Double Aneuploidy: Trisomy 18 and XXY in a Boy

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The simultaneous occurrence of double aneuploidy in the same individual is a relatively rare phenomenon. Most of the previously reported cases of double trisomy were found in spontaneous abortions. We report on a male newborn presenting with typical clinical features of Edwards syndrome (trisomy 18), resulting from de novo, non-mosaic 18 trisomy with an additional X in the karyotype: 48, XXY, +18. Besides the typical features of trisomy 18 (prominent occiput, clenched hands, rocker-bottom feet, congenital heart disease, diaphragmatic hernia and recurrent respiratory tract infections), the patient has overlapping features with Klinefelter syndrome (cryptorchidism). A molecular cytogenetic method with digoxigenin-labeled probes D18Z1 and DXZ1 was used to confirm the diagnosis, and to clarify the non-mosaic status of Edwards syndrome and the coexistence of Klinefelter syndrome. The XXY constitution may have contributed to the development of normal height and absence of microphthalmia in this patient with trisomy 18. This patient remains alive up to the present time (21 months). To our knowledge, this is the first case of Edwards syndrome together with Klinefelter syndrome in Taiwan. The literature regarding double aneuploidy, which combines both autosome and sex chromosome aberrations, was also reviewed. *(Chang Gung Med J 2006;29(4 Suppl):6-12)*

Key words: double aneuploidy, Edwards syndrome (trisomy 18), Klinefelter syndrome (XXY).

The occurrence of double aneuploidy i.e. the existence of two chromosomal abnormalities in the same individual, is an uncommon phenomenon.[1,2] Most reported cases of double aneuploidy are presented in the form of spontaneous abortions.[1,2] The reported cases involving autosome and/or sex chromosome aneuploidy, such as double autosomal trisomy and autosomal trisomy with sex chromosome monosomy or trisomy, are extremely rare in live newborns. These syndromes include Edwards-Down,[3] Down-Klinefelter,[4,5] Down-Turner mosaicism,[6] Down-XYY,[7] Patau-Klinefelter,[8] Edwards-Turner mosaicism,[9] Edwards-XXX,[10,11] Edwards-Klinefelter,[12-15] and Edwards-XYY.[16] The patient with double aneuploidy may have manifestations of both chromosomal anomalies. Further malformations, early death or different phenotype may be seen due to gene interaction between the two chromosomal abnormalities.[1-3] To date, only four cases of Edwards-Klinefelter syndrome with neonatal death have been described in the literature.[12-15] We report a new case of 48, XXY, +18 in a male infant with longer survival. The clinical manifestations are compared with those of trisomy 18 and Klinefelter syndrome, respectively.

CASE REPORT

This male patient, the first child of young, healthy and non-consanguineous parents, was born via cesarean section, after 39 weeks of gestation, due to fetal distress. The pregnancy was uneventful,

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except for intrauterine growth retardation (IUGR) with polyhydramnios in late gestation. The mother denied alcohol or drug exposure. The patient's birth weight was 2040 g (< 3rd percentile), body length 49 cm (25th percentile) and head circumference (HC) 29.5 cm (< 3rd percentile). After birth, he suffered from respiratory distress, and a single umbilical artery (absence of the left umbilical artery) and diaphragmatic hernia were noted. An emergency operation to repair the hernia was performed. Echocardiography showed a patent ductus arteriosus (PDA), ventricular septal defect (VSD) and pulmonary valvular stenosis (PS). Ligation of the PDA and pulmonary artery (PA) banding were done at two months due to pulmonary hypertension and heart failure. The patient was admitted to hospital several times for recurrent pneumonia. Marked motor delay was noted (head control at six months, walking at 15 months). At the age of one year, his growth parameters for weight and HC were still far below the 3rd percentile.

At the age of 15 months, the patient suffered fever and dyspnea, and pneumonia and urosepsis with E. coli infection were noted. Tracheostomy with aided mechanical ventilation was performed owing to his poor respiratory condition. Physical examination showed a small cachexic baby with multiple congenital anomalies and marked hypotonia. Body weight was 3.8 kg (far < 3rd percentile) and length 73 cm (5th percentile). The head was asymmetrical and small (HC 37.2 cm) with prominent occiput (Figs. 1A and 1B). The face was round without microphthalmia (Fig. 1A) with heavy eyebrows over the proximal one-third area, hypertelorism, a small nose with hypoplastic alae nasi, dysplastic ears (Fig. 1B), small mouth with high-arched palate and micrognathia. He also had a short neck, small chest with a short sternum, hypoplastic nipples, a grade II-III pansystolic murmur over the left sternal border, umbilical hernia, bilateral clenched hands with overlapping fingers (Fig. 1C), rocker-bottom feet, hypoplastic scrotum and cryptorchidism, and normal penis size (Fig. 1D). The anterior fontanel was nearly closed.

