PUBERTY DISORDERS IN GIRLS

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Abstract:
Introduction: During puberty, menarche represents the most important event in females. Amenorrhea is defined as the absence of menstruation during puberty. Aim: To evaluate the adolescents with amenorrhea and to analyzed the management of these patients. Material and method: We analyzed 216 patients admitted to the Endocrinology Department over a period of five years, from 2007 to 2012. The study protocol was complex and it consisted in the patients’ history, physical examination and anthropometric measurements. Laboratory evaluation included the measurements of LH, FSH, estradiol, testosterone, DHEA, 17 OH progesterone, TSH, prolactin. Karyotypes, imagistic studies, gynecological and psychological consult were performed in selected cases. Results: Out of 216 adolescents studied with a mean age of 13.8 ± 0.8 years old, 74% of girls were diagnosed with secondary amenorrhea, while the rest had primary amenorrhea. Regarding the etiology of the secondary amenorrhea, 156 patients had secondary amenorrhea caused by stress and 4 cases had mental anorexia. The majority cases of primary amenorrhea were secondary to polycystic ovaries syndrome (60.71%), late form of 21 hydroxylase deficit (7.41%) or Turner syndrome (25%). Therapeutic strategy for patients with secondary amenorrhea consisted in psychotherapy and sedative medication while the treatment of the patients with primary amenorrhea depended of form and etiology. Conclusions and discussions: Amenorrhea can hide behind a symptom complex pathology. A complex evaluation of the patients with irregular menstruation is required. Treatment should be as early as possible.
Key words: puberty, adolescents, amenorrhea

Introduction:
Puberty is a stage of life characterized by hormonal changes and physical and psychological modifications leading children from childhood to adolescence. During this period, menarche represents the most important event in females. Age of menarche is different among populations and it is useful marker of socio-economic status, as well as dietary and environmental patterns. Generally, the first menstrual cycle takes place between 12 and 13 years of age, with 98% of girls having menarche by 15 years of age. The normal range for menstrual cycles is between 21 and 45 days, with flow length varying from 2 to 7 days. During the first 2 years after menarche, menses length is often abnormal due to immaturity of the hypothalamic-pituitary-ovarian axis.

Amenorrhea is defined as the absence of menstruation during puberty. It can be presented in girls with their age over 14 years without the development of the sexual characters or in teenagers over 16 years with normal development of secondary sexual characters presented. Amenorrhea may be primary or secondary. The primary amenorrhea is characterized by the absence of installation cycle.

For the diagnosis of the amenorrhea is important two etiological coordinates: the presence of secondary sexual characteristics and the serum follicle stimulating hormone (FSH). Based on these criteria we have the following cases:

A. Primary amenorrhea with normal pubic development and normal or low FSH level

It implies the presence of anatomical abnormalities such as labial agglutination, hymen aplasia, and agenesis of the uterus (Rokitansky syndrome). Also it was described adolescents with female phenotype but with 46XY genotype presents without menses secondary to Müllerian agenesis.

B. Primary amenorrhea with delayed development of sexual characteristics and increased FSH

This form can be congenital or acquired. Short stature associated with a particular phenotype with widely spaced nipples, the presence of pectus deformities and the 4th metacarpal shorter Turner syndrome may be suspected and the karyotype is required to be performed. Hypogonadism hypergonadotopic can be associated with Albright syndrome or a deficiency of 17 α hydroxilase. Autoimmune oophoritis, tumors, radiation to the pelvis are other causes of acquired ovarian failure.

C. Primary amenorrhea, delayed secondary sexual characters and decreased levels of FSH

These characteristics are described in Kallman syndrome (congenital absence of GnRH and anosmia) or Prader - Willi syndrome (obesity, hypogonadism, delayed puberty, small hands, round eyes, mental retardation), Laurence - Moon - Bardet - Biedl (mental retardation, retinitis pigmentosa).

D. Primary amenorrhea virilizing

It is caused by the deficit of the 21 - hydroxylase due to excess of adrenal androgen overstimulation induced by ACTH, cortisol deficiency.

Secondary amenorrhea is defined as no menstrual cycles for a period of four-six months that occurs after the first year of the onset of menarche. It may be due to polycystic ovaries, gonadal dysgenesis, anorexia - nervosa, stress, brain or adrenal tumors, late form of 21 hydroxylase deficit, hyperprolactinemia (functional or tumor) or due to pregnancy. Incidentally, it is also present in patients with X/ autosomal translocations.

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Figure 1: Five cases with Turner Syndrome from our study

Figure 2: B.R. and B.B - Late onset Form of 21 Hydroxilase deficiency
Materials and methods:
We analyzed 216 patients admitted to the Endocrinology Department of “Louis Turcanu” Children Emergency Department with abnormalities of the menstrual cycle. This study took place over a period of five years, from 2007 to 2012.

The study protocol was complex.
It consisted in the patients’ and their family history, their physical examination and anthropometric measurements (height, height standard deviation score, weight, body mass index, growth velocity). Also it was noted the stage of pubertal development according to the Tanner criteria, signs of androgen excess (acne, hirsutism, deepening of the voice), signs or symptoms of systemic diseases or endocrine disorders (goiter, central obesity, purplish skin striae, muscle weakness), and stigmata of genetic anomalies (short stature, misshapen ears, broad chest, widely spaced nipples, cubitus valgus). Hirsutism was quantified using Ferrimann - Galaway scale. Blood pressure should be measured in order to quantify hypertension.

