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ORIGINAL ARTICLE

Evaluation of etiology and clinical feature of precocious puberty among children presenting in a pediatric endocrinology department in a tertiary care hospital.

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ABSTRACT… Objective: To find the frequency of precocious puberty in children and to compare the clinicaland laboratory parameters of central & peripheral precocious puberty. **Study Design:** Cross-sectional study. **Setting:** Karachi's National Institute of Child Health's Paediatric & endocrinology Division. **Period:** December 2016 and 2021. **Material & Methods:** All patients with precocious puberty will be taken from files through non-probability convenience sampling method. Data was analyzed on SPSS version 22.0. **Results:** Total 65 patients were included. The mean age was 6+3.35years. Precocious puberty was classified as peripheral precocious puberty in 38 (58.4%), central precocious puberty in 20 (30.76%), premature thelarche in 5(7.69%) and premature1pubarche in 2 (3.07%). In the peripheral precocious1puberty group, CAH was found in 22(78.5%), out of which 2 patients were of rare mutation of CAH presenting with peripheral precocious puberty (DAX mutation and 11 B hydroxylase mutation, adenocarcinoma was observed in 2(7.14%) followed by Mu-cane- Albright syndrome was in4(14.28%) and van wykgrumbach syndrome in 10 patients. Central precocious puberty was found in 20 patients hypothalamic harmartoma in 4(20%), craniopharyngioma 3(15%), hypothalamic astrocytoma 1(5.0%), genetically proven neurofibromatosis in 1(5.0%) patient and hydrocephalus 1(5.0%) and in 10(50%) patients no cause was found. **Conclusion:** The conclusion of the study that Peripheral precocious puberty was more common than central precocious puberty. The common cause of peripheral precocious puberty was CAH, while central precocious puberty was idiopathic. Children with central precocious puberty had greater height SDS, weight SDS, FSH, and LH levels compared to children who had peripheral precocious puberty.

Key words: Central Precocious Puberty, Girls, Idiopathic, Peripheral.

INTRODUCTION

Precocious precocity is defined as the presence of secondary sexual features at an age which is less than 2-2.5 SD below the general population's average age of puberty or the start of menstruation before the age of 9.5 in girls.[1]

Precocious puberty (PP) is the development of secondary sexual characteristics at an abnormally early age in comparison to the general population. The start of puberty in females before the age of 8 and in boys before the age of nine is a common description.[2] In children, it is a difficult transitional phase that includes growth acceleration as well as the development of secondary sexual characteristics. It is a time of physical and psychological growth.[3] Precocious puberty is thought to occur in 1 in 5000–10,000 people. Despite the significance and relative occurrence of premature puberty, there is little information on its causes among Iranian patients, to our knowledge.[4] In Mashhad study, 55 girls and another study was also conducted in Tehran on 74 patients with precocious puberty.[5]

Precocious puberty has a complex pathophysiology; the two main categories are related to the activation or non-activation of brain pathways that control hypothalamic pituitary gonadal axis activity.[6] It's a difficult diagnosis to make since the difference includes everything from benign variations to catastrophic diseases

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like cancer. Precocious puberty is divided into two types. Peripheral precocious puberty (depending on GnRH) and central premature puberty (GnRH independent). When central precious puberty is followed by a central nervous system (CNS) lesion, it is defined as organic, and when there is no associated CNS lesion on computed tomography (CT) or MRI, it's classified as idiopathic (MRI).[7]

Peripheral precious puberty is defined by the appearance of secondary sexual characteristics prior to the start of GnRH pulsatile secretion, which is caused by the production of sex hormones from either endogenous or exogenous causes. It happens less often than the CPP. Congenital adrenal hyperplasia, McCune-Albright syndrome (CAH), Leydig cell tumours and Sertoli cell tumours are some of the common causes. Teratoma and embryonic tumours are all germ cell tumours. Exogenous exposure to sex steroids, Familial male limited precocious puberty Syndromes.[8]

Central precocious puberty can be caused by a known or specific underlying central nervous system disorder (neurogenic central precocious puberty) or it can be caused by no apparent issue (idiopathic central precocious puberty).

