Delusional disorder and estrogen withdrawal associated psychosis: The role of estrogen in psychosis: A case report

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Case Report

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Abstract

Background: Psychosis, a complex and debilitating condition, is associated with marked gender differences. Decades of research have established a link between sex hormones—particularly estrogen—and the psychosis. Both animal and human studies have demonstrated the significant influence of estrogen on the central nervous system, especially on neurotransmitter systems implicated in psychosis. In 2001, to explore this relationship, case reports emerged describing psychotic episodes associated with decreased estrogen levels in contexts other than the puerperium. These cases were later defined as estrogen withdrawal associated psychosis (EWAP).

Clinical Presentation: We present the case of a 51-year-old woman who had undergone bilateral oophorectomy and hysterectomy three years earlier due to dysfunctional uterine bleeding and had been on estradiol 10 mg since the procedure. A few days after discontinuing the medication, she developed disorganized behavior along with auditory hallucinations, persecutory delusions, and delusions of passivity. Following a discussion of the fundamental clinical evaluation steps for psychosis, we compare this case with previous reports linking estrogen deprivation to psychosis, highlighting both similarities and distinctions.

Discussion and Conclusions: Despite the heterogeneity of EWAP as a diagnostic category, the potential clinical relevance of this diagnosis in selected cases is emphasized. This case underscores that individuals with vulnerability to estrogen deprivation may be at increased risk for developing psychosis and that such presentations may exhibit distinct clinical features. Nevertheless, further studies are needed to clarify unresolved questions and to improve diagnostic and therapeutic approaches to estrogen-related psychotic disorders.

Introduction

Sex differences are observed in the incidence of various neuropsychiatric disorders. Men are at higher risk for neurodevelopmental conditions such as autism spectrum disorder and attention deficit hyperactivity disorder, as well as alcohol dependence. In contrast, women are more likely to develop Alzheimer's disease, anxiety disorders, and depression. The biological underpinnings of these differences are not fully understood but are likely to involve complex interactions between genetic, environmental, and hormonal factors in the brain (1, 2, 3). Estrogen, which crosses the blood–brain barrier, modulates several neurotransmitter systems including dopaminergic, noradrenergic, and serotonergic pathways—key regulators of mood and cognition (4, 5, 6). A rapid decline in circulating estrogen may lead to central neurotransmission changes due to diminished estrogen availability in the brain (7). Ahokas and Aito demonstrated that estrogen administration improved puerperal psychosis in women with low estrogen levels (8, 9, 10). Building upon this, Mahe and Dumaine proposed that the relationship between estrogen decline and psychosis may not be limited to reproductive events such as premenstrual or postpartum phases. Based on retrospective reports of psychosis following non-puerperal estrogen withdrawal, the concept of Estrogen Withdrawal Associated Psychosis (EWAP) was

introduced (11). In the present case report, we describe an acute psychotic episode in a female patient who was diagnosed with delusional disorder during the clinical evaluation. Given the clinical presentation and temporal association with estrogen discontinuation, the episode was evaluated within the framework of EWAP.

Case Presentation

A 51-year-old woman, married with one child, a high school graduate, and a retired teacher, residing in the city center of Rize, presented to our clinic with complaints that had begun approximately twenty days prior to admission. She reported hearing a voice, which she identified as belonging to her husband, describing it as sometimes commanding and at other times judgmental. The voice instructed her to perform various actions such as opening windows, closing doors, or walking down the hallway. She noted that she occasionally complied with these commands, although at times attempted to ignore them. The hallucinations became more intense when she was alone and diminished when she was engaged in activity.

The patient described increasing difficulty in focusing on daily tasks, often postponing or leaving them incomplete. The voice persistently criticized her, accusing her of performing household chores inadequately or neglecting them altogether. She reported that the voice claimed her husband could access her thoughts and was recording them using a phone application. On several occasions, the voice suggested that she harm herself or jump from a window; however, she firmly denied any suicidal ideation or attempts. She also reported that the voice told her the food she was eating had been poisoned, and that the water she was drinking contained lethal medication. As a result, she sometimes avoided eating and once went a full day without drinking water.

Further, the voice conveyed messages that her husband was involved with other women, planned to divorce her, expel her and their son from the home, and cohabitate with those women. The voice also stated that her husband could uncover her secrets by making her talk in her sleep. Over the preceding two nights, her sleep had been significantly disrupted, and she reported complete insomnia the night before admission. During the clinical interview, she avoided eye contact, stating that the voice warned her that eye contact would allow others to read her thoughts or hypnotize her. She had reportedly searched the house for hidden listening devices and believed that her husband had orchestrated the entire situation as part of a deliberate plan. Approximately one week prior to admission, she contacted law enforcement and requested a restraining order due to fears of potential harm from her husband.

