Familial XY Gonadal Dysgenesis*

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Gonadal dysgenesis is a condition characterized by streak gonads in subjects who present the phenotypic appearance of females. In pure gonadal dysgenesis, unlike Turner's syndrome, no associated somatic anomalies are found; the adult is of normal or above average stature and may have eunuchoidal proportions (Sohval, 1965).

The term 'XY gonadal dysgenesis' refers to patients with pure gonadal dysgenesis who are chromosomal males (Federman, 1967). In contrast, the term 'dysgenetic male pseudohermaphroditism' refers to an incomplete form of maldevelopment of the embryonic testis in patients in whom varying degrees of masculinization and genital ambiguity are found either at birth or at the time of puberty (Table I).

In this report we present a family in which three sibs have abnormal gonads and incomplete sexual development: two phenotypic females with pure gonadal dysgenesis and a phenotypic male with dysgenetic pseudohermaphroditism (Fig. 1 and 2: II.6; II.7; II.8). These two entities have been reported in sibs on only one previous occasion (Barr et al., 1967).

Case Reports

Case 1. The propositus (Fig. 1 and 2: II.7) is a 17-year-old phenotypic male who was admitted to the hospital for investigation of ambiguous genitalia. He was born after a full-term, uneventful pregnancy, and was pronounced a female by the attending physician. However, this was not accepted by his parents and he was raised as a boy. At 5 years of age, when first admitted to the Colorado General Hospital, he was thought to be a pseudohermaphrodite of undetermined sex; an exploratory laparotomy was refused by his mother. The child's behaviour pattern was definitely masculine. At puberty he developed masculine secondary sex characteristics, and showed heterosexual inclinations. At the time of admission at age 17 years, he was well masculinized and had the following pertinent physical findings: height 170 cm., arm span 183 cm., weight 52 kg., a moderate amount of facial and axillary hair, and a male escutcheon. Bilateral inguinal herniae were present, the left one containing a mass which was thought to be a gonad. He had an underdeveloped bifid scrotum, a large phallus with marked chordee, a perineal urethra, and a vagina and bilateral patent Fallopian tubes, as demonstrated by vaginogram. The remaining physical examination was non-contributory.

| TABLE I |
| GENITAL AND GONADAL FINDINGS IN SUBJECTS WITH GONADAL DYSGENESIS |

<table>
<thead>
<tr>
<th>Gonadal Dysgenesis</th>
<th>External Genitalia</th>
<th>Gonads</th>
<th>Sex Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner's syndrome Dysgenesis</td>
<td>Female</td>
<td>Streaks</td>
<td>XO and XY mosaicism</td>
</tr>
<tr>
<td>Pure gonadal</td>
<td>Female</td>
<td>Streaks and/or tumours</td>
<td>XY and XO/XY mosaicism</td>
</tr>
<tr>
<td>XY gonadal dysgenesis</td>
<td>Ambiguous</td>
<td>Maldeveloped testes</td>
<td>XY and XO/XY mosaicism</td>
</tr>
</tbody>
</table>

An exploratory laparotomy revealed a small uterus and two Fallopian tubes. The left hernia sac contained a small testicle, with vas deferens and epididymis; the right sac was empty. Attached to the right Fallopian tube was a second gonad (Fig. 3). The bilateral herniae were repaired; a left orchipexy was performed, and the uterus, Fallopian tubes, and vagina removed. Later surgical procedures focused on releasing the chordee and constructing a male urethra.

Histological examination of the biopsy of the left gonad and the extirpated right gonad revealed testicular tissue with inactive, partially hyalinized seminiferous tubules enmeshed in a greatly increased number of interstitial cells and containing Sertoli cells. Additional tubular structures resembled epididymis and also rete testis. In multiple sections, there was no evidence of ovarian or neoplastic tissue.

Diagnosis. Dysgenetic male pseudohermaphroditism.

