Growth hormone therapy for a patient with idiopathic Fanconi syndrome and growth hormone deficiency

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Abstract Idiopathic Fanconi syndrome (FS) is characterized by a generalized dysfunction of the renal proximal tubules. Patients with FS often exhibit growth retardation due to complex factors, such as hypophosphatemia, metabolic acidosis, disturbed vitamin D metabolism and hypokalemia. To date, one FS patient has been reported to exhibit growth failure due to growth hormone deficiency (GHD), but the long-term clinical course of recombinant human GH (rhGH) therapy has not been reported. At 10 months of age, the patient was admitted to our hospital due to growth failure. Blood and urinary biochemical abnormalities, such as hypophosphatemia, metabolic acidosis, glycosuria and low-molecular-weight proteinuria, indicated a generalized dysfunction of the renal proximal tubules. The presence of cystinosis, collagen diseases, toxic agents and metabolic diseases were excluded. These features are compatible with idiopathic FS. Treatment with high-dose alkali, potassium citrate, phosphate buffer, hydrochlorothiazide and vitamin D supplement was initiated. The biochemical abnormalities achieved nearly normal values, and the patient's height was within -2.5 SD at the age of 2 years. However, his height did not continue to increase at the same rate and gradually declined to -2.9 SD at 4 years of age. GH stimulation test demonstrated GHD. After initiation of rhGH therapy, his height improved to -2.0 SD at the age of 9 years with no adverse effects. In conclusion, we report the case of a patient with FS and GHD who continued rhGH therapy for 5 years. The differential diagnosis

of GHD should also be considered for FS patients with short stature.

Keywords Idiopathic Fanconi syndrome · Growth hormone deficiency · GHD · Recombinant human growth hormone

Introduction

Idiopathic Fanconi syndrome (FS) is characterized by generalized dysfunction of the renal proximal tubules. Patients with FS often exhibit growth retardation due to complex factors, such as hypophosphatemia, metabolic acidosis, disturbed vitamin D metabolism and hypokalemia [1]. To date, one FS patient has been reported to exhibit growth failure due to growth hormone deficiency (GHD) [2], but the long-term clinical course of recombinant human GH (rhGH) therapy has not been previously reported. Here, we present a male patient with a combination of FS and GHD. In addition, we also demonstrate the 5-year course of rhGH therapy.

Case report

The patient is the first son of unrelated parents. He was admitted to our hospital due to growth failure at 10 months of age. His body length was 64.4 cm (-3.3 SD), and his body weight was 7510 g (-1.7 SD). Physiological examination results were normal. Blood and urinary biochemical abnormalities, such as hypophosphatemia (serum phosphate, 1.7 mg/dl), metabolic acidosis (plasma bicarbonate, 13.3 mmol/l), glycosuria, generalized aminoaciduria and low-molecular-weight proteinuria (urinary

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β 2-microglobulin, 9073 μ g/l, normal <320 μ g/l) indicated generalized dysfunction of the renal proximal tubules. The existence of underlying disorders, such as cystinosis, collagen diseases, toxic agents and metabolic diseases were excluded. He had no ophthalmic abnormalities and his hearing was normal. These features were compatible with idiopathic FS. Treatment with high-dose alkali, potassium salt of citrate, phosphate buffer, hydrochlorothiazide and vitamin D supplement was started. The biochemical abnormalities achieved nearly normal values, and the patient's

Fig. 1 Growth chart of our patient with FS and GHD. Appropriate replenishment therapy, such as high-dose alkali, potassium salt of citrate, phosphate buffer, hydrochlorothiazide and vitamin D supplement was started at 1 year of age. The biochemical abnormalities achieved nearly normal values, and the patient's height was within -2.5 SD at 2 years of age. However, his height did not continue to increase at the same rate and gradually declined to -2.9 SD at the age of 4 years. He started rhGH therapy at the age of 4 years while gradually increasing the phosphate buffer and vitamin D levels to match his growth. After initiation of rhGH therapy, his height gradually increased, and finally reached -2.0 SD at 9 years of age

height was within -2.5 SD at 2 years of age. However, his height did not continue to increase at the same rate and gradually declined to -2.9 SD at the age of 4 years (Fig. 1). His serum IGF-1 level was in the low range of normal (32 ng/ml, normal 32–176), and the GH level response to two pharmacological stimuli was inadequate, exhibiting peak GH levels of 5.6 and 1.6 ng/ml (normal >10 ng/ml) after an arginine and an insulin tolerance test, respectively. Brain damage, pituitary tumors and infection were excluded. Based on the results, we diagnosed our patient with idiopathic GHD in addition to idiopathic FS, and started rhGH therapy (0.15–0.20 mg/kg/week) while gradually increasing the phosphate buffer and vitamin D levels to match his growth. After initiation of rhGH therapy, his height gradually increased, and finally reached -2.0 SD at 9 years of age (Fig. 1). No adverse effects or changes in laboratory parameters were observed, with the exception of elevated levels of alkaline phosphatase (ALP) (Table 1).