The psychiatric history revealed that the patient had long harbored jealousy-themed delusional beliefs, particularly involving accusations of infidelity against her husband extending back over two decades. She believed he had affairs with nearly every woman in their vicinity and had fathered children with them, hiding this from her. When apart, she frequently called him to monitor his activities. Due to her husband's profession, they had relocated multiple times, and in each new residence, she developed strong beliefs that he was engaged in relationships with female neighbors. In public settings, she interpreted

interactions with women as deliberate attempts to signal familiarity or communication with her husband. These persistent suspicions had caused significant marital conflict and recurrent discussions of divorce.

Upon admission to the emergency department, a comprehensive diagnostic work-up was initiated. Substance- or medication-induced psychosis was ruled out. Toxicological screening included evaluation for prescription, over-the-counter, and illicit substances, with urine drug screening and blood alcohol levels ordered. Endocrinopathies and other medical conditions were screened through glucose testing, urinalysis, CBC, CMP, thyroid function tests, and a pregnancy test, all of which were unremarkable. Neuroimaging revealed no organic pathology, and neurological examination was normal. There was no history of psychiatric treatment or psychotropic medication use, nor was there any substance or alcohol use. Three years earlier, the patient had undergone bilateral oophorectomy and hysterectomy due to dysfunctional uterine bleeding and had been maintained on 10 mg estradiol since. The estradiol was discontinued twenty days before admission under medical supervision, and no other medications had been added or withdrawn.

She was admitted with a provisional diagnosis of psychotic disorder. Pharmacologic treatment included risperidone 1 mg and clonazepam drops (2x3). On the third day, risperidone was titrated to 3 mg/day in divided doses. The patient reported that auditory hallucinations subsided at this dosage, along with improvement in sleep and appetite, and a marked reduction in anxiety. Two days later, she stated she was uncertain whether the voice she had heard was indeed her husband's, estimating a 50/50 likelihood. A rapid and robust response to treatment was observed.

By the end of the first week, her acute psychotic symptoms had resolved, and as of the second week, jealousy-related thoughts had become vague and significantly less intrusive. On the 22nd day of hospitalization, she was discharged on risperidone 3 mg/day and referred to gynecology for follow-up regarding long-term estrogen use. In outpatient follow-up visits, she remained in remission for four months, reporting a stable and mutually satisfying relationship with her husband.

Discussion

The present case highlights a diagnostically and etiologically complex intersection between delusional disorder and an acute psychotic episode potentially related to estrogen withdrawal. The patient's long-standing delusional beliefs, particularly jealousy-themed ideas, had not previously led to treatment-seeking behavior. However, the sudden onset of a florid psychotic state dominated by auditory hallucinations shortly after discontinuation of estradiol suggests an additional pathophysiological mechanism.

Clinical observations have long noted gender-related differences in psychotic disorders, including schizophrenia, in terms of symptom presentation, illness course, and treatment response (13). While the underlying etiological mechanisms are not yet fully understood, recent research has pointed to the neuroprotective role of estrogen, particularly estradiol, in psychosis. Estrogen has been shown to modulate neurotransmitter systems such as dopamine, serotonin, and glutamate, particularly in brain

regions implicated in psychosis, including the prefrontal cortex, hippocampus, and amygdala (14, 15, 16). It enhances neuroplasticity, synaptic connectivity, and emotional regulation and supports cognitive control and self-monitoring functions. Both in vivo and in vitro studies have shown that estrogenic compounds can protect against brain cell damage caused by factors such as excitotoxicity, oxidative stress, inflammation, and apoptosis. These effects are thought to involve multiple molecular pathways, including mitochondrial stabilization and anti-inflammatory effects (17, 18, 19).

In conditions of estrogen deprivation, such as menopause or surgical oophorectomy, this neuroprotective modulation is diminished, potentially lowering the threshold for psychotic decompensation in vulnerable individuals. The increased risk of psychotic relapse in the postpartum and menopausal periods further supports this association. To explore this hypothesis, case reports published in 2001 described acute, short-term, and reversible psychotic episodes associated with estrogen decline outside the puerperium, subsequently termed EWAP (11).

In the case described, the temporal proximity between the discontinuation of estradiol and the onset of acute psychotic symptoms supports the EWAP hypothesis. Notably, the hallucinations were not only perceptual disturbances but also thematically related to the patient's prior delusional content. While the voices mirrored aspects of her long-standing jealousy delusions—such as infidelity—they introduced additional content that exceeded the scope of her previous beliefs. This partial thematic overlap suggests a transformation and expansion of delusional structures under the influence of acute neurobiological stress. Emotional memory activation may have played a role in shaping this hallucinatory experience, with previously encoded emotionally salient themes being reactivated and reformulated under changing neurobiological conditions, especially in the context of estrogen withdrawal. Cognitive models may help elucidate the mechanisms by which these psychotic symptoms emerged. Frith's self-monitoring hypothesis posits a disruption in the ability to correctly attribute internally generated events, such as inner speech, as self-produced. In this case, the patient externalized her thoughts and assigned them to a familiar persecutory agent—her husband. Additionally, the auditory hallucinations may have gained meaningful content from autobiographical and emotionally charged material previously stored in memory, in line with the context memory hypothesis. The convergence of delusional themes and hallucination content supports the idea that these two phenomena may be cognitively and phenomenologically integrated (20, 21, 22).

