Singapore Med J 2007; 48(5) : e146

Two cases of isochromosome 18q syndrome

Pal S, Siti M I, Ankathil R, Zilfalil B A

ABSTRACT

Patients with isochromosome 18q, a rare cytogenetic abnormality, also reported as Edwards syndrome, is the second most common autosomal trisomy. However, the phenotypic features and survival of these patients are not uniform and depend upon the portion of chromosomes getting duplicated or deleted. The survival of these children may be longer, hence a good cytogenetic diagnosis is a must. Morphological characteristics of isochromosome 18q are not yet fully delineated because of the rarity of the cases and as most cases are aborted medically or terminate spontaneously. We report two cases of isochromosome 18q, one male aged two years old and the other a male aged eight months old, and review the literature on this rare syndrome.

Keywords: autosomal trisomy, Edwards syndrome, isochromosome 18q, phenotype

Singapore Med J 2007;48(5):e146–e150

INTRODUCTION

Patients harbouring isochromosome 18q, a rare cytogenetic abnormality, also reported as Edwards syndrome, is the second most common autosomal trisomy with an occurrence rate of nearly one in 8,000 live births. Edwards syndrome is associated with a distinct pattern of congenital abnormalities, which results in early death. Marked growth deficiency is a major trait and other striking clinical features include congenital heart abnormalities, mental and developmental delays, prominent occiput, faun-like ears, micrognathia, short sternum, narrow pelvis, overlapping-finger and rocker-bottom feet. Though isochromosome 18q is viewed as Edwards syndrome, it may be associated with longer survival and a better prognosis than the latter; hence the importance of early and accurate diagnosis.

Morphological characteristics of isochromosome 18q are not yet fully delineated. The features of this chromosomal abnormality are variable, and overlap with 18p deletion and trisomy 18 or monosomy 18p. Unique features include holoprosencephaly, cebocephaly and cyclopia, which are rarely described in trisomy 18 and are only occasional findings in monosomy 18p. The phenotypical features of isochromosome 18q are mostly reported from foetuses. Some of the cases of isochromosome 18q, which have been reported with longer survival, have had mosaic karyotype. In this article we report two cases of this rare syndrome of isochromosome 18q, both boys, aged two years old and eight months old, respectively. This article also reviews the literature on isochromosome 18q.

CASE REPORTS

Case 1

A boy born to Malay parents from a nonconsanguinous marriage was the third child, and he had three healthy siblings. Both the mother and father were each 33 years of age at the time of his birth. The baby was born by emergency lower segment caesarean section (LSCS) due to foetal distress at full term. He was kept in the neonatal intensive care unit (NICU) for 11 days because of respiratory distress, due to suspected meconium aspiration, but he did not require any ventilation. Syndromic features noted at birth included facial abnormalities of prominent occiput, hypoplastic mandible, microcephaly, small eyes, low-set ears and beaked nose. Digital abnormalities were broad thumbs, broad great toes and abnormal, zigzag palmar creases. On follow-up, he was noted to have global developmental delay, hypotonia and growth retardation. There was generalised hirsuitism. There were no skeletal or cardiac abnormalities. The baby had a left inguinal hernia, which was later operated successfully.

Subsequently, the baby developed stridor due to laryngomalacia. Visual evoked potential showed a delayed latency, consistent with lesions affecting both optic nerves. Magnetic resonance imaging of his brain showed generalised cortical atrophy. Audiometry elicited inconclusive response to loud sounds. The child needed two hospitalisations for bronchopneumonia and aspiration pneumonitis until his present age of two years. He is presently undergoing a neurodevelopment training programme. His weight at the age of two years is 8.5 kg and he is severely retarded. His facial features can be seen from recent photographs of the child (Fig.1), and his karyotype was 46, XY, i(18q),

Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian 16150, Malaysia

Pal S, MBBS, DCH, MSc
Postgraduate Student

Siti MI, DipMedLab
Medical Laboratory Technologist

Ankathil R, PhD
Professor in Cancer Cytogenetics

Zilfalil BA MBBS, MSc, MMed
Director

Correspondence to:
Dr Bin-Alwi Zilfalil
Tel: (60) 9766 3000 ext 4151
Fax: (60) 9765 8914
Email: zilfalil@kb.usm.my

Fig. 1 Case 1 (isochromosome 18q) (a) Lateral and (b) frontal facial photographs show the typical facial appearance of partial Edwards syndrome with small eyes, frontal prominence, short and broad nose, low-set ears, long philtrum, downturned mouth and micrognathia.

del(18p) on GTG-banded conventional cytogenetic analysis (Fig. 2).

