Cushing’s, Dilated Cardiomyopathy and Stroke: Case Report and Literature Review

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Abstract
Dilated cardiomyopathy (DC) is a rare complication of Cushing’s syndrome. Hypertension and coronary artery disease tend to persist even after treatment of source of hypercortisolism as evidenced by previous studies. Based on a few case reports, Dilated Cardiomyopathy appears to be completely reversible with treatment of Cushing’s. We suggest that, in patients with idiopathic dilated cardiomyopathy, Cushing’s syndrome should be considered in the differential diagnosis. In patients with clinical features of Cushing’s, appropriate screening tests for Cushing’s should be carried out, which are inexpensive, non-invasive and readily available.

Résumé
La myocardiopathie dilatée est une complication rare du syndrome de Cushing. Comme le démontrent les recherches antérieures, l’hypertension et la coronaropathie tendent à persister même après un traitement visant l’origine de l’hypercortisolémie. Or, plusieurs observations cliniques semblent indiquer que la myocardiopathie dilatée serait complètement réversible lorsqu’on traite un syndrome de Cushing. Nous proposons que le syndrome de Cushing soit un diagnostic différentiel envisagé chez les patients présentant une myocardiopathie dilatée idiopathique. Chez les patients présentant des caractéristiques cliniques du syndrome de Cushing, des tests de dépistage appropriés devraient être effectués, d’autant plus que ces tests sont peu coûteux, non effractifs et facilement disponibles.
Case Report

A 29-year-old male was admitted in our hospital under the cardiology service for a trans-esophageal echocardiogram after having a left middle cerebral artery stroke resulting in aphasia and mild right sided weakness. CT and MRI scan of the head showed findings consistent with a left sided infarct (Figure 1). A transthoracic echocardiogram performed after the stroke was consistent with dilated cardiomyopathy with ejection fraction of 25% (Figure 2) One year prior to the current admission he was diagnosed with diabetes and hypertension. Other issues included obesity of rapid onset, and dyslipidemia.

In view of a suspected cardioembolic stroke, the patient was anticoagulated with warfarin. Cardiac monitoring on the ward and a subsequent 48 hour holter monitor did not show any evidence of atrial fibrillation. He was also given appropriate therapy for congestive heart failure. The endocrinology service was consulted for management of diabetes. Findings upon physical examination were consistent with possible Cushing’s Syndrome (Figure 4,5). Further investigations showed a 24 hour urine cortisol level of 702 nmol (normal <230 nmol/L); am cortisol after 1mg dexamethasone suppression was 748 nmol/l (normal <50 nmol/l), ACTH<5ng/l(normal 10-80 ng/l), Salivary cortisol 11 pm -30.4 nmol/l (normal <2.8 nmol/l). CT Adrenal glands showed a large left adrenal mass consistent with an adenoma (Figure 3). Subsequently, the patient underwent unilateral adrenalectomy. Cortisol replacement was started to avoid adrenal crisis due to suppression of the contralateral adrenal gland. The patient was discharged home, and follow up was arranged in the Endocrinology and Stroke Prevention Clinic.

Over the next few months the patient was followed up in the stroke rehabilitation clinic resulting in marked improvement in speech and right sided weakness. A subsequent transthoracic echocardiogram after 5 months showed normal size of left ventricle and an ejection fraction of 50-55% (Figure 4). Warfarin was discontinued and the patient was started on aspirin. There was gradual improvement in his glycemic control with normalization of hba1c in 5 months. Therapy for diabetes was discontinued. Features of Cushing’s including red striae and obesity continue to improve.
**Discussion**

Endogenous CS is a rare condition with approximated incidence of 2-3/million.\(^1\) Exogenous/iatrogenic Cushing's is presumed to be more common than endogenous Cushing's. Increased Cardiovascular Risk related to CS is an established entity.\(^2\) Patients with CS have increased cardiovascular morbidity.\(^3\) Various studies indicate that cardiovascular risk remains elevated even after treatment of Cushing's.\(^4\) In contrast to hypertension and coronary artery disease, which are known to be more prevalent and tend to persist even after treatment of Cushing's syndrome, DC is a rare complication which appears to have a favorable outcome with treatment of Cushing's syndrome.

DC is a rare but significant complication of CS. DC is a potentially curable complication, after treatment of Cushing's.

