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Association Of Elevated Levels Of Inflammatory Markers And D-Dimer With Psychosis In COVID-19 Patients And A Brief Review Of Possible Underlying Mechanism Of COVID Psychosis: A Retrospective Study In A Tertiary Care Hospital.

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ABSTRACT

COVID-19 disease is caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). In most of the cases the patients present with typical symptoms of fever, cough, dyspnea, sore throat etc. The involvement of central nervous system by SARS-CoV-2 resulting in encephalopathy, encephalitis and neuropsychiatric symptoms such as anxiety, depression, panic attack and post traumatic symptoms have been described in the literature. But the clinical presentation of Psychosis as a neuropsychiatric manifestation in COVID-19 patients has been described in very few literatures. Our aim of the study was to find out the incidence of Psychosis in COVID-19 patients and its association with elevated levels of inflammatory markers such as IL-6, CRP etc, and with that of elevated coagulation parameter such as D-dimer values. Severity of Pneumonia (by HRCT thorax), neuropsychiatric presentation of Psychosis and the various interventions received by the COVID-19 patients with Psychosis were also studied. Out of 2752 COVID-19 cases new onset COVID Psychosis was seen only in 36 cases with an incidence of 1.308%. Out of these, 30 cases were aged > 60 years (83.3%) with male predominance (n=25)(69.44%) Psychotic manifestations such as delusion, hallucinations and mania were seen in 34 (94%), 32(88.8%) and 28 (77.7%) cases respectively.

Keywords: COVID-19, Psychosis, D-Dimer, IL-6.

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INTRODUCTION

Coronavirus is a single stranded RNA virus with a distinct crown like outer envelope [1]. Corona viruses cause a respiratory disease known as Severe Acute Respiratory Syndrome (SARS). In 2002-2004 there was an epidemic of SARS by a strain of corona virus known as SARS-Cov-1 with a case fatality Rate(CFR) of 11% [2]. In December 2019 another strain of SARS-CoV was identified causing SARS known as SARS-Cov-2 [3]. This new strain caused corona virus disease 2019 (COVID-19) which soon became a pandemic (COVID -19 Pandemic) [4]. SARS-Cov-2 predominantly involve the respiratory system with the typical presentation of fever, cough, shortness of breath, sore throat etc. Apart from the respiratory system COVID-19 infection affects multiple other systems such as cardiovascular, Gastrointestinal, hematological & neurological systems [5, 6]. Involvement of the nervous system in COVID-19 resulting in cerebrovascular disease, encephalopathy, encephalitis and new onset anosmia and dysgeusia has been documented in the literature [7-9]. Previous reports from epidemic caused by SARS-Cov-1 the range of Psychiatric complications include anxiety, depression, suicidal ideation, organic hallucinosis & organic manic disorders [10]. Use of high dose corticosteroid in SARS has been identified as a significant associated factor in Psychotic presentations [10-12]. In COVID 19 Disease acute neurological symptoms has been documented by Mrcpsych, et al 2020 [13]. To date psychiatry research has mainly focused on the emotional impact of the corona virus pandemic on the general population [14]. New onset Psychosis in COVID-19 patients has been documented only in few literatures [15]. Psychosis is a severe mental disorder in which thought and emotions of an individual are so impaired that contact is lost with reality. In this study we have retrospectively analyzed new onset psychosis in COVID-19 patients.

Our aim of the study was to find out the incidence of new onset Psychosis in COVID-19 patients and its association with elevated levels of inflammatory markers such as IL-6 & CRP and elevated D-dimer levels. We have also described in brief the various neuropathogenetic mechanisms of new onset Psychosis in COVID -19 patients.

MATERIALS AND METHODS:

Place of Study

This was a retrospective study done in College of Medicine and Sagore Dutta Hospital (CMSDH, Kolkata-58).

Duration

The study was conducted between June 2020 to June 2021 (a period of 1 year).

Study Population

Inclusion Criteria

Patients with the following criteria's

- Adult patients (age >=18 years with positive RT PCR test for COVID 19 infection) and
- Having Psychosis developed after or concurrent with COVID-19 infection were included in the study.

