When mania isn't what it seems

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How would you handle this case?

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Mr. S, age 22, has autism, bipolar disorder, and intellectual disability. He suddenly experiences increased impulsivity and agitation. What could be causing these symptoms?

CASE Aggressive, impulsive, and not sleeping

Mr. S, age 22, is brought by his family to his outpatient psychiatrist because he has begun to exhibit motor and verbal tics, excessive adherence to rules and routines, and increased impulsivity and agitation.

Mr. S has significant language impairment and is unreliable as a narrator. His family reports that Mr. S's behavior has resulted in declining academic performance, and they have curtailed his social activities due to behavioral issues. Both his family and teachers report that it is increasingly difficult to redirect Mr. S's behavior. Although not physically aggressive, Mr. S becomes verbally agitated when rituals are incomplete. He has gone from sleeping 8 hours each night to only 3 to 4 hours, but he does not appear tired during the day.

HISTORY Multiple hospitalizations

As a child, Mr. S had been diagnosed with autism and intellectual disability. When he was 13, he began exhibiting marked stereotypy, restlessness, impulsivity, frenzy, agitation, combativeness, and purposeless motor activity. At that time, he was not receiving any medications. Mr. S had not slept for 2 days and had been walking in circles nonstop. He became aggressive whenever anyone attempted to redirect his behavior. The family took Mr. S to the emergency department (ED), where clinicians ruled out organic causes for his behavioral disturbances, including infections, drug intoxication, and use of illicit substances. Mr. S was transferred from the ED to a child and adolescent psychiatry ward at a nearby university hospital for inpatient treatment.

On the inpatient unit, the treatment team diagnosed Mr. S with bipolar disorder and believed that he was experiencing a manic episode. He was prescribed quetiapine, 25 mg by mouth during the day and 75 mg by mouth at night, to stabilize his agitation, and was discharged with a plan to follow up with his outpatient psychiatrist. However, within 1 week, his symptoms returned, with markedly increased aggression and agitation, so he was readmitted, tapered off quetiapine, and prescribed valproic acid, 125 mg by mouth during the day and 375 mg by mouth at bedtime. With this regimen, Mr. S became calmer, but when he was discharged home, he was subdued and

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withdrawn, overly adherent to rules and routines, constantly irritable, and often unable to focus.

Two years later, Mr. S developed hyperammonemia. Valproic acid was discontinued, and many of his behavioral issues resolved. He flourished both academically and socially. He experienced no exacerbation of symptoms until his current presentation.

Which diagnosis best explains Mr. S's current symptoms?

a) behavioral exacerbation of autism
b) generalized anxiety disorder
c) schizoaffective disorder
d) hyperkinetic catatonia

EVALUATION Pinpointing the cause

Mr. S's physical examination reveals that his vital signs are within normal limits. Mr. S is mildly tachycardic (heart rate, 105 bpm), with regular rate and rhythm. No murmurs, gallops, or rubs are auscultated. The remainder of the physical exam, including a detailed neurologic exam, is normal.

On mental status examination, Mr. S makes limited eye contact. He has difficulty sitting in the chair, with increased rocking, finger flicking, and hand flapping from baseline. Some compulsive behaviors are noted, such as tapping his neck. He has increased tics (eye blinking and mouth opening) and increased verbigeration and repetitive verbal statements. He loudly and repeatedly demands to go home, and uses short sentences with incorrect pronouns. His affect is difficult to assess, but he is agitated. His thought process is concrete. There is no evidence of suicidal ideation, homicidal ideation, or psychosis. Mr. S denies auditory hallucinations. His insight and judgment are limited.

The psychiatrist rules out a behavioral exacerbation of autism based on an interview with Mr. S's family and established rapport from treating him for several years. Mr. S's family reports that many of his behaviors are not new but that the increased drive and intensity is worrisome. Further, his family cannot identify any stressors or precipitants for the behaviors and reports that offering preferred reinforcers did not help. An anxiety disorder is ruled out because according to the family, Mr. S's drive to constantly move and complete rituals is fueling his anxiety. Schizoaffective disorder is ruled out because Mr. S denies auditory hallucinations and has not been observed responding to internal stimuli.

His Bush-Francis Catatonia Rating Scale (BFCRS) score is 26, which suggests a high likelihood of catatonia. Based on the BFCRS score, Mr. S's psychiatrist makes the diagnosis of hyperkinetic catatonia.

The authors' observations

The psychiatrist determined that Mr. S had been misdiagnosed with bipolar disorder at age 13. At that time, he had experienced his first episode of hyperkinetic catatonia and his symptoms decreased after he received lorazepam in the ED. However, the treatment team did not correctly identify this, most likely due to limited knowledge of catatonia among emergency medicine clinicians.

