

Review

Catatonia Due to General Medical Conditions in Psychiatric Patients: Implications for Clinical Practice

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Abstract: Catatonic syndrome is frequently observed over the course of severe mental disorders and general medical conditions, but when catatonia occurs in psychiatric patients with co-morbid medical or neurologic conditions, diagnosis and management may be challenging. Several medical conditions may cause catatonia in psychiatric patients, but some, such as brain injury, infections, hyponatremia and critical illness, may be most relevant in this population. Alongside appropriate etiologic treatment, benzodiazepines and electroconvulsive therapy in refractory cases are effective and safe, and may resolve catatonic syndrome rapidly. When newly-onset psychotic symptoms in catatonic patients with established psychotic disorders occur, delirium should be suspected and appropriately managed. An extensive clinical and laboratory diagnostic workup to determine the underlying etiology of catatonic syndrome should be carried out. In cases of acute multi-morbidity, the exact cause of catatonic syndrome in psychiatric patients may be unclear. It is recommended to avoid antipsychotic drugs in acutely catatonic patients, because they may exacerbate the catatonic symptoms. The akinetic type of catatonia should be differentiated from hypoactive delirium, as treatments for these syndromes differ substantially. When a psychiatric patient presents with symptomatology of both catatonia and delirium, treatment is particularly challenging.

Keywords: antipsychotics; benzodiazepines; catatonia; critical illness; general medical condition; hyponatremia; psychiatric patients

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1. Introduction

Motor abnormalities are frequently observed in patients with schizophrenia and related psychoses and may have clinical and prognostic relevance [1]. Of these, catatonia may be the most intriguing and challenging in terms of presentation and diagnosis. Catatonia is a psychomotor syndrome that comprises a broad range of symptoms, such as mutism, posturing, negativism, staring, rigidity and stupor, sometimes along with echolalia or echopraxia [2]. According to the motor behavior of the patients and other clinical symptoms and signs, catatonic syndrome may be divided into subtypes. Retarded (or stuporous or akinetic) catatonia is the more frequently observed subtype, and is characterized by a paucity of movement, including immobility, staring, mutism, rigidity, withdrawal and refusal to eat [3]. The second subtype is excited catatonia, which is characterized by severe psychomotor agitation with pointless, impulsive movements and combativeness [4]. The last subtype is malignant catatonia, which may be life-threatening and is associated with hyperthermia, altered consciousness and autonomic instability. Symptoms are similar to neuroleptic malignant syndrome and may signal a potential lethal underlying cause of catatonia, if not appropriately treated [3,4]. In terms of time-course, catatonia may be periodic. This is a rare form in which symptoms present in phases and may disappear completely in between episodes [4].

Although catatonic syndrome has been originally described as a subtype of schizophrenia, it is no longer considered as such. Rather, it is currently widely considered that catatonia

may be mostly observed in patients with general medical conditions and neurologic diseases. With regard to psychiatric disorders, catatonia may be more common in patients with mood disorders rather than schizophrenia [5]. Accordingly, catatonic syndrome may be diagnosed in patients attending not only psychiatric wards, but also several other clinical settings, such as the consultation–liaison psychiatric service [6], the emergency ward [7], the general hospital [8] and the intensive care unit (ICU) [9,10].

In a recent meta-analysis of catatonia prevalence over time, throughout several medical and psychiatric settings, the mean catatonia prevalence was found to be 9.2%. Despite the significant heterogeneity across studies, the prevalence of catatonic syndrome did not seem to decrease over time and did not seem to depend on different rating scales and criteria [11]. The prevalence and clinical significance of catatonic signs in patients with mental illness may differ across studies in different treatment settings and patient populations, but it seems that catatonic syndrome occurs in 9–17% of patients with acute psychiatric illnesses, and that the retarded subtype is the more frequently observed subtype, as aforementioned [3].