The T4, T3 and thyroid-stimulating hormone (TSH) blood levels were within normal ranges. Image studies revealed mild cardiomegaly, scoliosis of the thoraco-lumbar spine and a small narrow pelvis. The brain ultrasonography and eye ground examination were normal. Babinski sign was present. Echocardiography showed an atrial septal defect (3.7 mm), a VSD (10 mm) and PA banding with distal migration (Vmax 3.9 m/sec). Ultrasonography of the kidneys showed hypoplasia of the left kidney and atrophy with hydronephrosis of the right one. The hearing test by brainstem auditory evoked potential was abnormal. Visual evoked potential stimulation was normal. Chromosome study from the peripheral lymphocytes using G-banding showed the karyotype 48, XXY, +18 analyzed in 100 metaphases (Fig. 2). Parental chromosomes were normal. By using Fluorescent In Situ Hybridization (FISH) method with the digoxigenin-labeled probes D18Z1 and DXZ1, no mosaicism could be demonstrated. Electroencephalogram showed mildly diffuse cortical dysfunction without abnormal epileptiform discharges. Hemogram, electrolytes, blood glucose and metabolic screening were all normal. The patient failed to thrive and suffered severe constipation with poor weight gain, despite adequate nutritional support via nasogastric tube. Hypotonia was persistent with poor head control. He continues to have no developmental progression. Table 1 shows his clinical characteristics with comparisons to both aneuploidy syndromes.

DISCUSSION

A rare case of double chromosome aneuploidy including Edwards syndrome (trisomy 18) and Klinefelter syndrome was described highlighting the patient's longer life span. Most cases of double aneuploidies in liveborns involve the sex chromosomes combined with either trisomy 13, 18 or 21, i.e. XXX/18, XXX/21, XXY/13, XXY/18, XXY/21, XYY/13, XYY/18 and XYY/21.[4-16]

Trisomy 18 syndrome (Edwards syndrome) is the second most common multiple malformation with a 3:1 preponderance of females to males.[17] Babies with this disease are usually feeble and have a limited capacity for survival. Poor sucking power may necessitate nasogastric tube feeding but, even with optimal management, they fail to thrive. Fifty percent die within the first year as severely mentally defective individuals. Partial trisomy 18 or mosaic trisomy 18 infants may survive for a longer period. Patients with trisomy 18 usually have flexion deformity and overlapping fingers. The reported cases with XXY/+18 all have overlapping fingers

