DUPLICATION DEFICIENCY OF AN X-CHROMOSOME WITH AND WITHOUT 45,X MOSAICISM IN THREE GIRLS

Cytogenetic, Clinical, and Hormonal Findings

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In three girls, aged 14, 15 and 16 years, the chromosome analysis revealed a morphologically abnormal, enlarged X-chromosome resembling in size and centromere position the chromosome no. 2. The translocation points were different in all three cases. The Barr-bodies were enlarged. In two girls a 45,X mosaicism (25% and 10%) was found in lymphocyte cultures.

The length at birth was 43, 47 and 48 cm, and none of the girls was born before term. The main clinical abnormalities in all three cases were a marked growth retardation, slight morphological dysplasias, lack of sexual development and social immaturity. GH and cortisol secretion during an insulin tolerance test were normal. LH and FSH were elevated and showed an exaggerated reaction on LH-RH. Oestrogens were low normal and androgens within the normal range. At laparatomy the gonads were found to be streak gonads.

For two girls cell cultures of gonadal tissue were set up, the chromosome findings of which corresponded to those of the lymphocyte cultures.

The abnormality of the gonosomes reported here seems to represent a special form of gonadal dysgenesis. Although the translocation points were different in the three patients and one had no mosaic, while the other two showed 45,X/46,XX mosaicism, the clinical and hormonal findings were nearly the same for all three girls.

For three girls, aged 14, 15 and 16 years, a chromosome analysis revealed a morphologically abnormal, enlarged X-chromosome, resembling chromosome no. 2 in size and centromere position. The translocation points were not the same for all three patients. The Barr-bodies were enlarged.

CASE REPORT

1. Patient A.M. (Fig. 1)

The patient was born 4 weeks after term, after an uneventful pregnancy, with a birth weight of 2000 g, length 43 cm, and showed delayed mental and physical development. She was 15 years old at the time of the investigation (Fig. 1) and showed a marked growth retardation with a height of 134 cm, weight of 37 kg, and a head circumference of 51 cm.

The following *clinical symptoms* are apparent: Naevus flammeus over the root of the nose and on the neck, numerous small pigment naevi all over the body. High-arched palate, abnormalities of the teeth, " shield " chest, cubitus valgus. Sidney line on both hands, long, narrow fingers, shortened and curved 5th fingers on both hands, webbed toes between the basal bones of the 2nd and 3rd toes both sides, proximal insertion of the 4th toes both sides.

Asymmetry of the body: The left arm is 1.5 cm shorter than the right one, and the left leg 1.0 cm shorter than the right one. There is no evidence for congenital heart disease. Breast development: Stage 3 according to Tanner. Pubes: Stage 3 according to Tanner.

X-ray-examination: Pelvis: Flattening of the acetabulum both sides. Retardation of the bone age by about four years.

Laboratory investigations: Thyroid function, as judged by binding-index (1.06) and thyroxin-level (10.4 µg%) is within the normal range. The insulin tolerance test shows a normal rise of growth hormone (GH max 12.4 ng/ml) and a subnormal rise of plasma cortisol (F max 18 µg%). There is a normal excretion of 17-ketosteroids (3.5 mg/d) and 17-hydroxycorticosteroids (5.7 mg/d).

At 14 years and 6 months the *IQ* was found to be 90.

The *dermatoglyphics* are within the range of variability of the normal population and correspond well to those of the other members of the family (mother and two brothers).

Chromosome analysis: The mitoses from lymphocyte cultures show a Turner mosaic. The first investigation gave a value of 28% cells with the karyotype