Laboratory evaluation of amenorrheic adolescents included the measurements of LH, FSH, estradiol, testosteron, DHEA, 17 OH progesterone, TSH, prolactin. Also fasting insulin and glucose, insulin and HOMA index, adrenocorticotropic hormone, cortisol were performed. Because pregnancy represents the most frequent cause of secondary amenorrhea, pregnancy test was done in all cases.

Karyotypes were generated from the peripheral blood lymphocyte cultures and the cytogenetic analysis was performed. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Chromosomal analyses were performed by G-banding using trypsin and Giemsa at approximately 400 – 450 band level. Further nucleolar organizing regions staining and C-banding and heterochromatic region.
Gynecological consult performed a careful examination of the external genitalia to assess clitoris, hymen permeability and vaginal and uterine development.
Psychological consult were performed in selected cases.
Pelvic transabdominal ultrasonography scanning measured the length of uterus and ovaries and endometrial thickness while magnetic resonance imaging of the hypothalamus and pituitary gland, and magnetic resonance imaging of the pelvis played an important role in the evaluation of an adolescent with irregular menses. Osteodensitometry was performed for obtaining information about the structure of the bone.
Written consents were taken from all the patients of their parents or legal tutor.

Results and Discussion

The mean age of patients analyzed was 13.8 ± 0.8 years old. 77% of them were from rural areas.
Out of 216 adolescents studied, 74.04% (160 cases) of girls were diagnosed with secondary amenorrhea, while the rest had primary amenorrhea.
56 adolescences had primary amenorrhea. The cases secondary to polycystic ovaries syndrome, Turner syndrome (Figure 1) or late onset form of 21 hydroxylase deficit (Figure 2) are shown in Figure 3.
The distribution of ethnologic of primary amenorrhea show a high incidence of PCOS and Turner syndrome and the low incidence of other cases like Rokytskyne syndrome, 46XY DSD and Prader Willi syndrome.

Other causes of primary amenorrhea were 46XY DSD (Figure 4). In these cases we have severe emotional problem in the girls and their family.
Regarding the etiology of the secondary amenorrhea, 156 patients had secondary amenorrhea caused by stress and psychological problems and 4 cases had mental anorexia.

In all cases, patients showed osteoporosis or osteopenia.

Therapeutic strategy for patients with secondary amenorrhea consisted in psychotherapy and sedative medication.
The treatment of the patients with primary amenorrhea depended of form and etiology.

Patients with Turner syndrome received Etrimil Estradiol orally, 10μg/day, continuously for 1 year. After this period, estrogen administration was discontinuous from day 1 to 21, then Medroxyprogesterone 5 mg/day from day 15 to 21 was prescribed, while no hormone was given from day 21 until day 28. The patients with polycystic ovaries syndrome received first treatment with progesterone and after that with an estrogen and progesterone mixed (Yos, Yasmine, Diane). Late form of 21 hydroxylase deficiency received hydrocortisone replacement therapy. In depress girls specific was administrated.

Under etiological treatment, the menstrual cycle occurred in almost all patients, except those with anatomical defects and 8 patients with Turner syndrome.

Patients diagnosed with Rokitanski syndrome and 46XY patients received psychotherapy.

According to WHO, amenorrhea stands as sixth largest major cause of female infertility. Genetic factors like single gene disorders, chromosomal or multifactorial disorders are contribute to the constitutional etiology of amenorrhea. Cytogenetic investigations have underlined the importance of chromosomal abnormalities as a major cause of amenorrhea. In the medical literature it is described that the percentage of chromosomal abnormalities varies from 15.9% to 63.3 % in the primary amenorrhea and 3.8% to 44.4 % in secondary amenorrhea.

In many studies reviewed, the most frequent chromosomal anomaly in amenorrhea patients is Turner syndrome (45, XO) followed by a male karyotype. In this study the prevalence of Turner syndrome (25%) was higher, followed by male karyotype 46 XY DSD (3.57%).
The major cause of the primary amenorrhea in our study was polycystic ovarian syndrome (60.71%). It is an interesting fact that many investigators have suggested that this syndrome may be genetically determined. Some reports
have also shown chromosome alterations in a few patients with POS, secondary to X chromosome deletions or translocations. Detection of such chromosomal abnormalities at an early stage helps in surgery, counseling, and if mosaic to state the reproductive stages and premenopausal details. The karyotype aids in the confirmation of the diagnosis, a better phenotype-genotype correlation for a better understand of the clinical form heterogeneity, and in genetic counseling. Genetic counseling should include the risk of gonadal malignancy for patients with 46 XY DSD gonadal dysgenesis, the risk of premature menopause for patients with TS and the use of hormonal replacement therapy.

Conclusions:
1. Amenorrhea can hide behind a symptom complex pathology.
2. A complex evaluation of the patients with irregular menstruation is required.
3. Treatment should be as early as possible.

References:

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