



## > THE PATIENT

58-year-old woman

## > SIGNS & SYMPTOMS

- Paranoid delusions
- Ideas of reference
- Sleep problems
- Multiple, vague somatic symptoms

# CASE REPORT

ONLINE EXCLUSIVE

**Sandy Chan, BS; Ivan Chik, MD; Barbara A. Wilson, MD**

Geisel School of Medicine at Dartmouth, Hanover, NH; Department of Psychiatry at Dartmouth-Hitchcock Medical Center, Lebanon, NH

[Sandy.Chan@umassmemorial.org](mailto:Sandy.Chan@umassmemorial.org)

*The authors reported no potential conflict of interest relevant to this article.*

## > THE CASE

A 58-year-old married Asian woman with no apparent psychiatric history presented to the emergency department (ED) in an acute state with ideas of reference, paranoid delusions, and multiple, vague somatic symptoms.

Based on information in the patient's medical record, there had been suspicion of an underlying psychiatric disorder 6 years earlier. At that time, the patient had presented to her primary care provider (PCP) with vague somatic complaints, including diffuse body pain, dry cough, chills, weakness, facial numbness, and concerns about infections. A physical examination and work-up did not reveal the source of her complaints. Unfortunately, the patient's complaints increased in number and severity over time.

Her medical records also indicated that she had been assessed for depression severity using the Patient Health Questionnaire-9 (PHQ-9), with scores of 0 (4 years earlier) and 3 (3 years earlier). The scores suggested that she was not suffering from depression.

During this time, the patient also saw a psychiatrist; however, it was unclear whether her symptoms met the criteria for delusional disorder or schizophrenia because she did not exhibit negative symptoms or sensory hallucinations. In addition, the patient was extremely high-functioning in the community—she participated in dance classes and other social events—and had the equivalent of a medical degree from another country. Based on chart review, when she went to the psychiatrist 3 years prior to her current presentation, there were no antipsychotics prescribed.

In the weeks leading up to her current presentation, the patient reported that she was struggling with sleep, sometimes spending days in bed and other times needing unspecified medication obtained overseas to help her sleep. Her husband reported that she had become increasingly withdrawn and stopped attending her dance classes and social events.

The patient believed the government was trying to poison her via radiation and that unknown people were trying to harm her via an online messaging application. Immediately prior to her arrival in the ED, the police were called to pull her away from oncoming traffic because she ran into the road to find the assassins that were stalking her.

**■ During this recent visit to the ED,** the patient presented with labile affect, rapid speech, and anxious and angry mood. She complained about darkened spots on her arm (inflicted through radiation by the media), vaginal bleeding, paralysis below the waist (although she was pacing around), and unspecific pain around her belly. Physical examination revealed no obvious signs of head trauma, intact extraocular movements, no coughing or wheezing, regular heart rate and rhythm, a nontender abdomen to palpation, and normal bowel sounds. No focal neurological deficits were appreciated. She had no rashes, bruises, or skin abrasions on her abdomen or upper extremities.

The patient tried to leave the ED, saying that her third eye could see the radiation. She required medication and 4-point restraints.

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➤ Patients with late-onset schizophrenia often have paranoid or partition delusions and believe people or objects can permeate through barriers and access their home with malignant intent.

■ Her initial laboratory work-up for heavy metals, Lyme disease, human immunodeficiency virus (HIV), syphilis, delirium, and drug use were all negative. She also underwent head imaging studies that were also found to be negative. Her mental status exam was notable for a tangential thought process, preservation of delusions with loose associations, labile mood, and dysphoric affect. The patient demonstrated limited insight and judgment, although she was fully oriented to person, place, and time, which suggested against delirium at the time of evaluation.

## THE DIAGNOSIS

Based on the patient's current presentation and in light of her medical history, the health care team arrived at a working diagnosis of late-onset schizophrenia (LOS). The treatment team was able to identify that the current presentation in the ED was the patient's first episode of psychosis for LOS. The prior 5 to 10 years illustrated a slow progression of odd, yet feasible, chief complaints to multiple clinicians. Reaching the LOS diagnosis sooner had been complicated by the fact that the patient was extremely high functioning in the community.

## DISCUSSION

Schizophrenia is a severe, lifelong mental disorder characterized by at least 2 symptoms of delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms for at least 6 months, with significant social, occupational, and functional deterioration. Current models attribute the neurodevelopmental deregulation of the brain in patients with schizophrenia to dopaminergic hyperactivity and hypofunction of the glutamatergic neurotransmitter system, explaining why its onset is usually in adolescence or young adulthood.<sup>1,2</sup> However, 23% of patients present with symptoms after age 40, with 7% of patients being diagnosed between the ages of 51 and 60.<sup>3</sup>

■ **Late-onset vs early-onset schizophrenia.** LOS is often a missed diagnosis because the clinical presentation is different from

early-onset schizophrenia (EOS). Although the prodromal symptoms of EOS and LOS are similar and include marked isolation that subsequently progresses to suspiciousness and ideas of reference,<sup>4</sup> patients with EOS often also have prodromal negative symptoms. These prodromal negative symptoms associated with EOS may include loss of motivation, social passivity, and disorganized behavior. These symptoms are hypothesized to be caused by dopaminergic dysregulation in the anterior cingulate cortex. EOS is characterized by the patient experiencing more negative symptoms than LOS, which is characterized by the patient experiencing more positive symptoms.

