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CLINICO –ETIOLOGIC AND GENETIC PROFILE OF PRIMARY AMENORRHEA

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ABSTRACT **Background:** Primary amenorrhoea as a symptom may have many etiological factors. Though the incidence of primary amenorrhea is less than 1%, it accounts for significant amount of psychological trauma. As the condition requires extensive evaluation the girls are most often referred to tertiary care centres to have a comprehensive work up and management. **Objective:** To study the etiologic and genetic profile and different genetic abnormalities in primary amenorrhoea. **Methodology:** It is a descriptive cross-sectional study carried out in a tertiary care hospital in Kerala among 52 subjects who presented with Primary amenorrhoea, from November 2020 to July 2021. **Results:** The average age of presentation was 16.3 years . Amenorrhoea was the commonest complaint patients presented with accounting to 63.5% (n=33), followed by delayed secondary sexual characters in 23.1%(n=13) of cases. Out of the 52 subjects presented with primary amenorrhea, 14 patients (27%) were found to have Turner's syndrome, 8 (15.4%) patients had Müllerian agenesis, 6 (11.5%) had Turner mosaic genotype,6 (11.5%) had XY gonadal dysgenesis (Swyer syndrome), 6 (11.5%) patients had outflow tract obstruction, and 4 (7.7%) patient was found to have Testicular feminization. Other causes include constitutional delay in 5 patients (9.58%), panhypopituitarism in 2 patients (3.8%) and systemic disease in one patient. Karyotyping was done for 75% patient and the most common abnormality was 45,X (26.9%) of patients. **Conclusion:** Most common cause of primary amenorrhea in our study was Turner syndrome followed by Mullerian agenesis. It also signifies the importance of cytogenetics in primary amenorrhoea patients for understanding correct aetiology.

KEYWORDS : primary amenorrhoea, turner syndrome, karyotyping

INTRODUCTION

Primary amenorrhoea is defined as absence of menstruation and secondary sexual characteristics by the age of 14 and the absence of menstruation regardless of secondary sexual characteristics by the age of 16[1]. There is development of secondary sexual characteristics, onset of menstruation and also the sexual reproduction capability.

Previous studies have been reported from all parts of the world including the frequency of various aetiologies, cytogenetic abnormalities in cases of primary amenorrhea. Gonadal dysfunction has been considered as the commonest cause of primary amenorrhoea followed by out flow tract anomalies, hypothalamic and pituitary disorders. Literature showed greater prevalence of gonadal dysfunction leading to primary amenorrhoea in western countries while that of outflow tract anomalies in Asian African countries. Most of the studies from United States reported gonadal dysgenesis as the commonest cause while a larger study from Thailand of 295 cases showed Mullerian anomaly as commonest cause in Thailand [2]. Hence, racial and environmental factors may have role in the aetiology of primary amenorrhea.

There are reports from Indian literature elaborating the cytogenetic evaluation in primary amenorrhea patients and mentioning the contribution of chromosomal abnormalities in primary amenorrhoea. In 2010 Vijayalakshmi et al reported cytogenetic analysis study of primary amenorrhoea. The karyotype revealed 71.2% with normal composition, 27.8% with numerical aberrations, 26% with structural abnormality. X chromosomal abnormality was observed in 49% of study population [3]. After excluding non-genetic causes of primary a menorrhoea, the patients should receive prompt referral for genetic studies. Various other studies showing karyotype abnormalities from 14-42% [4,5,6].

Primary amenorrhea work up may seem to be complex, nevertheless a well elicited history, carefully conducted physical examination followed by use of imaging modalities and bioassays for endocrine abnormalities, permit the clinician to narrow the diagnostic possibilities and reach an accurate diagnosis quickly that help in choosing the appropriate management option. Primary amenorrhea affects physical, mental, psychological and social life of the patient, so a team approach involving gynaecologist, geneticist, psychologist and paediatrician is required. This study was conducted in a tertiary care hospital setting to evaluate various causes of primary amenorrhoea including chromosomal abnormalities

MATERIALS AND METHODS

Aim: To study the etiologic and genetic profile of primary amenorrhoea among patients attending in a tertiary care.