The biological background of catatonia has been the subject of extensive research. It has been observed that periodic catatonia may have a familial distribution [12], indicating a possible genetic contribution to this disorder. Indeed, previous research has yielded some evidence about the linkage of the periodic catatonia phenotype to chromosomes 15q15 and 22q13 [13,14]. The largest study of biomarkers in catatonia so far found that iron was low in patients with catatonia relative to psychiatric controls and this result remained after adjusting for demographic variables. This finding could not be attributed to inflammatory response or to malnutrition, and the authors favored the possibility that low iron causes hypodopaminergia in the basal ganglia, as several enzymes that interfere with dopamine synthesis are iron-dependent, thus generating hypokinetic symptoms. Moreover, there was no significant difference between serum iron levels during and between catatonic episodes which could indicate an underlying vulnerability, according to the authors [15]. Other research has suggested that the serum amyloid P component could be a potential disease-associated biomarker for catatonia [16]. In the largest study of catatonia neuroimaging on psychiatric inpatients to date, it was found that magnetic resonance imaging (MRI) scan abnormalities were common in patients with catatonia, and mostly consisted of diffuse cerebral atrophy rather than focal lesions. However, the rates of those abnormalities did not differ between patients with catatonia and other psychiatric inpatients [17]; thus, structural neuroimaging findings cannot be used as biomarkers in catatonia. On the other hand, studies with the use of functional MRI neuroimaging have found a cerebral blood flow increase in the left supplementary motor area and lateral premotor cortex in acute and remitted patients with periodic catatonia, suggesting that these findings could be used as diagnostic biomarkers [18].

With regard to pathophysiology, the precise underlying mechanisms of catatonic syndrome are still poorly understood, although there is some evidence from neuroimaging studies that catatonia in patients with schizophrenia may be associated with alterations of cerebral motor circuits [19], as aforementioned. Recent research has shown that alterations of neural activity in GABAergic and glutamatergic pathways may account for some of the catatonia phenotypes [20], while other studies have implied that manifestations of catatonia may be mediated through the activation of the innate immune system [21].

The presentation of catatonia in patients with mental disorders and co-morbid general medical conditions may be challenging for clinicians. Several medical conditions that are associated with catatonic syndrome may be encountered in patients with mental disorders. However, some of these may be particularly relevant in psychiatric patients. These patients may be prone to developing catatonic symptoms, due to their underlying mental illness that may itself be associated with catatonia. The present paper aims to provide an overview of the recent knowledge regarding catatonia due to general medical conditions in psychiatric patients, and to highlight the potential clinical implications of recognizing the precise cause of catatonic syndrome in psychiatric settings.

2. General Medical Conditions Associated with Catatonia

Several general medical conditions and neurologic syndromes have been implicated in the induction of catatonic syndrome [8,22]. Table 1 summarizes the most common medical and neurologic causes of catatonia. Those that are most relevant to psychiatric patients will be discussed further. It should be noted that some patients may be more likely to develop catatonic symptoms. In a recent prospective descriptive study with 241 psychiatric inpatients, it was found that male gender and younger age were associated with higher scores in catatonia rating scales [23]. Other variables that were examined, such as history of substance abuse and Human Immunodeficiency Virus (HIV) infection, were not statistically significantly associated with catatonia. The large study by Rogers et al. [15] that comprised 1456 patients yielded somewhat different results, as it found that patients with catatonia did not differ from the control group with regard to gender, but were younger and more likely to be from an ethnic minority background. Other recent research has suggested that cognitive impairment and physical morbidity may interfere with the development of catatonia in older adults, and that dementia could be a risk factor for catatonia [24].

Table 1. General medical and neurologic conditions associated with catatonia.

Condition	Comments
Critical illness	Catatonia prevalence up to 23%; may be underestimated in the ICU. Advanced age is associated with catatonia.
Encephalitis	The most common cause of autoimmune catatonia is NMDAR encephalitis.
Other neurologic conditions	CNS infections, neurodegeneration.
Structural CNS pathology	Space-occupying lesions, injury, vascular causes.
Hyponatremia	May be common in chronic schizophrenia.
Respiratory	Respiratory tract infection, respiratory failure; COVID-19 infection may be associated with catatonia and is more prevalent in psychiatric patients.
Medication and toxins	Alcohol or benzodiazepine withdrawal, lithium toxicity, inhalants.

CNS: Central Nervous System, ICU: Intensive Care Unit, NMDAR: N-Methyl-D-Aspartate Receptor.

2.1. Brain Injuries

There is evidence that patients with mental disorders, particularly those with psychotic disorders, may be prone to accidents, compared to the general population. Indeed, the risk of death by accident has been reported to be 2–4 times higher in patients with schizophrenia than in the general population [25,26]. Accordingly, brain injuries may be particularly relevant in these patients and such injuries may be associated with catatonic syndrome.

