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# Clinical and etiological insights into Central Precocious Puberty: Data from a Pediatric Endocrinology Service

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**Abstract**

***Background:*** *Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, due to early activation of the hypothalamic- pituitary-gonadal (HPG) axis. It is considered a multifactorial condition, associated with both physical and psychosocial challenges.*

***Objective:*** *To describe the epidemiological, clinical features, as well as the etiology of central precocious puberty (CPP) in patients followed at the Pediatric Endocrinology Service, University Hospital Center "Mother Teresa", Albania, during the period November 2012 to May 2020.*

***Materials and Methods:*** *A retrospective descriptive stuty including 33 children diagnosed with CPP. Data regarding age, sex, clinical signs, and etiology were obtained from patient follow-up records. Children diagnosed with peripheral precocious puberty and benign variants of puberty were excluded from the study.*

***Results:*** *Girls represented 93.9% of the cases (female-to-male ratio 15.5:1) with a mean diagnostic age of 6.26 ± 2.59 years. The most common initial sign in girls was thelarche, followed by pubarche and metrorrhagia. Less frequent signs included leukorrhea and characteristic body odor. In both boys, included in the study, genital enlargement and pubarche were observed, accompanied by neurological complaints such as vomiting, drowsiness, headache, and seizures. In 84.8% of cases (28 children), no organic cause was identified—classified as idiopathic CPP. All boys had neurogenic CPP, while 90.3% of girls had idiopathic CPP and 9.7% had neurogenic CPP. The most common CNS lesion was hypothalamic hamartoma.*

***Conclusion:*** *Central precocious puberty predominantly affects girls with idiopathic etiology, while boys more frequently have neurogenic causes. Brain MRI should be considered in all cases, even in the absence of neurological symptoms, to exclude CNS lesions. Early recognition and referral by pediatricians are crucial for optimal management of this condition.*

**Keywords:** Central precocious puberty, thelarche, pubarche, hypothalamic hamartoma

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**INTRODUCTION:**

Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.[1] These limits have been chosen to be 2 to 2.5 standard deviations (SD) below the mean age of onset of puberty. In most populations, the mean age of onset of puberty is approximately 10.5 years in girls and 11.5 years in boys, with a SD of approximately one year.[2] Precocious puberty is responsible for the early progression of secondary sexual characteristics, rapid bone maturation, reduced final height, inappropriate physical appearance for chronological age, and psychosocial problems. Underlying this process is premature activation of the hypothalamic-pituitary-gonadal (HPG) axis,which may occur due to central or peripheral causes.[3,4] Its cause can range from a variant of normal development (e.g.: isolated premature adrenarche or isolated premature thelarche) to pathological conditions with significant risk of morbidity and even death (e.g.: malignant germ cell tumor and astrocytoma).

Precocious puberty can be classified in Central precocious puberty (CPP), Peripheral precocious puberty and benign/ isolated variants of puberty.

CPP—also known as gonadotropin- dependent precocious puberty or true precocious puberty— is caused by early maturation of the HPG axis. CPP is characterized by the sequential maturation of the breasts and pubic hair in girls and the enlargement of the testes, penis, and pubic hair in boys. In these patients, sexual characteristics are always the same as the sex, i.e., isosexual. CPP is pathological in 40–75% of cases in boys,[5,6] compared with 10–20% in girls.[7,8]

The etiological causes of CPP include: idiopathic CPP, CNS lesions, CNS radiation, and congenital anomalies.

Lack of discovery of an identifiable cause leading to early activation of the HPG axis is considered the idiopathic form of CPP. Idiopathic form is present in 80–90% of cases in girls, but only in 25–60% of cases in boys.[7]

Many different types of intracranial lesions can cause precocious puberty. Hamartomas of the hypothalamus are benign tumors that may be associated with gelastic (laughing or crying) and other types of seizures. They are the most common type of CNS tumor that causes precocious puberty in very young children, although in most cases, the mechanism by which these tumors lead to CPP is unknown.

Other CNS tumors associated with precocious puberty include astrocytomas, ependymomas, pinealomas, hCG- producing germ cell tumors, and optic and hypothalamic gliomas.

Precocious puberty is a rare complication of CNS radiation, but when it occurs, it is usually associated with growth hormone (GH) deficiency.[9,10,11]

Acquired CNS lesions caused by inflammation, surgery, trauma, abscess and congenital anomalies (hydrocephalus, arachnoid cysts, suprasellar cysts, optic nerve hypoplasia) are rarer causes of CPP.

