Acta Med. Nagasaki 64: 31－34

Case Report

Genetic counseling for trisomy X syndrome diagnosed by amniocentesis: a case report

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[Introduction]

Trisomy X is a sex chromosome abnormality that occurs in approximately 1 in 1,000 female births. We provided genetic counseling to a pregnant woman and her husband following the prenatal diagnosis of trisomy X by amniocentesis.

[Case]

A 27-year-old pregnant woman, gravida 2, para 1, underwent a prenatal checkup by her general practitioner. Nuchal translucency (NT) of 3.4 mm was detected in the fetus at 11 weeks of gestation and had disappeared by 12 weeks of gestation. The pregnant woman and her husband consulted our unit for genetic counseling at 13 weeks of gestation. Although we did not detect any NT or other abnormality in the fetus, the parents were concerned about possible abnormalities and requested amniocentesis. Amniocentesis followed by chromosomal analysis at 16 weeks of gestation revealed a 47,XXX karyotype. We explained the results and characteristics of trisomy X to the couple. The frequency of trisomy X is 1 in 1,000, and it can be characterized by tall stature, developmental delay, learning disability, anxiety, and mood disorders. However, the features of trisomy X vary and we were therefore unable to predict the newborn's precise postnatal physical and psychological characteristics. The couple decided to continue the pregnancy, and a female newborn was delivered at 38 weeks of gestation weighing 2,418 g. The karyotype was confirmed as 47,XXX, but her development to date (age of 2 years) has been normal.

[Conclusions]

Careful genetic counseling is important for pregnant women and their partners following a prenatal diagnosis of trisomy X.

ACTA MEDICA NAGASAKIENSIA 64: 31－34, 2020

Key words: trisomy X syndrome, chromosome abnormality, genetic counseling, perinatal diagnosis

Introduction

Trisomy X was first reported by Jacobs et al.[1] in 1959. Trisomy X syndrome is a sex chromosome aneuploidy in females, with an incidence of 1 of 1,000 female births.[2] Trisomy X syndrome (including females with the 47,XXX karyotype and <20% mosaicism) is being prenatally diagnosed increasingly more often using techniques such as amniocentesis and noninvasive prenatal screening of maternal blood.[3] However, trisomy X syndrome is an unexpected prenatal diagnosis, and genetic counseling is therefore important for the pregnant woman and her family.[3]

Case

A 27-year-old pregnant woman, gravida 2, para 1, had undergone her first pregnancy without problems and delivered

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Received February 3, 2020; Accepted February 20, 2020

a healthy boy. She became pregnant again and underwent a prenatal checkup by her general practitioner. However, the doctor detected a 3.4-mm nuchal translucency (NT) in the fetus at 11 gestational weeks by ultrasonography. The doctor informed the patient of this finding, but the NT was no longer detectable at 12 weeks of gestation. The pregnant woman was anxious about the NT and visited our department, together with her husband, at 13 weeks of gestation. We were also unable to detect NT in the fetus and explained this to the couple. In addition, a genetic counselor counseled them on the meaning of NT, chromosomes, chromosomal abnormalities, and chromosome tests. The couple chose to undergo amniocentesis, which was performed at 16 weeks of gestation. The chromosome test revealed a 47,XXX karyotype (Figure 1). We explained the result to the patient and her husband and counseled them about the implications of trisomy X syndrome detected at 19 weeks of gestation. We explained that this syndrome may be associated with various morphological abnormalities and developmental disorders[3,4] (Table 1) but that the symptoms varied and did not all necessarily apply to their fetus. We also explained that trisomy X is not a rare disease, with an incidence of 1 in 1,000 female births, but that it remains undiagnosed in most girls.[4] The pregnant woman remained anxious but had no questions, while her husband said, "A lot of diagnosed cases means that there are many women who live normally."

Fetal ultrasonography screening at 20 weeks of gestation showed no abnormal findings. The couple discussed their options for 1 week and then decided to continue the pregnancy. Her husband said, "We decided to do our best with our baby."

The subsequent course of the pregnancy was uneventful, and a female newborn was born at 38 weeks of gestation, weighing 2,418 g. A chromosome test performed by a pediatrician after birth confirmed the 47,XXX karyotype. The newborn was diagnosed with mild pulmonary artery stenosis at 1 month of age on echocardiography, but the pediatrician decided that no treatment was necessary and opted for follow-up. He explained to the parents that there was no link between pulmonary artery stenosis and trisomy X. The child's height, weight, and development were all within the normal ranges at 2 years of age, and she was being regularly followed up in a pediatric outpatient setting at the time of this writing.

