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New-Onset Paranoia in an Elderly Woman With Bipolar Disorder: Differential Diagnosis, Evaluation, and Treatment

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Have you ever wondered how often paranoia develops in the elderly and in those with preexisting bipolar disorder? Have you considered what other conditions can contribute to or precipitate psychotic symptoms? Have you been uncertain about how best to evaluate and treat psychotic symptoms? If you have, the following case vignette and discussion should prove useful.

CASE VIGNETTE

Ms A, a 64-year-old woman with bipolar disorder, was admitted to the hospital with nausea, vomiting, and intractable right scapular pain. Her pain was thought to be secondary to an aggressive form of non-small-cell lung cancer of her right lung, which had been diagnosed 4 months earlier after she presented with right lower extremity weakness. During her initial oncologic workup, Ms A was found to have 2 brain metastases (1 in the left parieto-occipital area, which was resected, and the other in the left frontal lobe). Both sites were treated with stereotactic radiotherapy 1 month after her neurosurgery.

Although chemotherapy was scheduled to begin after her neurosurgery and radiation, she was lost to follow-up upon hospital discharge; she declined all phone calls from social services, declined visiting nurse services, and failed to attend multiple scheduled appointments in the cancer center. According to her son and daughter-in-law, Ms A became increasingly suspicious of them and of one of her best friends; she refused to speak with them and accused them of trying to break into her home and steal from her. She changed all the locks on her doors and declined to return to the hospital where she sought initial treatment because she felt that her providers could not be trusted.

When Ms A later self-presented to the emergency department for musculoskeletal pain and intractable vomiting, she was adamant that no one contact her son, daughter-in-law, or friend. Collateral from her family confirmed that this paranoia was new and uncharacteristic for Ms A. Her outpatient psychiatrist similarly noted she had been asymptomatic, with no mood episode on her psychiatric regimen for over a decade. She had no history of paranoid or persecutory delusions. The oncology team wondered whether her new-onset paranoia was related to her longstanding bipolar disorder, or whether it was secondary to her cancer and its treatments. Psychiatry and palliative care were consulted.

In addition to lung cancer and bipolar disorder, her past medical history was notable for diabetes mellitus type 2, peripheral arterial disease, asthma, and hyperlipidemia. Home medications included lamotrigine (100 mg twice/d), ziprasidone

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Clinical Points

- Paranoia can arise in those with serious mental illness, as well as in those with medical and neurologic conditions and as a side effect of medications and other treatments.
- Since any structural or physiologic disruption of brain functioning can lead to paranoia, neuroimaging is vital to understand the neurobiology of psychotic symptoms; however, no specific abnormal neuroimaging findings have been identified as pathognomonic for paranoia.
- Although treatment of paranoia is predicated on etiology, symptomatic treatment may be required before an etiology has been established; antipsychotic medications are the mainstay of treatment for paranoia.

(80 mg twice/d), gabapentin (300 mg 3 times/d), methadone (5 mg every 8 hours), acetaminophen (975 mg 3 times/d), oxycodone (5–10 mg every 4 hours as needed), and hydromorphone (0.3 mg every 3 hours as needed).

The initial examination demonstrated a cachectic woman who appeared older than her stated age and restless while in bed due to pain. She was alert, cooperative, and oriented to self, situation, place, season, and year but not to the month or date. The mental status examination was notable for rapid but interruptible speech, an anxious affect, and ruminative thinking, as well as persecutory delusional beliefs about her family wanting to harm and steal from her. She endorsed low energy, poor sleep, and poor appetite related to her physical symptoms. No increases in goal-directed activity, mood elevation, grandiosity, decreased need for sleep, or perceptual disturbances were noted.

Her medical workup included a computerized tomography (CT) scan and a magnetic resonance imaging (MRI) scan of her head and chest, as well as laboratory tests (eg, electrolytes, hemogram, urinalysis). While the laboratory tests were unremarkable, the brain MRI showed an interval increase in the size of an extra-axial collection with air and fluid concerning for an infection as well as new areas of focal enhancement along the margins of the left temporal parietal resection cavity that was suspicious for tumor recurrence.

DISCUSSION

What Is Paranoia?

