



# Acute Psychosis Following Hydrocortisone Replacement in a Patient with Secondary Adrenal Insufficiency Due to Recurrent Postoperative Pituitary Macroadenoma

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## Authors' contributions

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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Case Study

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## ABSTRACT

Acute psychosis in patients receiving physiological corticosteroid replacement is rare. The exact mechanism of this disorder is not clear. We report a case of a 50 year old female with recurrent post operative pituitary macroadenoma who had presented to us with features of adrenocortical insufficiency. The patient was started on intravenous (iv) hydrocortisone and after receiving six doses, she developed features of acute psychosis. She was put on anti-psychotics and hydrocortisone was withheld for 24 hrs. The patient recovered in a couple of days and oral hydrocortisone was re-started at 5 mg per/day and increased to 15 mg/day without recurrence of symptoms of psychosis.

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## 1. INTRODUCTION

Psychiatric disorder is one of the serious complications of glucocorticoid therapy. The average incidence of psychiatric disorders due to steroid therapy is reported to be about 6% [1]. Psychiatric side effects were reported in 1.3% of the patients receiving prednisone  $\leq$ 40 mg and 18.4% of those who received more than 80 mg of prednisone in the Boston Collaborative Drug Surveillance Program [2]. However psychiatric disorder with replacement doses of glucocorticoid is rare. Few case reports have shown that transient psychiatric symptoms may develop even on physiological replacement dose of glucocorticoids [3,4,5].

We describe a post operative case of recurrent pituitary macroadenoma with hypopituitarism who developed glucocorticoid induced psychosis after hydrocortisone replacement.

## 2. PRESENTATION OF CASE

A 50 years old female presented to the endocrinology clinic of Gauhati Medical College, Assam, India, in January 2015 with amenorrhoea for 12 years, headache and right hemianopia for 2 months, anorexia, nausea and generalised weakness for 2 weeks. On examination her BMI (Body Mass Index) was 20.95 kg/m<sup>2</sup>. Her blood pressure was 94/72 mmHg without any postural fall. Her mental state examination revealed that she was fully conscious and oriented to time, place and person. Her Psychomotor activity was mildly decreased and she was little worried about her illness thinking that it has probably relapsed again although no clinically significant mood disturbance was found. She did not have any thinking or perceptual disturbances. Her speech was relevant and coherent with little decreased tone and volume (may be attributed to her physical weakness). Her field of vision was restricted in the superior and temporal fields in both the eyes, the right eye being affected more severely. Motor system, sensory system and reflexes were normal. Respiratory system, cardiovascular and abdominal examination was unremarkable. Investigations revealed hyponatremia (serum Na 112 mmol/L). Blood glucose was normal (92 mg/dL on admission). Hormonal parameters were suggestive of hypopituitarism (Table 1). The clinical symptoms along with the low plasma cortisol (3.78 ug/dL)

were suggestive of adrenal insufficiency. A Thyroid stimulating hormone (TSH) level of 2.1 mIU/L and a low Free Thyroxine (FT4) level of 0.467 ng/dL suggested secondary hypothyroidism. The patient had secondary amenorrhoea and her Follicle stimulating hormone (FSH) was also low which was indicative of secondary hypogonadism. Other laboratory parameters are described in Table 2. The patient had been earlier operated twice for non functioning pituitary macroadenoma. In 1998, she had presented with headache and field defects in the left eye. She underwent right frontal craniotomy and subtotal excision of tumour and was discharged on prednisolone 5 mg once daily, which she discontinued after 2 months. Thirteen years later (in 2011) she developed headache and visual defects of the right eye and was again operated for recurrence of the tumour (transsphenoidal endoscopic assisted microsurgical excision). Histo-pathological examination was consistent with Gonadotropin producing adenoma. Following the second surgery she gradually developed symptoms of hypopituitarism but she was not on any replacement therapy or any other long term medication till she presented to us in January 2015. There was no history of any psychiatric illness in the past neither did she have any family history of any psychiatric illness.

Magnetic Resonance Imaging (MRI) Brain (January 2015) showed a heterogeneous predominant peripheral enhancing sellar mass lesion (1.8 x 1.6 x 2.6 cm) with suprasellar extension abutting and compressing the optic chiasma (Figs. 1 and 2).

