Diagnosis of Precocious Puberty in Girls

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Abstract: Puberty is one of the most astonishing periods of human life, when significant physical alterations occur along with psychosocial maturation. Precocious Puberty (PP) is defined as the appearance and progressive development of secondary sexual characteristics at a younger age than the general population, *i.e*. for Caucasian girls before 8 years of age. Untreated precocious puberty usually leads to short stature and can also cause significant emotional and behavioral issues. In recent years, an increased incidence of PP has been found in many countries although several studies now suggest that this trend has slowed down over the last decade in most industrialized countries, while persisting in other countries. Some girls with idiopathic precocious puberty may also have slowly progressive pubertal development without deterioration of their predicted height over a 2-year follow-up period. It is important to determine which girls to treat and the role of the clinician remains crucial. The clinician also needs to be familiar with the terminology of pubertal progression.

The aim of this review was to examine the diagnosis of central precocious puberty (CPP) taking in account clinical practice and international literature.

Keywords: Puberty, Thelarche, Precocious puberty, Pubertal progression, Early puberty, Gonadotropin-releasing hormone (GnRH), GnRH agonists.

INTRODUCTION

Puberty usually occurs when the hypothalamus-pituitary-gonadal (HPG) axis is activated and the pulsate secretion of the gonadotropin-releasing hormone (GnRH) starts. The neuropeptides kisspeptin and neurokinin B appear to play an important role in initiating GnRH release from the hypothalamus [1, 2]. During this phase of pubertal development, individuals attain secondary sexual characteristics and reproductive capacity. The onset of puberty is clinically defined as the first appearance of breast buds and is affected by many factors including genetic, metabolic, environmental, ethnic, geographic, and socioeconomic conditions [3, 4]. So, in girls the gonadotropin-dependent increase of ovarian estradiol secretion causes breast development (thelarche) at a mean age of 10 years (range: 8-12 years) and menarche typically follows 2.5 years later, at an average age of 12.5 years. Pubic hair appearance, which is adrenal androgen-dependent, may begin before, together with or after the clinical onset of puberty. The pubertal growth spurt typically occurs during Tanner stages II–III, before the first menstrual period, called menarche, which usually occurs at Tanner stage IV. After the first menses, girls continue to grow an average of 5-7 cm before reaching their final height.

Early-onset of puberty (EP) in girls ranges from common variants including premature thelarche (*i.e*. isolated non-progressive breast increase), adrenarche (driven by adrenal androgens leading to progressive appearance of pubic and axillary hair) and menarche (*i.e*. isolated prepubertal vaginal bleeding not caused by trauma) to rare pathologic processes such as

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precocious puberty (PP). Causes of abnormal EP maturation may be divided into GnRH-dependent and GnRH-independent processes. The former, known as central precocious puberty (CPP), results from the activation of the hypothalamic-pituitary-gonadal (HPG) axis due to abnormalities in the central nervous system while the latter originates outside of the HPG axis due to adrenal hyperplasia. A particular form of gonadotropin-independent precocious puberty is McCune–Albright syndrome, which is associated with mosaic cafe-au-lait skin pigmentation and fibrous dysplasia of bone [5].

It has been reported that puberty occurs earlier in girls with early maternal menarche, low birth weight or excessive weight gain in infancy, after international adoption, and after exposure to estrogenic endocrine-disrupting chemicals [6, 7]. Although the exact threshold for "normal" pubertal timing has been a subject of some debate, PP is normally defined as the appearance and progressive development of secondary sexual characteristics at a younger age than that of the general population, *i.e*. for Caucasian girls before 8 years of age [8]. PP is classified, according to the underlying physiopathological process, as CPP when early maturation of the HPG axis occurs. A girl with CPP typically follows the standard pubertal progression, which begins with breast budding, an increase in growth velocity from rising estrogen and insulin-like growth factor-I, and progressive breast enlargement culminating in menarche around 2.5 years later.

EP may be observed in girls with a progressive development of secondary sexual characteristics after eight years of life but before the age of ten. This condition is self-limiting in most girls but may progress into PP in a subset of girls [9]. Therefore, it must be monitored and if a progression towards PP is observed, the pediatric endocrinologist has to evaluate whether treatment to slow down puberty should be started. The incidence of PP has increased throughout the 20th century. Previously, these trends were largely explained by improved public health and nutrition, but endocrine disrupting chemicals (EDCs) are recently drawing public scrutiny [10]. Several studies now suggest that while this trend has slowed down over the last decade in most industrialized countries, it persists in other countries. On the other hand, some girls with idiopathic precocious puberty may experience slowly progressive pubertal development without deterioration of their predicted height over a 2-year follow-up period [11].

