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»MIXED« GONADAL DYSGENESIS,
A CASE WITH MALE PHENOTYPE AND 45,X/46,XY MOSAICISM

By
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ABSTRACT

A 48-year-old male with 45,X/46,XY mosaicism and mixed gonadal dysgenesis is presented. His height was 157 cm he had a shield-like chest and multiple skin naevi. The patient had been operated on for hypospadias. At 44 he became mildly diabetic.
On the left side of the scrotum there was a testicle measuring 2 cm, showing a histological picture of the »Sertoli cell only« syndrome. Laparotomy revealed a uterus, a vas deferens and a Fallopian tube. A streak gonad was located on the right side. Histologically the streak gonad resembled those typical of female Turner's syndrome, and the histology of the testis resembled that commonly found in male Turner's syndrome.
Cultures of lymphocytes from the peripheral blood made in 1961, 1962 and 1969 revealed 6, 31 and 12 per cent respectively of cells with the karyotype 46,XY. The remainder of the cells had the karyotype 45,X. Fibroblasts grown from skin biopsies invariably showed only 45,X cells. Mitoses from tissue cultures of the testis showed 29 % cells with the karyotype 46,XY. The apparent variations in the proportions of the different stem-lines between different tissues and at different times in mosaicism are emphasized.
Other reports on phenotypic males with the clinical picture of »mixed« gonadal dysgenesis and X/XY mosaicism or related karyotypes are

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briefly reviewed with emphasis on the testicular histology and the presence of congenital anomalies other than those connected with the genital system.

The term »mixed« gonadal dysgenesis (m. g. d.) was introduced by Sohval (1964) to describe cases with various degrees of hermaphroditism which can neither be classified as pseudohermaphrodites (with bilateral gonads) whether male or female, nor as hermaphrodites (with both testicular and ovarian tissue). Their main feature is a mostly undescended testis on one side and a »streak« gonad on the other. Among 27 cases collected by Sohval (1969) 12 patients had a female phenotype whereas the phenotype was ambiguous in 10 and male in 5 cases.

Among 19 cases studied cytogenetically in Sohval’s series (Sohval 1964) the karyotype was X/XY mosaicism in eight, XY alone in five, X alone in four and one case each of X/XXXX and X/XY/XX mosaicism respectively. The sex chromatin was negative in all cases.

Five patients in Sohval’s series were listed as having a male phenotype but with the same intra-abdominal findings including a uterus as in the female patients. Subsequently other cases of m. g. d. with male phenotype and mostly X/XY karyotype have been reported (Table 2).

A case briefly described previously (de la Chapelle & Hortling 1962, 1963) of »mixed« gonadal dysgenesis is now described again in detail following laparotomy and with additional karyotype determinations. The patient, now 48 years of age, had a male phenotype with X/XY karyotype, hypospadias, typical intra-abdominal findings and a descended testis showing no signs of spermatogenesis. The clinical features of our case are compared with those of previously reported male individuals with m. g. d., particular emphasis being paid to the location and histology of the testis.

1. Clinical data

The patient is a 48-year-old unmarried clerk, the seventh of eight children, four boys and four girls. Paternal and maternal age at his birth were 36 and 25 years respectively. The mother was diabetic. The maturation occurred to age. At the age of 33, a histologically malignant skin naevus was extirpated and treated with X-rays. At the age of 35, a Denis Browne urethroplasty was successfully performed for hypospadias. At the age of 44, mild diabetes was diagnosed with morning blood sugars of 169, 185 and 196 mg/100 ml and a maximum daily excretion of 27 g glucose. The blood sugar became normal following treatment with 250 mg of chlorpropamide every second day. The patient is of short stature (157 cm) and in 1964 was somewhat obese, weighing 67.6 kg. Since that time, his weight gradually decreased and in 1966 was 56.5 kg. He complained of periodic upper abdominal distress. He had taken testosterone preparations periodically since 1961. In 1966 laparotomy was performed.