Exclusion Criteria

- Individuals having medication induced Psychotic symptoms and Psychotic symptoms due to another medical conditions were excluded [16].
- Psychosis entirely to delirium are excluded as COVID-19 is a well established cause of delirium [17] & Psychotic symptoms are common in delirium [18].
- Patients with previous history and/or family history of severe mental disorders were also excluded.

Study Variables

The following study variables (parameters) were taken into consideration in this study.

- Clinical presentation with respect to respiratory symptoms and neuropsychiatric manifestations.
- Therapy for COVID 19 infection
- Antipsychotic therapy received.
- Hematological parameters - CBC
- D-dimer level.
- Biochemical Parameters-IL -6,CRP
- Radiological report : HRCT OF lungs
- Histopathological examination of the brain tissue obtained after autopsy.

Data collection

- The data on clinical presentation of the patients were retrieved from the clinical records of the COVID wards and the critical care unit(CCU) of our hospital.
- Treatment history in terms of therapy for COVID infection itself and antipsychotic therapy received were obtained from the clinical records.
- D-dimer level estimation was done by fully automated coagulation analyzer, STA Satellite Max, Stago, France by utilizing CL89050422.
- D-dimer levels were analyzed because of the hypercoagulable state induced by it leading to microvascular damage and hypoxia in the brain tissue.
- Biochemical parameters such as
  - IL-6 were measured by Cobas using CLIA principle.
  - CRP was measured by ERBA XL640/ ERBA-EM 360 by utilizing Turbi principle.

Severity of Pneumonia was assessed by analyzing the HRCT reports.

For histopathological examination of brain tissue samples were obtained by autopsy of died COVID patients which were hospitalized in our institution. Considering the recommendations provided by WHO (World Health Organization) [19] for performing autopsies on highly infectious disease and COVID-19 guidelines for Dead Body Management [20] a protocol was prepared and complete pathological autopsy was performed. Brain tissues obtained by autopsy were processed following routine tissue processing methods and hematoxylin and eosin (H&E) stained histopathological slides were prepared and examined under the light microscope.

Data Collection Sheet

- Age & Sex.
- Clinical presentation in terms of severity of respiratory symptoms.
- Therapy received for COVID Infection
- Antipsychotic symptoms.
- Antipsychotic therapy received
- Findings of HRCT of thorax .
- D-dimer levels.
- IL-6, CRP levels.
- CBC.
- Histopathological findings of brain tissue.
- Other analytical markers - like creatinine and transaminase.
- Presence of co-morbid conditions.
- CT/MRI of brain.

Statistical Analysis

All the data collected were analyzed by using the software SPSS version 20.0 and the values were represented and numbers(n) and percentage(%). Comparison was done by x^2 test.

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P-Value

<0.05 was considered statistically significant.

Ethical Consideration

The study was approved by the Institutional Ethical Committee (IEC) of our Institute.

RESULTS

In our study out of 2752 COVID cases only in 36 cases new onset COVID Psychosis seen(1.3%).

In our study majority of the COVID 19 patient with new onset COVID psychosis were above 60 years of age (n=30, 83.3%), only few cases seen in young patients. Increase incidence of new onset psychosis in older individuals reflects the underlying vulnerability to develop Psychosis while they are medically ill.

Most of the patients (n=29, 80.55 %) had any one of the underlying co-morbid conditions such as Diabetes Mellitus, HTN, IHD, COPD, Bronchial asthma, CKD etc. presence of these co-morbid conditions in COVID-19 patients (who had developed new onset Psychosis) is important from clinical point of view because these conditions can lengthen the duration of Psychosis. (28,29). High flow Oxygen(>20L/min) therapy given in the critical care unit (CCU) in 29 cases(80.55%).

