PURE GONADAL DYSGENESIS : CASE REPORT AND REVIEW

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In 1957 Hoffenberg and Jackson[1] drew attention to the tall patient who presents with primary amenorrhoea, eunuchoid features, and in whom primitive gonadal ridges are present instead of ovaries. In 1959 Harnden and Stewart[2] labelled this syndrome 'pure gonadal dysgenesis'. Chromosomal studies have been carried out on patients presenting with this syndrome from 1959.

In adulthood these individuals are of average (exceeding 59 inches) or tall stature.[3] The phenotype is female and they often have an attractive appearance. Hypogonadism and lack of breast development is a feature of the condition and associated somatic abnormalities are usually absent.

CASE REPORT

The patient was a 23-year-old female who had never menstruated spontaneously. From the age of 18 years she had scanty withdrawal bleeding after the administration of cyclical hormone therapy. For the past 10 months, since discontinuing hormone therapy, she had remained amenorrhoeic. Her general health was good, except for occasional migraine headaches.

When she was 6 years old, an appendicectomy had been performed and no abnormality of the ovary was noted. At the age of 19 years, a ventral hernia had been repaired. The patient was an only child. No family history of any menstrual upsets in the mother was available.

The general appearance of the patient (Fig. 1) was of a thin, attractive female of normal stature. The height was 65 in. and the weight 110 lb. The features were eunuchoid and a normal amount of axillary hair was present. The pubic hair was sparse but feminine in distribution and the breasts were grossly undeveloped. The external genitalia were hypoplastic and no clitoral enlargement was noted. The vagina admitted 1+ fingers. A small cervix protruded into the fornix and it was felt that the uterus was infantile in type. The ovaries were not felt on bimanual palpation.

Special investigations. The urinary FSH levels were 12 - 24, 24 - 48 and over 48 mouse units on three separate readings (normal laboratory levels—6 to 48 m.u.). The 17-ketosteroids

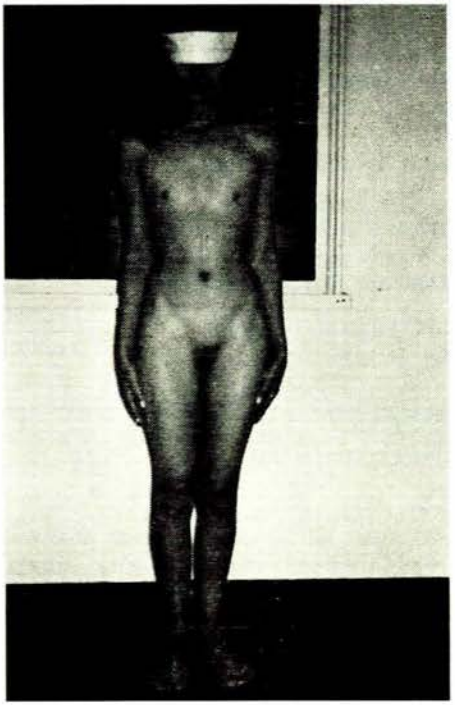

Fig. 1. Appearance of patient with pure gonadal dysgenesis.

and 17-hydroxycorticosteroid levels were within normal limits. The cytology of the vaginal smear showed minimal oestrogen activity. The patient was chromatin-positive on evaluation of the epithelial cells of the buccal smears, vaginal mucosa and polymorphonuclear leucocytes. The blood count, blood pressure and urine analysis were normal. The protein-bound iodine was 4·8 μg./100 ml. and the cholesterol 194 mg./100 ml. The blood urea and electrolytes were within normal limits. X-ray studies of the chest, sella turcica and osseous system were within normal limits, with a normal bone age.

On examination under anaesthesia the uterus measured 1¼ in. in length and no endometrium was obtained on curettage. At laparotomy the presence of an infantile uterus was confirmed and elongated fallopian tubes measuring 4 in. were found. Bilateral rudimentary streak gonads were present in each mesosalpinx. The streak on the right measured 1 in. and that on the left 1½ in. A biopsy was taken from the right gonadal streak.

Chromosomal analysis of the skin and fascia established the presence of 46/XX karyotype with normal chromosomal patterns, consistent with a normal female pattern. No structural abnormality of the chromosomes was observed. The nuclear sexing was chromatin-positive in the skin, fascia and muscle.

