GONADAL DYSGENESIS – A CASE SERIES FROM A SINGLE VILLAGE

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ABSTRACT: AIM: To describe the clinical features of patients presented with primary amenorrhoea and streak gonads from a single village and their response to treatment in a tertiary care hospital, thenceforth trace the source of genetic insult. **METHODOLOGY:** Patients attending outpatient department with primary amenorrhea and absent or poorly developed secondary sexual characters were examined clinically for height and genital development. They were evaluated with pelvic ultrasound, serum Follicle Stimulating Hormone, and karyotyping. **RESULTS:** Four patients presented at the age of more than 24 years with primary amenorrhea and poorly developed secondary sexual characters who were from a single village at Puducherry. On evaluation, pelvic ultrasound revealed streak gonads and serum FSH levels were elevated in all of them. Out of four, three of them had normal stature and one patient was short statured despite her genotype revealing 46XX. Among the patients with normal height, one had 45 X0 genotype. Thus they had unusual genotypic and phenotypic combinations. All of them responded well to hormone treatment. **CONCLUSION:** Diagnosis of pure gonadal dysgenesis must be done earlier for initiation of hormonal treatment. Search for teratogenic aetiologies for gonadal dysgenesis in that locality needs to be done.

KEYWORDS: primary amenorrhea, gonadal dysgenesis

INTRODUCTION: Primary amenorrhea is defined as absence of menses at age 13 years when there is no visible secondary sexual characteristic development or age 15 years in the presence of normal secondary sexual characteristics.^[1] Approximately 30% of patients with primary amenorrhea have an associated genetic abnormality.^[2] Turner syndrome (45 X0) is the most common chromosomal abnormality causing gonadal failure and primary amenorrhea.^[2, 3] The incidence of gonadal dysgenesis with Turner syndrome is 1:2000 whereas the occurrence of pure gonadal dysgenesis with 46 XX genotype is extremely rare.^[1] Yet we came across four patients with gonadal dysgenesis within a short span of time, all from a single village. All were diagnosed to have gonadal dysgenesis with unusual genotypic and phenotypic combinations. This case series describes the clinical features of patients presented with primary amenorrhoea and streak gonads from a single village and their response to treatment in a tertiary care hospital, and also to trace the source of genetic insult.

MATERIAL AND METHODS:

Study Design: Descriptive case series

Study Setting: Tertiary care centre, Puducherry

Between July 2011 and December 2011, four women presented to our gynaecology outpatient department with primary amenorrhea and poorly developed secondary sexual characters. Detailed history was taken and they were examined clinically for height, Turners stigmata and genital development. Then they were evaluated with serum Follicular Stimulating

Hormone (FSH) level, pelvic ultrasound and buccal smear for barr body. Finally the diagnosis was confirmed with karyotyping. The results are summarised in tables. (Table 1 and 2)

Interestingly, we found that all of them belonged to the same locality (Kirumampakkam village of Puducherry).

RESULTS: The mean age at the time of presentation was 23.5 years (Range 21-27). All the four patients gave the history of consanguineous parentage. On examination, secondary sexual characters were poorly developed in all of the patients with breast development Tanner's stage I-II and pubic hair development of Tanner's stage II. Of the four patients, one was short statured despite her genotype revealing 46XX. Pelvic ultrasound revealed streak gonads with hypoplastic uterus in all of them (Figure 1). Serum FSH levels were elevated with mean FSH level of 42.7 mIU/ ml (Range 28.2-70). Buccal smear for barr body were positive in all of them.

After having established that they had hypergonadotropic hypogonadism, suggestive clinical features prompted the investigation of karyotyping. A 72 hour PHA stimulated lymphocyte culture showed a chromosomal pattern of 46 XX in three patients (Figure 2) whereas 45XO [46XX/45XO (1:1)] suggestive of mosaic Turners (Figure 3) in one patient in spite of normal stature and absent Turner stigmata.

With the working diagnosis of gonadal dysgenesis, hormone treatment was initiated in them. They were prescribed conjugated oestrogen (0.625 mg) for 6 months, followed by Medroxy progesterone acetate (10 mg) for 10 days. Response to treatment was good in them with the onset of menses and improvement of secondary sexual characteristics. In patient with mosaic turners, breast development was slow and now attained Tanner's stage III. They are on cyclical estrogen and progesterone therapy and on regular follow up.