Paranoia is an irrational and persistent thought process involving feelings (of fear) and thoughts (of persecution, conspiracy, or threats).¹ Paranoia is one of the most common delusions in people with schizophrenia-spectrum disorders. However, patients with bipolar disorder, major depressive disorder (MDD), and other forms of mental illness and substance use disorders can also experience paranoia. Untreated paranoia often leads to social isolation, emotional distress, poor quality of life, and psychiatric hospitalizations.² Psychotic symptoms, including paranoia, are linked to neurodevelopmental deficits, alterations in the neurocircuitry of the central nervous system, environmental factors, and insecure attachments during childhood.^{3,4}

Table 1. Psychiatric, Medical, and Neurologic Conditions and Drugs Associated With Psychosis, Including Paranoia

Primary psychiatric disorders
Schizophrenia
Schizoaffective disorder
Bipolar disorder
Major depressive disorder
Delusional disorder
Medical disorders
Infectious diseases
Syphilis
Lyme disease
Meningitis
Brain abscess
Endocrine disorders
Addison's disease
Cushing's syndrome
Hypothyroidism and hyperthyroidism
Hypoparathyroidism and hyperparathyroidism
Vitamin deficiencies
Thiamine deficiency
Niacin deficiency
Vitamin B ₁₂ deficiency
Other disorders
Heavy metal toxicity
Neurologic disorders
Dementia
Alzheimer's disease
Lewy body disease
Vascular dementia
Parkinson disease
Normal pressure hydrocephalus
Huntington disease
Wilson's disease
Systemic lupus erythematosus
Drugs (due to intoxication or withdrawal)
Alcohol
Amphetamines
Cocaine
Hallucinogens
Sedative-hypnotics
Steroids

How Often Is Paranoia Seen in Isolation or With Other Manifestations of Psychosis?

Paranoia occurs on a spectrum of severity, with suspiciousness, mistrust, and self-consciousness on one end and delusions of persecution on the other.^{1,5} It also generates feelings that vary from mild discomfort to intense distress. Some degree of paranoia is common in the general population, with mild symptoms in 20%–30% and severe symptoms in ~2%.⁵ Several demographic, social, and economic risk factors for paranoia have been identified.⁶ Paranoia can arise in those with serious mental illness (SMI), including delusional disorder (previously called paranoid disorder), which is often characterized by one dominant delusion (ie, a fixed, false belief) without other psychotic symptoms or signs of mental illness. Delusional disorder often occurs in mid to late life and is more common in women than in men.⁷ Paranoia is more frequently seen along with other manifestations of psychosis among those with a major psychiatric illness. For example, paranoid delusions often coexist with other psychotic symptoms (eg, disorganized speech, auditory/visual hallucinations) in those with schizophrenia.

Who Develops Paranoia?

Paranoia is best thought of as a symptom rather than a diagnosis. Moreover, any person can develop paranoia given the right circumstances. Table 1 lists psychiatric, medical, and neurologic conditions associated with new-onset paranoia. Severe and persistent paranoia is most often associated with primary psychiatric disorders, including psychotic disorders (eg, schizophrenia, schizoaffective disorder, and delusional disorder) and mood disorders (eg, bipolar disorder and MDD). When psychosis arises in the setting of a psychiatric disorder, it is often referred to as a “primary psychotic illness.”

However, paranoia also develops in the setting of myriad medical conditions. When psychosis emerges independently from a psychiatric disorder, it is referred to as a *secondary psychosis* (ie, secondary to another condition or substance). Although the term *organic* is still used interchangeably with *secondary* by many clinicians, the term *organic* reflects a false dichotomy between “structural” and “functional” in our current understanding of the neurobiological basis of psychiatric illness.⁸

Alterations in dopaminergic neurotransmission have also been implicated in the development of psychotic symptoms, like paranoia.⁹ Any condition that impacts brain activity and structure in dopamine-rich areas can result in psychotic symptoms.

An evaluation for underlying (ie, secondary) causes of psychoses should be considered whenever atypical features are present. Notably, it is uncommon for a first episode of psychosis due to a primary psychiatric illness to develop in those of advanced age. Similarly, it is unusual for paranoia from a primary psychiatric illness to present with fluctuations in arousal and attention, abnormal physical findings, or significant laboratory abnormalities. Therefore, when these features become evident, a more thorough investigation of underlying conditions or exposures should be conducted.

What Might the Workup of Paranoia Entail?

