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A CASE OF GONADAL DYSGENESIS IN A PATIENT
WITH A 46/XY KARYOTYPE, PHALLIC ENLARGEMENT AND
ABSENCE OF SEMINIFEROUS TUBULES

By

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ABSTRACT

Among the patients with gonadal dysgenesis, the cases with phallic
enlargement, but without the somatic malformations seen in Turner's
syndrome, are classified as a special group. This group includes chroma-
tin-negative as well as chromatin-positive cases.

A patient is described with gonadal dysgenesis, XY karyotype, absence
of seminiferous tubules in streak gonads, presence of female internal and
external genitalia and phallic enlargement.

The problems of sex-determination and differentiation are discussed with
regard to this patient.

The term gonadal dysgenesis only indicates that the gonadal tissue is not
normally developed.

This term should not be used as is often done, to denote a clinical syndrome
which has been given the name of Turner's syndrome. This syndrome is
characterized by infantilism, gonadal dysgenesis, and short stature as well as
other somatic malformations.

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In contrast to Turner's syndrome many authors now talk about a syndrome of pure gonadal dysgenesis. This condition is characterized by poor development of the breast, the presence of scanty pubic and axillary hair and external genitalia of normal female type with a normal clitoris. The uterus is hypoplastic but endometrial bleeding may occur following oestrogen withdrawal, although the patient has primary amenorrhoea when untreated. The patient is of a normal height with eunuchoidal body proportions. The urinary excretion of gonadotrophins is usually raised. At laparotomy typical dysgenetic streak gonads are found. There are no somatic malformations.

Cases of pure gonadal dysgenesis may be chromatin-positive or chromatin-negative. One of us (J.T.) studied 11 such cases, classified as an eunuchoidal form of gonadal dysgenesis, in the period from 1956–1958. Four of these patients had a negative sex-chromatin pattern. Chromatin-positive cases with streak gonads, a female phenotype and with no somatic malformations have been described by Hoffenberg & Jackson (1957), Teter (1960), Jones et al. (1963). It is also possible that case 2 of Jacobs et al. (1960) and case 18 of Jacobs et al. (1961) with the karyotype XX could be included in the group.

Chromatin-negative cases with pure gonadal dysgenesis have been described by Harnden & Stewart (1959), Stewart (1960), de Grouchy et al. (1960), de la Chapelle (1962) (case no. 24). Jones et al. (1963) found 1 chromatin-negative case among several chromatin-positive cases. In all the chromatin-negative cases referred to above an XY-complement was found.

A variant of the group of gonadal dysgenesis is called gonadal dysgenesis with phallic enlargement (Grumbach & Barr 1958). The phallic enlargement may be present together with the usual malformations (Grumbach et al. 1955). Such patients are diagnosed as Turner's syndrome with phallic enlargement. In contradistinction to this, patients with no somatic malformations, but with gonadal dysgenesis plus phallic enlargement should be diagnosed as gonadal dysgenesis with phallic enlargement.

A chromatin-positive patient with this clinical picture was described by Greenblatt et al. (1956). Sayer's (1955) case of «male pseudohermaphroditism» may have been a chromatin-negative case of this kind.

The aim of the present study was to describe a chromatin-negative case with an XY-karyotype of gonadal dysgenesis with phallic enlargement, and also by correlating the sex-chromosome complement and structure of the gonad to gain further knowledge about sex determination and differentiation in man.

**CASE REPORT**

Patient H.A., aged 43, was examined seven years ago because of primary amenorrhoea, and underdeveloped genitalia. Growth and body development during childhood had been regarded as entirely normal. Axillo-pubic hair accompanied by some slight
growth of the breast and enlargement of the clitoris occurred at the age of approximately 14 years. However, full female secondary sex development did not follow. From the age of seventeen a rapid body growth occurred. Particularly marked was the growth of the extremities. She married at the age of 21. Due to a narrow and non-elastic vagina, sexual intercourse was impossible. After a few unsuccessful attempts, the couple gave up trying and was divorced. When the patient was 24 years of age she married again. Because of pain, sexual intercourse was again impossible. After a dinner with large quantities of alcoholic drinks, full coitus was attained, but a large rupture of the posterior fornix with haemorrhage occurred. Suture was performed in the Municipal Hospital. During the operation it was found that the uterus was very small, rather of foetal type and that the «ovaries» were extremely elongated and thin.

