

Ring Chromosome 15 Syndrome: Case Report and Literature Review

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Abstract

Objective: This report aimed to add our knowledge on the clinical features, diagnosis and management of ring chromosome 15 syndrome. **Methods:** Case report and literatures review. **Results:** A 4.5-year-old girl was admitted to our unit because of short stature. She was 86 cm in height and 9 kg in weight. Physical examination showed sparse temporal hair, right simian crease, fifth finger clinodactyly, and many irregular café-au-lait spots on the chest, abdomen, and inner thigh. Mental retardation was found. The results of cranial magnetic resonance imaging (MRI) as well as abdominal and cardiac ultrasonography were normal. Growth hormone (GH) provocative tests showed normal GH peak. Karyotyping of the lymphocytes showed 46,XX, r(15) pattern. Recombination human GH (rhGH) with a dose of 0.1 U/kg⁻¹·d⁻¹ was administered for 4 months with height increment of 3 cm. **Conclusion:** Ring chromosome 15 syndrome should be considered in patients with short stature and café-au-lait spots. Timely recognition and hereditary tendency counseling is required. rhGH therapy may improve the growth velocity.

Key words

Child; Growth hormone; Short stature; Ring chromosome 15

Introduction

Ring chromosome 15 (r(15)) syndrome is an uncommon chromosome anomaly first described by Jacobsen in 1966.¹ Less than 50 patients have been reported up to now,² and only 3 cases have been reported in China.³⁻⁵ Growth deficiency, mental retardation and congenital malformation were common phenotypes.⁶⁻⁸ Congenital malformations

included eye anomalies (e.g. macular defects, hyperopia, strabismus and heterochromia), ear abnormalities (e.g. dysplastic ears and hearing loss), café-au-lait macules and cardiac anomalies.^{2,6,7} Intrauterine growth retardation, high arched palate, brachydactyly and infantile seizures were also reported in some cases.^{6,7} However, it was still unclear whether these manifestations were really associated with r(15) as it was so rarely reported. Misdiagnosis and missed diagnosis can often occur because the clinical features are varied and nonspecific. There is only one reported case of r(15) syndrome with recombination human Growth hormone (rhGH) therapy.⁹

Herein, we reported a case of r(15) syndrome with 46,XX, r(15) karyotype and reviewed the associated literatures to add to the knowledge of the clinical features, laboratory findings and rhGH management of this rare event.

Case Report

A 4.5-year-old girl was admitted to our unit for short stature. She was born at 36 weeks' gestation via normal

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Received December 16, 2010

spontaneous vaginal delivery following an uncomplicated pregnancy. The girl was born without asphyxia history, and her birth weight was 2.6 kg. Her family history was unremarkable and her mother did not use alcohol, drugs or medications during the pregnancy. The height of her father and mother was 171 and 161 cm, respectively. On physical examination, she was 86 cm in height (<3rd centile) and 9 kg in weight (<3rd centile). She was symmetrically growth retarded. Distinctive features included sparse temporal hair (Figure 1a), right simian crease and fifth finger clinodactyly (Figure 1b), many irregular café-au-lait spots on the chest, abdomen, and inner thigh (Figures 1c-1d). She presented female external genitalia with Tanner I of breast and external genitalia. No webbing of neck was found. No remarkable neurological, aural, ocular, nasal, thoracic, cardiac and pulmonary manifestations were found.

Hormonal assays showed normal basal luteinizing hormone (0.3 IU/l), follicle-stimulating hormone (8.8 IU/l) and testosterone (<200 ng/l), and normal prolactin levels (11.2 mg/l) and human chorionic gonadotropin levels (<1 IU/l), and high basal estrogen levels (58.4 ng/l). Triglyceride level was 2.29 mmol/l. Growth hormone (GH) provocative tests (arginine stimulating test and levodopa stimulation test) were performed after an overnight fast, the GH peak were 18.7 µg/l and 28.0 µg/l, respectively. Insulin-like growth factor-1 (IGF-1) was 213 µg/l. Screening laboratory test results for blood cell count, liver and kidney function, glucose, insulin, triiodothyronine, thyroxine, thyroid-stimulating hormone, adrenocorticotropic hormone, cortisol, TORCH antibodies, series mass spectrum for amino acid and carnitine levels were all within normal limits or were negative.

Chromosome analysis of lymphocytes for this patient and her parents revealed a karyotype of 46,XX, r(15)(p11.2q26.3) pattern (Figure 1e) for this patient without mosaicism. The karyotypes of her parents were normal.

Bone radiographic imaging showed delayed bone age (about 3 years of age). S-M infantum-junior high school students social living ability testing revealed low intellectual functioning (standard score 10). The brain magnetic resonance imaging, abdominal, cardiac and pelvic ultrasonography were unremarkable.

After diagnosis, rhGH with a dose of 0.1 U/kg⁻¹·d⁻¹ (rhGH aqua mistura, GeneScience Pharmaceuticals Inc. China) was administered for 4 months with height increment of 3 cm. No obvious side effect was noted. Consent was obtained from the parents and the Ethical Committee of the Children's Hospital of Zhejiang University School of Medicine.

Discussion

Ring chromosomes have been identified for all human chromosomes.² The term "ring syndrome", initial described by Coté on 1981, was proposed to describe a phenotype of primordial growth failure without major malformations due to a ring autosome.¹⁰ Since first described by Jacobsen in 1966, less than 50 patients of r(15) have been reported. The average age at diagnosis was 8.1 years.⁶ We reviewed the available literatures since 1980, only 31 cases of r(15) syndrome had been reported with the gender information.^{2-6,9-25} They were 15 females and 16 males without gender predilection.