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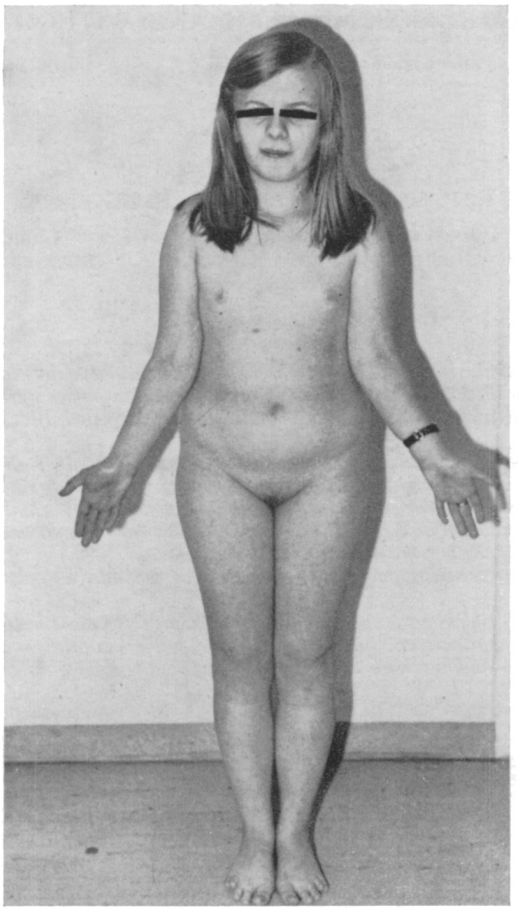

Fig. 1. Patient A.M., 14.7 years old.

45,X, the second investigation 22% 45,X. In the metaphases with 46 chromosomes the second X-chromosome is morphologically abnormal and appears to be a short arm-to-short arm X-X translocation with deletion of the terminal part of Xp (Fig. 2).

2. Patient B.N. (Fig. 3)

The patient was born after an uneventful pregnancy with a weight of 3000 g and length 48 cm. She shows normal mental, but retarded physical development. At the age of 15 years she shows a marked growth retardation with a height of 141 cm and a weight of 39 kg.

Clinical symptoms: Pigment naevi, abnormalities of the teeth, retardation of bone age by about 4 years, according to X-ray examinations. Breast development: Stage 1-2 according to Tanner. Pubes: Stage 3-4.

Laboratory investigations: Thyroid function is within the normal range (Thyroxin 8.9 μg%, PBI 5.9 μg%). Growth hormone shows a subnormal rise after arginine application (HGH max 15.0 ng/ml). There is a low, but still normal excretion of oestrogens (14 μg/d). The plasma values of gonadotropins LH (9.7 ng/ml) and FSH (44.0 ng/ml) were elevated and the urinary excretion of gonadotropins was also higher than normal. LH-RH application produces an exaggerated increase (LH max 26.1 ng/ml; FSH max 100 ng/ml).

Gynaecological investigations: Laparoscopy revealed streak gonads, the left having a more pronounced structure than the right one. Histological analysis of a biopsy of the left gonad showed a structure of menopausal ovary. Some follicles could be seen and the cortex of the ovary appeared to be stimulated. The *dermatoglyphics* show no peculiarities and correspond well to those of the parents.

Chromosome analysis: A Turner karyotype (45,X) is seen in 18% of the lymphocyte culture cells. The remaining cells have 46 chromosomes and, as in our first case, the second X-chromosome is a translocation chromosome X-X with a deletion of the terminal segments of the short arm.

Application of H_3-thymidine showed that it is late replicating. For this patient, chromosome analysis of the other tissues could also be performed:

(*a*) Skin biopsy: 58% cells have a 45,X karyotype, 42% have 46 chromosomes with the abnormal X-chromosome.

(*b*) and (*c*) Right and left gonads: Only cells with the atypical X-chromosome were seen, all having 46 chromosomes.

One of the metaphases from lymphocyte culture showed selective endoreduplication of Xq of the translocation chromosome.

3. Patient B.v.H. (Fig. 4)

The patient was a breech baby, born after an uneventful pregnancy, having a birth weight of 2700 g and a length of 47 cm. She shows normal mental, but retarded growth development. At the age of 16 years growth is markedly retarded with a height of 141 cm, but at 45 kg the patient is overweight for her height. Breast development: Stage 4 according to Tanner. Pubes: Stage 5.

X-ray examination showed a normal bone age of 13.5 years for a chronological age of 14 years.

