PRECOCIOUS PUBERTY AMONG GIRLS IN SULAIMANI: CAUSES AND ANTHROPOMETRIC FEATURES

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ABSTRACT

Background

Girls who reach puberty early can fail to reach their expected final height. In addition, they are prone to negative psychological behavior and there is an association with the future development of other negative health outcomes such as diabetes and heart disease.

Objectives

To determine the causes of precocious puberty in female patients and address some anthropometric features of the studied patients.

Patients and Methods

Data of 63 female patients who presented with signs and symptoms of puberty before the age of 8 years between the years 2012 and 2018 were collected and analyzed to find the percentages of certain etiologies and features and compare them to similar studies conducted in other countries.

Results

Central idiopathic precocious puberty (CIPP) was the main diagnosis of the cases and other causes also were identified. Causes from the most prevalent to the least prevalent include premature adrenarche, premature thelarche, functional ovarian cysts, and brain tumors. The study also showed a significant relationship between the body weight represented by Body Mass Index (BMI) at the time of presentation and the incidence of central idiopathic PP. Moreover, patients with premature adrenarche also had significantly higher BMI than their peers with normal puberty timing. In addition, the mean height at the time of diagnosis of the PP patients, in general, was significantly higher than their peers with a normal onset of puberty. Furthermore, the heights of the patients with CIPP is significantly negatively correlated with the age at which symptoms of puberty appeared. Finally, the bone ages of girls with PP with the different etiologies were significantly higher than the chronological age.

Conclusion

Precocious puberty in girls is an important condition in Sulaimani and it has different etiologies. Central idiopathic precocious puberty is the most common etiology. Girls with PP tend to be significantly taller at the time of the diagnosis, have heavier weights and have more advanced bone ages than the normal population.

Keywords: *Precocious puberty, Premature thelarche, Premature adrenarche, Bone age.*

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INTRODUCTION

While recent secular trends try to define Precocious puberty for females as the appearance of sexual characteristics at an earlier age, this research depends upon the classical definition by Marshal and Tanner as the start of secondary sexual characteristics such as the development of breasts (thelarche) or the pubic and axillary hair (adrenarche) before the age of 8 years in white girls and 6.5 years in black girls [1, 2] or at an age of less than 2 to 2.5 standard deviations from the general population [3, 4], or the onset of menstruation before the age of 10.5 [5].

PP in females can be classified into [6, 7]:

- Central PP (gonadotropin dependant PP) or True PP which can be: Idiopathic 90%, Organic brain lesions like hypothalamic hamartoma, brain tumors, hydrocephalus, severe head trauma, and myelomeningocele, and Hypothyroidism if prolonged and untreated.

- Peripheral PP (gonadotropin-independent) or precocious pseudopuberty:

Isosexual (feminizing): examples: McCune Albright syndrome, Autonomous ovarian cyst, ovarian tumors, Granulosa-theca cell tumor associated with Ollier disease, Teratoma, chorionepithelioma, exogenous estrogens.

Heterosexual (masculinizing): examples: Congenital adrenal hyperplasia, Adrenal tumors, ovarian tumor, and exogenous androgens defects.

Incomplete (partial) precocious puberty, premature thelarche, premature adrenarche, and premature menarche

Some risk factors early puberty in girls, Genetic factors [8], Mother's menarche age [9], Ethnicity [1, 2, 10], Parental income [9], Increased BMI [11, 12], Diet and behavior [9], Heavy study burden [9], Small for gestational age [11], Child adoption [11], Chemical exposure [12].

Diagnosis of PP

Patients' history

Usually the patients' chief complaint is breast enlargement [1, 6, 7] or appearance of pubic hair or axillary hair before the age of 8 years. Menses can be the first alarming symptoms in some patients [6, 7]. However, many patients visit a doctor for other complaints such as obesity, short stature, pelvic or abdominal pain, acne, facial hair, headache, visual disturbance or a regular doctor's visit.

Physical examination

Careful thorough examination of the patient is mandatory as well as determining the Tanner [7, 13] stage for breast, pubic hair and axillary hair development, as well as any other hinting features.

