PRIMARY AMENORRHOEA : A MANIFESTATION OF PRIMARY GONADAL FAILURE

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SUMMARY

During a study of 74 cases of primary amenorrhoea who came with abnormalities of pubertal sequencing, 23 were eventually diagnosed to have primary gonadal failure, partial or complete. The clinical features, somatic abnormalities, endoscopic and ultrasound findings, karyotyping and serum gonadotrophin levels are presented.

The presenting complaint was stunted growth in 8 cases, absent sexual development in 3 cases, and infertility in 1. Uterus was absent in 5, of whom 2 had a 46 XY karyotype the other three being 46 XX. Vagina was absent in 2 patients with hypoplastic uterus and in one with absent uterus and only lower 1/3 vagina was developed in 4 patients with absent uterus . Hypergonadotrophic status was found in 18 and renal anomalies in 3. In all but 3, the gonads were streak bilaterally. Two had bilateral small gonads and the remaining one had unilateral small gonad with streak and absent gonad on contralateral side.

Primary gonadal failure was thus the cause of primary amenorrhoea in 31.08% of patients. Of these 56.52% had abnormal karyotyping while 43.48% had normal 46 XX.

INTRODUCTION

Impaired steroid secretion due to primary gonadal failure leads to abnormal pubertal sequencing, sexual infantilism and finally presents as primary amenorrhoea in the second decade of life.

The commonest form of primary gonadal failure is gonadal dysgenesis described as Turner's syndrome of 45 XO. The structural chromosomal abnormalities of 45 XO, 45 XO/XX, XX_p and XX_q XX isochromosome contribute to the `chromosomally incompetent' gonadal failure.

In another relatively common condition, the chromosomal complement is normal, the 46 XX or 46 XY, the gonads fail to develop into either the ovary or testes and remain streak. These fall into the category of `pure gonadal dysgenesis'. The condition may be sporadic or familial, phenotypically both are females with normal or tall

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structure, normal mullerian ductal growth, sexual infantilism and cunchoid habitus. With XY dysgenesis, there may be a slight clitoromegaly and there is a greater preponderance of neoplastic change in the streak gonad.

A third, less common group of condition in the mixed gonadal dysgenesis group in which the chromosomal complement is 45 X/46 XY, variable gonadal growth seems from bilateral streak to unilateral streak with contralateral testes of variable size. The subjects are short statured, phenotype is female with clitorial hypertrophy at puberty, mullerian ductal development and delayed puberty.

MATERIAL AND METHODS

Patients with primary amenorrhoea, attending Sassoon General Hospitals, Pune between January 1986 and July 1990 were evaluated.

A detailed history was taken and clinical examination was done with special emphasis on sexual development, skeletal deformities, stature etc. Investigations like diagnostic endoscopies, ultrasonography, intravenous pyelography, hormonal assays and genetic study were undertaken whereever possible.

OBSERVATIONS AND RESULTS

Of the 74 patients of primary amenorrhoea attending the Endocrine Clinic at Sassoon General Hospitals, 23 were eventually diagnosed to have primary gonadal failure giving an incidence of 31.08%.

The following observations were made.

1. Age - 52.17% of the patients reported before the age of 18 years (Table 1).

2. Associated symptoms - Eight patients had consulted their own family physician for stunted growth which they had thought was not familial. Three patients complained of absence of sexual development and one of infertility.

3. Height (Table 2)

Except for the 4 patients with 46 XY, 9 of our chromosomally incompetent group were below 147 cms. One of the 46 XY was below 147 cms.

TABLE I

Age of Patients

Age (Years)	No.
-16	5
17-18	7
19-21	11

TABLE II

Height of Patients

Height (Cms.)	No.
121-130	6
131-140	8
141-150	3
151-160	3
161 -	3

TABLE III

Dysmorphic Features

Features	No.
Neckwebbing	2
Short neck	2
Cubitus valgus	1
Pectus excavatum	1
Wide carrying angle	2
Nystagmus	1
Squint	1
Finger toe anomalies	4
Masculine features	2
Clitoromegaly	1

TABLE IV

Karyotype

Karyotype	No.
46, XY	5
45 ,X	4
45, X/46, XX	1
45, X/46, XX, inv (X_{q})	1
46, X i (X_{q})	1
46, XX_{q22}	1
46, XX	10

TABLE V

Mullerian Abnormalities

Organ	Absent		Hypoplastic
Uterus	5		18
Tubes	Unilateral	1	15
	Bilateral	2	
Vagina	Partial	4	-
	Complete	3	

4. Dysmorphic features (Table 3)

5. Karyotype - Cytogenetic studies by Q-R banding of 100 cells of lymphocytic cultures detected chromosomal abnormalities in 56.52% while 43.48% had 46 XY karyotype (Table 4).

