Is growth hormone deficiency contributing to heart failure in patients with β-thalassemia major?

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Abstract
A 21-year-old woman with β-thalassemia major (β-TM) and GH deficiency developed end-stage heart failure, New York Heart Association (NYHA) functional class IV, within 3 months after withdrawal of recombinant human growth hormone (GH). A myocardial biopsy excluded myocarditis and showed moderate iron deposit in the heart. Before her admission, intensified treatments with digoxin, angiotensin-converting enzyme inhibitor, diuretics and extra chelation therapy (desferrioxamine (DFO)) had not improved her progressive heart failure. At admission, GH was reinstituted together with intensified treatment of cardiac drugs and low doses of DFO, and her heart failure reversed. Four months later, NYHA functional class II was reached and within 1 year her cardiac function was normalised. We suggest that GH deficiency due to iron-induced damage to the hypothalamic–pituitary axis can contribute to heart failure in adult patients with β-TM.

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Introduction
Homozygous β-thalassemia major (β-TM) is a transfusion-dependent, autosomal recessive haemoglobinopathy with highest prevalence in the Mediterranean countries, India and South-East Asia. Worldwide, 60 000 children are born each year with β-TM. The primary abnormality in β-TM is a wasteful, ineffective erythropoiesis resulting in a 10–15-fold expansion of the erythroid bone marrow and a drastic increase in haemoglobin catabolism (1). Iron accumulation is a consequence of blood transfusions as well as increased iron absorption caused by erythropoietic activity. Post-transfusion iron accumulation is a constant threat to these patients, and the most serious damage of iron overload appears in the liver, endocrine organs and myocardium (2). Pathological findings in the heart include dilated, thickened ventricular walls with particularly heavy iron deposits in the ventricles, epicardium and papillary muscles. These cellular deposits induce increased membrane lipid peroxidation in the sarcolemma, resulting in impaired Na, K, ATPase activity (3), increased lysosomal fragility (4) and, in particular, impaired mitochondrial inner-membrane respiratory chain activity (5).

Endocrine problems caused by direct accumulation of iron in endocrine glands or indirectly through the hypothalamic–pituitary axis are common. Growth retardation, delayed puberty, hypothyroidism, hypoparathyroidism and diabetes mellitus are all well-established complications of transfusional siderosis (6). Because diabetes mellitus and hypothyroidism appear when most endocrine cells are destroyed and replaced by fibrosis, these complications are rarely reversible (2).

Survival has improved with the introduction of iron-chelation therapy, and especially since the introduction of subcutaneous desferrioxamine (DFO) infusion by portable pumps only 20 years ago. Increased myocardial lipid peroxidation and abnormal contractility are reversed in vitro by DFO (7). Response to treatment may be assessed by serum ferritin measurements, and protection from cardiac complications may be achieved when ferritin levels are kept at <2500 μg/l (8). However, mortality is still high, often appearing in the second and third decades of life, and heart failure and ventricular arrhythmia is the main cause of death (9), but other mechanisms, such as immunogenic factors, may also be involved (10).

The first case report of reversible severe heart failure associated with GH deficiency due to primary pituitary failure concerned a man who improved within days on 12 IU daily of subcutaneous GH (11). Furthermore, in a similar GH-deficient patient with severe dilated cardiomyopathy, with left ventricular ejection fraction (LVEF) of 15%, intramuscular treatment with 4 IU daily of GH resulted in a marked improvement in
cardiac function within 2–3 weeks; after 3 months of treatment, a dramatic improvement in myofibrillar content in myocardiocytes was recorded (12).

We now report a case of a 21-year-old woman with β-thalassemia major who developed end-stage heart failure classified as NYHA IV (New York Heart Association functional classifications I–IV), within 3 months after withdrawal of GH. Before admission, intensified treatments with digoxin, angiotensin-converting enzyme (ACE) inhibitor, diuretics and extra DFO therapy had not improved her progressive heart failure. At admission, GH was re instituted together with intensified treatment of cardiac drugs and low doses of DFO, and her heart failure reversed. Four months later, NYHA II was reached, and within 1 year her cardiac function was normalised and has remained normal to date.

