

## PSYCHIATRIC DISORDERS ASSOCIATED WITH CUSHING'S SYNDROME

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### SUMMARY

**Background:** Cushing's syndrome is the term used to describe a set of symptoms associated with hypercortisolism, which in most cases is caused by hypophysial microadenoma over-secreting adrenocorticotrophic hormone. This endocrine disorder is often associated with psychiatric comorbidities. The most important include mood disorders, psychotic disorders, cognitive dysfunctions and anxiety disorders.

**Subject and methods:** The aim of this article was to review the prevalence, symptoms and consequences of psychiatric disorders in the course of Cushing's syndrome. We therefore performed a literature search using the following keywords: Cushing's syndrome and psychosis, Cushing's syndrome and mental disorders, Cushing's syndrome and depression, Cushing's syndrome and anxiety.

**Results:** The most prevalent psychiatric comorbidity of Cushing's syndrome is depression. Psychiatric manifestations can precede the onset of full-blown Cushing's syndrome and therefore be misdiagnosed. Despite the fact that treatment of the underlying endocrine disease in most cases alleviates psychiatric symptoms, the loss of brain volume persists.

**Conclusions:** It is important to be alert to the symptoms of hypercortisolism in psychiatric patients to avoid misdiagnosis and enable them receiving adequate treatment.

**Key words:** Cushing's syndrome - psychiatric disorders – depression – anxiety - psychosis

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### INTRODUCTION

Cushing's syndrome (CS) is the term used to describe a set of symptoms associated with hypercortisolism, in the majority of cases due to hypophysial microadenoma over-secreting adrenocorticotrophic hormone (ACTH). ACTH-independent endogenous hypercortisolism is caused in a majority of cases by adrenal gland tumors (Newell-Price 2006), while the most common exogenous cause of CS is glucocorticoids supplementation (Raveendran 2014). Pseudo-Cushing's syndrome is a condition in which symptoms of CS with functional hypercortisolemia are not caused by hypothalamic-pituitary-adrenal axis dysfunctions and is observed in a number of psychosomatic disorders (depression, anxiety disorders, alcoholism, anorexia nervosa, bulimia) (Sawicka 2013, Hatakeyama 2014). Hormonal disturbances associated with CS include insufficient reactivity of growth hormone (GH), thyroid stimulating hormone (TSH) and gonadotropin-stimulating factors; the lack of circadian rhythm of ACTH and cortisol secretion; a negative feedback exerted by glucocorticoids on ACTH secretion; the excessive secretion of ACTH with bilateral adrenal hyperplasia and the lack of ACTH and cortisol responses to stress (Raff 2015). Apart from somatic symptoms, patients with CS often experience a variety of mental health problems, on which this review is focused. Patients' complaints often include emotional lability and irritability, fatigueness, decreased energy, lower libido, anxiety, tearfulness, attention problems, and sleep disorders (shorter REM sleep latency and REM sleep period) (Kelly 1996).

### RESULTS

#### Mood disorders

Mood disorders are the most common psychiatric representation of CS (Krysta 2010). According to the prospective studies, over a half of CS patients (range from 50 to 62%) meet the diagnostic criteria of mood disorders (Sonino 1993, Dorn 1995, Sonino 1998, Bolanos 2004). Additionally, depression occurs in approximately 25% of the patients in the prodromal phase of Cushing's syndrome (Sonino 1993). It was observed that the incidence, type of mood disorders, and response to treatment are not related to the etiology of Cushing's syndrome (Sonino 2001). Atypical depression probably occurs more often than in the general population, and is characterized by irritability, hyperphagia, hypersomnia and increased fatigability, which may be associated with reduced secretion of CRH (Dorn 1997). The risk factors for depression in the course of Cushing's syndrome are still under investigation. Among the potential risk factors are older age, female sex, higher levels of cortisol in the urine before treatment, and more severe clinical condition (Sonino 1998). The question emerges whether depressive disorders results directly from the hypothalamic-pituitary-adrenal axis disorders or secondary to disfigurement, pain and a lack of self-acceptance. Discovering the link between high cortisol levels and the occurrence of depression more than a half a century ago initiated the research on the role of the hypothalamic-pituitary-adrenal axis in psychiatric disorders. A phenomenon of functional hypercortisolism in major depression was described, forming so-called pseudo-Cushing's syndrome (Carroll 2012, Tirabassi 2014). It

