Cushing’s syndrome manifesting as chronic insomnia caused by ad-renal cortical adenoma with incidental pituitary microadenoma

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Case Reports

Cushing's syndrome manifesting as chronic insomnia caused by adrenal cortical adenoma with incidental pituitary microadenoma

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Abstract

Background: Cushing's syndrome is a condition caused by excessive glucocorticoid with insomnia as one of its neuropsychiatric manifestation. Cushing's syndrome may be caused by excessive adrenocorticotropin hormone (ACTH-dependent), for example from ACTH producing pituitary tumors, or by overproduction of cortisol by adrenocortical tumors. In this report, we presented a case with Cushing's syndrome manifesting as chronic insomnia with adrenal cortical adenoma and pituitary microadenoma.

Case presentation: A 30-year-old woman was consulted from the Neurologic Department to the Internal Medicine Department with the chief complaint of insomnia and worsening headache for 6 months prior to the admission. She had undergone head MRI and abdominal CT scan previously and was found to have both pituitary microadenoma and left adrenal mass. From the physical examination she had clinical signs of Cushing's syndrome like Cushingoid face and purplish striae on her stomach. Midnight cortisol serum examination was done initially and showed high level of cortisol. High dose dexamethasone suppression test or DST (8 mg overnight) was later performed to help determine the main cause of Cushing's syndrome. The result failed to reach 50% suppression of cortisol serum, suggestive that the Cushing's syndrome was not ACTH-dependent from the pituitary but potentially from overproduction of cortisol by the left adrenal mass. Therefore, left adrenalectomy was performed and the histopathological study supported the diagnosis of adrenal cortical adenoma.

Conclusion: Chronic insomnia is a very important symptoms of Cushing's syndrome that should not be neglected. The patient had both microadenoma pituitary and left adrenal mass thus high dose DST test (8 mg overnight) needed to be performed to differentiate the source of Cushing's syndrome. The result showed only little suppression therefore the pituitary microadenoma was not the source of Cushing's syndrome and more suggestive from the adrenal etiology.

Keywords: Cushing's syndrome; insomnia; adrenal cortical adenoma; pituitary microadenoma; dexamethasone suppression test
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INTRODUCTION

Cushing's syndrome is described as a condition caused by high level of glucocorticoid hormone in the blood. The condition may be caused by over secretion of

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endogenous cortisol by the adrenal gland or administration of exogenous glucocorticoid agents meant for treatment of certain diseases[1]. Endogenous hypercortisolism can be further classified into ACTH-dependent Cushing's syndrome, where the adrenal gland secretes excessive amount of glucocorticoid hormone under the stimulation of ACTH overproduction commonly from pituitary tumor or ectopic ACTH production, and ACTH-independent Cushing's syndrome which caused by adrenal hypersecretion of cortisol, commonly happens in benign adrenocortical adenoma[2]. Cushing's syndrome, aside from the usual signs and symptoms such as Cushingoid face and purple striae, can also manifest in neuropsychiatric symptoms which can be mistakenly diagnosed as another disease. Cushing's syndrome patients appear to manifest, at minimum, the triad of irritability, insomnia, and decreased libido and may persist as the disease progresses[3]. These neuropsychiatric symptoms should not be ignored and need to be explored holistically from every aspect in order to establish the right diagnosis.

The diagnosis of Cushing's syndrome can be made initially through several tests, for examples Urine Free Cortisol (UFC), late-night salivary cortisol, and dexamethasone suppression test or DST (overnight 1-mg or longer low-dose). Giving a supraphysiological dose of exogenous glucocorticoid in healthy population suppresses ACTH production that subsequently decreases cortisol secretion. Patient with endogenous Cushing's syndrome of any reason will fail to achieve this suppression when low dose of exogenous glucocorticoid is given[4,5]. Patient with ACTH-dependent Cushing's syndrome commonly caused by pituitary microadenoma, also known as Cushing's disease, overnight 1-mg DST will not suppress the cortisol level but it will be suppressed by overnight 8 mg-high dose DST[6]. Decrease of cortisol level by 50% from the baseline level after the administration overnight 8-mg dexamethasone supports the diagnosis of ACTH-dependent Cushing's syndrome. The failure to reach the 50% suppression of cortisol level after overnight 8-mg DST suggests ACTH-independent Cushing's syndrome possibly from adrenal tumors[6,7]. In this case report, we presented a of 30-year-old woman with Cushing's syndrome manifesting as chronic insomnia with pituitary microadenoma and adrenal cortical adenoma, conditions which could both contribute to Cushing's syndrome but very different in origin cause and later the management.

