

"Beyond the Onset: A Comprehensive Analysis of Risk Factors and Etiological Mechanisms in Central Precocious Puberty"- A systematic review

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Abstract

Objectives: The purpose of this systematic review is to understand the recent advances that have been made in understanding the risk factors and etiology behind the rising incidence of precocious puberty in children. The key goals are to assess to understand the normal physiology of the hypothalamic-pituitary-gonadal (HPG) axis and the various theories that have been proposed that influence the normal functioning of the HPG axis leading to central precocious puberty.

Methods and Results: A systematic search was undertaken across various databases including Pubmed, Scopus, Embase, Web of Science, and Medline following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The initial search yielded 9097 articles. After removing the duplicates and title/abstract screening, the remaining articles were assessed for quality appraisal based on the AMSTAR checklist. Of these, 15 articles met the inclusion criteria and were included in this study.

Conclusion: Central Precocious Puberty is caused by an early activation of hypothalamic-pituitary-gonadal (HPG) axis. This review focuses on the abnormalities in the regulation of HPG axis leading to early puberty especially the molecular interactions between the HPG axis and GnRH neurons. Recently, mutations in MKRN3 and DLK1 have been implicated in both familial and sporadic CPP which significantly changed the current treatment strategy of CPP. Several syndromic illnesses and anomalies of the central nervous system are also associated with CPP. These diseases can have detrimental effects on one's physical, psychological, and physical health if they are not treated.

Categories: Pediatrics, Endocrinology, Adolescent medicine

Keywords: Central precocious puberty, risk factors, pediatric population, adolescent, endocrinology

Introduction

One of the more prevalent problems seen in pediatric endocrinology practice is precocious puberty. New stories about increasingly early pubertal development have appeared in the press, increasing the frequency with which families inquire about their children's pubertal growth. New knowledge has been available in the recent two years, notably about medicines and results, making an update in this sector timely.

Precocious puberty is described as the production or exposure to sex hormones happening earlier than the standards for gender and racial or ethnic origin. What is the prevalence of precocious puberty? On the basis of a population-based registry, the prevalence of all forms of precocious puberty in Denmark has been estimated as 0.2% of female children and < 0.05% of male children. Over an 8-year period, the annual incidence of premature puberty in female children ranged from 15 to 29 per 100,000 girls. The incidence was roughly 10- to 15-fold lower in male children [1]. These percentages of children diagnosed with all forms of precocious puberty include children with premature thelarche (PT), premature adrenarche (PA), and early normal maturing youngsters, as well as 46% with true central precocious puberty (CPP). Estimates from a large hospital-based registry in Spain recently estimated the annual incidence of CPP in female children at 1.1 per 100 000 [2]. Although this appears to be far lower than the Danish study, there were important methodological variations, such as limiting data collection to tertiary care facilities with pediatric endocrinology services, including only those with CPP, and using a stricter diagnosis of precocious puberty.

This paper will provide a brief overview of the changes that occur during pubertal development in normal children, as well as some of the neuroendocrine systems that regulate this process. The question of how early is too early for puberty has sparked significant debate. Due to space limits, a comprehensive study of this debate is impossible, although some recent pieces will be discussed. The emphasis will then transition to precocious puberty, with a focus on recent advances in identifying the risk factors and etiology.

Methods

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3].

Databases: A systematic search was conducted on Pubmed, Scopus, Embase, Web of Science, and Medline and focused on papers that were published between 2018 to 2023.

Search Strategy: The following search keywords were used on the databases - Risk factors, etiology, central precocious puberty, OR "Puberty, Precocious/etiology"[Majr:NoExp] OR "Puberty, Precocious/genetics"[Majr:NoExp])

Screening: After removing the duplicates, two reviewers (1st and 2nd Authors) independently checked the titles and abstracts of the publications for eligibility after eliminating duplicates. When there was no agreement, the eligibility was evaluated by a third reviewer who was not involved in the initial review.

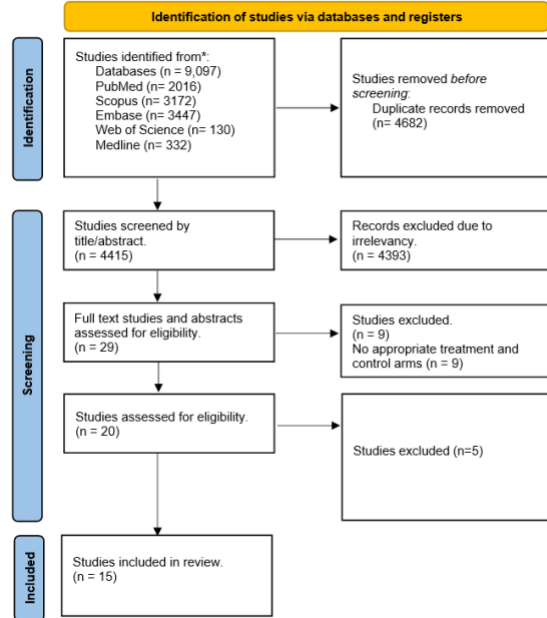
Inclusion Criteria: This study includes papers that are written and published in the English language, papers focusing on the pediatric age group, papers that have been published in the last five years, papers involving studies on humans and mice, and papers involving full-text.

