PRIMARY AMENORRHOEA—ETIOLOGICAL ANALYSIS

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Amenorrhoea, though in essence only an outstanding symptom, assumes the proportion of a clinical entity because of its association with infertility and other serious systemic or endocrine disorders. The purpose of this paper is to present the etiological factors in 66 cases of primary amenorrhoea, seen over a period of 3 years, in the endocrine clinic of Postgraduate Institute of Medical Education and Research, Chandigarh.

A detailed clinical history and physical examination were found to be helpful in selecting investigations to determine the underlying cause of amenorrhoea. Haemoglobin, E.S.R., urine examination, X-ray chest and buccal smear for sex chromatin were done for all the patients. Ancillary investigations like vaginal smears, endometrial biopsy, intravenous pylography, X-ray skull and hormone assays like serum gonadotrophins, T3, T4, TSH and 17-Ketosteroids were carried out according to plan in selected cases. Laparotomy to assess the status of the genital tract, as well as for gonadal biopsy was undertaken where possible.

Table I shows the age of the patients at first hospital visit. Thirty patients were unmarried and rest were married.

TABLE I

Age at First Hospital Visit

Age	Less than 15 yrs.	16-20	21-24	25-29	30 & above
Number	2	29	21	9	3

Table II shows the classification of etiological factors and sexual development. Patients with normal breasts, external genitalia and with normal growth of pubic and axillary hair are considered as sexually mature.

Hypogonadotrophic Hypogondism: There were 2 cases of hypogonadotrophic hypogondism. These patients were comparatively taller, (height 5′ 7″) than average without any development of breast or other secondary sexual characters. The serum gonadotrophins were very low, and sex chromatin was positive in both the cases.

Primary Ovarian Failure: All 5 cases were married. The sexual development was normal in 2 cases, while there was poor sexual development in 3. They were of average height. All showed minimal oestrogenic activity in the cervical mucus and vaginal smear and had

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TABLE II
Classification of Etiological Factors and Sexual Development

Etiological factors	No. of patients	Sexual Development		
		Normal	Hyposexual	Poor Development
Hypogonadotrophic Hypogonadism	2	–	–	2
Primary ovarian failure	5	2	–	3
Stein Leventhal syndrome	2	2	–	–
Gonadal dysgenesis				
i. Pure gonadaldysgenesis	16	–	–	16
ii. Turner Mosaic	3	1	2	–
Testicular feminisation	2	2	–	–
Incomplete testicular feminisation	1	–	–	1
True hermaphroditism	1	–	1	–
Mullerian dysgenesis	31	28	2	1
Genital tuberculosis	1	1	–	–
Cryptomenorrhoea	2	2	–	–

withdrawal bleeding by progesterone alone, indicating some ovarian activity. All were sex chromatin positive. The serum gonadotrophins were high in all cases. Two patients gave history of long fever during late adolescence.

Gonadal Dysgenesis: There was not a single case of typical Turner's syndrome. There were 16 cases of pure gonadal dysgenesis. Table II shows the sexual development of these patients. In 11 cases the buccal smear was negative, while in the other 5 it was positive. The vaginal smears done serially were found to be atrophic. Gonadotrophin activity was not uniformly high in these patients. In 13 cases the gonadotrophin levels were normal, and in 3 cases the levels were comparatively low.

Mosaic Turner's Syndrome: 3 cases. Stigmata peculiar to Turner's syndrome were not present, except poor breast development and short stature in 2 cases. The buccal smear was positive in all, and Karyotype was XO/XX. Surprisingly serum gonadotrophins were absent in all these 3 cases.

Prepubertal Polycystic Ovaries: 2 cases. Both were 23 years old, and 1 of them was unmarried. Buccal smears were positive. Serum gonadotrophins were variable. In 1 case gonadotrophins were normal, while in the other values were low. 17-Ketosteroids were on higher side of normal range. Both cases had laparatomy and wedge resection of ovaries, and presently are on clomid therapy.

Mullerian Dysgenesis: 31 cases. The age ranged between 18 to 37 years. Sixteen were unmarried and 15 were married. All were chromatin positive. I.V.P. was done in all the cases and only one was abnormal in which there was single pelvic kidney. Mullerian agenesis was present in 25 patients. Malformation due to irregularities of fusion in the lower portion of mullerian duct was observed in the remaining 6 cases. In 1 case whole genital tract showed extreme hypoplasia, the uterine length as measured by sound being 2.5 cm. Serum gonadotrophins were done in 11 cases out of which levels were subnormal in 2.

Testicular Feminisation: There were 2 cases with this entity and both were

unmarried. They sought advice early for primary amenorrhea and labial swellings. Body hair was sparse in 1, and absent in other. Buccal smears were chromatin negative. The gonadotrophins were normal in 1 and high in the other. Laparotomy showed a fold of peritoneum at the site of uterus and broad ligament. Gonadectomy was performed. Section of gonads, showed testicular tissue without spermatogenesis.

True Hermaphroditism: 1 case. This patient presented at the age of 20 years with amenorrhoea, having female habitus with hypoplastic sexual development. Buccal smear was chromatin positive. At laparotomy, uterus was atrophic. Section of gonads showed ovotestis on both sides. Serum gonadotrophins were normal in this case.