Case 2

The second patient is a boy born to a 28-year-old mother and 25-year-old father. He was their first baby, and his mother had no previous history of abortions nor was there a family history of congenital malformation. There was no history of consanguinity. The baby was born by emergency LSCS. He was admitted in NICU for eight days for asphyxia and neonatal jaundice. His main clinical features at birth were: weight 3.3 kg, head circumference 35 cm, length 53 cm, abdominal distension, prominent occiput, short sternum, 11 ribs, single palmar crease, hypoplastic fifth fingers, hypoplastic toe nails, very short big toes, small feet, micrognathia, low set and poorly formed ears, hirsuitism, low hairline, widely-spaced nipples, minimal rugae on scrotum, small penis (< 2 cm) with no hypospadias and well-descended testis. There was no cardiac abnormality. He had no feeding problems and had normal muscular tone.

At three months of age, the child developed seizures and noisy breathing, gurgling sound due to probable laryngomalacia and difficulty in feeding, which required hospitalisation. At the time of this report, the infant was eight months old and clinical features were prominent frontal bones, triangular facies, long filtrum, upturned nose, small eyes, large anterior frontanelle, stubby fingers, rocker bottom feet, severe head lag, normal tone and delayed developmental milestones. Unlike the previous case, this child had no history of recurrent infections. Conventional GTG-banded chromosomal analysis of the child showed 46, XY, i(18q), del(18p) karyotype pattern (Fig. 3).

DISCUSSION

Edwards syndrome (trisomy 18) is the most common autosomal abnormality among live births after Down syndrome (trisomy 21). Most trisomy 18 cases result from total trisomy 18. A fraction of trisomy 18 cases result from mosaicism and translocation.[1] Most trisomy 18 foetuses detected in mid-trimester do not survive to term[2] or have poor postnatal survival. The

