Trisomy 18 mosaicism: report of two cases

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Background: **Mosaic trisomy 18 has a wide phenotypic spectrum ranging from near normal to early death. We report two cases that add to our knowledge of the disease.**

Methods: **Patient 1 was a girl with a tracheoesophageal fistula, horse-shoe kidneys and a ventricular septal defect. Karyotyping of her lymphocytes showed complete trisomy 18. Due to her milder phenotypes, skin fibroblasts were karyotyped. Patient 2 was a boy with biventricular hypertrophic cardiomyopathy, patent ductus arteriosus, ventricular and atrial septal defects and significant feeding problems.**

Results: **Karyotyping of the skin and lymphocytes in patients 1 and 2 respectively revealed trisomy 18 mosaicism. Both children had only mild learning problems and were generally healthy with satisfactory growth. Patient 1 illustrates the possibility of significant discrepancy between the levels of trisomic cells in skin fibroblasts and lymphocytes leading to misdiagnosis. This finding has significant implications in medical management and counselling. Hypertrophic cardiomyopathy in patient 2 is recognized as a novel finding for this condition.**

Conclusion: **There is the possibility of good outcome for patients with mosaic trisomy 18, even in the presence of multiple congenital anomalies.**

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Introduction

Trisomy 18 is well-known human aneuploidy with a short life expectancy.[1] Pregnancies with trisomy 18 are characterized by low fetal activity, polyhydramnios and a small placenta.[2] Abnormally shaped head, micrognathia, widely spaced nipples, cryptorchidism, hypoplastic nails, characteristic hand posture with overlapping fingers and clubfoot are common features on examination. Frequent congenital heart anomalies in trisomy 18 include valvular defects, patent foramen ovale and ventricular septal defect. Additionally, malformations of the central nervous system, urogenital system and alimentary tract are not uncommon. The median life expectancy of live born infants with trisomy 18 is 4 days. Failure to thrive and severely delayed development are present universally in survivors.

Mosaicism is presence of more than one cell-line in the same individual. Mosaic trisomy 18 has a wide spectrum of phenotypes, ranging from near normal to early death.[3] Since the clinical outcomes of full and mosaic trisomy 18 can be different, it is essential to achieve a correct diagnosis because of the implications in medical management and counselling.

We report two cases that add to our knowledge of the spectrum and natural history of trisomy 18 mosaicism. Our first case illustrates the possibility of significant discrepancy between the levels of trisomic cells in skin fibroblasts and lymphocytes, leading to misdiagnosis. The second case adds a novel finding to the list of phenotypic features of this condition and highlights the possibility of good outcome for patients with mosaic trisomy 18, even in the presence of multiple congenital anomalies.

Case report

Case 1

The patient is the first child, a girl, born to Caucasian parents at 37 weeks of gestation via emergency lower segment caesarean section for fetal distress. Her mother had pre-eclampsia during the pregnancy, and antenatal scans had shown polyhydramnios and intrauterine growth retardation. The birth weight of the girl was 2030 g (0.4th centile) and head circumference was 34.5 cm. The girl was diagnosed with a tracheo-

esophageal fistula after birth, which was corrected surgically. Renal ultrasonography showed horse-shoe shaped kidneys and echocardiography showed a peri-membranous ventricular septal defect (VSD). On examination, she had a globular head with a prominent occiput, short sternum and small facial features. She held her fingers flexed and thumbs adducted, similar to, but not as striking as seen in trisomy 18. She also had minor 2-3 toe syndactyly with short dorsi-flexed great toes, hypoplastic nails and nipples.

Karyotyping of the cultured lymphocytes was done at five days of age and was reported as 47,XX,+18 in all 10 cells examined. The girl made good developmental progress in the first few months and therefore a possibility of mosaicism of trisomy 18 was considered. Skin biopsy was performed and the karyotyping of cultured skin fibroblasts showed 47,XX,+18[15]/46,XX[35]. Following this result, her original blood sample was reviewed with examination of 50 cells and reported as 47,XX,+18[44]/46,XX[6]. Karyotypes of both parents were examined and found to be normal.

She continues to make good progress at a mainstream school with extra help. She is growing along the 9th centile for height, 25th centile for weight, and between 50th and 75th centile for head circumference. At 11 years of age, she was noted to have typical features of mosaicism-skin pigmentation in the form of Blaschko's lines and mild asymmetry of the face and hands (Fig. 1). Her general health was good apart from mild asthma, mild constipation, and frequent infections.

Case 2

The patient is the second son born to South Asian parents. He was delivered at 38 weeks of gestation by elective lower segment caesarean section because of mother's history of a previous section. Antenatal scans had shown that the baby was small for dates. He was born in good condition with a birth weight of 1850 g (below 0.4th centile) and head circumference of 31.5 cm (0.4th centile). A karyotype analysis of lymphocytes was done in the second week of life, which revealed a mosaic karyotype 47,XY,+18[12]/46,XY[18] (Fig. 2). Both parents had normal karyotypes.

Echocardiography in the neonatal period showed biventricular hypertrophic cardiomyopathy that resolved after treatment with frusemide and captopril at two years of age. The boy also had a patent ductus arteriosus, a small VSD, and an atrial septal defect. The patent ductus arteriosus was closed surgically at the age of three years while the VSD closed spontaneously. A left inguinal hernia was diagnosed in the neonatal period and was repaired in the first year of life. He also needed a right inguinal herniotomy at five years of age. His left kidney was noted to be smaller on a renal ultrasound scan at five years, measuring 4.7 cm in length compared to 7.6 cm for his normal right kidney. His renal function was normal. He had generalized joint laxity and low muscle tone.