Case report

A 21-year-old woman born in Sweden to Indian parents was diagnosed with β-TM in her infancy. Since diagnosis, she had had regular blood transfusions and, from age 8 years, regular DFO therapy. At age 14, she experienced her first episode of heart failure, which slowly developed over 2–3 months and which finally resulted in hospitalisation. She recovered after 3 days of intensified treatment with diuretics and with the introduction of digoxin, and was retrospectively classified as NYHA functional class III. Echo investigations showed markedly reduced ventricular function with severely impaired contractility.

Between 14 and 16 years of age, she was diagnosed with primary hypothyroidism, diabetes mellitus and GH deficiency. Her GH deficiency was confirmed with a glucagon test, showing a maximum GH response of 2.0 mIU/l. When the patient was 16 years old, GH treatment (Genotropin, Pharmacia) was started to improve her final height. Later the same year, sex-steroid therapy was initiated for pubertal development, and treatment (Table 2), which after discharge (60 days) was switched from 15 mg/kg per day intravenous to 15 mg/kg per day intramuscular (1.6 IU = 0.53 mg, twice daily). Continuous intravenous low-dose DFO therapy (15 mg/kg per day) was started on day 3 of admission. The day before (550 mg) and after (470 mg) reintroduction of GH, the infusion of furosemide was very high, the heart failure had developed so rapidly, coincidence with the withdrawal of GH could not be excluded. Thus, GH was re instituted on day 2 of admission and, due to pronounced peripheral oedema, it was given intramuscularly (1.6 IU = 0.53 mg, twice daily). Continuous intravenous low-dose DFO therapy (15 mg/kg per day) was started on day 3 of admission. The day before (550 mg) and after (470 mg) reintroduction of GH, the infusion of furosemide was very high, and on the day of GH start, metolazone was given once (Table 2). Furthermore, after admission, she continued on spironolactone, which was given intermittently, enalapril and digoxin. Amlodipine was started on day 3 of admission, and a beta-blocker (carvedilol) was introduced only from day 13 of admission (Table 2). Levotiroxine was withheld during the 5-day critical period. On day 4 of admission, she could sit upright and had regained intellectual capacity, and the infusion of furosemide could be reduced. On day 5 of GH administration, Echo showed cardiac improvement, and a clear reduction of peripheral oedema was noted. Echo revealed a slightly enlarged left ventricle with general severe hypokinesia and inverse septal movement, and LVEF of 20%. The right ventricle was at least moderately dilated with more than modest hypokinesia.

The GH dose was changed to 2.8 IU (0.93 mg) once daily subcutaneously from day 6 of admission. By day 8, the patient had lost 8 kg in weight and could walk. A month later, Echo showed further cardiac improvement, and the patient was discharged from the hospital. She continued with GH treatment, cardiac drugs and DFO treatment (Table 2), which after discharge (60 days) was switched from 15 mg/kg per day intravenously to her previous subcutaneous dose (35 mg/kg per 8 h, 5 days a week). Echo at 4 months of GH...
Table 1 Cardiac function parameters, desferrioxamine (DFO) and recombinant growth hormone (GH) treatment, and serum ferritin and insulin-like growth factor I (IGF-I) concentrations over time with respect to substitution of GH in a 21-year-old woman with β-thalassemia major. (Reference values within brackets.)

