Diabetic ketoacidosis and hypogonadotropic hypogonadism in association with transfusional hemochromatosis in a man with beta-thalassemia major

Jin-Yng Lu, Ching-Chung Chang, Hsing-Chen Tsai, Kai-sing Lin, Yuk-Ming Tsang, and Kuo-Mou Huang

Abstract: We report a 23-year-old man with beta-thalassemia major and transfusional hemochromatosis, which manifested as diabetic ketoacidosis and hypogonadotropic hypogonadism. This unusual presentation of diabetic ketoacidosis in hemochromatosis has rarely been reported. Magnetic resonance imaging of the abdomen showed decreased signal intensity in the liver, spleen, and pancreas. In addition, the pituitary gland also showed heterogeneous low signal intensity, compatible with hemochromatosis. He was treated with insulin supplements and pulsatile human chorionic gonadotropin administration. Clinical improvement was noted after hormone replacement. Intensive iron chelation therapy was given to prevent cardiac complications, and to restore his gonadal function. During follow-up, the patient experienced improvement in libido and sexual potency.

Hemochromatosis is a disorder of iron accumulation with tissue damage, which most commonly affects the liver, pancreas, heart, and pituitary, resulting in liver cirrhosis, diabetes mellitus, cardiomyopathy, and hypogonadotropic hypogonadism. However, the occurrence of diabetic ketoacidosis is rare [1–3]. We describe a patient with an initial presentation of diabetic ketoacidosis who was found to have hypogonadotropic hypogonadism.

Case Report

A 23-year-old man was admitted because of abdominal pain and shortness of breath for 2 days. Beta-thalassemia major had been diagnosed since birth. He had been receiving blood transfusions regularly at a frequency of 1 unit washed red blood cells (RBC) every 2 weeks since he was 5 years old. Iron chelation therapy had been administered (desferrioxamine 1.5 g three times per wk) since the age of 14 with poor compliance. He denied the presence of other major systemic diseases such as hypertension, asthma, heart, liver, or kidney problems. He had only one previous hospitalization at the age of 10 years for surgical removal of an epidural hematoma after a head injury. He had never smoked or drunk alcohol. He had no family history of diabetes, hypertension, or chronic hepatitis. His older brother had also had beta-thalassemia major and had died of heart failure at a young age.

About 2 months prior to admission, the patient experienced general malaise and poor appetite with a weight loss of about 12 kg over 2 months. He denied fever, diarrhea, chronic cough, or history of drug abuse. One week before admission, he experienced constipation, increased urine output, and intermittent abdominal pain. The pain was dull in character, unrelated to meals or posture, and mainly located in the lower abdomen without radiation. He visited our thalassemia clinic 2 days before admission, when his fasting plasma glucose was 21.26 mmol/L on routine biochemistry screen. Diffuse abdominal pain, postprandial vomiting, and shortness of breath developed afterwards, and he was brought to the emergency department of our hospital in February 2000.
On arrival, his blood pressure was 112/62 mm Hg, pulse rate 131/minute, respiratory rate 22/minute, and body temperature 36.2°C. On examination, the patient looked acutely ill. He was 170 cm tall and weighed only 45 kg. He was alert and oriented. His pupils were isocoric and both reacted promptly to light. His neck was supple, although there was a grade II/VI systolic murmur at the left sternal border. His abdomen was soft and flat with hypoactive bowel sounds and diffuse tenderness. There was no rebound tenderness or muscle guarding. The liver and spleen were palpated 8 cm and 5 cm below the costal margin, respectively. His extremities moved freely without pitting edema. There was no pigmentation on his skin. His beard and pubic hair were scanty and his testes were abnormally small (Fig. 1).