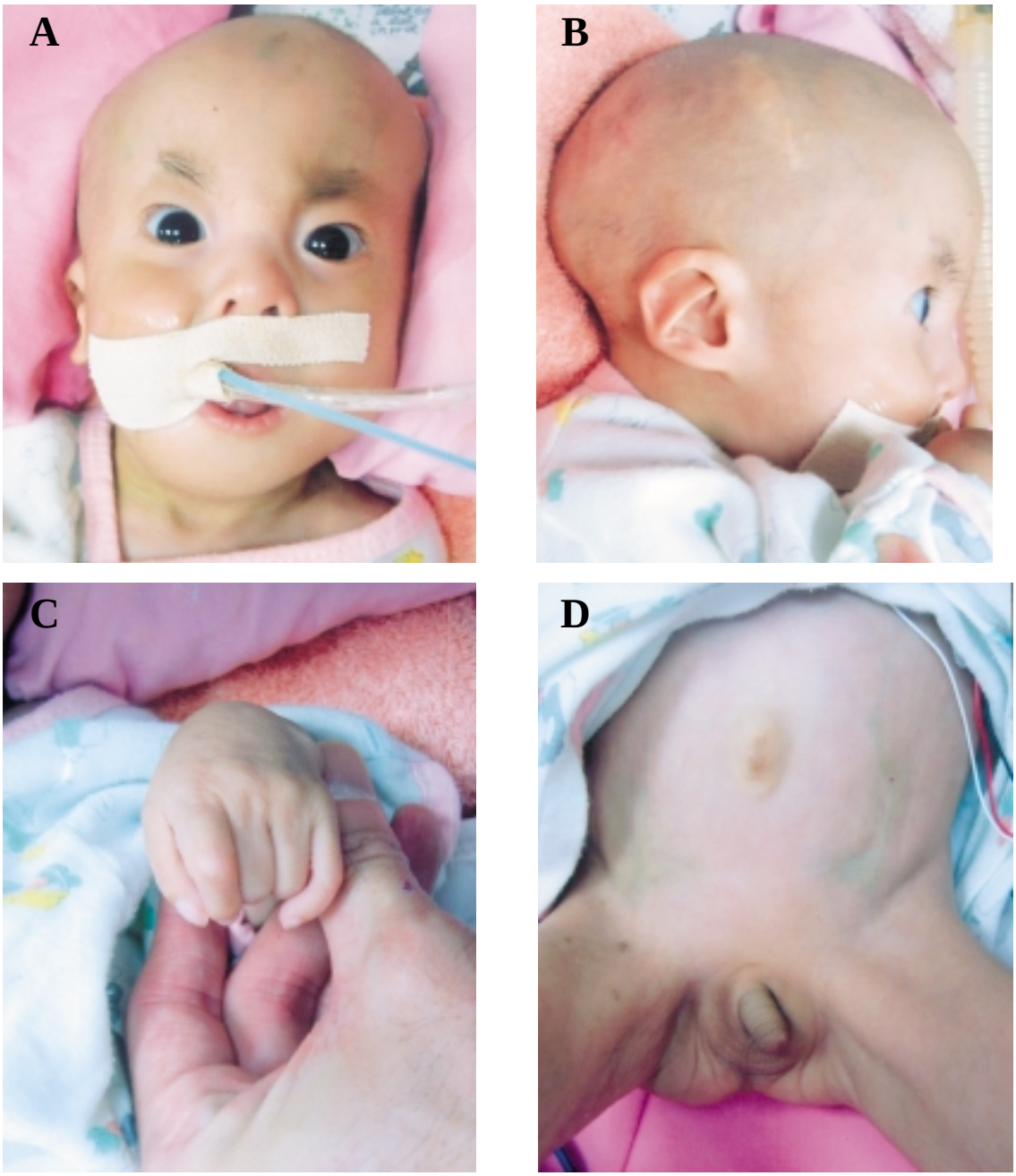

Fig. 1 Patient at 15 months of age: (A) asymmetric face without microphthalmia; (B) long skull with prominent occiput and dysplastic ears (the scar on the right side of the scalp was the result of extravasation of intravenous infusion); (C) clenched hands with overlapping fingers; (D) umbilical hernia, small pelvis, cryptorchidism and normal penis size.

(clenched hands).[12-15] Klinefelter syndrome is the most common single cause of hypogonadism and infertility.[18] Variable features are noted in these patients: they have a wide range of IQ levels, with a mean full-scale IQ between 85 to 90, and a tendency from childhood toward long limbs, with low upper to lower segment ratio and a relatively tall, slim stature.[18] Usually most 47, XXY boys have a nor-