Their condition is benign since they achieve their genetically determined height potential and reach normal adult height without treatment [12, 13]. Therefore, there is a subgroup of patients in whom treatment may not be necessary in order for them to achieve normal growth and reach their target height. However, patients with PP need to be monitored closely, because treatment may be necessary in up to a third of cases [14].

The aim of this review was to examine the diagnosis of CPP taking in account clinical practice and international literature**.**

DIAGNOSTIC APPROACH

Clinical Assessment

The Diagnostic approach in evaluating girl with precocious puberty is schematized by Figure **1**.

The first step in evaluating a girl with precocious puberty is to obtain a complete family history, *i.e*. age at onset of puberty in parents, and personal history, including the age at onset of puberty and progression of pubertal signs in the girl.

When precocious puberty is suspected, the pediatric endocrinologist needs to consider a number of questions:

- "How long ago (weeks or months) did the mammary gland appear?" and "Is pubertal development likely to progress?" In at least 50% of cases of precocious pubertal development, pubertal manifestations will regress or stop progressing, and no treatment is necessary [15]. Although the mechanism underlying these cases of nonprogressive precocious puberty is unknown, it has been observed that the HPG axis is not activated in these girls. On the other hand, for cases in which precocious puberty progresses, concerns include early menarche in girls and short adult stature due to early epiphyseal fusion.
- "Is it associated with a risk of other serious conditions, such as headache, loss of balance, visual impairment, clear changes in personality?"
- "Is there a family history of precocious puberty?"
- "Did the parents notice a sudden spurt of growth in their daughter?" The Clinician should evaluate growth patterns because progressive precocious

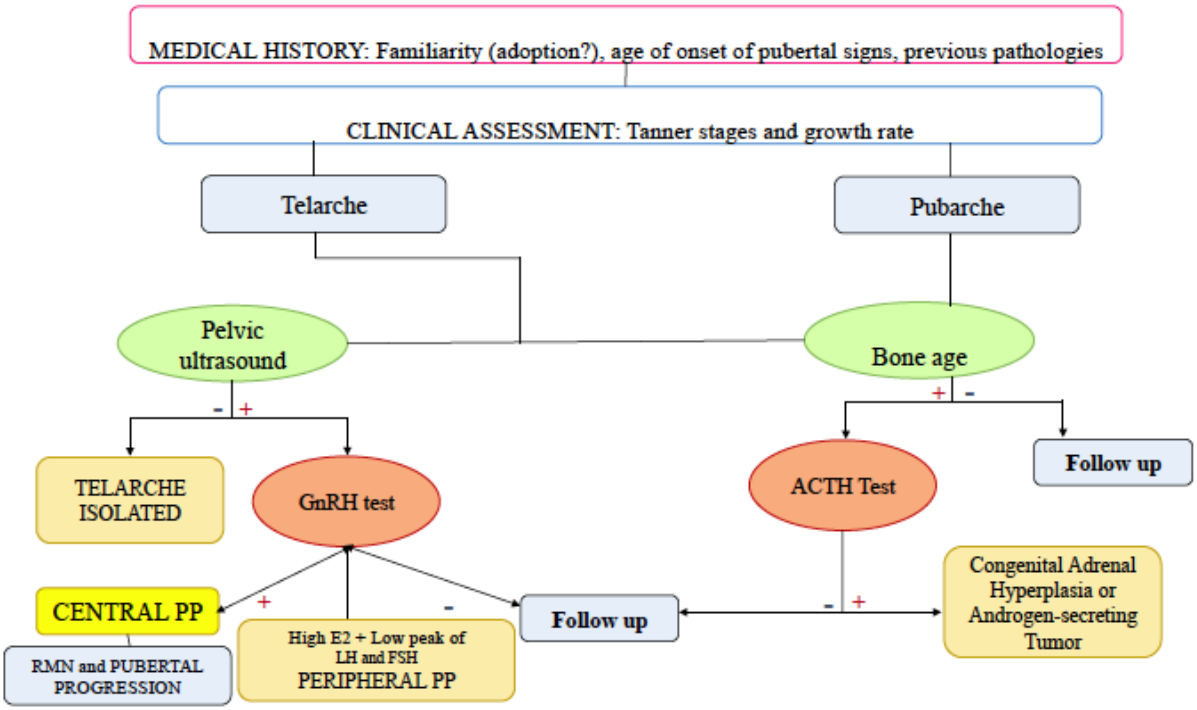

Figure 1: Diagnostic approach in evaluating girls with precocious puberty.

puberty is almost invariably associated with a high growth velocity that may also precede the onset of pubertal manifestations.