Understanding puberty timing differences, and also increasing referrals of children to suspected premature puberty, is critical because a younger age at puberty is associated to psychosocial problems and is a risk factor for an earlier age at first sexual intercourse. It also has long-term health consequences, including a greater risk of type 2 diabetes, increased abdominal obesity, short stature, excess weight, heart disease, anxiety, and premature death. According to huge genetic data, early puberty is connected to an increased risk of breast cancer, which is consistent with extensive epidemiological evidence that early menarche elevates the risk of breast cancer. In boys, early puberty may increase the risk of prostate cancer.[9,10]

The common cause of peripheral precocious puberty was CAH, while the common cause of central precocious puberty was idiopathic. Central precocious puberty was associated with high SDS for height, weight, FSH, and LH than peripheral precocious puberty. CAH was identified as the primary cause in 81.7% of cases of peripheral precocious puberty and idiopathic in 67.64% of cases of central precocious puberty.[11]

Precocious puberty is a neglected topic in Pakistan, and little research has been conducted to find its origin in our population. Puberty is associated with accelerated growth and bone maturation, as well as the onset of secondary sexual characteristics. This can result in a reduction in adult height.[12] Only a few epidemiological studies on the prevalence of PP have been published. The objective of the study is to find the frequency of precocious puberty in children and to compare the clinical and laboratory parameters of central and peripheral precocious puberty.

MATERIAL & METHODS

This cross sectional study was conducted from December 2016 to 2021 in National institute of child health Karachi (Ex-21/2021). Sample size 65 was calculated with 95% confidence interval and 5% margin of error by taking expecting prevalence of 4.4%[13] precocious puberty.

Inclusion Criteria

All patients with premature puberty diagnosed with the emergence of secondary sexual features in females younger than 8 years old and boys younger than 9 years old will be drawn from files using a non-probability convenience sampling method were included.

Exclusion Criteria

Children with head trauma, cranial radiation, previous CNS infections (meningitis, encephalitis), neurofibromatosis, tuberous sclerosis and severe hypothyroidism were excluded.

Central Precocious Puberty (CPP) was named after the usual pubertal development sequence and iso-sexuality of puberty. Peripheral Precocious Puberty (PPP) was defined as an aberrant pubertal development sequence with loss of pubertal synchrony or contra-sexual

development.[14]

Age, weight, height, skeletal age (in accordance with the Greulich & Pyle Atlas), history of disease, pubertal status (according to the Tanner category), baseline values of LH and FSH, testosterone, thyroid profile, androgens and adrenaline, pelvic ultra-sonography & Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain were noted. Premature pubarche diagnosed as the appearance of axillary hair, pubic hair or both before the age of18 years, bone age within+2 SDs of the average for the chronological age, pre-pubertal height velocity < 6 cm/year & pre pubertal response to the GnRH test.

The status of puberty was staged according to Tanner. Height was measured in centimeters in children over the age of two, and length was measured in children under the age of two. Electronic scales were used to measure weight in kg. A single observer measured both height & weight. Height, weight & BMI were all reported as standard deviation scores in comparison to the UK standard.

Data were analyzed on SPSS version 22.0. Age, weight, bone age etc. were presented as mean and standard deviation. Gender, clinical profile of signs and symptoms, type and etiology of PP were presented as frequencies and percentages. Effect modifiers age gender was controlled through stratification. Post chi-square test / t-test will be applied keeping P- value ≤10.05 as significant.