CASE REPORTS

A 30-year-old woman consulted from the Neurologic Department to the Internal Medicine Department with a chief complaint of insomnia and aggravating headache since 6 months prior to the admission. She also had difficulty to concentrate and muscle weakness. She reported that she gained 5 kg body weigh in a month.

She had visited some hospitals and doctors before and undergone medical check-ups but no abnormality was found. She was given sleeping medications but the symptoms weren't improved. She denied any history of consumption of over the counter drugs or herbal medicines. The physical examination showed she was overweight with the BMI of 27,34 kg/m^2 and had signs of hypercortisolism such as Cushingoid face (Figure 2) and reddish-purple striae (Figure 1) on her stomach. The vital sign was within the range of hypertension stage 1.

She had previously undergone examinations such as EEG, polysomnography, head MRI (Figure 5), and abdominal CT scan (Figure 6). EEG examination showed diffuse low voltage pattern on both brain hemisphere. Polysomnography examination revealed abnormal sleep architecture and she couldn't reach REM phase. Insomnia was confirmed with sleep efficiency was only 71%. She also had mild OSA (Obstructive Sleep Apnea) with AHI (Apnea-Hypopnea Index) 8,7. Oxygen saturation was quite low with level of 93% during sleep. A head MRI examination revealed a solid lesion on pituitary gland suspected of pituitary microadenoma with the diameter of 0,2 cm but no sign of increased intracranial pressure was found. The abdominal CT-scan revealed a solid left adrenal mass with the diameter of approximately 2,7 cm. Midnight cortisol serum was initially performed and showed elevated cortisol serum with the level of 19,8 μg/dL (normal level 2,9 – 17,3 μg/dL).

The patient had both pituitary microadenoma and left adrenal mass that could contribute to the development of endogenous Cushing's syndrome thus high dose dexamethasone suppression test (8 mg overnight) was performed to distinguish the main cause of Cushing's syndrome. The test resulted the failure to reach 50% suppression of serum cortisol from baseline level of 19,8 µg/dL to 18,1 µg/dL after the administration of overnight 8-mg dexamethasone. This concluded the Cushing's syndrome in the patient was not ACTH-dependent from the pituitary microadenoma and more implicative to the overproduction of cortisol by the left adrenal mass. The patient underwent left adrenalectomy and was treated with intravenous hydrocortisone 100 mg/day before the surgery to prevent adrenal insufficiency.

Post-adrenalectomy serum cortisol was lower than 0,8 μg/dL without any sign and symptom of adrenal insufficiency. The intravenous hydrocortisone 100 mg/day was continued until 3 days after the surgery and switched to oral hydrocortisone 20 mg/day in the morning. Patient was discharged from the hospital 7 days after the surgery. Oral hydrocortison 20 mg/day in the morning was continued until 1 month following the surgery. Histological analysis of the left adrenal mass showed diffuse cells with monotone oval nucleus and no sign of malignancy was present. Immunohistochemistry staining profile result showed Synaptopshysin was positive, Chromogranin-A was negative, NSE was negative, Calretinin was positive, and Ki67 was positive in less than 2% around the perinuclear area, supproted the diagnosis of adrenal cortical adenoma. The signs and symptoms of hypercortisolism, such as Cushingoid face and insomnia, were improved within 9 months after the surgery (Figure 3, Figure 4).

