Original Article

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Causes and Types of Precocious Puberty in North-West Iran

Siamak Shiva*, MD; Afshin Fayyazi, MD; Armen Melikian, MD, and Shadi Shiva, MD

Pediatric Health Research Center, Children's Hospital, Tabriz University of Medical Sciences, Tabriz, IR Iran

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Abstract

Objective: Precocious puberty is of concern because of the underlying disorders, the short adult stature, and the psychosocial difficulties. This study was carried out in order to evaluate the characteristics of children referred to pediatric endocrinology clinic with diagnosis of precocious puberty.

Methods: In a cross-sectional study between February 2007 and September 2009, all of the children referred to pediatric endocrinology clinic in North-West Iran with diagnosis of precocious puberty were recruited.

Findings: Data of 106 girls (82.2%) and 23 boys (17.8%) were analyzed. Mean age of the patients at the time of referral was 6.6±2.8 years (ranging 0.3-14 yr), which was 7±3.9 (ranging 0.3-14 yr) for boys and 6.6±2.5 (ranging 0.8-12 yr) for girls (*P*=0.6). Out of 129 subjects, 56(43.4%) had precocious puberty, 71.4% (35 cases) of them were due to central precocious puberty and 28.6% (16 cases) were pseudo-precocious puberty. 73 out of 129 subjects (56.6%) were due to normal variants of puberty, normal puberty, and no puberty. 87.5% of subjects with central precocious puberty were idiopathic.

Conclusion: Most of children referred with diagnosis of precocious puberty have benign normal variants. Most of cases with precocious puberty are affected with central precocious puberty, especially with idiopathic form of it.

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Key Words: Puberty; Precocious Puberty; Etiology; Children; Thelarche; Adrenarche; Menarche

Introduction

Puberty is a period in the life of a child when sex characteristics occur and growth velocity accelerates[1]. Precocious puberty (PP) refers to appearance of physical signs of sexual development in a child prior to the earliest accepted age of sexual maturation, 8 years in girls and 9 years in boys[2,3]. Precocious puberty currently affects 1 in 5000 children and is 10 times more common in girls than in boys[4] and is idiopathic in the majority of cases in girls[5]. Recent studies in the United States have suggested that girls are maturing at an earlier age than they were 30-40 years ago, and the number of girls with diagnosed PP is on the rise[6,7]. Results of a study from India have shown that the neurogenic central PP (CPP) is more common in boys than in girls. It was also suggested in that study that the most common cause of neurogenic CPP was hypothalamic hamartoma[8]. Hypothalamic hamartomas are rare congenital non neoplastic lesions of the tuber cinereum, which usually present as CPP[8]. Treatment of CPP with GnRH analog improves the final height and longstanding GnRH analogs have become the mainstay of

*** Corresponding Author;**
Address: Pediatric Health Research Center, Tabriz Children Hospital, Tabriz, Iran
E-mail: shivasiamak@yahoo.com

treatment of CPP[10,11]. On the other hand, peripheral precocious puberty is the result of the presence of PP due to the increase of sex steroids with no evidence of activation of the hypothalamic-pituitary-gonadal axis[12].

Results of a retrospective review of 104 children referred over a 3-yr period to a single clinician for signs of early puberty in Virginia revealed a low incidence of endocrine pathology and a high proportion of children with common benign variants[13].

PP is of concern because of the underlying disorders that may cause premature sexual development, the short adult stature that results from rapid skeletal maturation attributable to early secretion of sex hormone, and the psychosocial difficulties that the sexually precocious child may encounter[2].

It is necessary to continuously monitor premature puberty because of special threats that may result including early initiation of sexual life, increased risk of sexually transmitted infections, early teenage pregnancies, breast cancer, and obesity with all its consequences in adulthood[1].

The purpose of this study was to evaluate the characteristics of Iranian children referred to pediatric endocrinology clinic with diagnosis of PP. The objectives of the study were: 1) to determine the relative frequencies of the different diagnoses made; 2) to compare the different diagnostic groups in terms of age, reason for referral, and relative height; and 3) to determine the characteristics of idiopathic and neurogenic causes of CPP.

Subjects and Methods

Setting and participants:

The present study was conducted at the out-patient pediatric endocrinology clinic of Tabriz University of Medical Sciences which is the main tertiary pediatric care centre in the North-West of Iran. Between February 2007 and September 2009, all of the children referred with diagnosis of PP entered this cross-sectional study.

PP defined as breast or pubic hair development at Tanner stage 2 or more before the age of 8 years and/or menses before the age of 9 years in girls and development of genitalia or pubic hair at Tanner stage 2 or more before the age of 9 years in boys.