Laboratory investigations: Thyroid function is within the normal range (TSH 6.3 μ/ml; Thyroxin 9.5 μg%). The insulin tolerance test gives a normal rise of growth hormone (HGH max 18.0 ng/ml) and

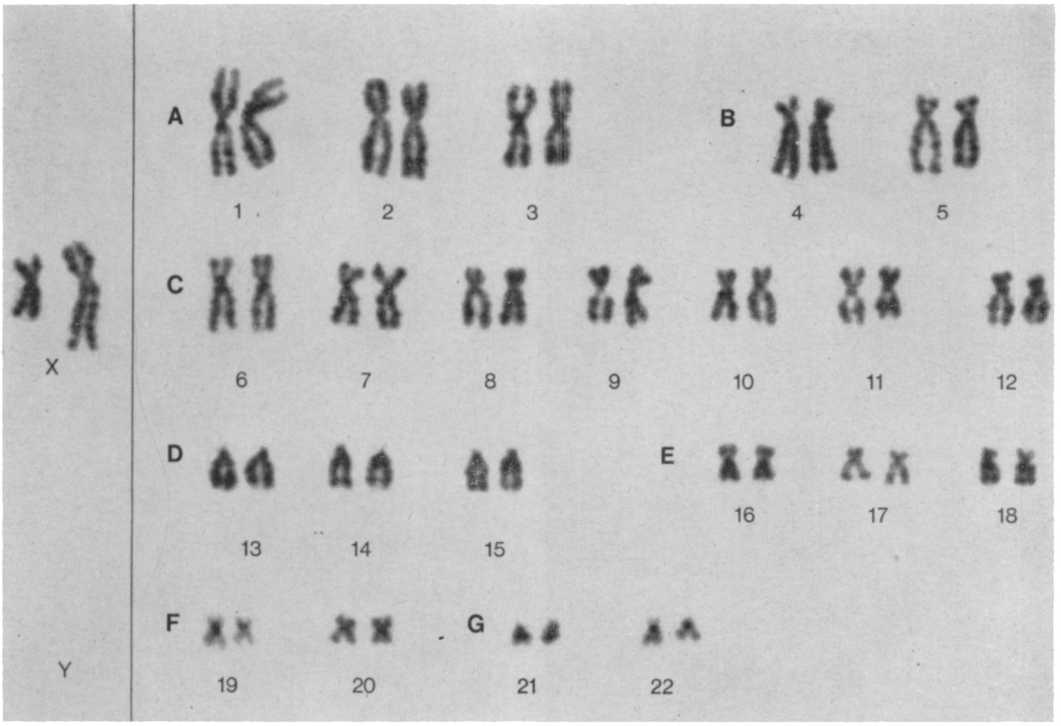

Fig. 2. Karyotype of the patient A.M. with translocation chromosome X-X (Giemsa banding technique).

of plasma cortisol (F max 26 μg%). Excretion of 17-ketosteroids (8.4 mg/d) and 17-hydroxycorticosteroids (9.1 mg/d) is normal and that of oestrogens (9.0 μg/d) is within the lower normal range. The plasma levels of the gonadotropins LH (12.7 ng/ml) and FSH (47.0 ng/ml) are elevated and LH-RH application produces an exaggerated increase (LH max 47.0 ng/ml; FSH max $>$ 50 ng/ml).

The patient had two spontaneous "menstrual" bleedings at 13.5 and 14 years.

Gynaecological examination: Laparoscopy revealed Turner-like gonads, an infantile uterus and normal Fallopian tubes. Histologically the streak-like gonads show remnants of ovarian tissue.

The *dermatoglyphics* of the patient correspond well to those of the parents.

Chromosome analysis: For the lymphocyte cultures the chromosome number was 46 for all cells analyzed. The morphologically abnormal X-chromosome is again very probably a short arm-to-short arm X-X translocation, but this time showing a larger deletion of the terminal segments of the short arm. This could also be ascertained by chromosome measuring. Tissue cultures of the left gonad show cells having the same karyotype.

Banding analysis in all three cases was performed using G-, Q- and C-banding techniques. The C-band method was particularly valuable, as it permitted the localization of a second functional inactivated centromere (Fig. 5).