It was a Descriptive cross-sectional study done at a tertiary care hospital at South Kerala. All patients attending to the OPD with complaints of not attaining menarche by the age of 16 or not having secondary sexual characteristics by the age of 14 and diagnosed as primary amenorrhoea for a period of one year from the time of approval of topic were included in the study.

Sample size:

Based on the study on Etiological factors of primary amenorrhoea: A prospective study published in an international journal of Obstetrics and Gynaecology; sample size was calculated.

N = the population size
P = the anticipated population proportion
Expected proportion (gonadal dysgenesis) = 0.50%
Relative precision = 20 %
Desired confidence level = (1-α) % - 95
Required sample size = 96

Sampling technique:

Patients who are presented to OP with complaints of primary amenorrhoea who met the inclusion criteria and who consented to take part in the study. Semi structured proforma was used to collect data.
Study variables

Clinical Parameters:

Age, BMI, symptoms like cyclical abdominal pain, head ache, vomiting, anosmia and signs like bulging hymen, palpable uterus

Biochemical Parameters: TSH, Hb, PCV, FSH, LH

Radiological Parameters:

USG findings – uterus, ovaries any structural abnormality and MRI abdomen (wherever available)

Data analysis:

Quantitative variables were expressed in mean and standard deviation and Qualitative variables in proportion. Chi square test was used to find association

RESULTS

Demographic data:
The age of patients presented with primary amenorrhoea ranged from 14 to 24 with mean age 16.35, standard deviation 1.86. Majority of patients presented in the age group of 16-18 year. Majority of patients are from middle socio-economic status 32.7 %(n=17) from upper middle and 32.7% (n=17) from lower middle socio-economic status.

Family History:
In our study 23.1% cases have family history of delayed puberty, 7.7% have family history of primary amenorrhoea, 7.7% have family history of infertility, and 61.5% have no significant family history.

Anthropometry:
In this study mean BMI is 19.946 and standard deviation 3.109. Minimum BMI in the study population is 13 and maximum is 26. Majority of patients are in normal BMI range. Mean height is 154.6 and standard deviation of 9.158, minimum height of 140 cm and maximum height of 172cm.

Puberty development by SMR staging:
Of the 52 patients, breast development was 44.2% in stage 2, 34.6% are in stage 3, and 21.2% are in stage 1. From this it's understood that majority of patients (65.4%) have poorly developed breast. For pubic hair staging majority are in tanner stage 2 (42.3%) followed by tanner stage 1 (28.8%) and tanner 3 in 26.9% followed by tanner 4 (1.9%). In the study population majority (69%) have adequate axillary hair growth and 21% have scanty growth and 10% have no axillary hair.

Hirsutism:
Ferryman Galway score is used to look for hirsutism and 75% were below the cut off value 8 and 25% were above 8 with features of hirsutism

Co-morbidities:
In this study hypothyroidism was the most common medical comorbidity (42.3%), followed by heart disease (17.3%), hyperprolactinemia 5.8%, history of head trauma in 3.8%, diabetes mellitus in 1.9%, hypertension in 1.9%. In 26.9% patients no known comorbidities were seen.

Other associated anomalies:
Of the total patients 5 (9%) had skeletal anomalies which include scoliosis, short metacarpal, polydactyly one patient with Mullerian agenesis fits into the phenotype of MURCS syndrome with Müllerian agenesis, unilateral renal agenesis, and anomalies of the cervicothoracic somites in the form of torticollis. Of the study population 6 (13%) patients have renal anomalies which include ectopic left kidney in 2 patients, Duplicated ureter in 3 patients and renal agenesis right side in one patient.

Hormonal profile:
Of the total study population 50% were hypergonadotrophic,46% were normogonadotropic and 4% were hypogonadotropic.

Imaging of Pelvis:
In this study the most common USG finding was streak gonads (46.2%) and 23.1% population no significant abnormality detected in USG,11.5% have absent uterus and ovary ,7.7% have absent uterus and 5.8% have other Mullerian anomalies and 5.8% have hematometra.

