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Cytogenetic, Morphological and Metabolic Abnormalities in Primary Amenorrhea

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OBJECTIVES - To report the clinical observation of cytogenetic and metabolic disorders that are seen in primary amenorrhea.**METHODS** - The study was conducted from January 2001 to September 2002 on 42 adolescents who presented with primary amenorrhea. All of them were subjected to thorough clinical examination, endocrine,cytogenetic and ultrasound assessment and if necessary a laparoscopic evaluation. **RESULTS** - The common age of presentation was between 19 and 20 years. The etiology of primary amenorrhea was Mullerian agenesis in 13 cases (30.9%), pure gonadal dysgenesis in 13 cases (30.9%), Turner's syndrome in five cases (11.9%) and Turner's mosaic in four cases (9.5%).Cytogenetic abnormalities were seen in 24% of cases. History of consanguineous marriage in the parents was present in 85% of cases who presented with pure gonadal dysgenesis. Heredo- familial disorder with diabetes and hypothyroidism was seen in 40 % of cases with Turner's syndrome. Renal abnormalities were seen in two cases with Meyer- Rokitansky-Kuster –Hauser (MRKH) syndrome. **CONCLUSION** - The commonest causes of primary amenorrhea in this study were pure gonadal dysgenesis and MRKH syndrome.

Key words : primary amnorrhea, cytogenetic abnormality, metabolic abnormality, consanguinity

Introduction

Adolescence is a time of emotional unrest, and during this period, failure to develop secondary sexual characteristics and failure to attain menarche cause profound distress to the individual and her parents who face uncertainty regarding the future of their daughter. Team work involving gynecologists, endocrinologists and geneticists is important in arriving at a correct diagnosis, which is imperative to offer various treatment modalities like hormone therapy and corrective surgery for sexual function. Establishing a correct diagnosis also helps in identifying those cases who need gonadectomy. The aim of this study was to evaluate the clinical observations, somatic abnormalities and cytogenetic and metabolic disorders seen in 42 cases who presented with primary amenorrhea.

Material and Methods

This study included 42 adolescents with primary amenorrhea who were admitted for investigations from January 2001 to September 2002. A detailed history was taken with special attention focusing on consanguineous marriage in parents, family history and pedigree analysis. A thorough general and gynecological examination was carried out, including height, span and body mass index (BMI). Various structural and somatic abnormalities were noted. Investigations were carried out for evidence of tuberculosis and endocrine problems. Ultrasound scan, radiological assessment of bone- age and karyotyping were carried out in all the cases. x-ray of the sella and CT scan were carried out in selected individuals.

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Observations and Discussion

During the study period, 41,711 gynecological cases were seen in the out- patient department, of whom 1000 cases were in the adolescent age group and primary amenorrhea constituted 4.2% of all the adolescent problems. Twenty six cases (62%) presented between 19 and 20 years of age, 12 cases (28.5%) between 17 and 18 years of age and four cases (9.5%) between 15 and 16 years of age for investigations. Besides primary amenorrhea, some of these cases also presented with other complaints. A history of stunted growth was seen in eight cases (19%), of which four were Turner's mosaics, three were Turner's syndrome and one was a case of pure gonadal dysgenesis (PGD) due to familial short stature. Absence of secondary sexual development was the main concern in four cases. It has been suggested that uncanalised myometrial tissue or a non-communicating rudimentary uterus with hematometra in Meyer- Rokitansky- Kuster- Hauser (MRKH) syndrome can cause characteristic pain of primary dysmenorrhea[1]. In our analysis, 3 of the 13 cases with MRKH syndrome presented with typical abdominal

pain. Anosmia and voice change were reported by one patient. Though initially it was thought of as a case of Kallmann's syndrome, further investigations revealed an adenoma of the pituitary. One patient presented with puffiness of face and abdominal swelling and investigations revealed chronic liver disease with anemia.

