OVARIAN NEOPLASMS IN CHILDREN*

BY

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Just over 100,000 cases have been admitted to the two main Liverpool Children's Hospitals during the last 10 years; amongst these were 21 children with ovarian new growths (Table 1).

TABLE 1
OVARIAN NEW GROWTHS, 1949-59

Tumour	No. of Cases	Left	Right
Cystadenoma	2	1	1
Teratoma:			
(a) Benign cystic	12	7	5
(b) Solid	1	—	1
Tumours of special morphology	3	3	—
Tumours of doubtful origin	3	3	1
(one case had bilateral tumours)			
Total	21	14	8

Cystadenoma

Cystadenoma, which accounts for 40-50% of all ovarian new growths, is a tumour of adult life, and uncommon in patients under 20 years of age. We have seen two cases, a girl (E.G.) of 13 with a right-sided, thin-walled, unilocular cystadenoma measuring $17 \times 13 \times 10$ cm., and a 12-year-old child (M.O.) with a small, left-sided, multilocular cystadenoma; neither of these two girls had menstruated.

Teratoma

Including all age groups, teratomas constitute 10-15% of ovarian tumours, but over 50% of the tumours of children are of this type. Willis (1955a) succinctly defines teratomas as 'embryonic tumours of pluri-potential, regionally non-specific tissue'. They possibly originate in foci of plastic polyvalent tissue, which escape the influence of the primary organizer (Willis, 1955b). Ovarian teratomas are arbitrarily divided into:

- (a) the common, benign, largely cystic tumours, in which tissue differentiates and matures

synchronously with the tissues of the host; and

- (b) the much less common solid or polycystic tumours, in which a great variety of tissue in different stages of maturity is found. They may grow rapidly and are usually malignant.

Though benign cystic teratomas consist largely of ectodermal tissue, skin with sweat glands and hair follicles, tooth buds or teeth and sebaceous material, endodermal and mesodermal tissue is always represented. Cartilage, muscle, intestinal and bronchial epithelium and nervous tissue are common. The contents of the cyst may be mucous or cerebrospinal fluid, in addition to or to the exclusion of the more usual sebaceous material.

The right ovary is affected more often than the left, and in 10% of cases there are bilateral tumours.

Radiological examination shows teeth, cartilage, bone or calcification in the cyst wall in 75% of cases.

Ovarian teratomas have been described in infants. They are, however, rarely encountered in children under 3 years of age. In a child the cyst is seldom larger than the patient's head.

Children with teratomatous cysts present in three ways: with enlargement of the abdomen; with abdominal pain, which may be either continuous or intermittent; or as urgent emergencies with torsion of the cyst pedicle.

Torsion is the commonest complication and is recorded in 1 in 4 or 1 in 3 of large series of cases (Peterson, Prevost, Edmunds, Hundley and Morris, 1955).

The development of carcinoma in a benign cystic teratoma is not uncommon in adults, usually in those past middle life, in whom the tumour has probably been present for a long time. It is doubtful whether this complication ever occurs before puberty.

We have seen 12 children with teratomatous cysts; the main features of these cases are summarized in Table 2.

Solid or polycystic teratomas are, by and large, rapidly growing and highly malignant. They tend to metastasize via the blood stream to the lungs.

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TABLE 2
BENIGN CYSTIC TERATOMAS

Case	Age (yr.)	History	Radiograph	Torsion	Side	Histology
S.J.	3	4 wk. pain, vomiting, constipation	Positive	Yes	Left	Teratomatous cyst; sebaceous material, hair, teeth, muscle
E.L.	10	3 yr. pain left-sided	Positive	No	Right	Teratomatous cyst; sebaceous material, hair, teeth
R.S.	5	Increasing abd. swelling; pain	—	No	Right	'Dermoid cyst', very large
H.C.	8	Increasing abd. swelling	—	Yes	Left	'Dermoid cyst'
C.P.	10	3 mth. intermittent left abd. pain; vomiting; pain on defaecation	—	Yes	Right	'Dermoid cyst', twisted with one horn of bicornate uterus
J.R.	7	Abd. pain and vomiting	Negative	Yes	Left	'Dermoid cyst'
C.W.	10	Abd. enlargement, pain	Positive	No	Left	Teratomatous cyst; skin, hair, cartilage, brain
B.G.	11	2 yr. abd. pain; nausea	Negative	No	Left	'Dermoid cyst'
W.T.	12	2 yr. vague pain; 3 wk. severe pain	Positive	No	Left	Teratomatous cyst; skin, teeth, hair, bone, cartilage, lung, nervous tissue
R.C.	5	Enlargement of abdomen since birth	Positive	No	Right	Teratomatous cyst; 12 × 1 × 6 in.
P.M.	11	Few mth. intermittent abd. pain	Positive	No	Left	Teratomatous cyst; calcified wall, bone, muscle, tooth, columnar epithelium 13 × 10 × 8 in.
L.S.	13	Few days left-sided abd. pain	Positive	No	Right	Teratomatous cyst; hair, sebaceous material, cartilage, mucous glands, columnar ciliated epithelium; cyst lined squamous epithelium 10 × 6 × 4½ in.