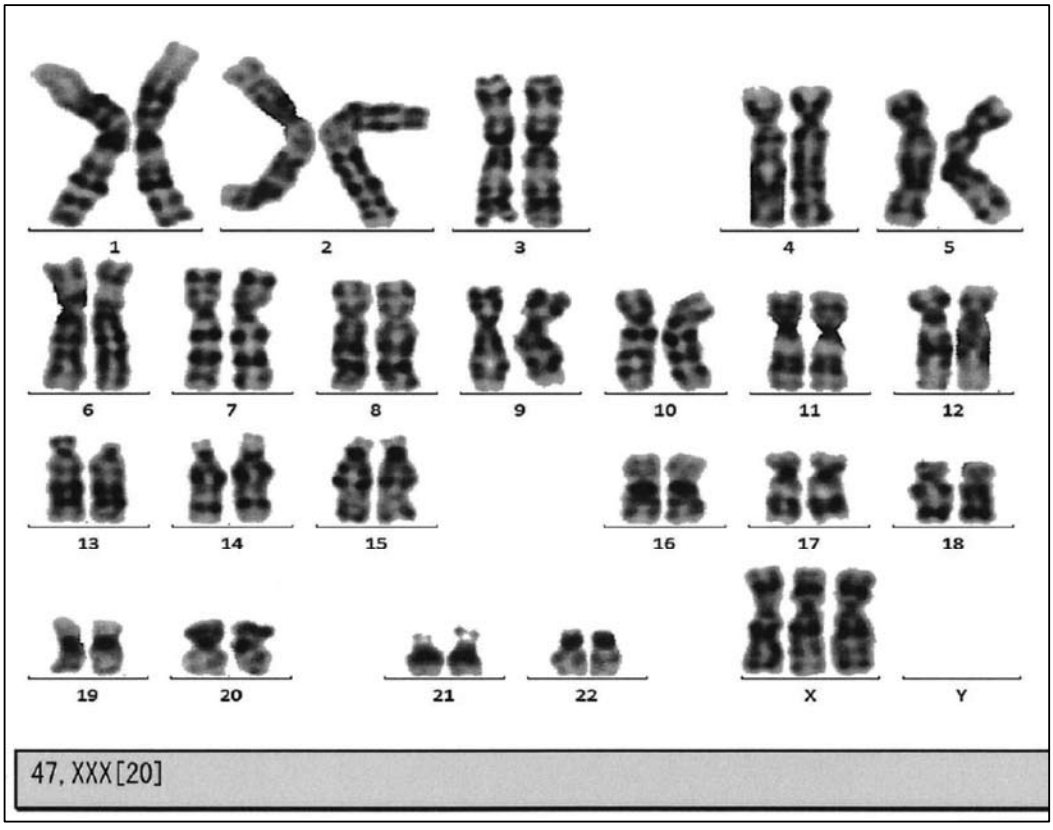

Figure 1. Karyotype analysis following amniocentesis

Table 1. Physical and medical features associated with trisomy X syndrome[3,4]

- Tall stature
- Epicanthal folds
- Clinodactyly
- Hypotonia in infancy
- Genitourinary malformations
- Renal anomalies
- Cardiac anomalies
- Constipation/abdominal pains
- Autoimmune problems
- Ovarian function/fertility problems
- Intention tremor
- Congenital hip dysplasia
- Seizure disorder
- Developmental delay
- Learning disabilities
- Attention-deficit/hyperactivity disorder, executive functioning problems
- Speech–language disorders
- Motor skills disorders
- Adaptive functioning problems

Discussion

Patients with trisomy X display a range of characteristics with varying frequencies.[4] Trisomy X can be associated with abnormal developmental and psychological features, but the phenotype varies widely from minimal involvement to clinically significant problems. It is therefore important to explain this syndrome carefully when counseling couples about trisomy X. The reported abortion rates for trisomy X vary from 16% to 70%.[5,6,7] Gruchy et al.[7] retrospectively reviewed 291 prenatally diagnosed cases of trisomy X in France during a 30-year period. In their report, the abortion rate decreased from 41.1% before 1997 to 11.8% after 1997, and the authors suggested that this change may have been due to better explanations to parents.[7]