At that time symptoms of climacteric molimina occurred.

In addition, the patient suffered from intestinal disturbances. Two years later she was operated on because of intestinal obstruction due to cicatrization following a chronic inflammation. Part of the ileum was surgically removed.

During the following years the patient suffered from sudden attacks of tinnitus and dizziness. Menière's syndrome was suspected and some relation with an absence of ovarian function was suggested by the neurologist.

Fig. 1.
Patient H. A., aged 43. Note eunuchoidal body shape.
When the patient was 36, the physical examination carried out at the Endocrine Department revealed a woman with masculine appearance and strong body build. Her height was 175 cm, her body proportions were eunuchoidal with prepubertal type of breast and scanty axillo-pubic hair. The clitoris was somewhat hypertrophied (Figs. 1 and 2) and the labia majora had a scrotal appearance. Gynaecological examination revealed a very narrow, non-elastic vagina and a very small but palpable uterus and cervix. No adnexal mass or gonads were found.

X-ray of the thorax and of the upper abdomen was normal. A urethrogram showed no congenital malformations of the urinary tract.

Urine gonadotrophin titer was raised to over 200 M. U. Urine 17-KS excretion amounted to 12.4 mg/24 h (slightly elevated). She had normal colour vision (tested with Ishihara's plates).

Examination of smears from the buccal mucosa showed a negative sex-chromatin pattern.

Laparotomy showed a foetal uterus and long thin fallopian tubes. In the place normally occupied by the ovary whitish streaks were found -- they were completely removed.

Histological examination of the right gonad revealed a cortical zone resembling ovarian connective tissue stroma (Fig. 3). The medullary zone contained nests of Leydig cells, which were rounded, eosinophilic and homogeneous with a slightly marked granularity. The nuclei were dark and spherical with a rather dense chromatin. Neither seminiferous tubules nor crystalloids of Reinke's were found. In the deeper layers numerous small tubules of mesonephric origin (Fig. 4) were seen. The lining epithelium of these tubular vestiges was composed of cuboidal cells, in some areas more columnar, but nonciliated. The lumen was highly convoluted. The mesonephric tubules were surrounded by poorly developed muscle sheaths.
Microphotograph of section of the gonad. It is composed of stromal tissue similar to that of ovarian cortex, but with no follicles. Note a small nest of Leydig-like cells in the medullary zone (bottom in the center).

Microphotograph of tubule of mesonephric origin.
Fig. 5.
Karyotype of cell with chromosome complement 46/XY.

The left gonad contained large nests of interstitial cells rather resembling theca-lutein cells, which originated from stromal cells. No primordial follicles were found in the gonads.

**Conclusion**

From the above findings it was concluded that this case should be classified as »The syndrome of gonadal dysgenesis with phallic enlargement«.

**Chromosomal analysis**

Leucocytes from peripheral blood were cultured by the method of Moorhead *et al.* (1960) with minor modifications. The skin was cultured as described by Philip (to be published).

Chromosomal analysis was performed with the aid of enlarged microphotographs.

**Results of the chromosomal investigations**

One hundred and four metaphases were counted. Ninety-six had 46 chromosomes. The karyotypes obtained from 12 cells, *i.e.* 7 from blood and 5 from skin, showed a typical male pattern (XY) (Fig. 5). The results are listed in Table 1.
Table 1.
Results of chromosomal counts.