The general appearance of the patient is typically male. He has a shield-like chest. He shaves daily and did so before androgen therapy was initiated. Axillary
and pubic hair are of normal masculine type. He has neither erections nor pollutions. There is a mild pseudogynaeacomastia without any palpable glandular tissue. There are numerous pigmented skin naevi. On the left side a soft gonad (2 cm) is palpable in the scrotum. The right gonad is not palpable. The penis is short (Fig. 1). No prostate can be palpated. Haemoglobin 13.9 g/100 ml. Electrocardiogram normal. Blood pressure 120/80 mm Hg. Creatinine 1 mg/100 ml, alkaline phosphatases 7.2 King-Armstrong units. X-ray investigation revealed a normal heart and lungs, hernia of the diaphragm, normal gall bladder and stomach. Urography showed the kidneys, ureters and urinary bladder to be normal. The calcium content of the vertebrae is increased rather than decreased. A standard oral glucose tolerance test revealed blood sugar values of 86 mg/100 ml before glucose, 178 mg/100 ml at 1 h and 169 mg/100 ml at 2 h after glucose. PBI 6 μg/100 ml, cholesterol 260 mg/100 ml.

X-rays of the skull revealed a normal sella turcica. The gonadotrophin excretion in the urine, assayed biologically according to the method of Pesonen et al. (1959) modified for routine use, was on two separate occasions greater than 40 and greater than 80 mouse units, respectively. Total 17-ketosteroids in the urine was 7.1 mg/24 h before androgen therapy. A loading test with 25 IU ACTH was administered intravenously and there was a rise in the plasma 11-hydroxycorticosteroids as determined according to a modified Spencer-Peet et al. (1965) technique, from an initial 9.2 μg/100 ml to 49.2 at 5 hours.

Psychologically he feels himself as male. As a child he was somewhat uncertain about his sex. As an adult he has felt himself to be male and has enjoyed female company, but has had no desire to advance in this respect.
2. Cytogenetic findings

The patient was found to be sex chromatin-negative. No Barr bodies were detected in the oral mucosa cells and there were no drumsticks in the polymorphonuclear leucocytes.

Chromosome preparations from leucocytes from the peripheral blood (Moorhead et al. 1960) and from the skin fibroblasts (Frøland 1961) were made on three occasions. Using the fibroblast method, tissue cultures were also set up from a biopsy of the left testis. After one subculture, mitotic cells were collected, processed and karyotyped. The results are shown in Table 1. Photographs of the 45,X and 46,XY karyotypes have been previously published (de la Chapelle & Horting 1963).

The great majority of cells from all the tissues studied (blood, skin and testis) had the karyotype 45,X. However, differences between the tissues were noteworthy. Moreover, the proportions of the two stem-lines in the lymphocytes were different on three occasions over a period of 8 years. Blood cultures in 1961 yielded 6 per cent XY cells, in 1962 31 per cent, and finally in 1969, the proportion of XY cells was 12 per cent. Although it is not possible to determine the causes or implications of this variation in the number of the XY cells, a genuine biological phenomenon is one possible explanation. In order to obtain a reliable assessment of the situation, repeated observations are obviously valuable.

In the three skin cultures, no 46,XY cells were found. It should be noted that skin from three different locations (forearm, abdomen and scrotum) behaved alike in this respect, showing regularly, over a period of 6 years, the karyotype 45,X only.

Both stem-lines were present in karyotyped cells from the cultures of testicular origin, the 46,XY cells making up 29 per cent of all the cells. At the stage when the mitoses were collected (after one month in vitro with one subculture) there were two populations of cells in the cultures of testicular origin. Morphologically, one type resembled fibroblasts whereas the other was larger and roundish. It was not possible to ascertain whether both types of cells were among those karyotyped. However, according to morphological assessment of the growing cultures, both types were equally numerous, displaying numerous mitoses, suggesting that both may have been represented in the population of mitotic cells used for preparing karyotypes (cf. Discussion).

3. Laparotomy and histological investigations

Before laparotomy the right inguinal canal was explored. In the canal a structure resembling ligamentum rotundum was found (containing connective tissue, blood vessels and atrophic smooth muscle cells) but no vas deferens.

Laparotomy disclosed a typical ligamentum latum and rudimentary female
Table 1.
Results of the cytogenetic investigations.

<table>
<thead>
<tr>
<th>Year</th>
<th>Tissue</th>
<th>Chromosome counts</th>
<th>No. of cells with Y chromosome</th>
<th>Per cent cells with Y chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 44</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>1961</td>
<td>Blood</td>
<td>1</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>1962</td>
<td>Blood</td>
<td>-</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>1963</td>
<td>Blood</td>
<td>-</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>1963</td>
<td>Skin (forearm)</td>
<td>1</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>1967</td>
<td>Skin (abdomen)</td>
<td>4</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>1969</td>
<td>Skin (scrotum)</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>1969</td>
<td>Testis</td>
<td>$^{1a}$</td>
<td>5$^3$</td>
<td>73$^3$</td>
</tr>
</tbody>
</table>

$^1$ Neither of these cells had a Y chromosome, the aberrant chromosome number apparently being due to chromosomes from other cells adjoining the metaphases in question.

