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Cushing's Disease with Cognitive Impairment Manifesting Post-Resection: A Case Report

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Abstract. In 2007, a 61-year old woman presented with clinical features of Cushing's Disease Syndrome. She underwent a diagnostic work up and was diagnosed with adrenocorticotropic hormone -producing pituitary adenoma, which was subsequently removed. Following surgery, the patient showed little recovery from her presenting neuro-cognitive symptoms, raising the question as to the effect of long term steroids on cognition, mood and behavior, and the potential for reversal of these effects.

Keywords: Cushing's disease, glucocorticoids, cognitive impairment.

Introduction

Hypercortisolemia is the state of biochemical excess of glucocorticoids. This may be classified into adrenocorticotropic hormone (ACTH)-dependent, in which there is an excessive ACTH production either from the pituitary gland (Cushing's Disease), or from ectopic sources. Thus, an excessive production of glucocorticoids from the adrenal glands with loss of regulation by

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ACTH, and loss of diurnal variation[1] or due to supraphysiologic doses of exogenous steroids[2]. Cushing's Disease accounts for approximately 70% of all cases of endogenous Cushing's Disease[2].

Clinical manifestations of glucocorticoid excess are many. However, the effect of hypercortisolism on behavior and cognition is less recognized. It is a highly variable manifestation of this disorder. Depression, psychosis, and dementia have all been reported as symptoms of cortisol excess[3].

This report presents a case of persistent depression and cognitive impairment, mainly executive dysfunction, due to ACTH-dependent Cushing's Disease.

Case Report

In 2007, a 61-year old retired registered nurse was presented to us with a three-year history of muscle weakness, fatigue, weight gain mainly in the truncal area and the face, spontaneous bruising, hirsutism, and a new diagnosis of type-2 diabetes. Past medical history was significant for quiescent ulcerative colitis, diet-controlled type-2 diabetes, osteopenia with subsequent history of multiple traumatic fractures, dyslipidemia, right mastectomy for ductal carcinoma in situ, and macular degeneration in the right eye. Review of her medications did not reveal chronic use of exogenous steroids. She did report requiring two doses of steroid enemas within the preceding five years. There was also a history of depression treated with citalopram (20 mg) at bedtime.

On physical examination, the patient had multiple physical manifestations suggestive of hypercortisolism, specifically; elevated blood pressure of 150/85, fullness in the face, mild dorsocervical fat pads, proximal myopathy in the lower limbs, noted by her having difficulty standing from a sitting position without using her hands for support. No proximal myopathy was detected in the upper limbs. She also had thin skin and multiple ecchymosis on the arms and legs that she indicated occurred spontaneously. There was evidence of truncal obesity; however she did not have abdominal striae. The rest of the physical examination was unremarkable.

Initial lab investigations revealed a serum cortisol at 1200 of 670 nmol/L, which was just within normal range [normal serum cortisol levels: 8 AM to noon: 5-25 mcg/dL (138-690 nmol/L)][4]. A diagnosis of Cushing's Disease was suspected but not confirmed at that time. Subsequently, the patient performed two 24-hr urine collections (reported as being adequate collections) for measurement of 24-hr urinary free cortisol. The highest reported value for her was 861 nmol/day (normal in that laboratory 189 nmol/day), indicating more than four-fold increase in 24-hr urinary cortisol, and diagnostic of Cushing's syndrome[5]. ACTH was also measured on two occasions; values of 6.9 and 7.7 (normal range in the lab 2.2 and 13.3 pmol/L) were reported, indicating lack of suppression by the elevated cortisol levels, consistent with a diagnosis of Cushing's Disease. A 1 mg dexamethasone suppression test showed lack of suppression of her 8 am cortisol with 1 mg of dexamethasone at 11 pm the preceding night, and an 8 mg dexamethasone suppression test was undertaken, showing a decrease in urinary cortisol by 87% and serum cortisol by 60%, indicating that the pituitary gland was the source of the elevated ACTH and not an ectopic source. Imaging using MRI with gadolinium showed larger bulk in the left side of the pituitary gland and deviation of the stalk to the right, with the post-contrast scan showing a 3.5 mm area of higher T2 signal in the left posterior region suggestive of a pituitary microadenoma on the left side. Inferior petrosal sinus sampling was not performed at that time as the management plan would not have changed.

Following discussion with an interdisciplinary team of Endocrinologists, Radiologists and Neurosurgeons, surgical resection was recommended. Consent was obtained from the patient, and surgery was performed and was uneventful. Pathology report confirmed an ACTH-producing pituitary adenoma.

Post-operatively, the endocrinology team follows the patient closely. Initially, she recovered well from the surgery, while on replacement dose of 30 mg hydrocortisone in the morning and 20 mg in the evening. However, one week postoperatively she presented to the emergency department with weakness, nausea and vomiting. She was treated with IV hydrocortisone, with symptomatic response, and

was discharged home on hydrocortisone (50 mg twice daily), with a slow taper planned. Over the subsequent months, it was evident that the patient had adrenal insufficiency requiring life-long replacement with hydrocortisone. She also suffered a stroke-like illness, with imaging revealing diffuse deep periventricular and subcortical white matter changes compatible with chronic ischemic changes, as well as lacunar infarcts in the anterior aspect of the internal capsules bilaterally. These were not felt to be acute at the time.