RESULTS

Total 65 patients were included. The mean age was 6+3.35 years. Age was categorized in 3 groups. Group 1 included participants between less than 3 years were 5(9.1%) of the entire data. Group 2 included participants between 3-6 years were 12(21.8%) and group 3 included participants between greater than 6 years were 38(69.1%). The mean of weight, height SDS, BMI, Bone Age, FSH Baseline and LH baseline are shown in Table-I. Precocious puberty was classified as peripheral precocious puberty in 38 (58.4%), central precocious puberty in 20 (30.76%), premature thelarche in 5(7.69%) and premature pubarche in 2 (3.07%).

In the peripheral precocious puberty group, 22(57.89%) were males and 16 (42.10%) were female. Less than 3 years were 4 (10.52%) children, 12 (31.57%) were between 3 to 5 years and 22(57.89%) were more than 5 years. Types of peripheral precocious puberty was as shown in Table-II. CAH was found in 22(57.89%) out of which 2 patients were of rare mutation of CAH presenting with peripheral precocious puberty (DAX mutation and 11 B hydroxylase mutation), adenocarcinoma was observed in 2(5.26%) followed by Mu-cane- Albright syndrome was in 4(10.52%) and van wykgrumbach syndrome in 10 patients (26.31%). CAH has 8 (36.3%) girls and 14 (63.6%) boys. Adenocarcinoma was found in a 7-year-old boy and a one-year-old child.

Central precocious puberty was found in 20 patients hypothalamic harmartoma in 4(20%), craniopharyngioma 3(15%), hypothalamic astrocytoma 1(5.0%) neurofibromatosis in 1(5.0%) patients and hydrocephalus 1(5.0%) and in 10(50%) patients no cause was found. 16(80%) females and 4(20%) males were identified as having hypothalamic central precocious puberty. Caniopharyngioma was observed in two female children aged 6 & 7 years, as well as one boy aged 8 years. A three-year-old girl was diagnosed with hypothalamic astrocytoma. (Table-III)

Comparison between the variables of central and peripheral precocious puberty as shown in Table-IV displays the difference was significant in the age of onset of puberty of central versus peripheral precocious puberty. (P<00.05) Children with central precocious puberty had greater height SDS, weight SDS, FSH and LH levels than those with peripheral precocious puberty. All the variables were significantly comparable with p-value1<10.05.

	Mean+ SD
Age	6+3.35
Onset age in years	5.36+2.39
Weight	20.92+6.17
Height SDS	110+20.49
BMI	16.4+2.36
Bone age	9.16+2.4
FSH Baseline	2.35+1.18
LH Baseline	0.77+0.70

Table-I. Descriptive of Age, Weight, Height etc.

	Yes
CAH	22(57.89%)
Adenocarcinoma	2(5.26%)
McCune- Albright syndrome	4(10.52%)
Vanwykgrumbach	10 (26.31%)

Table-II. Etiology of peripheral precious puberty

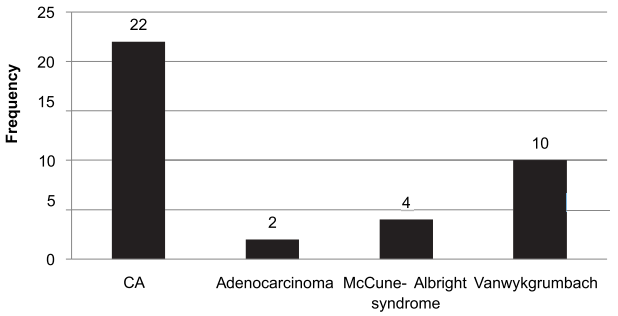

Figure-1. Etiology of peripheral precious puberty

	Frequency (%)
Hypothalamic	4(20%)
Craniopharyngioma	3(15%)
Hypothalamic Astrocytoma	1(5.0%)
Hydrocephalus	1(5.0%)
Neurofibromatosis	1(5.0%)
idiopathic	10 (50%)