Investigations and radiology

- Xray of the non-dominant hand to determine the bone age [6, 14, 15]

-Hormonal level: FSH, LH, Estradiol, testosterone, DHADS, progesterone,17-hydroxyprogesterone, prolactin, insulin-like growth factor, alpha-fetoprotein, and Thyroid function test [15]

- GnRH stimulation test [15]

- Ultrasound of the pelvis and abdomen [15]

- MRI of the brain [6, 15]

- GnRH stimulation test [6, 7]:

This is the gold standard test for diagnosing Central precocious puberty. It is performed by administration of GnRH analog such as Leuprolide and measuring the levels of FSH and LH before and after GnRH administration in certain time intervals. Usually, this test is diagnostic of Central Precocious Puberty if LH increase is more than FSH increase as well as this increase of LH is more than a certain laboratory level.

PATIENTS AND METHODS

Data from 63 girls, with the mean age of (7.3±2.3 SD) years (minimum 10 months and maximum 11 years), who presented with signs and symptoms of puberty (breast development or pubic/axillary hair) before the age of 8 years or menarche before the age of 10 and a half, were retrospectively reviewed. Written consent was obtained from the patients' families. The patients visited the endocrinology clinic in Shar Hospital in Sulaimani city. Some were seen in a private clinic by the same physicians who work in the mentioned hospital. The diagnoses were established for all of them based on clinical presentation, bone age estimation, investigations including hormonal essays such as GnRH stimulation test, and imaging including ultrasonography of the pelvis and brain MRI. The type of hormonal assay is chemiluminescent immunoassay. The device that was used in hormonal assays Liaison

XL 2015. These studies were performed at the patient's first visit and throughout the follow-up period. Tanner stage was recorded for every visit and the stage at which the patients had their first visit was entered in the database. The height and weight of the patients' first visits were recorded and plotted on percentile charts. The data were entered in the Program IBM SPSS 20 and were analyzed. Different statistical tests were done such as frequencies calculations as well as one sampled T-tests and bivariate statistical correlation studies. Moreover, charts and tables were obtained from the mentioned program and were placed throughout the text of the results section.

RESULTS

The mean age of the 63 female participants at the time of interview was 7.3 years (SD 2.3 years), ranging from 10 months to 11 years. They had their first symptoms at a mean age of 6.1 years (SD 2 years) (range from 9 months to 9.7 years) (Figure 2). Thirty-eight girls (64.4%) had breast enlargement, while 19 patients (32.2%) had axillary/pubic hair development, and only 2 patients (3.4%) had menses as their first symptoms (Figure 1).

Gonadotropin-dependent central precocious puberty made up the majority of the diagnoses in the study with 63.9% (40 cases). Sixty percent (38 cases) were idiopathic while central PP due to brain tumor made up only 3.2% (2 cases). Gonadotropin-independent PP made up 4.8% (3 cases) of the total population, all of which were due to the functional ovarian cyst(s). Premature thelarche comprised 13.3% (9 cases) of the population, while premature adrenarche represented 17.3% (11 cases) of the population. (Table1)

Regarding anthropometric features of the studied patients in general (Table 2), 46% (27cases) were normal, 17% (10 cases) were overweight and 36% (21 cases) were obese (figure3). In addition, the percentile means of weight, height, and BMI at the time of diagnosis were 72.6 percentile, 66.4 percentile and 70.9 percentile (Z score 0.9) respectively with a significant difference from the Centers for Disease Control and Prevention (CDC) means with P value less than 0.05 for all the mentioned variables. In addition, the bone age advancement mean of the population sample was 1.64 years with a standard deviation of 1.2 years (figure 4). Furthermore, the mean of the menarche age of the mothers of the studied patients was 13 years (SD 1.5 years) (Table 2).

Concerning central PP, central idiopathic PP was the most common diagnosis of all other etiologies. The mean BMI percentile (at the time of diagnosis) was 71.4 percentile (SD 31.4). One sample T-test was performed and it revealed a significant difference from the general population mean (50 percentile) with a P value <0.05. Therefore, there is a significant relationship between increased body weight and the incidence of idiopathic central PP. Similar tests were performed on the height percentiles of the studied cases (both at the time of diagnosis) and they revealed significant relationships between central idiopathic PP and increased height at the time of diagnosis, with P values < 0.05, and percentile means of 70.47 percentile. Consequently, a bivariate correlation statistical study was performed on height percentiles of the patients and the age at which the first pubertal symptoms emerged, and it revealed a negative correlation (Pearson correlation - 0.437) with a P value of 0.02 (<0.05). Thus, the taller the patients with central idiopathic PP are, the earlier the age at which they start their pubertal symptoms. Nevertheless, similar bivariate correlation statistical studies revealed no significant correlation between the age of start of pubertal symptoms with either weight or BMI. Finally, the mean bone age advancement in cases with central idiopathic PP was 2 years (SD 1.3 years). In addition to CIPP, Central Neurogenic PP (CNPP) was represented by 2 cases (3.2%), one of the girls had a hypothalamic hamartoma while the other one had a pituitary tumor.