2.2. Infections and COVID-19

Infections have been associated with the development of catatonic symptoms, and may be more relevant in causing severe morbidity and mortality to patients with psychotic disorders in developing countries [27]. Recently, in the era of the COVID-19 pandemic, there are several reports of catatonia associated with COVID-19 infection [28,29]. This may be relevant for people with severe mental illnesses, as there is evidence that they are more likely to suffer a COVID-19 infection, compared to the general population, and associated mortality rates are higher in these patients [30,31]. Moreover, these patients may be under-vaccinated for COVID-19 [32], although data are contradictory in this regard [33,34].

2.3. Hyponatremia

The most common electrolyte imbalance in patients with schizophrenia is hyponatremia, with a prevalence of 7–10% in inpatient settings [35]. The so-called psychogenic

polydipsia may sometimes cause hyponatremia, via excess consumption of water, and its incidence in chronic patients with schizophrenia may be up to 11–20% [36]. Additionally, antipsychotics and antidepressants can cause hyponatremia, because they may induce the syndrome of inappropriate antidiuretic hormone secretion [37]. This is also the case for some antiepileptic drugs that are used in the treatment of patients with bipolar disorders as antimanic agents and/or mood stabilizers [38]. Although hyponatremia as a cause of catatonia has only been rarely reported in the literature [39], such an association is relevant for clinical practice.

2.4. Critical Illness

It is alarming that there may be disparities in health and hospital care between patients with severe mental illnesses and the general population [40]. Indeed, there is some evidence that patients with schizophrenia may have reduced access to critical care [41]. On the other hand, it may be possible that these patients suffer a critical illness and need admission to the ICU, given their proneness to accidents and major injuries and the high rates of physical morbidity [42,43]. There are several studies on catatonic syndrome in critically ill patients, and the issues of multimorbidity and severe morbidity, alongside previous psychiatric history in catatonic critically ill patients, have been highlighted by the authors [9,44].

2.5. Withdrawal Catatonia

Patients with schizophrenia are particularly prone to alcohol/substance abuse disorders, with well-known negative effects on outcome and health [45]. Such misuse is also one of the leading causes of death in these patients [46]. Similarly, regular treatment with benzodiazepines may often be the case in these patients [47,48]. Moreover, a minority of patients with schizophrenia receive clozapine for the treatment of refractory symptoms. A comprehensive review of reported cases found that withdrawal catatonia was most commonly associated with the abrupt discontinuation of clozapine or benzodiazepines [49]. Abrupt discontinuation of alcohol or medication, such as benzodiazepines or clozapine, should always be suspected in acutely admitted psychiatric patients that present with catatonic symptoms.

3. Diagnosis of Catatonia

In clinical practice, catatonia may be diagnosed by referring to established diagnostic criteria, for example, the International Statistical Classification of Diseases, Tenth Revision, and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (ICD-10 and DSM-5, respectively), or with the use of clinical rating scales. However, the two major diagnostic systems differ substantially in their definitions and classifications of catatonia. That is, the DSM-5 conceptualizes catatonia as a widely independent syndrome, whereas the ICD-10 classifies catatonia only in the context of schizophrenia or as a syndrome due to an organic brain disorder [20]. In a previous review, six catatonia rating scales were critically evaluated, namely the Rogers Catatonia Scale, the Bush–Francis Catatonia Rating Scale (BFCRS), the Northoff Catatonia Rating Scale, the Braunig Catatonia Rating Scale, the Kanner Scale and the Modified Rogers Scale. The authors concluded that all scales were valid, reliable and useful in clinical practice, and their use improved the detection of catatonia. Of these, the BFCRS had been the most widely used in research as well as in clinical practice because of its ease of administration [50]. A recent study examined the use of different scales for the screening of catatonia, by comparing BFCRS and its screening instrument with the DSM-5. The BFCRS and the relative screening instrument showed the highest screening rate and a high inter-rater reliability, while the DSM-5 had deficiencies in screening for catatonia with low inter-rater reliability, which limited its utility in the assessment of catatonia in the clinical setting, according to the authors [51]. Very recently, the use of actigraphy as an objective measurement of physical activity was studied in patients with catatonic symptoms. The authors suggested that measuring

catatonia symptoms with actigraphy may aid the detection and staging of catatonia in clinical settings and may enable the monitoring of treatment effects in clinical trials [52].