Very rarely precocity and uterine bleeding have been associated with malignant teratoma containing areas of chorionic carcinoma.

We have seen only one solid teratoma; it occurred in a 12-year-old girl (J.N.) who had a large, easily visible, abdominal swelling. At operation there was bloody peritoneal fluid and the tumour had transgressed its capsule at two points; it was considered to be malignant. The pathologist, however, reported that, though the tumour contained the typical conglomeration of tissue, there was no definite evidence of malignancy. The child is well four years post-operatively.

Tumours of Special Morphology

(a) **Granulosa Cell Tumour or Granulosa Cell Carcinoma, and Theca Cell Tumour.** These tumours contain cells similar to those of the zona granulosa and theca interna of the normal ovary. Willis (1948) believes that they originate in normal follicular tissue or from the bi-potential formative ovarian stroma. Granulosa cell tumours usually contain some theca cells and, though theca cell tumours are more often 'pure', they often contain areas in which granulosa cells can be found. The rare luteal tumour causing similar symptoms is probably a granulosa-theca cell tumour which has undergone luteinization.

In keeping with tumours of other endocrine glands, granulosa and theca cell tumours may, or may not, produce hormones.

Granulosa cell tumours are said to constitute 10% of all solid ovarian tumours; 5% of the total number recorded have occurred in children (Morris and Scully, 1958a). This estimate of the relative fre-

quency of the tumour in children is probably too high. A hormone-secreting tumour in a child would almost certainly be published, whilst such a tumour in an adult might well cause less interest. Wilkins (1957) states that 33 granulosa cell tumours causing precocious puberty in children of 7½ years or under have been recorded. He has followed the exacting discipline of paediatric endocrinology for 20 years and has seen only a single case. Morris and Scully (1958b) state that 60 granulosa cell tumours and four theca cell tumours have caused precocious sex changes in prepubertal children. The disparity between 33 and 60 probably reflects a difference of opinion between the two authorities about the age at which sex changes are considered to be precocious. The youngest reported case of a granulosa cell tumour is a 14-week-old infant with bilateral tumours (Zemke and Herrell, 1941).

Uncommon as the granulosa cell tumour is, it is the most frequent ovarian cause of sexual precocity. The oestrogen-secreting tumour causes enlargement of the uterus, endometrial hyperplasia and bleeding, which may be slight or profuse, continuous or intermittent. In about half the reported cases it has been cyclical. Bleeding may occur only after removal of the tumour (oestrogen-withdrawal bleeding); on the other hand, it has often been the initial symptom; it is anovular and the other ovary remains normal for the child's age. There is development of the vulva and vagina and the vaginal cytology is of adult type.

Secondarily induced development of the breasts and growth of sexual hair commonly occur but are not invariable. Body growth is stimulated and the child is likely to be tall for her age.

Unfortunately few oestrogen assays have been made in children; in those recorded, the urinary oestrogen figures have varied from normal adult to very high levels (Wilkins, 1957).

As first pointed out by Gross (1953), all granulosa cell tumours, which have caused symptoms of oestrogism in children, have been readily palpable on abdominal examination. This is an important point in the differential diagnosis of bleeding or of sexual precocity.

In adults, symptoms of hyperoestrinism have been produced by tumours as small as 1.5 cm. in diameter. It is therefore possible that cell for cell the granulosa cell tumours of children produce less oestrogen than the tumours of adults.

In children under 8 or 9 years, the age at which the ovary normally begins to undergo pre-pubertal changes, regression of sexual development takes place after removal of a granulosa cell tumour. In children over this age little change occurs apart from cessation of bleeding and reduction in the size of the uterus.