Gonadotropin-Independent PP or Peripheral PP was represented by 3 cases of functional ovarian cyst(s) (4.8%). The mean height, BMI, and bone age advancement was 59.3 percentile, 38 percentile and 6 months respectively. One sample T-tests were run and these means were not significantly different from the general population means of the CDC with P values more than 0.05 for all of the given values.

In regards to pubertal variants, premature adrenarche was the second most common diagnosis after central idiopathic PP with 11 cases (17%). The mean BMI percentile for those patients was 82.2 with a significant difference from the CDC BMI mean of 50. The mean height percentile of these girls was 60.6 with an insignificant difference from the CDC mean of 50, P value=0.06. Moreover, the mean of the bone age advancement from the chronological age (BA-CA) for girls with premature adrenarche was 1.3 years with a P value less than 0.05.

Premature thelarche was the third most common etiology in general with 9 cases (13.3%) the mean BMI percentile of this group was 37.6 with an insignificant difference from CDC mean of 50 percentile, with P value more than 0.05. Additionally, the mean height percentile of this group was 44.6 with also an insignificant difference from the CDC mean of 50 percentile. Finally, the bone age advancement in girls with premature thelarche was 7 months with a P value less than 0.05.

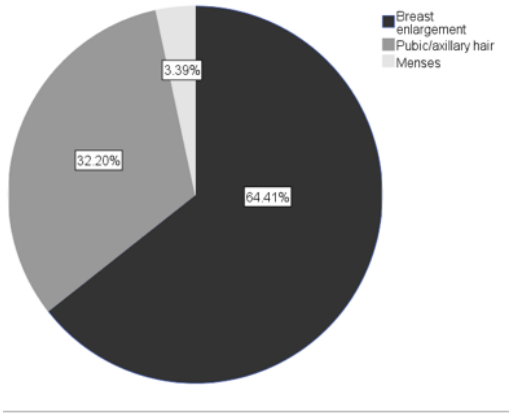

Figure 1. Presenting symptoms of precocious puberty