4. Complications of Catatonia

One of the core symptoms of catatonia, immobility, may increase morbidity in a psychiatric patient with an underlying medical illness already severe enough to have caused catatonia. Accordingly, a broad range of complications of catatonia can occur, such as aspiration pneumonia, dehydration, muscle contractures, pressure ulcers, nutritional deficiencies, severe weight loss, thiamine deficiency, electrolyte disturbances, urinary tract infections and venous thromboembolism [53,54], some of which may be life-threatening. These complications should be taken into consideration in the management of catatonic patients.

5. Treatment of Catatonia

Benzodiazepines, particularly lorazepam, are the first-line treatment for catatonia, regardless of the underlying cause. Their use is safe, easy and effective, with remission rates reported to be as high as 70–80% [54]. Resolution of the catatonic symptoms is usually rapid, within hours or days. Electroconvulsive therapy (ECT) should be used in cases that are refractory to benzodiazepines or in severe cases with life-threatening conditions such as malignant catatonia featuring high fever and autonomic instability, where a decisive and rapid response is required. ECT is also highly effective and may resolve catatonic syndrome rapidly [55]. There is no consensus on the duration of treatment of catatonia with benzodiazepines. Treatment is usually discontinued once the underlying illness that was thought to cause the catatonic symptoms remits, but if catatonia relapses, benzodiazepine treatment should be re-started, with no specific time-limit [4]. With regard to antipsychotic drugs, they are generally recommended to be avoided in acutely catatonic patients because of their potential of aggravating the catatonic symptoms. Once catatonic symptoms have improved with benzodiazepines or ECT, antipsychotic treatment can be initiated safely, preferably with a second-generation antipsychotic [3,54].

Obviously, when a medical cause of catatonia is suspected, etiologic treatment should occur concurrently, targeting the underlying cause. In addition, given the potentially life-threatening complications of catatonia, in several cases supportive care measures will be warranted such as intravenous fluids and nasogastric tube feeds, to maintain adequate hydration and nutrition. Mobilization and the repositioning of patients, as well as bowel regimens and anticoagulation prophylaxis, alongside high levels of nursing care, may be essential to prevent further complications [54].

6. Relapse and Recurrence

There are only a few data with regard to the recurrence of catatonia, but it has been suggested that the rate of relapses and recurrences are likely underestimated [56]. In a very recent prospective, observational study in an acute mental health unit in South Africa, the recurrence rate of catatonia over an 8-week follow-up was 2.3%, but involved just one patient [57]. Other research suggests that recurrence mostly involves the retarded catatonia subtype which responds well to benzodiazepines [56], and shows consistency of the catatonic signs and symptoms across different episodes [58]. In the largest clinical study so far on the presentation and correlates of catatonia in psychiatric inpatients, it was found that 25.1% of patients experienced at least two episodes within the 7-year follow-up period [15]. It seems that recurrence rates may be much higher, up to 10-fold in the long term, compared with the short-term rates. Most studied cases of recurrence involved patients with mental disorders, yet recurrence may also occur in cases of catatonia due to medical conditions [56].

7. Catatonia and Delirium

Another challenge for clinicians may be newly-onset psychotic symptoms in catatonic patients with established psychotic disorders. Such symptoms may develop in the context of an acute confusional state and may be difficult to distinguish from the symptoms of the underlying mental illness. The co-occurrence of the syndromes of catatonia and delirium may be encountered in several clinical settings [59,60]. Psychotic symptoms may be perceived as a sign of decompensation of the primary disorder in patients with an established psychotic disorder. In such cases, the inquiry for and the detection of confusion and disorientation could guide clinicians toward the diagnosis of an organic cause.

8. Discussion

Catatonia due to medical conditions in psychiatric patients is relevant and may be particularly challenging for clinicians. Patients with the most severe mental disorders may not receive appropriate medical care [61], yet they may be prone to developing catatonic symptoms in the context of a medical or neurologic disease. Several medical conditions may induce catatonic symptoms, regardless of underlying mental illness, but some are more relevant in this regard. However, this phenomenon is even more relevant in patients with a psychotic or mood disorder, which may itself induce catatonic symptoms.