Paranoia is a clinical diagnosis. However, learning how to conduct a diagnostic evaluation to rule out potential causes of paranoia is an important skill for clinicians. Given that roughly 3% of patients with psychotic illnesses have an underlying medical condition,¹⁰ organic brain diseases (manifest by paranoia and other psychotic symptoms) should be investigated and ruled out (often with the aid of neuroimaging studies).¹¹ Since any structural or physiologic disruption of brain functioning can lead to psychotic symptoms, neuroimaging has been a vital tool to understand the neurobiology of psychotic symptoms. Unfortunately, no specific abnormal neuroimaging findings have been identified as pathognomonic for the diagnosis of a primary psychotic disorder.^{3,12} Several conditions are worth noting. Autoimmune diseases can cause paranoia (as evidenced by autoimmune psychosis), and they should be ruled out during the diagnostic evaluation of secondary psychosis.¹³ Similarly, vitamin B₁₂ deficiency can lead to neuropsychiatric symptoms, including paranoia, and obtaining a vitamin B₁₂ level will be another diagnostic test reviewed while searching

for the etiology of paranoia.¹⁴ Moreover, hypothyroidism and hyperthyroidism can lead to psychotic symptoms; therefore, thyroid function tests are an integral part of the diagnostic evaluation of paranoia. Other causes of psychosis involve sexually transmitted illnesses; testing for neurosyphilis and HIV infection will also be a part of the diagnostic evaluation for paranoia. Use of multiple substances (including cannabis, hallucinogens, and stimulants) and withdrawal from alcohol is another cause of psychosis; urine toxicology testing should be considered in the diagnostic evaluation of paranoia. In addition, potential causes of acute encephalopathy should be investigated during the evaluation.

How Often Does Paranoia Develop in the Elderly or Those With Bipolar Disorder?

New-onset paranoia is common among older adults, as ~60% of late-life psychosis has an underlying medical or neurologic etiology. Paranoia is often observed along with dementia in older adults. The prevalence of psychotic symptoms, including paranoia, varies among different populations and settings. The overall point prevalence of paranoid ideation in the elderly is around 4%–6%; the prevalence rate increases with advancing age.^{15,16} Moreover, the prevalence of psychotic symptoms is often underestimated because older adults are often reluctant to report their psychiatric symptoms.¹⁶ Paranoia can persist and endanger those with psychiatric disorders, including bipolar disorder. The 12-month prevalence rate of bipolar disorder among adults aged 65 years and older is ~0.1%, which is lower than the prevalence rates among those aged 18–44 years (1.4%) and 45–64 years (0.4%).¹⁷ Despite the lower prevalence of bipolar disorder in older adults, data suggest that older adults experience paranoia more often than do younger individuals.¹⁷ More than half of patients with bipolar disorder develop psychotic symptoms during their lifetime. Moreover, paranoid delusions may arise during a manic or depressive episode in those with bipolar disorder. Delusions of grandiosity are the most common delusions experienced during episodes of mania.^{18,19} Furthermore, delusions of guilt are more often reported among those with psychotic bipolar depression.¹⁸ Although other types of delusions (eg, persecutory delusions, somatic delusions) are less frequently reported in bipolar spectrum disorders, they can be seen in patients with mixed bipolar states and with psychotic bipolar depression.¹⁸ A large body of evidence suggests that psychotic symptoms, including paranoia in bipolar disorder, lead to a less favorable clinical and neuropsychological outcome.^{20–22} However, longitudinal investigations are needed to mitigate methodological artifacts (eg, recall bias, misclassification bias) and to permit stronger causal inferences.

Which Treatments Reduce Paranoia?

Although treatment is predicated on etiology, symptomatic treatment may be required before an etiology has been established. Antipsychotic medications are the mainstay of treatment for paranoia. Second-generation

