Case reports

Ferguson-Smith⁹ hypothesised that short stature and other somatic abnormalities of Turner's syndrome can be produced not only by the absence of an X chromosome or the deletion of its short arm, but also by a deletion from a Y chromosome. He suggested that the Y may carry genetic material which prevents the expression of Turner's features. The high proportion of 46,XY cells in the gonads and skin of our patient may explain the absence of physical signs of Turner's syndrome and the possibility that he is indeed the biological father of two children. The latter was unconfirmed, as both his children were unavailable for paternity studies.

The patient's intelligence was normal and this is in keeping with the low percentage of 21 trisomic cells. However, his dermatoglyphic pattern was more typical of that found in trisomy 21 than in normal subjects.

M SPARAGANA, P W K WONG, T R DORSCH,
C CASTEN, M RAUER, AND K SZEGO
Medical Service, Veterans Administration,
Edward Hines Jr Medical Center, and the
Section of Genetics, Rush-Presbyterian St Luke's
Medical Center, Chicago, Illinois, USA

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Requests for reprints to Dr M Sparagana, Veterans Administration, Edward Hines Jr Hospital, Hines, Illinois 60141, USA.

Gonadal dysgenesis in a 46,XY female mosaic for double autosomal trisomies 8 and 21

SUMMARY The proband was evaluated at 19 years of age because of primary amenorrhoea and, on chromosomal analysis, was found to have a 46,XY karyotype in 75% of her cells and 48,XY,+8,+21 in 25% of her cells. She appeared normal at birth and exhibited normal intellectual and physical development until puberty when secondary sexual differentiation failed. This young woman showed none of the dysmorphic features associated with either trisomy 8 or trisomy 21. Her XY gonadal dysgenesis was manifested by late developmental problems of amenorrhoea, sexual infantilism, and gonadal neoplasia.

Double autosomal trisomy is extremely rare and has invariably been associated with significant physical abnormalities and limited viability.¹ XY gonadal dysgenesis is also uncommon, but it is compatible with normal longevity.^{2,3}

We now describe a young woman who has XY gonadal dysgenesis and, in addition, is mosaic for double autosomal trisomies 8 and 21. Until the time of failure of pubertal progression, she was considered quite normal.

Case report

The patient weighed 1818 g at birth and was delivered vaginally after the onset of premature labour at 36 weeks' gestation. The prenatal course had otherwise been uneventful. At conception her mother was 27 years old and her father was 31 years old. Except for her prematurity, the patient appeared to be normal at birth and her subsequent intellectual and physical development were entirely normal until puberty. At 13 years of age she had undergone a right adnexectomy for an 18 cm malignant teratoma and at that laparotomy the uterus, fallopian tubes, and left gonad appeared normal and prepubertal.

The patient was first evaluated by us at 19 years of age because of primary amenorrhoea. She appeared to be an intelligent female with a height of 152.5 cm, arm span of 151.4 cm, weight of 39.5 kg, and she was normotensive. Breast development and axillary hair were lacking, but a few pubic hairs were present. Although the vagina, cervix, and uterus were infantile, the clitoris measured 1.5 × 0.5 cm. No adnexal

Received for publication 17 January 1980

FIGURE Karyotype with Q banding showing 48,XY,+8,+21. (Reprinted by permission of the publisher from *Chromosomal Abnormalities Associated with Infertility* by Sulewski *et al*, vol 55, No 4, pp 469-75. Copyright 1980 by the American College of Obstetricians and Gynecologists.)

masses were palpable. She had persistent nystagmus and apparent micrognathia; in all other respects she appeared normal. Bone age was 12 years at the chronological age of 19 years. Serum oestradiol was less than 10 pg/ml (36 pmol/l) (normal range 10 to 770 pg/ml; 36 to 2828 pmol/l) and serum testosterone was 22 ng/dl (0.76 nmol/l) (normal range 20 to 80 ng/dl; 0.69 to 2.77 nmol/l) by radioimmunoassay (RIA). Serum FSH was greater than 1000 ng/ml (50 IU/l) by RIA and clearly in the menopausal range. Serum prolactin, TSH, thyroxine, and α -fetoprotein levels were normal. Intravenous pyelogram was normal. Blood type was A Rhesus positive. Haemoglobin, haematocrit, white blood cell count, and urine analysis were normal.