was observed in animal models that the hippocampus is particularly sensitive to hypercortisolism associated with exposure to exogenous glucocorticoids or heavy stress as hippocampal neurons have a high density of glucocorticoid receptors, which in the case of chronic hypercortisolism may lead to a selective atrophy of the hippocampus (Uno 1994). Clinical studies indicate the hippocampal dysfunctions and reduction in volume of the hippocampus in patients with depression (Sheline 1996, McEwen 1997). Langenecker et al. (2012) found that patients with Cushing's syndrome experience difficulties distinguishing emotional states and have impaired activation of brain structures responsible for perception, processing and regulation of emotions similar to those found in major depression. Normalization of cortisol level plays a crucial role in the treatment of mood disorders in the course of Cushing's syndrome. The correlation between reduction in the incidence of mood disorders and the normalization of cortisol level after surgery (pituitary surgery, bilateral adrenalectomy and others) was confirmed in studies with a follow-up (Espinosa-de-Los-Monteros 2013, Osswald 2014). In one study, a year after pituitary surgery the percentage of patients with depression decreased from 24% to 11% (Langenecker 2012), in another study after the same period of time, it went down from 51.5% to 17.2% (Dorn 1997). Antiglucocorticoids (metyrapone, mifepristone, ketoconazole) seem to be equally effective, especially in situations where the surgery can not be the treatment of choice (Lau 2015). Patients' quality of life after treatment also remains generally reduced, according to Osswald et al. (2004) in 45% of women and in 17% of men.

### Psychotic disorders

Psychosis is a rare manifestation of Cushing's syndrome, therefore the literature on the subject is limited and consists mainly of clinical case reports. In a study focused on psychiatric aspects of Cushing's syndrome (Kelly 1996) psychosis was diagnosed in 16 out of 209 patients studied and was found to be more common in adrenal carcinomas. Noteworthy, psychotic symptoms often precede the onset of full-blown Cushing's syndrome. Saad and colleagues (1984) reported a case of a 37-year old woman with acute psychosis and cognitive impairment. Performed diagnostic procedures strongly suggested Cushing's disease, although the patient had no cushingoid features, apart from mild generalized obesity. She underwent trans-sphenoidal resection of a pituitary macroadenoma, after which the neuropsychiatric manifestations resolved. Gerson & Miklat (1985) described a case of a 37-year old woman with Cushing's disease that first presented as a diagnostically confusing atypical psychosis. The patient died suddenly secondary to unexpected gastrointestinal bleeding. Pathological findings from a post-mortem examination confirmed the Cushing's disease diagnosis. Tang et al. (2000) presented two cases in which the diagnosis of Cushing's

syndrome was made when mental health problems became prominent. The patients were a 46-year old woman suffering from Cushing's syndrome due to an adrenal adenoma and a 25-year old woman with a psychosis secondary to Cushing's syndrome related to a metastatic adrenal carcinoma. In both cases psychiatric symptoms had eventually resolved after adrenalectomy.

Zielasek et al. (2002) reported a case of a 45-year old woman who developed persecutory ideas, social withdrawal, self-neglect and thought disorder over six years. After her psychiatrist noticed clinical features of Cushing's syndrome, she was admitted to the hospital, where a benign adrenal adenoma was detected and removed. After the surgery her mental state gradually improved. Tran and Elias (2003) described a patient with a pituitary macroadenoma which had an atypical clinical presentation, with no phenotypical signs of hypercortisolism and whose most prominent and distressing symptom was severe myopathy and psychosis.

However, it is not a rule that psychotic symptoms precede full blown Cushing's syndrome. Barnett and colleagues (1970) reported a case of a 23-year old female patient in which psychotic symptoms developed after rapid acceleration of Cushing's syndrome. She required transfer to acute psychiatric ward as she became paranoid, hallucinating, impulsive and suicidal, bilateral total adrenalectomy was then carried out. Terzolo et al. (1994) reported a case of a 35-year old female patient with an adrenal pheochromocytoma as a cause of ectopic Cushing's syndrome. As at admission to the hospital, clinical and hormonal data were unrewarding, it was decided to continue to observe the patient. Four months later, she became symptomatic with hypertensive and psychotic crises and glycemic decompensation. By that time, a full-blown Cushing picture was evident. When the left adrenalectomy was performed, signs and symptoms of Cushing's syndrome resolved.