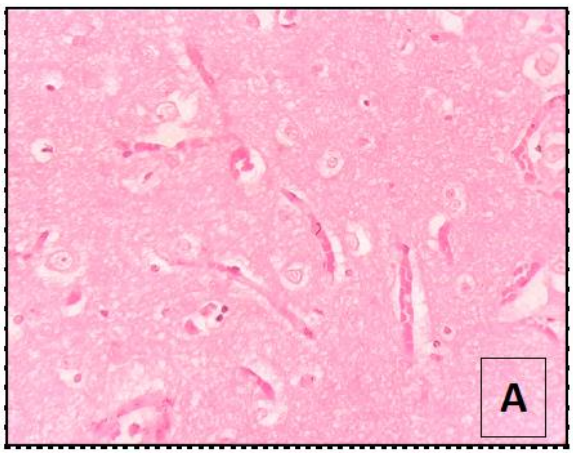
Out of 36 cases in 29 cases there were Severe COVID Pneumonia as evidenced on HRCT of thorax with a CT Severity Score(CTSS) of ≥18.

In our study all these patients received any one of the antipsychotic medications such as Olanzapine, Risperidone and Haloperidol in low dose.

In our study the patients who did not require CCU support (Mild to moderate COVID Pneumonia) the psychotic symptoms were mostly self limited (n=7, 19.44%). Patients with COVID Psychosis had significantly higher levels of IL-6, CRP and D-dimer levels. In our study other analytical markers such as Neutrophil to Lymphocyte ratio (N:L), creatinine, transaminase as a part of renal function test and liver function test respectively were also studied.

Out of 36 cases of COVID Psychosis 3 patients (who died suddenly) the autopsy pathological findings of brain tissues were available. The histopathological features include microvascular clogging by RBCs and fibrin thrombi contributing to brain ischemia. Along with this there were, hypertrophic astrocytes and perivascular lymphocyte aggregation as a response of brain tissue to ischemic injury.

In all the cases of COVID psychosis in our study the psychotic symptoms improved completely by low dose antipsychotics. So, no long term follow up records were available.



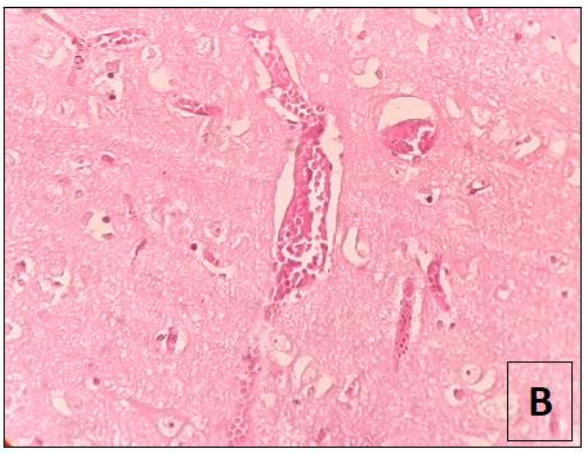


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Figure 1(A&B): Microvascular clogging by RBCs in brain tissue (H&E, 100X and 400 X)

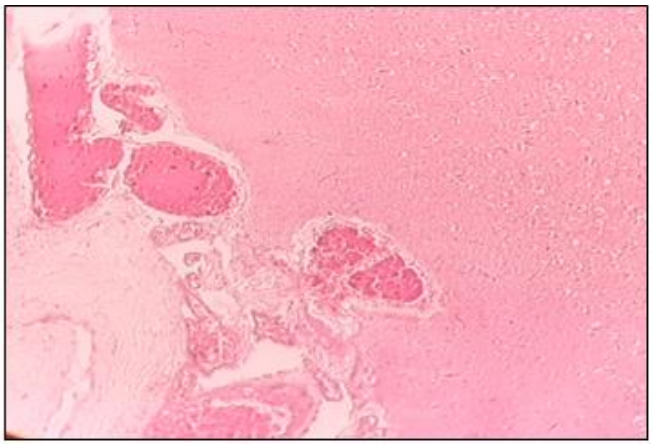

Figure 2: Microvascular clogging by fibrin thrombi in brain tissue (H&E, 100 X)

