

ULLRICH-TURNER SYNDROME, CHROMOSOME MOSAICISM AND PROPHYLACTIC GONADECTOMY

Maria Herbênia Oliveira Duarte¹, Ester Silveira Ramos¹, Odilon Iannetta² and
Iris Ferrari³

ABSTRACT

Twenty-four patients with Ullrich-Turner syndrome and its variants were analyzed to determine the mosaicism types and frequency and the X or Y origin of the chromosomal fragments in order to establish criteria for the indication of prophylactic gonadectomy. Twenty-one patients were mosaics, with a higher frequency of the 45,X/46,XX type. Six patients had cell lines with chromosome fragments: two X rings, two Y rings and two Y chromosomes of the pseudodicentric type. Thus, 17% of the cases had 45,X/46,XY mosaicism (with or without anomalous Y). The origin of the chromosome fragments was determined by the cytogenetic G-11 banding technique. On the basis of the cytogenetic results, the following clinical-surgical procedures were selected: group I (patients with mosaicism) was divided into two subgroups; subgroup A (45,X/46,XX) was followed clinically and treated hormonally; in subgroup B (45,X/46,XY) gonadectomy was followed by hormone treatment. Group II (patients with 45,X monosomy) was monitored at 6-month intervals with measurement of chorionic β -gonadotropin and peripheral blood α -fetoprotein levels and ultrasound examination.

INTRODUCTION

45,X/46,XX or 45,X/46,XY mosaicism represents the main cytogenetic alteration among patients with Ullrich-Turner syndrome, in contrast to isolated monosomy of

¹ Departamento de Genética, and ² Departamento de Ginecologia e Obstetria, Faculdade de Medicina de Ribeirão Preto, USP, 14049 Ribeirão Preto, SP, Brasil. Send correspondence to M.H.O.D.

³ Departamento de Genética e Biologia, Instituto de Ciências Biológicas, Universidade Federal de Brasília, 70910 Brasília, DF, Brasil.

the X (McDonough and Tho, 1983). The 45,X/46,XX type is more frequent and only 5 to 6% of the patients have the Y chromosome in one of the cell lines. Structural anomalies of the Y chromosome are proportionally more common than anomalies of the X and occur in a third of all 45,X/46,XY cases (Magenis and Donlon, 1982). Twenty-five percent of all dysgenetic patients with a Y chromosome in the karyotype develop gonadoblastomas (Curtis *et al.*, 1980). Thus, cytogenetic determination of the Y chromosome should be a fundamental criterion for the indication of prophylactic gonadectomy. However, the structural alterations of this chromosome and the low frequency of the XY line in mosaicism often prevent a cytogenetic diagnosis (Magenis and Donlon, 1982). Thus, the criteria for the indication of prophylactic gonadectomy are not uniform, with some physicians suggesting removal of the gonadal streaks for all dysgenetic patients and others only for virilized cases (Iannetta *et al.*, 1980).

Magenis and Donlon (1982) used the cytogenetic G-11 banding technique to determine the origin of chromosome fragments in these dysgenetic patients. The anomalous chromosomes presenting a small pericentromeric heterochromatin block (G-11 positive) are assumed to originate from chromosome Y through breaks and deletions. Y DNA probes are currently being used for this same purpose (McDonough, 1987) and can be employed together with G-11 banding to define the indication of surgery.

We carried out a clinical study of 24 patients with Ullrich-Turner syndrome and its variants, characterized the different types of chromosome mosaicism, and determined the X or Y origin of the chromosome fragments by G-11 banding in order to establish criteria for the indication of prophylactic gonadectomy.

SUBJECTS AND METHODS

The study was conducted on all patients with a clinical diagnosis of Ullrich-Turner syndrome who had been followed at the Sex Determination and Differentiation Ambulatory of the University Hospital of Ribeirão Preto, University of São Paulo, from 1984 to 1986. Each patient gave informed consent to participate in the study, which was approved by the Ethics Committee of our Hospital. Cytogenetic analysis was carried out on short time lymphocyte cultures with standard analysis of 100 metaphases in order to detect mosaicisms equal to or higher than 3% at the 0.90 confidence limit, or of 5% at the 0.99 confidence limit (Hook, 1977). G and C banding (Scheres, 1972; Sumner, 1972) was also performed in all cases, and G-11 banding (Magenis and Donlon, 1982) in those cases in which chromosome fragments were detected by standard analysis.

On the basis of the data obtained by cytogenetic analysis, the patients were divided into two groups. Group I consisted of patients with chromosome mosaicism (A, 45,X/46,XX; B, 45,X/46,XY) and group II of monosomic 45,X patients.

