulzacka *et al* [12] they have suggested that abnormal serum C-Reactive Protein level is associated with cognitive impairment in patients with schizophrenia. In their study, they included 369 schizophrenia patients. They used Wechsler Adult Intelligence Scale to measure the General Intelligence. Their study revealed that out of 369 patients, 104 patients (28.2% of sample size) had abnormal serum C - reactive protein levels. They found that cognitive functions were found to be significantly impaired in Schizophrenia subjects with abnormal CRP levels compared to those without abnormal CRP levels.

We are having similar results in our study indicating a cognitive impairment in those patients with an elevated serum C-Reactive protein levels. In the study conducted by Dorota Frydecka [13] they included 151 schizophrenia patients and 194 controls. The mean duration of illness was 12.2 years.

They measured hs - CRP in randomly selected subgroup of 88 schizophrenia patients and 88 controls. Cognitive performance in schizophrenia patients was assessed using Rey Auditory Verbal Learning Test (R, Trail Making Tests (TMT-A and TMT-B), Verbal Fluency Tests (FAS letters), Stroop test as well as selected Wechsler Adults Intelligence Scale (WAIS-R-Pl) subtests: Digit Symbol Coding Test, Digit Span Forward and Backward and Similarities.

They found significant impairment in schizophrenia patients with elevated serum CRP across all the domains tested. They revealed that, in Rey Auditory verbal learning test, there was lower scores on immediate recall span in the patients who were with high levels of serum C-Reactive

protein. They also concluded that the cognitive impairments observed in patients with schizophrenia might be the consequence of elevated serum C-Reactive protein levels which is an indicator of subclinical inflammation.

All the studies so far done in relation to the role of inflammation as the causative factor and cognitive impairment in schizophrenia has proved the role of serum C- Reactive protein in the cognitive impairment in schizophrenia patients. Our study with a sample size of 60, is also exhibiting a elevated serum C-Reactive protein levels in majority of the participants shows significant relationship between the cognitive impairment and serum CRP level, which is comparable with the previously done studies in this context.

Conclusion

This study supports the Neuroinflammatory theory of schizophrenia as evidenced by the rise in serum C- Reactive protein values in the course of illness and there exists a positive correlation between serum C-Reactive protein level and Cognitive deficits.

Serial measurements of serum C- Reactive protein and cognitive deficits are to be assessed, to know their fate longitudinally, over the period of time. Other inflammatory markers like Interlukin-6 also to be assessed in order to know the role of inflammation in the pathogenesis of cognitive impairment in schizophrenia.

Limitation of the study

This study was done as an cross sectional study, with a smaller sample size for a period of one year. If it's done as a prospective observational study with a follow up with a larger study group. There may be further insight of how disease progresses and there is an impact of cognitive memory at what stage and the trend of CRP in relation to that.

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