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Epidemiological characteristics of Patients with Central Precocious Puberty Attending Welfare Teaching Hospital / Baghdad / Iraq

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Abstract— Background: Central precocious puberty refers to early activation of the hypothalamic-pituitary-gonadal axis and occurs in 1 in 5000 to 10,000 children. **Aim of study:** To investigate the epidemiological characteristics regarding the demographic, clinical presentation, etiology of central precocious puberty, mode of treatment and, MRI findings. **Patients and Method:**A cross sectional study that conducted at Pediatric Endocrinology Outpatient Clinic in Children Welfare Teaching Hospital / Medical City from 1st of November 2018 to 30th of October 2019.Itincluded 83 patientspresented to the hospital because of early pubertal development and diagnosed with central precocious puberty.History was taken from patients' parents & file records. The following data were collected: age at time of onset of complain, gender, consanguinity, family history of similar conditions, main presenting symptom, mode of treatment, history of cranial irradiation, history of meningitis, and MRI findings. All patients underwent physical examination, based on physical findings, decision was made for additional evaluations. **Results:** In this study, 53% of patients aged> 6 years; 79.5% were females; consanguinity was positive in 33.7%; most common presentation in males was pubic hair (76.5%) and in females was thelarche (42.4%). Etiology in 84.8% of female patients was idiopathic, while idiopathic and CAH etiologies were presented in 94.2% of male patients (47.1% for each). **Conclusion:**Central precocious puberty is seen in girls in the majority of cases and is associated with a wide range of conditions.The most common underlying pathology was idiopathic in girls & boys followed by CAH in boys.

Keywords: Central precocious puberty,etiology, treatment, Iraq.

Introduction

Puberty is a period of physical, hormonal and psychological transition from childhood to adulthood, with accelerated linear growth and reproductive functionachievement [(1)]. Normal puberty in girls usually begins with thelarche (the onset of breast buds), followed within a few months by pubarche (the onset of pubic hair)[(2)].Precocious puberty is defined as the development of puberty younger than that which is expectedfor ethnicity and race,namely, before age eight years in girls and nine years in boys[(3)]. The accepted threshold to predict the condition is typicallytwo to 2.5 standard deviations younger than the mean [(4)].Precocious puberty is associated with accelerated growth, development of secondary sex characteristics, advanced bone age, and early closure of epiphysis. History should be taken for information about the onset of the signs, progression rate, and growth tempo in the last 6-12 months, presence of secondary sex characteristics (acne, oily skin, erection, night ejaculation and vaginal bleeding) in addition to the presence of pubertal signs[(5)].Itclassified into central or peripheral based on the etiology[(6)]. Central precocious puberty (CPP) refers to early activation of the hypothalamic-pituitary-gonadal (HPG) axis and occurs in 1 in 5000 to 10,000 children [(7)]. Compared to boyswhich had prevalence less than 5 per 10000, it is far more common in girlswhich is about 20 to

23 per 10000 girls, in whom it is usually idiopathic[8, 9].While the majority of girls have idiopathic CPP, boys are more likely to have a pathological source[10]. Risk factors for CPP include a history of international adoption, as well as congenital or acquired central nervous system insults, such as hypothalamic hamartoma, septo-optic dysplasia, tumor, trauma, infection, or ischemia. Several genetic syndromes, including neurofibromatosis type 1, tuberous sclerosis, and Sturge–Weber syndrome, are associated with CPP [3]. Apart from recognized genetic syndromes, anywhere from 5.2 to 27.5 % of cases have been reported to be familial[11]. The mainstay of treatment for CPP is GnRH analogs (GnRHa). This group of drugs provides constant serum levels of GnRHactivity and thus overrides the pulsatility of endogenous GnRH. Although there are many different analogs with different routesof administration, the primary agent in the United States for many years was depot IM injections of leuprolide acetate administered every four weeks[12]. The aim of this study is to investigate theepidemiologicalcharacteristics regardingthe demographic, clinical presentation, etiologyof CPP,mode of treatment, and MRI findings.

Patients and Methods

Study design, setting, and time: This was a cross sectional study conducted at Pediatric Endocrinology Outpatient Clinic in Children Welfare Teaching Hospital / Medical City in Iraq from 1st of November 2018 to 30th of October 2019.

Study Population and sample size: The study included 83 patients. All of them were children presented to the hospital because of early pubertal development and diagnosed with CPP. Any case of peripheral PP which convert to CPP like CAH &MacCune - Albright syndrome was also included in this study. All cases of peripheral PP which not convert to CPP and cases of premature thelarchewere excluded from the study. All patients' parents signed an informed consent to participate and allows us to review their medical records for research purposes as long as the patient anonymity and confidentiality of their medical records are maintained.

Diagnosis of CPP was achieved when girls presented with breast development with orwithout pubic hair. When present, clinical evidence of bothestrogen and androgens is important in differentiating CPPfrom benign premature thelarche. Boys were presented with bilateraltesticular enlargement as opposed to boys with peripheralPP in whom the testes are prepubertal or only slightly enlarged.CPP is also characterized by ongoing pubertal progression aswell as growth acceleration and advanced skeletal maturation[13].

Data collection: Done after history taking from patients' parents & file records. The following data were collected: Age at time of onset of complain, gender, consanguinity, family history of similar conditions, main presenting symptom, mode of treatment, history of cranial irradiation, history of meningitis, and MRI findings.TreatmentwithGnRH agonist (goserelin acetate [Zoladex]) in dose of 3.6 mg every four weeks or 10.8 mg every 12 weeks were administered to all patients.All of the patients underwent physical examination, based on physical findings, decision was made for additional evaluations.Brain MRI imaging was done to look for any brain pathology as a cause of PP in order to differentiate them from idiopathic PP.