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Fig. 1. The three patients: II.6, pure gonadal dysgenesis; II.7, dysgenetic male pseudohermaphroditism; II.8, pure gonadal dysgenesis. II.6 and II.8 were on cyclic hormone therapy at this time.

Fig. 2. Pedigree.
Case 2. The older sister of the propositus (Fig. 1 and 2: II.6) is a 19-year-old phenotypic female who had primary amenorrhoea and lack of spontaneous development of secondary sex characteristics. She had been on cyclic oestrogen/progesterone therapy for six months before admission, and since then had regular withdrawal bleeding and development of breasts and pubic hair.

Physical examination revealed a tall, bony female, with eunuchoidal proportions, height 185 cm., arm span 193 cm., and weight 56 kg. She had multiple small naevi on her skin, with no special distribution, and a hairy naevus on the anterior portion of her right thigh. Her ears were large, with hypoplastic antihelices, and the mandible was slightly prognathic. She had a mild conductive hearing loss probably secondary to recurrent otitis in childhood. A type I bifid uvula was found in the otherwise unremarkable palate. Cubitus valgus was present. Axillary hair and pubic hair were abundant and of normal distribution. The breasts were normally developed, with pigmented areolae. Her external genitalia were female with normal labia majora and minora and a moderately hypertrophied clitoris.

An exploratory laparotomy revealed bilateral streak gonads which were removed. A normal-sized nulliparous uterus and normal Fallopian tubes were present. Histological examination of the streak gonads revealed ovarian type stroma which contained scattered tubular elements lined by columnar epithelium, presumably of cervicovaginal origin. No ova, follicles, or neoplastic tissues were seen.

Diagnosis. Pure gonadal dysgenesis.

Case 3. The younger sister of the propositus (Fig. 1 and 2: II.8) is a 14-year-old phenotypic female who had not menstruated and had not developed secondary sex characteristics. She too was placed on cyclic oestrogen/progesterone therapy for six months before admission, and since then had withdrawal bleeding and breast development. At 8 years of age, a dysgerminoma of the right gonad was removed. On the left was a streak gonad which was left in situ.

Physical examination revealed a normal appearing female. Her height was 171 cm., weight 52 kg., and arm span 175 cm. She had multiple small naevi on her skin. There was slight clinodactyly of the fifth fingers. Axillary hair was sparse, but pubic hair was adequate and of female distribution. The breasts were normally developed. On rectal examination, a small firm uterus was felt, without adnexal masses. The external genitalia were normal for a female, without clitoral enlargement.

Diagnosis. Pure gonadal dysgenesis. Right dysgerminoma.

Family History

The three patients (Fig. 2: II.6; II.7; II.8) are the last three sibs in a sibship of seven. Of the other four sibs, two are married and have children (Fig. 2: II.2; II.3); one, who died at 11 years of age from a ruptured appendix (Fig. 2: II.4), was said to have normal early breast development, and the other (Fig. 2: II.5) is a normally developed female.

All seven sibs were purportedly conceived by the same father, who died in an accident at 62 years of age (Fig. 2: I.2). He worked in a uranium mine from one year before the conception of the affected sibs until death.

The mother (Fig. 2: I.3) was 37 years old at the time her youngest daughter was born. She was examined by us at 51 years of age and found to be a normal postmenopausal female.

Laboratory Studies

The following laboratory tests were within normal limits on all three patients: complete blood count,
urinalysis, blood urea nitrogen, creatinine, serum electrolytes, and total carbon dioxide, and skull and chest x-rays. Case 2 (II.6) had a retarded bone age (bone age 13 years at chronological age of 19 years), whereas the other two patients had normal bone ages.

Dermatoglyphic analyses were not unusual. Perceptual and psychological tests revealed that all three patients were of normal intelligence. The two sisters have problems with visual integration, more marked in the younger one (Case 3: II.8).

