The angry disciple

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Mr. J, age 54, is agitated, disruptive, and claims to be the 'son of Jesus Christ.' He left his job and family to travel to the Middle East to be baptized. What could be causing his symptoms?

CASE Disorganized thoughts and grandiose delusions

Mr. J, age 54, presents to the psychiatric emergency department (ED) with agitation and disruptive behavior. He claims that he is "the son of Jesus Christ" and has to travel to the Middle East to be baptized. Mr. J is irritable, shouting, and threatening staff members. He receives olanzapine, 10 mg IM, which helps to alleviate his disruptive behaviors. Laboratory results reveal a blood alcohol level of 231 mg/dL, indicating intoxication, which may be contributing to his disruptive behaviors. Mr. J is monitored and observed overnight.

The next day, he is calm and cooperative, but continues to express the same religious delusions. Mr. J is admitted to the psychiatric inpatient unit for further evaluation.

On the unit, Mr. J is pleasant and cooperative, but tangential in thought process. He reports he was "saved" by God 4 years ago, and that God communicates with him through music. Despite this, he denies having auditory or visual hallucinations.

Approximately 3 months earlier, Mr. J had stopped working and left his home and family in another state to pursue his "mission" of being baptized in the Middle East. Mr. J has been homeless since then. Despite that, he reports that his mood is "great" and denies any recent changes in mood, sleep, appetite, energy level, or psychomotor agitation. Although no formal cognitive testing is performed, Mr. J is alert and oriented to person, place, and time with intact remote and recent memory, no language deficits, and no lapses in concentration or attention throughout interview.

Mr. J says he has been drinking alcohol regularly throughout his adult life, often a few times per week, up to "a case and a half" of beer at times. He claims he's had multiple periods of sobriety but denies having experienced withdrawal symptoms during those times. Mr. J reports 1 prior psychiatric hospitalization 25 years ago after attempting suicide by overdose following the loss of a loved one. At that time, he was diagnosed with posttraumatic stress disorder (PTSD). During this admission, he denies having any symptoms of PTSD or periods of mania or depression, and he has not undergone psychiatric treatment since he had been diagnosed with PTSD. He denies any family history of psychiatric illness as well as any medical comorbidities or medication use.

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Disclosures
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How would you handle this case?

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Clinical Point

Although it is possible to develop psychotic symptoms due to severe alcohol withdrawal, Mr. J had no other signs of withdrawal

Table 1

Differential diagnosis of delusions

Substance-induced psychosis
Psychosis secondary to a general medical condition
Schizophrenia (or schizophreniform if duration <6 months)
Schizoaffective disorder
Major depressive disorder with psychotic features
Bipolar disorder with psychotic features
Delusional disorder

Which diagnosis would you consider for Mr. J?

a) substance-induced psychosis
b) primary psychotic disorder
c) psychosis secondary to a medical or neurologic condition
d) delusional disorder

The authors' observations

Mr. J's presentation had a wide differential diagnosis (***Table 1***). The initial agitation Mr. J displayed in the psychiatric ED was likely secondary to acute alcohol intoxication, given that he was subsequently pleasant, calm, and cooperative after the alcohol was metabolized. Despite this, Mr. J continued to demonstrate delusions of a religious and somewhat grandiose nature with tangential thought processes, which made substance-induced psychosis less likely to be the sole diagnosis. Although it is possible to develop psychotic symptoms due to severe alcohol withdrawal (alcoholic hallucinosis), Mr. J's vital signs remained stable, and he demonstrated no other signs or symptoms of withdrawal throughout his hospitalization. His presentation also did not fit that of delirium tremens because he was not confused or disoriented, and did not demonstrate perceptual disturbance.

While delusions were the most prominent feature of Mr. J's apparent psychosis, the presence of disorganized thought processes and impaired functioning, as evidenced by Mr. J's unemployment and recent homelessness, were more consistent with a primary psychotic disorder than a delusional disorder.[1]

Mr. J began to exhibit these psychotic symptoms in his early 50s; because the average age of onset of schizophrenia for males is approximately age 20 to 25, the likelihood of his presentation being the result of a primary psychotic disorder was low.[1] Although less common, it was possible that Mr. J had developed late-onset schizophrenia, where the first episode typically occurs after approximately age 40 to 45. Mr. J also described that he was in a "great" mood but had grandiose delusions and had made recent impulsive decisions, which suggests there was a possible mood component to his presentation and a potential diagnosis of schizoaffective disorder or bipolar disorder with psychotic symptoms. However, before any of these diagnoses could be made, a medical or neurologic condition that could cause his symptoms needed to be investigated and ruled out. Further collateral information regarding Mr. J's history and timeline of symptoms was required.

