Case Report

Isolated ACTH deficiency presenting with severe myocardial dysfunction

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KEYWORDS
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Summary We present a case of isolated adrenocorticotropic hormone (ACTH) deficiency complicated by acute adrenal crisis and severe myocardial dysfunction. A 54-year-old woman developed consciousness disturbance, hypoglycemia, hyponatremia, and rhabdomyolysis. Initial echocardiographic examinations on the sixth hospital day revealed marked right-sided atrial and ventricular dilatation and severe tricuspid regurgitation. A computed tomography scan for pulmonary embolism was negative. On the 14th hospital day, she became dyspneic and hypotensive. Repeated echocardiographic examinations demonstrated diffuse and severe hypokinesis of the left ventricle. The previous right-sided chamber dilatation became less apparent. Congestive heart failure and severe hypotension were refractory to catecholamines, while she was eventually diagnosed as having acute adrenal crisis due to isolated ACTH deficiency. Hydrocortisone replacement therapy was started, and echocardiographic examinations revealed that the left ventricular dysfunction completely returned to normal in the following eight days. Severe myocardial dysfunction is an uncommon but serious complication of acute adrenal insufficiency. The present case was unique in that diffuse left ventricular dysfunction was preceded by right ventricular dysfunction.

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Introduction

Isolated adrenocorticotropic hormone (ACTH) deficiency is a rare cause of secondary adrenocortical insufficiency. The etiology of this disease is uncertain, but an autoimmune mechanism has been inferred from histological evidence of lymphocytic adenohypophysisitis and selective loss of ACTH-immunopositive cells. The basal plasma levels of cortisol and ACTH are normal in some patients, and early diagnosis is still a challenge in many instances [1]. Patients with
this disease have a relatively higher tolerance to stress as compared to those with primary adrenal insufficiency. However, acute adrenal crisis is still a life-threatening condition. In adrenal insufficiency, hemodynamic impairment is characterized by volume depletion and low cardiac output, but severe myocardial dysfunction is very uncommon. We present a case of isolated ACTH deficiency complicated by acute adrenal crisis and severe myocardial dysfunction.

Case report

A 54-year-old woman was admitted to the hospital because of consciousness disturbance on September 3, 2008. She had complained of low-grade fever and general fatigue and stayed in bed after dinner on the previous day. She was found unconscious by a family member and taken by ambulance on the following morning. Until then, she had noticed some easy fatigability, while she had been working as an obstetric nurse for over 30 years and performing night shifts without difficulties. She had one daughter, and her postpartum course was uncomplicated. On admission her conscious level was JCS-III by Japan coma scale. Heart rate was 96 bpm, and blood pressure was 84/62 mmHg. She was febrile with a body temperature of 38.9 °C, and athetotic movements were seen in the bilateral upper limbs. Laboratory tests revealed severe hypoglycemia and mild hyponatremia (133 mEq/L), whereas hyperkalemia or eosinophilia were not present. The transaminases were moderately elevated along with elevated creatine kinase (CK) (aspartate transaminase 389 IU/L, alanine transaminase 139 IU/L, CK 4855 IU/L, CK-MB 63 IU/L), suggesting rhabdomyolysis. The C-reactive protein was 3.02 mg/dL. Cerebrospinal fluid examination revealed no remarkable changes except for low glucose levels, and computed tomography of the brain showed no abnormal findings. An electrocardiogram showed inverted T waves in leads II, III, and aVF. A chest X-ray film revealed clear lung fields and a normal cardiac shadow. She was given intravenous glucose and infused with maltose lactated Ringer’s solution, but complete recovery of consciousness was delayed for several days. On the sixth hospital day, she was still febrile. Echocardiography revealed marked right-sided atrial and ventricular dilatation and severe tricuspid regurgitation with an estimated pressure gradient of 29 mmHg. The right ventricular wall motion was impaired, and the short-axis diameter of the right ventricle was 31 mm (Fig. 1). A computed tomography scan with contrast enhancement was negative for pulmonary embolism. On the 14th hospital day, she became dyspneic and hypotensive. The chest radiograph showed cardiac enlargement and left pleural effusion. Electrocardiogram showed no additional ST-segment changes. Repeated echocardiographic examinations demonstrated diffuse and severe hypokinesis of the left ventricle along with right ventricular dysfunction (Fig. 2). Left ventricular end-diastolic and end-systolic dimensions were 41 mm and 36 mm, and fractional shortening was 12%. The short-axis diameter of the right ventricle was 29 mm. Laboratory findings demonstrated CK 4403 IU/L, sodium 126 mEq/L, potassium 3.8 mEq/L, and C-reactive protein 4.46 mg/dL. Although her hypotension was refractory to both volume expansion and catecholamines, she was eventually found to have an adrenal insufficiency as endocrinological examination revealed low levels of ACTH (5.9 pg/mL) and cortisol (0.6 μg/dL). Steroid therapy, initiated with 100 mg of intravenous hydrocortisone every 8h, immediately improved the patient’s general condition. Intravenous catecholamines were discontinued, while rhabdomyolysis and hyponatremia disappeared promptly after the initiation of steroid replacement therapy. Echocardiography showed that the global myocardial dysfunction completely returned to normal in the following eight days. The intravenous hydrocortisone was changed to oral hydrocortisone 15 mg/day. Endocrinological study of the pituitary gland showed that ACTH did not respond to corticotropin-releasing hormone and plasma cortisol responded slightly after a bolus ACTH injection. Plasma LH, FSH, PRL, and TSH responded normally after stimulation with TRH and LHRH. Magnetic resonance imaging revealed no pituitary lesions. These findings indicated that the acute adrenal crisis in the present patient was due to isolated ACTH deficiency. The patient was followed for two years under steroid replacement therapy without any complications or relapse of heart failure.