All of the referrals with diagnosis of PP were included. Those refused to participate in the study and those that did not complete the study course were excluded. Written informed consent was obtained from all participants, and the study protocol was approved by local ethic committee and research vice chancellor office of medical school, Tabriz University of Medical Sciences. Out of 135 children with diagnosis of PP, two of them refused to participate in the study and four did not complete the study course. Finally, 129 subjects were included in the analysis.

Study design:

After history taking, all of the subjects underwent thorough physical examination. Based on physical findings and accelerated or not accelerated growth, decision was made for additional evaluations. X ray of left wrist and hand, and abdominal ultrasonography were used for evaluation of skeletal growth acceleration and uterine growth respectively. Serum levels of THS, FSH, LH and testosterone were measured in boys with testicular enlargement. In girls with breast development serum levels of THS, FSH, LH and estradiol were measured and LHRH stimulation test (if needed) ordered. Uterus length of ≥35mm[14], LH/FSH peaks ratio after GnRH test ≥0.66, and plasma estradiol levels ≥15 pg/ml[15], were considered to be pubertal.

In patients with pubic hair only and growth acceleration, dehydroepiandrosterone sulfate, testosterone, and 17-hydroxyprogesterone were measured to identify non-classical congenital adrenal hyperplasia or a virilizing tumor.

All patients with CPP underwent brain magnetic resonance imaging and if findings were normal they were classified as idiopathic CPP. Follow-up visits were scheduled when the diagnosis was not clear at the first visit.

Early appearance of pubic hair without breast development in girls and without penile and testicular enlargement in boys was considered

premature adrenarche (PA), and appearance of breast tissue in a girl under 3 yr of age without rapid progression or growth acceleration was considered premature thelarche. In girls with one or more episodes of vaginal bleeding without breast development, and normal physical, laboratory, and imaging findings, it was diagnosed as premature menses. Normal puberty defined as breast development in girls above 8 yr of age and genital enlargement in boys above 9 yr of age. Girls without pubic hair and breast tissue and boys without pubic hair and genital enlargement were considered prepubertal.

Seca balance and studiometer was used for weight and height measurement. The body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). NCHS charts were used for defining overweight (85^{th} centile≤BMI<95^{th} centile for age and sex), and obesity (95^{th} centile≤BMI), and determination of height standard deviation score (SDS).

Statistical analyses:

The data were analyzed using SPSS software version 16. Statistical procedures used to analyze the data included chi-square test and t-test. Differences between groups were considered significant when P<0.05.

Findings

Data of 106 girls (82.2%) and 23 boys (17.8%) were analyzed. Mean age of the patients at the time of referral was 6.6±2.8 years (ranging 0.3-14 yr), which was 7±3.9 (ranging 0.3-14 yr) for boys and 6.6±2.5 (ranging 0.8-12 yr) for girls (P=0.6). Out of 129 subjects, 56 (43.4%) had PP, 71.4% (35 cases) of them were due to CPP and 28.6% (16 cases) because of pseudo-PP (PPP). 73 out of 129 subjects (56.6%) were due to normal variants of puberty, normal puberty, and no puberty. Idiopathic CPP constituted 87.5% of subjects with CPP.

Tables 1 and 2 illustrate some of the main characteristics of the patients. It is apparent from these tables that the girls had been more affected with CPP than the boys. This difference was statistically significant (P<0.001). Comparison of mean age between subjects with idiopathic CPP and those with neurogenic CPP, showed no statistically meaningful difference (P=0.08).

Organic brain lesions that we found in five cases of neurogenic CPP were hydrocephaly in a 7.5 year old girl, radiotherapy for brain tumor in a 7.5 year old boy, suprasellar tumor in a 7 year old girl, leukomalacia in a 3 year old girl with history of hypoxic-ischemic encephalopathy, and hypothalamic hamartoma in a 17 month old girl, the youngest subject.