EVALUATION Family history reveals clues

All laboratory studies completed during Mr. J's hospitalization are unremarkable, including complete blood count, basic metabolic panel, hepatic function panel, gamma-glutamyl transferase test, magnesium, phosphate, thyroid-stimulating hormone, vitamin B_{12}, thiamine, folate, urinalysis, and urine drug screen. Mr. J does not undergo any head imaging.

Mr. J has not been in touch with his family since leaving his home approximately 3 months before he presented to the ED, and he gives consent for the inpatient team to attempt to contact them. One week into hos-

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pitalization, Mr. J's sibling informs the team of a family history of genetically confirmed Huntington's disease (HD), with psychiatric symptoms preceding the onset of motor symptoms in multiple first-degree relatives. His family says that before Mr. J first developed delusions 4 years ago, he had not exhibited any psychotic symptoms during periods of alcohol use or sobriety.

Mr. J does not demonstrate any overt movement symptoms on the unit and denies noting any rigidity, change in gait, or abnormal/uncontrolled movements. The inpatient psychiatric team consults neurology and a full neurologic evaluation is performed. The results are unremarkable outside of his psychiatric symptoms; specifically, Mr. J does not demonstrate even subtle motor signs or cognitive impairment. Given Mr. J's family history, unremarkable lab findings, and age at presentation, the neurology team and inpatient psychiatry team suspect that his psychosis is likely an early presentation of HD.

What are the most common psychiatric manifestations of Huntington's disease?

a) psychosis and/or paranoia
b) depression
c) obsessive-compulsive behavior
d) irritability and/or anxiety

The authors' observations

Genetics of Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats within the Huntingtin (HTT) gene on chromosome 4, which codes for the huntingtin protein.[2,3] While the function of "normal" huntingtin protein is not fully understood, it is known that CAG repeat expansion in the HTT gene of >35 repeats codes for a mutant huntingtin protein.[2,3] The mutant huntingtin protein causes progressive neuronal loss in the basal ganglia and striatum, resulting in the clinical Huntington's phenotype.[3] Notably, the patient's age at disease onset is inversely correlated with the number of repeats. For example, expansions of approximately 40 to 50 CAG repeats often result in adult-onset HD, while expansions of >60 repeats are typically associated with juvenile-onset HD (before age 20). CAG repeat lengths of approximately 36 to 39 demonstrate reduced penetrance, with some individuals developing symptomatic HD while others do not.[2] Instability of the CAG repeat expansion can result in genetic "anticipation," wherein repeat length increases between generations, causing earlier age of onset in affected offspring. Genetic anticipation in HD occurs more frequently in paternal transmission—approximately 80% to 90% of juvenile HD cases are inherited paternally, at times with the number of CAG repeats exceeding 200.[3]

Psychiatric manifestations of Huntington's disease

Huntington's disease is characterized by motor, cognitive, and behavioral disturbances (***Table 2***,[2,4] ***page 40***). Motor symptoms include a characteristic and well-recognized chorea, often predominating earlier in HD, that progresses to rigidity, spasticity, and bradykinesia later in the disease course.[2] Cognitive impairments develop in a similar progressive manner and can often precede the onset of motor symptoms, beginning with early executive dysfunction. Thinking often becomes more rigid and less efficient, causing difficulty with multi-tasking and concentration, and often progressing to subcortical dementia.[2]

Psychiatric symptoms have long been recognized as a feature of HD; the estimated lifetime prevalence in patients with HD ranges from approximately 33% to 76%.[4] Depressed mood, anxiety, irritability, and apathy are the most commonly reported symptoms, while a smaller percentage of patients with HD can experience obsessive-compulsive disorder (10%

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Approximately 3% to 11% of patients with Huntington's disease experience psychotic symptoms

Table 2

Symptoms of Huntington's disease

Motor	Cognitive	Psychiatric
Chorea	Executive dysfunction (rigid thinking, difficulty multi-tasking and concentrating)	Depressed mood
Dystonia	Memory loss	Apathy
Myoclonus (more common in juvenile-onset HD)	Subcortical dementia	Irritability and agitation
Parkinsonian symptoms, including rigidity, spasticity, and bradykinesia (later in progression of adult-onset HD)		Anxiety
		Obsessive-compulsive behaviors
		Psychosis

HD: Huntington's disease

Source: References 2,4

Clinical Point

Family history is a major risk factor for HD-associated psychosis, as is early-onset HD

to 52%) or psychotic symptoms (3% to 11%).[4] A more specific schizophrenia-like psychosis occurs in approximately 3% to 6% of patients, and often is a paranoid type.[5,6] Positive psychotic symptoms, such as hallucinations and delusions, typically become less overt as HD progresses and cognitive impairments worsen.[7]