DISCUSSION: Primary amenorrhea is one of the important reasons for distress of family and patient herself. Literature review has shown that low frequency and fear of exposure of defect may be the reason for not seeking medical advice. In a study by Rizwan, most of the patients presented with primary amenorrhea were of age ranging from 16-20 years. [4] Primary amenorrhea creates problems such as social, psychosexual, infertility, osteoporosis and genital atrophy.

Few problems in gynaecologic endocrinology can present a diagnostic challenge to clinicians like that of amenorrhoea. However, when approached logically and systematically, the diagnostic evaluation of amenorrhoea truly is straight forward. The causes of primary amenorrhea include disorders of genital outflow tract and uterus, ovaries, anterior pituitary and hypothalamus out of which ovarian cause is common. [4]

Gonadal dysgenesis is defined as an incomplete or defective formation of the gonads, resulting from a disturbance in germ cell migration or organization. Approximately, 25% of affected individuals have a normal 46 XX karyotype and may harbour a more subtle abnormality involving one or more specific genes on the X chromosome required for normal ovarian function. [5] The most common form of gonadal dysgenesis is Turner's syndrome. The classical phenotype of Turner's syndrome include short stature, absent sexual development, webbed neck, low set ears, posterior hairline, widely spaced nipples, short fourth metacarpals and an increased carrying angle.[3] None of the patients in our case series had those Turner's stigmata.

46XX individuals with partial deletions of the X chromosome have variable phenotypes depending on the amount and location of the missing genetic material. Patients with a deletion of the long arm of X chromosome from Xq13 to Xq26 have sexual infantilism, normal stature, no somatic abnormalities and streak gonads.^[6] Majority of our patients had a similar clinical presentation. In those with mosaic 46XX cell line, the gonad may contain functional ovarian cortical tissue, resulting in some degree of sexual development, or even menses and the possibility of pregnancy.^[7]

The initial laboratory test should be assessment of serum FSH levels unless the history and physical examination suggest otherwise. If serum FSH levels are elevated, karyotyping should be obtained which will be the key to the diagnosis.^[5] Individuals with primary amenorrhea associated with all forms of gonadal failure and hypergonadotropic hypogonadism needs cyclic estrogen and progestin therapy to initiate, mature and maintain secondary sexual characteristics. Therapy is usually initiated with 0.625 mg/day of conjugated estrogens or 1 mg/day of estradiol. Medroxy progesterone acetate may be administered at a dose of 2.5mg daily or 5 to 10 mg for 12-14 days every 1-2 months.^[1]

CONCLUSION: Even though gonadal dysgenesis has been very well studied in literature, the exact aetiology is still unclear. This case series highlights that consanguinity and locality with possibility of teratogenic effect of some environmental hazard in a particular area may be the probable underlying cause. Since our sample size is small, further studies are required to prove the relation. Also, Search for teratogenic aetiologies for gonadal dysgenesis in that locality needs to be done.

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Table 1: Clinical summary of patients presented with primary amenorrhea

	Age (years)	Consanguineous Parentage	Height (cms)	Breast development (Tanner's Stage)	Pubic hair development (Tanner's Stage)	Turner's stigmata	External genitalia
Case 1	21	Present	162	II	II	Absent	Under-Developed
Case 2	24	Present	160	I	II	Absent	Under - Developed
Case 3	22	Present	132	I	II	Absent	Under-Developed
Case 4	27	Present	158	II	II	Absent	Under-Developed

Cms- Centimeters

Table 2: Summary of Investigations in patients presented with primary amenorrhea

	Uterus on pelvic ultrasound	Ovaries on pelvic ultrasound	Serum FSH levels (mIU/ml)	Buccal smear for Barr body	Karyotyping
Case 1	Hypoplastic	Streak	28.2	Positive	46 XX
Case 2	Hypoplastic	Streak	70.0	Positive	45 X0 [46 XX/45 X0(1:1)]
Case 3	Hypoplastic	Streak	34.2	Positive	46 XX
Case 4	Hypoplastic	Streak	38.4	Positive	46 XX

FSH- Follicular Stimulating Hormone

mIU/ml- milli International Units/ milliliter

Figure 1: Pelvic Ultrasound illustrating hypoplastic uterus

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Figure 2: Metaphase analysis revealing normal karyotype (46 XX)

Figure 3: Metaphase karyotyped showing a chromosomal pattern of 46 XX/ 45 X0 (1:1)

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