DISCUSSION

Cortisol is the main glucocorticoid hormone produced by the adrenal cortex and very important for maintaining most physiological state. The cortisol secretion is controlled by illustration of a hypothalamic-pituitary-adrenal axis (HPA axis). High level of cortisol whether caused by the excessive use of exogenous glucocorticoids (iatrogenic) or overproduction of endogenous cortisol can cause adverse effects on organ systems, a condition defined as Cushing's syndrome[2].

The incidence of Cushing's syndrome is 0,7-2,4 per million population per year. ACTH-independent Cushing's syndrome makes up for 15%–20% of Cushing's syndrome in adults; in which 90% are caused by unilateral adrenal tumors[4,8].

Cushing's syndrome has unique manifestations which are quite distinctive, for examples purple striae, facial plethora, proximal muscle weakness, easily bruising without evident of trauma, and unexplained osteoporosis[4,9]. These manifestations of Cushing's syndrome, though, can be diverse by individuals. The patient in our case first consulted from Neurologic Department with the chief complaint of insomnia and headache. She already went to consult with several doctors and hospitals before and was only given sleeping medications but didn't show any improvement. With thorough physical examination she actually showed several signs of Cushing's syndrome such as purple striae, Cushingoid face, and muscle weakness, which could allude establishing the diagnosis.

Insomnia is a sleep disorder described by problems in falling or staying asleep or having restorative sleep accompanied by daytime impairment. There are suggestions that HPA axis disturbance and elevation of evening cortisol are contributive to the development of insomnia. Although there are still limited number of studies, changes of polysomnography in Cushing's syndrome have been apparent thus proving the adverse effect of high level of glucocorticoid on sleep architecture. The changes may include reduction of Slow Wave Sleep or SWS, disruption of sleep continuity (increased sleep latency, enhanced waketime) and disturbance in Rapid Eye Movement or REM (shortened REM latency, elevated REM density). Oddly enough, these sleep disturbances are indistinguishable from those existing in major depression[10].

Cortisol decreases REM phase in sleep and excessive concentrations in blood can cause insomnia and strikingly increase or decrease mood[11]. Cushing syndrome may also present as psychiatric and cognitive disorders in up to 70%–85% of the patients. Depression, emotional lability, and irritability are the most frequent presentations; anxiety, panic attacks, acute psychosis, mania, paranoia, and suicidal tendencies are uncommon[12]. Reduced in brain volume, especially the hippocampus, has been linked to the high level of cortisol, and associated with learning disability and short-term memory impairment. This psychiatric and cognitive manifestations may improve after remission but many are still persist[5,13].

Patient suspected of ACTH-dependent Cushing's syndrome should be evaluated with a pituitary imaging with the MRI. However, ACTH-producing pituitary tumors can be quite hard to be detected even with advanced MRI methods because they commonly present as small lesions[14]. Furthermore, around 10% of healthy and normal population may possess incidental pituitary lesions equal to 6 mm in size[15]. Therefore, diagnosing ACTH-dependent Cushing's syndrome can be quite arduous. Head MRI and abdominal CT-scan results showed the patient had pituitary microadenoma and left adrenal mass respectively. Both conditions can lead to excessive cortisol level which present as Cushing's syndrome in this patient.

