Long-Acting Gonadotropin-Releasing Hormone Analogue Treatment for Central Precocious Puberty in Maternal Uniparental Disomy Chromosome 14

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Uniparental disomy (UPD) is the inheritance of a chromosome pair from one parent and is increasingly recognized as a cause of abnormal phenotypes either due to imprinted genes or, in the case of isodisomy, to homozygosity of recessive alleles. Maternal uniparental disomy for chromosome 14 (matUPD[14]) may cause a characteristic phenotype including precocious puberty. Central precocious puberty (CPP) was diagnosed in a 6-year-old girl with some dysmorphic features, truncal obesity, small hands, and small feet. Cytogenetic analysis of her peripheral blood demonstrated chromosomal rearrangement: Robertsonian translocation 45, XX, der(13;14)(q10;q10). MatUPD(14) was demonstrated in the patient by haplotype analysis of chromosome 14, showing that the CPP is one of the features caused by matUPD(14). The CPP was successfully treated with higher dosage of long-acting gonadotropin releasing hormone (GnRH) analogue, Leuprolide®, 90 μg/kg/month. This is the first report that describes GnRH analogue treatment for CPP associated with matUPD(14), suggesting that the GnRH analogue treatment is appropriate even for such a specific type of CPP.

Central precocious puberty (CPP) is the premature onset of puberty caused by precocious activation of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus. The majority of cases are idiopathic and almost all cases have been found in girls. A few of the cases were secondary to cerebral lesions including hydrocephalus, tumors, and trauma (Junier et al. 1992). Uniparental disomy (UPD) is the inheritance of a chromosome pair from one parent and is increasingly recognized as a cause of abnormal phenotypes either due to imprinted genes or, in
the case of isodisomy, to homozygosity of recessive alleles. Maternal uniparental disomy chromosome 14, designated as matUPD(14), is a genetic cause of disease with a recognizable phenotype including a number of consistent features, intrauterine growth retardation, CPP, short stature, hypotonia, developmental delay, scoliosis, and characteristic facies consisting of a high, broad forehead, and fleshy nasal tip (Temple et al. 1991; Antonarakis et al. 1993; Healey et al. 1994; Tomkins et al. 1996; Fokstuen et al. 1999; Falk et al. 2005). This disease should be considered in the differential diagnosis of Prader-Willi syndrome (PWS), because these syndromes have clinical overlap with each other (Berends et al. 1999; Hordijk et al. 1999). However, in later childhood, matUPD(14) shows some distinctions from PWS in certain features. While delayed puberty or hypogonadism is frequently recognized in PWS, premature puberty is a main finding in matUDP14. The causative mechanism of CPP complicating matUDP14 is unknown, but expected to be related to some imprinted gene in chromosome 14 (Tomkins et al. 1996; Fokstuen et al. 1999). We herein report a girl with matUPD(14) who was treated for CPP with long-acting GnRH analogue.

CASE REPORT
The patient was a 6.0-year-old Japanese girl with premature puberty. She was born to non-consanguineous Japanese parents at 40 weeks of pregnancy. Birth weight was 2,276 g (−2.2 s.d.), and birth length 46 cm (−2.0 s.d.). There was nothing remarkable during her infancy. She was referred to the hospital because of short stature, 90.1 cm tall (−2.3 s.d.), at the age of 4.0 years. She was endocrinologically evaluated as normal, but bone age was advanced (5.5 years) and Robertsonian translocation 45, XX, der(13;14)(q10;q10) was recognized on chromosomal analysis (Fig. 1). At the age of 6.0 years, she showed abrupt increase of height velocity and pubertal development of breasts (Tanner stage 3). Her height and weight were 111.2 cm (+0.3 s.d.) and 24.9 kg (+1.7 s.d.), respectively. Her bone age was far advanced, 9.6 years. Serum estradiol (E2) was increased to the pubertal level, 22.6 pg/ml and an GnRH test induced pubertal gonadotropin responses (basal luteinizing hormone [LH], 3.0 mIU/ml, and peak LH, 15.0 mIU/ml; basal follicle-stimulating hormone (FSH), 8.2 mIU/ml, and peak FSH, 13.0 mIU/ml), leading to a diagnosis of central precocious puberty (Table 1). The

Fig. 1. Karyotype of the patient showing der(13;14)(q10;q10). A balanced 13;14 Robertsonian translocation made a derivative chromosome by fusion of the two acrocentric chromosomes 13 and 14.
patient did not present any neurodevelopmental abnormality or any abnormal MRI image of the brain including pituitary gland. At the age of 6 years, dysmorphic evaluation demonstrated bi-temporal narrowing, frontal bossing, low nasal bridge with mildly anteverted nasal tip, and small mouth. Although she had truncal obesity, her hands were very small. Lengths of the right and left hands were 12.2 cm (−2.2 S.D.) and 11.8 cm (−3.6 S.D.), respectively. Her feet were also small, 16.0 cm (−2.1 S.D.) bilaterally. Three clinical features of the patient, characteristic dysmorphism, complication by CPP, and Robertsonian translocation 45, XX, der(13;14)(q10;q10), suggested a diagnosis of matUPD(14). We performed molecular studies to analyze UPD. The karyotypes of the parents were not determined, but they were apparently healthy, without any specific phenotypes suggesting chromosomal or imprinting abnormalities.

