CASE REPORT

Immune Rebound: Multiple Sclerosis after Treatment of Cushing's disease

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ABSTRACT

High cortisol level in endogenous Cushing's syndrome suppresses the immune system and after treatment there may be an over activity of immune reaction leading to autoimmune diseases mostly thyroid and rheumatologic disorders. This is the second reported case of multiple sclerosis developing after treatment of Cushing's syndrome. A 42-year old man is reported who presented with bone fracture and osteoporosis and diagnosed with Cushing's disease. Six months after surgical treatment of his pituitary adenoma, he developed progressive multiple sclerosis. We conclude that after treatment of endogenous Cushing's syndrome, the patients should be watched for development of autoimmune disorders including those affecting the central nervous system.

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Keywords: Multiple Sclerosis, Cushing Disease, Autoimmune Diseases

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INTRODUCTION

Glucocorticoids have profound suppressive effects on the immune system. In Cushing's syndrome elevated cortisol level suppresses the immune system and after treatment and resolution of hypercortisolemia there may be an overshooting of the immune reaction leading to development of autoimmune diseases (1). There have been reports of development or exacerbation of autoimmune diseases after treatment of endogenous Cushing's syndrome. These diseases mostly included autoimmune thyroid diseases and rheumatologic disorders (1). Here we present the second reported case of multiple sclerosis occurring after treatment of Cushing's syndrome.

The Case

In September 2010, a 42-year old man had a wrist fracture after falling down. X-Ray of the wrist showed osteopenia; bone densitometry revealed osteoporosis and therefore he was referred to endocrine clinic for evaluation of its cause. History of the patient was significant for the presence of weight gain and easy fatigability. In physical examination, blood pressure was 150/95 mmHg, he had mild plethoric face, and abdomen was slightly protruded with purplish striae. There was no proximal muscle weakness or atrophy. Neurologic examination was normal. He was evaluated for Cushing's syndrome and lab data are shown in Table 1.

Table 1. Initial laboratory results of the patient.

Hemoglobin g/dL	16.8
White blood cell per µL	9800 PMN:85%,Lymphocyte:15%
Blood urea nitrogen mg/dL	15
Creatinine mg/dL	1.3
Sodium meq/L	138
Potassium meq/L	3.8
Fasting blood sugar mg/dL	118
Basal cortisol µg/dL	21
Cortisol after 1mg dexamethasone Suppression test µg/dL	12.5
24 hour urinary free cortisol(normal<50 µg)	184
Cortisol after standard low dose dexamethasone Suppression test µg/dL	12
Cortisol after high dose dexamethasone Suppression test µg/dL	7
ACTH (normal:8-60 pg/mL	64

Thyroid function tests and other pituitaryhormone levels were normal. According to laboratory data he was diagnosed as a case of Cushing's disease. Pituitary MRI showed a 7 mm adenoma in right side of pituitary (Figure 1).

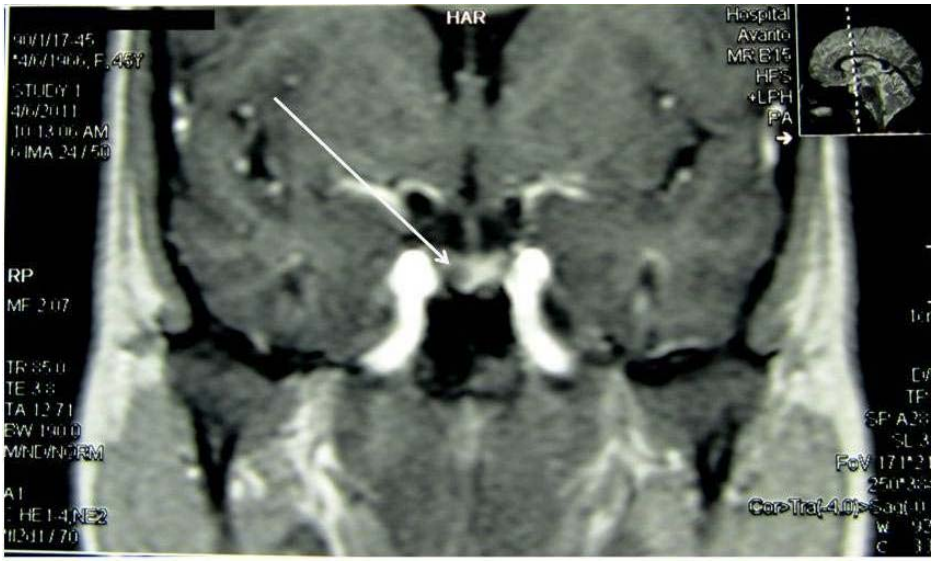

Figure 1. MRI of pituitary gland shows an adenoma in right side.

Trans sphenoidalsurgery was performed. The pathology report was basophilic pituitary adenoma. Four days after surgery, his basal cortisol was 2.0 µg/dL and he was prescribed prednisolone 30 mg/day to be tapered gradually to5 mg daily. Three months later he referred with good general condition. He had discontinued prednisolone after two weeks. His basal morning plasma cortisol was 9 µg/dL and 24-hour urinary cortisol was 38 µg. Four months later, he referred with one week history of blurred vision, difficulty in walking and severe vertigo. He reported a similar but milder attack lasting a few days one month previously. In initial evaluation there was weakness and spasticity of lower extremities and his gait wasataxic.