As a young child he had significant feeding problems which gradually improved. His weight gain was poor along the 0.4th centile. Although he did not have evidence of growth hormone deficiency, he was started on growth hormone treatment at five years of age on the basis of being small for gestation with failure to show catch-up growth. Following this he has only a small growth spurt. He is a pleasant and interactive boy with mild global developmental delay. He has bushy eyebrows, long eyelashes, slightly up-slanting palpebral fissures, prominent heels and overriding toes. He has areas of streaky, mottled, hypopigmentation of skin consistent with pigmentary mosaicism.

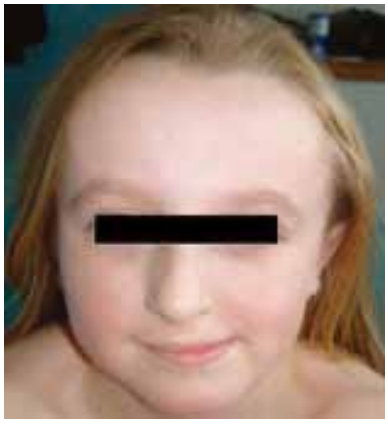

Fig. 1. Face of patient 1 showing no apparent dysmorphism apart from facial asymmetry due to mosaicism.

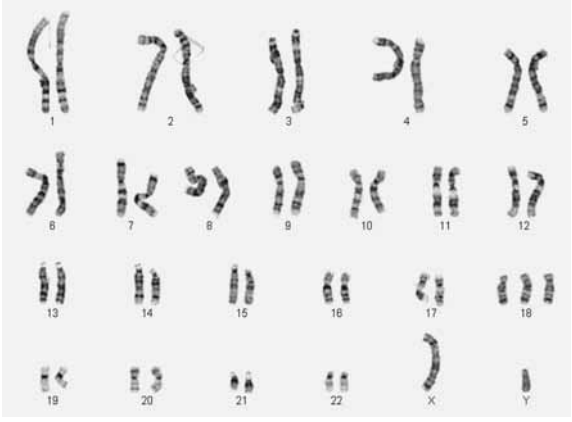

Fig. 2. Karyotype from a trisomic cell of patient 2 demonstrating three chromosome 18s.

Discussion

The earliest cases of trisomy 18 mosaicism were reported in 1965.[4,5] Since then at least 40 more cases have been described.[3] Most recently, Tucker et al[3] added two more cases in 2007 and reviewed 33 reported cases of mosaic trisomy 18. They demonstrated that in mosaic trisomy 18, if a majority of examined lymphocytes were of normal karyotype, the patient was likely to have normal intelligence. On the other hand if a majority of lymphocytes had trisomy 18, then the patient was more likely to have some learning problems. Apart from this, they did not find any correlation between other phenotypic features, including survival and level of trisomy.

Tucker et al[3] also showed that there is a significant discrepancy between the levels of trisomy in different tissues. This difference is highlighted by our first case, where 88% (44/50) of the patient's lymphocytes were trisomic for chromosome 18 whereas she had only 30% (15/50) trisomic skin fibroblasts. Routine karyotyping involves examination of only 10 lymphocytes unless mosaicism is suspected. Therefore some cases of mosaicism may be missed, resulting in misdiagnosis.

This case also highlights the importance of re-evaluating the diagnosis in trisomy 18 cases with milder phenotype or unusual clinical course. Achieving an accurate diagnosis is important in such cases because of serious implications in medical management and counselling of the family. Although this patient has a very high proportion of trisomic cells in her lymphocyte karyotype she has done well in terms of her growth, learning ability and general health.

Our second patient suffered from significant feeding problems, hypertrophic cardiomyopathy, multiple cardiac anomalies and bilateral inguinal herniae. Despite these, his overall outcome has been relatively good in terms of his general health and development. This illustrates that the outlook for children with trisomy 18 mosaicism can be good even in the presence of multiple congenital malformations.

He was treated with growth hormone even though his growth hormone levels were normal. There is only one reported case of trisomy 18 mosaicism treated with growth hormone. Sarigol and Rogers[6] reported a 13-year-old girl with normal intelligence, delayed pubertal development and growth failure with trisomy 18 mosaicism. She had a small anterior pituitary gland resulting in growth hormone deficiency, and growth hormone treatment resulted in a significant increase in her growth rate.

Hypertrophic cardiomyopathy in the second patient has never been reported in cases of trisomy 18 mosaicism although there is one report on an 18-year-old woman with full trisomy 18.[7] From the age of the described patient, it seems more likely that she had mosaic but not full trisomy 18. Hence, hypertrophic cardiomyopathy may be part of the phenotype of this condition.

Bass et al[8] reported a patient with mosaic trisomy 18, who had a small left kidney with normal function. This is similar to the finding in our second patient. Patient 1 has horse-shoe shaped kidneys. There are no other reports of renal malformations in cases of mosaic trisomy 18. Renal anomalies are common in patients with full trisomy and therefore renal findings in our patients are not surprising.

Routine karyotype from lymphocyte culture may not be sufficient to diagnose mosaicism in some cases. Hence, it is important for clinicians suspecting a diagnosis of mosaic trisomy 18 to consider karyotype from skin-fibroblasts. These two further patients add to our knowledge of the spectrum and natural history of trisomy 18 mosaicism.

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Contributors: KM and JCS diagnosed the patients. SB, KM and JCS examined the patients and counselled the families. SB prepared the manuscript and KM and JCS reviewed it.

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