<table>
<thead>
<tr>
<th>No. of chromosomes</th>
<th>43</th>
<th>44</th>
<th>45</th>
<th>46</th>
<th>47</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>46</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>50</td>
<td>1</td>
<td>54</td>
</tr>
</tbody>
</table>

Follow-up
The patient has received hormonal treatment for six years. Oestrogens with vitamin E and progesterone were given in a cyclic fashion. This treatment has resulted in a good development of the mammary glands and external genitalia. The climacteric symptoms and discomfort of pseudo-Meniére’s syndrome disappeared. When treatment was suspended all the above symptoms re-appeared. Cyclic artificial menstruations were also obtained. The patient married for the third time. At present she is able to have normal satisfactory sexual intercourse. Five years ago a cancer of the lower eyelid was diagnosed and was successfully treated by radiotherapy.

Discussion
There is good evidence that the Y-chromosome is important in the determination of sex in man. Although several cases have now been published in which testicular tissue has been present and in which a Y-chromosome has not been found (Atkins & Engel 1962) it is possible that this can be explained by the presence in these cases, of mosaicism or by translocation of parts of the Y-chromosome to other (autosomal) chromosomes. Such mosaicism will always be difficult to exclude, and even if more than one tissue has been investigated with regard to chromosomes, a gonosomic mosaicism cannot be ruled out.

Mosaicism in different tissues is occasionally seen; in one of our cases of male pseudohermaphroditism the chromosomal complement was a »two tissue« mosaic: 45/XO in the blood, but 45/XO, 46/XY in the skin.

As evidence for the importance of the Y-chromosome in sex determination it should be mentioned that cases with several X-chromosomes have a male phenotype, when a Y-chromosome is also present and that XO subjects have a female phenotype.

Although it is generally believed that the Y-chromosome is definitely significant for sex determination in man, there is now a good deal of evidence
for the suggestion of Harnden & Stewart (1959), that the Y-chromosome itself is not sufficient to ensure the male phenotype. This has been amply confirmed by the many cases of male pseudohermaphroditism with a female phenotype details of which have now been published. In this connection it may be mentioned that at least 17 cases with classical testicular feminization and an XY-chromosome complement are now on record. The fact that a subject with XO/XYY or XO/XY/XYY (Jacobs et al. 1961) and subjects with pure gonadal dysgenesis and an XY karyotype presents a female phenotype, is further evidence that the Y-chromosome is not sufficient for male differentiation. Vaharu et al. (1961) and Ferrier et al. (1962), however, suggest that the presence of even slight signs of virilization may be taken as evidence that chromatin-fragments of unknown origin may be deleted Y-chromosomes. In the present case it is obvious that the Y-chromosome is not even sufficient to ensure the development of seminiferous tubules.

Provided that the normal looking Y-chromosome does not mask invisible structural abnormalities, then either genetic factors located on other chromosomes or environmental factors during embryogenesis may play a part in the abnormal development of such patients. As Harnden & Stewart (1959) point out, an analogy with the experiments of Jost on rabbits, would explain the syndrome of pure gonadal dysgenesis, independently of the genetic sex of the patient. »Gonadectomy« in the early foetal state leads to an individual with a female phenotype which is independent of the genetic sex.

Unexplained, however, by this theory is the fact that chromatin-positive as well as chromatin-negative cases of gonadal dysgenesis can have an enlargement of the clitoris. There is no need to suggest the presence of a Y-chromosome in chromatin-positive cases of this kind. The sex differentiation is of course not independent of the genetic sex, but is, however, strongly influenced by other (especially hormonal) factors. As there is no agreement in the literature as to the source of androgens and oestrogens from the gonad, it is not possible to decide whether the Leydig-like cells present in the gonad of our patient produced the androgenic hormone which may have been responsible for the enlargement of the clitoris, but it is possible that this was the case. As Leydig-like cells may also be present in a female gonad, the same considerations may be valid in patients with male as well as female genetic sex.

Another possibility is that the adrenal gland is the source of androgenic hormones. Goldzieher & Rodgers (1963) found hypertrophy of the clitoris in one of a pair of dizygotic twins, and were able to show that this was caused by an enzyme-defect in the adrenal gland with increased excretion of 17-ketosteroids and pregnanetriol (congenital adrenogenital syndrome).

Finally the possibility of extrafoetal androgen sources must be mentioned.

In this case no definite conclusions as to the aetiology of the enlargement of the clitoris can be drawn.
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