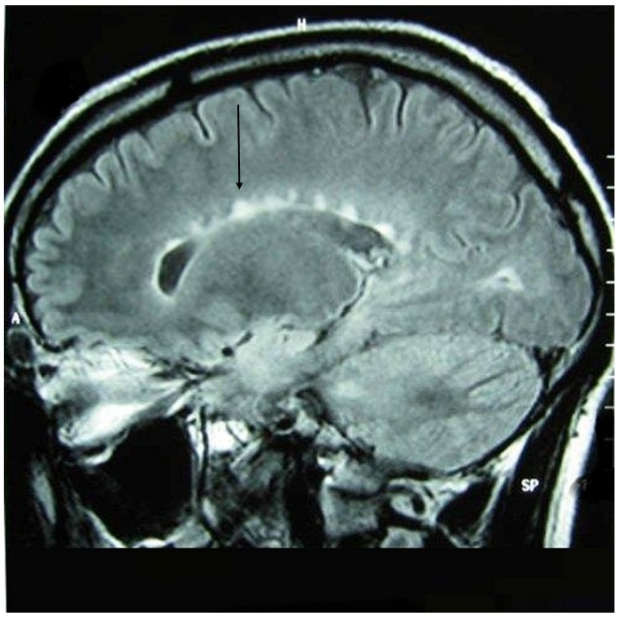

Figure 2. Brain MRI, parasagittal view shows plaques in periventricular area.

He was referred to the neurologist and was admitted in neurology ward. According to neurologist note, he also had abnormal cerebellar tests and hyperreflexia in legs. Brain MRI showed multiple plaques in periventricular area (Figure 2).
Visual evoked potential test was abnormal. In cerebrospinal fluid analysis there were 12 lymphocytes per microliter, protein was 32 mg/dL and sugar was 75 mg/dL. There were 8 oligoclonal bands in cerebrospinal fluid. Serum had 4 oligoclonal bands. IgG index was 1.6 (normal<0.66). In order to rule out other diseases with similar neurologic manifestations screening tests for presence of human immunedeficiency virus infection, anti-phospholipid syndrome, Behcet disease, systemic lupus erythematosus, and celiac disease were done and the results were negative. Serum vitamin B12 level was 650 pg/ml (normal: 280-900). He was diagnosed and treated as a case of multiple sclerosis. Despite treatment, the course of his disease was progressive and he was unable to walk after two years.

DISCUSSION

Cortisol, which is increased in endogenous Cushing's syndrome, has potent immune modulatory effects. It has suppressive effect on pro-inflammatory T-cells and stimulate regulatory T cells. It also causes apoptosis of auto-reactive B cells (2). The effect of glucocorticoids is mainly on T lymphocytes by inhibition of production of interleukin (IL)-1 and IL-2 by monocytes and activated T cells (2). After treatment of Cushing's syndrome and resolution of hypercortisolemia, there may be over activity of immune system. Transient thymus hyperplasia can be seen after treatment of Cushing's syndrome (1). It mimics what happens in post partum period. During pregnancy there is immune suppression due to increased level of cortisol and other immune suppressive factors followed by postpartum immunologic rebound and development or exacerbation of autoimmune diseases (3). The immunologic rebound has been reported in both ACTH dependent and independent types of Cushing's syndrome (4).There are several case reports of exacerbation or development of autoimmune hypothyroidism and Graves' disease (4,5), rheumatoid arthritis (6), systemic lupus erythematosus (7), sarcoidosis, and psoriasis (1) after surgical treatment of Cushing's syndrome. In one study the frequency of positive thyroid autoantibodies increased from 26.7% to 86.7% after treatment of Cushing's syndrome. In that study the mean interval between resolution of hypercortisolemia and diagnosis of primary thyroid disease was 9.8 and range of 2-18 months (4). In another study 40% of patients with Cushing's syndrome developed anti-thyroid antibodies 6 months after treatment (8). Thyroid diseases are the most frequent autoimmune disorder occurring after treatment of Cushing's syndrome. Our patient developed progressive multiple sclerosis about 6 months after treatment of his disease and this time interval favors a cause and effect relation between them. Too rapid discontinuation of prednisolone by the patient may be a factor. This is the first report of occurrence of multiple sclerosis after treatment of Cushing syndrome by surgical removal of a pituitary adenoma. Markou *et al.* reported a woman who developed multiple sclerosis 6 months after the removal of an adrenal adenoma, which was producing cortisol, aldosterone and androgen (9). Another author has reported a fatal case of disseminated encephalomyelitis (ADEM) which is an autoimmune demyelinating disease in a 34 years old woman, four months after treatment of Cushing's disease (10). This disease

has some similarities with multiple sclerosis. Multiple sclerosis is a multifocal demyelinating disease which is caused by autoimmune reaction to self antigens in the central nervous system. Both humoral and cell mediated immunities are involved in the disease process. The diagnosis of multiple sclerosis as in our case is based on the presence of neurologic symptoms and signs, which are disseminated in space and time, characteristic radiologic findings, presence of oligoclonal bands in cerebrospinal fluid and abnormal visual evoked responses (11). The course of autoimmune thyroid and rheumatologic diseases developing after treatment of Cushing's syndrome is generally mild (1), but as illustrated in our case and that reported by Chevalier *et al.* (10), in cases with central nervous system involvement the disease course can be aggressive. We conclude that after treatment of endogenous Cushing's syndrome, the patients should be watched for development of autoimmune disorders including those affecting central nervous system.

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