Blood groups from the mother and all her children were determined, as well as haptoglobin, G6PD, colour blindness, and phenylthiourea tasting test. Since neither the father nor a paternal uncle were available, these studies were not revealing.

**Cytogenetic and Endocrine Studies**

Buccal smears for sex chromatin bodies and lymphocyte and fibroblast cultures were performed by modifications of standard techniques (Moorhead et al., 1960; Tjio and Puck, 1958). The three patients were chromatin negative, and chromosome analysis of all examined tissues revealed a 46,XY karyotype, with no evidence of mosaicism. Their mother and one normal sister were both chromatin positive, and had a normal 46,XX karyotype (Table II).

A series of steroid analyses was carried out on blood and urine samples from the three patients (Table III). Testosterone was determined by gas chromatography equipped with an electron capture detector (Exley, 1967). The fractionated 11-deoxy-17-ketosteroids were estimated using a combination of glass fibre paper chromatography and gas liquid chromatography equipped with a flame ionization detector (Wotiz and Martin, 1962).

The blood and urinary testosterone levels showed some interesting abnormalities. They were low in the propositus when compared to a normal male; the corresponding values in the two sisters (on therapy) were much lower than those of the propositus, but still higher than normal female values. Other steroid levels were low to normal.

In order to investigate the source of the androgens in the propositus, dexamethasone was given to suppress adrenal synthesis of testosterone. Two days later, while continuing the dexamethasone, human chorionic gonadotropin (HCG) was also given in order to stimulate the testicular production of testosterone (Table IV; Fig. 4). The patient’s urinary levels of testosterone fell

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**TABLE II**

**CYTOGENETIC STUDIES**

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Sex Chromatin (buccal smear)</th>
<th>Tissue</th>
<th>No. of Cells</th>
<th>&lt;45</th>
<th>45</th>
<th>46</th>
<th>47</th>
<th>&gt;47</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.3</td>
<td>Positive</td>
<td>Lymphocytes</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>II.5</td>
<td>Positive</td>
<td>Lymphocytes</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>II.6</td>
<td>Negative</td>
<td>Lymphocytes</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Fallopian tube</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>15</td>
<td>46,XY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>28</td>
<td>1</td>
<td>46,XY</td>
<td></td>
</tr>
<tr>
<td>II.7</td>
<td>Negative</td>
<td>Skin</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>46,XY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gonad</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>46,XY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.8</td>
<td>Negative</td>
<td>Lymphocytes</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>46,XY</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE III**

**HORMONE LEVELS**

<table>
<thead>
<tr>
<th>Urinary Excretion (mg./24 hr.)</th>
<th>Patients</th>
<th>Normal Adult Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 2</td>
</tr>
<tr>
<td>Total 17-ketosteroids</td>
<td>11/2</td>
<td>46/5</td>
</tr>
<tr>
<td>Total 17-OH corticoids</td>
<td>13/5</td>
<td>8/8</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>1.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Etocholanolone</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Dehydroisoandrosterone</td>
<td>0.67</td>
<td>0.55</td>
</tr>
<tr>
<td>Pregnanediol</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>11-OH androstenedione</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>11-O androsterone</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>11-OH etiocholanolone</td>
<td>0.95</td>
<td>0.45</td>
</tr>
<tr>
<td>11-O etiocholanolone</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>FSH (m.U.)</td>
<td>+6/105</td>
<td>50/100</td>
</tr>
<tr>
<td>Testosterone Blood (µg./100 ml.) (±0.05 = 2 SD)*</td>
<td>0.44</td>
<td>0.04</td>
</tr>
<tr>
<td>Urine (µg./24 hr.) (±3 = 2 SD)</td>
<td>39.5</td>
<td>19.4</td>
</tr>
</tbody>
</table>

*SD, standard deviation.
from a basal value of 39.5 µg./24 hours to a suppression value of 5.4 µg./24 hours, and did not rise with HCG stimulation. Blood testosterone and other steroid fractions followed a similar pattern. All levels returned to their previous values only after cessation of the dexamethasone administration. The values of the other steroid fractions showed the same pattern as did testosterone. In contrast, the normal control male responded to dexamethasone with a similar drop in testosterone, which rose considerably after HCG stimulation.