The data from this study showed that the most common complaint of patients was breast enlargement in girls (64.9%), and pubic hair growth in boys (50%). Mean height SDS of the patients with congenital adrenal hyperplasia (CAH) (1.91±1.67) was significantly (P=0.02) greater than those with CPP (0.74±1.11). About 46% of cases with idiopathic CPP and 21% of

Table 1: Patients' characteristics regarding their final diagnosis

Final diagnosis		n (%)	Male/ Female	Mean age (year)
True or Central Precocious Puberty	Idiopathic	35 (27.1)	1/34	7.0 (1.9)
	Organic brain lesion	5 (3.9)	1/4	5.3(2.8)
Pseudo or Peripheral Precocious Puberty	CAH	12 (9.3)	8/4	6.0 (2.3)
	Hypothyroidism	3 (2.3)	0/3	6.2 (0.7)
	Adrenal Tumor	1 (0.8)	1/0	2.5
Normal Variants of Puberty	Premature Thelarche	23 (17.8)	0/23	3.4 (2.4)
	Premature Adrenarche	13 (10.1)	5/8	6.5 (2.3)
	Premature Menarche	3 (2.3)	0/3	9.3 (1.0)
Other	Normal Puberty	17 (13.2)	3/14	9.7 (1.3)
	Prepubertal	17 (13.2)	4/13	8.0 (2.3)
Total		129 (100)	23/106	6.6 (2.8)

CAH: Congenital Adrenal Hyperplasia

Table 2: Evaluated parameters of patients

Parameter	n	Mean (SD)
Age (year)	129	6.6 (2.8)
Height (m)	129	0.3 (1.4)
Bone age advance (year)	129	1.4 (1.5)
Uterus length (mm)	66	35 (6)
LH peak (IU/L)	66	12.0 (12.8)
FSH peak (IU/L)	66	13.8 (8.0)
LH/FSH peak ratio	66	0.9 (0.75)
Estradiol (pg/ml)	66	17 (15)
TSH (µU/mL)	66	3.7 (5.2)

SD: Standard Deviation

those with normal puberty were over-weight or obese. This difference was not statistically significant (*P*=0.1). Table 3 shows the BMI of different groups of patients.

Discussion

According to research findings, PP currently affects 1 in 5,000 children and is 10 times more common in girls[4]. True or central PP is the premature onset of puberty due to a precocious activation of gonadotropin-releasing hormone neurons in the hypothalamus[16] and represents 80% of PP cases[17]. Estimates of the frequency of central nervous system pathology causing CPP vary widely. In girls estimates of idiopathic CPP range from 69 to 98%, compared with 0 to 60% in boys[18,19]. The findings from this study indicate that CPP occurs above 2 times more than pseudo PP (PPP) and is more common in girls. As a result, idiopathic CPP is more common and occurs in upper ages in comparison with PPP. These findings are similar to those of other studies[20-23].

Previous studies have shown that patients with neurogenic CPP start their puberty earlier than those with idiopathic CPP[24,25]. In present study, although the mean age of patients with idiopathic CPP (7 yr) was greater than those with neurogenic CPP (5.3 yr) but this difference was not statistically significant. A possible explanation for this finding might be that the number of cases with neurogenic CPP was small (5 cases) in present study.

Results of a recent study from USA have shown that adiposity is associated with earlier pubertal development in girls[26]. An association between early sexual maturation and obesity is widely accepted, although the direction of causality has not been established[27]. About half of our patients with idiopathic CPP were over-weight or obese, this finding further supports previous studies[26-28].

Peripheral or pseudo-PP results from sex steroid exposure by process other than activation

Table 3: Body mass index of patients

Cases	n	85≤BMI<95 (Over weight)		BMI≥95 (Obese)	
		n	%	n	%
All	129	15	11.6	27	21
Male	23	2	8.7	6	26.1
Female	106	13	12.3	20	18.9
Idiopathic CPP	35	8	22.9	6	17.1
Organic CPP	5	0	0	1	20
Premature adrenarche	13	1	7.7	6	46.2
Premature thelarche	23	2	8.7	0	0
Premature menarche	3	0	0	0	0

BMI: Body mass index; CPP: central precocious puberty

of the hypothalamic-pituitary-gonadal axis, which is much less common than CPP. Causes of PPP range from well-characterized genetic mutations to those conditions without a known etiology[29]. In present study, the most common cause of PPP was CAH which was followed by hypothyroidism as the second common cause. In a study from India, PPP was secondary to adrenal causes in boys and ovarian cysts in girls[8]. In our study, ovarian cysts were due to hypothyroidism and all of the cysts and signs of puberty regressed with thyroxin therapy. The findings emerging from the present study showed that the majority of children referred for evaluation of precocious puberty have benign normal variants. These findings are consistent with those of Kaplowitz's[13].

The major limitation of the present study was the small number of cases with neurogenic CPP.

Conclusion

Most of the children referred to pediatric endocrinology clinic with diagnosis of PP have benign normal variants, normal puberty, and no puberty. Most of cases with true PP are affected with CPP, especially with idiopathic CPP which is commonly seen in over-weight and obese girls.

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Conflict of Interest: None

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