45,X/46,XY mosaicism

A clinical review and report of ten cases

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Abstract. The clinical findings in ten patients with 45,X/46,XY mosaicism are described. Three girls presented with short stature, delayed sexual development or Turner-like stigmata without signs of virilization. Bilaterally gonadoblastomas were found in two girls, and the gonads in one of these girls also contained mucinous cystadenomas. The remaining seven patients were raised as boys. Three had scrotal hypospadias and mixed gonadal dysgenesis. Three presented as male pseudohermaphrodites with scrotal or penoscrotal hypospadias and bilateral testes. One male was diagnosed in adulthood because of gynecomastia, but had normal male external genitals. The clinical findings illustrate the wide spectrum of phenotypic manifestations of 45,X/46,XY mosaicism, ranging from females with Turner-like phenotypes, phenotypic males and females with mixed gonadal dysgenesis, male pseudohermaphroditism to almost phenotypic normal males.

Key words: Mosaicism 45,X/46,XY - Gonadal dysgenesis - Mixed gonadal dysgenesis - Pseudohermaphroditism - Gonadoblastoma

Introduction

45,X/46,XY mosaicism is found in patients with gonadal dysgenesis [12, 19, 20], mixed gonadal dysgenesis [7, 9, 27], male pseudohermaphroditism [10], hypospadias [1] and gonadoblastomas [4]. Reports on the clinical findings of 45,X/46,XY mosaics based on original patients [3, 6, 8, 11, 15] and collected cases from the literature [8, 14, 17, 26] indicate that 45,X/46,XY mosaics have a wide spectrum of phenotypic appearances. The patients may present as almost complete phenotypic males, as cases with sexual ambiguity or as females with or without Turner-like stigmata. The stature may be short or normal, and eunuchoid proportions have been reported [5, 13, 16, 20, 25]. The aim of the present article is to review the phenotypic manifestations of 45,X/46,XY mosaicism based on the clinical findings in ten patients identified at our department during the last 18 years, and to compare them with previously reported cases. A special feature of our material was the predominance of males, since seven of the ten patients were raised as boys.

Methods and clinical material

Ten patients with the karyotype 45,X/46,XY mosaicism were identified among a total of about 2900 chromosomal analyses, carried out at the department since 1962. Chromosome analyses were performed in cultured lymphocytes from peripheral blood as reported previously [1].

Laparotomy and microscopic investigations of internal genital organs removed at surgery were carried out in eight patients (patients 1–7 and 9). Laparotomy is pending in patient 8 and was not found necessary in patient 10. A series of microscopical sections were made of the different structures in order to identify possible testicular, ovarian, Wolffian and Mullerian tissues.

The clinical and cytogenetic features of the patients have been summarized in Table 1. They may be divided according to four main diagnoses: gonadal dysgenesis (patients 1–3), mixed gonadal dysgenesis (patients 4–6), male pseudohermaphroditism (patients 7–9) and presumably phenotypic normal males (patient 10). Patients 7 and 9 have been reported previously [1].

Bone age was determined in patients 1, 2, 4, 5 and 6, and corresponded to chronological age. Five patients had heights near or below the 2.5th percentile (patients 1–5, Table). Four patients had Turner-like stigmata (patients 1, 2, 7 and 9, Table 1).

Patient 5 developed an autoimmune thyroiditis with goitre, increased thyroidal antibodies and slightly elevated thyrotropin (10.8 mU/l), whereas triiodothyronine and thyroxin levels were normal, 3.5 and 87 nM, respectively.

None of the patients was mentally retarded.

Urinary malformations were demonstrated in four patients with duplication of the renal pelvis (patient 5), horseshoe kidney (patients 3, 4 and 7) and vesicoureteric reflux (patient 4).

A human chorionicgonadotropin stimulation test was performed in patients 4, 6, 7 and 9 (1500 IU Physex twice a week for 3 weeks). In patients 4 and 6 the gonadotropin administration resulted in increases in the size of penis. In patients 7 and 9 the plasma levels of testosterone increased from 0.7–1.4 µg/24 h and from 0.2–2.1 µg/24 h, respectively. Elevated follicle-stimulating and/or luteinizing hormone levels were found in patients 2, 3 and 10, whereas patients 1, 4–7 and 9 had normal/low normal values.