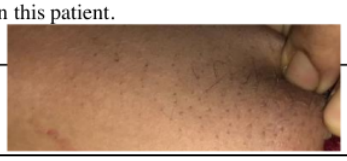

Figure 1. Reddish purple striae

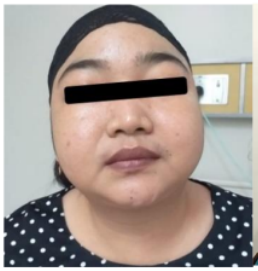

Figure 2. The patient's face before the treatment

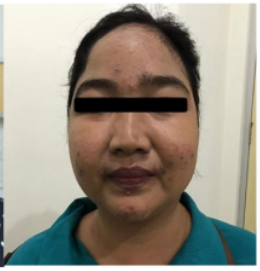

Figure 3. The patient's face 2 months after the left adrenalectomy

Figure 4. The patient's face 9 months after the left adrenalectomy

Dexamethasone suppression test or DST is one of the tests recommended as initial examination for diagnosing Cushing's syndrome. DST works on the principle of glucocorticoid suppressibility in adrenal function through the suppression mechanism of ACTH production by the pituitary. The test can be done either in overnight 1-mg test or longer and lower dose (2 mg/day over 48 hours). The overnight 1-mg test is a simple and can be done in outpatient setting. One mg dexamethasone is usually given around 11 pm, and cortisol level is evaluated between 8-9 am the following morning. Experts have recommended a limit for suppression of the post dexamethasone serum cortisol to lower than 1,8 μg/dl to attain higher sensitivity of more than 95%[4,5].

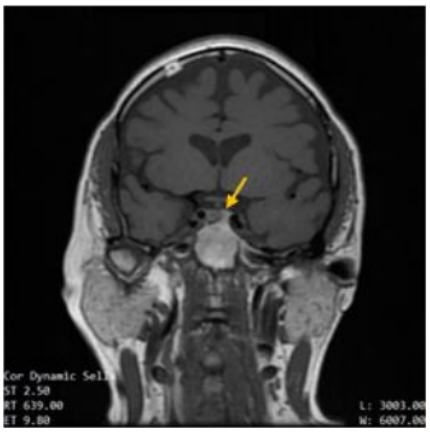

Figure 5. Head MRI

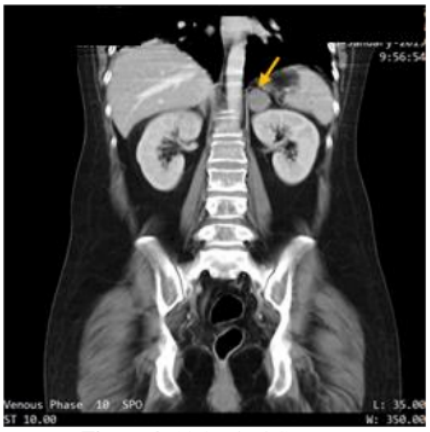

Figure 6. Abdominal CT-scan

However patient with ACTH-dependent Cushing's syndrome, overnight 1-mg DST will not suppress the cortisol level and particularly need higher dose with overnight 8 mg high dose DST[6,16]. Reduced cortisol level by 50% from the baseline after the overnight 8 mg high dose DST supports the diagnosis of ACTH-dependent Cushing's syndrome. The failure to reach the 50% reduction of cortisol after overnight 8-mg DST suggests ACTH-independent Cushing's syndrome which may arise from adrenal tumors[6,7]

In this patient, midnight cortisol serum examination initially performed and showed high level of cortisol. Apparently, from the previously done imaging examinations she was found to have pituitary microadenoma and left adrenal mass that could both become the possible sources of Cushing's syndrome. Overnight 8 mg high dose DST was later performed to distinguish the main cause of Cushing's syndrome in this patient. The result showed failure to reach 50% of decrease of cortisol serum from the baseline. This result implied that the source of Cushing's syndrome was not ACTH-dependent from the pituitary microadenoma and possibly ACTH-independent from the left adrenal mass. Left adrenalectomy was done to remove the source of excessive cortisol level and hydrocortisone therapy was given to prevent adrenal insufficiency. The histological study and immunohistochemistry staining of the adrenal mass supported the pattern of adrenal cortical adenoma. Her signs and symptoms, including the Cushingoid face and the insomnia, were improved gradually within 9 months after the surgery.

CONCLUSION

Cushing's syndrome may present as neuropsychiatric disorders, as in this case being chronic insomnia, and should be explored thoroughly accompanied by adequate physical examination to establish the proper diagnosis. High dose dexamethasone suppression test (8 mg overnight) can help distinguishing the main etiology of Cushing's syndrome in this case where the patient had more than one possible source of cortisol overproduction. The lack of cortisol suppression after high dose dexamethasone administration concluded the source of cortisol excess was not ACTH-dependent from the pituitary microadenoma and indicatory of adrenal etiology.

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FINAL GRADE

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GENERAL COMMENTS

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