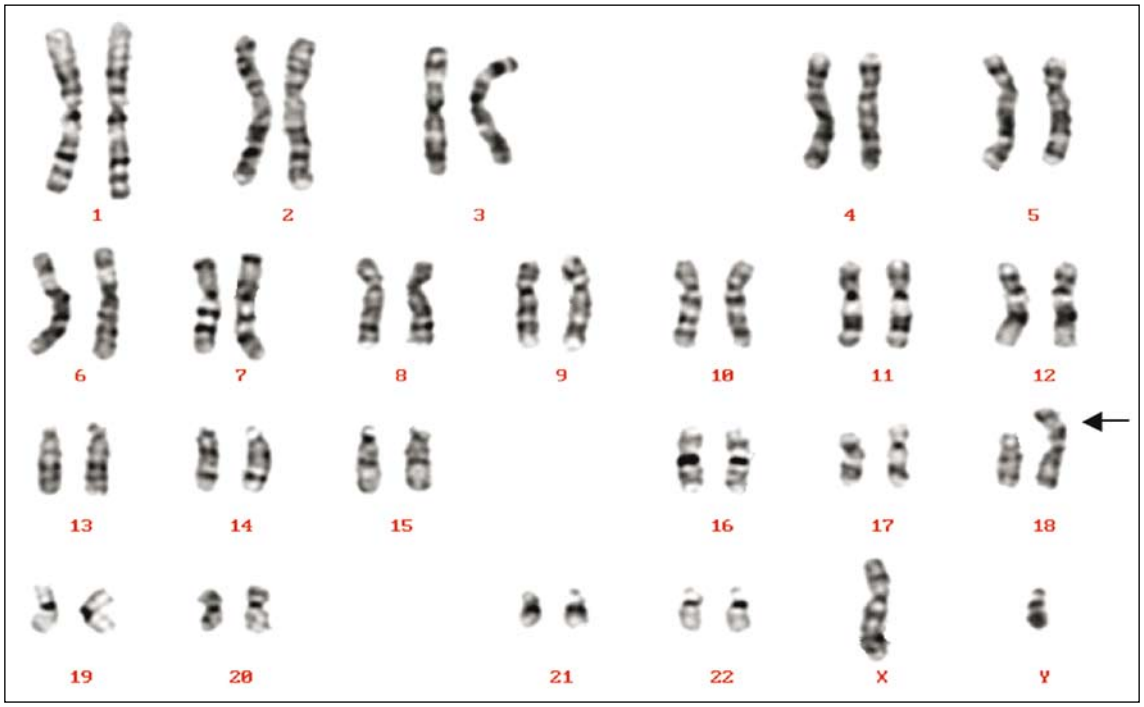

Fig. 2 Case 1. GTG-banded karyotype shows 46, XY, i(18q), del(18p). Arrow shows isochromosome 18q. There is an accompanying deletion of the p arm of chromosome 18.

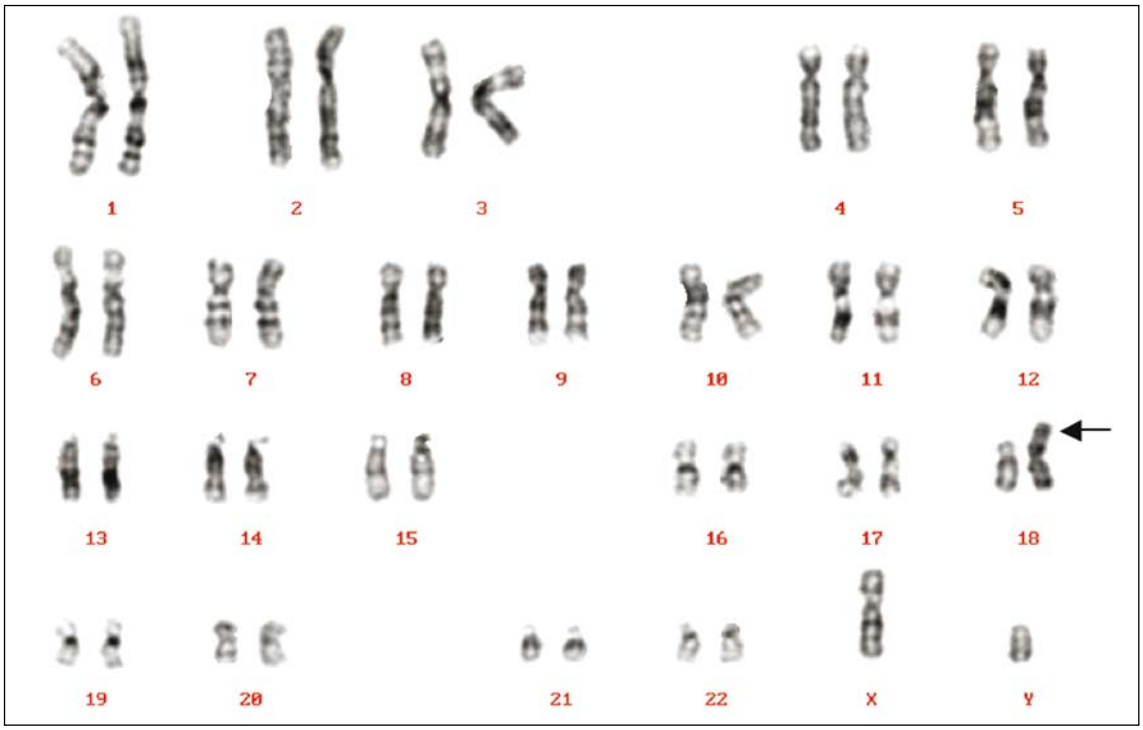

Fig. 3 Case 2. GTG-banded karyotype shows 46, XY, i(18q), del(18p). Arrow shows the isochromosome.

