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A Study of Primary Amenorrhea Cases in North Coastal Andhra Pradesh

Padmavathi Kallepalli[1], Deepak Kallepalli[2]
[1]*Associate Professor of Obstetrics and Gynecology, Guntur Medical College. Guntur. A.P. India.*
[2]*MBBS Andhra Medical College. Visakhapatnam. A.P. India.*

Abstract: ***Background:*** *Primary Amenorrhea is of varied aetiology, genetic factors being the major cause. These patients require good counseling from the medical professional who should be empathetic towards the patient. Primary Amenorrhea is not a terminal disease that kills a person. It is a clinical condition that affects the suffering individual psychologically and emotionally resulting in bringing down the morale of the person. It has a heavy social impact , as it takes them away from normalcy regarding pubertal growth and maturity of reproductive system and development of secondary sexual characters. The affected individuals feel heavily depressed and many of them show signs of suicidal tendency. Owing to the social stigma attached to this condition, all the sufferers do not come out and approach the medical institutional for a help.*

Methods: *In the present study 58 cases of primary amenorrhea were studied for various etiological causes. All the patients were studied for these causes retrospectively . They were from Department of Gynecology ; Andhra medical college Visakhapatnam and from Private Hospitals along the North Coastal Andhra Pradesh within the time period spanning from October 2013 to October 2015 . They were analysed under the following headings clinical profile, secondary sexual characters, physical examination,pelvic and rectal examination,hormone profile, USG and cytogenetic study.*

Results: *Among the 58 primary amenorrhea cases 24 Gonadal dysgenesis cases, 17 Mullerian duct anomalies, 3 Testicular feminization syndrome, One Polycystic ovarian syndrome and 4 pure Gonadal dysgenesis cases were noted.*

Conclusion: ***The*** *most common cause of these cases is gonadal dysgenesis and mullerian anomalies.Genetic and environmental factors might be he major factor for the above causes.*

Keywords: *Primary amenorrhea; mullerian anomalies, gonadal dysgenesis, genetic factors.*

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I. Introduction

Amenorrhoea is absence of menses in women of reproductive age. Primary amenorrhea is defined either as absence of menarche by 14 years of age in the absence of secondary sexual characteristics or absence of menses by 16 years in the presence of normal growth and secondary sexual characteristics . According to World Health Organization estimates, amenorrhea stands as sixth largest major cause of female infertility and affects 2.5% of all women in the child bearing age.

About 2.5% of adolescent girls present with primary amenorrhea. The incidence is increasing because of increased reporting, better utilisation of healthcare, declining trend in child marriage and increased awareness due to social media. Amenorrhoea is a symptom that reflects some underlying disease anywhere in the hypothalamic-pituitary-ovarian-uterine axis. There are different causes of primary amenorrhoea. It includes anomalies of mullerian development, gonadal dysgenesis, constitutional delayed puberty, tuberculosis, CNS tumors, idiopathic etc . A case of primary amenorrhoea should be evaluated thoroughly as it has impact on both physical and psychological well being of the patient. Early diagnosis and timely intervention is necessary to prevent long term health and social consequences. As soon as the etiology is established in a particular case, the patient can be counselled regarding the prognosis and future fertility options.

Aim : To study the details of clinical features, development of secondary sexual characters, biochemical and imaging techniques.

II. Material and methods

In the present study 58 cases of primary amenorrhea were studied. These patients have been referred to the Department of Gynecology King George Hospital Visakhapatnam by various Gynecologists both from Government Institutions and Private Hospitals along the North Coastal Andhra Pradesh from October 2013 to October 2015. Demographic study, hormonal and USG studies are done.

Inclusion criteria:
1. All cases of primary amenorrhea referred to the Department of Gynecology, Andhra Medical College, Visakhapatnam.
2. Only North coastal Andhra Pradesh Districts viz Srikakulam, Vizianagaram, Visakhapatnam were included.

Exclusion criteria:
1. Areas other than Srikakulam, Vizianagaram, Visakhapatnam Districts of Andhra Pradesh.
2. Phenotypic male general.
3. Age group below 13 Years.

III. Results

Among the 58 primary amenorrhea cases 24 Gonadal dysgenesis cases, 17 Mullerian duct anomalies, 3 Testicular feminization syndrome, One PCOS and 4 pure Gonadal dysgenesis cases were noted.
The clinical abnormalities observed were cubitus valgus (14 cases) webbing of neck (6 cases) dental anomalies (2 cases) : mental retardation (2 cases) : digital anomalies (1 cases) : short neck (25 cases) : obesity (3 cases) : shield shaped chest (5 cases), low set ears (3 cases), low hair line (2 cases), squint (2 cases) and the remaining cases (7) were without any apparent malformation.

