Challenging the Standard Psychiatric Illness Script of Catatonia: Beyond a Syndrome of Psychomotor Disturbance

George E. Sayde, MD, MPH and Sarah Miletello, MD
Department of Internal Medicine and Psychiatry, Tulane University School of Medicine, New Orleans, LA

Highlights

- **Life-threatening catatonia is often misdiagnosed or diagnosed rather late in the patient's hospital course.**
- **Catatonia is particularly nuanced with regard to underlying etiology, which is not entirely captured by the standard screening tools available to psychiatrists.**
- **C-L psychiatrists must incorporate neurobiologically-informed approaches to their clinical reasoning to avoid delays in life-saving therapies and pave the way for novel treatment modalities.**

Introduction

Catatonia is characterized by a spectrum of clinically-observable signs and correlating neurobiological etiologies which transcend the psychomotor disturbances described in the DSM-5 or BFCRS. We include two unique presentations of ***malignant catatonia*** refractory to benzodiazepines to highlight the intricate neurophysiologic underpinnings of the condition, enhance its nosology, and guide alternative targeted treatment considerations.

Autonomic instability in the presence of fever and stuporous (or excited) catatonia is defined as *malignant*, or life-threatening, catatonia (Philbrick, 1994).

The juxtaposition of Case 1 with Case 2 deepens our understanding of life-threatening catatonia. The first case is medically complex, involves a drug overdose inciting hypoxic respiratory failure and leukoencephalopathy, and entails a prolonged hospitalization. The second patient is an otherwise healthy woman with bipolar type I disorder, whose mania quickly progresses to life-threatening catatonia requiring intensive care and emergent ECT. **We can conceptualize two separate neurobiological mechanisms converging to a common clinical phenotype, yet each case warrants a unique treatment approach**.

Cases

Case 1: A 30-year-old woman with a history of polysubstance use, major depressive disorder, and hepatitis C cirrhosis was brought in by emergency medical services after being found unresponsive in her car. Her clinical course is depicted in **Figure 1**.

On arrival, the patient had a seizure and fell into multiorgan failure, requiring intubation and intensive care. Urine drug screen was positive for MDMA, amphetamine, cocaine, and opioids. Blood/urine cultures and routine CSF studies (including cell counts/cultures) were normal.

She was extubated on day 2. The patient appeared withdrawn, internally preoccupied with a flat affect, and responding to internal stimuli. Citalopram 20 mg/day and quetiapine 50 mg nightly were initiated. She suffered an opioid overdose leading to a prolonged hypoxic state (**Figure 2**). The patient continued to have intermittent fevers without an identifiable etiology. Her kidney and liver function ultimately improved, no longer requiring CRRT. On day 19, the patient was discharged to a rehab facility, where she slowly became more withdrawn and ultimately stuporous and confused with autonomic instability.

She was readmitted to our hospital on day 26. Infectious and immunologic workup were unremarkable. She exhibited **rigidity**, **flushing**, **mutism**, and **autonomic changes**. Creatine kinase was normal. Brain MRI (**Figure 2**) confirmed the diagnosis of **delayed post-hypoxic leukoencephalopathy** (DPHL). The patient continued to demonstrate symptoms of **malignant catatonia**, which may accompany DPHL. A lorazepam trial up to 2 mg IV q4hr showed no clinical benefit.