This case exemplifies a cognitive error of premature closure. Rather than considering catatonia as a complication of autism when Mr. S was 13, the clinicians added a second psychiatric diagnosis of bipolar disorder. Although premature closure errors generally occur when the physician assumes the patient is having a common complication of a known illness,[1] in Mr. S's case, the opposite occurred.

Conceptualizing catatonia

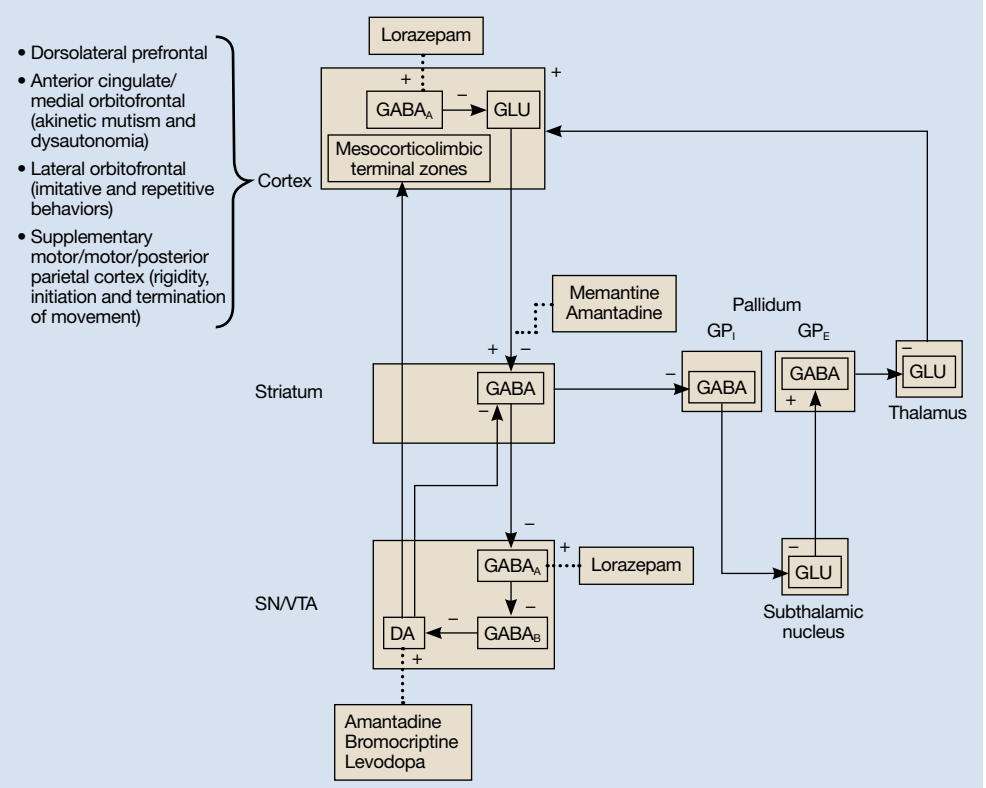
One helpful model for conceptualizing catatonia is to think of it as a basal ganglia disorder, with lesions in the basal ganglia thalamocortical tracts and the anterior cingulate/medial orbitofrontal circuit. Disrupting these pathways can result in symptoms such as mutism or repetitive and imitative behaviors. This is likely due to decreased disinhibition by gamma-aminobutyric acid (GABA), resulting in a hypodopaminergic state.

Clinical Point

Although not physically aggressive, Mr. S becomes verbally agitated when rituals are incomplete, and he sleeps only 3 to 4 hours each night

Figure

The neurobiologic pathophysiology of catatonia



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Source: Reference 2

DA: dopamine; GABA: gamma-aminobutyric acid; GLU: glutamate; GP$_I$: globus pallidus interna; GP$_E$: globus pallidus externa; SN: substantia negra; VTA: ventral tegmental area

Clinical Point

Catatonia is often seen in individuals with an underlying psychiatric condition such as schizophrenia, a mood disorder, or autism

This explains why benzodiazepines, which act to increase GABA, are effective for treating catatonia, and antipsychotics that act to decrease dopamine can exacerbate symptoms. Fricchione et al[2] developed a model to visually represent the neurobiologic pathophysiology of catatonia (***Figure***[2]).