6. Serum Gonadotrophins - Serum FSH ranged from 42-95 I.U. in 19 patients. (Normal S. FSH 10-30 I.U.)

7. Mullerian Abnormalities (Table 5).

Out of 23 patients 5 did not have uterus. Two of these had their karyotype 46 XY. 3 of them had karyotype 46 XX. The status of the tube was ascertained in 18 patients at laparoscopy. In 2 patients the tubes were absent along with the uterus whereas in 2 patients there was hypoplastic development of tubes in absence of uterus. Unilateral development of fallopian tube on the side of gonad was present in 1 case. Vagina was absent in 2 patients with hypoplastic uterus and 1 with absent uterus and only lower 1/3 vagina was developed in 4 patients of absent uterus.

8. Gonads - In the patients subjected to laparoscopy, bilateral streak gonads were found in 15, bilateral small gonads in 2 and unilateral small with contralateral streak gonad was found in 1.

9. Renal anomalies - The incidence of renal anomalies in our patients was 13.04%.

Horse shoe shaped kidney was found in 2 patients while in one patient there was unilateral agenesis and hypertrophy of contralateral kidney.

There was no history of consanguinity in our series. Two of our patients with 46 XY were the only daughters of parents. Family study of one was negative. There is no facility for detection of XY antigen in our laboratory.

10. Treatment - Four patients with 45 xo and mosaicism are on Ethinyl estradiol 10-30 mg/day orally for 21 days for the first 3-6 months. When breakthrough bleeding occurs medroxy progesterone 5 mg-day is added from day 12 to 21.

The duration of therapy in our series varies from 3 to 18 months. They are being assessed for response to therapy in the form of psychological relief and development of secondary sexual characters and undesirable side effects.

The 5 patients with 46 XY were advised gonadectomy, however, only 2 of them underwent the operation. 2 of them are still making up their mind. One patient is lost to follow up.

DISCUSSION

Incidence of primary gonadal failure (PGF) in our series is 31.08%. In literature the reported incidence is 9.4% (Chandrawati and Joshi, 1987), 43% (Reindollar et al, 1981), 34.44% (Kole et al, 1988). More than half of the patients reported to our clinic at or before age of 18 and even before 16.

Short stature and non development of secondary sexual characters had already alterted this group of young girls and their parents seeking early medical help. With increasing literacy and great awareness, girls with abnormal puberty are likely to attend early and require to be differentiated from those of delayed puberty.

In our series, the incidence of primary gonadal failure with normal karyotype is 43.48%. In literature the reported incidence is 59% (Pal, 1984), 36.5% (Aleem, 1981), 14.2% (Shearman, 1982).

Two out of 5 patients with absent uterus had karyotype of 46 XY. Krishna Kumari et al (1986) have suggested cytogenetic studies in patients with absent uterus. She has also suggested screening of family members for genetic counselling.

It is necessary to rule out abnormal karyotypes of 46 XY before instituting therapy for development of secondary sexual characters and maintenance of skeletal structure. The withdrawal bleeding every month in patients of gonadal agenesis has great psychological benefit. Successful prognancies have been reported in 2% of women with Turner's syndrome.

The risk of neoplastic change in streak gonad of 46 XY cell line and the need to replace hormone therapy in chromosomally competent group calls for early and thorough investigations of all cases of primary amenorrhoea to whom these disorders contribute 25-30%. Such patients seek early counselling and treatment.

Although at present there is very little to offer to this group of patients, it is necessary to investigate them for the malignant potential in 40-50% of male dysgenetics, for detection of similar condition in siblings and appropriate genetic counselling.

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