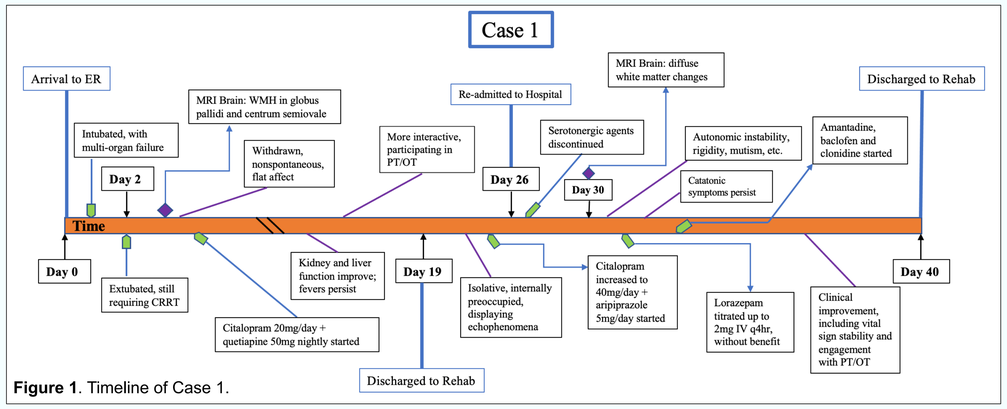

Figure 1. Timeline of Case 1.

Thus, alternative agents were started: baclofen (to alleviate spasticity), **amantadine** (for its activating properties and glutamatergic modulation) and clonidine (to treat autonomic instability). The patient had slow, clinical improvement as baclofen was titrated to 10 mg BID and amantadine to 100 mg BID. Clonidine was stopped, as the autonomic instability resolved. The patient was discharged to a skilled facility for therapy.

Case 2: A 60-year-old woman with bipolar I disorder and stage 1a breast cancer (in remission) presented for worsening bizarre behavior (hyperactivity, confusion, insomnia) over 2 weeks. Her course is depicted in **Figure 3**.

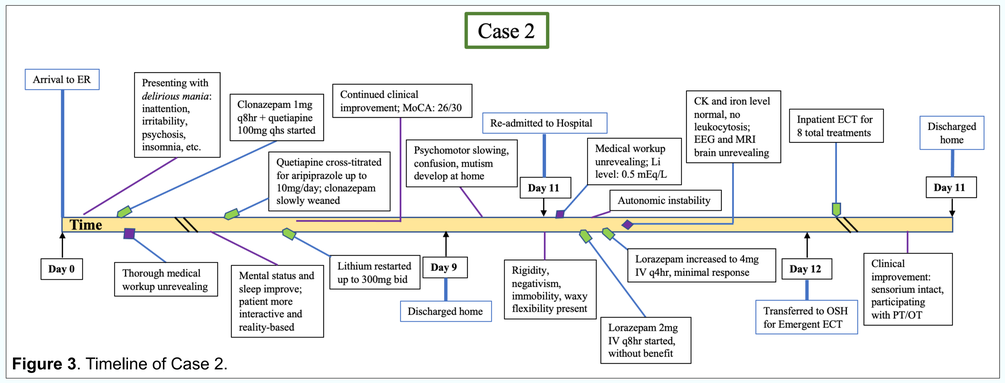

Figure 3. Timeline of Case 2.

On arrival, she was responding to internal stimuli and exhibited visual hallucinations. The constellation of inattention, fluctuating sensorium, perceptual disturbances, and insomnia was consistent with **delirious mania**. A thorough **medical workup proved unrevealing** - including vitals, physical exam, and routine bloodwork. Serum TSH, vitamin B12, and folate were normal. Toxicology screening was negative. Li level was therapeutic. Blood and urine cultures were normal. CK, ESR, and CRP were normal. Other infectious workup, including HIV, RPR, and hepatitis serology, was normal. Brain MRI was unremarkable.

The patient was started on clonazepam 1 mg q8hr and quetiapine 100 mg qhs. Sleep and mental status improved. She became more interactive and showed insight. Clonazepam was slowly weaned and quetiapine was cross-titrated for aripiprazole 10 mg/day prior to discharge. Home lithium was restarted up to 300 mg BID (Li level: 0.7 mEq/L). The patient became more reality-based and hallucinations remitted. Her cognitive function improved (MoCA score from 13/30 to 26/30 over 2 days). She was discharged home on day 9.