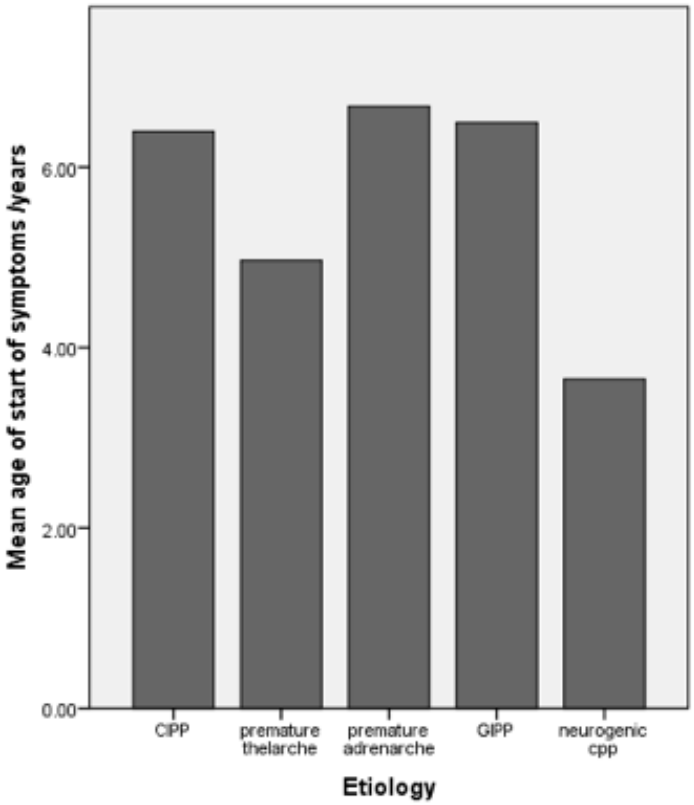

Figure 2. The Mean Age of Start of the Symptoms According to the Etiology of PP

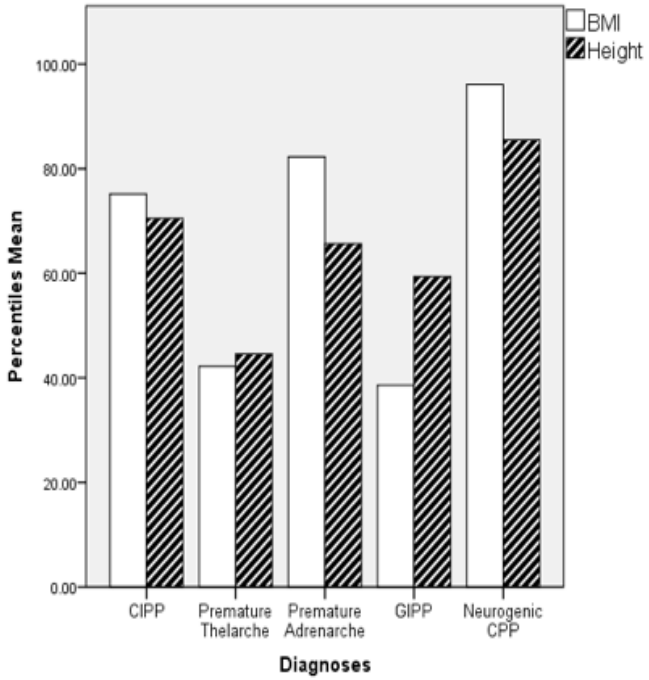

Figure 3. Height and Body Mass Index percentile Means According to the Etiology of CIPP, CPP, GIPP

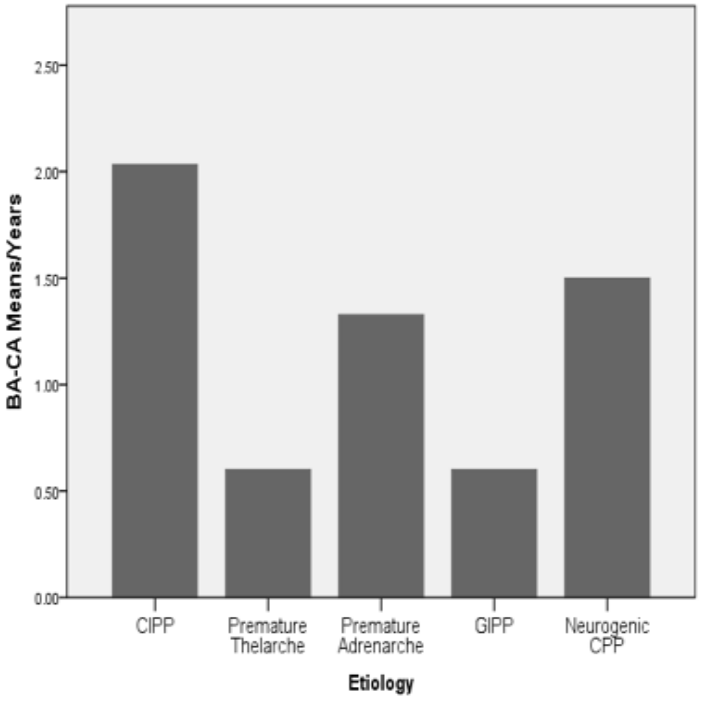

Figure 4. Bone Age Advancement According to the Etiology

Table 1. Etiologies of Precocious Puberty

Diagnosis Category	Diagnosis	Frequency	Percent
Central Precocious Puberty (Gonadotropine dependent PP)	Central idiopathic	38	60.3%
	(Central Neurogenic PP) hypothalamic hamartoma	1	1.6%
	(Central Neurogenic PP) pitutary tumor	1	1.6%
Peripheral-PP (Gonadotropine Independent PP)	Ovarian cyst	3	4.8%
Puberty Variants	Premature thelarche	9	14.3%
	Premature adrenarche	11	17.5%
Total		63	100%

Table 2. Anthropometric features of Precocious Puberty Patients According to the Diagnosis

Diagnoses		Height percentile	Weight percentile	BMI percentile	BMI Z-scores	Bone Age advancement/ years (BA-CA)
central idiopathic	**Mean**	70.5	78.8	75.2	1.2	2
	N	36	36	36	36	32
premature thelarche	**Mean**	44.6	35.6	42.2	- 0.2	0.6
	N	7	7	7	7	7
premature adrenarche	**Mean**	65.6	82.5	82.3	1.2	1.3
	N	11	11	11	11	9
ovarian cyst	**Mean**	59.3	34.3	38.6	- 0.9	0.6
	N	3	3	3	3	2
Central Neurogenic PP: hypothalamic hamartoma	**Mean**	96	98	97	2	1.1
	N	1	1	1	1	1
Central Neurogenic PP:pitutary tumor	**Mean**	75	95	95	1.7	1.9
	N	1	1	1	1	1
Total	**Mean**	66.4	72.7	71.4	0.95	1.6
	N	59	59	59	59	52