Underlying causes of catatonia

Catatonia is most often seen in individuals with an underlying psychiatric condition such as schizophrenia, mood disorders, or autism. However, catatonia also occurs in the context of general neurologic and medical disorders, including (but not limited to) infections, metabolic disorders, endocrinopathies, epilepsy, neurodegenerative diseases, delirium, hypertensive encephalopathy, autoimmune encephalitis, and liver and kidney transplantation.[3]

Subtypes of catatonia include[4]:

- hypokinetic catatonia, which presents as stupor, mutism, and negativism
- hyperkinetic catatonia, which presents as hyperactivity, agitation, and stereotypy (as observed in Mr. S)
- malignant catatonia, which is a potentially lethal form of catatonia that occurs when hypo- or hyperkinetic catatonia is accompanied by autonomic instability such as tachycardia, tachypnea, hypertension, fever, and muscle rigidity

• periodic catatonia, which is characterized by brief episodes of stupor or excitatory catatonia lasting 4 to 10 days. These episodes recur over weeks to years, with patients remaining asymptomatic between episodes, or showing mild symptoms, such as facial grimacing or negativisms. Periodic catatonia often is autosomal dominant, involves linkage for the long arm of chromosome 15, and has a better prognosis than the other forms.

Autism and catatonia

Most individuals with autism who experience a catatonic episode first do so between age 10 and 19, and many episodes are precipitated by sudden changes in routine resulting in stress.[5] An estimated 12% to 18% of patients with autism are diagnosed with catatonia in their lifetime, but the actual prevalence is likely higher.[4]

One of the reasons for this might be that although catatonia is well known in the psychiatric community, it is relatively unknown in the general medical community. Children and adolescents with psychiatric illness are likely to have symptoms of catatonia overlooked because catatonia often is not included in the differential diagnosis.[6]

In Mr. S's case, it became clear that he did not have a mood disorder, but was prone to episodes of hyperkinetic catatonia due to his autism.

Better recognition of catatonia

As catatonia becomes better elucidated and more clearly described in the literature, there is increasing awareness that symptoms do not always involve stupor, mutism, and slowed motor activity, but can include increased motor activity, agitation, and stereotypies. The BFCRS is extremely useful for quantifying symptoms of catatonia. The best way to confirm the diagnosis is to use a lorazepam challenge in an inpatient setting, or a trial of lorazepam in an outpatient setting.[5]

Related Resources

- Dhossche DM, Wing L, Ohta M, et al. International Review of Neurobiology: Catatonia in autism spectrum disorders, vol 72. New York, NY: Academic Press/Elsevier; 2006.
- Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. Am J Psychiatry. 2003;160(7):1233-1241.

Drug Brand Names

Amantadine • Symmetrel
Bromocriptine • Parlodel
Clonazepam • Klonopin
Lorazepam • Ativan
Memantine • Namenda
Oxazepam • Serax
Quetiapine • Seroquel
Valproic acid • Depakene, Depakote
Zolpidem • Ambien

Although lorazepam is often a first-line treatment for catatonia, which of the following have also been shown effective?

a) clonazepam
b) oxazepam
c) zolpidem
d) all of the above

The authors' observations

Lorazepam is often considered the first-line treatment for catatonia because it is one of the most widely studied medications. Other benzodiazepines, such as oxazepam and clonazepam, and the sedative/hypnotic zolpidem have also been shown to be effective. Antipsychotics with dopamine-blocking mechanisms can exacerbate symptoms of catatonia and should be avoided in these

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Clinical Point

There is increasing awareness that the symptoms of catatonia can include increased motor activity, agitation, and stereotypies

Bottom Line

Hyperkinetic catatonia is easily overlooked, especially in the emergency setting. Catatonia should always be ruled out, particularly in patients with underlying conditions associated with it. Hyperkinetic catatonia is an underrecognized comorbidity in patients with autism.

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patients. Furthermore, in cases of refractory catatonia, bilateral electroconvulsive therapy is an important and necessary treatment.[7]

TREATMENT Pharmacologic agents decrease BFCRS score

Mr. S is prescribed a regimen of lorazepam, 2 mg by mouth daily, and the supplement *N*-acetylcysteine, 600 mg by mouth daily. Within 2 weeks of starting this regimen, Mr. S's BFCRS score decreases from 26 to 14. After 6 months of treatment with lorazepam, Mr. S shows considerable improvement. The stereotypic behaviors and impulsivity decrease significantly, leading to improved sleep and performance in school. After 6 months Mr. S is successfully tapered off the lorazepam, with a complete return to baseline.

Clinical Point

Within 2 weeks of starting lorazepam and *N*-acetylcysteine, Mr. S's BFCRS score decreases from 26 to 14

References

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4. Wijemanne S, Jankovic J. Movement disorders in catatonia. J Neurol Neurosurg Psychiatry. 2014;86(8): 825-832.
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7. Seinaert P, Dhossche DM, Vancampfort D, et al. A clinical review of the treatment of catatonia. Front Psychiatry. 2014;5:181.