Patients with LOS typically do not exhibit negative symptoms because remodeling and myelination of neuronal circuitry matures by late adulthood, and thus becomes more resistant to impairment of motivational processes in the anterior cingulate gyrus.<sup>4,5,6</sup>

LOS is characterized by paranoid personality with predominantly positive symptoms, likely due to disruptions in cortico-striato-pallido-thalamic circuitry that manifest in increased frequency and severity of acoustic, tactile, or olfactory hallucinations and persecutory delusions.<sup>1,6,7</sup> Patients with LOS often have paranoid or partition delusions and believe people or objects can permeate through barriers and access their home with malignant intent.<sup>8</sup> The prevalence of delusions positively correlates with increased age at diagnosis.<sup>9</sup> Patients with LOS also often develop comorbid schizoid or schizotypal personalities.<sup>8</sup> In contrast, patients with EOS primarily present with disorganized behavior and speech; hallucinations; and delusions.

■ **Other features of LOS** include a high female:male ratio and symptomatic improvement with antipsychotics.<sup>7,10</sup> Studies show that the LOS ratio of women:men can range from 2.2:1 to 22.5:1, which could be explained by the effect of dopaminergic-modulating estrogen from different sex-specific aging brain patterns.<sup>8,11,12</sup> Finally, patients with LOS are less likely to seek care for sensory deficits than their age-equivalent counterparts.<sup>8,10</sup> Fortunately, many of the characteristics of LOS predict good prognosis: Patients are usu-

TABLE

## Differential diagnosis for psychosis<sup>8,13-18</sup>

	Late-onset schizophrenia	Early-onset schizophrenia	Alzheimer disease	Delusional disorder	Major depressive disorder with psychotic features
Age (y)	40-60	16-25	70-80 (early onset 40-50)	40	More dependent on length of untreated MDD and number of MDD episodes than age
Prevalence (%)	1	1.1	6.4	0.05-0.1	2.4-2.9
Female-to-male ratio	2.2:1 to 22.5:1	No significant differences	1.56 to 1	3:7	1.3 to 3
Prodrome	Marked isolation, suspiciousness, ideas of references	Negative symptoms (loss of motivation, social passivity, disorganized behavior)	Some subjective awareness of memory difficulties initially; difficulties with instrumental activities of daily living (eg, managing money)	Difficult to assess as patients tend to exhibit normal behaviors and appearance with their delusions	Typically has an insidious onset with progressive loss of function and worsening depressive symptoms
Associated personality types	Schizoid/schizotypal personalities	Disorganized personalities	---	---	---
Symptoms	Paranoid or partition delusions, may be bizarre	Delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms > 6 months	Confusion in evening hours, loss of appetite, restlessness, aggression, irritability; eventually progression to disorientation, inability to recognize common objects, meaningless repetition of words	Non-bizarre delusions > 1 month	Typical psychotic features are extensions of an individual's depressed mood with themes of inadequacy, guilt, disease, death, or deserved punishment. Can also have mood-incongruent features
Function in community	High-functioning	Social, occupational, and functional deterioration	Social, occupational, and functional deterioration	High-function with social impairment	Episodic deterioration in social, occupational, and functional ability
Prognosis	Improvement with antipsychotics	% of patients with persistent/fluctuating symptoms despite optimal antipsychotic medication	No current treatment; life expectancy 3-10 years	No effective treatment; antipsychotics may reduce rumination and anxiety associated with the delusional thoughts	Associated with high mortality; recurrence is high if depressive symptoms are not completely remitted

MDD, major depressive disorder.

ally female, display positive symptoms, have acute onset of symptoms, and are married with social support.<sup>10</sup>

### Diagnosing LOS

LOS can be challenging to diagnose because of its atypical presentation compared with EOS, relative rarity in the population, and its propensity to be confused with progres-

sive Alzheimer disease/dementia, delusional disorder, and major depressive disorder with psychotic features.<sup>3,6</sup> Patients with no prior psychiatric history often do not have ready access to psychiatrists and depend on PCPs and other clinicians to identify mental health issues. A careful history, including familial involvement, utilization of the Montreal Cognitive Assessment (MoCA) test, and evaluation

➤ **Delusional disorder and late-onset schizophrenia are often more challenging to differentiate because symptoms can overlap.**

of environmental factors, are crucial to arriving at the proper diagnosis.