Analysis of the cause of primary amenorrhea showed that Mullerian agenesis with MRKH syndrome was seen in 13 cases (30.9%) and gonadal dysgenesis in 22 cases (52.3%) The cause of gonadal dysgenesis was PGD in 13 cases (30.9%), Turner's syndrome in five cases (11.9%) and Turner mosaic in four cases (9.5%). Testicular feminisation syndrome was seen in one patient. Though the common presentation in polycystic ovarian disease (PCOD)is secondary amenorrhea, pre-pubertal polycystic ovarian disease was the cause of primary amenorrhea in one case. She had normal secondary sexual characteristics with varying degrees of acne and hirsutism. Her BMI was 30 with acanthosis nigricans, mullerian and ovarian development were normal and ultrasound showed evidence of PCOD and endocrine assessment showed elevated LH levels. Constitutional delay was diagnosed in three cases, and in two of them there was family history of delayed menarche in the mother and in the sibling. Two girls were aged 16 years and as all investigations were within normal limits they were reassured and advised to await spontaneous menarche. The third girl who was 18 years old attained menarche during the process of investigation. There were no cases of genital tract tuberculosis or outflow tract obstruction in our study. (Table I)

Pedigree analysis and history of consanguineous marriage in the parents were studied in all the 42 cases. Though intra- uterine infection and childhood mumps are rarer causes of PGD, autosomal recessive mode of inheritance is seen in most of the cases[2].

History of consanguinity in the parents, mostly 2nd degree or 3rd degree consanguinity was seen in 11 out of the 13 cases of PGD (85%). The etiology of MRKH syndrome is multifactorial. One of the possible causes is sporadic gene mutation which is transmitted by an autosomal dominant gene by the male relatives[1]. In our analysis history of consanguinity was elicited in 7 of the 13 cases (53.8%) with MRKH syndrome. In one case with testicular feminization syndrome there was a history of 3rd degree consanguinity. (Table II).

In 10 out of the 42 cases (24%), karyotyping showed cytogenetic abnormalities, Turner's syndrome with 45X was seen in five cases, Turner mosaic with 45X/46XX was seen in four cases, and testicular feminization with 46 XY was seen in one case. All the 13 cases with PGD showed 46 XX chromosomal pattern. (Table III).

All the cases with either 45X or 45X/46XX were short statured, height varying from 125 cms to 139 cms. Dysmorphic features such as webbing of the neck, low set ears, widely placed eyes and high arched palate were seen in four cases with Turner syndrome and one of them showed clemodactly of the little finger and sandal cleft of foot. Unilateral pelvic kidney was seen in two cases of MRKH syndrome, and cardiac anomaly with VSD was seen in one case with MRKH syndrome. In a study of 52 cases 37.5% of the patients with MRKH syndrome had renal anomaly of which lateral renal agenesis was the commonest[3].

Table I : Primary Amenorrhea: Causes and Consanguinity

Condition	Number	Percentage	Consanguinity		Non-Consanguinity	
			Number	Percentage	Number	Percentage
Pure gonadal dysgenesis	13	30.9	11	84.6	2	15.4
MRKH	13	30.9	7	53.8	6	46.2
Turner's syndrome	5	11.9	3	60	2	40
Turner's mosaic	4	9.5	2	50	2	50
Testicular feminisation syndrome	1	2.4	1	100	–	–
Others	6	14.4	1	16.6	5	83.4
Total	42	100	25	50.6	17	40.4

Table II : Cytogenetic Abnormality in Primary Amenorrhea

Condition	Karyotyping	No.	%
Turner's syndrome	45X	5	11.9
Turner's mosaic	45X/46XX	4	9.5
Testicular feminisation syndrome	46XY	1	2.4

In 24% of cases (10/42) abnormal karyotyping was seen.

Studies have shown that auto- immune thyroiditis with or without hypothyroidism and other metabolic disorders such as diabetes are seen more often in patients with Turner syndrome and also in parents of these patients (heredo- familial disorder).The possible mechanisms that are postulated are - a) the presence of autoantibody directly affecting the development of germ cells and b) some fault in the genetic stability which could lead both to the occurrence of autoantibody and to the existence of abnormal gamete[2]. In our analysis, out of the five cases with Turner syndrome two (40%) were suffering from both diabetes and hypothyroidism. On pedigree analysis, in one of them there was history of diabetes in the mother, in two in maternal uncles, in one in the maternal aunt, in the grandmother and in the great grand mother.

Absence of menstruation in a teen-ager is an extremely stressful problem and should be handled with care and sensitivity. Counseling and psychological support are paramount in the management of these cases. Family history plays a major role in identifying autosomal inheritance .Careful pedigree analysis will give a clue to the underlying heredo-familial disorder in the affected individual as well as their family members. HRT forms an essential part of treatment in cases presenting with hypogonadism. It is imperative to make a cytogenetic diagnosis as in cases with XY chromosomes removal of the gonad is mandatory to prevent the occurrence of malignant tumors.

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