RESULTS

Twenty-one of 24 patients were mosaics, with a higher frequency of the 45,X/46,XX type. Lines with chromosome fragments occurred in six cases; G-11 banding showed the presence of two X rings, two Y rings and two Y chromosomes of the pseudodicentric type. Thus, four patients had fragments originating from the Y, representing 19% of the mosaic cases. Patient M.V. had three cell lines, 45,X/46,XX/46,X, fra(Y); no case of normal Y was detected. Figure 1 shows the 46,X, fra(Y) line of patient M.V. with G, C and G-11 bands (series A) compared with those of her father (series B). The Y chromosome of the proposita was larger than her father's and exhibited different banding patterns. Figure 2 shows patient M.V. at 20 years and 7 months of age.

Three patients with Y-derived chromosome fragments (two rings and a pseudodicentric Y) were gonadectomized, and the following histopathological results were obtained: *case S.H.R.* (45,X/46,X, r(Y)), fibrous tissue with a cellular streak stroma; *case C.A.M.* (45,X/46,X r(Y)), fibrous tissue with Leidig cell clusters; *case M.V.* (45,X/46,XX/46,X, pseudic Y), microgonadoblastoma on the right and gonadal streak on the left.

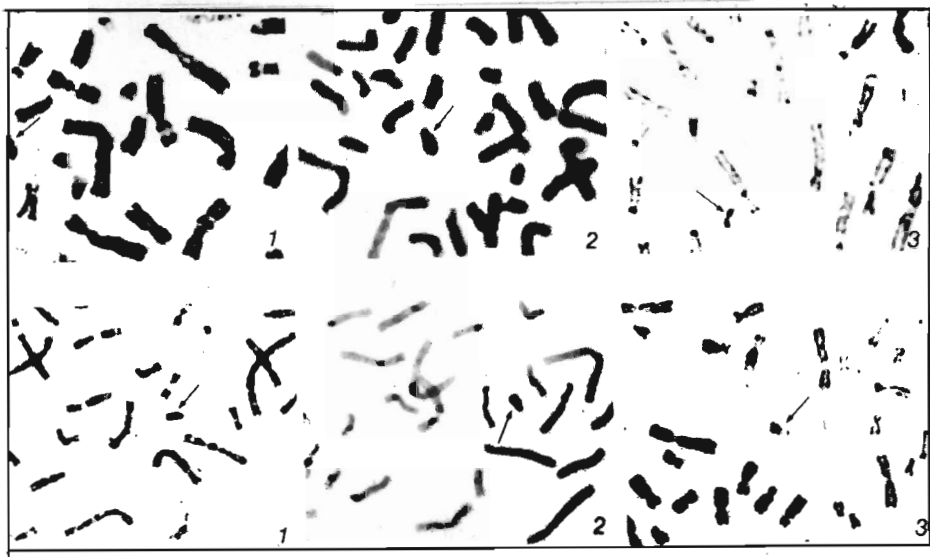


Figure 1 - Series A presents chromosome Y of patient M.V. submitted to G, C and G-11 banding (arrows). Series B presents metaphases of M.V.'s father with the same banding patterns. Chromosome Y of the patient is larger than her father's and shows a C band in the middle portion of the long arm (series A, photograph 2), as well as two pericentromeric G-11 bands of the pseudodicentric Y, according to Magenis and Danlon.



Figure 2 - M.V. at 20 years and 7 months. The patient had been treated with synthetic estrogen and showed mammary development. Note the short height (130 cm), short neck, wide-spaced nipples (IMD = 22 cm above 97%), and cubitus valgus.

DISCUSSION

We investigated 24 dysgenetic patients classified as cases of Ullrich-Turner syndrome or its variants (9). Non-virilized patients with 45,X/46,XY chromosome mosaicism are called Ullrich-Turner variant cases because they exhibit an external phenotype similar to that of 45,X/46,XX patients but run a risk of tumor transformation of their gonadal streaks (Curtis *et al.*, 1980).

A large percentage of our patients (87.5%) had mosaicism with one 45,X line and a 46,XX line in more than 80%. 45,X/46,XY mosaicism with structural anomalies of chromosome Y was present in 17% of our cases. McDonough and Tho (1983) reported similar data and stated that better clinical understanding of gonadal dysgenesis and the development of new cytogenetic techniques have confirmed mosaicism to be the main chromosome alteration in Ullrich-Turner syndrome.