Incomplete Testicular Feminisation: 1 case. This girl, an athelete and brought up as female, presented at the age of 18 years with hirsutism, voice changes, clitoromegaly and partially fused labia. The vagina was blind and much shorter than that seen in complete testicular feminisation. The uterus was absent. The testes were present in the labia. Buccal smear was chromatin negative. Patient refused admission and did not come for follow up.

In one case tubercular infection of pelvis was discovered as the cause of amenorrhoea.

Two cases of cryptomenorrhoea have been included in this series. Both had thick vaginal septum with stenosis of cervix in one case, and had hematometra and hematosalpinx. Reconstructive surgery was done in both these cases.

Discussion

It is essential to establish the diagnosis of the cause of primary amenorrhoea, prior to induction of menstruation or ovulation. In contrast with patients of secondary amenorrhoea in whom definite causes for the condition were ascertainable in only 50% of cases (Townsend *et al* 1966), it was possible in the present study, to determine the etiological factors for primary amenorrhoea in all patients.

As is evident from Table II, about 50% of the patients were of Mullerian dysgenesis. This relatively high incidence of mullerian dysgenesis is explained by the fact, that these cases were mostly referred for surgical reconstruction of vagina. Chawla *et al* (1963) reported an incidence of 55% urinary tract abnormality in mullerian dysgenesis cases. In the present series, 1 case of single pelvic kidney was seen. The observations obtained on the cytogenetical studies indicate that abnormalities of the sex chromosome complement do not usually occur in these patients. All the patients in this group showed normal female pattern. The cause of arrest of development of mullerian duct in presence of normal ovaries which are as yet thought to govern the development of mullerian system is difficult to explain.

It has been shown in literature at London Conference "The normal human Karyotype (1963)'", that 80% of the patients with gonadal dysgenesis are chromatin negative. The remaining 20% are chromatin positive, which suggests that there are non-chromosomal determinants of an individual sex. In 5/16 cases of pure gonadal dysgensis, buccal smear was chromotin positive. Unfortunately, only in 2/5 cases, Karyotypic analysis was done which showed 46 XX pattern, and laparotomy showed streak ovaries. The low gonadotrophin levels in 3/16 cases, in presence of streak ovaries is very difficult to explain. The presence

of bilateral streak gonads must be confirmed histologically and complete karyotypic analysis must be done to make an absolute diagnosis. In any patient with this syndrome who is found to have a Y-containing cell line, regardless of whether or not there is associated chromosomal mosaicism, laparotomy and prophylactic gonadectomy must be performed.

Mosaics form the largest number of the sex chromatin positive patients of gonadal dysgenesis, and among these the common karyotype is XO/XX, as in 3 of our cases, who had positive buccal smear (counts ranging from 8-15%) Ferguson-Smith (1965) estimated that 80% of XO/XX mosaics are short and 66% have somatic anomalies. Two of the mosaics in the present series were short.

The presence of an XY karyotype, bilateral testes and normal gonadotrophins, in a well-developed phenotypic female allows for a ready diagnosis of testicular feminisation syndrome. Two of our cases did not pose any difficulty in diagnosis. An incomplete form of testicular feminisation also exists, in which clitoris is enlarged and masculinisation occurs at puberty. There was only one such case in our series who failed to come for follow-up. It is important to make a distinction between the two types of testicular feminisation. However, an early gonadectomy should be performed in patients with the incomplete form to prevent virilisation at puberty. The complete and incomplete testicular feminisation syndromes often occur in multiple sibs and their "maternal aunts", indicating X linked recessive or male limited autosomal dominant inheritance (Philip and Trolle, 1965). Our cases did not have family history of similar syndrome.

High incidence of tubercular endometritis in cases of primary amenorrhoea is reported by Malkani and Rajani (1953) and Hafeez *et al* (1973). In our series only in 1 case genital tuberculosis causing amenorrhoea was discovered.

The thick transverse vaginal septum, lying higher than the normal hymen, was the obstructing lesion in 2 of our cases of cryptomenorrhoea. This septum presumably arose from failure of lumen to develop in the vaginal anlage.

Summary

Sixty-six cases of primary amenorrhoea were studied. The causative lesions of primary amenorrhoea were attributed to pure gonadal dysgenesis in 16 cases, Turner's mosaicism in 3, primary ovarian failure in 5, testicular feminisation in 2, ovotestis in 1, partial testicular feminisation in 1, hypogonadotrophic hypogonadism in 2, prepuberal polycystic ovaries in 2, Mullerian dysgenesis in 31, tuberculosis of pelvis in 1 and cryptomenorrhoea in 2 cases.

References

1. Chawla, S., Gadekak, M. G., Nirula, R. and Hingorani, V.: Indian J. of Surgery 25: 600. 1963.
2. Ferguson-Smith, N. A.: J. Med. Genet. 2: 142, 1965.
3. Hafeex, M. A., Tandon, P. L. and Muntal, S.: Ind. J. of Pathology & Bacteriology, 54: 16, 1973.
4. London Conference on Normal Human Karyotype Cytogentics. 2: 264, 1963.
5. Malkani, P. K. and Rajani, C. K.: Proceedings Indian association of Pathogists Fourth Meeting, November 1953.
6. Philip, J. and Trolle, D.: American J. Obst. Gynec. 93: 1076. 1965.
7. Townsend, S. L., Brown, J. B., Johnstone, J. W., Adey, F. D. and Evans, J. H.: J. Obst. Gynec. of Brit. Cwlth., 73: 529. 1966.