Although the onset of motor symptoms leads to diagnosis in the majority of patients with HD, many patients present with psychiatric symptoms—most commonly depression—prior to motor symptoms.[8] An increasing body of literature details instances of psychosis preceding motor symptom onset by up to 10 years.[6,9-12] In many of these cases, the patient has a family history of HD-associated psychosis. Family history is a major risk factor for HD-associated psychosis, as is early-onset HD.[7,9]

TREATMENT Antipsychotics result in some improvement

On Day 1 or 2, Mr. J is started on risperidone, 1 mg twice daily, to manage his symptoms. He shows incremental improvement in thought organization. Although his religious and grandiose delusions persist, they become less fixed, and he is able to take the team's suggestion that he reconnect with his family.

Mr. J is aware of his family history of HD and acknowledges that multiple relatives had early psychiatric manifestations of HD. Despite this, he still has difficulty recognizing any connection between other family members' presentation and his own. The psychiatry and neurology teams discuss the process, ethics, and implications of genetic testing for HD with Mr. J; however, he is ambivalent regarding genetic testing, and states he would consider it after discussing it with his family.

The neurology team recommends against imaging for Mr. J because HD-related changes are not typically seen until later in the disease progression. On Day 9, they recommend changing from risperidone to quetiapine (50 mg every night at bedtime) due to evidence of its effectiveness specifically for treating behavioral symptoms of HD.[13]

While receiving quetiapine, Mr. J experiences significant drowsiness. Because he had experienced improvement in thought organization while he was receiving risperidone, he is switched back to risperidone.

Which antipsychotics have evidence of efficacy for treating HD-associated psychotic symptoms?

a) haloperidol
b) risperidone
c) clozapine
d) quetiapine

The authors' observations

Currently, no treatments are available to prevent the development or progression of HD. However, symptomatic treatment of motor and behavioral disturbances can lead to functional improvement and improved quality of life for individuals affected by HD.

There are no extensive clinical trials to date, but multiple case reports and studies have shown second-generation antipsychotics (SGAs), including quetiapine, olanzapine, aripiprazole, and risperidone, are moderately effective in improving HD-associated psychotic symptoms.[9,12-16] Quetiapine is often suggested at lower doses because it has the least extrapyramidal effects of the aforementioned SGAs and will not cause worsening of bradykinesia or rigidity, which have been associated with later-stage HD.[13] Multiple case reports have noted that risperidone, which Mr. J tolerated and responded to, improved both psychiatric symptoms and motor symptoms.[9,12] A retrospective study found that risperidone use over 15 months reduced psychiatric symptoms and stabilized motor decline.[14] Varying dosages of risperidone, from 1 mg/d to 4 mg/d, were used in these case reports and study. Olanzapine and aripiprazole have been similarly effective in improving HD-associated psychosis as well as movement symptoms.[15,16] Clozapine is generally not recommended in patients with HD because high doses are required to achieve similar improvements in movement symptoms, which places patients at increased risk for adverse dose-dependent reactions, including agranulocytosis.[17]

Related Resources

- Huntington's Disease Society of America. http://hdsa.org.
- National Institute of Neurological Disorders and Stroke. Huntington's disease information page: What research is being done? https://www.ninds.nih.gov/Disorders/All-Disorders/Huntingtons-Disease-Information-Page.
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Drug Brand Names

Aripiprazole • Abilify	Olanzapine • Zyprexa
Clozapine • Clozaril	Quetiapine • Seroquel
Haloperidol • Haldol	Risperidone • Risperdal

OUTCOME Discharge despite persistent delusions

Mr. J's religious and grandiose delusions continue throughout hospitalization despite treatment with antipsychotics. However, because he remains calm and cooperative and demonstrates improvement in thought organization, he is deemed safe for discharge and instructed to continue risperidone. The team coordinates with Mr. J's family to arrange transportation home and outpatient neurology follow-up.

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Clinical Point

Certain second-generation antipsychotics are moderately effective in improving HD-associated psychotic symptoms

Bottom Line

Psychiatric manifestations, including psychosis, are prominent symptoms of Huntington's disease (HD) and may precede the onset of more readily recognized motor symptoms. This poses a diagnostic challenge, and clinicians should remain cognizant of this possibility, especially in patients with a family history of HD-associated psychosis.

Clinical Point

Clozapine is not recommended to treat HD because high doses are required to achieve similar improvements in movement symptoms

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