Severe psychosis in patients with Cushing's syndrome is generally difficult to treat and in most cases there is little or no response to antipsychotic drugs. Symptoms often resolve after the resection of tumor. Górniak and Rybakowski (2005) reported a case of a 24 year old woman with an acute paranoid syndrome in the course of Cushing's syndrome caused by a hypophysial adenoma. She was treated without improvement with haloperidol and fluphenzine and successfully with clozapine. After resection of the hypophysial adenoma no relapse of the psychotic disorder was noted despite discontinuing clozapine. Several case reports indicate that the mifepristone-induced receptor blockade may lead to significant clinical improvement in patients with Cushing's syndrome in whom surgery and inhibitors of adrenal steroidogenesis fail to control hypercortisolism (Johanssen 2007). Mifepristone is an antiprogesterin which at higher doses competes with glucocorticoids for binding to their receptor. Due to its rapid onset of

action, mifepristone may be particularly useful in acute crises, like cortisol-induced psychosis (Johanssen 2007). Van der Lely and colleagues (1991) reported two patients with adrenal carcinoma in whom mifepristone reversed acute cortisol-induced psychosis within 24 h. Chu et al. (2001) reported a case of a 51-year-old, severely ill male with an ACTH-secreting pituitary macroadenoma suffering from cortisol-induced psychosis. Transsphenoidal resection of the tumour was incomplete, ketoconazole was not tolerated and mitotane failed to control hypercortisolism, while treatment with RU 486 resulted in clear clinical improvement. Combined use of mifepristone and etomidate has been reported in successful treatment of severe psychosis unresponsive to treatment with conventional antipsychotic drugs caused by an ectopic ACTH-producing lung carcinoma and Cushing's syndrome (Bilgin 2007). Mifepristone was also found to be effective in treatment of psychotic symptoms in major depression in a double-blind, placebo-controlled study on five patients with psychotic major depression (Belanoff 2001).

### Cognitive dysfunctions

Cushing's syndrome is associated with brain atrophy and subsequent cognitive impairments. The region particularly sensitive to cortisol is the hippocampus (Sapolsky 1994). Hypercortisolemia impairs the ability of hippocampal neurons to survive various neurological insults (Sapolsky 1985), impairs the uptake and the metabolism of glucose (Paquot 1995) and cause retraction and simplification of dendrites in the hippocampus (Magariños 2000). However, the loss of hippocampal volume associated with sustained hypercortisolemia is at least partially reversible when the cortisol levels decrease (Starkman 1999, Gnjidic 2008, Toffanin 2011), it was observed that cognitive function, reflecting memory and executive functions, is impaired in patients despite long-term cure of Cushing's disease (Tiemensma 2010; Ragnarsson 2012). Regarding exogenous CS, Brown et al. (2004) found that patients receiving chronic corticosteroid therapy had impaired declarative memory compared to healthy controls which remained at the same level in a 4 years follow up (Brown 2007). Coluccia et al. (2008) after investigating the correlation between the memory and the corticosteroids dose-dependent hippocampal volume in patients receiving chronic corticosteroid therapy suggest that the effect of corticosteroids on the hippocampus is associated rather with acute than cumulative effects of these drugs.

### Anxiety disorders

Existing literature on anxiety disorders among patients with CS is rather limited. Starkman & Schteingart (1981) reported symptoms of anxiety in 66% of examined CS patients. In 34% of patients symptoms were mild, in 26% moderate, in 29% severe and in 11%

very severe. The severity of symptoms depended on the level of cortisol and ACTH – in patients with high levels of cortisol, but with low ACTH anxiety symptoms were milder. Loosen et al. (1992) examined 20 patients based on clinical history and SCID (Structured Clinical Interview for DSM-III). The vast majority of patients (79%) were diagnosed with generalized anxiety disorder (GAD) and 53% with panic disorder.

### CONCLUSIONS

Disorders of hypothalamic-pituitary-adrenal axis may lead to neuropsychiatric disorders, psychiatric symptoms may precede full-blown CS by months or even years. Treatment of psychiatric disorders occurring in the course of Cushing's syndrome requires stating an accurate diagnosis, undiagnosed hypercortisolemia leads to numerous somatic complications. Erroneous recognition of symptoms as solely psychiatric can lead to secondary complications arising from neuroleptic treatment - hyperprolactinemia, metabolic syndrome and functional secondary hypercortisolism. Treatment of the underlying disease (operational or pharmacological) in most cases alleviates psychiatric symptoms. While diagnosing and treating CS, it seems very important to carefully assess the patients' mental state, to implement appropriate strategies for treatment and rehabilitation, including psychiatric and psychological care, not only during an active phase of CS, but also suitably long after this treatment.

