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Concurrent catatonia and COVID-19 infection – An experiential account of challenges and management of cases from a tertiary care psychiatric hospital in India

ARTICLE INFO

Keywords

COVID
Catatonia
Neuropsychiatric
Benzodiazepines
Electroconvulsive therapy
ECT

ABSTRACT

Catatonia has been reported as one among many neuropsychiatric manifestations associated with COVID-19 infection. Catatonia and COVID-19 co-occurrence remain clinical concerns, often posing challenges pertaining to diagnosis, and especially management. Limited information is available regarding the appropriate approaches to the management of catatonia in COVID-19 infection, particularly with reference to the safety and efficacy of benzodiazepines and Electro-convulsive therapy (ECT). We present our experience of five patients with catatonia consequent to heterogeneous underlying causes and concurrent COVID-19 infection, who received care at the psychiatric COVID unit of our tertiary care psychiatric hospital. An interesting observation included varying underlying causes for catatonia and the potential role that COVID-19 infection may have played in the manifestation of catatonia. In our experience, new-onset catatonia with or without pre-existing psychiatric illness and concurrent COVID-19 can be safely and effectively managed with lorazepam and/or ECTs. However, critical to the same is the need to implement modified protocols that integrate pre-emptive evaluation for COVID-19 disease and proactive monitoring of its relevant clinical parameters, thereby permitting judicious and timely implementation of catatonia-specific treatment options.

1. Introduction

Catatonia is a complex syndrome of specific psychomotor abnormalities occurring in the context of various medical and neuropsychiatric illnesses (Padhy et al., 2014). Untreated catatonia is associated with significant risks of mortality and morbidity, secondary to medical complications, such as malnutrition, infections, contractures, metabolic disturbances, and severe presentations such as malignant catatonia (Padhy et al., 2014).

Catatonia has been previously associated with viral influenza (encephalitis lethargica) (Scheiner et al., 2021). Similarly, new-onset catatonia with other psychiatric symptoms or worsening of previous psychiatric disorders with COVID (Coronavirus disease) – 19 infection has been reported (Torrico et al., 2021; Zandifar and Badrfam, 2021). Proposed mechanisms include inflammation, stress, and psychological factors (Scheiner et al., 2021). Catatonia, in particular, has been reported either as a primary manifestation, co-occurrence, or sequelae of COVID-19 (Amouri et al., 2021; Caan et al., 2020; Mulder et al., 2021) with unfavorable outcomes in most. For management of catatonia, irrespective of cause, parenteral benzodiazepines and/or Electroconvulsive therapy (ECT) are primary treatment options (Rasmussen et al., 2016). However, providing these interventions in the background of COVID-19 infection poses several challenges (Gouse et al., 2020). Benzodiazepines increase the risk of respiratory depression while general anesthesia for ECT increases the risk of aerosol-based spread, in addition to inherent risks in medically ill/unstable patients (Surve et al., 2021).

In this paper, we share our experience of five patients who were admitted to the Psychiatric Covid Unit (PCU) (Navin et al., 2021) at the National Institute of Mental Health and Neuro Sciences (NIMHANS) which is a tertiary care psychiatric hospital in Southern India. Our set-up

was unique, wherein medical management for COVID-19 was provided concurrently with treatment for catatonia by the psychiatry team. Transfers to multi-specialty hospitals were made only when severe COVID-19 infection was noted or if progressive clinical deterioration occurred despite relevant treatment. Requisite medical care and evaluation were provided for all patients as per the Indian Council of Medical Research (ICMR) COVID management guidelines (Ministry of Health and Family Welfare India, 2021). These included monitoring of vitals 6th hourly, including oxygen saturation, respiratory parameters, and assessment of oral intake and clinical status by a nurse and on-duty medical officer (resident in Psychiatry). All patients received oral multivitamin and zinc tablets (100 mg per day). Oral Ivermectin up to 24 mg per day for 5 days/ Oral Doxycycline 200 mg per day for 5 days/oral Azithromycin 500 mg per day for 5 days either alone or in combination were given as per existing universal recommendations prevalent at the time, to prevent secondary infections. Baseline assessment of blood parameters (denoted as COVID workup henceforth) included hemogram, renal and liver function tests, serum electrolytes, D-dimer, Lactate Dehydrogenase, Serum Ferritin, and Serum C-reactive protein, repeated 3–5 days later or as clinically warranted, if continued inpatient care was deemed necessary. Additional clinical investigations were undertaken, based on the patient's medical history or clinical findings.

