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ORIGINAL ARTICLE

Etiological profile of precocious puberty in children at a Tertiary Care Hospital.

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ABSTRACT... Objective: To determine the etiological profile of precocious puberty in children. **Study Design:** Cross-sectional study. **Setting:** Department of Endocrinology, National Institute of Child Health, Karachi, Pakistan. **Period:** October 2023 to September 2024. **Methods:** Children of either gender, girls aged below 8 years, boys below < 9 years, and newly diagnosed cases of precocious puberty were analyzed. At the time of enrollment, demographic and clinical features were documented. Radiological and hormonal profiling were performed for the confirmation of etiology and type of precocious puberty. **Results:** In a total of 48 children, 23 (47.9%) were boys, and 25 (52.1%) girls. The mean age was 5.72±1.78 years. The most frequent clinical features were rapid height growth, adult body odor, and breast enlargement, noted in 48 (100%), 42 (87.5%), and 25 (52.1%) cases, respectively. Precocious puberty type was central, and peripheral among 25 (52.1%), and 23 (47.9%) children, respectively. Among central precocious puberty cases (n=25), the evaluation of etiology revealed that idiopathic in 17 (68.0%) children, hypothalamic hemartoma 3 (12.0%), mitochondrial encephalopathy 2 (8.0%), craniopharyngioma 2 (8.0%), and arachnoid cyst 1 (4.0%). Among 23 peripheral puberty cases, congenital adrenal hyperplasia was identified in 18 (78.3%) children, adrenocorticol carcinoma 2 (8.7%), ovarian teratoma 2 (8.7%), and Mccune-Albright syndrome in 1 (4.3%). **Conclusion:** Idiopathic central precocious puberty and congenital adrenal hyperplasia emerged as the most common causes of central and peripheral precocious puberty, respectively.

Key words: Congenital Adrenal Hyperplasia, Etiology, Hypothalamic Hemartoma, Mitochondrial Encephalopathy, Precocious Puberty.

INTRODUCTION

Precocious puberty (PP) refers to the early development of secondary sexual characteristics, occurring significantly earlier than the average onset age for the general population, typically by 2 to 2.5 standard deviations.[1] In girls, puberty is considered PP if it begins before the age of 8, and in boys, before 9.[2,3] This condition not only accelerates the development of physical traits associated with puberty but also leads to premature bone maturation, potentially limiting final height, causing concerns with physical appearance, and contributing to psychological and behavioral challenges.[2,3]

Data on the trends and prevalence of PP is scarce, however, existing global reports indicate that an earlier onset of puberty is more frequently observed in girls than in boys.[4] A study conducted on the Korean population found a prevalence of central precocious puberty (CPP) at 55.9 per 100,000 girls and 1.7 per 100,000 boys. The overall incidence was reported as 15.3 per 100,000 girls and 0.6 per 100,000 boys.[5] Another large data reported the prevalence of CPP as 193.2 per 100000 including 410.6 girls and 10.9 boys, whereas overall incidence was 122.8 per 100000 including 262.8 girls and 7.0 boys.[6]

The PP is classified into either "central precocious puberty (GnRH-dependent)", or "peripheral precocious puberty (GnRH-independent)". CPP occurs due to a disturbance in the "hypothalamic-pituitary-gonadal axis". In females, it is commonly idiopathic, while in males, it is often associated with an underlying pathology. Peripheral precocious puberty (PPP) arises from disruptions outside the hypothalamic-pituitary-gonadal axis,

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usually due to the production of sex steroids from either endogenous or exogenous sources. CPP accounts for approximately 80% of cases.[7-9] Atta et al. identified congenital adrenal hyperplasia (CAH) as the most frequent cause (81.8%) of PPB, followed by adenocarcinoma (9.1%), ovarian teratoma (6.1%), and McCune-Albright syndrome (3.0%). In CPP, the idiopathic cause was most common (67.74%), followed by hypothalamic hamartoma (12.90%), craniopharyngioma (9.67%), arachnoid cyst (3.22%), hypothalamic astrocytoma (3.22%), and hydrocephalus (3.22%).[9] A study by Osman HA et al. from Saudi Arabia reported that in CPP, 68% of girls had an idiopathic cause, while 50% of boys had pathological causes. In PPP, CAH was present in 42% of cases, and chronic hypothyroidism in 26%.[10] There are very limited studies available throughout the world and in Pakistan on aetiology of PP in children. The aim of this research was to determine the etiological profile of PP in children.

