

## **Acute psychosis in the course of treatment of acute adrenal crisis with hydrocortisone in the patient with secondary adrenal insufficiency – a case study**

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### **Summary**

**Aim.** Presentation of the risk of psychosis induced by the treatment of adrenal crisis with high doses of hydrocortisone.

**Method.** A case analysis in the context of the literature

**Results.** There are reported psychoses in the patients with adrenal hypofunction and hyperfunction. Psychoses following implementation of substitution with small doses of corticosteroids due to adrenal insufficiency were also observed. The hypereactivity of the glucocorticoid receptor is supposed mechanism. We have not found any description of psychosis connected with steroid administration in adrenal crisis. We present a case of 55 years old female, so far mentally healthy with untreated adrenocortical insufficiency secondary to radiotherapy of pituitary adenoma (prolactinoma) performed 3 years ago. She was admitted to the hospital because of acute adrenal crisis provoked by infection. In the fourth day of treatment with intravenous Hydrocortisone (up to 400mg/24 hours) there occurred acute psychosis with hallucinations, delusions and life-threatening behaviours. The patient was admitted to the psychiatric inpatient unit. Following 3 days of treatment with haloperidol, and decreasing the steroid dosage – the psychosis disappeared, without recurrence, despite of discontinuation of haloperidol.

**Conclusions.** The case focuses attention on the risk of psychosis connected with the treatment of the adrenal crisis with high doses of Hydrocortisone. Because of the risk of psychiatric complications, the patients treated with high doses of corticosteroids, require an evaluation of risk factors for mental disturbances, and safety precautions in cooperation of endocrinologist and psychiatrist.

**Key words:** glucocorticosteroids, acute psychosis, adrenal crisis

## Introduction

### Mental disorders and endocrinopathies

In 1963 Manfred Bleuler described mental disturbances coexisting with endocrine gland disorders as so-called psychoendocrine syndrome, which include disturbances of emotions, drives, circadian rhythms and mood [1].

In the following years many cases of various psychiatric disorders co-existing with abnormal function (hypofunction or hyperfunction) of adrenal, thyroid, pituitary and parathyroid glands have been reported [2].

In the cases of increased secretion of endogenous cortisol (Cushing's syndrome or disease), depression occurred the most often; anxiety disorders psychotic disorders, manic episodes and disturbances of consciousness were less frequent [3].

In adrenal insufficiency – primary (Addison disease) and secondary (impairment of the pituitary gland) – mild disturbances of mood, motivation and behaviour were reported most often. Dysthymic, depressive and manic syndromes were less frequent. Single cases of psychotic disorders or disturbances of consciousness were also reported [4–6].

### Mental disorders during steroid anti-inflammatory therapy

Hormones of adrenal glands – glucocorticoids – have been used in medicine to treat different illnesses, mostly those with underlying immunologic and inflammatory pathogenesis, both acute (e.g. anaphylaxis, hypersensitive reactions, asthma) and chronic (e.g. lupus, rheumatoid disorders), for over 50 years. Psychiatric symptoms were observed since the beginning of treatment with steroids. Different authors estimate frequency of occurrence of symptoms and disorders in the mental health to be 5% to 75% of all cases of corticosteroid treatment [7–9]. These differences depend on the criteria of diagnosis of particular mental disorders. Most prevalent are mild, with no clinical significance, disturbances of mood, behaviour, attention, memory, sleep and appetite. Psychiatric syndromes, mostly mood disorders (mostly depressive, sometimes manic or mixed episodes) are less frequent. Sometimes anxiety disorders are also observed. Prevalence of psychotic disorders is estimated to be 5–6% of the cases of corticosteroid treatment. There were reports of consciousness disorders (delirium) [10] and suicidal tendencies (especially among adolescents) [11–13]. Mild symptoms, i.e. insomnia, attention deficit, irritability, apathy, might be preliminary symptoms of more severe disorders, such as depression, mania, psychosis, delirium [10]. Some researchers use the term 'steroid psychosis' for common description of heterogeneous psychopathological syndromes connected with glucocorticoids treatment [7, 9, 10], which is not correct because the term 'psychosis' should be related to disorders with psychotic symptoms (delusions, hallucinations) [14].