Hematologic tests revealed a hemoglobin concentration of 106 g/L, a white cell count of 15.84 x 10^9/L, and a platelet count of 117 x 10^9/L. The differential count showed segment forms 70%, eosinophils 2%, basophils 2%, monocytes 2%, and lymphocytes 24%. Biochemical tests revealed the following concentrations: albumin 32 g/L, globulin 24 g/L, total bilirubin 23.94 µmol/L (direct form 23.94 µmol/L), aspartate aminotransferase 33 U/L, alanine aminotransferase 26 U/L, alkaline phosphatase 156 U/L, γ-glutamyl transpeptidase 96 U/L, blood urea nitrogen 9.28 mmol/L, creatinine 33.04 µmol/L, sodium 138 mmol/L, potassium 4.7 mmol/L, chloride 102 mmol/L, calcium 2.37 mmol/L, and glucose 34.69 mmol/L. The ferritin concentration was more than 10,000 µg/L. Hemoglobin A1C was 15.1%.

Fig. 1. A) Facial appearance and B) external genitalia. Note the feminine appearance and scanty pubic hair. The testes were small and soft, measuring 3.0 cm x 1.4 cm x 0.8 cm.

Initial arterial blood gas analysis revealed a pH of 7.261, partial pressure of oxygen (PO2) 132.1 mm Hg, partial pressure of carbon dioxide (PCO2) 11.9 mm Hg, bicarbonate 5.4 mEq/L, and calculated anion gap 30.6 mmol/L. Urine ketone bodies were +++. Regular insulin was infused continuously at a rate of 0.1 unit/kg body weight/hour after an intravenous bolus of 10 units (about 0.3 unit/kg body weight), to treat the observed diabetic ketoacidosis. Elevated amylase and lipase concentrations (1,337 U/L and 14,343 U/L, respectively) were also noticed. Abdominal ultrasound showed multiple gall stones, hepatosplenomegaly, edematous pancreas, and minimal ascites. Aggressive fluid and potassium supplementation was given through a central venous catheter. On the second hospital day, acidosis was corrected and dyspnea improved. The baseline C-peptide concentration was 0.55 nmol/L (normal, 0.6–1.4) and insulin concentration was 1.1 mIU/L (normal, 5–20). Six minutes after a 1-mg glucagon injection, C-peptide was 1.5 nmol/L, demonstrating poor insulin reserve. Abdominal magnetic resonance (MR) imaging, used to survey the cause of diabetes mellitus, revealed overall decreased signal intensity over the liver, spleen, and pancreas, which was suggestive of hemochromatosis (Fig. 2). Desferrioxamine was administered intensively during hospitalization for iron chelation. In addition, an endocrine survey was performed for hypogonadism. The results of endocrinologic tests are summarized in Table 1. The testosterone concentration was less than 0.89 nmol/L (normal, 13.40–53.60), and the luteinizing hormone releasing hormone (LHRH) test showed hypogonadotropic hypogonadism (Table 2). Brain MR imaging revealed heterogeneous low signal intensity over the anterior lobe of the pituitary gland, possibly related to hemochromatosis (Fig. 3). Therefore, human chorionic gonadotropin was administered and subcutaneous insulin (regular insulin before each meal and neutral protein Hagedorn insulin in the evening) was used to control blood glucose. During hospitalization, intermittent atrial fibrillation was also noted. However, cardiac ultrasound revealed good left ventricular contractility. Intensive iron chelation therapy was suggested. He was discharged on the 18th hospital day. During follow-up in the clinic, he experienced improvement in libido and sexual potency.
Fig. 2. Abdominal T2-weighted magnetic resonance image reveals severely decreased signal intensity over the liver (L), spleen (S), and pancreas (P), compatible with hemochromatosis.

**Discussion**

Hemochromatosis is an iron storage disorder resulting from excessive iron deposition and results in eventual tissue damage to the liver, pancreas, heart, and pituitary. It can be divided into two types: hereditary or genetic hemochromatosis and secondary iron overload due to iron-loading anemia, such as thalassemia. In Taiwan, the hereditary type of hemochromatosis is rare; our patient had thalassemia major, which was associated with transfusional hemochromatosis.