METHODS

This cross-sectional study was conducted at the department of endocrinology, National Institute of Child Health, Karachi, Pakistan during October 2023 to September 2024 after the approval from "Institutional Ethical Review Board" (IERB-46/2022, dated: 19-09-2023). The sample size was calculated to be 48 using the Open EPI software for "Sample size calculation" by taking the proportion of Arachnoid cyst as 3.22% patients of CPP[9], with 95% confidential level and 5% margin of error 5%. Non-probability consecutive sampling technique was used. Inclusion criteria were children of either gender, girls aged below 8 years, boys below < 9 years, and newly diagnosed cases of PP. Exclusion criteria were children with head trauma, cranial radiation, previous central nervous system infections (meningitis, encephalitis), neurofibromatosis, tuberous sclerosis, or severe hypothyroidism. Parents of children not unwilling to take part in the study were also excluded. PP was described as children (girls < 8 years and in boys < 9 years) who presented with secondary sexual characteristics like rapid height growth, acne or adult body odor. In girls, it is manifested as breast start to grow and menstruation, while in boys, testicles, penis and scrotum start to grow and voice deepening. Informed and written consents were sought from all parents.

Children fulfilling the eligibility criteria were included. At the time of enrollment, gender, age, weight (kg) and height (cm) were noted. Physical examination was performed. Clinical and medical history was documented with the help of parents. X-ray of hands and wrists were performed for the evaluation of skeletal age of the children. Blood sample of each child was collected in aseptic conditions in sterilized container and sent to the institutional laboratory for relevant hormonal screening. Pelvic ultrasound, along with CT or MRI of the brain, were conducted in conjunction with hormonal profiling to confirm the etiology and type of PP. PP was classified into two types: central and peripheral. CPP was diagnosed based on the typical sequence of pubertal development, which isosexual, similar to normal puberty. The etiologies for CPP were evaluated, including idiopathic causes, hypothalamic hamartoma, craniopharyngioma, arachnoid cyst, hypothalamic astrocytoma, and hydrocephalus. PPP was identified based on an atypical pubertal development sequence, characterized by the loss of synchronicity in pubertal changes or contrasexual development (such as virilization in girls or feminization in boys). The causes of PPP were investigated, including congenital adrenal hyperplasia (CAH), adenocarcinoma, ovarian teratoma, and McCune-Albright syndrome.

Data analysis was performed utilizing IBM-SPSS Statistics, version 26.0. Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. Chi-square test was applied to compare categorical data taking $p<0.05$ as significant.

RESULTS

In a total of 48 children, 23 (47.9%) were boys, and 25 (52.1%) girls. The mean age, height, weight, and skeletal age, 5.72±1.78 years, 22.21±4.20 kg, 120.81±14.40 cm, and 7.46±1.85 years, years, respectively. The most frequent clinical features were rapid height growth, adult body odor, and breast enlargement, noted in 48 (100%),

42 (87.5%), and 25 (52.1%) cases, respectively (Table-I).

Characteristics		Frequency (%)
Gender	Boys	23 (47.9%)
	Girls	25 (52.1%)
Age (years)	<5	15 (31.3%)
	5-8	33 (68.7%)
Skeletal age (years)	<5	4 (8.3%)
	5-11	44 (91.7%)
Clinical features	Rapid height growth	48 (100%)
	Adult body odor	42 (87.5%)
	Breast enlargement	25 (52.1%)
	Voice deepening	23 (47.9%)
	Rapid growth of testicles, penis and scortum	23 (47.9%)
	Menstruation	11 (22.9%)
	Facial hairs	19 (39.6%)
	Acne	4 (8.3%)

Table-I. Characteristics of children (n=48)

Distribution of clinical features with respect to gender showed obvious and distinct pattern and the details are shown in Table-II.

