Case Report

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The benefit of rhGH therapy in a Chinese child with 12q14 microdeletion syndrome: a case report

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Abstract

Objectives: The 12q14 microdeletion syndrome is a rare genetic condition characterized by intrauterine growth restriction, proportionate short stature, failure to thrive, and intellectual disability. Few reports have discussed the therapeutic aspect of patients with 12q14 microdeletion syndrome. Herein, we report the first case of 12q14 microdeletion patient treated with rhGH without growth hormone deficiency.

Case presentation: The patient presented with feeding difficulties during infancy, failure to thrive, intellectual disability and subtle dysmorphic facial features. The patient first visited the clinic at 5 years and 3 months, his height was 91.4 cm (−4.9 SD) and weight 10.0 kg (−2.86 SD). The growth hormone level was within the normal range. Bone radiological testing revealed no significant abnormalities. Genetic analysis identified a 6.97 Mb deletion at the chromosome 12q14.1–q14.3 region in the proband. Recombinant human growth hormone therapy was initiated, which lasted for 12 months, and the new height was 101.0 cm (−4.0 SD) and weight 12.0 kg (−3.6 SD).

Conclusions: This report first showed that patient with 12q14 microdeletion, although without growth hormone deficiency, can benefit from human growth hormone therapy.

Keywords: 12q14 microdeletion syndrome; children; growth hormone; short stature; therapy.

Background

12q14 microdeletion syndrome is a rare genomic disorder described initially by Menten et al. in 2007, and it is characterized by growth restriction, proportionate short stature, failure to thrive and developmental delay [1]. Although relatively rare worldwide, subsequent reports further expanded the phenotypic presentation of this syndrome, including osteopoikilosis, feeding difficulty, macrocephaly, subtle dysmorphic features, speech delay, and different degrees of intellectual disability [2]. Previous reports have identified several candidate causal genes, including LEMD3, HMGA2 and GRIP1 [2]. Haploinsufficiency is likely the main disease mechanism for the syndrome, whereas LEMD3 is probably responsible for abnormal skeletal maturation, HMGA2 for failure to thrive and short statures, and GRIP1 for developmental delay [1]. However, there are no defined genotype-phenotypic correlations for this microdeletion syndrome to date.

Almost all reports showed short stature or failure to thrive as the most common clinical feature of the syndrome, but few studies have examined the efficacy of recombinant human growth hormone (rhGH) for 12q14 microdeletion syndrome. Here, we conducted rhGH treatment on one patient with 12q14 microdeletion syndrome but without growth hormone deficiency. Our study demonstrated the growth-promoting benefit of rhGH for individuals with the 12q14 microdeletion.
**Case presentation**

This six-year and four-month-old boy is the second child of nonconsanguineous parents. He was born full term with normal vaginal delivery. There were no complications during pregnancy or delivery except intrauterine growth retardation. His birth weight was 2,200 g (−3 SD), and his body length was 48 cm (−1 SD). He presented with feeding difficulties during the neonatal period that improved over time; thereafter, development delay, failure to thrive and frequent obstipation were noticed. He sat unsupported at 7 months of age, walked independently at 12 months of age, and said his first words at 18 months of age. He first visited the behavior and development department at the age of five years and one month. Physical examination revealed proportionate short stature with a height of 91.4 cm (−4.9 SD), and a weight of 10.0 kg (−2.86 SD). His head circumference (47.2 cm, −2 SD) suggested microcephaly but was proportionate for his small habitus. Moreover, he presented with mild dysmorphic features, including a distinct inverted triangle face, narrow chins, wide forehead, frontal bossing, deep-set eyes, and a single palmar flexion crease. No other chronic diseases, including chronic renal insufficiency, inflammatory bowel disease, celiac disease and endocrine disorders, were noticed. Family history was negative for neurologic disease or intellectual disability. His mother had a normal height, and his father was short (160 cm, <−2 SD).

His routine blood test, thyroid hormone levels and IGF-1 level were normal. Insulin and arginine growth hormone stimulation tests indicated that he had no growth hormone (GH) deficiency (peak GH: 28.300 ng/mL). Bone radiography (Figure 1), abdominal ultrasound, and pituitary MRI revealed no abnormalities. The Wechsler Intelligence Scale for Children in Chinese (WISC-C) showed that his overall intelligence quotient was 56. Trio exome sequencing identified a 6.97 Mb deletion at the chromosome 12q14.1-q14.3 [chr12: 59,704,802–66,679,145] region in the proband, which occurred de novo (Figure 2). No other clinically significant variant was identified through a thorough analysis of the exome data. This deletion contains 24 OMIM genes, including *HMGA2* and *LEMD3* (UCSC GRCh38/hg38, https://genome.ucsc.edu/), and partially overlaps with previously described deletions in patients with 12q14 microdeletion syndrome [1]. Integrating the clinical presentations and the molecular findings, this proband was diagnosed with 12q14 microdeletion syndrome.

With informed consent and counseling, we administered rhGH therapy for the proband at a dose of 0.2 mg/kg per week at the age of five years and three months and evaluated the growth rate and adverse events during the course. After receiving rhGH therapy, the growth velocity was significantly increased (Figure 3). At the end of the 12-month period, the proband’s height increased to 101.0 cm (−4.0 SD), and his weight to 12.0 kg (−3.6 SD). During rhGH treatment, his routine blood test, IGF-1 level, thyroid hormones, and insulin levels were all within the normal range. His bone age was similar to his chronological age.