In 90% of cases, psychiatric disorders start within 6 weeks since the initiation of steroid treatment, but sometimes might start within 3–4 days [15, 16]. Consciousness disturbances usually last a couple of days, psychotic disorders last about a week,

manic episodes about 2–3 weeks, depressive mood disorders sometimes longer than a month [15, 16].

Epidemiological studies revealed that psychiatric disorders due to steroid therapy, especially depression, occur more often (60%) among women. Mania or delirium is more frequent among males [11].

Risk factors for psychiatric disorders during steroid therapy are high doses of corticosteroids [10, 17] and past history of mental disorders [13]. On the other hand, discontinuation (especially rapid one) of steroid administration among patients undergoing long term steroid treatment have been reported to be connected with occurrence of depression (especially among younger patients) and delirium (among elderly) [18].

### Mental disorders during steroid replacement therapy

In contrast to quite abundant literature describing mental disorders treated with corticosteroids due to non-endocrinological diseases, reports regarding mental disorders during steroid replacement therapy are rare.

Steroid replacement therapy among patients with adrenal insufficiency is aimed to normalize previously decreased blood levels of glucocorticoids and mineralocorticoids. Most frequent cause of primary adrenal insufficiency is autoimmune inflammation (Addison disease), and most frequent cause of secondary adrenal insufficiency is pituitary tumour, or its removal [19]. Replacement therapy should normalize the deficit, without causing increased blood concentration of cortisol. Therefore, it should not result in post-steroid mental disorders.

Moreover, there are data indicating that adrenal insufficiency (both primary and secondary) itself might cause mental disorders which mask the symptoms of hormonal dysfunction [20–22].

Epidemiological data reveal that 68% of patients with adrenal insufficiency (primary or secondary) who had been consulted 3 times by primary care physicians have been misdiagnosed, predominantly with diagnosis of mental disorders. These were mostly diagnoses of problems with emotion, mood and behaviour, rarely psychotic symptoms [4, 23].

In these cases hormone replacement therapy could result in the improvement of the mental state of the patient.

However, during hormone replacement therapy it is hard to obtain physiological blood concentration of cortisol and recreate natural circadian rhythm of cortisol secretion. Secretion of endogenous cortisol is lowest late at night and around midnight, it increases in the second half of the night and early in the morning (between 2:00 a.m. and 4:00 a.m.), reaches its peak in the morning after awakening, then decreases during the day, till the evening. Patients undergoing hormone replacement therapy might have periods of having abnormally decreased and increased cortisol levels [24]. Benson et al., while comparing different schemes of hydrocortisone dosing revealed that patients' mood and functioning correlated with the used scheme of dosing [25]. There are data revealing that interference of circadian rhythm of cortisol concentration in patients

treated with hormonal replacement therapy might cause decreased mood, poor functioning, depression, insulin resistance and osteoporosis [25, 26].

Untreated adrenal insufficiency might, due to long term deficit of glucocorticoids deficiency, lead to hypersensitivity of glucocorticoid receptor, and then to overreaction even to small doses of glucocorticoids [27]. This thesis might be supported by reports of mental disorders induced with the initiation of replacement therapy in patients with primary and secondary adrenal insufficiency even when very small daily doses are used. In the literature, we have found 5 such casuistic reports (2 cases of manic episodes, 2 psychotic syndromes, and 1 report of delirium). Among these reports, 3 were reports of patients with primary adrenal insufficiency soon after starting replacement therapy with physiological dose of glucocorticoids. There was one case of delirium [28] and 2 cases (previously presenting depression symptoms) of acute manic episodes [27, 29].

Two other cases were patients with secondary adrenal insufficiency connected with postpartum pituitary insufficiency (Sheehan syndrome) [30, 31]. In both cases there were acute psychoses with hallucinations following initiation of treatment with small doses of prednisone. In one of the cases symptoms of psychosis occurred on 5<sup>th</sup> day of replacement therapy with prednisone and diminished in 4 days following discontinuation of prednisone treatment and administration of 5 mg of haloperidol and 4 mg of lorazepam. In the next 2 weeks prednisone was reintroduced in dose up to 7.5 mg per day (split dose). Mental state of the patient was stable despite discontinuation of haloperidol [31].