Chromosomal analysis of the peripheral blood with Q banding showed a 46,XY karyotype in 44 of 69 cells studied; 15 cells contained additional chromosomes 8 and 21, 48,XY,+8,+21 (figure). Karyotypes of her parents were normal.

On histological review of the previously removed gonadal tumour, a gonadoblastoma was found with associated dysgerminoma and benign cystic teratoma. Because of the XY chromosomal components, laparotomy was performed to remove the remaining left gonad. It measured 0.5 $\times$ 3 cm and appeared to be a fibrotic streak gonad. Serial histological sections of the tissue showed a small gonado-

blastoma. Examination of 30 metaphases of skin fibroblasts at the third passage of cells and 30 metaphases of gonadal cells at the third passage of cells showed a 46,XY karyotype in each culture. The patient was H-Y antigen positive.

Postoperatively she was treated monthly with 1.25 mg conjugated oestrogen for 20 days followed by 5 mg norethindrone for five days. This cyclic regimen was associated with light withdrawal uterine bleeding. She grew 5 cm in height within 2 years and Tanner stage IV breast and hair development occurred. However, the serum FSH level remained greater than 1000 ng/ml (50 IU/l) despite concomitant development of breasts, pubic hair, and linear growth. She has been followed for 52 months without any change in her peripheral blood count or karyotype and without evidence of any other abnormalities. She has enjoyed a happy marriage for 8 months.

Discussion

Our patient had none of the typical phenotypic features of trisomy 8 or 21, the trisomic cells found only in her blood cultures. Grosse and Schwanitz¹ and Wilson *et al*⁴ reviewed the features of 18 patients with double autosomal trisomy, including

one patient with trisomies 8 and 21. They found that these subjects exhibited phenotypic characteristics of at least one of the trisomic conditions. Since the trisomic chromosomes have involved groups D, E, and G, the patients have primarily had features of the Patau (trisomy 13), Edward (trisomy 18), or Down (trisomy 21) syndromes. Our patient had none of these features and her early development was entirely normal. At the time of her evaluation, she was a successful college student. Haemopoietic chimerism rather than mosaicism may be an alternative explanation of the peripheral blood karyotype.

Her late developmental problems were amenorrhoea, sexual infantilism, and gonadal neoplasia which are the hallmarks of XY gonadal dysgenesis.^{2,3} The 46,XY cells presumably represent the predominant cell type in all tissues of her body. The presence of H-Y antigen indicates that early programming for testicular differentiation occurred in our patient. However, because of a lack of specific H-Y antigen receptors, testicular development was nullified.^{2,5} In the absence of Sertoli cells with the consequent lack of Mullerian inhibiting activity, Mullerian duct differentiation occurred.⁶

Although sexual target organ maturation was achieved with exogenous oestrogens, the patient's serum FSH level persisted in the menopausal range. One explanation for this is that the threshold for the oestrogen suppressive effect on gonadotrophin secretion may be higher than the oestrogen stimulating effect on sexual target organ maturation. However, an alternative possibility is that in the absence of secretion of folliculostatin/inhibin by the follicles/Sertoli cells, an otherwise effective level of oestrogen is insufficient for suppression of serum FSH to a normal range.^{7,8}

We are grateful for the expert technical assistance of Ms Helen Herr and Mr Joseph Rokita.

JOAN M SULEWSKI,* THAO PHUONG DANG,*

SAMUEL WARD,† AND ROGER L LADDA‡

*Division of Endocrinology and Infertility,

Department of Obstetrics and Gynecology;

†Department of Pathology; and

‡Division of Genetics, Department of Pediatrics,

Pennsylvania State University, College of Medicine,

The Milton S Hershey Medical Center,

Hershey, Pennsylvania 17033, USA.

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Requests for reprints to Dr J M Sulewski, Department of Obstetrics and Gynecology, The Milton S Hershey Medical Center, Hershey, Pennsylvania 17033, USA.