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### References

1. Barnett IG, Nabarro JD, LeQuesne LP: *Fluctuating Cushing's syndrome, acute psychosis, aminoglutethimide therapy. Proc R Soc Med* 1970; 63:338-9.
2. Belanoff JK, Flores, BH, Kalezhan, M, Sund, B, Shatzberg, AF: *Rapid reversal of psychotic depression using mifepristone. J Clin Psychopharmacol* 2001; 21:516-21.
3. Bilgin YM, van der Wiel HE, Fischer HR, De Herder WW: *Treatment of severe psychosis due to ectopic Cushing's syndrome. J Endocrinol Invest* 2007; 30:776-9.
4. Bolanos SH, Khan DA, Hanczyc M, Bauer MS, Dhanani N, Brown ES: *Assessment of mood states in patients receiving long-term corticosteroid therapy and in controls with patient-rated and clinician-rated scales. Ann Allergy Asthma Immunol* 2004; 92:500-5.
5. Brown ES, J Woolston D, Frol A, Bobadilla L, Khan DA, Hanczyc M et al.: *Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol Psychiatry* 2004; 55:538-45.
6. Brown ES, Vera E, Frol AB, Woolston DJ, Johnson BJ: *Effects of chronic prednisone therapy on mood and memory. Affect Disord* 2007; 99:279-83.

