

# First-Episode Psychosis and Cushing Syndrome

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Cushing syndrome, a state of hypercortisolism, has multiple etiologies, including ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS). EAS is a frequently severe emergency related to the degree of hypercortisolism. Neuropsychiatric symptoms of Cushing syndrome are well-documented, including irritability, anxiety, depressed mood, and cognitive impairment.<sup>1</sup> A few prior case reports have described first-episode psychosis associated with Cushing syndrome,<sup>2</sup> sometimes leading to delayed or misdiagnosis of Cushing syndrome.

Here, we report a case of a 72-year-old man diagnosed with EAS caused by excessive ACTH secretion by a metastatic neuroendocrine tumor. Our report aims to add to the body of evidence indicating that Cushing-associated psychosis can cause acutely severe paranoia and delusions that significantly impact management.

## Case Report

Mr A, a 72-year-old retired physician with no prior psychiatric history, was diagnosed with new-onset psychosis in the setting of hypercortisolism. He initially presented with weakness secondary to hypokalemia and was found to have Cushing syndrome. On psychiatric evaluation, he demonstrated paranoia and delusions as well as illogical, concrete, and limited thought content. Laboratory workup, neurocognitive examination, and collateral history ruled out delirium or dementias. His morning cortisol levels were up to 162 µg/dL, and ACTH levels were greater than 2,000 pg/mL.

Mr A's cortisol levels were not suppressed with a high-dose dexamethasone test, supporting

ectopic ACTH production. He was found to have a metastatic ACTH-secreting large cell neuroendocrine tumor, responsible for his hypercortisolism. Magnetic resonance imaging of his brain demonstrated a pituitary mass, and a bilateral adrenalectomy revealed a small focus of neuroendocrine carcinoma on his left adrenal gland.

Mr A was treated with haloperidol for hallucinations, delusional features, and paranoia; ramelteon for delirium prophylaxis; and suvorexant for sleep initiation. His endocrinology team ultimately started him on osilodrostat (decreases cortisol synthesis via 11 β-hydroxylase inhibition), which led to improvements in his cortisol levels, and his psychotic features subsequently diminished and resolved by the fourth day. All medications for psychiatric symptoms were successfully discontinued without symptom recurrence.

## Discussion

Hypothalamic-pituitary-adrenal axis abnormalities, including hypercortisolism, have been well-documented in first-episode psychosis cases.<sup>3</sup> This includes increased morning cortisol levels in the blood in individuals with first-episode psychosis and increased baseline cortisol levels in the saliva for individuals at a clinical high risk of psychosis.<sup>4</sup> There are multiple proposed mechanisms for how excess exposure to cortisol leads to psychosis. Theories include structural and chemical changes such as abnormal regulation of neurotransmitters, impaired neurogenesis, decreased brain volume in the hippocampus, abnormal loss of synapses, and dendritic atrophy. However, these changes are typically in the setting of

prolonged exposure to high levels of cortisol.

There are a limited number of case reports regarding Cushing syndrome and acute psychosis.<sup>2</sup> Past case reports that have described Cushing syndrome and acute onset of psychosis endorse severely high levels of cortisol, which may be a driving factor, and patients presented with less profound delusional and paranoid content.<sup>2</sup> In this case, the patient presented with severe paranoia and delusions in the setting of excess cortisol and metastatic malignancy. Similar cases have been reported and focus on reducing cortisol levels to help manage the psychiatric symptoms.<sup>2,5,6</sup> Psychotropic management can assist with symptoms; however, the ultimate treatment remains to address the endocrinologic abnormality. While most cases have reported improvement of neuropsychiatric symptoms with resolution of hypercortisolism, others have described persisting or even exacerbation of psychiatric symptoms even after resolution of the high cortisol levels.<sup>5-7</sup> Most importantly, we must recognize Cushing syndrome and its hormonal derangements as a possible underlying etiology of psychosis to guide effective diagnostics and therapeutic management.

## Article Information

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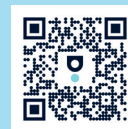
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