Clinical / Presenting Features	Boys (n=23)	Girls (n=25)	P-Value
Rapid height growth	23 (100%)	25 (100%)	1
Acne	4 (17.4%)	-	0.029
Adult body odor	20 (87.0%)	22 (88.0%)	0.913
Breast enlargement	-	25 (100%)	<0.001
Menstruation	-	11 (44.0%)	<0.001
Voice deepening	23 (100%)	-	<0.001
Rapid growth of testicles, penis and scortum	23 (100%)	-	<0.001
Facial hairs	19 (82.6%)	-	<0.001

Table-II. Distribution of clinical features with respect to gender

The comparison of relevant hormone parameters with respect to gender is shown in Table-III.

PP type was central, and peripheral among 25 (52.1%), and 23 (47.9%) children, respectively. Among CPP cases (n=25), the evaluation of etiology revealed that idiopathic in 17 (68.0%) children, hypothalamic hemartoma 3 (12.0%), mitochondrial encephalopathy 2 (8.0%), craniopharyngioma 2 (8.0%), and arachnoid cyst 1 (4.0%). Among 23 PPP cases, CAH was identified in 18 (78.3%) children, adrenocorticol carcinoma 2 (8.7%), ovarian teratoma 2 (8.7%), and Mccune-Albright syndrome in 1 (4.3%).

DISCUSSION

Our study included 48 children, of whom 52.1% were girls and 47.9% were boys. Ahmed et al.[11], observed that 71.8% of PP cases were female. Bajpai et al.[12], reported a female predominance with a 4.4:1 ratio of girls to boys, evaluating PP cohort. This gender bias is widely recognized and is attributed to the fact that girls often experience puberty earlier than boys due to earlier maturation of the hypothalamic-pituitary-gonadal axis.

In our cohort, 52.1% of the children had CPP, while the remaining 47.9% had PPP. This distribution is comparable to findings from Aftab et al.[13], where CPP was reported in 55.8% of the cases. In a study conducted by Dayal et al.[14], CPP accounted for 62% of the cases, with idiopathic causes being predominant. These similarities suggest that CPP is a significant concern in pediatric populations across diverse geographic regions. The distinction between CPP and PPP is essential, as it informs the diagnostic workup and management strategies.

Laboratory Parameters	Male	Female	P-Value
Lutenizing hormone (U/ml)	1.44±1.37	5.39±2.34	<0.001
Follicle stimulating hormone (U/ml)	1.60±1.15	6.97±1.49	<0.001
Estradiol*	-	134.07±132.54	-
Testosterone (ng/dl)#	517.17±218.39	-	-
Thyroid stimulating hormone (mIU/L)	1.69±0.75	1.48±0.52	0.250
17-Hydroxyprogesterone (ng/ml)	150.36±91.14	0.78±0.16	<0.001

Table-III. Comparison of laboratory parameters with respect to gender distribution in children with precocious puberty (N=48)
***only assesed in females; #only assessed in males**

Our study found that idiopathic causes were the most common etiology in children with CPP, comprising 68.0% of the cases. This finding mirrors that of Atta et al.[9], who identified idiopathic causes in 67.7% of their CPP cases. Ahmed et al.[11], reported that 86.3% of their CPP cases were idiopathic. These consistent findings across various studies suggest that idiopathic CPP is the leading cause in most populations, possibly due to the intrinsic variability in the timing of pubertal onset.