<table>
<thead>
<tr>
<th></th>
<th>2 months before GH withdrawal</th>
<th>2–3 months after GH withdrawal</th>
<th>Admission 4 months after GH withdrawal</th>
<th>5 days of GH treatment</th>
<th>22 days of GH treatment</th>
<th>4 months of GH treatment</th>
<th>1 year of GH treatment</th>
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<tbody>
<tr>
<td>NYHAa (I–IV)</td>
<td>I</td>
<td>III</td>
<td>IV 'Very low' &lt; 20</td>
<td>II</td>
<td>II</td>
<td>I</td>
<td></td>
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<tr>
<td>LVEFb% (&gt;55%)</td>
<td>65</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>40–45</td>
<td>50–55</td>
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<td>Cardiac index I/min/m²</td>
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<td>(38–67)</td>
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<td>Stroke volume index ml/m²</td>
<td>(33–67)</td>
<td>12</td>
<td></td>
<td></td>
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<td>LVIDc (d)/BSA mm/m²</td>
<td>30.6</td>
<td>31.9</td>
<td>34.4</td>
<td>32.5</td>
<td>30.0</td>
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<td>(&lt;32 mm/m²)</td>
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<td>PCWPd mmHg</td>
<td>28</td>
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<td></td>
<td></td>
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<td>(4–12)</td>
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<tr>
<td>CVPe mmHg</td>
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<td>(1–5)</td>
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<tr>
<td>Ferritin µg/l (6–81)</td>
<td>3570</td>
<td>8074</td>
<td>27</td>
<td>4120</td>
<td>7640</td>
<td>2470</td>
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<td>GH treatment</td>
<td>0.60 mg q.d., s.c.</td>
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<td></td>
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<tr>
<td>DFO treatment</td>
<td>Recommended 35 mg/kg/8 h, 5 days/week, s.c.</td>
<td>0.93 mg q.d., s.c. continuous i.v. infusion</td>
<td>0.93 mg q.d., s.c. continuous i.v. infusion</td>
<td>0.93 mg q.d., s.c. continuous i.v. infusion</td>
<td>0.93 mg q.d., s.c. continuous i.v. infusion</td>
<td>0.93 mg q.d., s.c. continuous i.v. infusion</td>
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<td>IGF-I µg/l (122–400)</td>
<td>180</td>
<td>51</td>
<td>298</td>
<td>57</td>
<td>59</td>
<td>60</td>
<td>477</td>
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<tr>
<td>Weight kg</td>
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<td>65</td>
<td>57</td>
<td>59</td>
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</table>

aNYHA I–IV; New York Heart Association functional classification I–IV; bLVEF, left ventricular ejection fraction; cLVID(d), left ventricular inner diameter (diastole); BSA, body surface area; dPCWP, pulmonary capillary wedge pressure; eCVP, central venous pressure.
treatment showed further improvement; at 1 year, her cardiac status was normal (Table 1).

