

•Case report•

Case report of Cushing's syndrome with an acute psychotic presentation

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Summary: A 36-year-old Chinese woman was brought to the emergency department of a general hospital with a 3-day history of mania, persecutory delusions, and suicidal ideation; she also had a 6-month history of disrupted sleep, hypervigilance, and somatic symptoms. Her physical exam on admission to the psychosomatic ward identified a moon-shaped face, exophthalmos, and purple striae on her legs, so acute psychiatric symptoms secondary to Cushing's syndrome was suspected. Elevated plasma cortisol and adrenocorticotropic hormone (ACTH) and identification of a mass on her left adrenal gland on the computed tomography (CT) scan of her abdomen confirmed the diagnosis. Low dose quetiapine (75-125 mg/d) and alprazolam (0.4 mg/qn) were prescribed to control the psychotic symptoms and improve her sleep. After surgical removal of a benign ACTH-independent adrenal tumor, her cortisol and ACTH levels returned to normal and her psychiatric symptoms gradually diminished over a one-month period, at which point she was discharged. Low-dose quetiapine was continued for 2 months after discharge and then discontinued; by this time her psychiatric symptoms had completely disappeared. In this case the patient had pathognomonic symptoms of CS, so it was relatively easy to make the diagnosis; but acute psychotic symptoms in CS can be life-threatening and may not be associated with the typical physical symptoms of CS (if there is only modest hypercortisolemia), so psychiatric clinicians should always consider CS among the possible differential diagnoses for unexplained acute psychosis.

Keywords: Cushing's syndrome; psychosis; differential diagnosis; case report; China

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1. Case report

A 36-year-old Chinese woman was brought to the emergency department of a large general hospital with a 3-day history of acute irritability, mania, aggressive behavior, persecutory delusions, and suicidal ideation. Over the prior 6 months she had had disrupted sleep, hypervigilance, and somatic complaints for which she had irregularly taken over-the-counter benzodiazepines. Three years previously she had had diabetes during a pregnancy. More recently she reported hypertension and menstrual irregularity for which she had been treated with felodipine and ethinylestradiol. She had no

history of smoking or drinking and no family history of serious physical or psychiatric illness.

She was initially admitted to the psychosomatic ward where her physical examination revealed a moon face, exophthalmos (abnormally protruding eyeballs), central adiposity, and purple striae on her legs. Her blood pressure was 140/106 mm Hg and her blood sugar was 6.88 nmol/L (normal range, 3.89-6.11 nmol/L). An acute episode of Cushing's syndrome with psychiatric manifestations was the provisional diagnosis. Her plasma cortisol levels were grossly elevated: the early a.m. (8:00) and midnight (24:00)

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values were $>46.7 \mu\text{g/dl}$ and $>50 \mu\text{g/dl}$, respectively (normal range, $2.5\text{-}12.57 \mu\text{g/dl}$). However, her adrenocorticotrophic hormone (ACTH) levels were low: the early a.m. and midnight values were both $<5 \text{ pg/ml}$ (normal range, $5\text{-}46 \text{ pg/ml}$). In addition, her cortisol levels were not suppressed after the administration of dexamethasone (DST) 1 mg (the cortisol level remained at $>50 \mu\text{g/dl}$). Computerized tomography (CT) scan of her abdomen revealed a $2.5 \text{ cm} \times 2.8 \text{ cm}$ tumor on her left adrenal gland.

The adrenal tumor was the presumptive cause of the physical and psychiatric symptoms, so on consultation with an endocrinologist and surgeon an elective surgery was scheduled one week later, at which point she was transferred to a surgical ward. In the intervening week she was started on low-dose quetiapine ($75\text{-}125 \text{ mg/d}$) and alprazolam (0.4 mg/qn), which partially reduced the severity of her psychotic symptoms and improved her sleep. The resected tumor was a benign ACTH-independent adrenal adenoma. One week after surgical removal of the adrenal tumor, her plasma cortisol and ACTH levels in the early morning (8:00) were $<1 \mu\text{g/dl}$ and 8.93 pg/ml , respectively, and at midnight (24:00) they were $1.01 \mu\text{g/dl}$ and 5.81 pg/ml , respectively. She remained hospitalized for one month after the surgery; during this time her physical symptoms were treated with prednisolone, felodipine, metoprolol, and omeprazole, and her psychiatric symptoms and sleep disorder were treated with quetiapine and alprazolam. On discharge her physical symptoms had resolved and her persecutory delusions, mood dysregulation, and insomnia, had disappeared, though she continued to have some non-specific somatic complaints such as fatigue and backache. After discharge she continued to take quetiapine 75 mg/qn but discontinued the alprazolam. After two months of outpatient follow-up her psychiatric symptoms had completely resolved, so the quetiapine was stopped. On telephone follow-up several months later she reported no recurrence of any symptoms.

