


True Hermaphroditism: Cytogenetic Analysis, Surgical Repair, and Social Implications

True hermaphroditism is rarely encountered in man. Whenever this condition exists the contradiction between genotype and phenotype stimulates an extensive investigation of such an affected individual.

The chromosomal findings of true hermaphroditism were first reported by Hungerford et al. (1959) who demonstrated a 46,XX chromosomal complement in the leucocytes of peripheral blood. An attempt to simplify the nomenclature and assign a specific term to this anomaly (gonadal intersexuality) was made by Russell (1954). Overzier (1964) reviewed the findings of 171 authenticated cases of true hermaphroditism reported in the literature and of these cases only 14 had the benefit of cytogenetic analysis. However, with the progress in cytogenetic techniques and the incorporation of gonadal biopsies more comprehensive analyses have been reported. From this it has become apparent a normal female 46,XX karyotype is the usual finding in true hermaphroditism with the exception of a limited few who demonstrate a 46,XY chromosomal complement or a variant due to mosaicism.

The diagnosis of true hermaphroditism requires the demonstration of both ovarian and testicular tissue in the same individual. These patients usually have varying degrees of ambisexual development. The testicular tissue is generally located in the scrotum or outside the abdomen, while the ovarian tissue is usually found in an intra-abdominal position.

Himman (1935) classified true hermaphroditism into four categories. (1) Bilateral with testis and ovary or ovotestis on each side and usually demonstrating a uterus and tubes. (2) Unilateral with ovotestis on one side and an ovary or testis on the other side (these appear to be the most frequent). (3) Lateral with testis on one side and an ovary on the other side. (4) Indeterminates with no conformity as to location or type of gonadal tissue.

Case Report

Clinical History and Details of Surgical Repair.

The patient was a well developed, well nourished, alert, cooperative 3-year-old Tunisian child with no visible anatomic abnormalities other than ambiguous genitalia. He was the 3rd sib of a normal healthy young mother aged 26 at the birth of the propositus. There was no history of hormonal therapy or other medication taken prenatally. The pregnancy was normal and delivery in a local Tunisian hospital was without incident with a sage-femme (midwife) in attendance. There was no history of consanguinity nor was there a history of any similar defect in the family. The child progressed normally, walked and talked at approximately one year. This child was being reared as a male despite the fact that the ambiguous genitalia were noted at birth.

Physical examination of the external genitalia revealed a small phallus which lacked a penile aperture. A slit-like mucosal lined aperture resembling a urogenital sinus was located on the ventral side at the base of the phallus. Urine was voided through this slit-like aperture and caused the child no discomfort. The scrotum was not fused and gave the appearance of labia. Palpable masses in both inguinal areas could be expressed downward into the labia like structures. A chordee was present.

Laboratory examinations were not remarkable; creatinine, urea, total protein, and electrolytes were all within normal range. Urinary excretion of 17-ketosteroids (2.8 mg/24 hr) was within normal limits for age of the patient. No tests for 17-hydroxycorticoids or gonadotropins were available. Retrograde cystography and voiding urethrography indicated a normal male-type urethra with no unusual bladder neck obstructions. There was no evidence of urethral reflux. Intravenous pyelograms showed bilateral reduplication of the renal system.
collection systems. This is a normal variant and was not thought to be relevant, apart from this the urinary tract appeared functionally and anatomically normal. Radiology showed a normal bone age and no abnormalities in the thorax.

Laparotomy revealed bilateral cryptorchid ovotestes; there was no evidence of a uterus. A right and left vas deferens were present along with a male type bladder and prostate. Bilateral gonadal biopsies were taken. The gonads, both grossly ovotestis, were then delivered through an incision in the tunica vaginalis and placed in the under developed scrotal sack and fixed. The chordee deformity was corrected.

Biopsy material showed: On the right side a 0.7 cm irregular nodule of tissue with a generally roughened surface showing areas of a smooth shiny white membrane or capsule. Histological sections showed a typical infantile ovarian pattern with many ova and a few small follicles in the cortex, as well as infantile testicular tissue. The left side showed 4 pieces of tissue ranging from 0.3 to 0.8 cm. Histological sections showed infantile ovarian tissue, Fallopian tube type tissue, and a small portion of infantile testicular tissue. These are usual findings when ovotestes are present (Fig. 1).

A second surgical procedure for removal of the ovarian tissue was performed. On the right a 1 x 0.5 cm mass of gritty yellow ovarian tissue was removed in toto from the newly fixed testis. On the left the ovarian portion of the ovotestis was not well demarcated and appeared fused with the testicular tissue, however the ovarian tissue was removed as completely as possible from the newly fixed testis. Following an uneventful recovery the child was discharged in good condition.