**RESULTS:**

During the study period, 33 children were diagnosed with central precocious puberty. Of these cases, 31 were female (93.9%) and 2 were male (6.1%), giving us a female-to-male ratio of 15.5/1. (Figure 1)

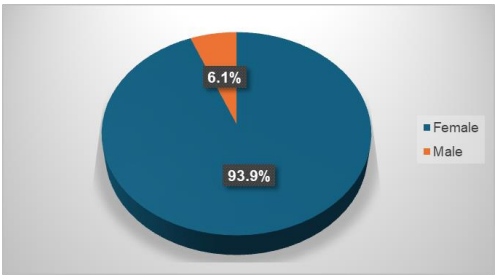


**Figure 1**

The results show a strong predominance of the female gender in children with CPP. The mean age of children was 6.26±2.59. The youngest child was 6 months old and the oldest one was 10 years old.

Of the 33 patients included in the study, the age group with the highest number of patients was 6-8 years old, with 16 cases or 48.5% of the total. The age groups with the fewest cases were those > 8 years old and those < 6 years old, respectively with 8 cases or 24.2% and 9 cases or 27.3% of the total. (Figure 2)

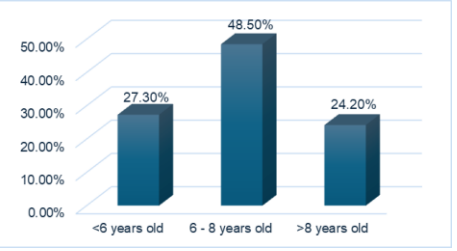


**Figure 2**

Physical examination of children reveals the presence of secondary sexual characteristics. One or more of these characteristics may be present in the same child. Figure 3 shows the clinical presenting features of girls with CPP.

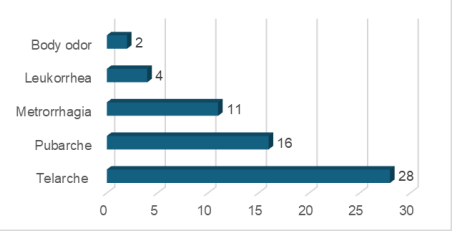


**Figure 3**

The most common presenting clinical feature noted during physical examination of girls is thelarche. In our study, thelarche was present in 28 cases or 90.3% of girls diagnosed with CPP. The other clinical feature most frequently encountered after thelarche is the development of pubic hair or pubarche. Pubarche was evident in 16 cases or 51.6% of girls. 11 girls had metrorrhagia, or 35.5% of them. The rarest clinical features are

leukorrhea and characteristic body odor, respectively in 4 girls (12.9%) and 2 girls (6.5%).

In both boys diagnosed with CPP, secondary sexual characteristics were present along with neurological signs and symptoms. Enlargement of the genital organs associated with the development of pubic hair was present in both cases. While, accelerated growth and characteristic body odor were evident in only one case. The accompanying neurological signs and symptoms of the boys were vomiting, drowsiness, headache and seizures.

Of the children analyzed with central precocious puberty, in 28 of them (84.8%) no cause of the disease was identified (i.e., they are idiopathic forms), while in 5 cases (15.2%) an organic cause was identified. (Figure 4)

Idiopathic CPP was present in 28 girls (90.3% of cases) and in no case in boys. Neurogenic CPP, with the presence of an organic cause, was seen in 3 girls (9.7% of cases) and in both boys.

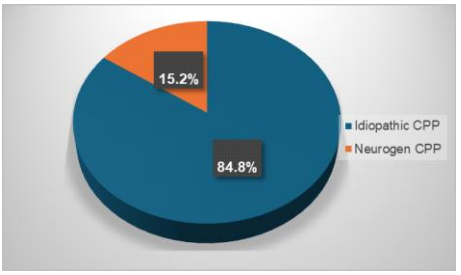


**Figure 4**

From the neuroradiological examinations of the patients, a lesion in the central nervous system (CNS) was found in 5 of them. Two girls resulted with hypothalamic hamartoma and one with septo-optic dysplasia. Hypothalamic hamartomas are benign tumors and often cause CPP. The two girls who resulted with hypothalamic hamartoma did not have associated neurological signs. Hypothalamic hamartoma and craniopharingeoma were found in the boys. (Table 1)

