

Confirmation of mosaic trisomy 22 in an infant with failure to thrive

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Introduction

Chromosome mosaicism is defined as the presence of two or more karyotypically different cell lines in an individual¹. These two cell lines occur as a post zygotic event but other mechanisms are also described². Mosaicism is associated with the live birth of infants with chromosome anomalies that are not detected in non-mosaic forms and the mosaicism may be present at low levels in tissues making cytogenetic confirmation difficult. In some cases, the mosaicism is confined to a single tissue adding to the complexity of diagnosis³. We report a child with clinical features of mosaicism in whom the diagnosis of mosaic trisomy 22 was confirmed.

Case report

A 4 ½ year old girl who was the second child of healthy, unrelated parents presented for further evaluation of poor growth. She was born at term with symmetrical intrauterine growth retardation: birth weight 1.8 kg (<-3SD), occipito-frontal circumference (OFC) 31cm (<5th centile) and length 46cm (<-3SD). She had a cleft of her soft palate which was repaired at nine months of age and ventricular septal defect closed at 10 months of age. She also had severe feeding difficulty associated with severe gastro-esophageal reflux disease and complicated with recurrent aspiration pneumonias necessitating gastrostomy feeding.

On examination, she had severe growth retardation with a weight of 8.8 kg (<-3SD), height of 85cm (<-3SD) and an OFC of 41 cm (<-3 SD). She had linear hypopigmentation along the lines of Blaschko in both upper limbs, left sided facial, limb and trunk hypoplasia [with leg length discrepancy of 3 cm] and a mild scoliosis. The hypoplasia of the left lower limb is shown in Figures 1 and 2.

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Figure 1: Hypoplasia of left lower limb



Figure 2: Hypoplasia of left lower limb

She also had hypertelorism, micrognathia and bilateral pre-auricular pits. Her development was globally delayed (gross motor 1 year, fine motor 1 ½ years, speech 1 ½ years, social 2 years). She had central hypertonia with joint hypermobility and bilateral genu recurvatum. Her neck and posterior hairline were normal.

Initial echocardiography revealed a restrictive perimembranous ventricular septal defect and

hypoplastic transverse aortic arch. Hearing assessment using audiometry, ultrasound scan of renal tract, magnetic resonance imaging of brain and electroencephalogram were normal and eye examination showed no colobomata. Chromosome testing revealed mosaic trisomy 22 syndrome (47, XX, +22 (03)/ 46, XX)

Discussion

Trisomy 22 is the second most common autosomal trisomy found in fetal life and accounts for 3-5% of all spontaneous abortions⁴. However, mosaic trisomy 22 in live born infants has been reported in only around 20 cases as per recently published reviews⁵. The clinical features of Trisomy 22 are variable and are presumed to be dependent on the proportion of the trisomic cell line in each tissue. They include constant features such as mental retardation, growth retardation, microcephaly, cryptorchidism (males), very frequent (>80%) features such as muscle underdevelopment/hypotonia, micrognathia, cleft palate, large low-set malformed ears, pre-auricular tags and/or sinuses, long slender fingers and/or finger-like thumbs, congenital heart disease, congenital hip dislocation and frequent (>60%) features such as craniofacial asymmetry, long and beaked nose, long philtrum and strabismus^{6,7}. Described clinical manifestations include microcephaly, hypertelorism, epicanthic folds, hypoplastic or low set ears, mid-face hypoplasia, hypoplastic distal phalanges, abnormalities of male genitalia, pre and postnatal growth retardation, cleft palate, cardiac and/or renal anomalies and anal atresia/stenosis⁸. This case did not have the major anal, ear or eye malformations [especially the 'cat eye' sign caused by iris coloboma] that are classically associated with this syndrome. The presence of some but not all the described malformations is consistent with the variability of the condition, which in turn reflects the proportion of the trisomic cells in each tissue or organ.

The presence of linear pigmentary anomalies [either hyper or hypopigmentation] along the lines of Blaschko associated with the presence of asymmetry of the body is typical of a mosaic genetic disorder. Such mosaicism could be due to a chromosome disorder⁹ or a single gene disorder¹⁰. Some of the mosaic disorders are clinically distinct and therefore recognizable^{11,12} while many are less easily diagnosed due to the nonspecific nature of the findings.

Establishing a genetic diagnosis enables better management including investigations for the associated problems as well as more accurate counselling of the parents regarding the prognosis and recurrence risks. Genetic testing in a child with developmental delay and features suggestive of a

mosaic disorder would begin with karyotyping but it is necessary to alert the laboratory for the need to count a larger number of cells on blood karyotype to identify a mosaicism of low frequency¹³. When available, comparative genomic hybridization is the preferred method of diagnosis¹⁴ as its positive yield is higher than with conventional karyotyping. In addition, the use of a buccal cells¹⁵ or fibroblasts¹⁶ for testing is more likely to identify the abnormality.

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