Discussion

The present patient developed severe myocardial dysfunction and refractory hypotension unresponsive to catecholamines. The underlying cause was eventually found to be acute adrenal crisis due to isolated ACTH deficiency. Although cardiac failure has been described as a coexisting illness in adrenal insufficiency, it has not been subjected to detailed analysis [2,3]. Severe myocardial dysfunction is uncommon but serious complication of adrenal insufficiency. Only sporadic cases have been reported: a total of 8 cases (4 children and 4 adults) were found in the literature (Table 1) [4–11]. The causes of underlying adrenal deficiency include isolated ACTH deficiency, Addison’s disease, congenital adrenal hyperplasia, and hypopituitarism due to pituitary adenoma. Congestive heart failure develops after the preceding symptoms of adrenal insufficiency such as fatigue, hypoglycemia, and impaired consciousness. Profound hypotension is refractory to catecholamines because it is also associated with secondary volume depletion due to adrenal failure. The electrocardiogram shows non-specific ST-T changes which are not analogous to those seen in acute coronary syndrome. Echocardiography demonstrates diffuse severe myocardial dysfunction with or without chamber dilatation, but it is not of diagnostic help in revealing the underlying adrenal insufficiency. The myocardial dysfunction and severe hypotension may lead to a fatal course if underlying adrenal insufficiency is unrecognized and left untreated [2], whereas glucocorticoid treatment rapidly improves the myocardial dysfunction within several days to weeks. Furthermore, refractory heart failure and severe hypotension usually respond to the replacement therapy. It is to be noted that a few reported cases manifested congestive heart failure even after the preceding glucocorticoid therapy within 24–48h (Table 1: cases 2, 5 and 8). Some of the authors suspected that glucocorticoid therapy may have a detrimental hemodynamic effect such as water and sodium retention. Nonetheless, the myocardial dysfunction in these cases was successfully reversed during the steroid
Table 1  Reported cases of severe but reversible myocardial dysfunction associated with adrenal insufficiency.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Cause of adrenal insufficiency</th>
<th>Symptoms</th>
<th>Clinical course</th>
<th>Recovery of ventricular wall motion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Newborn</td>
<td>Congenital adrenal hyperplasia: 21-hydroxylase deficiency</td>
<td>Shock</td>
<td>Dilated cardiomyopathy normalized after replacement with hydrocortisone and fludrocortisone</td>
<td>4 days</td>
<td>Boston et al. [4]</td>
</tr>
<tr>
<td>2</td>
<td>11/male</td>
<td>Addison’s disease</td>
<td>Cachexia, rhabdomyolysis, shock</td>
<td>Markedly diminished cardiac function occurring 24 h after initial hydrocortisone therapy</td>
<td>8 days</td>
<td>Derish et al. [5]</td>
</tr>
<tr>
<td>3</td>