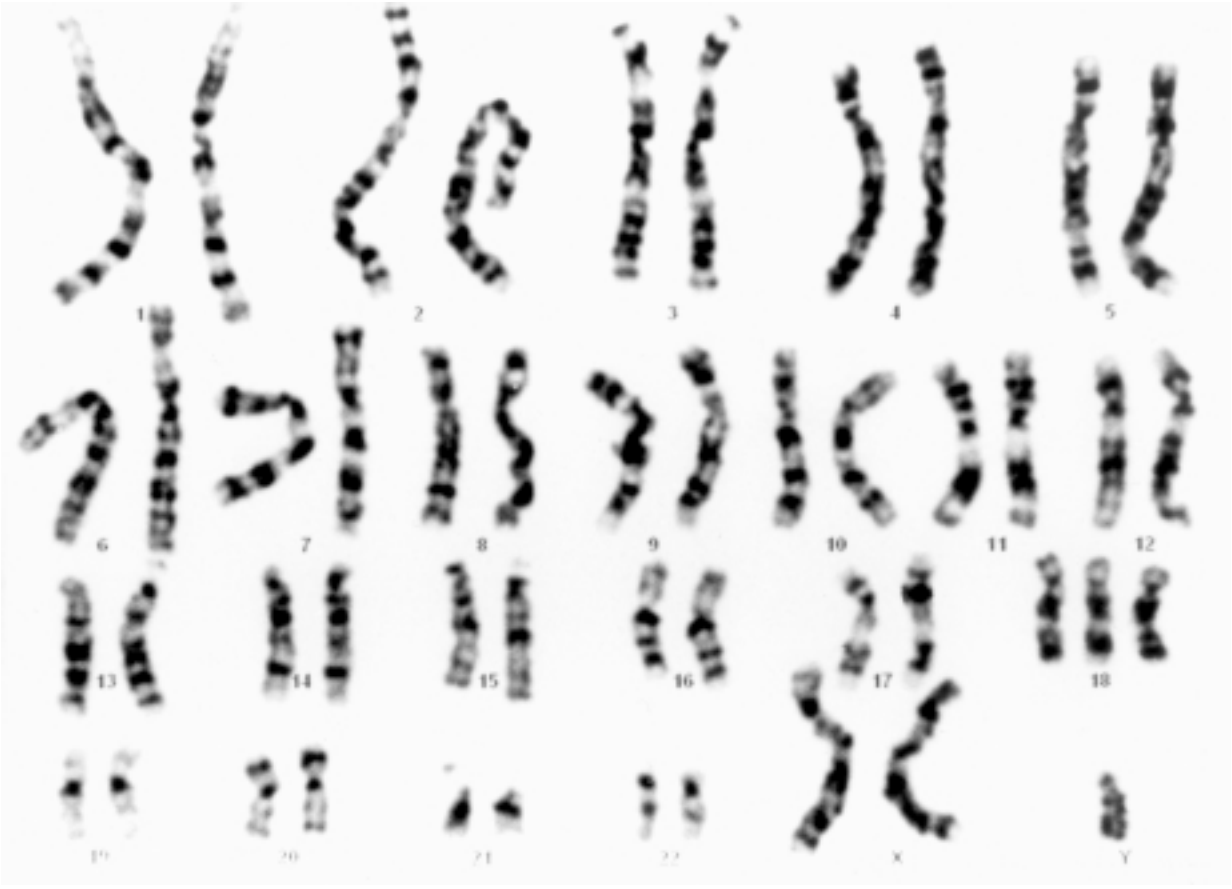

Fig. 2 Karyogram of the proband shows the concurrence of trisomy 18 and XXY.

mally developed penis and small firm testes of about 2.5 ml, and infertility is the rule, although they may enter puberty normally. The majority of affected individuals require some help in school, particularly in reading and spelling. The 47, XXY males have a higher than normal incidence of minor structural abnormalities, such as elbow dysplasia and fifth finger clinodactyly, and major external genitalia problems.

Infants with XXY/+18 usually manifest typical abnormalities of trisomy 18, such as IUGR, typical facial appearance (prominent occiput, microphthalmia, small mouth, micrognathia and malformed ears), congenital heart defects, overlapping and flexion deformity of fingers, rocker-bottom feet and renal abnormalities,[12-15,17] with similar conditions as XXX/+18 or XYY/+18.[10,11,16] Further disorders, such as hypogenitalism, hypogonadism and long legs, are also present.[12-15,18] A non-mosaic type of Edwards syndrome and the coexistence of Klinefelter syndrome, confirmed by the FISH study, did not lead to early death or spontaneous abortion in the present case. This boy continued to survive beyond his first year but was unable to walk. The clinical presentation of this patient was consistent with reported cases of trisomy 18 or XXY/+18 (Table 1)[12-15,17,18] but with a longer lifespan. The combination of trisomy 18 and sex chromosome polysomy (e.g. XXY, XYY or XXX) leads to either mild or more severe phenotypes depending on the composition of different cell clones.[10-16] The different forms of double aneuploidy cannot be explained by any single combination of nondisjunctional errors.[1-3]

Given the rarity of the disorder and scant published data, the incidence, phenotype and recurrence risk are difficult to establish. Genetic counseling and prognosis remain challenging. Prognosis for trisomy 18 or XXY/+18 patients depends on the severity of

Table 1. Comparison of Trisomy 18, Klinefelter syndrome, XXY/+18 and the Present Case

