



## A Case of Psychomotor Dysfunction in Medical Intensive Care Unit

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### ABSTRACT

Psychomotor dysfunction manifesting with disturbances of sensorium, cognition, tone, and movements is a commonly faced condition among the critically ill patients admitted in intensive care units. It may present as agitation or retardation and can imitate delirium, extra-pyramidal syndrome, akinetic mutism, neuroleptic malignant syndrome, or in extreme cases, catatonia. Up to a third of these patients have pre-existing psychiatric illnesses that get aggravated due to organic disorders including but not limited to drug interactions, metabolic encephalopathy, central nervous system infections, sepsis, cerebrovascular accidents, nonconvulsive status. In addition, the ICU environment may itself initiate or aggravate psychotic symptoms. The alteration of gamma aminobutyric acid, glutamate, serotonin and dopamine transmissions have been implicated in its pathogenesis. We report a patient, a known case of schizophrenia, who developed catatonia after starting antitubercular treatment consisting of rifampicin, isoniazid, pyrazinamide and ethambutol. He was admitted in medical ICU in catatonic state. His response to lorazepam challenge was suggestive of catatonia. He was managed with satisfactory outcome.

**Key words:** Psychomotor Dysfunction, Dystonia, Catatonia, Drug Interaction, Antitubercular therapy, Antipsychotics

### INTRODUCTION

Psychomotor dysfunction is a commonly encountered condition in patients admitted in intensive care units and can present as agitation or retardation. Delirium is the most faced psychiatric disturbance in the critically ill and occurs in over 80% [1,2] out of these up to a third have pre-existing psychiatric illness that gets aggravated due to organic insult [3-5].

There are many diseases that present with altered sensorium, cognition, tone, and movement owing to their common characteristics. The organic diseases that may present with neuro-psychiatric presentations include metabolic encephalopathy, central nervous system (CNS) infections like tubercular meningitis leading to vasculopathy leading to multiple infarcts (13-57%), sepsis (70%), cerebrovascular accidents (CVA) (20-80%) and nonconvulsive status (10-22%) [6-9]. In addition, the ICU environment itself can aggravate/precipitate neuropsychiatric abnormalities in the seriously ill, especially the elderly [10]. This often complicates the diagnostic work-up and management plan and

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finally the overall prognosis of the ICU patients. A thorough history, noted with the help of a dependable informant about previous psychiatric illness, prescription and illicit drug use, comorbidities, old medical records, recent changes in behaviour and need for hospitalization, and comprehensive neuro-psychiatric evaluation can help arrive at a definite diagnosis.

## CASE REPORT

A 56-year-old male, retired clerk, known case of paranoid schizophrenia for 20 years was on regular treatment with olanzapine, trihexyphenidyl and propranolol. He had no other known comorbidities or addictions. He developed dry cough, malaise, feverishness and anorexia of two months duration. HRCT Thorax showed mediastinal lymphadenopathy and hence antitubercular therapy (ATT) consisting of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol (HRZE) was started 15 days prior to admission. Five days after starting ATT, he developed psychomotor retardation that progressed over a next 10 days. There was slowing down of movement and speech, associated with stiffness of the body. Eventually he was unable to identify family members and interact with them. He was brought to the hospital by his wife, when he had stopped eating, talking, passing urine, all movements and had a persistent blank stare.

Clinically, he was ectomorphic, lying totally immobile and expressionless in bed, staring uncomprehendingly. Flattening of affect was present. Core temperature was 100°F, pulse 110/min, respiratory rate 18/min, blood pressure 130/70 mm of Hg, and oxygen saturation (SaO<sub>2</sub>) was 96% on room air. Bilateral multiple, discrete, firm, non-tender, sub-centimetric cervical lymph nodes were palpable. Neurologically, he appeared awake but was totally unresponsive to verbal and noxious stimuli. Pupils were normal in size and reactive to light. Ophthalmoscopy ruled out raised intracranial tension. Lead pipe rigidity was present. Deep tendon reflexes were brisk. Plantar reflex was not elicitable. There were no focal neurological signs. There was mild pleural effusion on the right.