**Table 1. Hormonal investigations of the patient**

Hormone (serum)	Patient value	Reference range
Cortisol (Morning)	3.78 ug/dL	5-25 $\mu$ g/dL
TSH	2.1 mIU/L	0.4-4.0 mIU/L
Free T4	0.467 ng/dL	0.89-1.7 ng/dL
Prolactin	7.5 ng/mL	5-20 ng/mL
FSH	0.412 mIU/L	1.1-11.6 mIU/mL

She was started on IV fluids and IV hydrocortisone 50 mg 8 hourly. It was tapered to 50 mg 12 hourly on the next day and then to 50 mg once daily on the 3<sup>rd</sup> day. There was marked clinical improvement. Her electrolyte

abnormalities improved gradually. However, after receiving 6 doses of IV hydrocortisone, on the 3<sup>rd</sup> day, i.e. after around 48 hours, although she showed significant improvement in her general condition, she started showing some psychiatric symptoms. Her Psychomotor activity increased significantly and she started talking more and more and was observed to be easily distractible. She became over familiar with the hospital staff and the other patients and attendants of the ward. Her speech became fast, over detailed with frequent change of topics showing pressure of speech, flight of ideas and loosening of associations. Her mood which was initially anxious became elated and changed to irritable by the end of the 3<sup>rd</sup> day. She also developed some visual hallucinatory behaviour. She did not sleep for the whole day and gradually became irritable and restless. It is when the psychiatrist was consulted and her thought process revealed Delusion of reference, Ideas of grandiosity (spiritual) and Ideas of persecution. Her affect was found to be inappropriate to her thought content and a diagnosis of Acute and Transient Psychosis, polymorphic type was made according to ICD-10. She was given a stat dose of injection Haloperidol and injection Lorazepam. The next day, the restlessness and irritability decreased, although her over familiarity and

increased talking persisted. She was then commenced on tablet Olanzapine 5 mg once daily at bed time along with tablet Lorazepam 1 mg twice daily which was gradually tapered off. Hydrocortisone was withheld for 24 hrs and was re-introduced at 5 mg per/day and increased to 15 mg/day in divided doses. The patient was discharged from the hospital on the 12<sup>th</sup> day on hydrocortisone and thyroid hormone replacement. She was reviewed by the Psychiatrist periodically and olanzapine was stopped after 4 weeks. There was no recurrence of symptoms of psychosis. The patient has been referred to the neurosurgeon for further management.

### 3. DISCUSSION

Glucocorticoids are steroid hormones secreted by the adrenal cortex. Although it is well-known that psychiatric manifestations can occur in patients receiving corticosteroids, the precise mechanism of this association is poorly understood. The neuropsychiatric effects of glucocorticoids may include depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia and psychosis [6,7].

**Table 2. Other laboratory parameters (Blood)**

Variables and reference range	On admission	2 <sup>nd</sup> day	3 <sup>rd</sup> day	4 <sup>th</sup> day	7 <sup>th</sup> day
Total leucocyte count (4.0 x 10 <sup>3</sup> -11.0 x 10 <sup>3</sup> ) per µL	7.14 x 10 <sup>3</sup>		8.43 x 10 <sup>3</sup>		8.2 x 10 <sup>3</sup>
<b>Differential count (%)</b>					
Neutrophils	66				71
Lymphocytes	19				22
Monocytes	6				4
Eosinophils	9				3
Serum Creatinine (0.6 -1.25 mg/dL)	1.0		0.9		0.8
Blood Urea (19 – 42 mg/dL)	36				29
Sodium (137 -145 mmol/L)	112	119	127	134	140
Potassium (3.5 - 5.0 mmol/L)	5.1	4.9	4.1	4.2	3.7
Calcium (8.4 – 10.2 mg/dL)			9.2		
Magnesium (1.7 – 2.4 mg/dL)			2.1		
Random Blood Glucose (mg/dL)	92		124		
Fasting Blood Glucose (mg/dL)		86			94
2 hrs post prandial Blood Glucose (mg/dL)		108			134
Aspartate transaminase(17-59 U/L)	28				
Alanine transaminase (21-72 U/L)	34				
Alkaline phosphatase (38-126 U/L)	133				
Serum albumin (3.5- 5.0 g/dL)	3.9				



**Fig. 1. MRI (T2 weighted sagittal image) showing the pituitary macroadenoma with suprasellar extension**



**Fig. 2. MRI (Post contrast coronal image) showing heterogeneously enhancing pituitary macroadenoma with compression of optic chiasma**

In a retrospective study of 14 cases and 79 published case reports conducted by Lewis and Smith, [1] it was found that the most common psychiatric disorders were depression (35%) followed by mania (31%), psychosis (14%), delirium (13%), and mixed states (6%). Lewis and Smith found that 73% of manic patients and 56% of depressed patients treated with steroids had psychotic symptoms [1]. Our patient was diagnosed to have Acute and Transient Psychosis, polymorphic type according to ICD-10.

The dose of glucocorticoids appear to be one of the most important risk factors for development of neuropsychiatric symptoms [6]. The Boston Collaborative Drug Surveillance Program [2] carried out in 1972 included 718 consecutive hospitalized patients receiving prednisone therapy. Psychiatric symptoms were reported in 1.3% of the patients receiving prednisone  $\leq$ 40 mg, 4.6% of those receiving 41-80 mg/day and 18.4% of those who received more than 80 mg of prednisone per day. Lewis and Smith [1] reported that 77% of patients developed psychiatric symptoms when prednisone doses of  $\geq$ 40 mg/day were used. The onset of corticosteroid-induced neuro-psychiatric symptoms may vary from within hours of initiation of treatment until after the cessation of therapy. Lewis and Smith [1] reported a median of 11.5 days, from initiation of steroids to onset of psychiatric symptoms (range: hours to 210 days).