**TABLE IV**

<table>
<thead>
<tr>
<th>Urinary excretion (mg./24 hr.)</th>
<th>1*</th>
<th>2†</th>
<th>3‡</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 17-ketosteroids</td>
<td>12.7</td>
<td>5.3</td>
<td>4.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Total 17-OH corticoids</td>
<td>14.5</td>
<td>4.8</td>
<td>3.6</td>
<td>13.9</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>2.7</td>
<td>0.9</td>
<td>0.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Etiocholanolone</td>
<td>2.3</td>
<td>0.5</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Dehydroisoandrosterone</td>
<td>0.8</td>
<td>0.2</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>11-O androsterone</td>
<td>0.8</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>11-O androsterone</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>11-O etiocholanolone</td>
<td>1.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.52</td>
<td>0.13</td>
<td>0.13</td>
<td>0.56</td>
</tr>
<tr>
<td>Blood (µg./100 ml.)</td>
<td>39.5</td>
<td>5.4</td>
<td>5.4</td>
<td>35.0</td>
</tr>
</tbody>
</table>

* Baseline levels.
† During adrenal suppression.
‡ During adrenal suppression and HCG administration.
§ Baseline levels, 10 days after ‡.

**Discussion**

The familial occurrence of XY gonadal dysgenesis in a single as well as in different sibships has been reported by several authors (Barr et al., 1967; Bartlett et al., 1968; Brogger and Strand, 1965; Cohen and Shaw, 1965; Fine, Mellinger, and Canton, 1962; Frasier, Bashore, and Mosier, 1964; Sternberg, Barclay, and Kloepfer, 1968). Before the present report, no phenotypic males had been described in association with familial XY gonadal dysgenesis, though the first case of Barr *et al.* (1967) showed definite signs of masculinization at the onset of puberty. This patient was a male pseudohermaphrodite; the sister had pure gonadal dysgenesis. All the other patients have had pure gonadal dysgenesis, and 46,XY karyotypes. In the only reported 45,X/46,XY mosaic in this group (Cohen and Shaw, 1965), the 45,X line was found in 50% of the mitoses from one gonad only. Table V summarizes the principal characteristics of all these patients, including our three cases. Only in the cases reported by Cohen and Shaw (1965) and by Brogger and Strand (1965), were marker chromosomes found.

In our patient with dysgenetic male pseudohermaphroditism, there was no response to gonadotropin after dexamethasone administration, and testosterone levels did not rise until adrenal suppression was terminated. The primary source of testosterone, therefore, is the adrenal, and the patient has little if any steroid of testicular origin. The serum and urinary testosterone values in the two sisters were raised as compared with a normal female, but lower than a normal male. High urinary testosterone levels in phenotypic females with male karyotypes have been reported on several occasions (Federman, Davidoff, and Ouellette, 1967; Ismail et al., 1968; Josso *et al.*, 1969). The adrenals of chromosomal males (whether phenotypically male or female) produce more androgens than those of chromosomal females. The reason for this is not completely understood. The foetal testis synthesizes testosterone early during differentiation (Villee, 1969), and Tata (cited by Max Hamburgh, 1969) hypothesized that the primary action of these hormones on developing target structures is the stimulation of some transcriptional RNA synthesis. These data suggest that the foetal testis programs the adrenal for increased testosterone production at a later developmental stage.