Patients with CS have twice the mortality rate compared to controls. Studies have shown that patients with CS are at increased risk for venous thromboembolism, myocardial infarction, stroke, peptic ulcers, fractures, and infections.\(^2\) Patients on exogenous steroids who have iatrogenic Cushing's have also been shown to have increased cardiovascular events including coronary artery disease, heart failure and ischemic stroke.\(^4\) Steroids are also known to increase the risk of thrombosis.\(^5\)

Endogenous causes of CS include ACTH dependent Cushing’s syndrome (80%) and ACTH independent Cushing's syndrome (20%). ACTH dependent CS includes Cushing's disease (68%), ectopic ACTH (12%) and ectopic CRH (<1%). ACTH independent causes include: adrenal adenoma (10%) adrenal carcinoma (8%) micro and macro nodular hyperplasia (<1%).

The cardiovascular complications from CS have been mainly attributed to hypertension and include left ventricular hypertrophy, diastolic heart failure, and myocardial ischemia. Isolated DC due to CS in the absence of other cardiovascular complications is rare, and is potentially completely curable with treatment of Cushing's.

Studies specifically looking at the persistence of cardiovascular morbidity after treatment of Cushing's have shown that patients fully treated and achieving normal serum and urinary cortisol levels for at least 5 years have an increased prevalence of atherosclerosis and obesity, hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability.\(^3\)

DC is a rare complication of Cushing’s with less than 10 cases reported so far.\(^7\)-\(^14\) Although the exact mechanism is unknown, it is likely secondary to hypercortisolism induced myopathy of the cardiac muscle, independent of the effects of cortisol on vasculature.\(^6\) The reversal of Cardiomyopathy after treatment of hypercortisolism is likely similar to improvement in proximal myopathy after treatment. This reversibility makes DC a unique complication in Cushing's syndrome patients.

In some reported cases, patients identified later with CS were diagnosed previously as idiopathic DC. In 1 case, the adrenal adenomas had been found incidentally as part of heart transplant work up for DC.

These cases indicate that there is a possibility that Cushing’s syndrome as a cause of dilated cardiomyopathy is under estimated. Also, given the prevalence of obesity is increasing, a patient with high BMI and diabetes may not trigger the thought of Cushing’s initially.

We suggest that, in the case of in-patients who have Dilated Cardiomyopathy but no other identifiable cause, Cushing’s Syndrome should be considered in the differential diagnosis and patients should be carefully evaluated with screening tests which are readily-available, non-invasive and in expensive.

**References**

9. Peppa, Melpomeni MD; Ikonomidou I, Dilated Cardiomyopathy as the Predominant Feature of Cushing’s Syndrome. The American Journal of the Medical Sciences Issue: 2009 Sep;338(3):252-3
Table 1. Cases of Dilated Cardiomyopathy associated with Cushing’s Syndrome.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Source of hypercortisolism</th>
<th>EF before treatment</th>
<th>EF after treatment</th>
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<tbody>
<tr>
<td>1. Shibusawa et al</td>
<td>2013</td>
<td>Pituitary Adenoma</td>
<td>18%</td>
<td>51%</td>
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<td>2. Rotondi et al</td>
<td>2011</td>
<td>Pituitary adenoma</td>
<td>25%</td>
<td>64%</td>
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<td>3. Ma et al</td>
<td>2010</td>
<td>Pituitary Adenoma</td>
<td>-Reduced-</td>
<td>58%</td>
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<td>4. Peppa et al</td>
<td>2009</td>
<td>Adrenal adenoma</td>
<td>45%</td>
<td>60%</td>
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<td>5. Yong et al</td>
<td>2009</td>
<td>Adrenal adenoma</td>
<td>34%</td>
<td>67%</td>
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<td>6. Petramala et al</td>
<td>2007</td>
<td>Adrenal adenoma</td>
<td>35%</td>
<td>60%</td>
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<tr>
<td>7. Marazuela et al</td>
<td>2002</td>
<td>Adrenal adenoma</td>
<td>25%</td>
<td>69%</td>
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<tr>
<td>8. Hersbach et al</td>
<td>2001</td>
<td>Pituitary adenoma</td>
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<td>50%</td>
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<td>9. Current study</td>
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<td>25%</td>
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