A PROSPECTIVE STUDY OF ETIOLOGY OF PRIMARY AMENORRHEA WITH ESPECIAL EVALUATION FOR NON CLASSIC CONGENITAL ADRENAL HYPERPLASIA DUE TO 21 HYDROXYLASE DEFICIENCY

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Abstract- ***Amenorrhea, an absence of menses is a symptom that generally brings teenagers for evaluation. This study was undertaken to determine the etiology of primary amenorrhea with especial concern to non classic congenital adrenal hyperplasia (NC-CAH)- due 21 hydroxylase deficiency among female adolescents refered to clinics of Pediatric Endocrinology of Tehran and Iran University of Medical Sciences and private office. One hundred and five female adolescents were studied . All patients were examined by pediatric endocrinologist. Routine lab tests, FSH, LH, Prolactin, T4, TSH, 17-hydroxyprogesterone and in some cases ACTH Stimulation Test for screening of NC-CAH due to 21 OH deficiency were performed. Chromosomal analysis, sonography of the ovaries and CT scan or MRI of the brain was performed in some of them. Forty three patients (41%) had hypergonadotropic hypogonadism and sixty two patients (59%) had hypogonadotropic hypogonadism. Turner's syndrome and constitutional delay of puberty were the most common causes of primary amenorrhea in our study. The frequency of primary amenorrhea due to 21-OH deficient NC-CAH was 6.6% in overall (105 cases).***

This study shows that in a population with high incidence of consanguineous marriages, some rare genetic disorders such as 21 OH deficient NC-CAH are relatively common.

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Key Words: ***Primary amenorrhea, hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, non classic congenital adrenal hyperplasia (NC-CAH).***

INTRODUCTION

Amenorrhea is defined as the absence or cessation of menstrual bleeding. Most investigators agree that failure of menarche by age 16, regardless of the presence or absence of secondary sexual characteristics or absence of menstruation in a woman with previous periodic menses or lack of menstruation by age 14 years in the absence of breast devlopment merits evaluation (1,2). Amenorrhea is traditionaly categorized as either primary (no history of menstruation) or secondary (cessation of menses after a variable time). Normal menstrual cycles requires normal function of the hypothalamus, pituitary, ovaries and out flow tract. Failure of menses can be due to a problem at any of these levels (2,3). Individuals with poorly controlled or undiagnosed 21-OH deficient form of congenital adrenal hyperplasia (CAH) may suffer from either delayed puberty (due to suppression of gonadotropins by adrenal androgens) or true precocious puberty (consequent upon premature activation of gonadal axis secondary to rapid maturation), the latter typically predominates. Although certain classical forms of CAH may not be diagnosed until later life, non classical varients produce symptoms in later childhood or beyond (1-3). It must be considered that symptoms and findings in patients with non-classic 21-OH deficient congenital adrenal hyperplasia (NC-21OHD CAH) may be similar to those in women with polycystic ovary syndrome (PCOS). (1,2). It must be noticed that in NC-21OHD CAH there are low levels of gonadotropins before begining of puberty and high levels of gonadotropins after starting of puberty. Spaiser and coworker estimated that NC-21OHD CAH is the most common recessive disorder in humans. The frequency being 1% in all ethnic groups. (2-5). We have conducted this study in order to determine the etiology of primary amenorrhea with especial concern to NC-CAH due to 21 hydroxylase deficiency in 105 female patients with primary amenorrhea.

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MATERIALS AND METHODS

In a prospective and observational study from September 1995 to September 2001, 105 female

patients with primary amenorrhea have been seen in pediatric endocrine clinic and private office. The patients' ages ranged from 13 to 19 years with the majority between 14-16 years of age. A careful complete history and physical examination were taken. The height, weight, blood pressure were measured and all patients were examined for hirsutism and other signs of virilization. The extent of breast, axillary hair and pubic hair development were determined by an endocrinologist. The thyroid gland and breasts were examined for goiter and galactorrhea. When history and physical examination were completed and systemic chronic disease were excluded, baseline FSH, LH and estradiol were measured in all patients to determine whether the patient had hypogonadotropic (FSH ↓ , LH ↓) or hypergonadotropic hypogonadisem (FSH ↑ , LH ↑). In hypergonadotropic patients with short stature with or without other stigmata of Turner's syndrome, chromosomal analysis was performed. Seventeen hydroxyprogesterone (17 OHP) was measured in the morning and in patients especially with evidences of androgen excess (hirsutism, acne ....). 17 OHP levels was greater than or equal to 200 ng/dl (6 nmol/l). ACTH stimulation test was performed and baseline 17 OHP and cortisol and stimulated 17 OHP and cortisol after 30 minutes 250 microgram short acting ACTH (Cosyntropin) IV bolus injection were measured for screening of 21-OH deficient NC-CAH. In hypogonadotropic patients with or without galactorrhea and goiter, prolactin, T4 and TSH assays were performed. The uterus and ovaries were visualized in 73 patients and in 26 patients with hypogonadotropic hypogonadism and unknown etiology, CT Scan or MRI of the brain was performed.