<table>
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<tr>
<th>Hormonal evaluations of the patient</th>
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<tr>
<td><strong>Chronological age (years)</strong></td>
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<tr>
<td>4.0</td>
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<tr>
<td>LH (mIU/ml)</td>
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<tr>
<td>FSH (mIU/ml)</td>
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<tr>
<td>Estradiol (pg/ml)</td>
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<td>Bone age (years)*</td>
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ND, not determined. *Evaluated by TW2 (20 bones)-method.

![Fig. 2. Haplotypes of the patient and her parents.](image)

In this family, eight markers were informative, and five showed heterodisomic maternal UPD (D14S990, D14S258, D14S74, D14S280, and D14S65), while three showed isodisomic maternal UPD (D14S70, D14S288, and D14S292).
The patient was enrolled in a study approved by the Ethics Committee of Akita University School of Medicine. Informed consent was obtained from the parents. Genomic DNA was extracted from peripheral blood lymphocytes obtained from the patient and her parents. Fifteen highly polymorphic dinucleotide markers spanning all of chromosome 14 were selected from the NCBI-UniSTS website. Chromosomes 2, 9, and 13 were also analyzed using 4, 4, and 8 dinucleotide markers, respectively. After amplification by PCR, fluorescence-labeled products were mixed and electrophoresed on an ABI 377 DNA sequencer. Results were shown in Fig. 2. In this family, eight markers were informative, and five of these showed heterodisomic maternal UPD (D14S990, D14S258, D14S74, D14S280, and D14S65), while three showed isodisomic maternal UPD (D14S70, D14S288, and D14S292). UPD was not recognized in chromosomes 2, 9, 13.

Since precocious puberty was expected to cause poor growth prognosis, we started administration of a long-acting GnRH analogue (Leuprolide®) to CPP at the age of 6.0 years. This GnRH analogue is used to treat a wide range of sex hormone-related disorders including prostatic cancer, breast cancer, endometriosis and precocious puberty. It acts primarily on the anterior pituitary, inducing a transient early rise in gonad-

Fig. 3. Growth chart for the patient. Abnormal acceleration of height velocity associated with puberty improved after long-acting GnRH analogue treatment.
otropin release. With continued use, it causes pituitary desensitization and down-regulation, leading to suppressed circulating levels of gonadotropins and sex hormones. The starting dose of Leuprolide® was 30 μg/kg/month, but serum levels of LH, FSH, and E2 remained elevated at 8.2 mIU/ml, 5.1 mIU/ml, and 10.1 pg/ml, respectively, 140 days after treatment was started. Increase of Leuprolide® dosage in 60 μg/kg/month still did not sufficiently suppress the hypothalamic-pituitary-gonadal axis and the dosage was finally increased to 90 μg/kg/month. The serum levels of LH, FSH, and E2 were sufficiently suppressed to 3.1 mIU/ml, 4.8 mIU/ml, and < 10.0 pg/ml, respectively, 1.5 years after the treatment (Table 1). Abnormal acceleration of height velocity associated with puberty has been improved after treatment was initiated (Fig. 3).

**DISCUSSION**

Clinical features of a girl with matUPD(14) were described in this report. Although the patient demonstrated some dysmorphic features that suggest the diagnosis of matUPD(14), we considered it difficult to establish the diagnosis only based on these features. In our case, Robertsonian translocation 45, XX, der(13;14)(q10;q10), which was found on chromosomal analysis routinely performed for female patients complaining of short stature, was one key to the diagnosis. Acrocentric chromosomes involved in Robertsonian translocations are prone to being affected by mis-segregation events, resulting in UPD. In the 14 patients with matUPD(14) reported to date, DNA analysis for matUPD(14) was performed after cytogenetic analysis showed a Robertsonian translocation (13;14, 14;14, 12;21) (Berends et al. 1999). Prader-Willi syndrome (PWS) is the most common pathological obesity syndrome presenting as pediatric obesity, and is characterized by some dysmorphic features including narrow forehead, olive-shaped eyes with antimongoloid slant, small hands and feet, mental retardation, hypotonia and feeding difficulty in infancy, obesity in the second year of life, and hypogonadism. Since matUPD(14) has some clinical overlap with PWS, differential diagnosis of matUPD(14) and PWS becomes necessary. One group systematically tested samples from 35 patients with normal karyotypes and unexplained PWS-like phenotypes (Cox et al. 2004). However, none of the samples tested showed evidence of matUPD(14). They concluded that matUPD(14) is not a common explanation for the phenotype in patients referred for PWS testing. Another report also indicated that the incidence of matUPD(14) is likely to be low among patients referred for PWS (Dietz et al. 2005). In our case, complication by CPP was the other key for diagnosis, suggesting matUPD(14) as the etiology. CPP is one of the most common endocrine diseases in children, especially in girls. MatUPD(14) should be considered in the differential diagnosis of CPP associated with characteristic dysmorphism and features frequently described in matUPD(14). In the present patient, the hypothalamus-pituitary-gonadal axis was successfully suppressed with long-acting GnRH analogue. This is the first report describing GnRH analogue treatment for CPP associated with matUPD(14).

**References**


Healey, S., Powell, F., Battersby, M., Chenevix-Trench, G. &