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages.Chi square test was used to assess the association between gender and certain information, while fisher exact test was used instead when the expected frequency was less than 5.A level of P – value less than 0.05 was considered significant.

Results

In this study, the most common age of patients was > 6 years (53%); 79.5% of them were females; consanguinity was positive in 33.7%; 6% had positive family history of PP; most common presentation in males was pubic hair (76.5%) and in females was thelarche (42.4%); GnRH agonist alone was received in 85.5% of patients and with growth hormone injection in 14.5% as shown in table (1).

Table 1: Distribution of study patients by general characteristics

Variable		No. (n= 83)	Percentage (%)
Age (Year)			
<3		10	12.0
3 - 6		29	35.0
> 6		44	53.0
Gender			
Male		17	20.5
Female		66	79.5
Consanguinity			
Yes		28	33.7
No		55	66.3
Family history			
Yes		5	6.0
No		78	94.0
Presentation			
Male	**Pubic hair**	13	76.5
	Testicular enlargement	4	23.5
Female	**Thelarche**	28	42.4
	Thelarche and pubic hair	23	34.8
	Menarche	4	6.1
	Thelarche and menarche	5	7.6
	Pubic hair	6	9.1
Type of treatment			
GnRH agonist		71	85.5
GnRH agonist + Growth hormone		12	14.5

As shown in table (2), the etiology in 84.8% of female patients was idiopathic, while idiopathic and CAH etiologies were presented in 94.2% of male patients (47.1% for each) and this difference was statistically significant (P= 0.001). Most of MRI findings were normal in both females and males (94% and 100% respectively).

Table 2: Etiology and MRI findings according gender

	Gender		Total (%) n= 83	P - Value
	Female (%) n= 66	Male (%) n= 17		

Etiology				
Idiopathic	56 (84.8)	8 (47.1)	64 (77.1)	
CAH	1 (1.5)	8 (47.1)	9 (10.8)	
Meningitis	2 (3.0)	1 (5.8)	3 (3.6)	
Micro adenoma	3 (4.5)	0 (0)	3 (3.6)	**0.001**
Hamartoma	1 (1.5)	0 (0)	1 (1.2)	
Meningocele	1 (1.5)	0 (0)	1 (1.2)	
McCune- Albright syndrome	2 (3.0)	0 (0)	2 (2.4)	
MRI finding				
Normal	62 (94.0)	17 (100.0)	79 (95.2)	
Pituitary micro adenoma	3 (4.5)	0 (0)	3 (3.6)	**0.582**
Hypothalamic hamartoma	1 (1.5)	0 (0)	1 (1.2)	

Discussion

In this study, most common age of patients was more than six years and the majority of them were females. This results agreed with studies conducted by Çatlı G et al 2019 in Turkey, when showed that 72.5% were aged between 7-8 years[14]& by Ng S et al 2003 in England asreported that the mean age of onset of puberty was 6.2 years [15].This may be due to the fact that most families don't seek medical help early but only when more signs of puberty become apparent. The high predominance of females in this study was in accordance with several studies as in a Korean study by Kim SH et al 2015 [16], Teilmann G et al study 2005 in Denmark [9], and in Spain by Soriano-Guillén L et al 2010[17] when estimated much more prevalence of CPP in girls compared to that in boys. In regard to the consanguinity of the parent, this study showed that about 33.7% were positive & this much higher than result obtained byHashemipour M et al study in Spain 2015 when they concluded that there was no association with parental consanguinity among patients[18].This might due to that some secondary causes of PP like CAH related to consanguinity marriage which is common in our community.

Regarding the main presenting symptom of the male, this study revealed that 76.5% of boys had pubic hair as primary complaint & only 23.5% with enlargement of testis, which is similar to Prété G et al study in 2008 when found that 67% of patients presented with pubic hair [19]. While in girls; thelarche represent the main initial complaint (42.4%) followed by thelarche&pubarche (34.8%).This is similar to Giabicani E et al study in 2013 which reveal that breast development was the first sign of puberty in 69.2%of girls [20]& in Shiva S et al study in 2012 was 64.9%[21].This is the commonest presenting feature of CPP & goes with definition of precocious puberty.

In the current study, the most common cause of precocious puberty in girls was idiopathic (84.8%) and it was the cause in 47.1% of boys; while CAH was the most common cause in males as the etiology of precocious puberty (47.1%) and only in 1.5% of girls.In Moayeriet al study, 40% of female patients had CPP, 90% of which were idiopathic PP. Furthermore, 61% of boys with CPP had idiopathic CPP[22].

In this study, the result of MRI finding revealed that 6 % of femalesshowed positive findings including4.5% with pituitary micro adenoma & 1.5% of them with hypothalamic hamartoma. No male with brain pathology.These finding similar to finding in Ng S et al study as most patients were female with PP and MRI abnormalities were present in 10 (15%) of male patients [15]. These MRI findings might be due to large number of female patients in comparison to male patients.Higher percentage of patientsin this study were treated with GnRH agonist alone (85.5%) in comparison with those treated by addition of GH to the treatment regimen (14.5%); while in Pucarelli I et al study in 2003,(47%) of patients treated by GnRH agonist plus GH[23]; and this might due to late presentation of

our patients & interruption of GH treatment availability in our hospital. Family history of patients with similar condition was detected in 6%, in contrast to Giabicani E et al study in 2013; the family history of PP present in 41.4%[20]but agreed with Hashemipour M et al study in 2015 in which there was no any case of familial PP[18].In conclusion,CPP is seen in girls in the majority of cases and is associated with a wide range of conditions.

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