There was a wide spectrum of clinical findings in patients with r(15) syndrome encompassing a near normal phenotype to multiple malformations. In Butler's report, the commonest features included short stature (27/27), mental retardation (20/21), microcephaly (21/24), low birth weight (<2.5 kg, 19/26) and birth length (≤46 cm, 14/17), bone age delay (6/8), hypertelorism (11/24), brachydactyly (12/27), triangular facies (10/24) and broad nasal bridge (10/27). Other common features were speech delay (9/23), cardiac abnormalities (8/27), frontal bossing (8/22), anomalous ears (8/27), hypotonia (7/27), micrognathism (7/24), fifth finger clinodactyly (7/27), high-arched palate (6/27), small hands (6/26), café-au-lait spots (5/21), and talipes equinovarus (4/27).⁶ Achromic areas (3/21), simian crease (3/25), 2nd and 3rd toe syndactyly (3/27), renal malformations (2/25), cryptorchidism (2/9) and hypospadias (1/9) were also reported.^{6,26} In addition, several diseases, included congenital diaphragmatic hernia (CDH),^{4,11,12,26-28} Russell-Silver syndrome,^{2,29,30} Prader-Willi syndrome (PWS)¹³⁻¹⁹ and autism,²⁰ were reported to be related with r(15). Our case showed low intellectual functioning, short stature, bone age delay, simian crease, fifth finger clinodactyly and café-au-lait spots, which were consistent with the features of r(15) syndrome. The versatility of clinical findings in patients with r(15) syndrome is associated with the mosaicism level of the ring chromosome, tissue-specific variation in this mosaicism, variation in the amount of euchromatin, the mitotic instability and parents' origin of the r(15).^{6,7,9,25} Two mechanisms of ring chromosome formation were proposed. One is regarded that the ring chromosomes is the result of breakage in both arms of a chromosome, with fusion of the points of fracture and loss of the distal fragments.³¹ These patients had gene deletions presenting with severe features. Another mechanism is the simple fusion of chromosome ends with preservation of telomeric and subtelomeric sequences. This would result in alteration of the structure



Figure 1 Clinical features of the patient. (a) Short stature and sparse temporal hair. (b) Right simian crease and fifth finger clinodactyly. (c) and (d) Many irregular café-au-lait spots on the chest, abdomen and inner thigh. (e) The karyotype of 46,XX, r(15) pattern.

of the genetic material rather than a pure deletion with slight features.^{32,33} Our case was characterised by growth deficiency, café-au-lait spots, simian crease and bone age delay without major malformations, which suggested less genetic material loss and may be associated with the second mechanism of ring formation.

It is difficult to make a complete correlation between the size of deletion and the phenotypes, because the clinical features are not complete in all cases and the exact size of the deletions are not determined. By comparative genomic hybridization array, some cases have determined the size of the associated deletion and facilitated the phenotype-

genotype correlations at the molecular level. Previous studies showed that cardiac abnormalities due to the hemizygosity/haploid sufficiency of the NR2F2/COUP-TFII gene in r(15) patients.^{8,34} PWS results from the absence of paternal contribution in the imprinted region at 15q11-13.^{18,35} The malformations of CDH were frequently associated to 15q interstitial or terminal deletions, and the critical region localised in 15q26.1-q26.2.^{11,27,28,36} The genes on 15q26 were involved in the most basic steps of kidney abnormalities.³⁷ Growth deficiency is a common finding in r(15) because 15q terminal deletions involve loss of the IGF-1 receptor gene (IGF-1R) located at 15q26.3.^{2,26,38-40}

However, another study did not agree a loss of the IGF-1R gene.⁹ In our case, a normal IGF-1 and peak GH levels in stimulation test, and good response of rhGH were noted. These did not support the abnormality of GH, IGF-1 and IGF-1R, or other reasons which may result in the severe postnatal growth failure.

The clinical features of r(15) syndrome were varied and nonspecific. Therefore, some medical staffs may neglect it and misdiagnosis or delayed diagnosis occurs frequently. The average age at diagnosis was 8.1 years.⁶ Most cases were diagnosed postnatally, and only 4 cases were diagnosed prenatally.^{2,4,11,41} Fetus with thickened nuchal fold, single umbilical artery, CDH, and intrauterine growth retardation by fetal ultrasound at 16-24 weeks required further investigations for chromosomal abnormalities.^{2,4,11,41} Unfortunately, neither current maternal serum screening nor ultrasonographic findings can be served as a marker for the prenatal diagnosis of r(15).⁴¹ For patients with growth deficiency, café-au-lait spots, bone age delay, simian crease or other dysmorphic features, r(15) syndrome should be considered.

The experience for management of these cases is limited. rhGH therapy is widely used for Turner syndrome, another chromosome disease. However, the efficacy of rhGH on Turner syndrome is less than that for growth hormone deficiency (GHD) patients. To our knowledge, only one case with r(15) syndrome has been reported with rhGH therapy. It was a 4-year-old boy, whose peak GH response to clonidine stimulation was good (35.6 µg/l), but low (5.3 µg/l) in response to insulin induced hypoglycaemia. He was treated with rhGH at a daily dose of 1 U at the age of 2 years 3 months. During the two years of treatment, his growth velocity increased from 5.9 cm per year to 8.5 cm per year, his relative height improved from -6.2 SD to -4.4 SD and the predicted adult height increased from 159.6 cm to 163.5 cm. His bone age advanced only one year.⁹ Our case had a good response to low dose rhGH.

In summary, r(15) syndrome should be considered in patients with short stature, bone age delay, café-au-lait spots, simian crease and fifth finger clinodactyly. Timely recognition and hereditary tendency counseling is required. rhGH therapy may improve the growth velocity.

Acknowledgments

We thank the children and their parents for permitting the use of her data. This work is supported by grants from the Zhejiang Health Bureau Fund (2006QN017).

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