A summary and comparison of clinical variables and investigations of the 5 cases are presented in Table 1 and Table 2, respectively.

Case 1. A 21-year-old single male, presented in October 2020 with a 2-month history characterized by mutism, withdrawal, staring, posturing, urinary incontinence, autonomic instability, immobility, rigidity, negativism, waxy flexibility, and postural instability with symptomatic worsening over the preceding 4 days. The Bush Francis Catatonia Rating

<https://doi.org/10.1016/j.ajp.2022.103004>

Received 17 November 2021; Received in revised form 29 December 2021; Accepted 1 January 2022

Available online 4 January 2022

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Scale (BFCRS) score at baseline was 22. Systemic examination was unremarkable. There was no prior history of psychiatric illness, psychotropic drug use, head trauma, fever, seizures, or disorientation.

The COVID RT-PCR (Reverse Transcription Polymerase Chain Reaction) test was positive and hence admitted to PCU for evaluation and management of catatonia. COVID workup did not reveal any abnormality. His vitals were within normal limits throughout inpatient care (except for intermittent tachycardia-between 100 and 110/min). The patient was initiated on oral Lorazepam but switched to intravenous Lorazepam (6 mg daily) in three divided doses due to inadequate response (BFCRS=17). Bitemporal ECTs, administered thrice weekly were commenced further following non-response to lorazepam (BFCRS=9). A delayed response to ECT (improvement after the 10th ECT session) was observed, wherein followi wherein, following course of 13 ECTs, all catatonic symptoms resolved, except for rigidity (BFCRS=0). Lorazepam per oral (p.o.) 2 mg daily was continued due to worsening of catatonia on attempted cessation, and subsequently discontinued after a month. Serum and Cerebrospinal fluid (CSF) anti-N-methyl-D-aspartate (NMDA) and Voltage-Gated Potassium Channel (VGKC) antibodies were negative. CSF cytology and biochemistry were unremarkable. Fungal, Treponemal, and Cryptococcal infections were ruled out. Antinuclear Antibody (ANA), Antineutrophilic cytoplasmic antibody (ANCA), Anti-Thyroid peroxidase (TPO) antibody, Paraneoplastic profiles were negative. Given persistent rigidity and gait instability, a neurology opinion was obtained and a diagnosis of atypical Parkinson's disease was considered. Amantadine 50 mg and Selegiline 10 mg were initiated along with gait training. PLA2G6 homozygous gene mutation (R741Q) identified, suggested Early onset Parkinson's disease (EOPD). At the time of discharge, there were no catatonic features and patient has shown improvement in motor symptoms with the above antiparkinsonian medications. However, gait instability persisted during follow-ups.

Case 2. A 26-year-old gentleman, with nicotine dependence and a history of psychotic depression in his mother, presented with a 10-year illness suggestive of Paranoid Schizophrenia, having failed trial of Risperidone. At admission in January 2021, he had stupor, mutism, staring, posturing, and grimacing suggestive of catatonia. The above developed over a one-month history preceding presentation to hospital. He was non-adherent to medications. There was no prior history of catatonia. BFCRS at presentation was 10. Whilst catatonic signs improved significantly with the lorazepam challenge (2 mg IV), inpatient care was planned for the management of residual catatonia and psychotic illness. RT-PCR for COVID-19 was positive, with no respiratory or systemic symptoms noted. Lorazepam p.o. (6 mg daily in divided doses) resulted in the resolution of catatonia over 2 days (BFCRS=0). Vitals remained within normal limits. Antipsychotic medications were reinitiated (Amisulpride up to 600 mg and Injection Fluphenazine Decanoate 25 mg fortnightly administered depot) with Lorazepam tapered to 4 mg and discharged with advice for home isolation. No side effects to treatment with above were noted. The patient did not follow up with our services subsequently, and hence further clinical details were unavailable.