In the current case, NT was detected by ultrasonography during early pregnancy, and trisomy X was subsequently diagnosed by an amniotic fluid chromosome test. The result was unexpected for the couple, and they were worried about whether to continue their pregnancy. After the birth, the mother read about trisomy X on the Internet and was disturbed by comments regarding developmental disorders associated with the condition. She felt that her child was developing language more slowly than her brother and reported her concerns to the pediatrician. Tartaglia et al.[4] pointed out that information on the Internet might be biased. Importantly, the frequency of trisomy X is high (1 in 1,000 female births), and the couple was informed that most girls with the condition remain undiagnosed. Berglund et al.[8] reported that the incidence of trisomy X was 1.6 per 1 million females, and no change in the incidence was observed from 1970 to 2010. This report implies that there are many women who have not been diagnosed with trisomy X. Furthermore, patients with trisomy X do not necessarily present with all the symptoms listed. In our case, the parents were very concerned about developmental disorders. Prenatal ultrasound findings of trisomy X reportedly include thickening of the NT and fetal growth restriction. However, we explained that developmental disorders cannot be diagnosed before birth. Tartaglia et al.[4] reported that the mean full-scale IQ score of individuals with trisomy X was 85 to 90 and that approximately 5% to 10% had intellectual disability. We therefore spent a long period of time counseling the couple appropriately to ensure that they understood the implications of the diagnosis of trisomy X, after which they decided to continue the pregnancy.

We have summarized the postnatal characteristics of trisomy X from previous reviews in Table 2.[2-4,9] Women with trisomy X reportedly have various physical characteristics,

developmental disorders, and emotional disorders. However, all affected women do not have all reported characteristics; therefore, close long-term observation of newborns with trisomy X is required. Careful personal follow-up is important because of insufficient reporting on adult women with trisomy X.[2]

In conclusion, patients with trisomy X can present with various characteristics, and careful genetic counseling is needed for pregnant woman and their partners following a prenatal diagnosis of trisomy X.

Acknowledgments

The authors have no conflict of interest with regard to this report. We thank Susan Furness, PhD and Angela Morben, DVM, ELS, from Edanz Group (https://en-author-services.edanzgroup.com/), for editing a draft of this manuscript.

Table 2. Postnatal characteristics of trisomy X reported in previous reviews

Medical features	Estimated frequency (%)
Tall stature[4]	80–89
Epicanthal folds[4]	32–46
Clinodactyly[4]	42–65
Hypotonia in infancy[4]	55–71
Genitourinary disorders[3,4]	5–16
Congenital hip dysplasia[3,4]	2–12
Constipation/abdominal pain[3,4]	12–45
Seizure disorder[3,4]	11–16
Tremor[3,4]	6–20
Developmental characteristics	
Attention-deficit/hyperactivity disorder[3,4]	25–48
Low verbal IQ of teenage girls[2,3]	86
Low performance IQ of teenage girls[2,3]	90–95
Language difficulties[2,3]	72–75
Learning disability[2,3,9]	37–74
Any psychiatric mood disorder[2,3]	30–37

References

1) Jacobs PA, Baikie AG, Brown WM, Macgregor TN, Maclean N, Harnden DG. Evidence for the existence of the human "super female." *Lancet* 2: 423-425, 1959
2) Otter M, Schrander-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. *Eur J Hum Genet* 18: 265-271, 2010
3) Wigby K, D'Epagnier C, Howell S et al. Expanding the phenotype of Triple X syndrome: a comparison of prenatal versus postnatal diagnosis. *Am J Med Genet A* 170: 2870-2881, 2016
4) Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). *Orphanet J Rare Dis* 5: 8, 2010
5) Forrester MB, Merz RD. Pregnancy outcome and prenatal diagnosis of sex chromosome abnormalities in Hawaii, 1986–1999. *Am J Med Genet A* 119A: 305-310, 2003
6) Hamamy HA, Dahoun S. Parental decisions following the prenatal diagnosis of sex chromosome abnormalities. *Eur J Obstet Gynecol Reprod Biol* 116: 58-62, 2004
7) Gruchy N, Blondeel E, Le Meur N et al. Pregnancy outcomes in prenatally diagnosed 47,XXX and 47,XYY syndromes: a 30-year French, retrospective, multicentre study. *Prenat Diagn* 36: 523-529, 2016
8) Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet J Rare Dis* 14: 16, 2019
9) Freilinger P, Kliegel D, Hänig S, Oehl-Jaschkowitz B, Henn W, Meyer J. Behavioral and psychological features in girls and women with triple-X syndrome. *Am J Med Genet* 176: 2284-2291, 2018