The dose dependent effect of growth hormone therapy in patients with IGF-1 receptor haploinsufficiency due to heterozygous deletion

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【Background 】 The IGF-1 receptor (IGF1R) gene is located on the distal long arm of chromosome 15 (15q26.3). Heterozygous inactivating mutations of the IGF1R gene cause intrauterine and postnatal growth failure and mental retardation. Patients with heterozygous deletion of IGF1R gene treated with growth hormone have been reported in only several cases[1-3)].

【Objective 】The purpose of this research is to determine the most effective GH treatment for patients with IGF1R haploinsufficiency due to heterozygous deletion.

【Patients and Method】

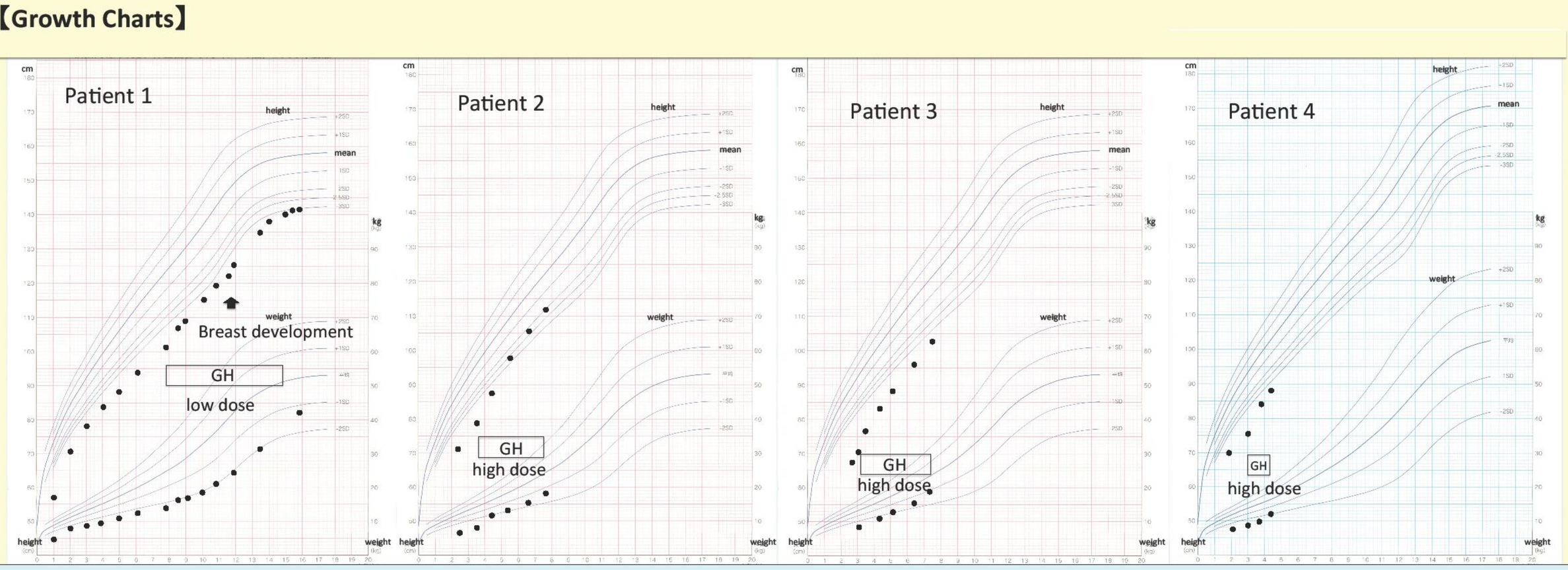
We investigated the clinical course of four patients with IGF1R haploinsufficiency due to heterozygous deletion diagnosed by array CGH analysis. All four patients were born with severe intrauterine growth failure and revealed mental retardation.

Patients	sex	Gestational age (week)	Birth weight (g)	Birth length (cm)	Karyotype	Onset of GH therapy (year)	Serum IGF-1 levels before GH therapy (ng/mL)
1	female	41	1858	41.0	46,XX,der(15)t(4;15) (q33.2;q26.3)mat	7	375
2	female	39	1634	41.5	46,XX,der(15)t(4;15) (q33.2;q26.3)mat	3	260
3	female	37	1746	38.0	46,XX,r(15)(p11.2q26.3)[27]/45,XX,-15[3]	3	177
4	male	35	1420	38.5	46,XY,der(15)(q26.1)	3	128

【Results】

One female patient (patient 1) at 7 years of age, with height 101.3 cm (−4.2 SD), was administered 0.18 mg/kg/week of GH and increased to 0.20 mg/kg/week. Her serum IGF-1 was 375 ng/ml before GH treatment. Her adult height was 141.1 cm (−3.2 SD). During GH treatment, high levels of IGF-1 persisted (380-730 ng/ml before the development of secondary sexual characteristics and 648–1030 ng/ml since then). The other three patients (two female and one male) at 3 years of age, with height SDS ranging from −4.7 SD to −6.4 SD, were administered 0.25 mg/kg/week of GH and increased to 0.35–0.47 mg/kg/week. The serum IGF-1 was 128–260 ng/ml before GH treatment. One female patient (patient 3) improved from -6.4 SD to -3.5 SD after 5 year of GH treatment. Her maximum IGF-1 was 877 ng/ml during GH treatment. The male patient (patient4) improved from −5.1 SD to −4.1 SD after 1 year of GH treatment. His maximum IGF-1 was 513 ng/ml during GH treatment. The other female patient (patient 2, younger sister of patient 1) improved from −4.7 SD to −1.9 SD after 4 year of GH treatment. Her maximum IGF-1 was 701 ng/ml during GH treatment. However, there was no obvious improvement of mental retardation in the four patients.

【Growth Charts】



【Conclusions】Long-term GH therapy causes growth acceleration during childhood in a dose-dependent manner. Earlier onset of therapy may provide better results.

【References】

1. Okubo Y et al., Cell proliferation activities on skin fibroblasts from a short child with absence of one copy of the type 1 insulin-like growth factor receptor (IGF1R) gene and a tall child with three copies of the IGF1R gene. J Clin Endocrinol Metab. 2003 Dec;88(12):5981-8.
2. Walenkamp MJ et al., Successful long-term growth hormone therapy in a girl with haploinsufficiency of the insulin-like growth factor-I receptor due to a terminal 15q26.2->qter deletion detected by multiplex ligation probe amplification. J Clin Endocrinol Metab. 2008 Jun;93(6):2421-5.
3. Ester WA et al., Two short children born small for gestational age with insulin-like growth factor 1 receptor haploinsufficiency illustrate the heterogeneity of its phenotype. J Clin Endocrinol Metab. 2009 Dec;94(12):4717-27.

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