pathognomic segment responsible for Edwards phenotype is thought to be located in the q arm. Hence, isochromosome 18q is diagnosed as Edwards syndrome (complete triplication of q arm). Surprisingly, triplication of various segments of the q arm does not produce the same phenotype. Several individuals having partial trisomies of chromosome 18, such as 18q2 trisomy, 18p and q1 trisomy, have been reported in literature. These patients displayed a range of severity from a relatively mild phenotype with no internal organ malformations to the classic characteristics of Edwards syndrome. For example, partial Edwards syndrome due to trisomy of the distal one-third to one-half of the long arm of chromosome 18 have the clinical features of longer survival, less profound mental retardation, prominent orbital ridges, prominent nasal bridge, everted upper lip, poorly modelled ears, short neck, long hyperextensible fingers and sometimes seizures.[3] Review of the phenotypes produced by various triplicated 18 regions was supportive of the hypothesis that no one chromosome 18 region is sufficient to produce the phenotype of trisomy 18.[4]

Isochromosome 18q, which is formed by deletion of the p arm and triplication of the q arm due to misdivision during meiosis, shows a variety of phenotype ranging from mild facial dysmorphism to severe organ malformations precluding postnatal survival. Mechanism of formation is by centromeric (centric) fission. This is also known as transverse or lateral centric misdivision, and has been defined as the splitting of one functional centromere of a metacentric or submetacentric chromosome to produce two derivative centric chromosomes. Phenotypically, isochromosome 18q may sometimes have similar features like the partial Edwards syndrome which was noted in our second case (prominent frontal bones, triangular facies, long philtrum, upturned nose, small eyes, down-turned mouth, micrognathia and seizures). Patients of isochromosome 18q may also present with features of deletion of 18p, which has a variability of phenotypes, and life expectancy of these patients does not seem to be affected. In fact, deletion of the p arm of chromosome 18 always accompanies isochromosome 18, and probably reduces the devastating effects of duplication of the entire q arm of chromosome 18, thereby improving the outlook.

Our first case had some phenotypic features of Edwards syndrome, like prominent occiput at birth, severe growth and mental retardation, micrognathia and overlapping fingers but showed more manifestations of 18p deletion syndrome as he grew older (Fig. 1). On reviewing the literature, the few reported cases of i(18q) surviving in infancy included a case of a newborn girl with holoprosencephaly, microcephaly, and absent right radius.[5] Another girl with de novo isochromosome 18q had radial/thumb aplasia and thrombocytopenia, in addition to multiple congenital anomalies. Here, comparison with reported cases suggested that the genes for such features were located on the 18q arm.[6] Hypopituitarism was first described in patients with i(18q) syndrome by

Table Ia. Summary of reported cases of isochromosome 18q surviving in infancy and their phenotypes.

Case 1 (Present report)	Case 2 (Present report)	Bass et al[8] (1979)	Calvano et al[9] (Mosaic) (2003)	Turan et al[7] (Mosaic) (2005)	Spinner et al[5] (2005)	Sahoo et al[6] (2005)
Micrognathia	Micrognathia		Moderate developmental delay	Hypopituitarism	Alobar holoprocencephaly	Thrombocytopenia
Low set/large ears	Low set/large ears	Low set/large ears			Absent radius	Radial and thumb aplasia
Overlapping fingers	Overlapping fingers	Overlapping fingers	Facial dysmorphism, epicanthic fold and unilateral ptosis	Facial dysmorphism		
	Rocker bottom feet	Rocker bottom feet				
High forehead	High forehead	High forehead				
	Low hairline	Low hairline				
	Widely-spaced nipples	Widely-spaced nipples				
	Micropenis	Cardiovascular anomaly			Microcephaly	Multiple anomalies
Severe developmental delay	Short sternum, absent rib					