**Discussion**

12q14 microdeletion syndrome is a rare genetic disease. Previous literature reported about 30 patients with 12q14 microdeletion syndrome. Here, we report another patient with a consistent clinical presentation of previously reported cases with 12q14 microdeletion.

Previous reports showed that 87.1% of patients with 12q14 microdeletion syndrome had short stature or a failure to thrive, 80.6% were born small for gestational age (SGA), 58.1% had feeding difficulties in infancy or early childhood, 35.4% had intrauterine growth retardation (IUGR), and 19.3% had GH deficiency (Supplementary Table 1). Previous
reports have identified several candidate causal genes, including LEMD3, HMGA2 and GRIP1. Several studies have suggested HMGA2 as a candidate gene for intrauterine and postnatal growth retardation in patients with 12q14 microdeletion syndrome. The HMGA2 gene encodes a member of the “high-mobility group AT-hook” (HMGA) family. The HMGA protein is highly expressed in early developmental stages in embryos and mesenchymal stem cells [3]. HMGA2 has been shown to be essential in regulating cell growth, proliferation, differentiation and death, playing a crucial role in embryonic development and growth regulation [3]. In mice, inactivation of one or both alleles of Hmga2 results in body-size reductions of 20 % and 60 %, respectively [4]. In humans, association studies have shown that HMGA2 is associated with height variation in the general population. Overall, these findings further support the association between haploinsufficiency of HMGA2 and short stature and growth restriction.

To date, growth hormone deficiency (GHD) was reported in only six patients with 12q14 microdeletion syndrome [5–9]. Only five cases administered GH treatment have been reported; all of them presented with short stature and growth restriction, and four of them showed growth hormone deficiency [5–7, 9] (Supplementary Table 2). All deleted regions identified in these patients contain HMGA2, with deletions ranging from 1.83 to 10.11 Mb in size. However, growth hormone levels were reported in two brothers only [9]. Buysse et al. [6] reported a boy with short stature, failure to thrive, hypotonia and global developmental delay. The boy was treated with GH at 27 months of age, and after...
10 months of treatment, GH treatment resulted in a mild to moderate response [6]. However, the patient reported by Mari et al. [5] was started on growth hormone treatment at age 3 yrs 7 months; after 7 months of treatment, the growth velocity did not change, but his overall conditions seemed to improve slightly. Furthermore, two brothers reported by Fischetto et al., presenting with IUGR, severe short stature, failure to thrive and GHD, carried a 1.9 Mb maternal microdeletion [9]. Stature improved after GH therapy in the older brother; however, no obvious benefit was found in the younger sib [9]. Finally, one case yielded no conclusive result due to insufficient treatment duration [7]. However, it is worth noting that one patient would have a normal IGF-1 level despite a low result on a stimulation test, which suggesting a probably false positive diagnosis of GHD and may need a second GH stimulation test [9]. Even though, most short children with 12q14 microdeletions had normal growth hormone levels. Therefore, it is not certain whether GH therapy would be beneficial to those patients without GHD. However, considering response to first-year rhGH treatment is an important indicator of future gains in height. What's more, previous research shows that rhGH is safe and increases short-term height gain and adult height across GHD and non-GHD conditions [10]. So, we empirical conducted rhGH treatment on the patient without growth hormone deficiency. Our trial demonstrated a height gain of +0.9 SD with height increased from 91.4 cm to 101.0 cm after the first year of GH therapy, which could be regarded as effective. Moreover, his overall conditions seemed to improve, and his eating habits and digestive function improved significantly, which may be one of the promoting factors for his stature improvement. A previous study showed that adverse events were reported for approximately 3.1 % of pediatric patients with growth hormone deficiency. The most common adverse events include headache, scoliosis, infections, elevated IGF-1, pain, and vomiting [10]. However, no rhGH-related adverse events were observed in our case.

Taken together, these reports showed that GH therapy response was different in different patients with 12q14 microdeletion who presented with short stature and GHD, even within familial cases. More patients need to be reported to establish better correlations between GH therapy response and multiple factors, including sex, deleted region size, degree of GHD, initiation age, and duration of GH therapy. Therefore, it is uncertain whether the rhGH therapy benefit in our case will be sustained or catch-up with genetic height at his adult stage, which requires long-term follow-up. It should be noted cautiously that growth in our patient may also be influenced by the short stature of his father since we cannot rule out a possible phenotypic contribution of any other genetic variant that was not identified.

In conclusion, this is the first report of a 12q14 microdeletion patient treated with rhGH without growth hormone deficiency, and the results demonstrated a beneficial effect on height improvement without overt short-term side effects. Our findings suggest that GH therapy could be considered to improve short stature in patients with the 12q14 microdeletion, even without growth hormone deficiency. More trials will be necessary to determine the correlation between GH therapy effectiveness and other factors among 12q14 microdeletion patients.
Learning points

– 12q14 microdeletion syndrome should be considered in those patients who present with growth restriction, proportionate short stature, failure to thrive and developmental delay.
– Haploinsufficiency of HMGA2 associated with short stature and growth restriction in patients with 12q14 microdeletion.
– Growth hormone therapy could be considered to improve short stature in patients with the 12q14 microdeletion, even without growth hormone deficiency.

What’s new

– This report first showed that patient with 12q14 microdeletion, although without growth hormone deficiency, can benefit from human growth hormone therapy.

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References


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