RESULTS

Among 105 female patients who were studied, 43 cases (41%) had hypergonadotropic and 62 cases (59%) had hypogonadotropic hypogonadism. In hypergonadotropic patients Turner's syndrome was the most common cause (53.5%) and other causes in decreasing frequency were: Late onset congenital adrenal hyperplasia due to 21 hydroxylase deficiency (16/3%), polycystic ovary syndrome (11.6%), idiopathic ovarian failure (9.4%), testicular feminization syndrome (4.6%), 17 hydroxylase deficiency (2.3%) and mixed gonadal dysgenesis (2.3%) (Table 1). In hypogonadotropic patients constitutional delay of growth and puberty was the most common cause (22.6%) and other etiologies in decreasing frequency were: isolated gonadotropin deficiency (17.7%), hypopituitarism (12.9%), major thalassemia (11.3%), hypothyroidism (9.7%), diabetes mellitus (6.5%), hyperprolactinemia (4.8%), rheumatoid arthritis (4.8%), kallmann's syndrome (3.2%). chronic renal failure (3.2%). and inflammatory bowel disease (3.2%) (Table 2).

Table 1. Etiologies of hypergonadotropic hypogonadism in 43 female patients

Etiology	No	Percent (%)
Turner's syndrome	23	53.5
NC-CAH (210H)	7	16.3
PCO(1)	5	11.6
Idiopathic	4	9.4
T.F. S(2)	2	4.6
17OH deficiency	1	2.3
M.G.D(3)	1	2.3
Total	43	100

(1) Polycystic ovary syndrome
(2) Testicular Feminization Syndrome
(3) Mixed Gonadal Dysgenesis

Table 2. Etiologies of hypogonadotropic hypogonadism in 62 female patients

Etiology	No	Percent (%)
Constitutional	14	22.6
Idiopathic gonadotropin deficiency	11	17.7
Kallmann's syndrome	2	3.2
Hypopituitarism	8	12.9
Hypothyroidism	6	9.7
Hyperprolactinemia	3	4.8
Chronic systemic disease	18	29
Total	62	100

The most frequent stage of breast development in our patients was stage 2 and other stages in decreasing of frequency were: stage 3 (33.3%), stage 4 (11.4%), stage 1 (9.5%) and stage 5(4.8%) (Table 3).

Table 3. Stages of breast development in 105 female patients with primary amenorrhea

Stage	No	Precent
1	10	9.5
2	43	41
3	35	33.3
4	12	11.4
5	5	4.8
Total	105	100

DISCUSSION

Primary amenorrhea refers to a lack of menstruation by age 16 years in the presence of breast development or by age 14 years in the absence of breast development (1-5).

Turner's syndrome is the most common cause of primary ovarian failure (Hypergonadotropic hypogonadism) and constitutional delay of puberty is the most common cause of secondary ovarian failure (Hypogonadotropic hypogonadism) (1-4). Spaiser and co-workers (2,4) estimated that incidence of NC-21OHD CAH in patients with primary amenorrhea is 1-5%, (The frequency is higher in Ashkenazi Jews, Hispanics and Yugoslavs). These patients most often have a reduction in P450 21 (21 hydroxylase activity). This defect in cortisol synthesis leads to an increase in ACTH and 17-hydroxyprogesterone (17 OHP) production. The latter is the basis for diagnosis. Levels of 170HP below 300 ng/dl are normal and levels of more than 800 ng/dl are considered to be diagnostic. When levels fall between these values, ACTH test is required to make the diagnosis (4,6). We have conducted this study in order to determine the etiologies of primary amenorrhea with special concern to NC-21OHD CAH in 105 females with primary amenorrhea. Age of puberty in Iran is similar to other countries according to investigation which had been performed on natural age of puberty in Tehran, Hamedan, Mashhad by our cooperators (10). Therefore we can use same universal definitions for diagnosis of precocious or delay puberty and so primary amenorrhea. Age of our patients was between 13-19 years and mean referal age was 14.2 years. In our study and other study that was performed (10) in Mashhad university by Dr. Vakily et al the most common cause was Turner's syndrome and constitutional delay of puberty that is compatible with international references (1-5). In this study the most cammon cause of primary amenorrhea in 105 patients was Turner's syndrome (21.9%) which displays requirement for further investigation and national supports for these patients in our country. The incidence of 21-OH deficient NC-CAH in our study was 16.3% in hypergonadotropic patients and in 105 patients was 6.6%. In another study that was peformed on etiologies of hirsutism by Moayeri et al , the frequency of 21-OH deficient NC-CAH was 5.4% (11). Spaiser and co-workers (2,4) estimated that the incidence of NC-21NHD CAH in patients with primary amenorrhea is 1-5% (the frequency is higher in Ashkenazi Jews, Hispanics and Yagoslavs). In conclusion, it seems that the incidence of this enzymatic defect may be higher in Iran, perhaps because of the high incidence of consanguineous marriages in Iran. Therefore, we recommend to think about the non classic form of CAH (late onset) especially 21-OH deficient type in female adolescents with primary amenorrhea especially when accompanied with hirsutism, acne and short stature that can be confirmed with ACTH stimulation test. We do not recommend the routine use of this test in all patients, rather this test should be performed only when the morning 17 OHP level is greater than or equal to 200 ng/dI (6 nmol, l).

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