**Discussion**

This is the first report of GH treatment in a patient with β-TM and end-stage heart failure, and it warns that sudden withdrawal of GH in patients with β-TM and GH deficiency may result in life-threatening heart failure. However, reinstitution of GH, together with intensified treatment with cardiac drugs and low-dose DFO, reversed and continuously stabilized the heart failure. The development of severe heart failure in this patient occurred at a time when her compliance with DFO therapy was low. The serum ferritin levels were extremely high when she had manifest heart failure, although the levels remained high even when the heart failure was reversed (Table 1). This is in accordance with the rather unreliable time relation between heart failure and serum ferritin levels in these patients (13). Furthermore, extra DFO therapy shortly before admission did not improve the progressive heart failure. On day 3 of admission, the patient was given a low dose of DFO, and 15 mg/kg per day intravenously was continued for 60 days. Thereafter, subcutaneous treatment was reintroduced. Aggressive DFO treatment of 85–200 mg/kg per day intravenously was reported to reverse established symptomatic myocardial disease in three of five patients (14). However, the grade of heart failure was less severe than in the present case, with LVEF of 39–52% before treatment and improvement only after 1 year of DFO therapy. In the literature, we can find no case of β-TM in which end-stage heart failure was reversible on DFO therapy. In the majority of cases, long-term, continuous, 24-h DFO infusion in high doses (>50 mg/kg per day) decreased serum ferritin levels within the first months and improved LVEF from 36% to 49%. In the present case, improvement of heart failure was seen within hours to days of reinstituting GH, together with intensive treatment with diuretics, even before the start of DFO therapy, and this improvement continued even when DFO treatment was switched from intravenous to subcutaneous. The iron content in the biopsies was graded as moderate in the present case. An uneven distribution of iron can make quantification in biopsies unreliable, but a significant correlation between serum ferritin and myocardial iron grade in biopsies has been reported (13). Compared with matched controls, GH-deficient patients have shown an impaired left ventricular mass and LVEF (15–18). A recent meta-analysis has shown GH treatment to be associated with a significant positive effect on left ventricular mass, interventricular septum thickness, left ventricular posterior wall, left ventricular end-diastolic diameter and stroke volume when assessed by Echo (18). In contrast, GH treatment was not found to have a significant impact on systolic parameters. However, it is worth noting that
childhood-onset, GH-deficient patients, as illustrated by the present case report, have lacked physiological GH secretion during developmental age, a lack which provokes more marked alterations of cardiac structure and function that seem to be more responsive to GH treatment (18, 19). In animal models, the beneficial effects of GH in heart failure are significant increase in left ventricular wall thickness and decreased systolic and end-diastolic wall stress, improved left ventricular function, with increased fractional shortening, mildly increased myocardial contractility and enhanced left ventricular relaxation (20). Furthermore, decreased systolic and end-diastolic wall stress was recorded, with increased cardiac output. An increased Ca\(^{2+}\) responsiveness in cardiomyocytes has been suggested as an underlying cause (21). Acute improvement of cardiac index has been shown after continuous intravenous infusion of GH in men with chronic congestive heart failure, due to ischaemic or idiopathic causes, on unchanged heart failure medication (22). It was suggested that GH might have a place among inotropic drugs in the short-term treatment of chronic heart failure (22). Furthermore, in two men with end-stage heart failure due to ischaemic heart disease, an improvement was achieved within weeks on GH doses of 10–14 IU/day subcutaneously; one patient was successfully bridged to transplantation and the other was delisted (23).

There are reasons to believe that the withdrawal of GH was of importance for the rapid development of end-stage heart failure in our patient. Firstly, at withdrawal of GH, the patient was most probably GH deficient, in view of a very low serum IGF-I level, which has a very high predictability for GH deficiency (24). Although no retest of GH secretion was performed at withdrawal, our patient had been tested at age 16 years and found to be severely GH deficient (25). Furthermore, all her other endocrinological problems, that is, diabetes mellitus, primary hypothyroidism and secondary gonadal insufficiency, still needed treatment. This accords with previous findings in β-TM, that these endocrine abnormalities are likely to be irreversible (2). In addition, the timing of the development of NYHA functional class IV fits well with a previous case report showing that about 3 months after GH withdrawal cardiac functional indices worsened in a GH-deficient patient (26). Secondly, other causes of heart failure, such as myocarditis, were excluded. At admission, the patient had for several months been treated with enalapril, spironolactone, digoxin, furosemide and DFO, but her heart failure progressed. Fluid retention with increase in extracellular water is an acute effect of GH treatment but seems to be physiological and does not affect blood pressure (27). In the state of the extreme heart failure, the infusion rate of diuretics was kept at a high level to allow a continuous diuresis of 2–300 ml per h.

In conclusion, during intensified treatment with cardiac drugs and low-dose DFO, together with reconstitution of GH, the heart failure resolved. A remarkable improvement was seen within days, improvement was continuous, and the NYHA functional class II was reached after 4 months. Within a year, complete normalisation was achieved and is still present. The present case report cannot prove the significance of GH in this patient group, as several concomitant medications known to affect the heart function were used. However, this report supports a randomised, placebo-controlled study with GH in patients with β-TM, GH deficiency and heart failure.

Acknowledgements

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