■ **Differential diagnosis.** When psychosis appears later in life, it is important to consider a broad differential (TABLE<sup>13-18</sup>), which includes the following:

**Alzheimer disease.** LOS can be easily differentiated from psychosis associated with Alzheimer disease or dementia through findings from neuropsychologic assessments and brain imaging. The initial first-line assessment for Alzheimer disease includes determining time course of daily living impairment and memory with follow-up brain imaging. Magnetic resonance imaging of patients with Alzheimer disease shows clear atrophy of the medial temporal lobes and general brain atrophy.<sup>19</sup> Other than hypoperfusion in the frontal and temporal area, brain imaging of patients with LOS will not reveal any pathology.<sup>1</sup>

**Delusional disorder** and LOS are often more challenging to differentiate because symptoms can overlap, and many of the negative symptoms that would otherwise help clinicians diagnose schizophrenia in a younger population are absent in LOS. The milder symptoms of LOS may also lead clinicians to favor a diagnosis of delusional disorder. However, the following differences can help physicians differentiate between LOS and delusional disorder. Delusional disorder<sup>20-22</sup>:

- often will include paranoid beliefs, but these beliefs will not be bizarre, and the patient's daily functioning will not be impaired, whereas patients with schizophrenia would have an increase in isolation and impairment in functioning that tends to be distinct from baseline.
- is more rare than schizophrenia. Delusional disorder has a prevalence of 0.05% to 0.1% compared to 1% for schizophrenia.

**Major depressive disorder (MDD) with psychotic features.** Major depressive disorder with psychotic features is an important differential to consider in this setting because the treatment intervention can be considerably different. Among patients

who have MDD with psychotic features, a significant mood component is present, and treatment typically focuses on optimizing a selective serotonin reuptake inhibitor (SSRI); depending on severity, electroconvulsive therapy (ECT) also may be warranted.<sup>19</sup>

For patients with LOS, optimizing an antipsychotic medication is the typical course of treatment, and ECT would likely have less of an impact than it does with MDD with psychotic features. Furthermore, in the case of our patient, her medical records showed that she was evaluated with the PHQ-9 in the outpatient setting prior to hospitalization. The patient's PHQ-9 scores ranged from 0 to 3, suggesting against any significant depressive symptoms.

**Other.** Finally, in an acute setting, other differential diagnoses for mental status changes (depending on clinical findings) might include:

- drug/medication use
- delirium
- nutrient deficiencies
- acute head trauma
- chronic subdural hematoma
- syphilis
- Lyme disease
- HIV encephalitis
- heavy metal toxicity.

### Treatment involves antipsychotics—especially certain ones

Antipsychotic medications are utilized for the treatment of patients with LOS. A Cochrane review concluded that there are no trial-based evidence guidelines for the treatment of patients with LOS, and that physicians should continue with their current practice and use clinical judgment and prescribing patterns to guide their selection of antipsychotic medications.<sup>22,23</sup> Pearlson et al<sup>24</sup> found that 76% of patients with schizophrenia achieved at least partial remission and 48% achieved full remission with antipsychotic treatment.

The preferred treatment for patients with schizophrenia is low doses of newer antipsychotics (atypical or second-generation antipsychotics [SGAs]) because they are less likely to cause extrapyramidal symptoms/adverse effects than first-generation antipsychotics. Examples of SGAs include aripipra-

zole, risperidone, olanzapine, quetiapine, and ziprasidone.

Effective treatment for LOS includes antipsychotics at a quarter to one-half of the usual therapeutic doses. In patients with very late-onset schizophrenia, doses should be started at a tenth of therapeutic dose.<sup>1,23</sup> Physicians should titrate up carefully, as needed.

As with any significant mental illness, to improve clinical outcomes, family support may help patients' medication adherence and ensure they attend scheduled medical appointments.

■ **Our patient** was eventually stabilized on long-acting injectable risperidone, 25 mg, with improvement in symptoms. Unfortunately, she was not convinced that her symptoms were psychiatric in nature and did not continue with her medications as an outpatient.

The patient's nonadherence to her medication regimen led to 2 more hospitalizations with similar presentations over the following 2 years. On her most recent discharge, she was stabilized on oral olanzapine, 10 mg every night at bedtime, with close outpatient follow-up and family education.

## THE TAKEAWAY

The prodromal phase of patients with LOS is similar to patients with EOS and includes withdrawal and isolation from others, making it difficult for physicians to evaluate and treat patients. Patients with LOS predominantly experience positive symptoms that may include delusions and hallucinations. Brain imaging studies can help rule out progressive dementia diseases. A neuropsychological evaluation can assess the patient's functional level and types of delusions, which helps to differentiate LOS from other late-age psychoses. Treatment with SGAs make for a good prognosis; however, this requires patients to be adherent to treatment. **JFP**

### CORRESPONDENCE

Sandy Chan, MD, Department of Internal Medicine, UMass Memorial Medical Center, 55N Lake Avenue, Worcester, MA 01605; Sandy.Chan@umassmemorial.org

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