Table 1: MALFORMATIONS

S.No	MALFORMATIONS	No. of cases	PERCENTAGE
1	Cubitus Valgus	14	24.13
2	Webbing of neck	06	10.34
3	Dental anomalies	02	3.44
4	Mental retardation	02	3.44
5	Digital anomalies	01	1.72
6	Short neck	10	17.24
7	Obesity	03	5.17
8	Sheild shaped chest	05	8.62
9	Low set ears	03	17.24
10	Low hair line	02	3.44
11	No abnormality	07	12.06

Majority of cases of PA have Gonadal Dysgenesis (28 out of 58) 48.27%.Mullerian Duct Anomalies constituted 29.31%(17 out of 58). 5.17 % Cases of Testicular Feminization Syndrome were found in this study. Mosaics constituted 6.89% of cases. Other causes included 03 cases of Delayed Periods due to anemia, Malnutrition, 01 case of Pulmonary Tuberculosis, 1 case of Birth trauma and 01 case of Myxedism. (Table 2).

Table 2 : AETIOLOGY

S.N0	**AETIOLOGY**	**No.of** cases	**PERCENTAGE**
1	Gonadal dysgenesis Tumer's(45xo)	28	48.27%
2.	Mullerian duct anomalies(46xx)	17	29.31%
3.	Testicular feminization syndrome(46xy)	03	05.17%
4.	Mosaic Turner's(45xo/46xx)	04	6.89%
5.	Cases without any above abnormalities or pure primary amenorrhea cases. (46xx)	06	10.34%

Among the secondary sexual characters breast development was the most affected with 22 patients normal breast development.30 patients showed poorly developed breasts,5 cases showed non development and one case showed fibroadenosis. 22 cases showed normal axillary hair,20 cases showed scanty axillary hair and 16 were with absent axillary hair. Pubic hair was normal in 29, scanty in 8 and absent in 21 cases. Demographically stature was normal 149-152cm in 15 cases, tall 159 -167cm in 3 cases ,moderately tall 156-158 in 11 cases, short 140-148cm in 21 cases and very short 121-139cm in 8 cases(table 3).

Table 3-Stature

Category	**Range**	**Number**	**Per cent**
Very short	121-139	08	13.79
Short	140-148	21	36.20
Normal/medium	149-152	15	25.86
Moderately tall	156-158	11	18.96
Tall	159-167	03	5.17

The mean age at marriage was 16.22 years ranging 14-18 years. Only 9 patients were married in this study. Two individuals are said to be consanguineous if they have at least one ancestor in common. Two of the

marriages were consanguineous and the rest were affinal. Of all the 9 married couples 4 demanded medical tests, 3 were separated, one divorced and one was disputed . In the present study (n-58) we observed Hindus -54 .Muslims -02 .Christians -02 With help of pedigree charts we observed that 65.51%cases were products of consanguineous marriage ..Patients with Turner's syndrome who were chromatin negative were considered genetic males. There were 24 cases with 45 XO karyotype.

Laboratory investigations: The initial workup included serum luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone levels. Pelvic ultrasonography (transabdominal or transvaginal) was done for presence of uterus, adnexae, and any reproductive tract anomaly. In cases where USG was inconclusive, MRI was done to visualise Mullerian structures, gonads and renal anomalies. Laparoscopy and hysteroscopy was also done for diagnosis and management as and when indicated. Cytogenetic study for karyotype detection was done in cases of primary gonadal failure and those with symptoms of androgen excess. The causes of primary amenorrhoea are classified into five groups based on the organs involved in the etiology [4]:

Compartment 1: End-organ failure or out-flow tract obstruction
Compartment 2: Gonadal failure
Compartment 3: Pituitary cause
Compartment 4: Hypothalamic cause Other causes.

The patients were classified into 4 groups based upon the organ involved in the etiology of primary amenorrhoea. Hormonal analysis revealed one case of polycystic ovarian syndrome (1.72%). Hormonal analysis of these patients revealed elevated FSH levels in only 4 cases of Gonadal dysgenesis.

IV. Discussion

Rishma Dhillon and Virkud (1991) studied 52 cases of primary amenorrhea. Turner's syndrome and Mayer Rokitansky-Kuster-Hauser syndrome were the commonest aetiological factors in their series similar observation is seen in present study.

5.7% of the patients in their study were found to have Genital Koch's. Failure to obtain withdrawal bleeding after Progesterone plus estrogen challenge test one should suspect genital Koch's. They found 37.5% of patients with Rokitansky-Kuster-Hauser syndrome had renal anomaly, of which, lateral renal agencies was the commonest. They concluded that the commonest cause of primary amenorrhea was chromosomally incompetent ovarian failure and next comes the anatomical defect.