Karyotyping:
Of the total 52 patients karyotyping done for 37 patients (71%) and the most common abnormality seen is 45X0 (26.9%), followed by 46XY in 19.2% patients ,45XO/46XX karyotype in 11.5% and karyotype was normal in 12.5% patients. (Table 1)

Table 1: Karyotyping Reports In Study Population

KARYOTYPING REPORT	NUMBER	PERCENTAGE
46XX	7	13.5
45XO	14	27
46XX/45XO	6	11.5
46XY	10	19.2
Not Done	15	28.8
TOTAL	52	100

Aetiological Profile:
Systemic disease was found in 2% cases, constitutional delayed puberty in 9.58%cases, Panhypopituitarism in 3.8% cases, turner syndrome in 27% of cases, turner mosaic in 11.5% of cases and Swyer syndrome in 11.5% of cases. Rokitansky syndrome 15.4%%, androgen insensitivity in 7.7%, and Mullerian abnormality in 11.9% cases. (Table 2)

Table 2: An Etiological Classification Of Patients With Primary Amenorrhea.

Etiological classification	No. of patient	Percentage
Level 1 Utero-vaginal Normogonadotropic hypogonadism		
Rokitansky syndrome	8	15.4%
Testicular feminization	4	7.7%
Mullerian abnormality (out flow obstruction	6	11.9%
Total	18	35%
Level 2 – Ovarian Hypergonadotropic hypogonadism		
Turner syndrome	14	27%
Turner mosaic	6	11.5%
Swyer syndrome	6	11.5%
Total	26	50%
Level 3 –pituitary Hypogonadotropic hypogonadism Total	0	0%
Level 4 – Extrinsic to the HPO axis		
Systemic disease	1	2%
Pan hypopituitarism	2	3.8%
Constitutional delay	5	9.58%
Total	8	15.38%
Total	52	100.0

Systemic disease was found in 2% cases, constitutional delayed puberty in 9.58%cases, Panhypopituitarism in 3.8% cases, turner syndrome in 27% of cases, turner mosaic in 11.5% of cases and swyer syndrome in 11.5% of cases. Rokitansky syndrome 15.4%%, androgen insensitivity in 7.7%, and Mullerian abnormality in 11.9% cases.

DISCUSSION

This study was conducted among 52 subjects who presented to OPD with the complaints of primary amenorrhoea. The age of presentation ranged from 14 to 24, with mean age 16.35. Majority of patients were in the age group of 16-18 years. Thirty-four patients (65.4%) were from middle socioeconomic status. Ashok Krishna et al who did the similar study also noted that the average age of presentation was 17.23+/- 4.2 years [7]. We did not see any patients in the age group of 30 to 40 years because most of the inquisitive patients are diagnosed by then.

Most common presenting complaint was amenorrhea in 63.5% (n=33) of patients in our study, followed by delayed secondary sexual characters in 23.1% (n=13) of patients, cyclical abdominal pain in 11.5% (n=6) of patients, one patient was married and presented with infertility. This observation may be because of most of the patients and their relatives were more concerned about attaining menarche. Similar results were noted in studies done by Kripalini et al at AIMS Delhi[8]. Mean BMI and height in the study population was 19.9 Kg/m^2 and 154 cm respectively. 13 (25%) out of the total 52 patients have hirsutism.

For further evaluation, we divided the patients into two groups based on secondary sexual characters. In this study 34 patients (65.4%) were with absent secondary sexual characters and 18 patients (34.6%) with adequate development of secondary sexual characters. These results disagree with the studies conducted by Iqbal and Nahel where secondary sexual characters were well developed in 69% of cases. This disagreement is related due to frequency of type of amenorrhoea. Those with absent secondary sexual characters were further evaluated with FSH and LH, then patients were distributed based on this.50% were hypergonadotrophic,46% normogonadotropic and 4% hypogonadotropic. Those with adequate secondary sexual characters were primarily evaluated with USG abdomen and other investigations based on clinical indications.

Among the USG findings streak gonad seen in 46.2% of cases, uterus was not visualised in 11.5% of cases, Mullerian anomalies in 5.8% of cases, hematometra in 5.8% of cases and got normal USG findings in 23.1% of patients. This result agreed with study done by Porafkari in

2008 in which streak gonad seen in 50% of cases hematometra seen in 7 % of cases[9].

