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Tetrasomy X in a Child with Multiple Abnormalities: Case Report and Literature Review from China

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Abstract Polysomy of the X chromosome is a very rare disorder, and little information is available in the literature. Tetrasomy X was first reported in 1961 and only approximately 60 cases have been reported. Herein, we reported a 5-year-old girl with tetrasomy X, who presented to our clinics because of "short stature". She was born to a G2P2 mother at 39 weeks of gestation with a birth weight of 3.5 kg. She started walking at 16 months of age, and speaking at 18 months. She had syndactyly in both hands and patent ductus arteriosus (0.7 cm), which were corrected by surgery soon after birth and at 7 months of age, respectively. She also had a history of epilepsy for 3 years with 4 episodes of convulsion but none in the past two years, and depakine was administered till now. She was apt to get pneumonia. She was 105 cm in height and 13 kg in weight, showing a coarse face with ocular hypertelorism and epicanthus. She presented with female external genitalia with Tanner I breast and external genitalia development. Her pelvic ultrasound showed immature uterus and ovarian. Intelligence quotient test revealed low intellectual functioning (IQ: 51). Cytogenetic investigation revealed a karyotype of 48,XXXX. These data showed that in females with intellectual disabilities, abnormal height, microcephaly, skeletal and limb anomalies, and congenital heart defects, 48,XXXX karyotype should be considered although it is an extremely rare entity.

Key words 48,XXXX; Intellectual disabilities; Malformation; Sex chromosomal disease; Tetrasomy X

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Introduction

Chromosomal abnormalities include abnormal number or structure of the chromosomes, an important cause of congenital anomalies, psychiatric disorders, and intellectual disabilities.[1,2] The addition or deletion of an X or Y chromosome to a normal karyotype results in a sex chromosome abnormality (SCA) such as 45,X, 47,XXX, and 47,XXY. SCAs occur in at least 1 out of 400 births, and their phenotypes have been extensively described. Most common is deletion of an X or Y chromosome, namely Turner syndrome (45,X).[1] However, the addition of more than one extra sex chromosome is rare. Polysomy of the X chromosome, i.e. 48,XXXX (tetrasomy X) and

49,XXXXX (pentasomy X), is a very rare disorder, and little information is available in the medical literature. The first case of tetrasomy X was reported by Carr et al in 1961, and only approximately 60 cases have been reported.[3-7] Herein, we reported a case of tetrasomy X and reviewed literatures to emphasize the clinical features, diagnosis and management of this rare entity.

Case Report

A 5-year-old girl was presented to our clinic because of "short stature". She was born to a G2P2 mother at 39 weeks of gestation via normal spontaneous vaginal delivery following an uncomplicated pregnancy. Her birth weight was 3.5 kg without asphyxia history. She started walking and speaking at 16 and 18 months, respectively. She had syndactyly in both hands, which was corrected by surgery soon after birth. She was born with patent ductus arteriosus (PDA, 0.7 cm), which was closed by operation (ligation from left chest) at 7 months of age. She was apt to get pneumonia even after operation for PDA. She also had a history of epilepsy for 3 years with 4 episodes of convulsion but none in the past 2 years, and depakine was administered till now. Her family history was unremarkable and her mother did not use alcohol, drugs, or any medications during pregnancy.

Upon physical examination, the patient was 105 cm in height (standard deviation score, SDS, -1.47) and 13 kg in weight (SDS, -2.83) showing a coarse face with ocular hypertelorism and epicanthus. She presented with female external genitalia with Tanner I breast and external genitalia development. No webbing of neck, skeletal or limb anomalies was found. The dermal, aural, ocular, nasal, thoracic, cardiac, and pulmonary examination all showed normal results.

Screening laboratory test results were all within normal limits or were negative for liver and kidney function, thyroid-stimulating hormone, adrenocorticotrophic hormone and cortisol, and TORCH-IgM. Her pelvic ultrasound showed immature uterus and ovarian. Intelligence quotient test revealed low intellectual functioning (IQ: 51). Cytogenetic investigation using blood culture and G chromosome banding revealed a karyotype of 48, XXXX. All metaphases were found to have the same pattern. No mosaicism was detected.

Discussion

X chromosome tetrasomy is a rare gonosomal aneuploidy. Since the first case was reported in 1961, only approximately 60 cases of tetrasomy X have been reported. Tetrasomy X was reported in none of the 242 paediatric patients we reviewed with sex chromosome abnormalities from 1998 to 2008.[1] The mechanism of tetrasomy X is still unclear. It seems likely that most, if not all, tetrasomy X is attributable to successive non-disjunctional events involving the same parent. Indeed, the most likely mechanism is a nondisjunction of the maternal X chromosomes in both divisions of meiosis in order to produce a tetrasomy X ovum.

To our knowledge, this is the fourth case of tetrasomy X reported from China (Table 1).[5-7] All these four patients had a female phenotype. Unfortunately, none was diagnosed before 2 years of age, but between 2 and 14 years (2, 5, 8 and 14 years), despite of various clinical features. This may be due to the very low incidence of tetrasomy X, in combined with inconstant signs and insufficient awareness of this disease among paediatricians and other practitioners.