**Cytogenetics**

Buccal smears were taken from all members of the immediate family and showed the 2 normal female sibs as well as the mother to be sex chromatin positive. The father was sex chromatin negative. Repeated buccal smears from the propositus were sex chromatin positive. A known sex chromatin positive control was used to confirm all buccal smears results (Table I). The laboratory which did this study took a count of 15% to be sex chromatin positive.

Peripheral blood smears from the propositus showed 2% of the neutrophils to have sex chromatin appendages (drumsticks).

Analysis of 200 cells from three peripheral blood leucocyte cultures from the propositus showed only a normal female 46,XX chromosome complement (Table II and Fig. 2).

Fibroblast cultures were not available in Tunisia so that neither the biopsied gonadal tissue nor skin could be used to exclude the possibility of a Y chromosome being present in other tissues.

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**Fig. 1.** Photomicrographs of ovotestis. (x 150.)

Left: Testicular portion showing immature seminiferous tubules containing sertoli cells.

Right: Ovarian portion showing infantile ovarian tissue with a few primordial follicles.
TABLE I

SEX CHROMATIN DETERMINATIONS

<table>
<thead>
<tr>
<th></th>
<th>Number of Buccal Smears</th>
<th>Number of Cells Counted</th>
<th>Number of Cells with a Barr Body Present</th>
<th>Percentage of Barr Bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propositus</td>
<td>5</td>
<td>5000</td>
<td>773</td>
<td>15.46</td>
</tr>
<tr>
<td>Mother</td>
<td>2</td>
<td>500</td>
<td>109</td>
<td>21.8</td>
</tr>
<tr>
<td>Sib 1</td>
<td>2</td>
<td>500</td>
<td>148</td>
<td>29.6</td>
</tr>
<tr>
<td>Sib 2</td>
<td>2</td>
<td>500</td>
<td>163</td>
<td>32.6</td>
</tr>
<tr>
<td>Father</td>
<td>3</td>
<td>1000</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
<td>200</td>
<td>56</td>
<td>28.0</td>
</tr>
</tbody>
</table>

TABLE II

CHROMOSOME COUNTS OF CELLS FROM CULTURED PERIPHERAL BLOOD

<table>
<thead>
<tr>
<th>Chromosome No.</th>
<th>Number of Cells Analysed in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture 1</td>
</tr>
<tr>
<td>45</td>
<td>1*</td>
</tr>
<tr>
<td>46</td>
<td>66</td>
</tr>
</tbody>
</table>

* Thought to be random loss.

Discussion

The exact mechanism causing true hermaphroditism has yet to be fully understood. Pedigree studies have not shown conclusive evidence for a familial heritable factor, although a report of 3 affected brothers (Rosenberg, 1963) suggests such a mechanism. All 3 brothers were sex chromatin positive and had a 46,XX karyotype. This case has been listed by McKusick (1968) as an autosomal recessive. One autosomal recessive in each parent would produce one quarter affected genetic female sibs. Other explanations for such a heritable factor might be: a dominant mutant, X-linked or autosomal. The X-linked dominant mutant would produce one half affected genetic female sibs, while an autosomal or a maternal X-linked dominant mutant would produce one half affected genetic female sibs. A sex-linked recessive depressor gene in both parents would result in an expected one half affected genetic female sibs and all normal male sibs. This mode of inheritance would suggest a heterozygous female carrier, as well as an unaffected hemizygous male carrier which would result in more frequent appearance of affected genetic females (on a population basis) than would be expected with an autosomal recessive gene.

Approximately 80% of all true hermaphrodites have a 46,XX karyotype. Ferguson-Smith (1966) suggested that one of the X chromosomes contains the testicular determining gene, normally found on the Y chromosome, due to a DNA exchange during oogenesis.
meiosis thus providing a genetic make up of XX'Y. If the Lyon hypothesis is correct then variations in gonadal tissue could be accounted for by random inactivation of the X or X'Y chromosome.

Still another possible explanation, as suggested by McFeely, Hare, and Biggers (1967), is the presence of a mutant male derepressor gene present on one of the X chromosomes which would function in a manner similar to that of an active Y chromosome. Additional supportive evidence for a male derepressor gene has been given by Hamerton et al. (1969) in their work on genetic intersexuality in goats. Evidence was presented for a male derepressor gene tightly linked with the autosomal dominant 'P' (polled = lack of horns) gene. Phenotypic variability could be due to incomplete penetrance and degree of expressivity of a derepressor gene.