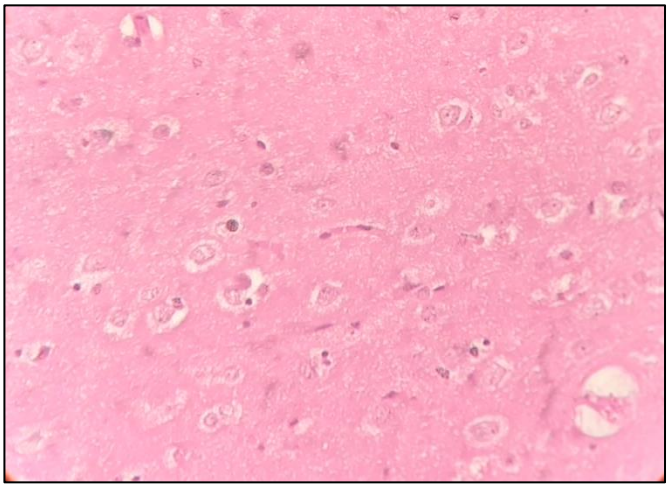

Figure 3: Reactive astrocytes as a response of hypoxic injury in brain tissue (H&E, 400 X)

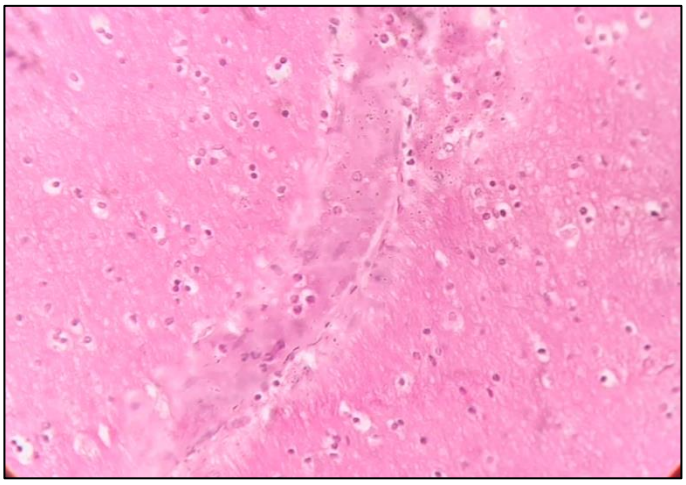

Figure 4: Perivascular lymphocytes as a response of hypoxic injury in brain tissue (H& E, 100X)

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Clinical presentation of the patients such as age, sex, respiratory, gastrointestinal and neuropsychiatric manifestations are described in Table-1 and represented as numbers(n) and percentage (%).

- Various interventions the Covid patients received are described in Table-2.
- Association of elevated levels of IL-6, CRP & D-dimer with that of Covid Psychosis are shown in Table-3.
- Severity of Pneumonia(on HRCT of thorax), co-morbid conditions and other laboratory findings in patients with Covid Psychosis are analysed in Table-4.

Table 1: Age, Sex and clinical presentation of patients with covid psychosis.(n=36)

Parameters	Number	%
i) Age		
>60 yrs.	30	83.3 %
<60 yrs.	6	16.66%
ii) Sex		
Male	25	69.44 %
Female	11	30.55%
i) Respiratory Symptoms		
Dyspnea, cough ,sore throat	30	83.33%
ii) Neuropsychiatric Presentations		
Delusion	34	94%
Hallucination	32	88.8%
Mania	28	77.7%
iii) Fever	32	88.8 %
iv) Gastrointestinal Symptoms :-		
Loose motion	6	16.66%

Table-2-Treatment (interventions) received by the patients with Covid Psychosis(n=36).