We noted that CAH was the predominant etiology among children with PPP, identified in 78.3% of cases. Rai et al.[15], Showed that CAH was reported in 78.5% of the PPP cases, and Atta et al.[9], found CAH to be the main cause in 81.8% of their PPP patients. Bolu et al.[16], reported late-onset CAH as a common cause of PPP, further affirming the association between CAH and peripheral forms of the condition. The high prevalence of CAH in PPP highlights the need for early screening and appropriate treatment for adrenal disorders, particularly in populations with a high prevalence of consanguinity, where autosomal recessive disorders like CAH are more frequent. Ahmed et al.[11], noted that CAH was the cause in 60% of their girls with PPP, reinforcing the importance of investigating adrenal causes in such cases. These findings are critical as they suggest the need for early recognition and hormone replacement therapy to mitigate the long-term impacts on growth and development.

The mean age of our patients was 5.72 ± 1.78 years, and the mean skeletal age was 7.46 ± 1.85 years, reflecting significant advancement in bone age relative to chronological age. This phenomenon is commonly observed in PP. Bajpai et al.[12], found that girls with neurogenic central isosexual PP had an average bone age advancement of 3.4 years, similar to our findings. Our results also align with those of Patel et al.[17], who reported a mean bone age advancement of 3.4 years in children with PP. Such accelerated bone maturation can result in reduced adult height if not appropriately managed, emphasizing the need for early intervention.
Neuroimaging plays a pivotal role in diagnosing the underlying cause of CPP.[18] In our study, hypothalamic hamartomas, craniopharyngiomas, and other brain lesions were identified in several children with CPP. This is consistent with Bajpai et al.[12], who found that hypothalamic hamartomas were a common cause of neurogenic CPP in both boys and girls. The presence of such lesions necessitates careful monitoring and, in some cases, surgical intervention to prevent further complications. Rai et al.[15], also reported hypothalamic hamartomas in 20% of their CPP cases, further highlighting the significance of neuroimaging in these patients. In boys, PPP was primarily associated with CAH and adrenal tumors, similar to the findings of Patel et al.[17], who identified hypothalamic hamartomas as the most common cause of CPP in boys. This highlights the need for targeted diagnostic investigations, such as adrenal imaging and hormonal assays, in boys presenting with PP. The high prevalence of idiopathic CPP and CAH in peripheral cases suggests the need for a standardized approach to the diagnosis and management of PP. Early identification of PP, followed by appropriate imaging and hormonal evaluations, can help clinicians distinguish between idiopathic and organic causes, allowing for timely treatment and intervention.[16,19] Our findings also underscore the importance of addressing the psychosocial impact of PP, particularly in girls. Early breast development and menstruation can be distressing for young girls, leading to emotional and psychological challenges.[20] Education and counseling for both parents and children are essential components of managing PP, particularly in cases where the condition is idiopathic or benign, as suggested by Cemeroglu et al.

One limitation of our study is the relatively small sample size, which may limit the generalizability of our findings to larger populations. Our study was conducted at a single tertiary care center, which may introduce referral bias, as more complex cases are likely to be referred to specialized centers. Another area for future research is the long-term follow-up of children with PP, particularly those treated with GnRH analogs. While short-term outcomes, such as the normalization of pubertal progression and

improvement in adult height, have been well-documented, there is a need for more data on the long-term health and psychosocial outcomes of these patients. In particular, future studies should examine the impact of early pubertal suppression on fertility, bone health, and metabolic outcomes in adulthood.

CONCLUSION

Idiopathic central precocious puberty and congenital adrenal hyperplasia emerged as the most common causes of central and peripheral precocious puberty, respectively. Our findings reinforcing the need for comprehensive evaluations in children presenting with early signs of puberty. Early diagnosis and appropriate treatment can mitigate the long-term effects of precocious puberty on growth and development, improving the quality of life for affected children.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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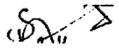
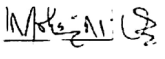
1	Sadia Mehak	Data collection, Drafting, Responsible for data, Approval for publication.	
2	Mohsina Noor Ibrahim	Study concept, Methodology, Proof reading, Approval for publication.	
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