The abdominal gonads present in patients 1–7 (Table 1), were removed before puberty. In patient 1 microscopic investigation of the abdominal streak gonads revealed nests of...
gonadoblastomas, whereas the abdominal gonads in case 2
contained both gonadoblastomas and mucinous cystadenomas
(Fig. 4).

Discussion

Both male and female embryos have an inherent tendency to
feminize, unless there is active interference by masculinizing
factors, including the histocompatibility-Y (H-Y) antigen,
anti-Müllerian hormone, testosterone and dihydrotestos-
terone [13, 23]. The mechanisms involved in the translation of
genetic sex into a testis or an ovary are poorly understood.
The H-Y antigen is present in all cell membranes from normal
XY males, and its synthesis and secretion is regulated by
genes on Y and X chromosomes. The H-Y antigen is the puta-
tive morphogenetic factor responsible for the differentiation
of the gonadal cells into testicular tissue. The Sertoli cells of
the testes are responsible for the secretion of anti-Müllerian
hormone, which prevents the development of female genital
ducts during a critical period of fetal life. Testosterone, se-
creted by the Leydig cells, stimulates the development of male
genital ducts. The conversion of testosterone to dihydrotestos-
terone at the end organ, is responsible for the masculinization
of the external genitals. The inhibitory influence of the fetal
testis on Müllerian duct development, and the stimulatory ef-
effect of testosterone on the development of male genital ducts,
are exerted locally and unilaterally. The masculinizing effects
of dihydrotestosterone on external genitals is, however, an
endocrine effect of testosterone. Two intact X chromosomes are
required for differentiation of the indifferent gonad as a nor-
mal ovary, and patients with a 45,X karyotype develop ab-
dominal streak gonads [7, 9, 13, 23].

The patients with 45,X/46,XY mosaicism listed in Table 1
show a wide spectrum of different expressions, which proba-
ably is explained by the predominance of the 45,X or 46,XY
cell-lines in the gonads and somatic tissues. The 45,X cell-line
is supposed to have determined the gonadal development into
abdominal streak gonads in patients 1-3. In patients 4-6,
46,XY and 45,X cell-lines had determined the development of
the gonads on each side of the body [9], resulting in a testis
and an abdominal streak gonad, respectively. In patients 7-
10, the 46,XY cell-line induced the development of testicular
tissue in both gonads. True pseudohermaphroditism with
ovotestes [14, 25] and a hernia uteri inguinalis [13, 20] have
also been reported in 45,X/46,XY mosaics.

Patients 1-3 had no testicular tissue, and the absence of
fetal testosterone and anti-Müllerian hormone had resulted in
the involution of the Wolfian ducts and the persistene of Fal-
popian tubes. In patients 4-6 with mixed gonadal dysgenesis,
testosterone secretion from the testis had induced the unilat-
eral development of a vas deferens, whereas a Fallopian tube
persisted on the side of the abdominal streak gonad due to ab-
sence of anti-Müllerian hormone. In many of the patients with
45,X/46,XY mosaicism, expression of the H-Y antigen is in-
sufficient, resulting in various degrees of dysgenetic testes
[13]. Reduced or delayed secretion of anti-Müllerian hormone
may result in persistence of Müllerian structures, like a uterus
in patients 4-7 and unilateral Fallopian tubes in patients 7 and
9. Similarly, reduced fetal testosterone secretion may explain
the absence of the right vas deferens in patient 9.

Some Müllerian structures could be demonstrated in all
patients subjected to laparotomy. Most of the patients with
45,X/46,XY mosaicism have a more or less developed uterus

![Fig. 1. Appearance of the external genitals of patient 8 at the age of 7
months. Bifid scrotum with scrotal hypospadia, but with a rather well-
formed phallus and bilateral scrotal testes](image1)

![Fig. 2a, b. Appearance of the external genitals of patient 6 at the age of 2
with a bifid scrotum with scrotal hypospadia, but with a rather well-for-
med phallus (a). A testis is present in the right scrotum. At the age of 16 years (b) the male external genitals have developed satisfactorily](image2)