The various types of gonadal dysgenesis here considered probably have their determining steps occurring early in foetal development. The experiments of Jost (1953) have shown that a functioning testis is essential for the stimulation of Wolffian duct derivatives and the inhibition of Müllerian duct derivatives. The foetal testis is thought normally to secrete an inducer or organizer substance which evokes these effects through a local action. Jost showed that early castration of male embryos prevents the resorption of the Müllerian
duct system with absent or abnormal masculinization of the external genitalia. It is therefore possible that the defect in the abnormal foetal gonad may lie in the structure, the amount, or the time of production of the inducer substance. Complete failure of inducer action would be analogous to early castration, in which a streak gonad is produced which is incapable of inducing masculinization even though a Y chromosome is present. A lesser abnormality of the foetal testis would then produce a dysgenetic male pseudohermaphrodite with varying degrees of masculinization of the genitalia. The aetiology of the defects in this family is unknown, but the involvement of three out of seven sibs suggests a genetic origin. Since the chromosomes appear normal, gene mutation seems a likely mechanism. The genes involved could be carried on the X chromosome as a sex-linked recessive trait or on an autosome and inherited in a sex-limited autosomal dominant manner. If this condition were transmitted by the father, a translocation must have occurred between the Y and the X chromosome during meiosis. This is most unlikely since three children are involved.

Of particular interest is the fact that the affected sibs have apparently identical X chromosome constitutions, and yet exhibit two different clinical types of gonadal dysgenesis. It is likely that these two clinical entities share a common genetic defect and that other modifying genetic or environmental factors may have influenced the various phenotypes.

**Summary**

A family is presented in which three sibs have dysgenetic gonads and abnormal sexual development. All have apparently normal male karyotypes. Endocrinological studies in the patient with dysgenetic male pseudohermaphroditism revealed a non-functioning testis, and it was shown that his testosterone was of adrenal origin. It is concluded that the various manifestations of pure gonadal dysgenesis and dysgenetic male pseudohermaphroditism differ only in the degree of severity. The genetics of this familial condition is unknown though a gene mutation is suggested.

Thanks are due to the Department of Obstetrics and Gynecology and the Department of Urology of the University of Colorado Medical Center for their cooperation in the study of this family; and to Dr. Theodore T. Puck for his suggestions and advice.

**REFERENCES**


### Familial XY Gonadal Dysgenesis

#### XY GONADAL DYSGENESIS

| Frasier et al. (1964) | Sternberg et al. (1968) | Bregger and Strand (1965) | Bartlett et al. (1968) | Relationship  
|----------------------|------------------------|--------------------------|------------------------|---------------  
| Monozygotic twins    | First cousins and maternal aunt | Sibs†                    | First cousins and maternal aunt‡ | Phenotype  
| F, F                 | 46,XY                  | 21                       | 24                     | Age (yr.)  
|                      |                        | F, F                     | F, F                   | Primary amenorrhea  
|                      |                        | +, +                     | +, +                   | Breast development  
|                      |                        | −, −                     | −, +                   | Areolar pigmentation  
|                      |                        | −, −                     | +, −                   | Axillary hair  
|                      |                        | −, +                     | +, +                   | Pubic hair  
|                      |                        | ±, ±                     | ±, ±                   | External genitalia  
|                      |                        | ±, ±                     | ±, ±                   | Enlarged clitoris  
|                      | 46,XY                  | S, S                     | S, S                   | Hypoplastic uterus  
|                      | 46,XY                  | D, D                     | D, D                   | Fallopian tubes  
|                      | 46,XY                  | Neg., Neg., Neg.         | Neg., Neg., Neg.       | Gonads  
|                      | 46,XY                  | 46,XY                    | 46,XY                  | Undifferentiated gonadal tumour  
|                      | 46,XY                  | 46,XY                    | 46,XY                  | Sex chromatin  
|                      | 46,XY                  | 46,XY                    | 46,XY                  | Karyotype    

**Symbols:**  
- M — Masculine  
- T — Testis  
- F — Feminine  
- S — Streak  
- D — Dysergimona  
- M/F — Ambiguous  

**Blank spaces** — No information available

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