Interventions	Number of patients received	%
(A) Oxygen Therapy (i) Low flow Oxygen (@5 to15 L/min) given in the general covid ward via Nasal Prong, Face Mask,NRBM	7	19.44%
(ii) High flow Oxygen(>20L/min) therapy given in the critical care unit (CCU) via Venturi Mask. - High flow nasal oxygen - Mechanical ventilation	29	80.55%
(B) Drug therapy for Covid 19 infection (i) Antibiotics- Azithromycin(500 mg ODx5d) Or Amoxycillin-Clavulinic acid(625 mg TDS X 6 days)	36	100%
(ii) Hydroxy Chloroquine (400 mg BD f/b 400 mg ODx4d)	36	100%
(i) Glucocorticoids (SPo_2<90%) (8 mg ODx3-5 days)	29	80.55%
(ii) LMWH (to combat hypercoagulability) (1 mg/Kg/day) (iii) Tocilizumab, Remdesvir [(If IL-6 level >5 times)]	18 6	50% 16.66%
C) Antipsychotic therapy		
Haloperidol (10 mg) Olanzapine (5 mg) Risperidone (2-4 mg/day)	12 14 10	33.33% 38.88% 27.77%

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Table 3: Association of inflammatory markers (IL-6, CRP) and D-dimer level with covid sychosis.(n=36)

Parameter		Number of patients received	%	P. Value
		Yes	No	
		Yes	No	
i)	IL-6 >35 pg/ml.	30(83%)	6(16.6%)	<0.001
ii)	CRP >10 mg/ml.	28(77.7%)	8(22.2%)	<0.001
iii)	D-dimer >2.4µg/ml.	24(66.0%)	12(33.3%)	<0.001

Table 4: Severity of Pneumonia(on HRCT of thorax), co-morbid conditions and other laboratory findings in patients with Covid Psychosis.(n=36)

Parameters	Number of patients	%
i) Severity of Pneumonia(HRCT)		
1. Mild (Score ≤ 7)	1	2.77%
2. Moderate (Score 8-17)	7	19.44%
3. Severe (Score ≥ 18)	29	80.55%
ii) Co-morbid conditions		
1. DM	9	25%
2. HTN	6	16.66%
3. Bronchial Asthma	3	8.33%
4. COPD	4	11.11%
5. CKD	3	8.33%
iii) CBC		
N:L Ratio ≥ 3.13	6	16.66%
iv) Raised creatinine (RFT)	4	11.11%
v) ↑ Transaminases (LFT)	2	5.5%
vi) CSF examination	Not available	-

DISCUSSION

Psychosis is a severe mental disorder which may occur as a result of an underlying psychiatric illness such as Schizophrenia or may be caused by medication, alcohol/or substance use or an underlying health condition.

In this study we have analyzed new onset psychosis in individuals having the underlying health condition as COVID-19 disease. Patients having psychosis have any one of the following symptoms such as

- Trouble thinking clearly or concentrating.
- Suspiciousness or unease around others.
- Lack of self care or hygiene.
- Spending more time alone than usual etc.

Various mechanisms have been postulated for the new onset psychosis in COVID-19 patients as discussed below:

- It has been hypothesized that human corona viruses and other respiratory viruses may act as opportunistic pathogens of the CNS as they have been shown to have neuroinvasive qualities due to autoimmunity or viral replication [21].
- According to Lee et al [12] and Troyer et al [22] CNS penetration and neuroinflammation by the corona virus has been associated with new onset psychotic disorders in COVID-19 patients .

- Elevated inflammatory markers particularly CRP and IL -6 raise the possibility of a virus associated inflammatory trigger. Profound inflammatory response to COVID-19 infection i.e "Cytokine Storm" has been postulated to produce neuropsychiatric symptoms through immunological mechanism [22, 23].
- Organoids (miniaturized clumps of brain tissue made by coaxing human Pluripotent stem cells to differentiate into neurons built by Muotris team showed that SARS-CoV-2 could infect neurons in these organoids, killing some of them and reducing the formation of synapses between them [24].
- Another evidence of corona virus affecting brain tissue was given by Mary Fowkers team who showed the presence of Corona virus in the brain tissue itself by Electron Microscopy. (Brain tissue obtained by post mortems in 67 people who had died of COVID-19 as posted in a reprint in late may) [25].
- SARS-COV-2 RNA has been recently isolated from the central Nervous system of the COVID-19 patients which provides the evidence of neurotropic nature of COVID-19 virus [8, 26].
- In a review of Literature Troyer et al [22], postulated that direct viral infiltration of CNS, transmigration into CNS through blood leukocytes, and central and peripheral cytokine activation causing CNS inflammation and blood brain barrier compromise are the possible mechanism for the neuropsychiatric manifestations.