Case 3. A 38-year-old woman presented in May 2021, with an abrupt onset illness of 4 days duration, with fearfulness, irrelevant talk, intermittent outbursts of laughter, elementary auditory hallucination, mutism, posturing, staring, withdrawal, immobility, and automatic obedience in the absence of any prior history of catatonia, or psychiatric illness. COVID exposure was present (immediate family member). The patient was diagnosed with Acute transient psychotic disorder with catatonia (baseline BFCRS score of 8).

RT-PCR test was positive. No respiratory or systemic abnormalities were noted. She was admitted to PCU and commenced on oral Olanzapine 10 mg daily, and Lorazepam 4 mg daily (divided doses). Metoprolol 25 mg daily was commenced following cardiology consultation for tachycardia and cardiac 2D-Echocardiogram was normal. Catatonia resolved over a week (BFCRS=0). Throughout inpatient care, vital parameters

remained within normal limits, except for persistent tachycardia. COVID workup did not reveal any abnormality. Lorazepam was tapered and stopped and the patient discharged on Olanzapine 10 mg per day.

On follow-up, two months later, the patient did not have a recurrence of psychotic or catatonic symptoms. However, extrapyramidal signs were noted and Trihexyphenidyl 2 mg p.o. per day was initiated.

Case 4. A 24-year-old male presented with 6 years of episodic illness suggestive of schizoaffective disorder with a catatonic presentation in the previous two episodes and poor inter-episodic recovery. Valproate 1 gm per day and Quetiapine 50 mg per day advised previously was discontinued by the patient, one year before the current presentation.

He presented in March 2021 with 2 weeks of immobility, mutism, staring, posturing, grimacing, mannerism, negativism, withdrawal, impulsivity, and ambitendency, and he was diagnosed with Schizoaffective disorder with catatonia (BFCRS baseline score 18). Intravenous lorazepam (8 mg in divided doses) was associated with improvement in food intake. Subsequently, it was replaced with oral lorazepam (8 mg daily) and Aripiprazole p.o. titrated to 20 mg. As inadequate response to lorazepam was noted, Bifrontal (BF) ECTs were commenced. Following the first ECT, he was identified as COVID-19 positive. Over the subsequent 2 weeks, no upper respiratory signs were noted and vital parameters remained within normal limits. COVID workup at baseline and on repeat testing revealed no abnormality. Cross titration of Tab Risperidone (up to 8 mg) with Tab Aripiprazole was undertaken given persisting psychotic and mood symptoms. Valproate p.o. 750 mg per day was added as a mood stabilizer. Despite the same, residual mutism, staring, grimacing, and impulsivity persisted (BFCRS score 6) and ECTs were commenced. A course of 5 BF-ECTs contributed to improvement in catatonia and mood symptoms. At discharge (BFCRS score of 2), he was advised daily dosage of Valproate 750 mg, Risperidone 8 mg, Trihexyphenidyl 2 mg, and lorazepam 2 mg.

On follow-up after 2 weeks, he was readmitted for worsening catatonia with immobility, mutism, staring, grimacing, ambitendency (BFCRS score of 7). Oral Lorazepam up to 6 mg and 9 BF ECTs were administered that improved both catatonic (BFCRS=0) and psychiatric symptoms. Other medications were continued and the patient was discharged for outpatient-based treatment.

Case 5. A 35-year-old lady, with hypothyroidism and schizoaffective disorder-depressive type (failed trials of Risperidone, Olanzapine, Amisulpride, Aripiprazole, Chlorpromazine, and multiple antidepressant medications) of 15 years duration had adequate improvement with a previous trial of Clozapine 300 mg; however, it had to be stopped due to excess sedation, weight gain, and constipation. A combination of Quetiapine (800 mg) and Sertraline (150 mg) had benefitted to some extent in the past. She had received ECT (3 courses of 5-6 ECTs) in the past for suicidality. No history of catatonia was noted in the past. In the background of medication non-adherence, the patient presented in September 2020, with a 1-month duration of depressive symptoms and 4 days of stupor, negativism, mutism, posturing, staring, gegenhalten, and withdrawal (BFCRS score was 18). In the emergency ward, catatonia responded to intravenous lorazepam (6 mg daily), however, negativism and withdrawal persisted for which inpatient care was planned. The RT-PCR test was positive, requiring admission to PCU. Sertraline (up to 200 mg) and Quetiapine (up to 600 mg) were initiated. A concurrent course of 7 Bitemporal ECTs (twice weekly with first 3 ECTs in the PCU with precautions) contributed to gradual improvement in catatonic (BFCRS - 0) and depressive symptoms. Parenteral lorazepam was switched to oral lorazepam 6 mg daily and gradually tapered and stopped over 2 weeks. No respiratory or systemic features of COVID-19 were noted. Vital parameters remained stable throughout the inpatient stay. COVID workup at baseline and on repeating on the 5th day did not reveal any abnormality. After completing treatment in the PCU, the patient was transferred to the inpatient psychiatry ward and subsequently discharged with significant improvement.