DISCUSSION

To date 59 cases of pure gonadal dysgenesis have been described in the literature. Sohval[3] reported on 35 cases which he analysed, added a further 8 which had come to his attention and included 7 from Russian reports. Engel and Forbes[4] described 6 cases (cases 43 - 48) with the features of pure gonadal dysgenesis. An additional 3 cases were recorded, 2 by Moszkowski *et al.*[5] and 1 by Graham *et al.*[6] In 17 cases there was no anatomical confirmation, which is one of the criteria for the diagnosis of the syndrome—cases 20 - 23 of Sohval,[3] 2 cases of De Lorzis *et al.* described by Sohval, 7 Russian reports described by Sohval and cases 43 - 46 of Engel and Forbes.[4]

Nuclear Sexing

The nuclear sex was determined in 56 of the 59 cases reported (in cases 5, 10 and 11 reported by Sohval, this investigation was not performed). Of the total of 57 cases, including the present case, 31 were chromatin-positive (54·4%) and 26 chromatin-negative (45·6%) (Table I).

TABLE I. REPORTED CASES OF NUCLEAR SEXING

Source	*Male*	*Female*
Original 35 cases reported by Sohval[3]	17	15
Additional 8 cases reported by Sohval[3]	5	3
Russian literature 7 cases reported by Sohval[3]	3	4
Cases 43 - 48, Engel and Forbes[4]	0	6
Moszkowski *et al.*[5]	0	2
Graham *et al.*[6]	1	0
Present case	0	1
Total (including present case)	26	31

The Karyotype

Of the 41 cases where chromosomal analysis was performed, the karyotype was that of a normal female, 46/XX, in 19 cases including the present report (49%) (Fig. 2). A normal male pattern, 46/XY, was recorded in 12 cases (29%); and a mosaic pattern was present in 9 instances (22%), 7 with two cell lines and 2 with three cell lines. A partial deletion of the X occurred in one instance, the karyotype being Xx (Table II).

TABLE II. CHROMOSOMAL STUDIES

Chromosomes	*No. of cases*
XX	19
XY	12
XO/XX	4
XO/XY	2
Xx	1
XO/Xx	1
XO/XX/XXX	1
XO/XY/XYY	1

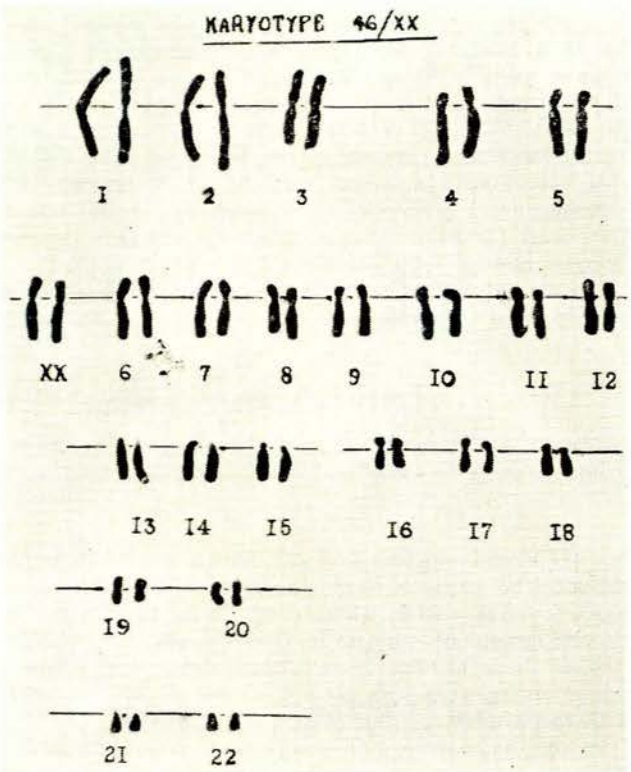

Fig. 2. Normal female karyotype 46/XX.

Streak Gonads

The gonads are represented by bilateral, elongated, white fibrous streaks situated in the position of the normal ovaries, which represent the rudimentary, non-functioning remnant of the gonadal ridge. The fibrous streak is not thickened and is non-functioning. This streak is also present in Turner's syndrome.

Microscopically, the streak consists of a spindle-celled stroma, arranged in whorls resembling ovarian stroma. Rete and hilar cells are also observed.

Biopsy of the fibrous streak of the present case showed remnants of early embryonic structures and rete ovarii were demonstrated (Figs. 3 and 4).

Clitoral Enlargement

This is not a constant feature of the condition and the clitoris may or may not be enlarged. There is no definite correlation between the chromosomal pattern and clitoral enlargement. An XY pattern has been found in association with an enlarged clitoris (3 Russian cases quoted by Soh-

val[3]). Moszkowski *et al.*[5] described an enlarged clitoris in a patient with an XX pattern. Warren *et al.*[7] described a case with clitoral enlargement and XO/XX mosaicism. In this case, however, a hilar cell tumour was found, which probably produced the virilism described.