$^2$ This cell had a Y chromosome.

$^3$ Two of these cells had a Y chromosome.
The female genitalia consisted of a uterus 3 cm × 2 cm in size, one Fallopian tube with fimbriae and beneath the tube an ovary-like formation (Fig. 2). From the uterus two strings extended down to the bladder neck. One of these, located more medially, was apparently a venous plexus, while the other, more to the right was a vas deferens, as shown histologically. Palpation at laparotomy revealed no prostatic gland.

The location of the structures found at laparotomy is depicted schematically (Fig. 3).

Histological investigation revealed the following: Relatively typical uterus tissue with normal myometrium but relatively low endometrium. The glands are ordinary and in some places slightly enlarged and resemble oestrogen-induced beginning hyperplasia. From the surface some polypoid structures extend into the lumen.

Fallopian tube with relatively normal ridge formation. Some of the epithelial cells show cilia, others are secretory cells with a clear cytoplasm. The muscle layer is normal. Alongside the Fallopian tube, tubule-like structures with cilia, in some places surrounded by smooth muscle tissue, are found. These structures resemble parovarian remnants of the Wolffian duct (epoophoron-paroophoron).

A section from the right string extending from the uterus revealed a tubule-like structure with simple cylindrical epithelium and in some places formations resembling cilia. The lamina propria mucosae is thick and peripherally surrounded by a thin muscle layer. This structure is interpreted as a vas deferens.

![Image](image_url)

**Fig. 2.**
Uterus, Fallopian tube and adjacent structures.
The intra-abdominal gonad (Fig. 4) revealed no tunica albuginea but connective tissue very much resembling ovarian stroma (C). Deeper in the specimen there are tubules covered with cylindrical epithelium like those beneath the tube (A). A further structure consisting of cell islands formed by a few cells with clear cytoplasm can be seen (B). This structure may be a primitive sex cord system. In at least one site a lumen can be observed in the middle of the cells. There are no oocytes. Scattered around the specimen are cells with eosinophilic cytoplasm and a relatively large rounded nucleus (D). These cells resemble Leydig cells but the cytoplasm is slightly granular. It is difficult to decide whether this structure originates from ovarian or testicular primitive tissue.

Biopsies of the left testicle (Fig. 5) in 1962, and 1969 gave identical results. There is an absence of spermatogenesis and thickening of the basal tubular membranes without any tubular fibrosis or sclerosis. Only somewhat atypical Sertoli cells are seen in the tubuli. The Leydig cells are hyperplastic and in some places form large areas of cells with relatively large amounts of brown pigment. The testicle can be classified as a »Sertoli cell only« syndrome. The patient did not receive any treatment during the months before biopsy.
Fig. 4.
The »streak« gonad.
A Tubules similar to those beneath the Fallopian tube (160 ×).
B Cell islands resembling primitive sex cord structures (266 ×).
C Connective tissue under the peritoneum (66 ×).
D Cells with eosinophilic cytoplasm and a large hyperchromatic nucleus (arrows) resembling Leydig cells (266 ×).
DISCUSSION

The male phenotype is less common than the female in m. g. d. and no comprehensive survey of the male cases has been made. Therefore the case reports found in the literature have been tabulated (Table 2) with special emphasis on the location, and histology of the testicle as well as on the presence of congenital anomalies.

6 out of 13 cases of m.g.d. in Table 2 showed 45,X/46,XY mosaicism, one each having a 45,X/48,XXXY, a 45,X/48,YYYY, a 45,X/46,XY/47,XXY/46,XX, a 45,X/46,XYqi?/47,X?Yqi?Yq- mosaicism and two a 46,XY karyotype

X/XY mosaicism has also been described in connection with other clinical syndromes, such as female and male Turner's syndrome, true hermaphroditism