Table 1
Clinical characteristics of patients with COVID-19 and catatonia.

	Case 1	Case 2	Case 3	Case 4	Case 5
Prior Psychiatric Diagnosis	Nil	Schizophrenia	Nil	Schizoaffective disorder	Schizoaffective disorder
Final Psychiatric diagnosis	Organic catatonia with Young-onset Parkinson's disease	Schizophrenia	Acute and transient psychotic disorder with Catatonia	Schizoaffective disorder	Schizoaffective disorder- depressive type
Family history of catatonia/ psychiatric illness	No	Yes (Psychotic depression in mother)	No	No	No
Prior history of catatonia	No	No	No	Yes	No
ILI symptoms	No	No	No	No	No
Covid Related metabolic derangement	Nil	Nil	Nil	Nil	Nil
Route of Administration of Lorazepam	IV	Oral	Oral	IV	IV
Highest dose of Lorazepam given	6 mg	6 mg	4 mg	8 mg	6 mg
Worsening of respiratory parameters and saturation with Lorazepam	No	No	No	No	No
Chest imaging	HRCT Chest- Few patchy areas of GGO in the superior segment of the left lower lobe (CO-RADS-6, CTSS-1/25)	Chest imaging not done	HRCT chest- Peripheral patchy GGOs in bilateral lung fields (CO-RADS-6, CTSS -6/25)	Chest X-ray- No abnormality detected	Chest X-ray- No abnormality detected
BFCRS (at baseline)	22	10	8	18	18
ECT administered	Yes	No	No	Yes	Yes
Adverse events during or after ECT	None	None	None	None	None

(ILI-Influenza like illness, CO-RADS: COVID-19 reporting and data system, CTSS- Chest CT severity score, GGO-Ground glass opacities, HRCT- High resolution Computed Tomography)

Table 2
Blood investigations performed during inpatient care.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
Hemogram	WNL	WNL	Elevated Total WBC count -13, 900/uL*, Neutrophil-50.6% Lymphocytes -44.2%*. Platelet count – 6,40,000/uL* Rest- WNL	Total WBC count – 5900/uL Neutrophil -35.4%*, Lymphocytes -49.1%*	WNL
	WNL	NA	Total WBC count-12, 600* Neutrophil count -75.7%*, Lymphocytes- 20.9%* Platelets-4,42,000/uL Rest -WNL	Total WBC count – 5300/uL Neutrophil – 44.6%, Lymphocytes -42.0%*	
Neutrophil-Lymphocyte Ratio	2.54	3.22	1.19	0.72	2.09
	NA	NA	3.62*	1.06	NA
Renal function test	WNL	WNL	WNL	WNL	WNL
	WNL	NA	WNL	WNL	NA
Liver function test	WNL	WNL	WNL	WNL	WNL
	WNL	NA	WNL	WNL	NA
Serum Electrolytes	WNL	WNL	WNL	WNL	WNL
	WNL	NA	WNL	WNL	NA
D- Dimer(<500ngFEU/ml)	355	NA	263	354	150
		NA	241	NA	NA
Serum Ferritin (10–150 ug/L)	29	NA	131	168*	25
		NA	107	NA	NA
Serum C reactive protein (<5 mg/L)	3	NA	3	5	< 1
	3	NA	2	NA	NA
Lactate Dehydrogenase (135–225 U/L)	204	NA	258*	245*	176
	279*	NA	264*	NA	NA

(NA-not available, WNL- Within normal limits, * indicates abnormal investigation findings)

2. Discussion and conclusions

In this paper, we describe case summaries of five patients, who presented with catatonia and COVID-19 infection and underwent inpatient treatment in our PCU.