### Table 1. Results of endocrinologic tests

<table>
<thead>
<tr>
<th>Component</th>
<th>Plasma concentration (normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-stimulating hormone (mIU/L)</td>
<td>1.62 (0.4–4.0)</td>
</tr>
<tr>
<td>Free thyroxine (pmol/L)</td>
<td>10.30 (7.72–22.52)</td>
</tr>
<tr>
<td>Triiodothyronine (nmol/L)</td>
<td>0.72 (1.25–3.07)</td>
</tr>
<tr>
<td>Thyroxine (nmol/L)</td>
<td>34.48 (57.92–154.44)</td>
</tr>
<tr>
<td>Cortisol 8 AM (nmol/L)</td>
<td>555.39 (137.95–689.75)</td>
</tr>
<tr>
<td>Cortisol 4 PM (nmol/L)</td>
<td>339.36 (68.98–344.88)</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (pmol/L)</td>
<td>7.77 (2.20–14.31)</td>
</tr>
<tr>
<td>Dehydroepiandrosterone sulfate (nmol/L)</td>
<td>&lt; 0.002 (0.0125–0.0364)</td>
</tr>
<tr>
<td>Prolactin (µg/L)</td>
<td>3.7 (≤ 15)</td>
</tr>
<tr>
<td>Human growth hormone (µg/L)</td>
<td>2.0 (≤ 5.0)</td>
</tr>
<tr>
<td>Intact parathyroid hormone (ng/L)</td>
<td>26.2 (12–72)</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>&lt; 0.89 (13.40–53.60)</td>
</tr>
</tbody>
</table>

Our patient had received blood transfusions regularly since childhood. Modern hypertransfusion and chelation therapy have shown benefits in growth and bone disorders [4]. Although it is associated with improved life expectancy, chronic complications such as liver cirrhosis, diabetes mellitus, cardiomyopathy, and endocrinopathy are becoming more common. Clinically, ferritin concentration is an indicator of iron overload. It has been shown that the mean percentiles for height and weight in patients with low ferritin concentrations (< 2,000 µg/L) are higher than for those with high ferritin concentrations (> 2,000 µg/L) [4]. However, in other studies, no correlation was found between total body iron load, the number of transfusions, and ferritin concentration or any endocrine function tested [5, 6].

In our patient, ferritin concentration was persistently high (> 10,000 µg/L), due to poor compliance with iron chelation therapy. Although general discomfort, decreased appetite, and weight loss were noted for more than 2 months, the patient did not seek help. This led to an initial presentation of severe insulin deficiency and overt diabetic ketoacidosis on admission. Diabetic ketoacidosis is rare in

### Table 2. Results of luteinizing hormone (LH) releasing test (100 µg intravenously)

<table>
<thead>
<tr>
<th>Minutes</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/L)</td>
<td>0.25</td>
<td>0.33</td>
<td>0.33</td>
<td>0.39</td>
<td>0.40</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>&lt; 0.7</td>
<td>&lt; 0.7</td>
<td>0.8</td>
<td>0.75</td>
<td>&lt; 0.7</td>
</tr>
</tbody>
</table>

FSH = follicle-stimulating hormone.

Fig. 3. Pituitary magnetic resonance image reveals heterogeneous low signal intensity over the anterior lobe of the pituitary gland (arrow), possibly related to hemochromatosis.
hemochromatosis, probably because advanced diabetic screening and intensive iron-chelation therapy are now used. However, the renal glucose threshold in thalassemic patients with glucose disturbances is high (> 99 mmol/L) [4], which can lead to inaccurate diabetic screening when using urine tests. For early diagnosis and appropriate treatment of glucose disturbances, the blood glucose should be regularly measured. In cases of hyperglycemia, an oral glucose tolerance test is indicated. Diet or exercise may be helpful in patients with impaired glucose function, and in cases of frank diabetes mellitus, a hypoglycemic agent or insulin should be administered. Intensive desferrioxamine (150 mg kg\(^{-1}\)d\(^{-1}\)) is recommended, as it may improve diabetes mellitus and the dosage of hypoglycemic agents may be decreased after intensive iron chelation therapy. Lethal acute complications of diabetes mellitus such as diabetic ketoacidosis and coma can be avoided with early detection and management of glucose disturbances [1–3, 5, 7].

