Three sisters with gonadoblastoma

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SUMMARY Three sisters with gonadoblastoma and an 46,XY karyotype are presented. This observation suggests that heredity may play an important role in the genesis of the tumour.

The number of gonadoblastoma cases reported so far is relatively small. Scully's review (1970) mentioned 101 cases to which at least 30 more have been added. From among these, only a few cases were familial. We had the opportunity of studying 3 sisters with tumours of this type and favour the conclusion that heredity may play an important part in tumorigenesis.

Present study

The 3 sisters studied by us were born to a non-consanguineous couple. In the same sibship there are 3 other sisters apparently normal, of whom 1 has 2 children.

CASE 1

C. Ve., aged 24, was born at term, weighed 3100 g, was 51 cm long, and had a normal childhood development. At puberty, however, she failed to develop menses and was admitted to hospital for primary amenorrhoea. The patient is of female appearance with feminine distribution of body fat and relatively long legs (Fig. 1). The secondary sexual characteristics are also female: breasts are pubescent (third degree) with small, pale areolae, and punctiform nipples. Pubic hair is of feminine distribution, almost normally developed (second to third degree). The external genitalia are pubescent female with normally developed vulva, and a 7 cm long vagina. Rectal palpation reveals a medial formation (uterus?) the size of a cherry; acidophil index 4%.

The sella turcica is of normal size and appearance; there is slight hyperostosis of the internal side of the skull; growth cartilages (knees) are persistent but much reduced in thickness; sex chromatin is negative and the karyotype in peripheral blood cultures is 46,XY.

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Digital dermatoglyphs (Dr M. C. Ciovirnache) show: 8 loops, 2 arches, and a total number of crests of 44.

Palmar dermatoglyphs—right-hand formula: a6, b11, c11, d12; left hand; a5, b7, c7, d11; axial triradii are proximal on both hands; palmar flexion lines are normal. Patterns: radial loops in both hypothenar regions; small loop in the II right interdigital space.

Plantar dermatoglyphs show ulnar loops on the big toes of both feet with a total number of crests (right + left) of 9; there is a distal loop in the thenar region and field I of the right foot; there is distal loop in the thenar region of the left foot.

Results of hormone examination are given in Table 1.

Fig. 1 Case 1.

Table 1 Hormone values before and after gonadectomy (on urine sample)

	Before gonadectomy	After gonadectomy	Normal ranges
Dehydroepiandrosterone (DHA)	0.54 mg/24 h	0.36 mg/24 h	0.6-1 mg/24 h
Aetiocholanolone (AE)	4.72 mg/24 h	2.25 mg/24 h	1.8-3 mg/24 h
11-oxogenic steroids (11-oxy)	2.15 mg/24 h	1.15 mg/24 h	1.2-2 mg/24 h
17 oxosteroids (total 17-OS)	7.41 mg/24 h	3.76 mg/24 h	4-6 mg/24 h
Total estrogens	22.7 µg/24 h	3.00 µg/24 h	10-30 µg/24 h
Urinary gonadotrophins	20 mouse units		5-25 mouse units

Laparotomy showed a congested hypoplastic uterus (4 cm/2.5 cm), with Fallopian tubes of normal form and development. In place of ovaries there were hard, calcified oval-shaped formations resembling hypoplastic gonads (1.5 cm/1 cm). Both gonads were removed.

Histological examination (Dr Taşcă) showed, in the gonadal fragments from the right side, small round cells with closed nuclei (Sertoli or granulosa-like cells) forming solid bands; in places they enclosed a microcavity with an amorphous content or included large clear cells with big, round nuclei (germinal cells). The stroma was fibrous and wavy; it contained interstitial cells resembling fibrocytes or Leydig cells (Fig. 2). The left side gonadal fragments closely resembled ovarian structure and contained structures which resembled involuted and atretic follicles. This would, of course, be inconsistent with an XY constitution.