Based on history and clinical findings, possibility of CNS infection, extrapyramidal syndrome (EPS) and catatonia were considered. Other possibilities of metabolic encephalopathy, electrolyte imbalance, cerebrovascular accidents, neuroleptic malignant syndrome (NMS), systemic infections (pneumonia, sepsis), and status epilepticus were also kept as other probable causes.

All ongoing medications were stopped in view of possible drug-drug interaction and psychiatric consultation was sought. While reports of other investigations were awaited, Lorazepam test dose of 02 mg was administered intravenously. He showed signs of improvement within minutes of lorazepam administration, and after two doses of lorazepam, he started responding to verbal commands and talking with family members. The positive response to lorazepam challenge and unremarkable investigations further confirmed the diagnosis.

The investigations revealed raised erythrocyte sedimentation rate (ESR) 80 mm at end of 1 hour and C-reactive protein (CRP) 12 mg/L. HRCT Thorax showed mild right basal pleural effusion and enlargement of mediastinal lymph nodes, 10-34 mm. Pleural fluid showed exudative fluid with markedly raised ADA (131 IU/L) and LDH (2130 IU/L), and CBNAAT positive for mycobacteria, sensitive to rifampicin. All other investigations (complete blood count (CBC), cultures, metabolic parameters, serum CPK, serum LDH, thyroid function tests, ultrasound scan of abdomen and pelvis, CSF analysis, neuroimaging, EEG, and viral markers) were unremarkable. Drug levels could not be obtained because of resource limitation.

Since the patient did not exhibit any psychotic symptoms, the antipsychotic medication were withheld as advised by the psychiatrist. ATT was restarted after seven days along with supportive care. Lorazepam was tapered off and stopped after three weeks. He was discharged after six weeks when he could manage his daily activities and was advised to attend psychiatric and pulmonology clinics for follow up.

## DISCUSSION

We have presented a case of catatonia that was aggravated due to drug-drug interaction after addition

of a new treatment regimen that is known to reduce therapeutic levels of the antipsychotics. The differential diagnoses that were considered included catatonia, EPS, akinetic mutism, NMS, CNS tuberculosis, and sepsis. The diagnosis of catatonia was established by the response to lorazepam administration and improvement after stopping ATT.

The prevalence of catatonia ranges from 5%-18% in inpatient psychiatric units, 8.9% in elderly patients and 3.8% in intensive care units [11]. Catatonia may manifest itself with features of psychomotor agitation or retardation [12]. The diagnostic criteria according to DSM 5 are given in **Table 1** [13]. Immobility, mutism, rigidity and staring are common presenting features. Catatonic stupor is a rare presentation. The appearance of any of these signs in the absence of an alternative definitive diagnosis is highly suggestive of catatonia [12]. Most patients present with subtle signs that can be easily missed, if not specially considered because, no specific sign is pathognomonic of catatonia [14,15].

**Table 1: Definition of Catatonia According to DSM-5**

CHARACTERISTICS	DESCRIPTION
Stupor	no psychomotor activity, no reactivity to the environment
Catalepsy	passive induction of postures held against the gravity
Waxy flexibility	slight and even resistance to repositioning by the examiner
Mutism	no or minimal verbal response-NA in established aphasia
Negativism	opposing or not responding to external stimuli or instructions
Posturing	spontaneous and active maintenance of posture against gravity
Mannerism	odd caricatures of ordinary actions
Stereotypy	repetitive, frequent, non-goal directed movements
Agitation	(not influenced by external stimuli)
Grimacing	Maintenance of odd facial expressions
Echolalia	repeating the words spoken by the examiner
Echopraxia	mimicking of movements made by the examiner
<b>*Catatonia is defined by the presence of at least 3 of the 12 characteristic symptoms</b>	

*Adapted from American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.*

The pathophysiology of catatonia is not yet clearly understood. The alterations of gamma aminobutyric acid (GABA), glutamate, serotonin, and dopamine transmissions have been associated with its pathogenesis. Functional MRI imaging may be suggestive of orbitofrontal and prefrontal cortex dysfunction [16,17]. Several drugs and withdrawal states can precipitate catatonia (**Table 2**) [18-21]. Rebound catatonia is seen commonly in withdrawal of clozapine and benzodiazepines. Concurrent administration of drugs acting as inhibitors or inducers of the enzymes involved in the metabolism of the antipsychotic drugs may decrease or increase their therapeutic level, as happened in our patient after starting ATT [22].

