13 Trisomy Born to a Mother Treated with Bromocriptine : Incidental or Not?

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IMAI, T., YASUDA, K., OHTA, T. and MIURA, K. 13 Trisomy Born to a Mother Treated with Bromocriptine : Incidental or Not? Tohoku J. exp. Med., 1987, 153 (3), 233-238 — A case of 13 trisomy born to a mother treated with bromocriptine is described. She, 27 years old, was treated with bromocriptine (5 mg/day) as a galactorrhea amenorrhea syndrome with hyperprolactinemia (basal 34-122 ng/ml). After the treatment for about a month, disappearance of galactorrhea and occurrence of menstruation were observed. She became pregnant on the second ovulation. On the 34th week she got a male 13 trisomy (47, XY, +13) baby with premature delivery. The baby died 11 hr after his birth. After the first delivery, bromocriptine was readministered. Following the induced abortion on the second pregnancy, she borned a healthy baby on the third pregnancy in spite of taking bromocriptine. This case of 13 trisomy might be incidental. However, the effect of bromocriptine on chromosome should be further evaluated in detail. ———— 13 trisomy ; bromocriptine ; hyperplolactinemia ; pregnancy ; congenital malformation

One of the greatest concern over the drugs administered for infertility or during pregnancy is adverse effects on pregnancy and teratogenic effects on fetus. Bromocriptine is now widely accepted for the treatment of normoprolactinemic as well as hyperprolactinemic infertility. Although the safety of bromocriptine has been reported in several survey works (Turkaji et al. 1982; Kurachi et al. 1983, 1986; Raymond et al. 1985), the follow-up period and the numbers of babies entered into the studies would not be fully satisfactory for the evaluation of the safety of this drug.

The authors present the suggestive baby of 13 trisomy delivered from the mother ingesting bromocriptine.
A nulliparous woman, 27 years old, visited Gifu University Hospital because of infertility and amenorrhea. She has had no particular familial and past histories, including consanguineous marriage. Her menstruation had been regular until 17 years old. At the age of 17 she developed irregular menstruation, several times a year. Since 19 years old she had noted amenorrhea. She got married at the age of 26 with 28 years old healthy man. She had no history of particular drug ingestion. She denied headache nor visual disturbance.

Her height is 156 cm and weight is 47.5 kg. Visual acuity and field on perimetry were normal. Bilateral galactorrhea was demonstrated by moderate massage. Otherwise physical examination revealed no remarkable findings.

Skull x-ray, sellar polytomography and CT scan revealed no abnormal findings. Basal plasma prolactin levels were high and ranged from 34 to 122 ng/ml (upper limit of basal level of normal subjects in our laboratory: 24 ng/ml). In TRH test (500 µg, i.v.) plasma prolactin decreased from 34 to 16 ng/ml. In metoclopramide (MTC) test (10 mg, i.v.) plasma prolactin increased slightly from 100 to 133 ng/ml at 90 min. On the other hand, plasma prolactin decreased from 122 to 23 ng/ml by a single ingestion of 2.5 mg bromocriptine. Plasma LH and FSH responses (21 to 145 mIU/ml and 10 to 31 mIU/ml, respectively) to LH-RH (100 µg, i.v.) and TSH response (3 to 18 µU/ml) to TRH were normal.

Clinical course is shown in Fig. 1. Bromocriptine was initially administered in dose of 2.5 mg/day for 7 days and increased to 5 mg/day as idiopathic galactorrhea amenorrhea syndrome. About a month after the treatment basal plasma prolactin normalized to 6 ng/ml, and disappearanc of galactorrhea and occurrence of menstruation were observed. She became pregnant on the second ovulation, as judged from basal body temperature (BBT), and bromocriptine was discontinued on the 20th day of conception. After the cessation of bromocriptine, plasma prolactin rose to 227 ng/ml in the 7th week of pregnancy, and was

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**Fig. 1.** Clinical course of the mother (Case H.K., 30 years, Female). Shaded area in the part of basal prolactin level shows the normal range during pregnancy. BBT, basal body temperature.
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1. Her pregnancy progressed normally. On the 34th week her pregnancy resulted in a premature delivery and got a male baby weighed 1,600 g. Apgar score was 6. The baby died 11 hr after his birth. The chromosomal study of the blood revealed 13 trisomy (47, XY, +13) (Fig. 2).

2. On the 28th day after the delivery basal plasma prolactin was 74 ng/ml (Fig. 1) and CT scan revealed the intracellular low density area by enhancement. Although she had had no menstruation with readministration of bromocriptine, she became the second pregnancy. Induced abortion was performed for her health.

3. Bromocriptine was intermittently readministered every month (Koike et al. 1980) for elevated prolactin and galactorrhea. Namely, daily 5 mg of bromocriptine was administered from the day of the end of menstruation to the 5th day of luteal phase as judged from BBT. With this therapy plasma prolactin lowered into normal range. However, prolactin response to MTC was still low (4 to 12 ng/ml). Galactorrhea disappeared and menstruation recurred. On the 9th ovulation with combined therapy of HCG (5,000 U, i.m. for 4 days) (Fig. 1) she became the third pregnancy, and bromocriptine was withdrawn. Plasma prolactin was 9 ng/ml before the conception but increased to 215 ng/ml during the first trimester with galactorrhea. Readministration of bromocriptine from the 11th week resulted in normalization of plasma prolactin level and disappearance of galactorrhea. She was delivered of a female baby weighed 3,620 g in the 40th week. The baby was physically normal and has been in good health.