The chromosome findings for the parents of patients 2 and 3 and for the mother of 1 were all normal.

DISCUSSION

The abnormality of the gonosomes reported here seems to represent a special form of gonadal dysgenesis. Clinically, the most obvious symptom is a marked growth retardation. About the time of puberty an ovarian insufficiency becomes obvious. However, other morphological symptoms typical of Turner syndrome are rare. The hormonal investigations show no peculiarities apart from a strongly increased excretion of gonadotropin characteristic of ovarian insufficiency. Examination of the gonads revealed either a typical Turner gonad or remnants

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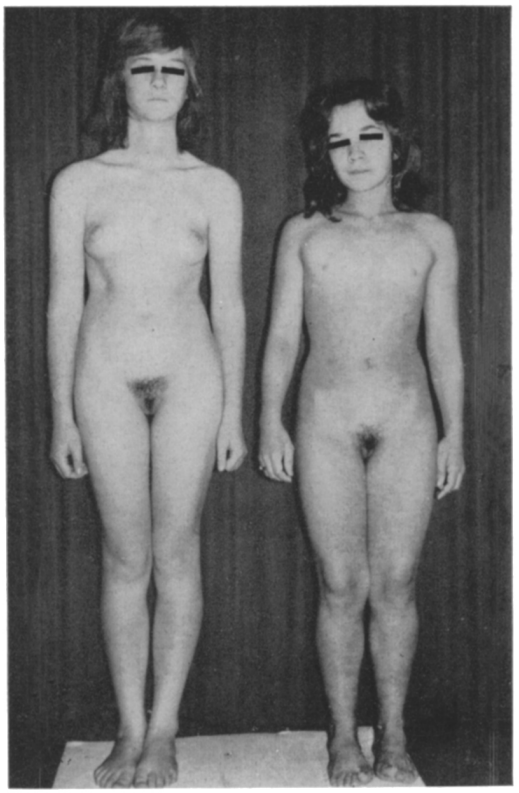

Fig. 3. Patient B.N., 15 years old (left, normal girl of the same age).

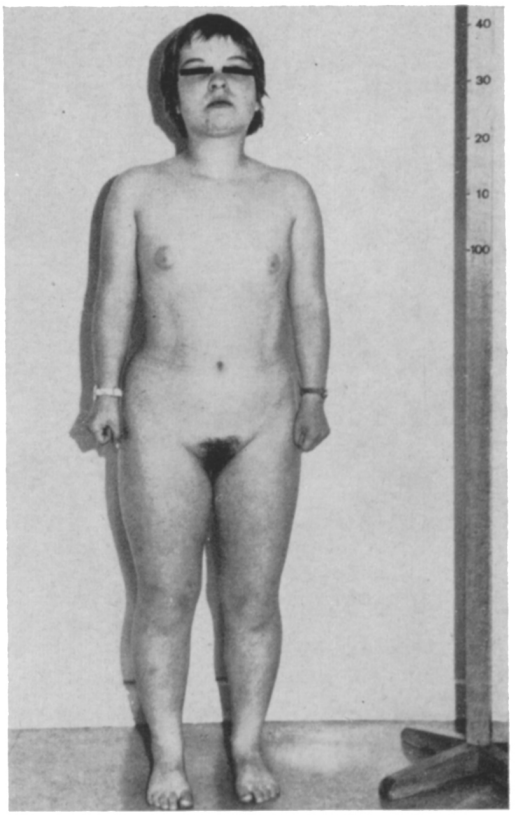

Fig. 4. Patient B.v.H., 16 years old.

of ovarian cortex, occasionally with ova and follicle cells. All three patients showed enlarged Barr bodies (Fig. 6), but these were homogeneous in size and not divided.

In all three cases, the X translocation chromosome is dicentric where one of the centromeres is functionally inactivated. As is well known for isochromosomes of the long arm of X (Xqi), the morphologically abnormal X is late replicating. For two of our patients we observed a Turner mosaic, the frequency of which varies for the different tissues examined. It is probable that these mosaics arose during early embryonic development, as the dicentric translocation chromosome would probably tend towards nondisjunction following anaphase-lagging. We have made similar observations for patients with an iso-X chromosome; 9 of 17 patients so far examined here showed Turner mosaicism.

