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Down's/Turner's mosaicism

Double aneuploidy as a rare cause of missed prenatal diagnosis of chromosomal abnormality

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SUMMARY Two babies with Down's/Turner's mosaic karyotype are reported. In each, because of advanced maternal age, chromosomal analysis had been carried out on the fluid obtained by amniocentesis in early pregnancy. Only the 46,X+21 cell line grew in the specimens and the extra 21 chromosome was wrongly identified as a Y chromosome, so that the fetus was thought to have a normal male karyotype, 46,XY. At birth both babies were phenotypically female with features predominantly of Down's syndrome and the correct karyotype was then identified. Twenty cases of this rare chromosomal abnormality are reviewed and one other living child who had been similarly wrongly diagnosed is reported.

Down's/Turner's mosaic is a rare chromosomal abnormality, occurring in about 1 in 2 000 000 births.¹ We report 2 babies born with this disorder in each of whom chromosomal analysis of amniotic fluid had mistakenly identified the fetus as a normal male.

Case 1

Amniocentesis was performed at 17 weeks' gestation at the mother's request in view of her age. This was the third pregnancy of a 36-year-old mother but the first child of her 65-year-old second husband. The karyotype of the fetus was reported as 46,XY. At 38 weeks' gestation a girl weighing 2590 g was born normally. The infant had the facial appearance of a Down's syndrome; she was markedly hypotonic

with a low hairline, and had pronounced webbing of the neck. The heart was normal. Karyotype was 46,X+21/47XX+21. The 46X+21 was present in 12% of the cultured cells. At age 11 months she had the appearance typical of Down's syndrome together with some webbing of the neck. Development was delayed at a 7-month level and she was growing in length along the 3rd centile.

Case 2

A 38-year-old mother in her second pregnancy requested amniocentesis at 15 weeks. The amniotic fluid karyotype was thought to be 46,XY. A girl weighing 1750 g was delivered at 36 weeks' gestation by caesarean section performed for intrauterine growth retardation. The infant had the facial appearance of Down's syndrome, a large clitoris, puffy hands and feet, and for a few days was cyanosed in air, and had a cardiac murmur. There was a single palmar crease and talipes on the right. She died from bronchopneumonia aged 15 weeks. The karyotype obtained in the neonatal period was 47,X iso X+21/46,X+21.

Discussion

In each instance the karyotype of the fetus after cell culture from amniotic fluid was thought to be 46,XY, because in each only the 46X+21 cell line had grown. The extra 21 chromosome was interpreted to be the Y chromosome in a normal total of 46 chromosomes, as the appearance of a 21 chromosome is very similar in size and shape to the Y chromosome. Chromosomal banding is not undertaken routinely in

amniotic fluid preparations in this laboratory as it is not thought to be cost effective to do so. Although the Y chromosome bands poorly it can generally be distinguished from the G group chromosomes which band more clearly. Nevertheless, if the phenotype of the fetus cannot be seen, banding techniques alone do not allow the conclusion to be confidently made that the Y chromosome is absent, nor do they identify an abnormal karyotype and justify termination of the pregnancy. The other important test for distinguishing the Y chromosome is the brilliant fluorescence of its long arms. Fluorescence of amniotic fluid preparations was adopted for a time in this laboratory as a routine procedure to confirm the presence of a Y chromosome but was subsequently stopped as there were some 'false negatives'—that is, although the Y chromosome might fail to fluoresce in the amniotic fluid cultures a normal boy was subsequently born. Thus the absence of fluorescence did not prove the absence of a Y chromosome. We do not fluoresce interphase nuclei for a Y chromosome in addition to culturing the cells, but we feel that the same argument would apply even more strongly if this were done: the absence of fluorescence would again not provide irrefutable evidence that there was no Y chromosome present.

The clinical features of Down's syndrome predominate in all the 20 cases of Down's/Turner's

mosaic that we could find reported, in which the karyotype may vary considerably (Figure). The appearance is typical of Down's syndrome but all are girls; generally they are of short stature with reduced or absent body hair, with minimal or absent breast development, absent menstruation, and often a shield-shaped chest. Mental handicap is moderate to severe. In some, neck folds, cubitus valgus, and neonatal lymphoedema are reported and gonadotrophic hormones may be increased.² In a girl¹ with a karyotype mistakenly interpreted as 46,XY, testicular feminising syndrome was diagnosed until repeat chromosomal analysis showed 46,X+21/45,X as the karyotype. A cell line of 46,X+21 can easily be mistaken as 46,XY but banding and fluorescence should provide the correct answer, provided the child can be seen to be a phenotypic female. One cell line was 46,X+21 in 13 of the 22 mosaic cases reviewed here.

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45XO/47XXG+ (n=5)
 46XOG+/47XXG+ (n=3)
 47XX21+/47XXp-q-21+ (n=2)
 45XO/46XOG+/46XX/47XXG+ (n=2)
 46XOG+/46XX/47XXG+ (n=2)
 45XO/46XOG+/47XXG+
 46XOG+/46XX
 46XX/45XO/47XXG+
 46XO21+/45XO
 46XOG+/47XXG+/48XXXG+
 47XXp-21+

Figure Karyotype variations in Down's/Turner's mosaic (20 case reports).¹⁻⁶