<td>62/female</td>
<td>Pituitary adrenal insufficiency caused by empty sella</td>
<td>General fatigue, appetite loss</td>
<td>Left ventricular systolic dysfunction and enlargement improved by hydrocortisone administration</td>
<td>By 2 months</td>
<td>Eto et al. [6]</td>
</tr>
<tr>
<td>4</td>
<td>36/male</td>
<td>Addison’s disease</td>
<td>Congestive heart failure</td>
<td>Globally reduced left ventricular systolic function normalized after steroid therapy</td>
<td>By 7 weeks</td>
<td>Afzal and Khaja [7]</td>
</tr>
<tr>
<td>5</td>
<td>13/female</td>
<td>Addison’s disease</td>
<td>Cachexia, respiratory distress, hypotension</td>
<td>Global left ventricular dysfunction occurring more than 24 h after institution of hydrocortisone therapy</td>
<td>12 days</td>
<td>Conwell et al. [8]</td>
</tr>
<tr>
<td>6</td>
<td>2/male</td>
<td>11β-Hydroxylase deficiency</td>
<td>Breathlessness</td>
<td>Dilated cardiomyopathy markedly improved after hydrocortisone therapy</td>
<td>3 months</td>
<td>Al Jarallah [9]</td>
</tr>
<tr>
<td>7</td>
<td>42/female</td>
<td>Biermer’s disease</td>
<td>Multiorgan failure, cardiogenic shock</td>
<td>Diffuse severe left ventricular hypokinesia completely reversed after hydrocortisone and fludrocortisone therapy</td>
<td>10 days</td>
<td>Mekontso-Dessap et al. [10]</td>
</tr>
<tr>
<td>8</td>
<td>42/female</td>
<td>Addison’s disease</td>
<td>Cardiogenic shock with low output</td>
<td>Severe left ventricular dysfunction occurring 42 h after hydrocortisone therapy</td>
<td>&gt; 9 days</td>
<td>Wolff et al. [11]</td>
</tr>
<tr>
<td>9</td>
<td>54/female</td>
<td>Isolated ACTH deficiency</td>
<td>Consciousness disturbance, fever, involuntary movement, hypoglycemia, hyponatremia, rhabdomyolysis, hypotension</td>
<td>Severe myocardial dysfunction preceded by right-sided atrial and ventricular dilatation; complete reversal after hydrocortisone therapy</td>
<td>8 days</td>
<td>Present case</td>
</tr>
</tbody>
</table>
Isolated ACTH deficiency presenting with severe myocardial dysfunction

replacement therapy. The patient was successfully weaned from catecholamines soon after hydrocortisone therapy, and complete reversal of myocardial wall motion was obtained in the following eight days.

In the present case, right ventricular dysfunction preceded the severe left ventricular dysfunction. To our knowledge, right ventricular dysfunction in adrenal insufficiency has not received attention in the previous literature. There were no other plausible causes for right ventricular dysfunction except for adrenal insufficiency. Pulmonary embolism was excluded by computed tomography. Isolated right ventricular ischemia/infarction is very rare and its electrocardiographic changes are usually seen in the precordial leads rather than in the inferior leads. The right ventricular function also recovered after steroid replacement therapy. Because of these reasons, we believe that the right ventricular dysfunction was the result of acute adrenal insufficiency.