These psychiatric symptoms described here are due to supraphysiological doses of glucocorticoid in patients without pre existing adrenal insufficiency. Our patient however developed psychosis after starting physiological steroid replacement following prolonged hypocortisolism.

Female gender has been implicated to be a risk factor for developing steroid induced neuropsychiatric complications [6]. In the study by Lewis and Smith [1], 68% of patients with psychiatric manifestation were women. There is no concrete evidence that a history of psychiatric disorders is a potential risk factor for steroid-induced neuropsychiatric effects [6].

Cognitive impairment as a result of steroid use is probably because of corticosteroids' effects on the hippocampus [6]. The hippocampus and the amygdala have high number of glucocorticoid receptors [8,9]. In patients receiving high-dose corticosteroids a reversible atrophy has been found in the hypothalamus and amygdala [10,11]. Hippocampal cell loss has been reported

in animals receiving glucocorticoids or subjected to prolonged stress [12]. Our patient however did not have cognitive dysfunction or memory loss and the MRI brain did not reveal any abnormality of the hippocampus.

Glucocorticoid acting on the receptor in the neurons lead to changes in the production of neurotransmitters (dopamine and serotonin) and neuropeptides (somatostatin, beta-endorphin) [6]. Altered concentrations of serotonin receptors at the synaptic cleft may also result in the mood symptoms found in corticosteroid-treated patients [8].

Acute psychosis in patients receiving physiological corticosteroid replacement is rare. The exact mechanism of this disorder is not clear. It has been suggested that long standing hypoadrenalism results in up-regulation of central glucocorticoid receptors [3]. Therefore, physiological doses of steroid result in a supra-physiological response in the neural pathways [3]. When hydrocortisone replacement is continued, there is gradual down-regulation of the receptors, and so the supraphysiological response is self-limiting and the psychiatric symptoms subside [3]. A few case reports have shown that patients with adrenocortical insufficiency have developed acute psychosis following hydrocortisone replacement.

Ur E et al. [3] reported a case of a 32 year old woman admitted with acute primary adrenocortical insufficiency with depressive symptoms. The patient was rehydrated with one litre saline and intramuscular hydrocortisone 100 mg 6 hourly was given for 24 hours, following which oral hydrocortisone 30 mg per day in divided doses was started. After 36 hours of oral therapy, the patient developed symptoms of acute mania, which subsided after treatment with oral pimozide 4 mg per day.

Mada S et al. [4] described a 72 year old lady with secondary adrenal insufficiency due to a large cystic pituitary mass. The patient was started on intravenous hydrocortisone, 50 mg once daily. Following 5 doses of intravenous hydrocortisone, the patient developed severe psychosis. The patient recovered after discontinuation of hydrocortisone for 48 hrs and treatment with haloperidol 2 mg/day.

Liu ES and Becker C [5] reported a case of a 48 year old male with panhypopituitarism due to pituitary non-secreting macroadenoma who

underwent transphenoidal resection of the tumour. Following surgery, the patient was started on IV hydrocortisone 50 mg BID. On the third post operative day the patient developed acute psychosis one hour after receiving the hydrocortisone infusion. On the next day the steroids were reduced to hydrocortisone 20 mg in the morning and 10 mg in the evening. The patient remained psychotic and the hydrocortisone replacement was stopped. The patient gradually recovered on the 7<sup>th</sup> post operative day.

Electrolyte imbalance may give rise to various psychological symptoms as well as psychiatric illness [13]. However, the acute episode in our patient began when the electrolytes were gradually improving. Rapid correction of hyponatremia can lead to osmotic demyelination syndrome [14]. In our patient, the rate of sodium correction was slow and the clinical picture was not consistent with the above syndrome.

Psychiatric disorders have been found to be an important presenting complaint in patients with long-term adrenal insufficiency [15]. Our patient however did not have any psychiatric symptoms on admission to the hospital and developed psychosis only after initiating treatment.

Our case is very much similar to that reported by Mada S et al. [4]. In both instances psychosis following steroid replacement improved after temporary discontinuation of hydrocortisone along with treatment with antipsychotics.

#### 4. CONCLUSION

This case report once again highlights the fact that patients with prolonged hypocortisolemia may develop acute psychosis even on physiological replacement doses of corticosteroid and need to be closely monitored. To the best of our knowledge, this is the first case reported from India. Further research is needed to explain the exact mechanism of this phenomenon.

#### CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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