Discussion

Our patient is the first case to be diagnosed as GHD in addition to idiopathic FS in Japan. Furthermore, to the best of our knowledge, this is the first report of long-term rhGH therapy over 5 years for a patient with GHD and idiopathic FS. Therefore, several findings are noteworthy.

First, our patient's height demonstrated increased growth after initiation of rhGH therapy, and no clinical adverse effects were reported. Although growth retardation is one of the features of FS [1], the differential diagnosis of GHD should also be considered in the case of FS patients with short stature despite appropriate treatments, such as vitamin D, high-dose alkali, phosphate buffer and potassium salt of citrate. Furthermore, similar to the previously reported case of FS and GHD [2], our patient also gradually demonstrated insufficient height increases. Therefore, gradual growth impairment is a possible indicator that can distinguish patients with both FS and GHD from patients with FS alone. Similar to the efficacy of rhGH therapy in GHD patients with other renal tubular disorders, such as

Table 1 Laboratory and radiological parameters in our patient with FS and GHD before and after rh-GH treatment

Age of years	1	4	5	6	7	8	9
IGF-1 (ng/ml)	10.7	32	76	96	75	183	100
IGF-1 (SD)	-1.8	-1.4	-0.9	-0.7	-1.6	+0.2	-1.3
ALP (IU/l)	1877	1222	1830	1774	1985	1865	1824
Ca (mg/dl)	9.8	9.7	9.5	9.7	9.2	9.6	9.2
P (mg/dl)	1.7	3.8	3.9	4.7	3.7	4.5	3.8
iPTH (pg/ml)		27	26	58	43	42	82
BMD (Z score)			-2.4		-3.9		-2.4
Bone age (years)			3.6			5.5	6.0

Dent disease and Bartter syndrome [3, 4], rhGH therapy is also effective for the patients with FS and GHD.

Second, elevated levels of serum ALP and slightly decreased levels of serum calcium were observed after rhGH therapy in our patient (Table 1). Serum phosphate and intact-parathyroid hormone (iPTH) levels exhibited little change over the 5-year period of rhGH therapy. We did not observe a consistent trend in bone mineral density (BMD), and the radiological findings did not demonstrate features of rickets or osteomalacia.

It is well known that the growth response to rhGH therapy in prepubertal children is significantly affected by age, glomerular filtration rate (GFR), target height, the pretreatment growth rate and comorbid conditions including syndromes [5, 6]. Furthermore, it is also known that increased levels of bone formation markers such as procollagen I N-terminal propeptide (PINP), osteocalcin and bone-specific ALP, are predictors of the effectiveness of rhGH therapy in children [7, 8]. Therefore, it is possible that an elevated ALP level is a good predictor of rhGH therapy effectiveness in patients with FS and GHD.

Third, despite the previously mentioned factors, a poor response to rhGH therapy in the first patient with elevated levels of ALP and iPTH was also reported [2]. In addition, the serum calcium level demonstrated a slight decrease in the patient as in previously reported GHD patients after rhGH therapy [9]. The height velocity of the patient demonstrated improvement after levels of phosphate and vitamin D were increased. We gradually increased the dosage of phosphate buffer and vitamin D in accordance with the patient's growth and carefully watched for an extreme elevation of ALP levels or a decrease in serum calcium.

Hypophosphatemia due to renal phosphate loss, severe acidosis and 1, 25-dihydroxyvitamin D3 deficiency is thought to induce osteomalacia in adult FS patients [10–12]. Therefore, the dosage of replenishment therapy should be modified, especially in pediatric patients with FS and GHD who demonstrate a poor response to rhGH therapy.

In conclusion, we present a male patient with FS and GHD who continued rhGH therapy for 5 years. His height demonstrated normal levels of growth after the initiation of rhGH therapy. The differential diagnosis of GHD should be considered for FS patient with a short stature. Appropriate replenishment therapy is especially important during rhGH therapy in patients with FS and GHD.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB Approval Number 016-0326) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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