DISCUSSION

Important results of this research were compared to results from other research conducted globally. First, the study showed that central idiopathic PP was the main etiology for the study group (60%). This is concordant with other research like the Rohani et al. [16] study on Iranian girls which showed 45.4% CIPP. Bridges et al [17] showed 43% in England, and Cisernino et al. that found 74% CIPP. In contrast, the main diagnosis was premature adrenarche according to the Kaplowitz et al [18] study in Washington, DC. Moreover, neurogenic PP due to a brain tumor was represented by only 2 patients, who comprised 3.2% of the total population and 5% of the cases diagnosed with central precocious puberty. In other words, the CIPP: CNPP ratio is 19:1. This was close to the Rohani et al. finding of 20:1, and Martin Chalumeau et al. [19] at a pediatrics hospital in Paris which revealed a CIPP to CNPP ratio of 17:1. However, Kaplan KL et al. [20] in the University of California showed a much less pronounced ratio of CIPP to CNPP with 2.6:1.

Regarding Gonadotropin Independent PP, the study encountered 3 cases with functioning ovarian cyst(s) that consisted 4.8% of the total population. Nevertheless, Bridges et al. found only 1 case of GIPP diagnosed with hypothyroidism that represented only 0.5% of the sample. Moreover, the Rohani et al. study revealed 2 cases of ovarian cysts that made up 4.45% of the population. Rohani also revealed 1 case of McCune-Albright Syndrome as well as 1 case of

adrenal carcinoma. Furthermore, in comparison with B.M Taher et al. [21] in Jordan, out of 54 girls that participated in Taher research, 4 cases of congenital adrenal hyperplasia were diagnosed as well as one case of hypothyroidism.

In regards to the anthropometric measures of PP, this study has shown a significant positive relationship between weight and body mass index with the incidence of precocious puberty in general and idiopathic central PP. This conclusion is consistent with Paul B. Kaplowitz et al. research in the United States [18] that showed a significant increase in BMI Z-scores in white and black girls who are more advanced in their Tanner stages in terms of breast development or pubic hair development or both. In addition, another American study by Youfa Wang [20] concluded that increased BMI has a positive association with premature sexual maturation in girls. Finally, according to meta-analysis research executed by Wenyan Li et al. [23], after analyzing different studies from China, Spain, Portugal, US, and Canada, increased weight is associated with early puberty including the age at which puberty symptoms starts. However, the age before 8 years at which symptoms of puberty start is not significantly correlated to the increased weight or BMI of the girls in our study group.

Consequently, comparisons were made between our results and others regarding the heights of the studied girls. In a comparison with research executed by Thais Della Manna et al. [24] in the University of São Paulo, Brazil, girls who had premature thelarche had compatible heights with the normal population while girls who had true precocious puberty had significantly higher heights than the normal population. Similarly, in our study, the mean height percentile of patients with true precocious puberty was 70.4 (P value less than 0.05). Nevertheless, patients with premature thelarche in our study were not significantly different in terms of height to the CDC general population. Furthermore, a study was done by Srinivasan P. [25] at the Tamil Nadu Dr.M.G.R university, Chennai, India, concluded that patients with Central PP as well as Central Idiopathic PP had mean heights more than the general population means at the time of the diagnosis.

Finally, regarding the features of PP, the results of our study were compared to others in terms of bone age difference from the chronological age. In comparison with Thais Della Manna et al. in Brazil, both studies showed a significant increase in bone age advancement in girls with true PP, while both studies showed no significant difference of bone age advancement than the normal population in patients with premature thelarche. Additionally, the Srinivasan P. study revealed that the means of bone age advancement patients with Central PP and Central idiopathic PP were 3.4 and 3.1 years respectively.

It is worth mentioning that the study compared values such as weight, height, and BMI percentiles to the values of CDC. It would have been more convenient if a control sample for these values were available that represented the general population in Sulaymaniyah region. Finally, more efforts are recommended to be paid to follow up with the patients who participated in the study in the following few years to obtain further results.

In conclusion, precocious puberty in girls is an important condition that needs to be better evaluated, followed up with, and treated. The most common cause for PP in Sulaimani province is idiopathic central PP and premature adrenarche is the second most common. Moreover, girls who start their puberty symptoms early tend to be taller and weigh more than their peers at the time of start of symptoms, with more advanced bone age.

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