**Table 1**

| | | |
|---|---|---|
| **Female** | Hypothalamic hamartoma | 2 |
| | Septo-optic dysplasia | 1 |
| **Male** | Hypothalamic hamartoma | 1 |
| | Craniopharingeoma | 1 |

**DISCUSSION:**

Puberty is a period of physical, hormonal, and psychological transition influenced by genetics, nutrition, ethnicity, lifestyle changes, and environmental factors. When the endocrine events responsible for these changes occur before the age of 8 in girls and 9 in boys, the condition is defined as precocious puberty. This situation often raises concerns

and uncertainties for both children and their parents, prompting them to seek medical attention.

Our study showed that girls are more frequently affected by this condition, accounting for 93.9% of cases, while boys made up only 6.1%. For reasons still not fully understood, precocious puberty is more commonly observed in girls. The appearance of breast buds— often unilateral or bilateral— is typically the first sign of puberty in girls. This physical change is usually noticed by parents and is concerning due to its early onset, prompting medical evaluation and diagnosis. In contrast, the initial sign of puberty in boys is an increase in testicular volume, a change that often goes unnoticed by parents, resulting in delayed diagnosis and an increased female-to-male ratio.

The mean age at diagnosis in our study was 6.26 ± 2.59 years. Notably, 24.2% of children were diagnosed after the age of 8, suggesting a delay in diagnosis. This may be attributed to late medical presentation due to parental unawareness or insufficient recognition of the condition by primary care providers. Delayed diagnosis and treatment can reduce the effectiveness of therapy.

Among the children diagnosed with CPP in our study, 28 (84.8%) had an idiopathic form, while 5 (15.2%) had an identifiable organic cause. Idiopathic CPP was present in 90.3% of girls and in none of the boys. Conversely, all boys and 9.7% of girls had neurogenic CPP. This reflects a significant association between gender and etiology: idiopathic CPP is predominant in girls, whereas neurogenic CPP is more frequent in boys.

Due to the high incidence of neurogenic CPP in boys, thorough evaluation— including brain MRI— is strongly recommended for all male patients. There is ongoing debate about whether all female patients, particularly those diagnosed after age 6, should undergo MRI due to conflicting data on the risk of CNS abnormalities in this group. A 2018 meta-analysis found a 3% prevalence of intracranial lesions in girls diagnosed after age 6, compared to 25% in those diagnosed earlier.[12] Another study reported brain abnormalities in 6.3% of girls with CPP onset after 6 years. Earlier onset of puberty and higher basal levels of LH and estradiol have been proposed as predictors of CNS lesions.[13] Some authors recommend MRI for all girls with CPP, even in the absence of neurological signs. In our study, no significant differences were found between girls with or without brain lesions in terms of age at diagnosis or clinical presentation. Therefore, we recommend brain MRI for all patients to rule out intracranial pathology.

In neurogenic CPP, a variety of CNS lesions can be identified via MRI, including hypothalamic hamartomas, optic gliomas, arachnoid cysts, astrocytomas, ependymomas, hydrocephalus, septo-optic dysplasia, pineal tumors, trauma, and infections. Among these, hypothalamic hamartoma is the most frequent cause. These are congenital, non-progressive lesions characterized by ectopic tissue growth at the base of the hypothalamus. The exact mechanism by which they activate the HPG axis is unclear. Clinically, they present with precocious puberty or gelastic seizures, which are often resistant to antiepileptic drugs. In our study, hypothalamic hamartoma accounted for 60% of neurogenic CPP cases.

Another concern in children with precocious puberty involves psychosocial and emotional wellbeing. The physical changes and the discrepancy between chronological and biological age can cause psychological stress. These children are at higher risk of difficulties in school, inappropriate sexual behavior, social maladjustment, substance abuse and mood disorders. Psychological support is therefore essential.[14,15]

**CONCLUSION:**

Central precocious puberty is significantly more prevalent in girls, with idiopathic forms being most common. Boys are more likely to have underlying CNS abnormalities. MRI should be considered in all cases, even in the absence of neurological complaints, to rule out organic causes. Routine monitoring of secondary sexual characteristics by general pediatricians and early referral to pediatric endocrinologists are essential for timely diagnosis and treatment.

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