The defects can be compartmentalised as given above and may lie within the uterus, ovaries, pituitary or hypothalamus. Genetic and chromosomal anomalies play a major portion of primary amenorrhoea especially in cases of gonadal failure. The study of primary amenorrhoea should be very meticulous including history, physical examination, hormone evaluation, pelvic imaging (either ultrasound or MRI). Dutta (1987) stressed the diagnostic importance of karyotyping in the evaluation of primary amenorrhea as he found chromosomal aberrations in 30.4% of patients among 23 cases of primary amenorrhea.

Previous studies have been reported from all parts of the world indicating the frequency of various etiologies, cytogenetic abnormalities in cases of primary amenorrhoea. Gonadal dysfunction has been considered as the commonest factor for primary amenorrhoea worldwide followed by pituitary/hypothalamic disorder and outflow tract anomalies. Literature shows 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 have mentioned gonadal dysgenesis as the most common cause of amenorrhoea while a large study from Thailand of 295 cases has shown Mullerian anomaly as the commonest cause in Thai population. In our study, we found gonadal dysgenesis and hypogonadotropic hypogonadism as the most common attributing factor to primary amenorrhoea followed by Mullerian anomalies. The proposed reason for this difference might be the environmental and racial or genetic influence. There are reports from India elaborating the cytogenetic evaluation of these patients and mentioning the contribution of chromosomal abnormalities in primary amenorrhoea.

A large study from Andhra Pradesh in India had earlier reported abnormal karyotype of 21.5% women presenting with primary amenorrhoea . Our findings were similar to the previous study of 48 cases of primary amenorrhoea reported in 1998 from the same centre in India where they have found mullerian anomalies in 54.2% cases followed by hypogonadotropic hypogonadism (22.9%), hypergonadotropic hypogonadism (16.6%) and genital tuberculosis (6.3%). Eren E et al. reported a study elaborating various causes of primary amenorrhoea in 39 cases. They showed chronic diseases, prolactinomas, insulin resistance and mullerian agenesis leading to normogonadotropic hypogonadism as the commonest cause. People have also studied the patterns of chromosomal abnormalities in cases of primary amenorrhoea and gonadal failure. A previous study from Turkey had shown high incidence of chromosomal abnormalities in one-fourth cases (25%) of primary amenorrhoea or premature ovarian failure. It affects all the reproductive organs including uterus, fallopian tubes,

and ovaries leading to amenorrhoea either primary or secondary infertility. It has worst outcome when endometrial lining is affected and it leads to endometrial damage thereby causing primary amenorrhea.

The consanguinity rate in Andhra Pradesh published by various research workers range from 22% - 50% as per study of chakravarthi et al 1971. The highest concentration of inbreeding is seen in the rural and tribal regions in Andhra Pradesh. The present study only includes three north costal districts of Andhra Pradesh.viz ,. Srikakulam, Vizianagaram and Visakhapatnam. Incidence of PCOS as a cause of PA - given by various workers ranged from 1.6% - 4.5%. In present study one case of PCOD was reported (1.72%) .It was compared with three other studies. The mean value of 3 various studies was 3.13 (table 4)

TABLE-*4* :INCIDENCE OF PCOS IN VARIOUS STUDIES

S.No	Reference	Total no.of cases	PCO syndrome	Percentage
1	Pal	62	01	1.60
2	Rajan et al	22	01	4.50
3	Parul shaw	60	02	3.30
4	Present study	58	01	1.72

In the present study serum Triido thyronine (T3), Thyroxine (T4) and thyroid stimulating hormone (TSH) and follicle stimulating hormone (FSH), Luteinizing hormone(LH) and Prolactin(PL) levels have been estimated in 58 primary amenorrhea cases.Only FSH values varied and were found elevated in just 4 cases. The FSH values have been elevated from 55.5 miu/ml to 150.0 miu/ml. It is interesting to note that all these 4 cases have same type of chromosomal abnormality 45X0 ,46XX and their stature ranges from medium to very short. Moreover, all the **4** cases have Gonadal Dysgenesis.

V. Conclusion

Significance of 'X' inactivation is dosage compensation variability of expression and mosaicism. Study of barr bodies in these cases of primary amenorrhea helps us to decide for further course of investigation of the individuals. Barr body study by the way of buccal smear examination is the fastest, cost effective, simple technique of preliminary examination of chromosomal disorders and genetic sex determination. It is highly useful in primary health centers, community health centers, during field medical camps (door to door screening programs) and Area hospital as a preliminary investigation. Individuals and family members can be counseled affirmatively regarding further investigations that have to be done**.**

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