Turan et al in 2005. This patient had i(18q)/del(18p) mosaicism. The dysmorphic findings were that of del(18p) syndrome as well as features of trisomy 18, Edwards syndrome.[7] A case of isochromosome 18q was reported by Bass et al in an infant who had features of both trisomy 18 and 18p-syndromes, similar to our first case. Those features of 18p-syndrome, resembled Turner syndrome, viz. downward obliquity to the palpebral fissures, short, webbed neck, low posterior hairline, and widely-spaced nipples. The infant died of heart failure at 3.5 months of age.[8]

In another case of a mosaic individual with isochromosome 18q described by Calvano et al in 2003, the patient was monosomic for 18p in both cell lines and trisomic for 18q in the minor cell line.[9] The girl had short stature, moderate developmental delay, and facial dysmorphisms. The major cell-line was characterised by the presence of a reciprocal balanced translocation (18q; 20p) resulting in the formation of a dicentric derivative chromosome. The minor cell-line carries an iso18q chromosome. No cell contained both abnormal chromosomes. This observation suggested that the minor cell-line could have derived from the major one after the breaking of the translocation with subsequent formation of the isochromosome 18q. This report also explains isochromosome formation in this case. The translocation could be the initiating event leading to the mosaicism.[9] The summary of these cases surviving postnatally is shown in Table Ia.

Of the cases of i(18q) reported by prenatal diagnosis, anomalies included congenital megacystis, intrauterine growth retardation, cloacal dysgenesis, high forehead, hypertelorism, a prominent nose with a bulbous tip, median cleft lip and palate, micrognathia, low-set ears, a short neck, a joint contracture, prominent heel, pseudohermaphroditism, clubbed feet, abnormal hand positioning, oedema of the scalp, cleft palate, polyhydramnios and major congenital anomalies of premaxillary agenesis, alobar holoprosencephaly, double outlet right ventricle, DiGeorge syndrome and streak ovaries.[10-12] FISH analysis on interphase amniocytes was done in two suspected cases, as reported by Graf et al.[13] In the first case, a 20-year-old woman had prenatal ultrasonography which showed a foetus with bilateral dilated ventricles, bilateral choroid plexus cysts, open neural tube defect, bilateral club feet, ventriculoseptal defect with endocardial cushion defect, Dandy Walker malformation and omphalocoele with overlapping fingers and clenched fists. The foetus had clinical trisomy 18 due to the presence of two isochromosomes (one isochromosome 18p and other iso 18q). Fluorescent in situ hybridisation (FISH) studies were done with centromeric probe for chromosome 18, which showed signals on both normal chromosome 18 and isochromosome 18 (three signals). In the second case, a 21-year-old woman went for prenatal diagnosis. Features on ultrasonography were holoprosencephaly, omphalocoele, and bilateral hypoplastic forearms with radial deviation of hands. Full cytogenetic analysis revealed 46, XX, i(18q10). Subsequent FISH studies on metaphase cells with probe (D18Z1) specific for centromeric region of chromosome 18 showed signals on both normal chromosome 18 and isochromosome 18. Signals on 18q were significantly smaller in all cells examined.[13] The

Table 1b. Summary of prenatally-reported cases of isochromosome 18q and their phenotypes.

van Essen et al[12] (1993)	Chen et al[10] (1998)	Habecker-Green et al[11] (mosaic) (1998)	Graf et al[13] Case 1 (2002)	Graf et al[13] Case 2 (2002)
Alobar holoprosencephaly		Oedema of the scalp	Hydrocephalus bilateral choroid plexus cysts	Holoprosencephaly
	Intrauterine growth retardation	Polyhydramnios	Open neural tube defect	
Streak ovaries			Dandy Walker malformation	
	Cleft palate facial dysmorphism	Cleft palate	Ventriculoseptal defect with endocardial cushion defect	
Double outlet right ventricle			Omphalocoele	
	Congenital megacystis cloacal dysgenesis		Bilateral club feet overlapping fingers, clenched fists	Omphalocoele
	Prominent heel a joint contracture	Clubbed feet abnormal hand positioning		Bilateral hypoplastic forearms with radial deviation of hands
DiGeorge anomaly	Pseudoherm-aphroditism			

summary of cases of isochromosome18q diagnosed prenatally is given in Table Ib.