Another aspect to consider is that in girls, pubic hair in the absence of breast development is suggestive of adrenal disorders, premature pubarche, or exposure to androgens.

Furthermore, the physical examination should include an assessment for facial acne or hyperpigmented skin lesions suggesting neurofibromatosis or tuberous sclerosis or the McCune–Albright syndrome (café-au-lait spots).

The bone age of patients with precocious puberty is generally advanced in relation to chronological age. On average, girls complete linear growth at 15 years of skeletal maturation. However, the absence of advanced bone age does not justify the interruption of the diagnostic process when increased growth velocity and other clinical symptoms of progressive puberty are present. Bone age advancement depends on how long before the clinical evaluation the HPG axis was activated. In fact, some parents do not give importance to the early signs of puberty, such as the appearance of the mammary gland or occurrence of pubertal spurt. Therefore, the girl's hormonal mechanism may have already been triggered by the time she is brought to the physician's attention. Although bone age is typically advanced, this is certainly not exclusive to CPP and may be seen to a milder degree in numerous other conditions [16]. Moreover, bone age is often used to predict adult height, although this prediction is rather unreliable as it tends to overestimate adult height [17].

Pelvic ultrasonography can be useful, mainly in girls with early pubertal development, as a means of identifying the presence of ovarian tumors or cysts. An ovarian volume of >1.8 mL and uterine length of >3.4 cm indicate hormonal stimulation and may be useful additional laboratory parameters to evaluate girls with precocious puberty [18]. Microcysts and ovarian follicles are normal findings in approximately 40% of prepubertal girls. Changes in uterine longitudinal diameter due to estrogen exposure can also be used as an index of progressive puberty in girls. However, pelvic ultrasonography alone cannot distinguish between prepubertal girls and early pubertal girls because of the overlap in uterine and ovarian dimensions in these two conditions [19]. Finally, clinicians should also bear in mind that ultrasound results may be technician dependent.

Magnetic resonance imaging (MRI) of the brain should be required to investigate possible hypothalamic lesions in all cases where diagnosis of cerebral abnormalities is associated with CPP. In particular, young age, rapid pubertal progression, and high

estradiol concentrations are factors that might predict an increased risk of brain abnormalities. The prevalence of such lesions is higher in boys (40–90%) than in girls (8-33%) and is much lower when puberty starts after 6 years of age in girls (about 2%) [20, 21]. The hypothalamic hamartoma is the most common organic cause in both sexes, usually manifesting before 4 years of age [22]. Surgical treatment is only indicated for large hamartomas with neurological symptoms (prevalence 4-5%), including refractory epilepsy and intracranial hypertension [23]. Among the most frequent incidental findings are pituitary abnormalities, including microadenomas and pineal cysts [24, 25].

Basically, to evaluate a patient with precocious puberty, the clinician must know the normal chronology of pubertal events and growth rate, and the progression of bone maturation. A progression from one stage to another in less than six months and a height velocity above the previous percentile characterize a progressive condition. Height, weight, and height velocity should be plotted in reference curves; height in patients with precocious puberty is generally found to be above the familial pattern.

Hormonal Assessment

The clinical suspicion of precocious puberty must be confirmed by laboratory results. The gold-standard biochemical diagnosis is based on the assessment of gonadotropins, mainly LH, after stimulation with exogenous GnRH or GnRH agonists [20]. The development of laboratory methods with high sensitivity and specificity has given rise to the suggestion that baseline random LH could be used to assess the activation of the gonadotropic axis, thus avoiding the need to test the GnRH-stimulated LH concentration [26, 27]. However, several studies have demonstrated that the diagnostic value of basal LH is variable [28,29]. Indeed, basal ultrasensitive LH is often within the prepubertal range in early CPP and thus may be falsely reassuring [30]. In the past the test with GnRH analogue has been proposed over the classical GnRH test to assess the ovarian response providing a comprehensive evaluation of HPG. Previous studies in girls with premature sexual development have shown that the stimulating effect on HPG achieved by a single injection of GnRHa induces a serum E2 rise [31].

Caution should be used when interpreting gonadotropin concentrations in children under 2 or 3 years of age, because baseline gonadotropin concentrations are usually high in this age group (20). Some investigators have suggested that a simplified test with a single measurement 30 or 40 minutes after GnRH is sufficient to confirm activation of the gonadotropic axis [32]. Cut-off values of an LH peak higher than 5 IU/L, assessed by ultrasensitive immunoassays, are usually indicative of an activated gonadotropic axis [33].