Cognitive Status

Eighteen months following the surgery, the patient was referred to a geriatrician for assessment regarding cognitive decline. During the assessment, a history of lack of concentration, difficulty with spelling, lack of attention to detail and forgetfulness was brought forth by the patient and her family. These symptoms were attributed, at least in part, to the persistent hypercortisolism she had been experiencing for a number of years, and were expected to improve over time postoperatively, but did not, and may have worsened. Along with the symptoms described, there were also behavioral changes (irritability, apathy, social isolation and impulsivity) and notable functional decline. On examination, she obtained a score of 26/30 on the Montreal Cognitive Assessment (MOCA) test, losing 2 points on recall, 1 point on placement of numbers and hands on clock-drawing. She scored 7/15 on the geriatric depression scale. The overall impression was of a lady with progressive cognitive decline involving multiple domains including language, memory and executive dysfunction, affecting her function. As such, she met clinical criteria for a dementing illness.

The patient underwent further neuropsychological evaluation, which concluded that while she did have evidence of executive dysfunction, this was neither due to a dementing illness nor to the lacunar infarcts noted on imaging. It was suggested that persistent cognitive decline was most likely to related prolonged hypercortisolism, however, lack of improvement post-resection of the tumor was unusual. It was also suggested that some of her symptoms

may be related to depression, anxiety and sleep disturbance, and further referrals were made.

A referral to a psychiatrist confirmed the above assessment, and no additional treatments were added. The hope was that her cognitive and functional symptoms would resolve or at least improve gradually post-resection of the ACTH secreting tumor. Unfortunately, despite ongoing follow-up for at least one year, no improvement was noted.

Discussion

The presence of an ACTH-producing pituitary adenoma leads to elevated levels of cortisol in humans. Cortisol is known to affect receptors throughout the body, including the nervous system. In the brain, there are two types of cytoplasmic receptors, namely mineralocorticoid (type I) and glucocorticoid (type II) receptors, which have different brain distribution and functional pattern. These receptors mediate the hormonal activity by either stimulation or suppression of target gene transcription, depending on cell type[6,7]. Normally, cortisol is tightly regulated via a feedback mechanism between the hypothalamus, pituitary gland and adrenal glands; when cortisol levels increase, CRH and therefore ACTH undergo negative feedback, which then decreases ACTH stimulation of the adrenal glands to synthesize and release cortisol, ultimately causing cortisol levels to go down to normal values[8]. Abnormal exposure of the nervous system to glucocorticoids has been implicated in several disorders, such as Alzheimer's Disease and depression[9]. Indeed, in Dr. Harvey Cushing's Disease initial description of this condition he describes symptoms of difficulty in concentrating, insomnia, visual disturbances, and 'fits of irritability that alternate with periods of depression[3]. By examining the specific areas of memory impairment, it has been suggested that the areas in the brain where type II receptors are more abundant are the areas mostly affected by glucocorticoid excess, namely the neocortex and the hippocampus[3,10]. Starkman *et al.*[11] noted that individuals with Cushing's Syndrome exhibited a decrease in hippocampal formation(HF) volume as measured by MRI, as well as variability in severity of learning and memory dysfunction as measured by

neuropsychologic testing. An association between reduced HF volume and lower scores on verbal learning and memory tests were also noted. Interestingly, an inverse correlation between HF volume and cortisol levels was noted. Others observed that there was some recovery of hippocampal size after treatment of Cushing's syndrome, directly proportional to the degree of lowering of serum cortisol levels[3,12,13].

Earlier work postulated mechanisms causing the decrease in hippocampal size, *i.e.,* Sapolsky *et al.*[14], suggested that it was due to loss of neurons. Exposure to high levels of glucocorticoids also reduces denditric length and branching morphology of adult hippocampal pyramidal cells according to Woolley *et al.*[15]. DeKosky *et al*.[16] found that elevated glucocorticoid levels, through inhibition of compensatory axodendritic sprouting, also impair neuronal capacity to recover from injury. Prolonged exposure to high levels of glucocorticoids is associated with impaired hippocampal long-term potentiation[17,18] and can decrease hippocampal synaptic plasticity[19]. It has also been documented that elevation of cortisol causes cerebral atrophy and ventricular enlargement[20-22].

Conclusion

Hypercortisolemia affects the body on many different levels. While many of the changes, such as insulin resistance and hypertension are for the most part reversible, some effects may not be completely reversible. It is unusual for any changes to worsen after treatment of the underlying condition, and while our patient's cognitive and mood changes may be attributed to multiple causes, an important contributor was the hypercortisolemic state, which was prolonged. Further research needs to focus and determine the time of resolution of cognitive and mood effects of exposure to high steroid levels once the exposure ceases is warranted.

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تقرير عن حالة تغير معرفي لم يتم علاجه بالرغم من استئصال ورم مسبب لداء كوشينغ

هلا هشام موصلي

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المستخلص. في عام ٢٠٠٧ تقدمت امرأة عمرها ٦١ عاماً بأعراض مطابقة لمرض كوشينغ. خضعت المريضة لعدة تحاليل و تم تشخيصها بمرض كوشينغ سببه ورم حميد صغير في الغدة النخامية و من ثم تم استئصال الورم. لم تظهر المريضة تحسناً واضحا بعد استئصال الورم في وظائفها المعرفية مما جعلنا نتساءل عن دور ارتفاع هرمون الكورتيزول المرضي في المسبب للإختلال المزمن للوظائف المعرفية ومدى احتمالية علاج هذا الاختلال.