2. Discussion

Cushing's syndrome (CS) is a clinical condition that results from chronic secretion of excessive levels of glucocorticoids by the adrenal glands which then directly influences the functioning of the hypothalamus and pituitary glands—the other components of the hypothalamic-pituitary-adrenal (HPA) axis. The hypercortisolism directly or indirectly results in the common clinical presentation of obesity, hypertension, diabetes, osteoporosis, amenorrhea, and hirsutism.^[1] In 80-85% of cases CS is adrenocorticotrophic hormone (ACTH) dependent, the result of a pituitary corticotrophic adenoma or an extra-pituitary corticotrophic adenoma (i.e., ectopic ACTH syndrome). In the remaining 10-20% of cases the disease is ACTH-independent (as was the case with this patient),

usually the result of an adrenal gland tumor or adrenal hyperplasia, which can be unilateral or bilateral and benign or malignant.^[2]

The insidious onset of prodromal fatigue and increased vigilance in CS are usually ignored by the individual and overlooked by clinicians.^[2] The subsequent emergence of more troubling symptoms (hypertension, diabetes, osteoporosis, fractures, easy bruising, peripheral edema, back pain, menstrual irregularity, muscle weakness, and acne) results in greater clinical attention, and the presence of specific physical signs of CS (purple striae, facial plethora, exophthalmos, proximal myopathy, hirsutism, truncal obesity, and buffalo hump) often leads to the diagnosis. The median delay from onset of first symptoms to treatment is two years.^[3] Clinical complications negatively impact the quality of life of individuals with CS and associated cardiovascular and infectious diseases substantially increase their morbidity and mortality (Hazard Ratio, $2.8\text{-}16$).^[4]

Premorbid, concurrent, and consecutive psychiatric symptoms occur in 40-86% of individuals with CS.^[3] A wide range of specific and non-specific psychiatric symptoms have been reported:^[1,5,6] hypervigilance, fatigue, irritability, somatic complaints, sleep disturbance, decreased libido, depression, mood dysregulation, anxiety, cognitive abnormalities, suicide intent, personality changes, psychotic episodes, and anorexia nervosa. The reported prevalence of these neuropsychiatric signs and symptoms in CS varies across studies. One review^[7] reported major depressive syndrome in 50-81% of individuals with CS, anxiety in 12-79%, cognitive impairment in 66%, and mania in 3%. The occurrence of depression in CS is significantly associated with female gender, older age, higher urinary cortisol levels, and more severe physical symptoms.^[8] These neuropsychiatric symptoms significantly impair the health-related quality of life (HRQOL)^[7] of individuals with CS.

The presumed cause of these neuropsychiatric symptoms in CS is chronic glucocorticoid-induced damage to the brain and the hippocampus. Research about depression in CS suggests that atrophy of the prefrontal cortex and/or suppression of neurogenesis in the dentate gyrus is a proximal cause of the depressive symptoms.^[7]

When CS is suspected, the first step is to exclude hypercortisolemia attributed to exogenous glucocorticoid exposure or a pseudo-Cushing's state^[4] (such as alcohol abuse). Then one of three biochemical screening tests is recommended: (a) the 24-hour Urinary Free Cortisol (UFC) test, (b) the late-night salivary cortisol test, or (c) the 1 mg overnight dexamethasone suppression test (DST). After a diagnosis of CS is made, the primary cause should be determined, typically by abdominal or pituitary imaging to identify tumors or adrenal hyperplasia. Recent clinical

practice guidelines for CS^[4] recommend that all patients with comorbid psychiatric disorders receive immediate and long-term monitoring and adjunctive treatment for the psychiatric condition. After effective treatment of the hypercortisolemia, the psychiatric symptoms usually resolve gradually,^[5] but these individuals are subsequently at increased risk of developing anxiety, depression, maladaptive personality traits, and cognitive impairment.^[4]

Acute psychotic episodes associated with CS, though relatively uncommon,^[5] require urgent treatment because they may be associated with a life-threatening acute infection, pulmonary thromboembolism, or other cardiovascular events.^[9] Acute psychosis with a high suicide risk can occur in CS with even modest hypercortisolism (which may have less prominent physical symptoms),^[10] so psychiatric clinicians must always consider CS as a potential differential diagnosis for any unexplained psychosis.

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Conflict of interest statement

The authors declare that they have no conflict of interest related to this manuscript.

Informed consent

The patient signed an informed consent form and agreed to the publication of this case report.

Authors' contributions

YJW wrote the first draft of the case report that was subsequently revised by JC and YCM. YCM and ZXC both treated the patient.

急性精神病性表现的库欣综合征：一例病例报告

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概述：一位 36 岁的中国女性因出现狂躁、被害妄想和自杀意念 3 天被送至某综合医院急诊。六个月来患者易醒、过度警觉并出现躯体症状。入心身病房后，体检发现该患者满月脸、突眼，且双腿有紫纹，因此考虑急性精神症状继发于库欣综合征。血浆皮质醇、促肾上腺皮质激素 (adrenocorticotrophic hormone, ACTH) 水平升高，腹部计算机断层扫描 (computed tomography, CT) 发现左肾上腺肿块，证实了该诊断。使用小剂量噻硫平 (75-125 mg/d) 和阿普唑仑 (0.4 mg/qn) 来控制精神病性症状并改善其睡眠。将一个良性的非 ACTH 依赖性肾上腺肿瘤手术切除后，患者的皮质醇和 ACTH 水平恢复正常，其精神症状也在一个月内逐渐减少，此时该患者出院。患者出院后一

直门诊随访，维持噻硫平治疗（因为担心停药对睡眠和情绪稳定的影响），总时间持续 1 年左右，剂量从 50mg 渐减至 25mg 至减停。这时她的精神症状已经完全消失。该病例中，病人具有库欣综合征的特殊症状，因此相对容易诊断；但在库欣综合征中急性精神病性症状可能会危及生命，也可能不出现库欣综合征的典型躯体症状（如果皮质醇增多症不严重），所以临床精神科医师在鉴别难以解释的急性精神病时，应该始终考虑将库欣综合征纳入可能的鉴别诊断。

关键词：库欣综合征；精神病；鉴别诊断；病例报告；中国

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