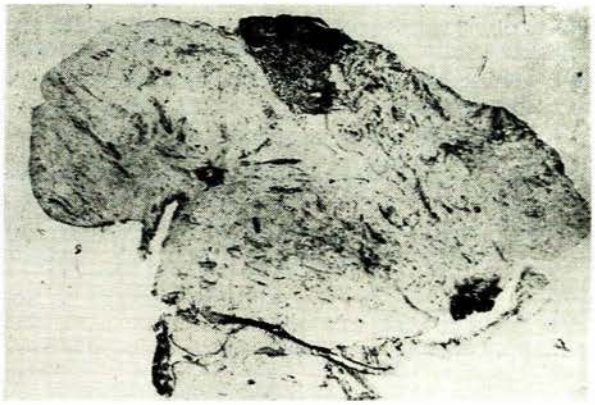

Fig. 3. Histology of streak gonad showing fibrous tissue and absent follicles.

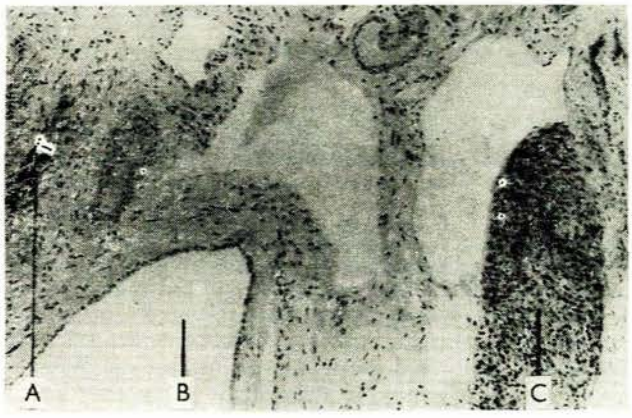

Fig. 4. Histology of streak gonad showing (A) rete ovarii, (B) simple inclusion cyst, and (C) cells with eosinophilic cytoplasm and hyperchromatic nuclei which may be hilar cells or mesothelial cells.

Pathogenesis

The pathogenesis of the condition is not at all clear. The finding of gonadal streaks in pure gonadal dysgenesis and Turner's syndrome is constant. The somatic abnormalities found in Turner's syndrome are absent or may be a solitary finding in pure gonadal dysgenesis. Abnormal karyotypes have been demonstrated in both syndromes.

The somatic gene (A) described by Hoffenberg and Jackson[1] and the gene for stature (S) appear to be closely linked. Sohval[3] has pointed out the fact that subjects with gonadal dysgenesis who are not short show no, or at the most, inconspicuous, somatic anomalies of the Turner's syndrome. Histology and chromosome studies have not been able to explain the difference in the two syndromes. As more data are accumulated, however, some correlation should be possible.

Management

Replacement therapy with oestrogens should be given at the time of puberty if the diagnosis is made in the prepubertal stage. A fortuitous finding of streak gonads at laparotomy provides the diagnosis. Administering oestrogens before puberty will prevent the development of the eunuchoid features. Oestrogen therapy after puberty may improve the secondary sex characteristics and in some instances may lead to normal breast development.

Prognosis

Patients with gonadal dysgenesis are old for their age and seldom reach 65 years.[4] The incidence of hypertensive disease is also increased even in patients who have received hormone replacement. The incidence of development of diabetes mellitus or thyroiditis is also increased.[4]

The incidence of malignancy occurring in gonadal dysgenesis has been pointed out by Sohval.[3] Four out of 22 cases of hilar cell tumour occurred in patients with gonadal dysgenesis.[7] Gonadal neoplasms were found in 8 out of 28 cases of gonadal dysgenesis.[5] Engel and Forbes,[4] however, found no cases with malignant change in 48 cases of gonadal dysgenesis. For this reason it may be wise to remove the gonadal streak and possibly the uterus, as prolonged oestrogen therapy may predispose to the development of endometrial carcinoma. Gusberg and Hall[9] reported 23 cases of endometrial carcinoma in patients who had prolonged oestrogen therapy for varying lengths of time.

SUMMARY AND CONCLUSIONS

A female patient fulfilling the criteria of pure gonadal dysgenesis is reported, characterized by normal stature, eunuchoid features with infantile genitalia and absent breast development. Nuclear sex determination was chromatin-positive and the karyotype was 46/XX. The presence of gonadal streaks was confirmed at laparotomy.

In a review of the literature, chromosomal investigations were performed in 41 out of 60 cases (including the present case) of pure gonadal dysgenesis. In 47% of these cases the sex chromosome pattern was XX and in 29% XY. Twenty-two percent of cases were mosaics, the most common mosaic pattern being XO/XX.

Nuclear sex determination in 57 cases showed that 54·4% were chromatin-positive and 45·6% chromatin-negative. Clitoral enlargement may or may not be present. There is an increased incidence of diabetes, thyroiditis and malignancy in cases of gonadal dysgenesis.

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