Figure 1  Initial echocardiographic examinations performed on the sixth hospital day demonstrate right-sided atrial and ventricular dilatation. The left ventricle is compressed at end-diastole by the dilated right ventricle. Severe tricuspid regurgitation is shown on the right of panel C. (A) Parasternal long-axis view. (B) Parasternal short-axis view. (C) Apical four chamber view. (Left: end-diastole, right: end-systole.)

Figure 2  Repeated echocardiographic examinations performed on the 14th hospital day demonstrate diffuse and severe hypokinesis of the left ventricle along with right ventricular dysfunction. Massive pleural effusion resulting from congestive heart failure is seen. (A) Parasternal long-axis view. (B) Parasternal short-axis view. (C) Apical four chamber view. (Left: end-diastole, right: end-systole.)

Isolated ACTH deficiency presenting with severe myocardial dysfunction
Glucocorticoids play an important role in myocardial contraction and sympathetic nerve regulation. Depletion of endogenous glucocorticoids is suggested to correlate with the development of myocardial dysfunction. Adrenalectomized rat models have shown that impaired myocardial contractility was associated with a depletion of microsomal phosphorylase activity and marked reduction in calcium uptake in the sarcoplasmic reticulum [12, 13]. These may lead to impaired glycogenolysis and depression of myocardial contractility. Furthermore, glucocorticoid deficiency downregulates expression of adrenergic receptors, decreases adrenaline synthesis, and blunts cardiovascular reactivity to catecholamines. It is speculated that glucocorticoid deficiency may lose protective effects against catecholamines [14, 15]. These underlying mechanisms could explain severe myocardial dysfunction associated with adrenal insufficiency.

Takotsubo cardiomyopathy is the other form of reversible cardiomyopathy seen in adrenal insufficiency [16]. It is characterized by left ventricular apical ballooning with an abrupt onset, whereas refractory hypotension may not be a predominating feature. Takotsubo cardiomyopathy in adrenal insufficiency occurs exclusively in adults. The electrocardiogram shows ST-segment elevations and giant negative T waves mimicking acute coronary syndrome. The apical ballooning in Takotsubo cardiomyopathy generally resolves spontaneously within several days to weeks. It remains unclear whether steroid replacement therapy is indispensable for the wall motion recovery in Takotsubo cardiomyopathy, as one of the reported cases has shown spontaneous improvement without glucocorticoid therapy [17]. As for the present case, serial electrocardiograms showed no ST-segment changes and echocardiogram demonstrated diffuse wall motion abnormalities instead of apical ballooning. Thus, we conclude that Takotsubo cardiomyopathy can be reasonably excluded in the present case.

We had difficulty in diagnosing adrenal insufficiency in the present case. Signs and symptoms of adrenal insufficiency may be diverse and nonspecific. The patient was not so conscious of easy fatigability prior to the disease onset. While hypoglycemia, consciousness disturbance, hyponatremia, and hypotension might give some clues to the diagnosis, other manifestations such as hyperkalemia, eosinophilia, and hyperpigmentation were absent. Moreover, there were some extraordinary findings, including fever, athetotic involuntary movement, rhabdomyolysis, and slightly elevated inflammatory parameters, all of which led us to differential diagnosis of miscellaneous diseases. Sekijima et al. demonstrated cases of isolated ACTH deficiency presenting with neuroleptic malignant syndrome-like symptoms [18]. Neuroleptic malignant syndrome is a potentially lethal neurological condition most often caused by an adverse reaction to neuroleptic or antipsychotic drugs, and it is characterized by hyperthermia, altered consciousness, extrapyramidal symptoms, autonomic dysfunction, and elevated creatine phosphokinase levels. Although extrapyramidal symptoms were not properly evaluated, fever and rhabdomyolysis may be attributable to neuroleptic malignant syndrome — like symptoms in the present case. It is likely that these difficulties may lead to delay in the diagnosis of underlying adrenal insufficiency and its appropriate management.

References