In the literature we found reports of 11 cases of X-X translocations which resulted in a large submetacentric chromosome. In four of these patients the translocation chromosome was shown to be due to fusion of the deleted short arms of two X chromosomes (Disteche et al. 1972, de la Chapelle and Stenstrand 1974, Ruthner and Cobb 1974, Becroft et al. 1977), as for our three patients. One case was considered to have a long arm-to-long arm fusion of two X chromosomes (Sinha et al. 1976). In all these cases the translocation chromosome was dicentric. The translocations most probably occurred during gametogenesis in one of the parents

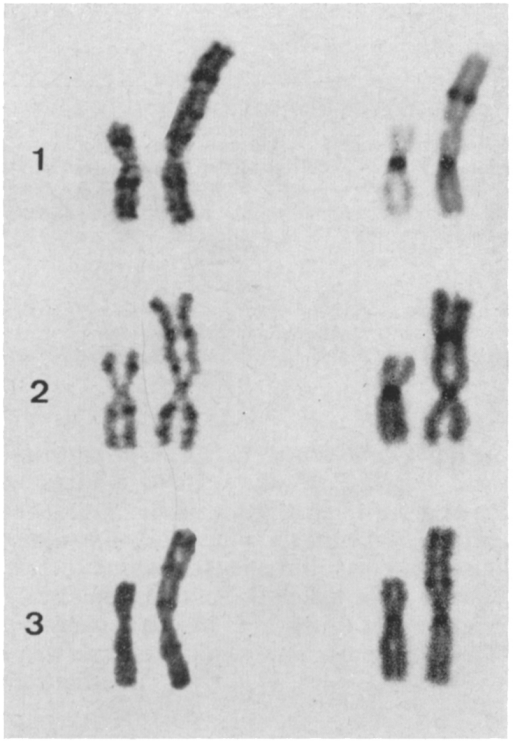

Fig. 5. Translocation chromosomes X-X of the three patients (G- and C-banding).

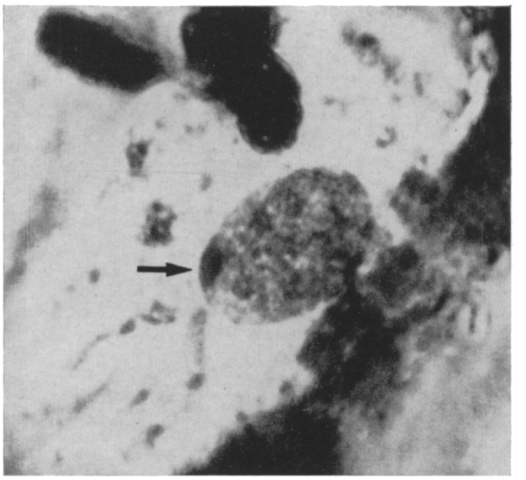

Fig. 6. Enlarged Barr-body of the patient A.M. in buccal smears.

of each patient, while the X0 cell line arose in the early stages of embryonic development.

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REFERENCES

Becroft D.M.O., Costello J.M., Shaw R.L. 1977. 46,XX-X terminal rearrangement / 45,X mosaicism in a child with short stature. Clin. Genet., 11: 122-127.

de la Chapelle A., Stenstrand K. 1974. Dicentric human chromosomes. Hereditas, 76: 259-267.

Disteche C., Hagemeijer A., Frederic J., Progneaux D. 1972. Abnormal large human chromosome identified as an end-to-end fusion of two X's by combined results of the new banding techniques and microdensitometry. Clin. Genet., 3: 388-395.

Ruthner U., Cobb E. 1974. Fusion of the short arms of one X chromosome in a patient with gonadal dysgenesis. Humangenetik, 24: 159-160.

Sinha A.K., Pathok S., Nora J.J. 1976. Fusion of two apparently intact human X chromosomes. Hum. Genet., 32: 295-300.

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