In our study majority of the COVID 19 patient with new onset COVID psychosis were above 60 years of age(n=30, 83.3%), only few cases seen in young patients. Increase incidence of new onset psychosis in older individuals reflects the underlying vulnerability to develop Psychosis while they are medically ill [27].

Most of the patients (n=29, 80.55 %) had any one of the underlying co-morbid conditions such as Diabetes Mellitus, HTN, IHD, COPD, Bronchial asthma, CKD etc. presence of these co-morbid conditions in COVID-19 patients (who had developed new onset Psychosis) is important from clinical point of view because these conditions can lengthen the duration of Psychosis [28, 29].

Out of 36 cases in 29 cases there were Severe COVID Pneumonia as evidenced on HRCT of thorax with a CT Severity Score(CTSS) of ≥18.

According to Ferrando et al, 2020 [15] patient with COVID Psychosis were asymptomatic from respiratory system infection point of view and the psychotic symptoms were characterized by thoughts of reference and structural delusional belief. In our study mostly the patient were very much agitated, there was disorientation to space and time, disorganized thinking and hallucinations. These features were similar to the study described by Martin recently [30]. All these features persisted for a very short period (<7 days). This is because probably most of the patients in our study had Severe Pneumonia(CTSS ≥18) requiring prompt management in the Critical Care Unit(CCU). Along with the improvement of the respiratory symptoms, Psychotic symptoms also subsided.

In our study all these patients received any one of the antipsychotic medications such as Olanzapine, Risperidone and Haloperidol in low dose.

In our study the patients who did not require CCU support (Mild to moderate COVID Pneumonia) the psychotic symptoms were mostly self limited (n=7, 19.44%) which was similar to the findings of Spanish Influenza pandemic review by Meninger et al [31].

Out of 36 cases of COVID Psychosis 3 patients (who died suddenly) the autopsy pathological findings of brain tissues were available. The histopathological features include microvascular clogging by RBCs and fibrin thrombi contributing to brain ischemia. Along with this there were, hypertrophic astrocytes and perivascular lymphocyte aggregation as a response of brain tissue to ischemic injury.

Patients with COVID Psychosis had significantly higher levels of IL-6, CRP and D-dimer levels.In our study other analytical markers such as Neutrophil to lymphocyte ratio (N:L), creatinine, transaminase as a prat of renal function test and liver function test respectively were also studied.

Follow Up

In all the cases of COVID psychosis in our study the psychotic symptoms improved completely by low dose antipsychotics. So, no long term follow up records were available.

Limitations

- In this study the data on CSF examination and virus PCR were not available restricting the data on complete neurological examination report.
- Data on follow up of these patients were not available.

CONCLUSION

Psychosis is a complex condition with many etiologies. The data on new onset psychosis in COVID-19 patients have been described in very few literatures. We had analyzed the potential neuropathogenesis of new onset psychosis in COVID-19 patients and its association with elevated inflammatory markers such IL-6 & CRP etc. This neuropathogenesis warrants further investigations such as measurement of broader array of cytokines such as TNF-α, Il-8, IL-10 and IL-2R along with IL -6 and CRP in peripheral blood and CSF would characterize immune activation both centrally and peripherally.

In our study Critically ill COVID-19 patients who received prompt therapy for the underlying COVID-19 infection and its associated inflammation the symptoms of Psychosis lasted for a very short period and improved along with the improvement of respiratory symptoms. This observation indicates towards a conclusion that the antipsychotic medications could likely be obviated or mitigated by the effective treatment of the underlying COVID-19 infection and its associated inflammation.

Considering the various neuropathogenetic mechanisms of COVID psychosis and its variable clinical symptoms larger prospective studies should be conducted for exploration of the various modalities of management and follow up of COVID-19 patients developing psychosis.

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