45,X/46,X dic (Y) mosaicism in a phenotypic male

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Abstract

Cytogenetic analysis, confirmed by in situ hybridisation studies, showed a mosaic 45,X/46,X dic (Y) (q12) karyotype in a 14 year old boy who was initially diagnosed as having Noonan's syndrome. He made an early response to recombinant growth hormone; this suggests that this treatment may improve final height.

The phenotypic expression of Noonan's syndrome and Turner's syndrome is similar and it is important to distinguish between them because of management and counselling. We present a teenage boy who was initially diagnosed as having Noonan's syndrome.

Case report

The boy was born at 41 weeks' gestation with a weight of 2500 g and length 48 cm. At the age of 4 years, his height was recorded as 87 cm (standard deviation score (SDS) -3.4) and at the age of 8.7 years as 109.5 cm (SDS -3.3). At the age of 13.1 years his height was 123.9 cm (SDS -4.3), weight 31 kg, and mean parental height 165 cm. He had a dysmorphic appearance with coarse skin, increased elbow carrying angle, webbed neck, widened nipple distance, and gaps between incisors. There was no shortening of the metacarpals, no audible heart murmur, and normal blood pressure. Axillary and pubic hair were absent, and his genitalia were Tanner stage 2 with testes 3 ml (left) and 5 ml (right) in volume.

Endocrine investigations showed normal thyroid and adrenal function and prolactin concentration. His testosterone concentration was 1.5 nmol/l, follicle stimulating hormone undetectable, and luteinising hormone 6 IU/l. There was a growth hormone peak of 20 μ g/l during sleep and a rise with insulin hypoglycaemia to 13.3 μ g/l (glucose nadir 2.1 mmol/l).

His growth velocity was 3.4 cm/year (SDS -3.0) before starting treatment with recombinant growth hormone. After 10 months' treatment (4 units five times a week for eight months then 4 units seven times a week) his growth velocity increased to 7.5 cm/year (SDS -1.4). At 14 years of age his bone age by the Tanner-Whitehouse 2 method was 12.4 years. He subsequently went abroad.

patient showed the presence of two cell lines. Approximately 40% of cells had a 45, X chromosome constitution while the remainder had 46 chromosomes, apparently with a Y chromosome (see fig 1). In a proportion of cells a second constriction in the Y chromosome was noted. C and Cd banding was performed and two dark staining bands and two pairs of centromeric dots respectively were seen in some cells. Quinacrine staining showed that the usually brightly fluorescent distal heterochromatic region of the Y chromosome was absent in all cells examined.

To confirm that the chromosome was indeed derived from the Y, presumed because the patient was phenotypically male, we undertook in situ hybridisation studies on metaphase spreads using the DNA probes pDP105 and pHY2.1, which map to the juxtacentromeric

Figure 1 Trypsin/Giemsa (G) and C banded (C) partial karyotypes showing chromosomes 21, 22, and abnormal Y (from left to right).

Figure 2 Autoradiograph of in situ hybridisation with DNA probe pDP105 on a metaphase spread from the patient. Note two clusters of silver grains over the abnormal Y chromosome (arrowed).

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Chromosome analysis of trypsin/Giemsa banded preparations of cultured lymphocytes from the

region of the Y chromosome and to the distal heterochromatic region respectively. In situ autoradiographs showed two clusters of silver grains over the dicentric chromosome with probe pDP105 (fig 2) and none with probe pHY2.1. The karyotype was thus interpreted as 45, X/46, X dic (Y) (pter → q12:q12 → pter).

Parental blood samples were not available.

Discussion

The similarity between the phenotypic expression of Noonan's syndrome and Turner's syndrome can lead to confusion. The familial occurrence of Noonan's syndrome would indicate a dominant mode of inheritance for this condition and the coincident appearance of neurofibromatosis I in some cases may indicate that the Noonan's syndrome gene is also on chromosome 17.

The presence of features similar to those of Turner's syndrome in a phenotypic male specifically provokes a diagnosis of Noonan's syndrome. Some of these phenotypic males, with varying degrees of virilisation, have, however, been shown to be more appropriately called male Turner's syndrome, resulting from the presence of 45, X/46, XY mosaicism. Like the case reported here several of these have shown a non-fluorescent Y chromosome and it has been suggested that they may be dicentric chromosomes derived by sister chromatid reunion in band Yq1. The expected mitotic behaviour and unstable nature of such a dicentric chromosome would predispose to the development of a 45, X cell line resulting, in some cases, in the stigmata of Turner's syndrome.²⁻³

We have been able to show in our case that the Y chromosome present, although not easily distinguishable from a normal Y on conventional trypsin/Giemsa banding, indeed did prove to be dicentric and to have lost the whole of the heterochromatic portion of the long arm when examined by C banding, Cd banding, and quinacrine fluorescence. This was confirmed by use of Y chromosome DNA probes that showed loss of the heterochromatic region recognised by the probe pHY2.1 and duplication of the region

near the centromere recognised by the probe pDP105.

Although we were not able, probably for technical reasons, to demonstrate two centromeres in all cells no Y chromosomes with normal heterochromatin were observed. Unfortunately we were not able to examine the paternal chromosomes but the father was reported to be of normal phenotype.

It is clearly important from management and counselling aspects to ensure that Noonan's syndrome and Turner's syndrome are distinguished in patients. The latter are at risk of gonadoblastoma when Y chromosomal material is present and the reproductive expectations and recurrence risks are different for the two syndromes.

It has been suggested that gonadoblastoma is less likely to develop in dysgenic gonads when the Y chromosome lacks the fluorescent region.⁴ The number of cases for which long term surveillance is available and which contribute to this conclusion is small, however, and there should be caution in adopting a policy of non-interference. In males with descended testicles, such as this case, long term observation of the testes should be feasible.

Recent evidence in the use of recombinant growth hormone in female patients with Turner's syndrome has indicated the beneficial effect of this treatment in improving growth velocity and final height.⁵ The initial response to growth hormone in our patient suggests that such treatment may also have an important role in treatment of males with this syndrome.

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- 1 Magenis E, Donlon T. Non-fluorescent Y chromosomes: cytogenetic evidence of origin. *Hum Genet* 1982;60:133-8.
- 2 Rosenberg C, Frota-Pessoa O, Vianna-Morgante A, Chu TH. Phenotypic spectrum of 45, X/46, XY individuals. *Am J Med Genet* 1987;27:553-9.
- 3 Kofman S, Perez-Palacios G, Medina M, et al. Clinical and endocrine spectrum in patients with the 45, X/46, XY karyotype. *Hum Genet* 1981;58:373-6.
- 4 Lukusa T, Fryns JP, Van den Berghe H. Gonadoblastoma and Y-chromosome fluorescence. *Clin Genet* 1986;29:311-6.
- 5 Rosenfeld RG. Update on growth hormone therapy for Turner's syndrome. *Acta Paediatr Scand [Suppl]* 1989;356:103-8.

Congenital parvovirus infection

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Abstract

A case of congenital parvovirus (B19) viraemia with associated thrombocytopenic purpura and platelet antigen incompatibility in an infant is reported. Results of laboratory investigations indicated that the baby was infected in utero.

A recent report has shown evidence of the sequelae of congenital parvovirus (B19)

infection.¹ Others have shown haematological consequences of infection in an otherwise normal infant.² We report a confirmed intrauterine infection with B19 in an infant, which was associated with thrombocytopenic purpura and platelet antigen incompatibility.

Case report

An infant boy was born at 37 weeks' gestation after a normal delivery. Pregnancy had been

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