antipsychotics, also called atypical antipsychotics (including risperidone, olanzapine, quetiapine, and lurasidone), are generally preferred over the first-generation antipsychotics (FGAs), also called typical antipsychotics (including haloperidol, perphenazine, and chlorpromazine), to treat paranoia, mainly because FGAs are more apt to induce tardive dyskinesia and extrapyramidal symptoms. In general, the drugs' side effect profiles and an individual's experience with an antipsychotic medication help to determine which medication to prescribe.²³ Common adverse effects of antipsychotics involve involuntary muscle movements, akathisia, sedation, weight gain, and constipation. Potential life-threatening adverse medication effects are agranulocytosis and myocarditis, especially with clozapine use. Tardive dyskinesia is one of the most troublesome long-term side effects from antipsychotics, and it should be discussed with patients before starting an antipsychotic. If a trial of one antipsychotic medication does not work, another antipsychotic should be tried before considering augmentation with a mood stabilizer (like lithium or valproic acid) or clozapine.²⁴ Similarly, electroconvulsive therapy (ECT) should be considered for treatment-resistant paranoia. If use of ECT is not feasible, combining 2 antipsychotics to address paranoia should be considered. However, the benefits of the antipsychotic polypharmacy have not been well established.²⁵

How Are Patients With Multiple Brain Metastases Managed?

The treatment of brain metastases has evolved over the past 2 decades with the advent of new targeted therapies and refinement of radiation techniques.²⁶ Historically, due to concerns of poor drug penetration through the blood-brain barrier, treatment modalities were limited to surgical resection and whole brain radiation therapy (WBRT). Surgical resection remains the mainstay of treatment for solitary or symptomatic brain metastases, as it can offer a rapid reversal of symptoms and the possibility of "cure" in oligometastatic disease. Stereotactic radiotherapy is used in the postoperative setting to the surgical bed, as it can reduce local recurrence. Since there is an increased awareness of significant cognitive decline and impairment in quality of life associated with WBRT, it is used only in carefully selected patients.²⁷ Steroids continue to be utilized for control of vasogenic edema and symptomatic relief, but prolonged use is associated with an extensive side effect profile, including anxiety, hypomania/mania, and impaired glycemic control.²⁸

In this current era of precision medicine, molecular advances have allowed us to shift toward utilizing targeted therapies in a subset of patients with driver mutations, such as epidermal growth factor receptor mutations, receptor tyrosine kinase, and anaplastic lymphoma kinase translocations.²⁹ Tyrosine kinase inhibitors in this setting can eliminate the need for radiotherapy and surgical resection altogether. Immunotherapy has also offered a marked survival benefit in many patients with non-small-cell lung

cancer; however, its role in the management of associated brain metastases is currently under investigation.³⁰

When Should Palliative Care Be Considered in a Patient With Widely Metastatic Cancer?

Research has demonstrated that early utilization of palliative care in patients with metastatic cancer enhances quality of life and decreases end-of-life hospitalizations.³¹ Integration of early palliative care is recommended by professional societies and integrated into general oncology practice.³² Whether what is needed involves symptom management, discussions of goals of care, identification of health care proxies, or a smoother transition to end-of-life care, there are multiple benefits in developing early rapport with a palliative care provider.

Unfortunately, inpatient palliative care services are often underutilized, in part due to prevalent geographical and racial disparities.³³ More effective integration of those services, both for inpatient and outpatient settings, can improve patient-centric care.

What Happened to Ms A?

Ms A's paranoia was thought to reflect a secondary psychosis due to progression of intracranial metastases. Collaboration among her multidisciplinary inpatient team and her outpatient psychiatrist led to additional treatment of Ms A's paranoia with olanzapine (2.5 mg every morning and 5 mg at bedtime). The downside of adding a second antipsychotic to her regimen was outweighed by her considerable functional decline due to her paranoia, as it might have interfered with her medical care and quality of life.

Throughout her hospitalization, Ms A's pain was better controlled, as was her distress. She became more meaningfully engaged with her health care team regarding her goals of care. While she continued to be suspicious of her family, the addition of olanzapine allowed her to tolerate the idea of her family becoming involved in her care. She preferred to focus on her comfort and returning to a setting wherein she could be surrounded by her friends and beloved pets. She was discharged to inpatient hospice care.

CONCLUSION

While paranoia is a common manifestation of psychosis in those with a primary psychiatric illness, paranoia also develops because of medical or neurologic conditions, especially when paranoia develops later in life or in the setting of impaired cognition or attention. Although there is no "gold standard" workup for the medical causes of paranoia, a comprehensive history and a physical and neurologic examination should be performed. Then, brain imaging, toxicologic screens, and basic laboratory screening tests should be obtained, as well as tests for syphilis and HIV infection and for deficiencies of thiamine, niacin, and vitamin B₁₂. Timely assessment and treatment (typically with an antipsychotic agent) will reduce suffering and facilitate improved quality of life.

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