No long-term follow-up of cases which have had granulosa cell tumours removed in childhood is available. It is, however, known that a second tumour may develop in the other ovary many years after a granulosa cell tumour has been removed, and that intraperitoneal recurrences may appear a long time after a patient is thought to be cured (Diddle, 1952). Distant metastases may occur but are not common. The mortality for granulosa cell tumour in adults is about 50% and the longer the follow-up the higher the mortality. The histology of the tumour may give some help in prognosis (Kottmeier, 1952).

We have seen only one child (C.E.) with a

granulosa cell tumour (Table 3). She was admitted aged 11 months with a cystic, easily palpable tumour which had undergone torsion. Enlargement of the breasts was just appreciable, and there was a faint down of dark pubic hair. There was no history of bleeding, but she had a slight blood-stained vaginal discharge for 48 hours after operation.

(b) Arrhenoblastoma, Hilar Cell or Sertoli-Leydig Cell Tumour. These tumours, which characteristically cause masculinization, are rare at any age, and excessively rare before puberty. An arrhenoblastoma in a girl of 11 years with symptoms of masculinization is, however, described (Thomas, Fisher, Turnbull and Krieger, 1952) and Morris and Scully (1958c) mention a Leydig cell tumour causing virilism in a girl of 4 years.

(c) Germinoma. This is a non-hormone-secreting tumour, composed of cells of embryonal type, resembling the sexually undifferentiated germ cells of the early gonad.

Disgerminoma of the ovary is histologically indistinguishable from seminoma of the testicle. The former has a high incidence in pseudo-hermaphrodites and patients with hypogonadism, and seminoma has a predilection for incompletely descended testes; either tumour is occasionally bilateral. Interesting differences are that, in spite of seminoma being more easily diagnosed whilst the tumour is small, the mortality for seminoma is higher than that for disgerminoma. The difference in age incidence is very remarkable. Disgerminoma is a tumour of the young; three-quarters of the cases recorded have been under 30 years and half under 20 years, though no instance of the tumour has been

TABLE 3
TUMOURS OF SPECIAL MORPHOLOGY

Case	Age	History	Clinical Findings	Treatment	Diagnosis	Side	Result
C.E.	11 mth.	Abdomen always prominent; rapid increase last few days; acute abdominal pain; vomiting	Large cystic lower abd. tumour; definite slight mammary enlargement; faint down of dark pubic hair	Oophorectomy	Granulosa cell tumour; large polycystic; uterus enlarged, other ovary normal; torsion	Left	Post-operative uterine bleeding; complete regression of sex changes; well 3 yr.
J.B.	12 yr.	Abdominal pain; dysuria; pyrexia	'As big as a child of 8 yr.'; large solid tender mass left lower abdomen and pelvis	Excision of tumour, uterus, ovary, part of bladder, sigmoid colon and parietal peritoneum; radiotherapy	Disgerminoma; solid tumour as big as large grapefruit; adherent to and infiltrating pelvic organs and parietal peritoneum	Left	Still very small; well 2½ yr.
J.D.	13½ yr.	(At 3 yr. undescended testes, right gonad biopsy, testes, repair hypospadias); acute abdominal pain 6 days	Large lower abd. tumour; urinary 17-ketosteroids 4 mg./day; sex chromatin —negative, male	'Oophorectomy'; radiotherapy	Germinoma; ? disgerminoma; ? seminoma; large solid tumour, small uterus, fallopian tubes and broad ligaments; torsion	Left	Well 6 mth; growth of penis and sexual hair

recorded in a child under the age of 7 years. Seminoma is most frequent early in the fifth decade, very rare before 20 years, and the youngest case recorded was 16 (Bell, 1938).

Disgerminoma is a smooth, solid tumour, grey or greyish-pink in section. It has a tendency to undergo necrosis, to transgress its capsule and invade neighbouring pelvic organs and sometimes lymphatic glands. Distant metastases occur, but uncommonly. In cases followed up over long periods the mortality is about 50% (Morris and Scully, 1958d).

Our first case (J.B., Table 3) apart from her tumour showed no abnormality except that she was very small for her age. She is chromatin-positive.

The second case (J.D., Table 3) occurred in a child who is chromatin-negative. The gonad on the left was entirely replaced by tumour, so that it is not possible to know whether it was an ovary, a testis or an ovo-testis. The tumour was intra-abdominal and there was a uterus and two fallopian tubes; the other gonad is, however, an incompletely descended testis. The child's development since the tumour was removed appears to be conforming to the male pattern. In view of the patient's age, this tumour is best designated a germinoma rather than either a seminoma or disgerminoma.