Of the five, one (Case 3) had new-onset catatonia; in the absence of any family or prior psychiatric history. COVID-19 infection is likely to have precipitated psychosis with catatonia, but a heightened sensitivity to atypical neuroleptics at follow-up suggests the additional possibility of persisting COVID-19 related neuropsychiatric sequelae. Another

patient (Case 1) had an underlying genetic condition (EOPD) presenting with catatonia. Given that catatonia is not a known symptom of EOPD (Getz and Levin, 2017), the concurrent diagnosis of acute COVID-19 infection highlights how the interplay between COVID-19 and genetic susceptibility to neurological disorders may influence clinical presentations. Of the remaining three, one individual (Case 4) had a prior history of catatonia, while the other two (Cases 2 and 5) developed catatonia for the first time despite having a long-standing psychiatric illness. Gene-environment interactions influencing COVID-19 disease severity have been identified, and loci corresponding to lung,

autoimmune, and inflammatory diseases were noted. This once again highlights how COVID-19 infection contributes to accelerating the development of, or altering the course (Quincozes-Santos et al., 2021) of pre-existing neuropsychiatric disorders. This might also explain the variable response to treatment for catatonia and psychiatric disorders seen in our patients.

Other than Case 2, all other patients were treated with antibiotics such as Doxycycline, Azithromycin, or Ivermectin in monotherapy/combination. Anti-inflammatory and immunomodulatory properties of these medications (Ali et al., 2021; Echeverría-Esnal and Grau, 2021) may have affected the course of catatonia, but we have inadequate evidence in this study to comment upon the same, and further studies are required to clarify this relationship. All patients were asymptomatic for the COVID-19 related systemic manifestations. However, whether this observation is incidental would be difficult to determine. The primary catatonia presentation may have led to an earlier presentation to the hospital thereby permitting timely treatment. Additionally, prior studies have noted that those with pre-existing psychiatric disease have lower severity of COVID-19 infection as well as lower mortality from same (Canal-Rivero et al., 2021; Dratcu and Boland, 2021; Moga et al., 2021).

Among our patients, the most common catatonic signs noted were posturing, immobility, mutism, staring, and withdrawal, similar to another study from our center examining catatonic syndromes (Subramaniyam et al., 2019). Three individuals required ECTs because of inadequate response to Lorazepam. Higher scores on BFCRS were associated with the need for ECT and slower resolution of symptoms in this case series, as has been reported previously (Raveendranathan et al., 2012). While it may be argued that lorazepam doses administered were lower, adopting a cautious approach and initiating ECTs early can offset the potential risks of using high-dose benzodiazepines. Also, lorazepam is a safer choice among benzodiazepines in those with COVID-19 infection, because of the absence of liver metabolism and therefore a decreased risk of prolonged action or drug-drug interactions as occurs with other drugs of this class (Shah et al., 2021). ECT administration in the presence of COVID-19 infection requires a coordinated approach that can ensure safety of both, the patient and the treating team, details of which have been elaborated on in a previous publication from our center (Surve et al., 2021). To summarize briefly, in our PCU, a team comprising of a psychiatrist, an anesthetist, and nursing personnel administered ECTs. All cases described in this series who were administered ECT, received Thiopentone (3–5 mg/kg wt.) and Succinylcholine (0.5–1 mg/kg wt.) as anesthetic and muscle relaxant respectively (similar to pre-COVID practices). NIVIQUE device, Technonivilak, Bangalore, India was used for ECT administration and a dedicated machine was allocated for the administration of ECT exclusively for PCU patients. The stimulus was delivered at 125 pulses per second, with a current of 800 mA and pulse width of 1.5 ms; and the train duration was altered to achieve the desired charge (Thirthalli et al., 2017). Additional COVID-specific modifications to ECT administration were made to improve the safety of the patient and decrease the risk of transmission to the staff. These included the use of Heat moisture exchange (HME) filters between the patient end of the anesthesia circuit and the reusable face mask, pre-oxygenation of all patients with 100% oxygen for 3–5 min, apnoea ventilation with restriction of bag-mask ventilation, avoidance of airway manipulation, pre-anesthetic administration of anticholinergic medications (glycopyrrolate) to minimize secretions in those with profuse oral secretions (as in Case 1). All staff personnel used personal protective equipment (PPE) during the time of the ECT procedure. Patients were monitored in the ECT room after the procedure for around 30 min and vitals monitoring, including oxygen saturation was undertaken by nursing personnel (initiated immediate post-procedure until recovery and transfer out from ECT room). Emergency resuscitation kits and other equipment with medications were kept ready for immediate access in case of rare cardiac or other adverse events. The seizure threshold estimated in previous sessions, if any, were considered, instead of a titration-based method, and the final current stimulus