Sex chromosome mosaicism has been demonstrated in true hermaphroditism by Mentz (1968), Butler et al. (1969), and Park, Jones, and Bias (1970). Mosaicism may result from the fusion of 2 blastomeres, each resulting from an individual fertilization of 2 ova or an ova and a polar body. Subsequent genetic competition between cell lines would determine which would predominate as suggested by Herschler and Fechheimer (1967). There is also the possibility of cells from a second embryo passing the placental barrier into the first embryo thus producing an organism genetically and chromosomally chimeric. Death and reabsorption of this second embryo would result in its loss accounting for a single chimeric offspring.

After a review of other studies done in both human and animal true hermaphroditism, it is suggested as a possible explanation for human familial transmission of this anomaly that a sex-linked derepressor gene may be present in the population.

This case report and its ensuing surgical repair is of interest for several reasons. A uterus is present in the vast majority of such patients (Butler et al., 1969; Federman, 1969). This patient showed no evidence of a uterus. The case study, counselling, and surgery were done in Tunisia by American medical personnel. The total management of this patient necessitated an entirely different approach due to the cultural, social, and economic differences. The need for familial genetic studies, beyond buccal smears, was not deemed necessary within the cultural pattern of this child's family. Such thinking of course ruled out a pedigree analysis or a more complete study. The child had been reared as an only son and the father felt strongly that this status must be preserved no matter what the genetic sex might be. Eventual sterility for this child would have no grave social consequences as a male, while as a female, sterility would result in severe social problems. To be a nonfecundating woman, proven or otherwise, would be a well grounded cause for the dissolution of her marriage. Which in turn would necessitate the ability and the opportunity for such a woman to be self supporting. Neither of these two conditions prevail at the present time for the vast majority of women in Tunisia. The American point of view in the assignment of sex is not necessarily that of, nor perhaps most efficacious for, peoples reared within the structure of other cultural patterns. The strong feelings of this devoted, well meaning father were no different than those of his fellow country men.

It was not an objective of the medical personnel involved with this case to offer suggestions that would be contrary to the normal concepts of this family, thus the immediate surgical repair decided upon was perhaps the most prudent for all concerned.

Summary

A 3-year-old child with ambiguous genitalia was found at laparotomy to have bilateral ovoid Fallopian tube type tissue but no uterus. Histological examination of the gonadal tissue revealed both ovarian and testicular tissue. There were 15% chromatin positive cells found in buccal smears. Cultured leucocytes consistently showed a 46,XX chromosome complement. The possibility of an X-linked derepressor gene for this anomaly is suggested. Indigenous social patterns were a contributing factor to the surgical course taken.

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REFERENCES
Case Reports

Two Cases of Trisomy D Associated with Adrenal Tumours*

It is becoming increasingly clear that congenital abnormalities due to chromosomal aberrations may be associated with a high incidence of neoplastic disease (Miller, 1966). In patients with Down’s syndrome, the prevalence of leukaemia is increased 20-fold compared with the general population (Wald et al, 1961) and recent reports indicate that other autosomal aberrations also may have a propensity for developing neoplastic disease (Schade, Schoeller, and Schultze, 1962; Zuelzer, Thompson, and Mastrangelo, 1968; Geiser and Schindler, 1969).

The present report describes two cases of trisomy D associated with adrenal tumours.

Case Reports

Case 1. The youngest of 6 sibs, this boy was born on 2 May 1965 to unrelated healthy parents aged 38 (mother) and 52 years (father). Birthweight was 2950 g; delivery was normal. There was no radiation exposure, viral infection during pregnancy, or previous fetal loss. The remaining sibs (3 sisters and 2 brothers) were normal.

Multiple abnormalities were present at birth. The head was small with several mid-line scalp defects. The face was moon-shaped with bilateral microphthalmia, corneal opacities, low-set abnormal ears, a left accessory auricle, a severe bilateral hare lip, and a wide cleft involving both hard and soft palate. There was an extra digit on the right hand and on the left foot. Fingers were tightly flexed and the elbows showed a flexion deformity. Testes were small and the penis showed a mild degree of hypospadias.

Skeletal radiology showed no abnormality other than a thin cranial vault. Chromosome analysis was done on preparations of peripheral blood. Of 30 metaphases studied, all but 2 cells, which had a normal diploid number, had 47 chromosomes with the additional chromosome in the D group (47,XY,D+). The chromosomes of both parents were normal.

![FIG. 1. Gross appearance of the adrenal tumour in case 1 showing the cystic and lobular nature.](http://jmg.bmj.com/)

Received 7 June 1971.

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