**Table 2: Drugs that may Precipitate Catatonia**

<b>Psychotropic drugs</b>	Fluphenazine, Haloperidol, Risperidone, Clozapine
<b>Non-psychotropic drugs</b>	Steroids, Disulfiram, Ciprofloxacin, Benzodiazepines
<b>Drugs of abuse</b>	Phencyclidine, Cannabis, Mescaline, LSD, Cocaine, Ecstasy
<b>Withdrawal states</b>	Clozapine, Benzodiazepine, Alcohol, Zolpidem, Gabapentin

Drug-induced parkinsonism may also present with immobility, staring, rigidity, and freezing and must be differentiated from catatonia. The posturing and immobility of catatonic patients may be confused with dystonia, while the psychomotor agitation of excited catatonia needs to be discerned from akathisia [12,23-25]. Unlike catatonia where patients are usually withdrawn and negativistic, parkinsonism patients are cooperative and interactive. Also, echo-phenomenon and posturing are not seen in parkinsonism. And lastly, the clinical features of parkinsonism usually worsen by benzodiazepines administration [12].

Out of the four first line antitubercular drugs, Isoniazid is an inhibitor of Cytochrome P450 1A2 and 3A4 (CYP1A2 and CYP3A4). Rifampicin, on the other hand, is a potent inducer of both, CYP1A2 and CYP3A4, and the P-glycoprotein (P-gp) transport system [22,26-28]. Rifampicin can accelerate the metabolism of the antipsychotics which are cleared by CYP enzymes and/or are P-gp substrates and cause therapeutic failure of several drugs. Full induction of enzymes usually occurs in about one week after starting rifampicin and the induction dissipates around two weeks after discontinuing rifampicin. The induction is near maximal at a dose of 300 mg/day [22,29]. Clozapine and olanzapine are mainly metabolized by CYP1A2. Rifampicin also induces uridine diphosphate glucuronosyl transferase (UGT) enzymes and can reduce efficacy of olanzapine and samidorphan significantly [30,31].

It is imperative for internists and general physicians to be able to diagnose catatonia in the ICU and among the critically ill, as early diagnosis and management prevent many complications, like development of neuroleptic malignant syndrome. Other complications are often due to severe immobility and refusal to eat or drink. These include exhaustion, hyperpyrexia, aspiration pneumonia, deep vein thrombosis, pulmonary embolism, decubitus ulcers, and contractures. Self-inflicted injuries and harm to others can also occur, particularly during periods of increased activity [32].

## MANAGEMENT

Various scales are used for diagnosis and assessment of severity of catatonia. The Bush Francis Catatonia Rating Scale (BFCRS) is commonly used because of its validity, reliability and ease of routine use [33-35]. The initial step in management is to stop the drugs that can potentially cause catatonia like neuroleptics, steroids, stimulants and anticonvulsants [36]. The diagnosis can usually be confirmed by lorazepam challenge [37]. A response of 50% or greater reduction in the score using BFCRS after lorazepam challenge establishes the diagnosis. However, absence of response to lorazepam does not exclude catatonia [38]. Other benzodiazepines are also effective, but lorazepam is preferred due to its action mainly on GABA-A, which is implicated in pathogenesis of catatonia [39]. Instead of sedating, it makes the patient more alert and interactive. Subsequent management includes use of electroconvulsive therapy, Glutamate antagonists, antiepileptic drugs, and atypical antipsychotics, depending on the response to the previously used modality [40].

## CONCLUSION

We have reported a case of catatonic stupor whose pre-existing schizophrenia, well controlled with antipsychotic drugs, worsened because of drug-drug interaction. The differential diagnoses in our case were CNS infections, EPS and catatonia. These and other age-related and comorbidity-related conditions were ruled out with the help of investigations. The final diagnosis was established by the lorazepam challenge. The aim of reporting this case is to emphasize the importance of recognizing psychotic symptoms and signs among patients attending medicine outpatients and admitted in general medicine wards, especially ICU.

### LIMITATION OF STUDY

Authors acknowledge that therapeutic levels of rifampicin, INH and anti-psychotic drugs should have been done to establish the cause of worsening of catatonia but could not be done due to resource limitation.

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