CASE 2

C.C. aged 22, born at term, weight 3100 g, length 49 cm. She had no significant family history. She

was admitted to hospital for primary amenorrhoea and lack of sexual development. The patient looked immature for her age, with narrow shoulders and thorax, narrow pelvis, and elongated lower limbs. The adipose tissue was poorly developed.

Sexual characteristics showed undeveloped breasts with very small pale areolae and invaginated punctiform nipples (degree 0); pubic hair was scanty (first degree), axillary hair was absent (Fig. 3).

External genitalia: infantile vulva with a 6 cm long vagina. Per rectum palpation revealed a medial formation (uterus?) the size of a pea; acidophil index: 2%.

The sella turcica was of normal size but with a double contour of the anterior slope; growth cartilages (knee) persisted partially; sex chromatin was negative; the karyotype in peripheral blood cultures was 46,XY.

Digital dermatoglyphs showed 4 loops, 6 arches, and the total number of crests 18; right hand palmar formula: a5, b7 c(x), d11, left hand; a5, b7, c(x), d11. Axial triradii were in the proximal position. Flexion lines were normal in both hands.

Fig. 2 Cell clusters resembling Sertoli-granulosa cells surrounding eosinophilic deposits simulating Call-Exner bodies and large cells with clear cytoplasm resembling germinal cells. (× 200.) (Case 1).

Fig. 3 Case 2.

Plantar dermatoglyphs showed the total number of crests to be 10 on the big toes; in field II-III on the right foot, there was a double-centred whorl; in field I and II on the left foot there was a proximal loop and a double-centred whorl.

Results of hormone examination are given in Table 2.

Laparotomy showed a hypoplastic uterus (1 cm × 0.5 cm) and Fallopian tubes. In the left ovarian position there was an ivory band 0.5 cm × 0.5 cm. On the right side there was a small fibrous formation. Both formations were removed.

Histological examination showed, on the left side, the formation of wavy fibrous stroma without follicles and on the right side the formation of abundant fibrous stroma filled with cysts and containing granulosa Sertoli-like cells and separate or conglomerated crystals.

CASE 3

C.Vi., aged 18, was born at term with normal weight and length. She was admitted to hospital for primary amenorrhoea. The patient was normally developed

Fig. 4 Case 3.

with a slight elongation of the lower limbs. Adipose tissue was moderately developed and had a non-characteristic topography (Fig. 4).

Secondary sexual characters showed, on the right side, hard discoidal tissue in the subareolar area (first degree) and on the left side, slightly developed mammary tissue (first and second degree); there are small unpigmented areolae with punctiform, invaginated nipples. Pubic hair was female but relatively sparse (third to fourth degree); axillary hair was also sparse.

External genitalia: the vulva was prepubescent, with a 6 cm long vagina. Per rectum palpation revealed a medial oval-like formation (uterus) of 1 cm diameter; acidophilic index: 8%.

The sella turcica was of normal size and appearance; growth cartilages (knee) are partially present; sex chromatin was negative, and the karyotype in peripheral blood cultures was 46,XY.

Digital dermatoglyphs showed 6 loops, 4 arches, and a total number of crests of 45. Palmar dermatoglyphs showed a right hand formula: a3, b8, c10, d11, left hand formula; a5, b7, cx, d11. The axial triradius was missing from the right hand, but was proximal

Table 2 Hormone values before and after gonadectomy

	Before gonadectomy	After gonadectomy	Normal ranges
Dehydroepiandrosterone (DHA)	2.31 mg/24 h	0.26 mg/24 h	0.6-1 mg/24 h
Aetiocholanolone (AE)	3.32 mg/24 h	0.32 mg/24 h	1.8-3 mg/24 h
11-oxogenic steroids (11-oxy)	1.97 mg/24 h	1.37 mg/24 h	1.2-2 mg/24 h
17 oxosteroids (total 17-OS)	7.60 mg/24 h	1.95 mg/24 h	4-6 mg/24 h
Total oestrogens	16.5 µg/24 h	0.4 µg/24 h	10-30 µg/24 h
Urinary gonadotrophins	20 mouse units		5-25 mouse units