In girls, serum levels of E2 are not used to diagnose CPP, considering their low sensitivity and the significant overlap between normal prepubertal and pubertal children [34]. Low concentrations of estradiol in girls do not rule out a diagnosis of precocious puberty. In fact, prepubertal estradiol concentrations are present in many girls affected by CPP. On the other hand, high concentrations of estradiol in the presence of low concentrations of gonadotropins strongly suggest a peripheral cause of precocious puberty [18, 20]. The criteria for assessing CPP's progress are shown in Figure **2**.

Diffrential Diagnosis of Precocious Puberty

Firstly, the pediatric endocrinologist might carefully discriminate between CPP and its common variants, such as premature thelarche or adrenarche [20, 27]. These conditions occur independently of the reactivation of gonadotropic axis. Premature thelarche is defined as an isolated development of breast tissue in absence of accelerated linear growth or rapid progression of breast development, or advanced skeletal maturation. It often occurs in girls during their first years of life and usually regresses over several months [35]. Premature adrenarche is characterized by gradually progressive pubic or axillary hair growth due to slightly increased concentrations of adrenal-derived androgens [36]. Therefore, girls with pubic hair or axillary hair and no breast development, are likely to have premature adrenarche or a peripheral cause of precocious puberty. Peripheral precocious puberty (PPP) occurs when hormonal influences originating outside of the HPG axis produce incomplete, atypically sequenced and rapid pubertal progression [37]. Quickly progressing or significant hyperandrogenic findings may warrant workup for congenital adrenal hyperplasia or an androgen-secreting tumor. Elevated estradiol levels may suggest an estrogen-secreting tumor [37]. Hypothyroidism and exogenous steroid use should be excluded. Multiple café-au-lait spots and fibrous dysplasia of bones may be indications of McCune-Albright syndrome or neurofibromatosis [37].