The risk of trisomy 18 is known to increase with increasing maternal age as well as increasing paternal age; however, in combination with high maternal age, association with paternal age tends to assume lesser significance.[14,15] On the other hand, the risk association of isochromosome 18q with maternal and paternal ages has not been studied. In these two cases reported in this study, both parents were less than 35 years of age. In the review of most other cases of i(18q), parents were of a young age. In conclusion, the absence of major internal organ malformations in a case of isochromosome 18q seems to indicate a better prognosis and postnatal survival. The variety of phenotypes found in our two cases and those reported earlier, is probably because there is possibly no phenotype-genotype correlation in triplication of various parts of the q arm of chromosome 18. Detailed molecular studies may provide the answer and should be done wherever possible.

ACKNOWLEDGEMENTS

We acknowledge all the staff of the cytogenetics division of our unit for their painstaking efforts in karyotyping the cases, and the Department of Paediatrics, Hospital USM for referring the cases for genetic follow-up.

REFERENCES

1. Forrester MB, Merz RD. Trisomies 13 and 18: prenatal diagnosis and epidemiologic studies in Hawaii, 1986-1997. Genet Test 1999; 3:335-40.
2. Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genet 1989; 45:855-61.
3. Jones KL. Smiths Recognizable Patterns of Human Malformations. 5th ed. Philadelphia: WB Saunders, 1997.
4. Wilson GN, Heller KB, Elterman RD, Schneider NR. Partial trisomy 18 with minimal anomalies: lack of correspondence between phenotypic manifestations and triplicated loci along chromosome 18. Am J Med Genet 1990; 36:506-10.
5. Spinner NB, Eunpu DL, Austria JR, Mamunes P. Holoprosencephaly in a newborn girl with 46,XX,i(18q). Am J Med Genet 2005; 39:11-2.
6. Sahoo T, Naeem R, Pham K, et al. A patient with isochromosome 18q, radial-thumb aplasia, thrombocytopenia, and an unbalanced 10;18 chromosome translocation. Am J Med Genet A 2005; 133:93-8.
7. Turan S, Saka N, Guney I, Bereket A. A patient with hypopituitarism and isochromosome 18q mosaicism. Horm Res 2005; 64:261-5.
8. Bass HN, Sparkes RS, Miller AA. Features of trisomy 18 and 18p-syndromes in an infant with 45,XY,i(18q). Clin Genet 1979;16:163-8.
9. Calvano S, Croce AI, Zelante L. Clonal evolution of an unbalanced structural rearrangement after telomeric fusion. 4th European Cytogenetics Conference; 2003 Sep 6-9; Bologna, Italy.
10. Chen CP, Chern SR, Lee CC, Town DD. Isochromosome 18q in a fetus with congenital megacystis, intra-uterine growth retardation and cloacal dysgenesis sequence. Prenat Diagn 1998; 18:1068-74.
11. Habecker-Green JG, Naeem R, Gold H, et al. Prenatal diagnosis and clinical features of an individual with tetrasomy 18p and trisomy 18q mosaicism. J Perinatol 1998; 18:395-8.
12. van Essen AJ, Schoots CJ, van Lingen RA, et al. Isochromosome 18q in a girl with holoprosencephaly, DiGeorge anomaly, and streak ovaries. Am J Med Genet 1993; 47:85-8.
13. Graf MD, Gill P, Krew M, Schwartz S. Prenatal detection of structural abnormalities of chromosome 18: associations with interphase fluorescence in situ hybridization (FISH) and maternal serum screening. Prenat Diagn 2002; 22:645-8.
14. Naguib KK, Al-Awadi SA, Moussa MA, et al. Trisomy 18 in Kuwait. Int J Epidemiol 1999; 28:711-6.
15. Baty BJ, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13. I. Growth, physical assessment, medical histories, survival, and recurrence risk. Am J Med Genet 1994; 49:175-88.