#### Treatment of post-steroid mental disorders

In most cases, a withdrawal of post-steroid mental disorders is observed after reduction of dose or discontinuation of glucocorticoids. Sometimes, there is a need to introduce psychotropic treatment (sedatives, antipsychotics, antidepressants, mood stabilizers, sleeping remedies). Full recovery was observed among 95% of patients in which steroid treatment had been discontinued, among 85% of patients who had been treated with antipsychotics, and 100 % of patients who had both procedures administered [14].

So far, haloperidol is antipsychotic most frequently used in treatment of post-steroid psychosis. In some cases, second generation antipsychotics: risperidone and olanzapine, were used [10, 32].

In the treatment of post-steroid depression, tricyclic antidepressants are not recommended. It is recommended to use selective serotonin reuptake inhibitors (SSRI) [10].

There were clinical trials showing beneficial effects of lithium in prophylaxis of psychiatric disorders in patients undergoing glucocorticoid therapy [33, 34]. There were observed some effects of lamotrigine and memantine on improvement in case of memory dysfunction connected with glucocorticoid therapy [34].

### Acute adrenal crisis – corticoid therapy and mental disorders

In replacement treatment of chronic adrenal insufficiency it is difficult to secure proper blood concentration of hormones in situations of rapidly increased need for this hormones, such as infection, trauma or other stress. In these situations, life-threatening deficit of cortisol – acute adrenal crisis, may occur [19]. Acute adrenal crisis is an acute, life-threatening situation. It occurs in the form of a shock with peripheral circulatory failure, electrolyte disturbances, (hyponatraemia, hyperkalaemia, hypoglycaemia), pain in the stomach, severe vomiting, diarrhoea, and consciousness disorders. Untreated adrenal crisis might lead to death. There are long lasting prodromal signs of adrenal crisis, such as loss of appetite and nausea (“stomach signs”), fatigue and muscle aches (pseudo-influenza symptoms). Abnormal levels of electrolytes (including hyperkalcaemia) already occur in this prodromal states [35].

Adrenal crisis is usually treated with large doses of hydrocortisone, starting with 100 mg intravenously administered immediately. This is followed by treatment with hydrocortisone in the dose of 200–400 mg per day, together with replenishment of fluids, sodium, glucose, and treatment of the cause of adrenal crisis e.g. infection (antibiotics). When the patient’s health improves and the cause of crisis is treated successfully, it is possible to gradually (2–3 days) decrease the dose of hydrocortisone aiming at replacement therapy dose, which can be administered orally [35]. On one hand, the treatment of adrenal crisis consists in glucocorticoid replacement therapy, on the other, due to treatment of circulatory shock there is a need to use high doses of glucocorticoids, much higher than physiological doses, which might lead to psychotic disorders.

However, according to Anglin, psychosis might be connected with adrenal crisis itself. Metabolic and water-electrolyte imbalance are important risk factors [4].

In available literature, we have not found any reports of psychosis during treatment of adrenal crisis with high dosages of glucocorticoids.

We present a case of the patient with no past history of mental disorders, with untreated secondary adrenal insufficiency after removal of pituitary tumour. In this patient acute adrenal crisis following infection had revealed. Paranoid syndrome requiring psychiatric hospitalization occurred on the 4<sup>th</sup> day of the treatment of adrenal crisis with intravenous hydrocortisone.

### A case study

The case concerns 55-years old female with university education, employed, with no past history of mental disorders. 3 years ago she underwent the pharmacological treatment and radiotherapy of pituitary tumour (prolactinoma), which was followed by secondary adrenal insufficiency. However, she has not been taking hormone replacement medications for 2 years. Her mental health was good, and her professional and social relations were also good. In 2010 She was admitted to endocrinology ward of the Bielanski Hospital due to symptoms of life-threatening adrenal crisis (stomach pain, hypotension, vomiting, hyponatraemia, hyperkalaemia), which occurred after the infection of upper respiratory tract.

After the treatment – intravenous hydrocortisone administration, initially 400 mg/daily, and since third day 200 mg/daily – an improvement in somatic health and normalization of electrolyte balance was observed, but on the third day of hospitalization acute psychotic symptoms emerged.

