49, XXXXY Syndrome

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49, XXXXY syndrome is a rare sex chromosomal disorder. A 5-month-old boy had failure to thrive and multiple congenital anomalies including microcephaly, facial dysmorphism (hypertelorism, megacornea, cleft palate, and micrognathia), obvious heart murmur, umbilical hernia, microphallus, and mild clenched hands. Chromosomal studies via techniques of G-banding and fluorescence in situ hybridization showed the constitution to be 47, XXXXY in all cells. Ventriculomegaly and congenital cardiac defects (patent ductus arteriosus, atrial septal defect, and peripheral pulmonary stenosis) were noted. He has severe atopic dermatitis with high IgE levels and psychomotor retardation. After heart surgery and nutritional support, he has better growth and the rehabilitation program is continuing. *(Chang Gung Med J 2004;27:551-4)*

Key words: sex chromosome, 49, XXXXY syndrome, Klinefelter syndrome.

The 49, XXXXY syndrome was first reported in 1960 by Fraccaro et al.[1] This rare sex chromosomal aneuploidy syndrome has an approximate incidence of 1 in 85000 male births.[2] Over 100 cases of 49, XXXXY syndrome have been published to date.[3-7] These patients are frequently diagnosed as having "Klinefelter variant". However the clinical features of 49, XXXXY are distinct, with emphasis on the prevalence of congenital heart defects,[4] and the classic findings including radio-ulnar synostosis, hypogonadism, and mental retardation.[2-6] I present a new case of 49, XXXXY syndrome and discuss the clinical course.

CASE REPORT

A 5-month-old boy was admitted due to multiple congenital anomalies, poor feeding, accompanied with bronchopneumonia. He was born to a gravida 2, para 1 24-year-old healthy mother, with birth body weight (BW) of 2600 g, body length (BL) of 45 cm, and head circumference (HC) of 30 cm, via cesarean section at 37 weeks of gestation because of fetal distress. Umbilical cord around the neck was noted at birth but without any hypoxic episode. His Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. There was no neonatal hyperbilirubinemia. After birth, facial dysmorphism and heart murmur were noted. Echocardiography showed a patent ductus arteriosus (PDA) with left to right shunt, a type II atrial septal defect, and peripheral pulmonary stenosis (pressure gradient 24.6 mmHg). Ligation of the open PDA was performed at 30 days old after the failure of three doses of indomethacin. Poor feeding and activity with severe gastro-esophageal reflux bothered him. Long-term naso-gastric tube feeding was used. At the age of 5 months, physical examination showed a small infant with severe seborrheic dermatitis (Fig. 1). His BW was 3.9 kg, BL was 55.5 cm, and HC was 36 cm (all below the 3rd percentile). He had a dysmorphic face including microcephaly, hypertelorism, downward slant, short palpebral fissures, low-set, dysplastic ears, megacornea, micrognathia, short neck, pectus excavatum, short sternum, large open anterior fontanelle (4×4.5 cm), cleft palate with central fissure, no heart murmur,

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laryngomalacia, short neck, umbilical hernia, simian crease on the left palm, pes planus, hypoplastic scrotum, microtestes (<1 ml), microphallus (1.2 cm), and clinodactyly or contracted digits. His blood pressure was 108/57 mmHg. The breathing sounds were coarse with diffuse rhonchi. Hemogram showed mild leukocytosis (11×10^9 cells/L), anemia (hemoglobin 11.0 g/dL), and thrombocytosis (434×10^9/L). Liver, renal function and electrolytes were all within normal ranges. Brain echography showed ventriculomegaly. X-ray studies of both upper extremities did not reveal radio-ulnar synostosis or other anomalies. Chromosome analysis from the peripheral blood culture showed a 49, XXXXY constitution in all his metaphases (Fig. 2). FISH study was performed to elucidate the possibility of mosaic sex aneuploidy, which may explain the absence of radioulnar synostosis in this case. However, there were four X chromosomes and one Y chromosome in all metaphases (100 cells) after FISH with the X and Y painting probes, respectively. His parents' karyotypes were found to be normal. The patient had mental and physical developmental retardation (sitting at 13 months, standing at 18 months, and no speech until 3 years). There were no seizures. Recurrent bronchopneumonia occurred to him before the age of 3 years. He has severe seborrheic and atopic dermatitis when persistent high platelet count ($450\text{-}500\times10^9$/L), high levels of immunoglobulin E (IgE, 750 IU/mL) and eosinophil count (660×10^6 cells/L) were noted. He was enrolled in a rehabilitation program. He now has better growth but the BW, BL, and HC were still below the 3rd percentile at 3 years of age.

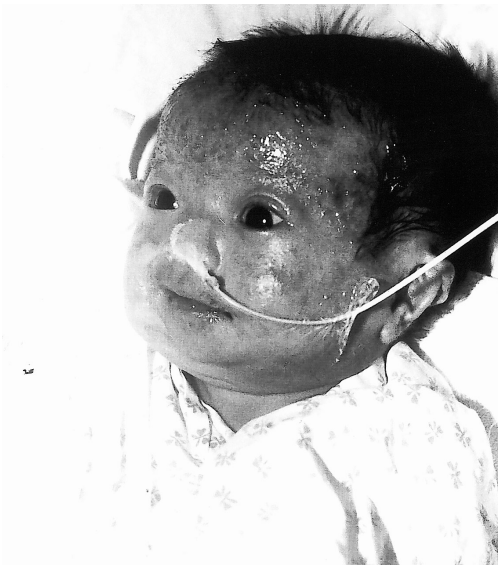

Fig. 1 The patient aged 5 months.