4. One month after the delivery, the mother's plasma prolactin was 17.6 ng/ml, and 7 months after the delivery plasma prolactin responded to MTC from 34 to 93 ng/ml. Puerperal lactation was good.

5. The baby with 13 trisomy exhibited many anomalies. Defects of skull skin and bone were remarkable. Bilateral anophthalmia, bilateral auricular deformation, marked cleft lip and palate, and retention of the testes were noted. Defects of two thoracic vertebrae and ribs were noted by whole body x-ray. In extremities polydactylies of both feet (each 6) were also found. Autopsy was not performed.

**DISCUSSION**

It seems likely that hyperprolactinemia in this mother is due to micro-
prolactinoma, as suggested by low or decreased responses of plasma prolactin to MTC and TRH, and low density area by CT scan after the first pregnancy.

Clinical course of the first pregnancy in this mother seemed to be comparable with those in several survey series on the pregnancy in the patients treated with bromocriptine. That is, period of bromocriptine administration during pregnancy in our case, 20 days after ovulation, was not different from mean values of 13.7 (Kurachi et al. 1983), 16.8 (Kurachi et al. 1986) and 21 days (Turkaji et al. 1982) after ovulation. The high plasma prolactin levels observed during the pregnancy in this mother was also applicable to those in the previous works.

Incidence of congenital anomalies in the mothers treated with bromocriptine was 2.2% in 134 babies (Kurachi et al. 1983), 3.5% in 1,241 babies (Turkaji et al. 1982), 6.3% in 64 babies (Raymond et al. 1985) and 1.8% in 448 babies (Kurachi et al. 1986). The incidences of premature delivery were 5.5% in 134 babies (Kurachi et al. 1983) and 11.1% in 1,241 babies (Turkaji et al. 1982) and 7.9% in 448 babies (Kurachi et al. 1986). All these figures corresponded to the normal pregnancy (Turkaji et al. 1982; Kurachi et al. 1983, 1986). In the study by rat no teratogenic activity was detected (Weinstein et al. 1982), although rabbits given bromocriptine during pregnancy have offspring with an unusually high incidence of cleft lip (Spark and Dickstein 1979). Based on these findings, there has been general agreement that bromocriptine does not increase the risk of congenital malformations when it was used for inducing ovulation. However, the administration of bromocriptine is generally discontinued as soon as pregnancy was confirmed. To our knowledge, chromosomal study with relation to bromocriptine treatment was performed in only 19 babies (Schellekens et al. 1977). All babies except one with hereditary pericentric inversion of the 6th chromosome showed normal chromosomal pattern (Schellekens et al. 1977). In the survey work of 1241 infants by Turkaji et al. (Turkaji et al. 1982), two cases of Down Syndrome (21 trisomy) were included. 13 trisomy, differed from 21 trisomy, is a relatively rare chromosomal abnormality, and the frequency was reported as one per 7,000 (Conen and Erkman 1966) or 145,000 (Taylor 1968) babies. The fact that chromosomal abnormalities observed during bromocriptine treatment were all trisomy may suggest the necessity of future study of the effects on chromosome. Most 13 trisomy is spontaneously aborted in the early period of pregnancy. However, chromosomal study of the aborted fetus from the mothers taking bromocriptine has not been performed. Anomalies found in the present baby were all typical for 13 trisomy. Trisomy, either 13 or 21 trisomy, of chromosome is caused by chromosomal non-disjunction at the first or the second meiotic division. It is well known that prevalence of 13 trisomy as well as 21 trisomy increased with advanced maternal age. In fact, the frequency of 13 trisomy increases in the mothers above 40 (Lenz et al. 1966). In the present case, however, the age of the mother was 28. A pair of the 13th chromosome in this baby should be derived from a mother or a father. The authors could not perform the
examination of Q-band or NOR + G band, and not confirm the origin of 13th chromosome in our baby. So there is no evidence of the positive participation of bromocriptine in 13 trisomy in our baby and it might be coincidental. Especially, the fact that healthy baby was born to the same mother treated by bromocriptine, support this possibility. However, it is conceivable that bromocriptine administered may affect on the early phase of the second meiotic division.

There are too small amount of studies to conclude the complete safety of the drug for chromosome. The necessity of further chromosomal investigations including various bands in the babies and also in the aborted fetus should be emphasized, and abnormal cases, even if it seemed to be incidental, should be accumulated in future.

Acknowledgments

This case was reported to the committee on the surveillance of bromocriptine treatment in Japan. This study was supported by grants from the Disorders of Adrenal Hormone Research Committee (Chief, Prof. R. Takeda) and from the Disorders of the Hypothalamo-Pituitary Gland Research Committee (Chief, Prof. N. Shimizu) of the Japanese Ministry of Health and Welfare.

References