Previous reports have suggested a direct relationship between the number of supernumerary X chromosomes and the phenotypic severity, whilst on the other hand many polysomy X syndromes carry a high level of variety within their physical and behavioural phenotype. However, Moraes et al showed that more than one X activation in most cell lines from their study on the X chromosome inactivation in patients with 49,XXXXX, which implied that the disruption of X inactivation was associated with severe phenotype.[8] Among these 4 patients reported from China, all had intellectual disabilities, including cognitive, language and/or motor, especially language retardation in case 3. Microcephaly and later start walking were noted in case 3 while epilepsy was reported in our case. The mechanism of epilepsy is still unknown. It is commonly regarded that it is not caused by the action of a single gene in single or triple dose, but is influenced by the combined action of a number of genes within and outside of the aneuploid segment.

Besides, other inconstant multiple malformations were noted. Ocular hypertelorism was noted in three patients, epicanthus and mild jaw prognathism in two, and depressed nasal bridge in one. Cleft palate was noted in two patients. Short finger of bilateral pinkie was found in two while less

number of fingerprint ridge lines, clinodactyly of fingers and toes, and syndactyly was found in one patient, respectively. Malnutrition and short stature were noted as well. These were similar to previous reports,[3,4] and some features were similar to patients with Down syndrome.[5,6] Moreover, it was notable that the PDA was the only reported type of congenital heart defects in 3 of the 4 patients (including current case). Whether PDA is associated with tetrasomy X requires further study.

The sex chromosome-related short stature homeobox-containing gene (SHOX) is associated with the height of some sex chromosomal abnormality, such as Turner syndrome. Many have suggested that tall stature in patients with additional sex chromosomes is associated with an overdosage of the SHOX gene, which may result in excessive growth.[9] Rooman et al reviewed 39 patients with 48,XXXX and found that most of them had normal or tall stature.[10] However, Ottesen et al showed that the median height standard deviation scores (SDS) was -0.6 (-1.9 to +2.1) in 13 patients with 48,XXXX karyotype.[11] Among the four cases reported from China, case 3 was 160 cm in height. No data on height and weight were available for case 1 and 2, which may imply that they had normal height. However, our current case had -1.47 SDS for height. The discrepancy on height is still unknown and the effect of an addition X or Y chromosome on height needs further investigation.

Whether the genital system is affected has been variably reported. Premature ovarian failure was reported in a patient with mosaic pentasomy X/tetrasomy X syndrome and complete tetrasomy X syndrome.[10,12] In the four studied patients, two patients (including the current case) had normal uterus and ovarian, and one patient (case 3) had menarche at 12 years of age. Genital system was not mentioned in the other patient. It was notable that naive vulvar and possible uterine agenesis were reported in one patient. To our knowledge, this is the second case of 48,XXXX aneuploidy with documented absence of ovaries. It may be associated with the levels of inactivation of X chromosome.

Table 1 The clinical data of the patients reported from China

	Case 1	**Case 2**	**Case 3**	**Current case**
Age (Years)	2	8	14	5
Neurodevelopmental features	Intellectual disabilities	Poor learning ability	Poor language and memory for digital, microcephaly (51 cm head circumference), start walking and speaking at 34 months and 10 years	Intellectual disabilities (IQ, 51), epilepsy, started walking and speaking at 16 months and 18 months
Facial features	Ocular hypertelorism, epicanthus, mild jaw prognathism, cleft palate	Long face, ocular hypertelorism, epicanthus, mild jaw prognathism, II° cleft palate	Small palpebral fissures, ocular hypertelorism (5.6 cm), small inner canthus, depressed nasal bridge	Coarse face with ocular hypertelorism and epicanthus
Hand and foot	Not available	Short finger of bilateral pinkie, less number of fingerprint ridge lines.	Short finger of bilateral pinkie, clinodactyly of fingers and toes	Polydactyly in both hands
Growth and pubertal development	Malnutrition, not available for pubertal development	Naive vulvar, possible uterine agenesis	160 cm in height, 31 kg in weight; menarche at 12 years	Short stature (105 cm), 3.5 kg birth weight; immature uterus and ovarian
Congenital heart disease	Patent ductus arteriosus	Patent ductus arteriosus	Not available	Patent ductus arteriosus
Reported year/Reference	1996[5]	2001[6]	2007[7]	2010

The prognosis of patients with tetrasomy X is associated with the karyotype, X chromosome inactivation and the malformations. Adult cases have been rarely reported and are usually due to mosaicism tetrasomy X. Some surgical intervention should be applied to correct the malformations. Sex hormones replacement therapy (estrogen) was suggested to promote the development of the second sexual characteristics in patients without ovarian. Genetic counselling is indicated during subsequent pregnancies. Besides somatic areas, mental development (cognitive, language and motor coordination) will be affected in patients with tetrasomy X.

In summary, our data showed that in females with intellectual disabilities, abnormal height, microcephaly, skeletal and limb anomalies, and congenital heart defects, 48,XXXX karyotype should be considered although it is an extremely rare entity.

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Contributors

Mrs. Zi Yan Jiang was responsible for protocol development and writing the manuscript. Mrs. Wen Yi Xiong was responsible for patient management. Prof. Chao Chun Zou supervised the design and execution of the study and writing the manuscript.

Conflict of Interest

There are no competing interests.

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