

Trisomy 22 and intersex

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Abstract

Complete trisomy 22, with or without mosaicism, has been reported as a distinct syndrome. In this report an infant is described who was externally male but with female rudimentary internal organs and whose karyotype was 47, XX+22.

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Trisomy 22 is a rare condition, with less than 20 reported cases¹ in the world literature and the intrauterine death rate is high. The phenotypic features are varied and include growth retardation, microcephaly, low set and malformed ears, micrognathia, cleft palate, anti-mongoloid slant eyes, long and sloping forehead, congenital heart disease, and hypotonia.² Hypoplastic genitalia have been described in a few cases of trisomy 22 but in none of these cases has histology of the gonads been reported. Detailed postmortem examination in our patient revealed the presence of testicular tissue in both gonads confirming gonadal sex status as male.

Case report

This infant was the second to be born to unrelated Nigerian parents (maternal age 31 years; paternal age 43 years), the previous sibling being a normal boy born at full term. There were no other pregnancies and the family history was not informative. The mother booked in the first trimester and routine maternal serum screening at 16 weeks for Down's syndrome (triple test) was positive (risk >1:250), but the couple declined further investigations after an anomaly scan at 18 weeks' gestation which showed no structural abnormality. The pregnancy was uneventful until 37 weeks' gestation when labour commenced spontaneously. At this time there was evidence on ultrasound scan of intrauterine growth retardation, the baby being equivalent to only 31 weeks in size. After an antepartum haemorrhage, the baby was delivered by emergency caesarean section. He required intubation briefly and was subsequently transferred to the neonatal intensive care unit. His birth weight was 1570 g and the occipitofrontal circumference 27 cm. Numerous malformations were found on physical examination: sloping narrow forehead, large anterior fontanelle, abnormal crease on right ear, broad and flat nasal bridge, flat nose, absent eyelashes and eyebrows, short and webbed neck, central cleft of hard and soft palate, small narrow chest, two vessels in the umbilical cord. The genitalia were male in appearance with fused scrotum and a micropenis containing

erectile (corporal) tissue. The testes were not palpable. He remained hypotonic and failed to gain weight in spite of nasogastric tube feeding. He developed a cardiac murmur in the first week of life and remained cyanosed in air. An echocardiogram showed an atrial septal defect and possible abnormal pulmonary valve. An ophthalmological examination revealed no abnormality and the ultrasound scan of the brain and renal system was normal.

A human chorionic gonadotrophin stimulation test was performed (500 IU×3) and the testosterone concentration rose to 2.0 mmol/l from a baseline concentration of 1.5 mmol/l. The serum 17 hydroxyprogesterone concentration of 18.7 nmol/l (normal <20 nmol/l) excluded 21-hydroxylase deficiency. The baby failed to make progress and died aged 3 months.

A postmortem examination revealed a small rudimentary vagina and uterus and both gonads which were located in the abdominal cavity contained testicular tissue (fig 1). The presence of an atrial septal defect was confirmed.

Cytogenetics

Chromosomal studies were performed on both short term peripheral lymphocyte cultures and on skin fibroblasts. The sex chromosomal constitution of the patient was XX using standard methodology including G banding without any evidence of a structural alteration of either X chromosome. Trisomy for chromosome No 22 was present (fig 2A) which was confirmed by chromosome painting (fig 2B). Application of Y specific probes for the centromere and GMGY10 did not reveal the presence of Y material either as a translocation to Xp or in a separate cell line in mosaic form. The probe GMGY3 which is closer to the testicular determining factor (TDF) locus was uninformative. The chromosome patterns of both parents were normal.

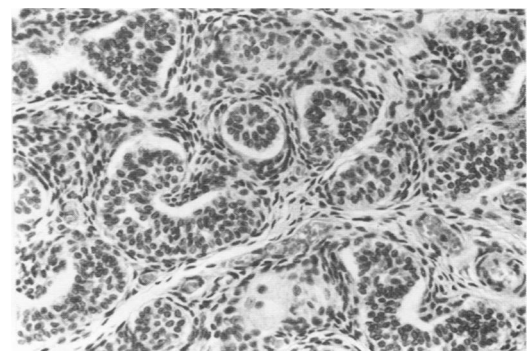


Figure 1 Histological section of left gonad showing seminiferous tubules (haematoxylin and eosin ×375).

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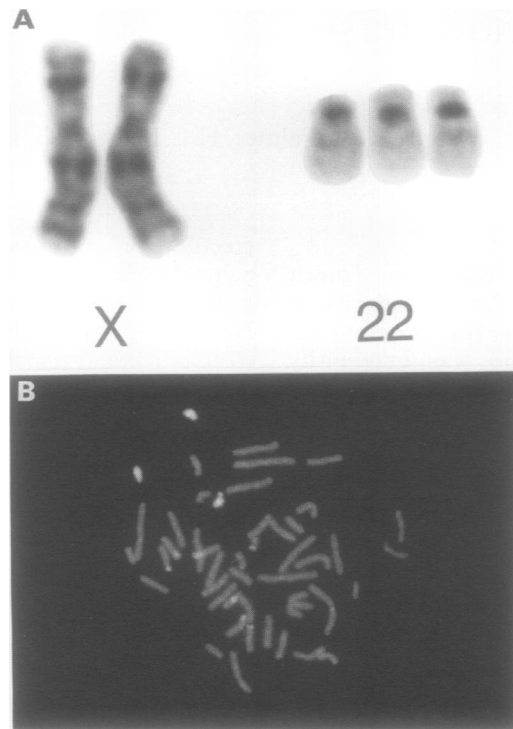


Figure 2 (A) Partial karyotype showing the X pair and trisomy 22. (B) Chromosome paint using a whole chromosome probe for No 22 showing three brightly fluorescent acrocentric chromosomes (top left).

Discussion

The testosterone response to human chorionic gonadotrophin stimulation was subnormal,³ suggesting that the origin of the incomplete male development may have been inadequate testosterone production.⁴

Abnormality of genitalia with intersex has previously been reported in a newborn with partial trisomy of 13 and 22.⁵ However, all previous reported cases of trisomy 22 with ambiguous genitalia have been male whereas in our patient the karyotype was female.

Despite the gonadal histology, the basic fluorescent in situ hybridisation tests including chromosome painting and conventional G banding did not reveal a structural anomaly of one of the X chromosomes involving an X-Y interchange or mosaicism. Ultimate proof would require the application of a probe close to, or for, the sex determining region of the Y chromosome; so-called SRY, which as yet has not been possible in this case. Stored material is available for further investigation at a later date. It is now evident that in some XX patients with testicular tissue where the patient has abnormal or ambiguous genitalia it is not possible to demonstrate Y sequences on either of the X chromosomes.⁶

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