Tumours of this group which, from their morphology, would be expected to secrete oestrogens or androgens may be inactive; less commonly, a tumour containing granulosa cells produces androgens and a tumour containing Sertoli-Leydig cells causes feminization.

Germinomas, which are characteristically non-hormone-secreting, have occasionally produced sex hormones.

Tumours of Doubtful Origin

Three cases have been grouped under this heading (Table 4).

One was a highly malignant anaplastic carcinoma in a girl (J.T.) of 13 months, which conformed histologically to the tumour described by Schiller (1939) as a mesonephroma. Morris and Scully (1958e) include this growth amongst the malignant teratoid tumours.

The second was a large, solid tumour in a girl (J.C.) of 8½ years. Histologically it was a highly malignant undifferentiated carcinoma. The possibility of its being a hormonally inactive granulosa cell carcinoma, or even a disgerminoma, is not excluded: in favour of one or other of these diagnoses is the fact that the child is well four and a half years after operation and radiotherapy.

The third child (V.T.) presented during life, and at autopsy, a picture so confusing that the case is left without comment.

Secondary malignant tumours of the ovary are common in adults, but in children they are very rare; Grob (1957) has described bilateral ovarian tumours secondary to lymphosarcoma of the neck. In this case a very careful search at autopsy disclosed no alternative primary growth.

Treatment

An ovarian tumour should be removed, and the sooner the better; it may be malignant and a few days may make a difference in prognosis. A large incision should be made, and the pedicle of the tumour should be clamped at the first possible

TABLE 4
TUMOURS OF DOUBTFUL ORIGIN

Case	Age	History	Clinical Findings	Treatment	Diagnosis	Side	Result
J.T.	13 mth.	Enlargement of abdomen	Firm, mobile abdominal tumour	Oophorectomy	Anaplastic carcinoma (mesonephroma)	Left	Death 4 mth. Abdominal metastasis
J.C.	8½ yr.	Enlargement of abdomen	Large, solid, lower abdominal tumour	Oophorectomy ; radiotherapy	Solid; tumour through capsule; blood and clumps of tumour cells in peritoneal fluid; undifferentiated carcinoma; ?? granulosa cells. W. 435 g.	Left	Well 4½ yr.
V.T.	13 yr.	2 mth. general ill health, pain, anaemia, intestinal bleeding	Abdominal and pelvic mass; ascites; clinical features and blood picture of widespread malignant process	Radiotherapy started but discontinued	Autopsy: bilateral ovarian tumours; search revealed no alternative primary growth. Histological features of anaplastic carcinoma rather than malignant reticulo-endothelial disorder; probably primary ovarian growth	Left	Death

moment to prevent dissemination of malignant cells via the blood stream.

The fallopian tube should be preserved in obviously simple cystic tumours. The second ovary should be examined; it may contain a small teratoma or granulosa cell tumour, removal of which by dissection will preserve some ovarian tissue.

Cases of granulosa cell tumour and disgerminoma have recovered when the tumour has spread beyond its capsule and invaded other pelvic organs so that radical excision is justified and may be rewarding.

There is little authoritative guidance about when to use, and when not to use, radiotherapy, and the decision may be very difficult. Not only will irradiation cause sterility, but growth and the pattern of growth may be impaired.

It is probably true to say that anaplastic carcinomas, malignant teratomas and tumours which histologically resemble chorionic carcinoma will be little influenced by radiotherapy.

Granulosa cell tumours and disgerminomas are radio-sensitive, and there is definite evidence that in adults the prognosis, after removal of these tumours, is improved by radiotherapy (Santesson, 1947). Therefore, if it has been necessary to remove as well as the tumour the uterus and second ovary, or if the peritoneal fluid contains tumour cells, or if the report of the pathologist suggests a highly malignant growth, radiotherapy should be given.

If the tumour is intracapsular and the pathological report is favourable, x rays should be withheld.

Girls who have had both ovaries removed, or one removed and the other destroyed by x rays, should have the benefit of endocrine treatment at 13 to 16 years of age so that they may, as far as possible, conform to the female pattern.

The literature shows that ovarian tumours are more frequently right- than left-sided, and this is especially true of teratoma and disgerminoma.

In this series of 21 cases (22 tumours), 14 were left-sided and eight right-sided (Table 1). This emphasizes the fallacies inherent in conclusions based on small series of cases.

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