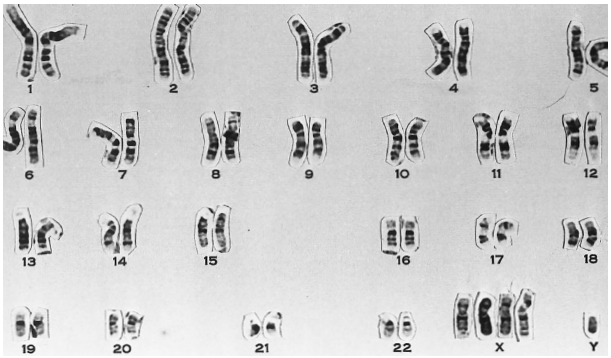

Fig. 2 The karyotype shows 49, XXXXY.

DISCUSSION

The previous reports describing children with 49, XXXXY syndrome have emphasized the "classic triad" of mental retardation, radio-ulnar synostosis, and hypogonadism.[2-6] Some recent reports have paid attention to the more distinctive phenotype of 49, XXXXY syndrome consisting of a characteristic facies and habitus, multiple skeletal anomalies, cardiac defects, genital abnormalities, a variety of mental deficits, and severe speech impairment.[4-7] Our patient did not have the triad but has typical features presented in patients with 49, XXXXY syndrome.

A 49, XXXXY karyotype is thought to arise from maternal non-disjunction during both meiosis I and meiosis II.[8,9] Such successive non-disjunction theoretically produces an egg with four X chromosomes, which, when fertilized by a Y bearing sperm, results in an embryo with 49, XXXXY syndrome.[8,9] Interestingly, the occurrence of this syndrome does not appear to be related to maternal age. Two prevalent theories have been made to account for the phenotype associated with a 49, XXXXY genotype as well as for other X chromosome aneuploidies: 1) increased dosage of active genes in regions which escape X inactivation, and 2) asynchronous replication of the extra X chromosomes.[4,10] In both cases, the amount and timing of genes expressed on the X chromosome is altered.

Compared with Klinefelter syndrome (47,

XXY), people with 49, XXXXY syndrome have characteristic facial features, particular habitus, cardiac defects, multiple skeletal anomalies, genital abnormalities, variable mental impairment, and speech problems apart from those seen classically in Klinefelter syndrome. The number of the always active regions (at the tip of Xp) is increased from one to four, which cause the abnormal phenotype.[10] The clinical phenotype changes as the person grows to an adult.[5,11,12] The characteristic facial appearance of a child with 49, XXXXY syndrome includes a full, round face, epicanthal folds, upward-slanting palpebral fissures, ocular hypertelorism, telecanthus, a broad and depressed nasal bridge, and micrognathia. Patients may also have microcephaly, cleft palate, and abnormally shaped or positioned ears.

Significant behavioral problems were common in older patients, such as emotional disturbances with low frustration levels, timidity and shyness, and the level of adaptive functioning was much higher than the cognitive level. The degree of mental retardation and impairment of language abilities with a remarkable discrepancy between language expression and comprehension were shown to be more severe in the older subjects as well.[6,11] Hypergonadotropic hypogonadism was evident after the puberty, and testosterone replacement therapy is recommended. Thorough endocrinological follow-up examinations in male patients with X polysomies are suggested.[12,13]

A rare condition, hyper IgE syndrome (HIE), is characterized by a recurrent staphylococcal abscesses of the skin, lungs, and other sites from infancy. A coexistence of pentasomy X and HIE syndrome has been reported.[14] Mildly elevated IgE and severe atopic dermatitis in this patient suggest sex chromosome aneploidy, either pentasomy X or XXXXY, may play an important role in the pathogenesis of atopy.

The diagnosis of 49, XXXXY syndrome is usually ascertained postnatally by the association of mental retardation, variable growth deficiency, Down syndrome-like facial dysmorphy, hypogenitalism and other malformations, especially involving the heart and skeletal system.[15] Prenatal diagnosis of the pentosomy 49, XXXXY is generally fortuitous. Detailed sonographic findings during the second trimester revealing a small penis and abnormal posturing of the lower extremities are very suggestive of this syndrome.[15] A subsequent amniocentesis is indicated to verify the results.

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染色體49, XXXXY症

侯家瑋

染色體49, XXXXY 症是一種極罕見的性染色體疾病。它被認爲是Klinefeter 氏症 (47, XXY) 的一變異型，但具有更嚴重的表現型。一名5 個月大男嬰因爲生長不良及先天多重畸形而住院，身體畸形包括小頭症、臉畸形 (包括眼距過寬、巨角膜症、顎裂及小下巴)、明顯心臟雜音、臍疝氣、外生殖器短小及手攣縮。經由染色體G-顯帶術及螢光性原位雜交法檢查所有細胞核型皆爲49, XXXXY。其他先天畸形包括腦室擴張、先天性心臟病 (開放性動脈導管、心房中膈缺損及周邊肺動脈狹窄)。病童有嚴重異位性皮膚炎及高免疫球蛋白E及精神運動發展遲緩，經由心臟手術及營養支持，病童有較好的成長，目前仍在復健治療中。(長庚醫誌 2004;27:551-4)

關鍵字：性染色體，染色體49, XXXXY症，Klinefelter 氏症。

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