An extensive clinical and laboratory diagnostic workup to determine the underlying etiology of catatonic syndrome should be carried out, considering the broad list of neurologic and general medical causes, as well as the complications of catatonia. Laboratory investigations should include a complete blood count, blood urea nitrogen, creatinine, creatine phosphokinase and hepatic enzymes, thyroid function tests, electrolytes and blood glucose, among others [3]. More specialized laboratory investigation, such as imaging of the brain, electroencephalogram and spinal fluid analysis should also be considered, according to indications.

In cases of acute multi-morbidity in psychiatric patients, the exact cause of catatonic syndrome may be unclear. Presumably, multiple causal factors, including the underlying mental illness per se, may act synergistically to cause catatonia. Clinicians should be aware of the medical causes that may induce catatonia in this vulnerable population, and newly-onset catatonic symptoms should not be perceived as a manifestation of the underlying psychotic or mood disorder without proper investigation for general medical conditions. Moreover, the presence of delirium may be an indication of a medical cause of catatonic features; thus, an extensive diagnostic workup toward potential medical causes should be performed in cases of delirium and catatonia co-occurrence [62].

Implications for Treatment

The treatment of catatonia in medically ill psychiatric patients may be challenging for clinicians. Of course, treatment should be etiologic, targeting the underlying medical cause of catatonia, if known. At the same time, there is a need for treatment of the mental disorder, even when the medication regimen may be accountable, at least in part, for catatonic syndrome. The commencement of lorazepam or other benzodiazepines as initial treatments of catatonic syndrome and the use of ECT in refractory cases seem plausible and may be safe. However, treating catatonic syndrome in medically ill patients with psychotic disorders may be even more challenging. These patients may need continuous antipsychotic administration, and this complicates treatment, as antipsychotics may precipitate neuroleptic malignant syndrome in patients with catatonia [3,63]. It is recommended to avoid antipsychotic medication in acute catatonic patients; when catatonic symptoms have been treated with benzodiazepines or ECT, antipsychotic treatment can be initiated safely [3]. The so-called withdrawal catatonia may occur in the context of the abrupt discontinuation of a treatment regimen that comprises clozapine or benzodiazepines. This is clinically relevant, because medication discontinuation by patients with psychotic disorders is common [64] and may result in psychotic relapse and hospitalization. In these

patients, the commencement of benzodiazepines and/or clozapine could be effective for the resolution of the catatonic symptoms.

The most common type of catatonia, that is, the akinetic subtype, should be promptly differentiated from hypoactive delirium, which may be common but under-recognized in hospitalized patients [65]. This could have important treatment implications. That is, in cases of delirium, treatment with antipsychotics is regularly employed for the management of psychotic symptoms and agitation [66,67], whereas, in catatonia, antipsychotics may precipitate neuroleptic malignant syndrome. In cases of delirium and catatonia co-occurrence, special consideration is warranted. Symptoms of catatonia and delirium may overlap, complicating diagnosis, whereas treatments for these two syndromes are different, making the management of these patients even more challenging. That is, while antipsychotics are typically employed in the treatment of delirium, the emergence of catatonia should raise caution against the use of these agents, as they may exacerbate the catatonic symptoms. On the other hand, benzodiazepines are not recommended for the treatment of delirium, and indeed may produce or worsen an acute confusional state, whereas they are an effective treatment for catatonia [54,62].

9. Conclusions

Catatonia is an epidemiologically and clinically relevant syndrome in patients with mental disorders that may be induced by several treatable medical causes, along with the well-known psychiatric causes. In cases of newly-onset catatonic symptoms in psychiatric patients, a number of general medical conditions should be considered and appropriately investigated. Simple tests, such as full blood count, could be suggestive of a possible cause and guide clinicians toward etiologic treatment of catatonic syndrome, whereas other more specialized examinations may be needed in some cases. Treating psychiatrists should co-operate with other physicians to ensure an accurate diagnosis of the underlying cause of catatonic syndrome in their patients. Treatment with benzodiazepines or ECT in refractory cases may suffice to eliminate catatonic syndrome, alongside the prompt management of the suspected underlying cause.

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