Six patients (28.5%) showed chromosome fragments which were identified by G-11 banding as two X rings, two Y rings and two Y chromosomes of the pseudodicentric or nonfluorescent type (Magenis and Donlon, 1982). Both pseudodicentric Y chromosomes and rings are formed by terminal deletions on the short and long arms of a normal Y chromosome (Magenis and Donlon, 1982). The wide phenotypic variation observed in 45,X/46,XY patients is presumably due to the different concentrations of cell lines in the various tissues. Verp and Simpson (1987) classified 45,X/46,XY patients into three groups: a) patients with female external genitalia and gonadal streaks; b) patients with ambiguous external genitalia generally associated with a streak and a testis or with bilaterally dysgenetic testes; and c) preponderantly male phenotype with bilateral testes. Group "a" in the classification of Verp and Simpson (1987) was a target of our study because of the similarity between these patients and Ullrich-Turner syndrome patients, even though the former are prone to the development of gonadal tumors. Structural anomalies of chromosome Y are also more common among 45,X/46,XY patients with a female phenotype than among virilized patients (McDonough and Tho, 1983), and specific cytogenetic techniques are needed to identify such anomalies (Magenis and Donlon, 1982).

According to Curtis *et al.* (1980), 25% of gonadal dysgenesis patients with a cell line containing a Y chromosome develop gonadoblastomas. This risk is directly proportional to age, being significantly higher after puberty (Manuel *et al.*, 1976) due to a lower degree of virilization of the external genitalia (Nagel *et al.*, 1984) and to the intra-abdominal localization of the gonad (Rutgers and Scully, 1987). Even though this type of neoplasm is not of an invasive type, its frequent association with other malignant forms such as dysgerminomas (Troche and Hernandez, 1986) justifies preventive gonadectomy. This should not be limited to virilized patients or extended to all Ullrich-Turner patients. Detection of chromosome Y either by specific cytogenetic techniques or using DNA probes should be the fundamental criterion for the indication of prophylactic gonadectomy, especially among the groups of 45,X/46,XY patients with a female phenotype.

Considering the relationship of gonadoblastoma with a normal or anomalous Y chromosome in dysgenetic patients, and the possibility of establishing the X or Y origin of chromosomal fragments, we decided to use the following approach for the two groups of patients: *Group I*, patients with chromosome mosaicism - A) 45,X/46,XX mosaicism (normal or anomalous X) are followed clinically. Estrogen treatment is started after age 12 years and sex hormones are measured every six months. Cases of long-arm X isochromosomes are also tested for thyroid function. B) 45,X/46,XY mosaicism (normal or anomalous Y) patients are informed about the risk of gonadal neoplasms and the need for surgery, which is performed before puberty or at the time of diagnosis. After surgery, they are submitted to the same clinical treatment as the patients with 45,X/46,XX

mosaicism. *Group II*, patients with 45,X monosomy, are monitored by measuring chorionic β -gonadotropin and peripheral blood α -fetoprotein levels at six month intervals, and ultrasound examinations is also performed at the same intervals to detect possible gonadal neoplasms not predicted cytogenetically. Hormonal treatment is the same as used for mosaic cases.

ACKNOWLEDGMENTS

Publication supported by FAPESP.

RESUMO

Vinte e quatro pacientes com Síndrome de Ullrich-Turner foram analisados, afim de se determinar a frequência de tipos de mosaicismo e a origem, X ou Y, de fragmentos cromossômicos, para o estabelecimento de critérios de indicação de gonadectomia profilática. Vinte e um pacientes eram mosaicos, com uma maior frequência do tipo 45,X/46,XX. Seis pacientes apresentaram linhagens celulares com fragmentos cromossômicos: dois com anéis de X, dois com anéis de Y e dois com cromossomo Y do tipo pseudocêntrico. Desta maneira, 17% dos casos apresentaram mosaicismo (com ou sem Y anormal). A origem dos fragmentos cromossômicos foi determinada por técnica de bandamento G-11. Baseados nos resultados citogenéticos, os seguintes procedimentos clínico-cirúrgicos foram selecionados: grupo I (pacientes com mosaicismo) dividido em dois subgrupos: subgrupo A (45,X/46,XX) seguido clinicamente e tratado com hormônios; subgrupo B (45,X/46,XY) no qual a gonadectomia seguiu-se tratamento hormonal. Grupo II (pacientes com monossomia 45,X) monitorizado, a intervalos de seis meses, com medidas de β -gonadotrofina coriônica e níveis, em sangue periférico, de α -fetoproteína, e ultrassonografia.

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(Received November 27, 1990)