Although the liver function tests in our patient seemed to be in the normal range, abdominal MR imaging revealed low signal intensity over the liver, spleen, and pancreas with various T1- and T2-weighted pulse sequences, compatible with very high iron deposition. It has been reported that semi-quantitative grading is clinically acceptable for a preliminary evaluation of hepatic iron overload, while quantitative SI measurements using T2-weighted spin echo pulse sequences with various echo times are likely to be more accurate not only in the diagnosis but also in the follow-up of patients under chelation therapy [8]. MR imaging may replace invasive needle biopsy of the liver for accurate determination and monitoring of iron overload [5, 8], even if liver function is within the normal range. Hepatic iron concentration also seems to be a reliable indicator of total body iron stores in patients with thalassemia major; repeated determinations of the hepatic iron concentration could provide a quantitative means of measuring the long-term iron balance [9].

Because of this patient’s feminine appearance, and small, soft testes (Fig. 1), baseline and LHRH-stimulated LH and follicle-stimulating hormone (FSH) concentrations were obtained. The low LH, FSH, and testosterone concentrations prompted us to search for pituitary hypogonadism. It has been reported that anterior pituitary function (LHRH stimulation test) correlates well with MR imaging results in homozygous β-thalassemia, and may be useful in predicting future impairment of pituitary function [10]. The detection of pituitary iron overload on gradient-recalled echo T2-weighted images has been reported to be consistent with a hypothesis of hypogonadotropic pituitary insufficiency due to iron-induced cellular damage [11, 12]. In our patient, although the LHRH stimulation test demonstrated the central origin of hypogonadism, it did not exclude iron deposition in the testes that might contribute to sexual dysfunction. Disturbances of both pituitary and end-organ function are observed in hemochromatosis [13]. In one study that evaluated a small group of patients with hemochromatosis and hypogonadism, MR imaging detected iron overload in the pituitary gland (with significant T2 shortening compared to control patients) and no iron overload in the testes, supporting the hypothesis of hypogonadotropic pituitary insufficiency due to cellular damage induced by iron overload in the anterior pituitary gland [14]. Hypogonadism or pubertal failure is related to the degree of liver fibrosis and it is often due to hypothalamic and/or pituitary dysfunction [15]. In our patient, although testicular MR imaging was not performed, because of the biochemical evidence of secondary hypogonadism, an intramuscular injection of human chorionic gonadotropin was administered instead of testosterone to restore testicular function and fertility. During follow-up, the patient experienced improvement in libido and sexual potency. In some cases, aggressive iron depletion can restore gonadotropin secretion [16, 17]. The age at diagnosis is critical and there are no proven cases of reversal of hypogonadotropic hypogonadism in men over the age of 40 years at the start of iron depletion therapy [18]. A low total sperm count and/or motility has been reported in a proportion of thalassemic patients, and reduced sperm mobility has been found mainly in patients with a low ferritin concentration, which was attributed to desferrioxamine toxicity [17]. Iron depletion therapy may restore the anterior pituitary function. However, once multifactorial infertility is diagnosed, and the patient desires fertilization, in vitro fertilization augmented with intracytoplasmic sperm injection and embryo transfer may be indicated [19].

Our patient’s other endocrinologic tests were all within normal limits, except for low triiodothyronine and thyroxine concentrations. However, free thyroxine and thyroid-stimulating hormone concentrations were both normal, which suggests that sick euthyroid syndrome may have contributed to the low triiodothyronine and thyroxine concentrations.

Hemochromatotic cardiomyopathy is the main cause of morbidity and mortality in patients with thalassemia major. Once heart failure develops, most patients die within a few months. It has been reported that intensive iron chelation therapy can reverse the clinical course of hemochromatotic cardiomyopathy [19]. In our patient, intermittent atrial fibrillation was noted. Although cardiac ultrasonography revealed good left ventricular contractility, intensive chelation therapy was necessary to prevent cardiac complications.
The prognosis of transfusional hemochromatosis has improved greatly since the advent of iron chelation therapy, because cardiac complications from iron deposition have declined. However, endocrinopathy such as hypogonadotropic hypogonadism, diabetes mellitus, and hypothyroidism have been diagnosed more frequently with the improvement in life expectancy [20]. Early diagnosis and treatment of these complications with hormonal therapy is important in the management of transfusional hemochromatosis [7].

References