In this study most common cause of primary amenorrhoea was hypergonadotropic hypogonadism which was 50% of total cases, among this turner syndrome was the commonest in 14 patients (27%). Studies of Akthar A et al, Kriplani A et al, Tahir et al and Shanoli et al showed an incidence of 13.3%, 20.5% and 23.9%, 35.8%, respectively and Studies done by Anita et al at Vani Vilas Government hospital showed an incidence of 32%[10]. 80% of patients with turner syndrome were short statured, all were with absent secondary sexual characters. 5 patients had skeletal anomalies which include scoliosis in 2 patients, short metacarpal, polydactyly and cubitus valgus were the other skeletal anomalies seen. One patient had left ectopic kidney. Regarding Echocardiographic findings bicuspid aortic valve in 2 patients, Left heart hypoplasia in 1 patient and coarctation of aorta were the other findings seen. Therefore, screening for CVS defects as early as possible is very important in these patients.

Other causes of hypergonadotropic hypogonadism seen include Turner mosaics in 6 patients (11.5%). One patient with Turner mosaic was married and presented with infertility. All patients with Turner mosaic lacked secondary sexual development.

Swyer syndrome seen in 6 patients (11.5%). They also lacked secondary sexual characters and all underwent gonadectomy and for one patient HPR report came as malignant gonadoblastoma.

Second most common type of amenorrhea in this study was normogonadotropic type which was seen in 15.4% (18) of total 52 patients, among these Mullerian agenesis was the commonest cause in 8 patients. 6 patients with Mullerian agenesis had renal anomalies, out of these ectopic left kidneys in 2 patients, Duplicated ureter in 3 patients, and right renal agenesis in 1 patient. One patient with Mullerian agenesis fits into the phenotype of MURCS syndrome with Müllerian agenesis, unilateral renal agenesis, and anomalies of the cervicothoracic somites in the form of torticollis.

Out flow tract obstruction was seen in 6 patients (11.9%) which include imperforate hymen in 4 patients and TVS in 2 patients. Study done by Tushar et al, showed three patients out of 25 (12%) had transverse vaginal septum. Study of Kriplani A et al, had five cases of transverse vaginal septum Androgen insensitivity syndrome was diagnosed in 4 subjects.

Constitutional delay was seen in 5 patients (9.58%), panhypopituitarism in 2 patients (3.8%), chronic systemic disease in one patient (chronic kidney disease).

37 out of 52 subjects underwent karyotyping, among this 13.5% (n=7) where of normal karyotype, 27%(n=14) 45XO,11.5% (n=6)45XO/46XX,19.2%(n=10) were 46XY. The 46XY karyotype has been reported in increasing percentage compared to previous studies. Although the reason for high incidence is unknown, application of FISH could be the one of the factors to detect Y chromosome.

After the diagnosis, counselling the patient is the most important integral component of management of primary amenorrhea [12]. All the patients and their families were counselled regarding their condition and their menstrual, coital and reproductive function. They were given psychological counselling to accept their condition and cope with it, maintaining their self esteem.The main limitation of this study was sample size, due to covid scenario. The study could have been better if a proper follow up and treatment outcome was also included.

CONCLUSION

Hypergonadotropic hypogonadism (50%) was the most common causative factor leading to amenorrhea followed by normogonadotropic hypogonadism of which uterovaginal anomaly (35%) of cases. Clinical pointers like age, height and Tanner staging at presentation, can help to indicate underlying aetiology in patients with primary amenorrhea. Normal stature and breast development at presentation point towards hypogonadotropic hypogonadism and Mullerian agenesis as the most likely causes. At the other end of spectrum, most common aetiology underlying primary amenorrhea with short stature and underdeveloped breasts is Turner syndrome or its variant. A multidisciplinary team approach, including gynaecologist, endocrinologist, geneticist, dietician, psychiatrist, and medical doctor, is needed to provide treatment and psychological support.

The goal of management should be to prevent problems related to the hypoestrogenic stages, to initiate pubertal development to maintain, to deal with sexual problems, to resume ovulation and menses, to deal with fertility problems and to manage problems from the nature of aetiology ,medical and surgical treatment.

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