Table 3 *Hormone values before and after gonadectomy*

	<i>Before gonadectomy</i>	<i>After gonadectomy</i>	<i>Normal ranges</i>
Dehydroepiandrosterone (DHA)	0.61 mg/24 h	0.21 mg/24 h	0.6-1 mg/24 h
Aetiocholanolone (AE)	4.95 mg/24 h	1.80 mg/24 h	1.8-3 mg/24 h
11-oxogenic steroids (11-oxy)	1.75 mg/24 h	1.29 mg/24 h	1.2-2 mg/24 h
17 oxosteroids (total 17-OS)	7.31 mg/24 h	3.30 mg/24 h	4-6 mg/24 h
Total estrogens	16.0 µg/24 h	3.60 µg/24 h	10-30 µg/24 h
Urinary gonadotrophins	20 m.u.		5-25 m.u.

on the left hand. Flexion lines were normal on both hands. Patterns: a small loop in the interdigital space III of the right hand, medial loop in the hypothenar area of the left hand.

Plantar dermatoglyphs showed on the big toes of both feet, an ulnar loop with a total number of crests of 11. Patterns: a double-centred whorl in field I of left foot and a distal loop in the thenar region; a double centred whorl in field II of right foot.

The results of hormonal tests are shown in Table 3.

Laparotomy revealed a hypoplastic uterus (2 cm × 1 cm) with normally shaped but hypoplastic Fallopian tubes. In the left ovarian position there was a flattened formation (2 cm × 1 cm); on the right side there was an oval shaped formation (3 cm × 2 cm) with a silvery-white capsule surrounded by an epididymis-like formation roughly resembling a testis. Both formations were removed.

Histological examination showed that the fragment from the left side contained abundant stroma resembling an ovary but lacked follicular formations; the right side fragment showed numerous amorphous calcifications in a very dense fibrous stroma; in

places the calcifications seem located in the lumen of cysts. There were also cellular fields with granulosa Sertoli-like cells that sometimes formed a follicle around hyaline material which was yellowish with Van Gieson staining and resembled Call-Exner bodies. In other areas these elements formed tubular structures. In the adjacent stroma were isolated groups of cells with yellowish cytoplasm (Van Gieson) of granular aspect resembling adult Leydig cells (Fig. 5).

Discussion

The three sisters presented above had certain characteristics in common that favoured the diagnosis of gonadoblastoma.

From a steroid hormonal standpoint the 3 sisters shared some characteristics such as:

(a) In the initial studies the 17-oxosteroids [17OS] were increased, exceeding the maximum values for women and coming within the range characteristic of men. In 2 cases (C.Ve. and C.Vi.) the raised 17 OS was the result of

Fig. 5 *Microcysts containing amorphous calcium deposits.*

the aetiocholanolone [AE] fractions; in 1 case (C.C.) dehydroepiandrosterone [DHA] was also raised as well as AE. Total oestrogens showed values specific of the normal adult woman in all the 3 sisters.

- (b) After gonadectomy the total chromatographic 17 OS value decreased to normal in 2 cases (C.Ve. and C.Vi.) and fell much below the normal in 1 case (C.C.). The decrease was due to a fall in the AE fraction but in case (C.C.) the HDA fraction also contributed. After gonadectomy the ratio between the 3 chromatographic fractions returned to normal.
- (c) The total oestrogens showed a pronounced decrease in all 3 cases.

The gonadotrophins were studied before gonadectomy in order to eliminate a hypogonadotrophic hypogonadism. They were normal.

Conclusions

Even at the time of the first tests, it was noticed in all the 3 sisters that there was an increased secretion of oestrogens and androgens from either the gonads or the adrenal cortex. This was confirmed by the significantly increased values of the AE fraction. Gonadectomy suggested that these steroid hormones were of gonadal origin: oestrogens fell and 17 OS decreased with a corresponding equilibration of the ratio between the 3 fractions.