Features/patients	Trisomy 18[17]	Klinefelter syndrome[18]	XXY/+18[12-15]	Present Case
Incidence	0.3/100 newborns	1/500 male newborns	very rare	
Psychomotor retardation	severe 100%	some dull mentality / psychosocial adjustment problems	severe	severe
Growth	IUGR, postnatal growth failure, microcephaly 100%	average 10 cm taller than XY males, normal HC	IUGR, postnatal growth failure, microcephaly	IUGR, poor weight gain, microcephaly, normal height
Genital malformation	cryptorchidism, micropenis 100%	cryptorchidism > 50%, normal penis	cryptorchidism	cryptorchidism, normal penis
Feeding difficulty	> 95%	nil	+	+
Congenital heart defects	VSD, PDA > 95%	not mentioned	VSD, PDA or complex heart defect	VSD, PDA, PS
Skull	prominent occiput with long skull, small biparietal diameter of skull > 80%	brachycephalic	prominent occiput with long skull	prominent occiput with long skull
Ear	fawn-like, pointed upper portion, low-set > 80%	normal or slight dysplasia	low-set, dysplasia	dysplastic
Eye	narrow palpebral fissures 40-60%, microphthalmia/ strabismus, hypo-/ hypertelorism, ptosis 10-50%	not mentioned	hypertelorism 100%, microphthalmia 50%	hypertelorism
Nose	upturned small nose, broad nasal bridge, 50-80%	normal	upturned small nose, broad nasal bridge	broad nasal bridge, small nose
Mouth	small mouth, micrognathia, narrow high palate > 80% short upper lip 10-50%	not mentioned	small mouth, micrognathia, high-arched palate	small mouth, micrognathia, high-arched palate
Neck	short neck 50-80%, web neck 40-60%	low hair line at times	short neck	short neck
Trunk/abdomen	short sternum, single UA > 80%, inguinal/umbilical hernia 50-80%, Meckel diverticulum 40-60%, diaphragmatic hernia 10-50%	gynecomastia after puberty	short sternum, hypoplastic nipples	short sternum, single umbilical artery, hypoplastic nipples, diaphragmatic hernia
Renal	horseshoe kidney, hydronephrosis, hydroureter 50-80%	not mentioned	not mentioned	renal hypoplasia (left), atrophy and hydronephrosis (right)
Skeletal	flexion deformity of fingers, overlapping fingers, small narrow pelvis, limited hip abduction > 80%, rockerbottom feet with prominent calcaneus 50-80%	altered body proportion (US/LS < 1), long limbs, vertebral collapse with osteoporosis, mild elbow dysplasia, scolios is, clinodactyly, radioulnar synostosis	flexion deformity of fingers, overlapping fingers, small narrow pelvis, limited hip abduction, rockerbottom feet with prominent calcaneus	clenched hands, overlapping fingers, small narrow pelvis, limited hip abduction, rocker-bottom feet, scoliosis, clinodactyly
Outcome	poor: often die of respiratory problems	relatively good, normal life span, incomplete virilization, variable eunuchoidism, diabetes 8%	poor	fair to poor

Abbreviations: IUGR: intrauterine growth retardation; HC: head circumference; VSD: ventricular septal defect; PDA: patent ductus arteriosus; PS: pulmonary stenosis; UA: umbilical artery. US:____, LS:____.

associated malformations (particularly of the heart) and episodes of infection.[12-15] Cardiac malformations in 41 autopsy cases of trisomy 18 showed a VSD in all tricuspid valve anomalies in 80%, pulmonary valve anomalies in 70%, aortic valve malformations in 68%, mitral valve anomalies in 66%, polyvalvular disease (i.e. malformations of more than one valve) in 93% and a subpulmonary infundibulum (conus) in 98%. These findings appear to be characteristic of all trisomies. These data suggest that excessive chromosomal material (as in trisomies) may result in situs solitus at all levels.[19] However, the prenatal diagnosis of double trisomy such as 48,XXY,+18 is not difficult. Both amniocentesis and cordocentesis could confirm the diagnosis. Furthermore, prenatal sonographic findings of increased nuchal translucency, IUGR, polyhydramnios and associated structural anomalies, such as brain malformation, diaphragmatic hernia and major cardiac defects, in late gestation indicate the possibility of certain chromosomal disorders.[20]

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雙非常數染色體：三染色體十八症及XXY於一男孩

侯家瑋

在同一個體出現雙非常數染色體 (double aneuploidy) 是相當罕見的一種染色體異常疾病，主要報告病例多出現在自然流產的胎兒，於活產兒極爲少見。一名男性新生兒表現典型三染色體十八症 (trisomy 18) 之臨床表徵，乃源於新發生的非拼湊型第十八號染色體三體症合併多一個 X 染色體，所以其核型爲 48,XXY,+18。此病人之臨床表徵符合第十八號染色體三體症之描述 (明顯枕骨部，重疊指，搖椅腳架狀後腳跟，先天心臟畸形，橫膈膜疝氣，與重複呼吸道感染並有 Klinefelter 症之隱睪症)。以螢光性原位雜交法 (探針 D18Z1 與 DXZ1) 證實此非拼湊型染色體雙非常數異常雙非常數另外，他的 XXY 變化可解釋此病人之較正常身高及沒有小眼症，與較長的存活時間 (迄今 21 個月大)。本報告爲台灣首例且做相關文獻回顧。(長庚醫誌 2006;29(4 Suppl):6-12)

關鍵字：雙非常數染色體，愛德華氏症(染色體十八三體症)，Klinefelter 氏症(XXY)。

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