* Cytogenic abbreviations are according to the Chicago Conference (Standardization in Human Cytogenetics, Birth Defects: Original Article Series, II:2. The National Foundation: New York (1966).
Cases of "mixed" gonadal dysgenesis with male phenotype. Including only individuals in whom laparotomy had been performed and the testicular histology described.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Anomalies</th>
<th>Testicles Location and size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warkany et al.  (1962)</td>
<td>2 weeks</td>
<td>Scrotum divided by raphe, ears prominent and low. Right ureter dilated. Penis normal.</td>
<td>Left inguinal.</td>
</tr>
<tr>
<td>Lewis et al.     (1963)</td>
<td>45 years</td>
<td>Hypospadias, bifid scrotum. No children, married.</td>
<td>At 27 operated on for ectopic testis. A malignant seminoma was found on the left side.</td>
</tr>
<tr>
<td>Guinet et al.    (1965)</td>
<td>18 years</td>
<td>Hypospadias. Bilateral inguinal herniation. Height 155 cm.</td>
<td>Right intra-abdominal.</td>
</tr>
<tr>
<td>de Grouchy et al. (1966)</td>
<td>12 years</td>
<td>Hypospadias, short metacarpals and metatarsals. Height 128 cm.</td>
<td>Left scrotal, size normal.</td>
</tr>
</tbody>
</table>

and male pseudohermaphroditism. Quite normal reproductive organs have been found in two males with the karyotype 45,X/46,XY (Kjessler 1966) and in one with 45,X/46,XY/46,XXp−q−/47,XXp−q−Y mosaicism (Ferrier et al. 1963).

The testis is most often intra-abdominal, inguinal or labial. Scrotal location occurred once in Sohval’s series. This patient was an infant of ambiguous phenotype (Conen & Erkman 1963). Later three male cases with a scrotal testis were described (Table 2). In our patient the testis was descended.

According to Sohval (1964) the location of the testicle determines the histological status. Apparently, however, the histological picture varies. Germinal elements more or less normal for the age have been described almost regularly
Table 2 (cont.).

<table>
<thead>
<tr>
<th>Histology</th>
<th>Other genital findings at laparotomy</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal tissue, intra-tubular ovoid bodies.</td>
<td>Uterus, vas deferens, Fallopian tube. Poorly differentiated gonad on the left.</td>
<td>Not investigated. Sex chromatin negative</td>
</tr>
<tr>
<td>Infantile.</td>
<td>Uterus, Fallopian tubes (two), a large urecholic cyst. No gonad on the right.</td>
<td>45,X/48,XXXXY</td>
</tr>
<tr>
<td>Malignant seminoma.</td>
<td>Uterus with adeno-carcinoma. On the right undifferentiated gonad and Fallopian tube.</td>
<td>45,X/46,XY</td>
</tr>
<tr>
<td>Sertoli cells among numerous spermatogonia. No Leydig cells.</td>
<td>Uterus, Fallopian tube and undifferentiated gonad on the left.</td>
<td>45,X/46,XY/47,XXY/46,XX</td>
</tr>
<tr>
<td>Immature spermatogenesis.</td>
<td>Uterus, two Fallopian tubes, »streak« gonad on the right.</td>
<td>46,XY</td>
</tr>
<tr>
<td>Spermatogenesis according to age.</td>
<td>Uterus, Fallopian tube, undifferentiated gonad on the right.</td>
<td>45,X/46,XY</td>
</tr>
</tbody>
</table>

In the male cases (Jackson et al. 1966; de Grouchy et al. 1966; Job et al. 1966), sometimes even if the testicle is ectopic (Cox & Berry 1967) and also in cases with ambiguous external genitalia (Bergada et al. 1962). Absence of germinal elements in an intra-abdominal testis may be seen in the female type (Turner et al. 1963, case 1; Greenblatt et al. 1964; Sohval 1964; Jackson et al. 1966; Zimprich 1969) but sometimes the tubules are well developed (Turner et al. 1963, case 2). The total absence of germinal elements despite the fact that the testis was descended is striking in our case. Leydig cells are as a rule to be found in cases of m.g.d. regardless of phenotype, as was also the case in the present patient.
Table 2.
Cases of "mixed" gonadal dysgenesis with male phenotype. Including only individuals in whom laparotomy had been performed and the testicular histology described.