delivered was erred towards the higher side. Electrode placement (Bitemporal) was prioritized for ECTs, given the need for urgent response and permitting administration of fewer ECTs (Kellner et al., 2010). None of the patients experienced any deterioration in respiratory functioning or any other adverse effects with the use of benzodiazepines or ECTs. This may have been related to the fact that our patients were predominantly asymptomatic for respiratory manifestations (although High-Resolution Computed Tomography (HRCT) in 2 patients showed evidence of COVID-related lung changes). Nonetheless, no complications were noted even in those individuals with chest imaging demonstrating COVID-related changes. Applying objective rating scales for catatonia (BFCRS) to monitor the progress and response to treatment, ensured optimal dosing of lorazepam and/or timely commencement/cessation of ECTs. Cautious use of benzodiazepines in lower daily doses, and prompt commencement of modified ECTs (under precautions) facilitated the quick resolution of catatonia.

Catatonia has previously been linked with infections and immune dysregulation. Catatonia as a severe acute phase response in terms of psychomotor retardation has been postulated (Rogers et al., 2019). Also, the elevation of serum markers of inflammation such as D-dimer, high sensitivity C-reactive protein (not absolute levels), increased ferritin levels have been previously reported in individuals with catatonia (Rogers et al., 2019). It is interesting to note that our patients had an overall normal profile of inflammatory markers. Case 3 had a Neutrophil-Lymphocyte Ratio (NLR) of 3.62 which is above the recommended cut-off of 3.3 that predicts conversion to severe COVID infection (Yang et al., 2020). However, this patient did not have clinical deterioration and responded well to treatment. Here we would like to stress that neurotropic infectious agents are also known to cause catatonia and other neuropsychiatric disorders. The same could also contribute to the presentation of catatonia via direct neuro-invasion by SARS-COV2 (severe acute respiratory syndrome coronavirus 2). Neuro-invasion by the hematogenous route via the altered blood-brain barrier and direct invasion by the virus via the olfactory route have been reported as possible pathways (Generoso et al., 2021). Angiotensin-converting enzyme 2 (ACE 2) receptors are expressed by neurons, glia, and endothelium making them a potential target for viral invasion, potentially contributing to neuropsychiatric manifestations such as catatonia (Generoso et al., 2021). These mechanisms in the context of COVID-19 infection and catatonia are yet to be understood but possibly point towards genetic, immunogenic, metabolic, and/or neurotoxic pathologies.

Whilst limitations of this study include small sample size, a retrospective chart review, limited/absence of follow-up data, nonetheless, this case series highlights the complex relationship between COVID-19 and catatonia and important challenges in its management that clinicians would face. Catatonia may at times be the sole manifestation of underlying COVID-19 infection and evaluation for the same needs to be a part of the workup in new-onset neuropsychiatric disturbances such as catatonia or worsening of course of a pre-existing psychiatric disorder. Our experience indicates that in the absence of respiratory compromise, ongoing close monitoring of COVID-19 illness can permit concurrent administration of parenteral benzodiazepines, such as lorazepam, and ECTs safely in catatonia.

3. Disclosures

Patient confidentiality has been maintained. Additionally, exemption has been granted by the institutional ethics committee for preparing this case series using information available exclusively from clinical records stored at the hospital.

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