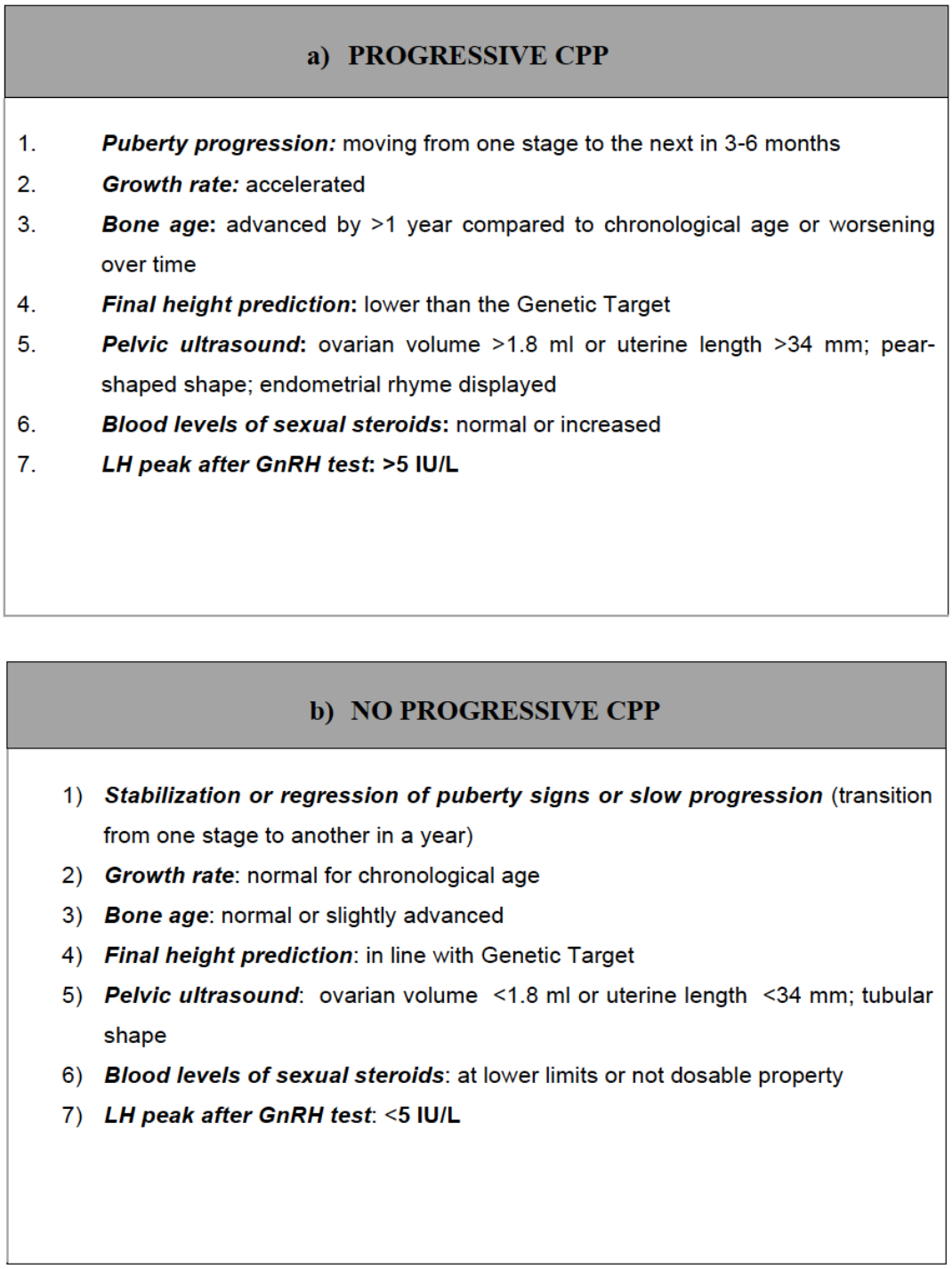

Figure 2: Criteria for assessing CPP's progress **a**) progressive CPP **b**) no progressive CPP.

Isolated prepubertal vaginal bleeding, with no other signs of puberty, are generally benign but must be distinguished as dependent or non-dependent on hormonal action. It is worthy of note that prepubertal vaginal bleeding rarely represents the first manifestation of CPP. In addition, recurrent or continuous bleeding requires further investigation.

GnRH-independent central precocious puberty must be distinguished from peripheral precocious puberty. Therefore, early breast development is not always a manifestation of CPP, and clinical and laboratory investigations are useful in reaching a diagnosis. Clinical indicators of pubertal progression carry more weight than hormonal tests and imaging. A period of

clinical observation is highly recommended before any pharmacological intervention.

Earlier pubertal timing in girls is one of the best-replicated antecedents of adolescent mental health problems, including depression, anxiety, disordered eating, delinquency, substance use, and school failure or dropout [38]. In addition, result from a recent study suggest that girls who experienced earlier menarche continued to report elevated psychopathology in early-to-middle adulthood even after accounting for demographic and contextual variables commonly associated with vulnerability for mental health. Earlier age at menarche was associated with higher rates of both depressive symptoms and antisocial behaviors in early-middle adulthood largely because difficulties that started in adolescence did not attenuate over time [39].

CONCLUSION

Precocious puberty is becoming increasingly common owing to a multitude of factors such as genetics, lifestyle changes, and exposure to endocrine-disrupting chemicals. It is a frequently encountered condition in pediatric endocrinology practice, and one which raises a number of concerns and uncertainties in parents and children. Emotional changes are the most important concerns of parents and patients. Therefore, the early recognition, sufficient understanding, and communication about physical development rates that differ from the norm are required for patients, parents, and medical care providers. Furthermore, patients should provide psychological support for the perception of a healthy self-image in patients. Longitudinal studies on changes in psychosocial problems and on the differences in the effects of GnRH agonist are required in patients with precocious puberty. Given research is scant regarding the relationship of negative outcomes of technology on puberty, greater attention might be placed on critical media literacy to help pubertal girls explore the role of media in their identity development and body ideal. Girls' pubertal timing is directly connected to mental health. The sequelae of earlier development are not transient growing pains but are predictive of difficulties and challenges that persist into adulthood. This revision offers practical information for pediatricians and adolescent health care providers. In fact, the diagnosis and taking charge with appropriate treatment of early puberty is essential to avoid permanent emotional sequelae.

This condition is best managed by an interprofessional team that includes an endocrinologist, pediatrician, nurse, surgeon (if involving masses or tumors) and a mental health counselor.

ABBREVIATIONS

FSH: Follicle stimulating hormone

LH: Luteinizing hormone

GnRH: Gonadotropin-releasing hormone

E2: Estradiol

aGnRH: GnRH analog

CPP: Central precocious puberty

PPP: Peripheral precocious puberty

EP: Early Puberty

AUTHORS' CONTRIBUTIONS

RG and VC wrote the manuscript and revised the literature; GF and MG analyzed data; CMM gave technical assistance; EB, AV and MB designed the study, revised the manuscript and gave conceptual advice. All authors read and approved the final version of the manuscript.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests.

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