Table-III. Etiology of central precocious puberty

Variables	Central	Peripheral	P-Value
Onset age	5.03+1.83	5.5 2+.66	*0.016
Height in cm	119.7 + 20.3	109.4 + 20.1	0.11
Height on SDS	1.12+0.76	0.92+ u	*0.005
Weight	23.37+6.8	20.5+6.38	0.174
Weight SDS	0.75+0.2	0.72+0.5	0.012
BMI	16.10+ 2.33	16.3 +2.49	*0.003
Bone age	9.37 +3.03	33.8 +41.6	*0.005
FSH Baseline	3.93 +3.4	1.15 +0.24	*0.002
LH Baseline	3.51 +0.7	0.35 +0.23	*0.003

Table-IV. Comparison between central & peripheral precocious puberty.
***Significant at p < .05**

DISCUSSION

Precocious puberty is a rare but curable endocrine condition in children. Because there is a lack of locally data on precocious puberty in Pakistan, the true importance of the disease, as well as the frequency of different types of precocious puberty, is unknown. Due to a lack of pediatric endocrinologists and specialized pediatric endocrine centers in Pakistan. In this study we have also included three genetically proven cases patients first time in the study from Pakistan.[15] One case of homozygous mutation of CYP11B11 with variant c45G < A (p.TrP15). Second case of hemizygous mutation of NROB1 gene of c.327 C>A variant. Third case of pathogenic heterozygous mutation of NF1gene with variant.

Precocious puberty can often be divided into two categories. Early maturation of the hypothalamic-pituitary-gonad axis known as central precocious puberty, which is defined by the normal sequential emergence of isosexual secondary sexual characteristics.[16] Excess sex hormone release from the gonads or adrenal glands causes peripheral premature puberty, sources of sex steroids from outside the body, or ectopic gonadotropin production from a germ cell cancer. It could be both isosexual and heterosexual.[5]

Overall, central precocious puberty is common than peripheral precocious puberty[17], and in our study where central precocious puberty accounted 30.7% and peripheral precocious puberty accounted 57.8%.

The frequency of various kinds of premature puberty in different studied populations shows greatly according to international data. In this study, peripheral precocious puberty 38 (58.4%) and central precocious puberty in 20 (30.76%). In peripheral precious puberty, 22(57.89%) were males and 16 (42.10%) were female. In central Precious puberty, 16(80%) females and 4(20%) males.

In 2015 study, children with PPP were 38.72% and CPP 36.57%.The underlying etiology of central precocious puberty was idiopathic in 83.3 percent

of cases. Male predominance was identified in 44.1 percent of individuals with peripheral precocious puberty. Congenital adrenal hyperplasia was the most common (12/19) underlying cause of peripheral precocious puberty. (18) In UK study, 197 (97.4%) of 213 individuals with premature puberty were girls, whereas 16 (7.5%) were males; 40.0% of the girls had CPP, 5.0% had PPP, and the rest had benign.[19]

Girls had central precocious puberty at a higher rate than boys did, as observed in this study, and peripheral precocious puberty was more prevalent in our study. In our situation, peripheral precocious puberty is a severe problem, and CAH is typically the underlying cause. As a result of delayed diagnosis and treatment, they eventually developed peripheral precocious puberty. In a study conducted in China, 91 cases of peripheral precocious puberty in children were shown and out of them CAH being the underlying cause in majority of them.[20]

LIMITATION OF STUDY

Although we have included genetically proven cases as well but Gnrh stimulation test was not possible due to unavailability of gnrh analogue in Pakistan.

CONCLUSION

The conclusion of the study that Peripheral precocious puberty was more common than central precocious puberty. The common cause of peripheral precocious puberty was CAH, while central precocious puberty was idiopathic. Children with central precocious puberty had greater height SDS, weight SDS, FSH, and LH levels compared to children who had peripheral precocious puberty.

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3	Roshia Parveen	Data collecion, Interpretation.	
4	Zubair Khoso	Article review.	
5	Taj Muhammad Laghari	Article writing & Data interpretation.	
6	Mohsina Noor Ibrahim	Article review, conception.	