Effect of growth hormone on fatty liver in panhypopituitarism

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Abstract

A 17 year old boy was admitted because of short stature and hepatomegaly. He was diagnosed with panhypopituitarism and fatty liver. The fatty liver improved, not with hydrocortisone or levothyroxine treatment, but with growth hormone administration. The fatty liver in this patient was attributable to a growth hormone deficient state.

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Keywords: fatty liver; growth hormone; growth hormone deficiency; hypopituitarism

It has become evident that besides its growth promoting action, growth hormone has several metabolic actions on adipose tissue.[1] Chronic exposure to growth hormone induces a decrease in lipogenesis and an increase in lipolysis.[2] As the lipolytic effect of growth hormone is more pronounced in the abdominal fat mass,[3–5] patients with growth hormone deficiency usually present with truncal-type obesity.[2] However, the massive deposition of fat in the liver, that is fatty liver, has not been reported in growth hormone deficient patients. We report a patient with panhypopituitarism who suffered from fatty liver that improved with growth hormone treatment.

Case report

A 17 year old boy was admitted to our hospital because of short stature and hepatomegaly. He was the product of a normal full term pregnancy with a breech presentation; his birth weight was 2690 g. At the age of 13 years he was diagnosed with tricuspid regurgitation, and a tricuspid valve repair operation was performed. At the same time he was noted to have hepatomegaly and hypothyroidism (serum thyroxine 44 nmol/l, serum thyroid stimulating hormone 2.9 mU/l). Therefore thyroid hormone replacement treatment (50 μg of levothyroxine) was begun. Though the tricuspid regurgitation completely resolved, the liver enlargement persisted.

On physical examination, his height was 154.4 cm (−2.7 SD), and weight 51 kg (−1.1 SD). A firm liver was palpable 10 cm below the right costal margin, although his spleen was not palpable. He did not show any signs of secondary sexual characteristics. Blood examination showed evidence of abnormal liver function (table 1). His total cholesterol concentration was 4.58 mmol/l (normal range 3.24–6.71 mmol/l) and free fatty acid, triglyceride, and high density lipoprotein cholesterol concentrations were 0.16 mmol/l (0.10–0.73 mmol/l), 2.06 g/l (0.17–1.98 g/l), and 1.53 mmol/l (0.78–1.81 mmol/l), respectively. The fasting serum glucose concentration was 4.6 mmol/l and the serum haemoglobin $A1_c$ was 5.3% (4.6–5.8%). Benedict's reaction of his urine was negative. His bone age was evaluated as 12.5 years using the Greulich-Pyle atlas. Ultrasonography of the liver showed increased echogenicity, suggestive of fatty infiltration. Histological examination of a biopsy specimen showed liver cells containing many fat droplets and fibrosis of Glisson's sheath (fig 1). On the bases of these findings, he was diagnosed with a fatty liver.

To evaluate his short stature we performed endocrinological examinations. Though he was given 50 μg of levothyroxine, serum thyroid hormone concentrations remained low (serum triiodothyronine 1.31 nmol/l, serum thyroxine 37 nmol/l). A thyrotrophin releasing hormone (TRH) stimulation test demonstrated a delayed and prolonged rise in thyroid stimulating hormone, indicating hypothalamic TRH deficiency. Administration of gonadotrophin releasing hormone showed no gonadotrophin response. His plasma cortisol was below the detection level, and insulin induced hypoglycaemia failed to increase the plasma cortisol concentration. A growth hormone provocation test using insulin, clonidine, and growth hormone releasing factor also failed to increase the serum growth hormone concentration. His serum insulin-like growth factor (IGF)-I concentration was 2.9 nmol/l. Based on these findings we made a diagnosis of panhypopituitarism. Magnetic resonance imaging of the brain did not show any abnormal findings.

Hydrocortisone (0.3 mg/kg) replacement therapy was begun, and the dose of levothyrox-

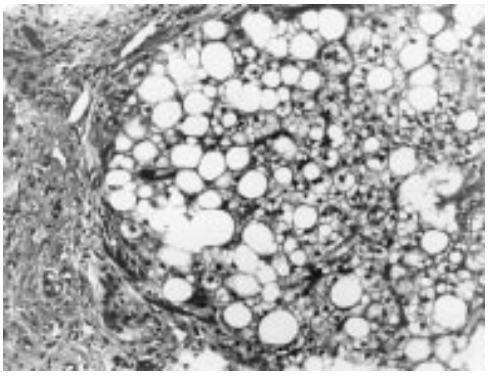

Figure 1 Histology of a biopsy specimen showing liver cells containing large lipid vacuoles and fibrosis of Glisson's sheath (× 50, haematoxylin and eosin staining). These vacuoles were not stained by periodic acid Schiff.

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Table 1 Changes in serum liver enzymes and IGF-I concentrations before and during hormone replacement

		Supplementation	
	Before treatment	*Levothyroxine and hydrocortisone (for 5 months)*	*Levothyroxine, hydrocortisone, and growth hormone (for 9 months)*
Aspartate aminotransferase (U/l)	94 (11-32)*	53	32
Alanine aminotransferase (U/l)	86 (6-39)*	113	47
γ-Glutamyltranspeptidase (U/l)	107 (3-40)*	162	65
Lactate dehydrogenase (U/l)	393 (236-455)*	503	335
IGF-I (nmol/l)	2.9 (37.4-82.0)*	2.1	19.3

*Normal range for the patient's age.

ine was increased to 100 μg. Though the serum thyroid hormone concentrations normalised and remained normal for five months, the liver enlargement did not improve and the liver enzymes remained raised (table 1). We then initiated growth hormone treatment using recombinant human growth hormone (0.5 U/kg/week divided into seven daily subcutaneous doses) in addition to continuing the hydrocortisone and levothyroxine treatment. After beginning the growth hormone a marked decrease in liver size was observed, and the liver enlargement resolved after four months of treatment. Within nine months of the start of growth hormone the liver dysfunction also had markedly improved (table 1), and ultrasonography of the liver showed almost normal echogenicity.

Discussion

Our case is particularly interesting as the fatty liver improved not with hydrocortisone or levothyroxine treatment, but with the administration of growth hormone. This fact strongly suggests that the fatty liver in this patient was attributable to the growth hormone deficient state. Although numerous metabolic and nutritional disorders have been known to cause fatty liver,[6] the fatty liver associated with growth hormone deficiency has not been reported. As adipocytes lack functional IGF receptors,[2] the lipolytic effect is a direct consequence of growth hormone rather than mediated through IGF-I given the evidence that IGF-I treatment in children with Laron's syndrome produces lipolytic effects.[7] Our case illustrates that growth hormone also plays an important part in lipid metabolism in the liver, which is a main target organ of growth hormone, and therefore has many growth hormone receptors.

It remains unclear why this represents the only reported case of the development of a fatty liver in a patient with growth hormone deficiency. A significant feature in this case is that the initiation of growth hormone treatment was extremely delayed. Fatty liver associated with a growth hormone deficient state may take a long time to manifest. Our case shows that a long term growth hormone deficient state increases fat accumulation in the liver as well as in adipose tissue, causing fatty liver and obesity.

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