The patient was consulted by a psychiatrist on the endocrinology ward. She was oriented to person, time and place. She had auditory and visual hallucinations. She presented delusions of thought insertion, religious and bizarre delusions. Disorganized thinking was also observed („I spited a witness, now You are a witness, please look in the mirror, they know”, “I have enough of this game, which the book says about, can You see the blood”). The patient was agitated, verbally and physically aggressive toward other persons.

Due to diagnosis of acute psychosis with paranoid symptoms and behaviour threatening the health of the patient and other people, she was transferred to the psychiatric ward without her consent (article 23 of Polish Mental Health Act). At the psychiatric ward, treatment with haloperidol (10 mg/daily i.m.) and diazepam (up to 15 mg/daily i.m.), was initiated and fluids were administered i.v. The dose of hydrocortisone was reduced to 10 mg/daily. Because of agitation and aggressive behaviour, the patient was restrained for a short time.

On the second day of hospitalization the patient improved, psychotic symptoms disappeared. There was no further requirement for antipsychotic medication. Stable patient, with normal mood, normal activity, calm, with no psychotic symptoms, was discharged from the hospital after 5 days of observation with the treatment recommendation as follows: 10 mg/daily of hydrocortisone in split doses, without further antipsychotic medication. The disturbances were differentiated with organic delirium, however, as her orientation and memory was not deteriorated and she presented paranoid syndrome (with typical delusions and hallucinations with elements of distraction), the “acute psychosis in the course of intravenous corticosteroid therapy due to acute adrenal crisis” was recognized. According to the ICD-10 classification the diagnosis was: “organic delusional disturbances (schizophrenia-like)” – F06.2. For 2.5 years long katamnestic period no recurrence of any psychiatric disturbances has been observed.

## Discussion

The described patient, with untreated secondary adrenal insufficiency had acute adrenal crisis following upper tract infection. On the fourth day of treatment with high doses of intravenous hydrocortisone, acute psychotic syndrome with aggressive behaviour threatening the health of the patient and other people, requiring psychiatric hospitalization occurred. The psychotic symptoms disappeared after 3 days of treatment with haloperidol and significant reduction of hydrocortisone dose.

In the literature, we have found case reports of psychoses in patients with primary (Addison disease) and secondary (Sheehan syndrome) adrenal insufficiency [4–6, 20–22]. In the presented case, however, the psychotic symptoms have occurred after 4 days of treatment with high doses of intravenous hydrocortisone and normalizing the water-electrolyte imbalance; moreover, these psychotic symptoms disappeared after

the reduction of hydrocortisone dose. Therefore, the development of the psychosis was probably caused by high doses of hydrocortisone rather than adrenal insufficiency. This is difficult to distinguish whether improvement was caused by the short term treatment with antipsychotic agent or by the reduction of the steroids dose. Most likely, it was the combined effect of both factors. Due to agitation and aggression of the patient, there was an urgent need of use antipsychotic and sedative medications. The presented patient had no past history of mental disorders and no family history of mental illness. Three years ago, after the treatment of pituitary adenoma, indicators of brain injury due to radiotherapy were not presented. She returned to her profession without any difficulties, and she had good interpersonal relations. Due to observed paranoid symptoms without any disturbances of consciousness and memory the acute psychosis related to steroid therapy of adrenal crisis was diagnosed and classified according to ICD as “organic delusional disturbances (schizophrenia-like)” F06.2 [36]. After discontinuation of treatment with antipsychotic medication (haloperidol) and reduction of hydrocortisone dose to oral replacement dose, no relapse of psychotic symptoms was observed. Within 2.5 years of follow-up there was no known relapse of mental disorders in that patient, what might indicate the relationship between acute psychosis and high dose of hydrocortisone in the course of adrenal crisis.

### Conclusions

The case focuses attention on the risk of triggering a psychosis by the treatment of adrenal crisis with high doses of hydrocortisone.

Because of the risk of psychiatric complications, the patients treated with high doses of corticosteroids, require an evaluation of risk factors for mental disturbances and safety precautions, as well as cooperation of endocrinologist and psychiatrist.

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