7. Carroll BJ, Iranmanesh A, Keenan DM, Cassidy F, Wilson WH, Veldhuis JD: Pathophysiology of hypercortisolism in depression: pituitary and adrenal responses to low glucocorticoid feedback. *Acta Psychiatr Scand* 2012; 125:478-91.
8. Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D: Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *Journal of Clinical Endocrinology and Metabolism* 2001; 86:3568–3573.
9. Coluccia D, Wolf OT, Kollias S, Roozendaal B, Forster A, de Quervain DJ: Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. *J Neurosci* 2008; 28:3474-8.
10. Dorn LD, Burgess ES, Dubbert B, Simpson SE, Friedman T, Kling M et al.: Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. *Clin Endocrinol* 1995; 43:433-42.
11. Dorn L, Burgess E, Friedman T, Dubbert B, Gold P, Chrousos G: The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *J Clin Endocrinol Metab* 1997; 82:912-9.
12. Espinosa-de-Los-Monteros AL, Sosa E, Martinez N, Mercado M: Persistence of Cushing's disease symptoms and comorbidities after surgical cure: a long-term, integral evaluation. *Endocr Pract* 2013; 19:252-8.
13. Gerson SN, Miclat R: Cushing Disease presenting as Atypical Psychosis followed by sudden death. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie* 1985; 30:223-224.
14. Gnjidic Z, Sajko T, Kudelic N, Malenica M, Vizner B, Vrkljan M: Reversible "brain atrophy" in patients with Cushing's disease. *Collegium antropologicum* 2008; 32:1165-1170.
15. Górniak M, Rybakowski J: Paranoid syndrome in the course of Cushing's disease. *Post Psychiatr Neurol* 2005; 14:18–20.
16. Hatakeyama M, Nakagami T, Yasui-Furukori N: Adrenal Cushing's syndrome may resemble eating disorders. *General Hospital Psychiatry* 2014; 36:760.e9–760.e10
17. Johanssen S & Allolio B: Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol* 2007; 157:561-569.
18. Kelly WF: Psychiatric aspects of Cushing's syndrome. *QJM* 1996; 89:543-51.
19. Krysta K, Górniak E, Furczyk K: Persistent depression in the course of Cushing's syndrome – a case report. *Post Psychiatr Neurol* 2010; 19:305-307.
20. Langenecker SA, Weisenbach SL, Giordani B, Briceño EM, Guidotti Breting LM, Schallmo MP et al.: Impact of chronic hypercortisolemia on affective processing. *Neuropharmacology* 2012; 62:217-25.
21. Lau D, Rutledge C, Aghi MK: Cushing's disease: current medical therapies and molecular insights guiding future therapies. *Neurosurg Focus* 2015; 38:11.
22. Loosen PT, Chambliss B, DeBold CR, Shelton R, Orth DN: Psychiatric phenomenology in Cushing's disease. *Pharmacopsychiatry* 1992; 25:192-8.
23. Magariños AM & McEwen BS: Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proc Natl Acad Sci USA* 2000; 97:11056–61.
24. McEwen BS: Possible mechanisms for atrophy of the human hippocampus. *Mol Psychiatry* 1997; 2:255-62.
25. Newell-Price J, Bertagna X, Grossman AB, Nieman LK: Cushing's syndrome. *Lancet* 2006; 367:1605–17.
26. Osswald A, Plomer E, Dimopoulou C, Milián M, Blaser R, Ritzel K et al.: Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. *Eur J Endocrinol* 2014; 171:209-15.
27. Paquot N, Schneiter P, Jéquier E, Tappy L: Effects of glucocorticoids and sympathomimetic agents on basal and insulin-stimulated glucose metabolism. *Clin Physiol* 1995; 15:231-40.
28. Raff H: Cushing Syndrome: Update on Testing. *Endocrinol Metab Clin North Am* 2015; 44:43-50.
29. Ragnarsson O, Berglund P, Eder DN, Johannsson G: Long-term cognitive impairments and attentional deficits in patients with Cushing's disease and cortisol-producing adrenal adenoma in remission. *The Journal of clinical endocrinology and metabolism* 2012; 97:1640-48.
30. Raveendran AV: Inhalational Steroids and Iatrogenic Cushing's Syndrome. *Open Respir Med J* 2014; 8:74-84.
31. Saad MF, Adams F, Mackay B, Ordonez NG, Leavens ME, Samaan NA: Occult Cushing's disease presenting with acute psychosis. *Am J Med* 1984; 76:759-66.
32. Sapolsky RM: Glucocorticoids, stress and exacerbation of excitotoxic neuron death. *Semin Neurosci* 1994; 6:323–331.
33. Sapolsky RM: A mechanism for glucocorticoid toxicity in the hippocampus: increased neuronal vulnerability to metabolic insults. *J Neurosci* 1985; 5:1228-32.
34. Sawicka N, Gryczyńska M, Sowiński J: Two diagnoses become one? Rare case report of anorexia nervosa and Cushing's syndrome. *Neuropsychiatr Dis Treat* 2013; 9:431-5.
35. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW: Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; 93:3908–13.
36. Sonino N, Fava GA, Belluardo B, Girelli ME, Boscaro M: Course of Depression in Cushing's Syndrome: Response to Treatment and Comparison with Graves' Disease. *Horm Res* 1993; 39:202–206.
37. Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F: Clinical correlates of major depression in Cushing's disease. *Psychopathology* 1998; 31:302-6.
38. Sonino N & Fava GA: Psychiatric disorders associated with Cushing's syndrome: epidemiology, pathophysiology and treatment. *CNS Drugs* 2001; 15:361-73.
39. Starkman MN & Scheingart DE: Neuropsychiatric manifestations of patients with Cushing's syndrome. Relationship to cortisol and adrenocorticotrophic levels. *Arch Int Med* 1981; 141:215-19.
40. Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Scheingart DE: Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biol Psychiatry* 1999; 46:1595-602.
41. Tang A, O'Sullivan AJ, Diamond T, Gerard A, Campbell P: Psychiatric symptoms as a clinical presentation of Cushing's syndrome. *Ann Gen Psychiatry* 2013; 12:23.
42. Terzolo M, Alè A, Pia A, Bollito E, Reimondo G, Paccotti P et al.: Cyclic Cushing's syndrome due to ectopic ACTH secretion by an adrenal pheochromocytoma. *J Endocrinol Invest* 1994; 17:869-74.
43. Tiemensma J, Kokshoorn NE, Biermasz NR, Keijser BJ, Wassenaar MJ, Middelkoop HA et al.: Subtle cognitive impairments in patients with long-term cure of Cushing's disease. *The Journal of clinical endocrinology and metabolism* 2010; 95:2699-2714.

44. Tirabassi G, Boscaro M, Arnaldi G: Harmful effects of functional hypercortisolism: a working hypothesis. *Endocrine* 2014; 46:370-86.
45. Toffanin T, Nifosi F, Follador H, Passamani A, Zonta F, Ferri G et al.: Volumetric MRI analysis of hippocampal subregions in Cushing's disease: a model for glucocorticoid neural modulation. *European psychiatry: the journal of the Association of European Psychiatrists* 2011; 26:64-67.
46. Tran M & Elias AN: Severe myopathy and psychosis in a patient with Cushing's disease macroadenoma. *Clin Neurol Neurosurg* 2003; 106:1-4.
47. Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O et al.: Neurotoxicity of glucocorticoids in the primate brain. *Horm Behav* 1994; 28:336-48.
48. van der Lely AJ, Foeken K, Van Der Mast RC, Lamberts SW: Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Annals of Internal Medicine* 1991; 114:143–144.
49. Zielasek J, Bender G, Schlesinger S, Friedl P, Kenn W, Allolio B et al.: A woman who gained weight and became schizophrenic. *Lancet* 2002; 360:1392.

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