The 3 cases also show a histological similarity. The histological features indicate a participation of the germinal cells, sex cord derivatives, and of the elements of mesenchymal origin, in addition to calcifications. All these elements, coming within the range of Scully's description of tumoral lesions, define the histopathological diagnosis of gonadoblastoma.

And, finally, it is worth noticing that in none of our cases did we find any virilization phenomena.

Cytogenetics

Almost all the female patients with gonadoblastoma, have a Y chromosome and most of them have a 46,XY karyotype (Brøgger and Strand, 1965; Frasier *et al.*, 1964; Freeman and Miller, 1969; Similä *et al.*, 1974) or are 45,X/46,XY mosaics (Teter, 1960; Siebenmann, 1961; Philip and Teter, 1964; Borghi *et al.*, 1965; Strumpf, 1965; Ionescu *et al.*, 1965; Teter and Boczkowski, 1967; Ferencz *et al.*, 1971; Shabrov, 1973). Other mosaics have also been reported: 45,X/46,XYq – (Desjeux *et al.*, 1969), 45,X/46,XY/47,XYy (Hirschhorn, 1969 cited by Freeman and Miller, 1969; Hsu *et al.*, 1968) and 45,X/47,XYy (Suné *et al.*, 1970). Very few cases are

chromatin positive, e.g. 5 of 63 reported by Talerma (1971). The existence of a 46,XX karyotype has been confirmed only twice, by Overzier (1964) and by de Bacalao and Dominiquez (1969).

The male sex chromosome complement of patients with gonadoblastoma is subject to various interpretations:

- (a) in the case of tumours appearing in the primitive gonad, the progonad genetically might have become testis;
- (b) in the case of tumours developing in a gonad whose sex cannot be defined histologically (and this is the most frequent situation), the respective gonad is in reality testis.

On the other hand, there have been published reports for a long time on the neoplastic potential of the dysgenetic testis (Melicow and Uson, 1959; Sohval, 1964; Milcu *et al.*, 1968; Schellas *et al.*, 1971) and naturally the role of the Y chromosome. According to Teter and Boczkowski (1967), 27% of individuals with gonadal dysgenesis and an XY karyotype have gonadal tumours.

Though hypothetically, a relation may be supposed to exist between abnormal sex chromosomes, gonadal dysgenesis, and the tumour, it is very difficult to prove and impossible to explain.

It seems that at least some of the cases are of genetic origin. In support of this idea are the familial cases and twin studies. Though their number is small these must not be overlooked taking into account the low incidence of gonadoblastoma.

From among the familial cases reported, mention must be made of those of Fine *et al.* (1962), Baron *et al.* (1962), Brøgger and Strand (1965), Cohen and Shaw (1965), Gagnon and Cadotte (1967), Talerma (1971), and Allard *et al.* (1972). In all these cases only 2 members of the sibship were affected. As far as we know, the family in our study is the only one to have 3 affected members.

Relevant observations on twins are extremely rare. Frasier *et al.* (1964) reported monozygous twins with pure gonadal dysgenesis and gonadoblastoma. It is worth noticing that one of the sisters described in our study was born of a dizygotic twin pregnancy; her twin sister has a normal phenotype and has regular menses.

It may be supposed, though the number of observations is very small, that some of the gonadoblastoma cases are the result of a genetic mutation which, according to Allard *et al.* (1972) has an autosomal recessive transmission. But, it seems probable from our studies that gonadal dysgenesis is itself genetically determined and thus, in our family too, the genetic constitution favours the development of the tumour. This idea is supported by other reports

of familial pure gonadal dysgenesis and by some sibships in which one of the members had gonadoblastoma and the other pure gonadal dysgenesis (Frasier *et al.*, 1964).

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