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BRIEF REPORT — CASE REPORT

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Prader-Willi syndrome in a child with XYY

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Abstract We report a 26-month-old boy with XYY syndrome, with the complication of Prader-Willi syndrome (PWS) due to uniparental maternal disomy of chromosome 15. To our knowledge, this is the first case of XYY syndrome and PWS. Clinical findings were fully compatible with the diagnostic criteria for PWS. Molecular analysis revealed a maternal heterodisomy of chromosome 15, indicating that non-disjunction of chromosome 15 had occurred at maternal meiosis I, and that the non-disjunction of chromosome Y and of chromosome 15 had occurred independently.

Key words XYY syndrome · Prader-Willi syndrome · Uniparental maternal disomy · Non-disjunction of chromosome

Introduction

Prader-Willi syndrome (PWS) was described in 1956 and its clinical features are neonatal hypotonia, mild-to-moderate mental retardation, hyperphagia with subsequent obesity, hypogonadism, short stature, mild facial dysmorphism, and a characteristic neurobehavior (Holm et al. 1993). Approximately 70%–80% of PWS patients have a paternal deletion of chromosome 15q11–q13, and a majority of nondeletion patients have maternal disomy of chromosome 15 or chromosome 15q11–q13. Several patients with Klinefelter syndrome and PWS and some with trisomy X syndrome and PWS have been reported (Butler et al. 1997). It was probable that non-disjunction of chromosome 15 and other chromosomes may have occurred coincidentally at some frequency. However, molecular analysis in these patients indicated that non-disjunction of the X chromosome and of chromosome 15 each occurred independently. We report here a PWS patient with XYY syndrome and discuss the non-disjunction events.

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Clinical report

The patient was born to a healthy 32-year-old mother and 32-year-old father who were unrelated. The parents had two other healthy boys. The mother felt decreased fetal movements during the pregnancy. The patient was born at 41 weeks of gestation by emergency cesarean section due to fetal distress. Birth weight was 2,486 g (−1.8 SD), length 50 cm (−0.2 SD), and head circumference 37.2 cm (+2.6 SD). Dolichocephaly and a narrow face was noted. The infant showed severe hypotonia and cried weakly like a cat. Nasogastric tube feeding was necessary for 1 week due to his inability to nurse or suck. Bilateral hip dislocation, right clubfoot, and bilateral cryptorchidism were detected. Brain echography revealed no abnormalities. Chromosomal analysis showed a karyotype of 47, XYY in 20 out of 20 metaphase cells. He was treated with an apparatus for bilateral hip dislocation at 4 months of age. Mild generalized hypotonia persisted until about 6 months of age. Feeding problems had resolved at 6 months of age and he showed an increased appetite, resulting in rapid body weight gain. Right clubfoot and bilateral cryptorchidism were treated surgically at 10 and 12 months of age, respectively. He showed developmental delay. He sat at 12 months and spoke several words at the age of 2 years. He received occupational therapy from the age of 19 months. Hypotonia persisted, but was less pronounced than during the infant period.

A genetic evaluation was requested at 17 months of age, at which time his height was 77 cm (−1.1 SD) and weight

Table 1. Microsatellite analysis in PWS family

	PWS family		
Markers	Patient	Father	Mother
D15S128	1/1	2/2	1/1
D15S210	1/2	2/3	1/2
D15S817	2/4	1/3	2/4
D15S97	1/1	2/2	1/1

PWS, Prader-Willi syndrome

was 11.8kg (+1.3 SD). He had a bland expressionless face with a history of skin picking. Bilateral epicanthal folds, almond-shaped palpebral fissures, small feet, and narrow hands with a straight ulnar border were noted. The patient had fair skin, light-colored hair, a small penis, and a small and flat scrotum with retractile testicles. Chromosomal analyses of his parents were normal. Clinically, he was suspected to be affected with Prader-Willi syndrome (PWS). Fluorescent in situ hybridization in the PWS critical region on chromosome 15q11.2 showed no deletion. Analysis of DNA methylation in the PWS locus on chromosome 15q11–q13 was performed by polymerase chain reaction (PCR) using genomic DNAs extracted from peripheral white blood cells of the patient and his parents (Glenn et al. 1996, Kubota et al. 1997). An exclusively maternal methylation pattern was observed in the small nuclear ribonucleoprotein polypeptide N (*SNRPN*) gene (data not shown). To distinguish uniparental disomy and an imprinting mutation, the polymorphic pattern using microsatellite DNA markers (D15S128, D15S210, D15S817, and D15S97) distributed along chromosome 15 was analyzed in both the parents and the patient. With three fully informative markers, D15S128, D15S817, and D15S97, only maternal alleles were detected, indicating the presence of maternal uniparental heterodisomy for chromosome 15 in peripheral white blood cells (Table 1).

Discussion

The clinical findings in the patient were fully compatible with the diagnostic criteria for PWS (Holm et al. 1993). The symptoms for XYY syndrome are known to be subtle and were not marked in our patient. Some clinical features, including mental retardation, cryptorchidism, and a small penis may be overlapping symptoms of PWS and XYY syndrome.

If non-disjunction of chromosome Y and chromosome 15 had occurred coincidentally by postzygotic missegregation, chromosomal change in our patient would have been explained by one event. Some maternal environmental factors or some endogenous factors in the female gamete itself may have led to non-disjunction of chromosome 15 during female gametogenesis and to non-disjunction of chromosome Y postzygotically. However, somatic mosaicism was not observed by chromosomal analysis. It is reasonable to consider that the non-disjunction of chromosome Y and of chromosome 15 occurred independently; the non-disjunction of chromosome 15 at maternal meiosis I and the non-disjunction of the Y chromosome at paternal meiosis II.

The incidence of PWS is about 1 per 10,000 live births, and maternal disomy 15 accounts for about 25% of those subjects. Therefore, the chance for a child to be born with PWS due to maternal disomy 15 would be about 1 in 40,000. The chance of having a child with XYY syndrome is 1 in 1,800 live births. Assuming that these non-disjunction events occurred independently, the odds of having a child with both PWS (due to maternal disomy 15) and XYY syndrome would be about 1 in 72,000,000. Studies of patients with PWS associated with other genetic diseases may provide genetic information useful for understanding the mechanism of uniparental disomy.

References

Butler MG, Hedges LK, Rogan PK, Seip JR, Cassidy SB, Moeschler JB (1997) Klinefelter and trisomy X syndromes in patients with Prader-Willi syndrome and uniparental maternal disomy of chromosome 15—a coincidence? Am J Med Genet 72:111–114

Glenn CC, Saitoh S, Jong MTC, Filbrandt MM, Surti U, Driscoll DJ, Nicholls RD (1996) Gene structure, DNA methylation, and imprinted expression of the human SNRPN gene. Am J Hum Genet 58:335–346

Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg (1993) Prader-Willi syndrome: consensus diagnostic criteria. Pediatr 91: 398–402

Kubota T, Das S, Christian SL, Baylin SB, Herman JG, LedBetter DH (1997) Methylation-specific PCR simplifies imprinting analysis. Nature Genet 16:16–17