<table>
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</thead>
<tbody>
<tr>
<td><em>Job et al.</em></td>
<td>8 years</td>
<td>Hypospadias. Bifid renal calix and ureter on the right. Short stature.</td>
<td>Left inguinal.</td>
</tr>
<tr>
<td><em>Josso et al.</em></td>
<td>3 years</td>
<td>Hypospadias. No other anomalies.</td>
<td>Left inguinal.</td>
</tr>
</tbody>
</table>

The testicular histology in this patient resembled the "Sertoli cell only" type. The smaller than normal testis and the increased excretion of gonadotrophins are not features of the original del Castillo's syndrome (del Castillo et al. 1947). Cases without any germinal elements have also been described in otherwise healthy males (Nelson 1950; Tillinger 1957) or in cryptorchism (Tillinger 1957; Hortling et al. 1967).

The streak gonad and short stature found in most cases of male m. g. d. are also features of the female Turner's syndrome. In the male Turner's syndrome a histological picture of Sertoli-cell-only syndrome or at least a deficient ger-
Table 2 (cont.).

<table>
<thead>
<tr>
<th>Histology</th>
<th>Other genital findings at laparotomy</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanty spermatogenesis.</td>
<td>Uterus, vas deferens, Fallopian tube, Müllerian duct, »streak« gonad on the right.</td>
<td>45,X/46,XY</td>
</tr>
<tr>
<td>Cells arranged in whorls in both gonads.</td>
<td>Uterus, Fallopian tube, Müllerian duct, »streak« gonad on the right.</td>
<td>45,X/46,XY</td>
</tr>
<tr>
<td>Immature spermatogenesis.</td>
<td>Uterus unicornus, Fallopian tube, »streak« gonad on the right.</td>
<td>45,X/46,XY</td>
</tr>
<tr>
<td>Immature spermatogenesis.</td>
<td>Fallopian tube on the right. No uterus. No gonad on the right.</td>
<td>46,XY</td>
</tr>
<tr>
<td>Well-formed testicular tubules.</td>
<td>Uterus, Fallopian tube, no evidence of ovarian stroma.</td>
<td>45,X/48,XYYY</td>
</tr>
<tr>
<td>Germinal cell aplasia.</td>
<td>Uterus, Fallopian tube, »streak« gonad on the right.</td>
<td>45,X/46,XY</td>
</tr>
</tbody>
</table>

Minal cell development is present (Schoen 1965; Chaves-Carballo & Hoyles 1966). In the series of male cases of m. g. d. (Table 2) anomalies such as short stature, brachymetacarpals and kidney anomalies often described in Turner's syndrome were frequently found. The combination in our case of absence of spermatogenesis, short stature, stocky build, numerous pigmented naevi and a »streak« gonad thus seems to indicate that the patient described here could be regarded as having features of both male and female Turner's syndrome. He also fulfils the criteria of »mixed« gonadal dysgenesis.

The histological pattern in the »streak« gonad is indistinguishable from that.
seen in Turner's syndrome (Sohval 1964) as was also the case in this patient. Total absence of the gonad is sometimes seen (Table 2).

With regard to the origin of the male phenotype and the degree of masculinization it is of interest that in a recent case with ambiguous phenotype the X/XY karyotype mosaicism was found in leucocytes and skin. The right gonad, of testicular type, had only 45,X cells (Ferrier & Kelley 1967). By contrast, in our case mosaicism was present in the lymphocytes and the testicular cells, but not in the skin cells. Thus the data available at present show no consistency in the distribution of the different stem-lines. It would appear logical that the presence of an XY stem-line induces masculinization of the gonad at the time of organogenesis with subsequent masculinization of the phenotype. Probably the production of a testicular inducer substance by the primordial gonad is involved (Dewhurst 1962). To explain why the phenotype is male in some m. g. d. patients and female in others, it may be postulated that this agent is defective or that the time sequence of events may be upset (Ferguson-Smith 1965; Federman 1967). Later changes in the proportions and distribution of the stem-lines may obscure the karyotypic picture. To solve these problems, many more cases will have to be studied. Early investigations of foetuses might be especially rewarding (Klinger & Schwarzacher 1962).

In an earlier report (de la Chapelle et al. 1964) it was shown histochemically that cultures of testicular origin from an XX male contained both fibroblasts and cells displaying steroid dehydrogenase activity presumed to be of Leydig cell origin. While it is not possible to prove that in the present case such cells were similar to those with the XY karyotype, this remains an attractive hypothesis.

The frequent combination of m. g. d. with gonadal blastomas is remarkable and is an indication for the removal of the intra-abdominal gonads. When tumour formation occurs it is often difficult or impossible to classify the basic type of hermaphroditism (Lewis et al. 1963; Sohval 1964).

REFERENCES


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