Taken together, the clinical course, symptom profile, hormonal history, and treatment response suggest that EWAP represents a valid explanatory model for this patient's acute episode. It is important to emphasize that hallucinations are not characteristic of delusional disorder and, when present, are typically limited to content congruent with the primary delusion (23). The prominence and complexity of hallucinations in this case, including elements that extended beyond prior delusional themes, underscore the likelihood of a distinct underlying process. The rapid resolution of symptoms with antipsychotic treatment, following a dramatic hormonal shift, further supports this hypothesis. Nevertheless, future studies should aim to clarify diagnostic criteria, investigate the neuroendocrinological underpinnings of EWAP, and explore the potential utility of serum estrogen monitoring and prophylactic interventions in at-

risk populations. It remains to be determined whether the onset or severity of psychosis is influenced more by the magnitude or the rate of estrogen decline. Comparative studies examining the efficacy of prophylactic hormonal versus psychopharmacological interventions in women at risk may offer new insights into prevention and management strategies for hormone-related psychosis (24).

Conclusions

Psychotic disorders exhibit significant sex differences in terms of onset, symptomatology, and treatment response. Estradiol has been proposed as a key neuroprotective factor contributing to these differences. This case illustrates the clinical deterioration of a woman who had not previously sought psychiatric care, following gynecological surgery and the abrupt discontinuation of long-term estradiol therapy. The emergence of florid psychotic symptoms—including a new cluster of delusions with marked behavioural disorganization and dominant auditory hallucinations—was temporally associated with estrogen withdrawal and evaluated within the framework of EWAP.

The patient's rapid and robust response to antipsychotic treatment parallels clinical features observed in other estrogen deprivation–related psychiatric syndromes. This underscores the importance of recognizing estrogen withdrawal as a potential precipitant of acute psychosis in susceptible individuals. Moreover, this case highlights the need for greater attention to women's mental health as a distinct neurobiological domain. Integrating hormonal factors into clinical risk assessments may lead to more effective strategies for the prevention, early identification, and treatment of psychosis in women—strategies that are not only clinically beneficial but also offer simple, cost-effective, and widely applicable solutions for preventing and managing psychosis in women.

Abbreviations

EWAP
estrogen withdrawal associated psychosis

Declarations

Ethical Approval and consent to participate

The patient provided consent for the case report through an informed consent form.

Clinical trial number: not applicable.

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Consent for publication

The patient provided consent for publication through an informed consent form.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Not applicable

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Figures

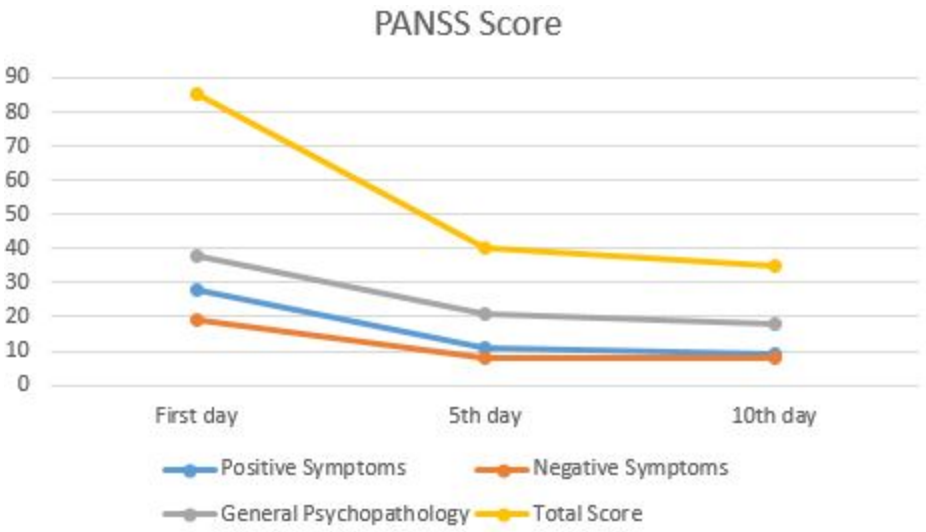

Figure 1

Change from baseline in PANSS scores