Two days later, the patient returned in a decompensated, catatonic state. Per family, in the hours preceding arrival, the patient developed confusion, psychomotor slowing, and mutism. On initial exam, she was **tremulous**, **rigid in all extremities**, and **hyper-reflexic**. The patient displayed **negativism** and **waxy flexibility**. Vitals and routine laboratory tests were again normal.

We started lorazepam 2 mg IV q8hr with continual up-titration. She showed minimal response to this over the next 24 hrs. The patient remained quite **diaphoretic**, **rigid**, **stuporous**, with ***Gegenhalten***, and a GCS of 10. Her vital signs became labile, and her condition progressed to **malignant catatonia.** EEG and repeat brain MRI were normal. Serum paraneoplastic/auto-immune encephalitis panel was normal. The patient was quickly transferred to a nearby facility for emergent ECT. She underwent 8 rounds of inpatient ECT with significant improvement and was discharged home.

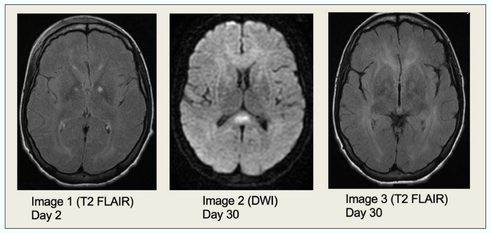

Figure 2. MRI brain at 2 days post-hypoxic event (Image 1). Note white matter hyperintensities in bilateral globus pallidi and centrum semiovale – a hallmark of DPHL. At 30 days, a new area of restriction has evolved in the corpus callosum (Image 2), in addition to progression of older white matter findings (Image 3).

Discussion

In **Case 1**, the underlying medical cause is more apparent as the driver of the catatonia phenotype: hypoxic brain injury → white matter inflammation → catatonic symptoms.

- The pathophysiology of **DPHL** involves a prolonged hypoxic state leading to **demyelination of white matter**, as **oligodendrocytes** are particularly vulnerable (Won, 2002).
- **Abnormalities of white matter** are also strongly associated with a **catatonic phenotype**, as seen in studies of genetically mutant myelinating proteins (CNP) in mice and humans (Pease-Raissi, 2018; Hagemeyer, 2012).

In **Case 2**, the primary systemic trigger is subtle, disguised by an unrevealing routine medical workup, and likely in part explained by **immune system dysregulation** and **neuroinflammatory processes** contributing to a decompensated primary psychiatric disorder.

- A strong association exists between severe catatonia and NMDA-R encephalitis, implicating the immune system and downstream glutamatergic or GABA-ergic modulation (Rogers, 2019). Increasing the NMDA-R blockade initially results in behavioral symptoms such as **delirious mania** – and at higher antibody titers, autonomic dysfunction and **malignant catatonia** (Dalmau, 2011; Restrepo-Martinez, 2020).
- An immune-mediated framework may allow the conceptualization of bipolar disorder (in part) as an inflammatory condition, where elevated cytokine levels are associated with manic episodes (Munkholm, 2013). Perhaps mania progresses to delirious mania, and ultimately catatonia with autonomic instability as the immune systems is recruited ➔ **overactivation of microglia** and **neuroinflammation** (Rosenblat, 2017).

Conclusions

These cases highlight the call for an integrative framework of catatonia that transcends a syndrome of cerebral motor dysfunction and encompasses other theories such as dysregulated immune system activation, disruption of the microglia, white matter inflammation, NMDA-receptor hypofunction, or glutamatergic modulation. This informs management: ECT is contraindicated in Case 1 due to its potential to worsen the underlying leukoencephalopathy, while it serves as life-saving treatment in Case 2.

C-L psychiatrists are challenged to consider diversified schemas for all psychiatric presentations which are evidence-based and neurobiologically-informed, especially in the acute medical setting. This will guide novel research and targeted treatment considerations.

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