Exclusion criteria: This study does not involve papers involving the adult population and papers that involve grey literature.

Quality Assessment Tools: Using the AMSTAR checklist, two reviewers (first and second authors) independently evaluated the quality of each chosen article. Using standardized forms, data was retrieved from and kept on an electronic database using Microsoft Excel (version 16.74; Microsoft Inc.). To resolve the differences in quality assessment and data extraction, the two reviewers convened a meeting to reach a consensus.

Results: A total of 9097 articles were found using a keyword search through five databases. There were 4682 duplicates removed, and 4393 articles were eliminated following title and abstract screening. We retrieved full-text articles of all the remaining 29 papers, and these were screened using the inclusion/exclusion criteria, with 14 articles removed that did not fulfill the inclusion criteria.

Flow chart depicting identification of studies through literature search



Finalized studies and their characteristics

Finalized Study	Study type	Aim	Year of participants	Age period of age	Follow up	Conclusion
1. Prevalence and Incidence of Precocious Pubertal Development in Central and Epiphyseal Study Based on National Registers	Epidemiologic study	estimate the prevalence and incidence of precocious pubertal development in Denmark in a 9-year period.	60	Girls 6-9 years Boys 6-9 years	9 years	0.2% of all Danish girls and 0.05% of Danish boys had some form of precocious pubertal development.
2. Central Precocious Puberty in Children Living in Spain: Incidence, Prevalence, and Relation of Adiposity and Intergenic Pathology	Observational study	assess the risk of developing CPP among children and teenagers, and study the relation of variables of CPP associated with intergenic pathology.	290	Girls 6-9 years Boys 6-9 years	12 years	Risk of CPP markedly increases with both national and international adiposity but is not influenced by migration, suggesting psychological influences on CPP.
3. Sexual precocity after menopause from developing countries to reduce evidence of previous exposure to organochlorine pesticides	Retrospectively study	mechanism of precocious puberty might involve previous exposure to organochlorine pesticides found in organochlorine pesticides	148	Girls 6-9 years Boys 6-9 years	9 years	A possible relationship between transient exposure to endocrine disruptors and sexual precocity was found.
4. Central precocious puberty: Recent advances in understanding the aetiology and the clinical approach	Systematic review	To understand various risk factors and etiology being CPP	NA	Girls 6-9 years Boys 6-9 years	NA	MRXN, DMF, AINS and KINS, mutation, NOTCH and SHOX have been implicated in the recent cases.
5. Obesity as a risk factor for central precocious puberty: a case-control study	Case-control study	To understand the role of obesity in CPP	88	Girls 6-9 years Boys 6-9 years	9 years	Precocious menarche and obesity in early childhood may be risk factors for CPP, especially in female children
6. The Congenital and Acquired Mechanisms Implicated in the Etiology of Central Precocious Puberty	Anatomic review	To understand the role of congenital and acquired mechanisms in CPP	NA	Girls 6-9 years Boys 6-9 years	NA	The etiology of CPP is multiple and heterogeneous, including diverse congenital and acquired causes that can be associated with different lesions or functional alterations of CNS.
7. A review of the genetics and epidemiology of central precocious puberty	Anatomic review	To understand the role of genetics and epidemiology in CPP	NA	Girls 6-9 years Boys 6-9 years	NA	Central precocious puberty may have multiple etiologies: developmental, anatomic, environmental, genetic, and idiopathic.
8. Genotype-Phenotype Correlations in Central Precocious Puberty Caused by MKRN3 Mutations	Case study	To describe the clinical and hormonal features of patients with CPP due to MKRN3 mutations.	70	Girls 6-9 years Boys 6-9 years	NA	Severe mutations in MKRN3 result in greater bone age advancement and higher basal LH levels in patients with CPP.
9. Endocrine-Disrupting Chemicals and Early Puberty in Girls	Anatomic review	To understand the role of EDCs in CPP	NA	Girls 6-9 years Boys 6-9 years	NA	The major determinant of early puberty, at least in girls, is the presentation of the growth pattern of constitutional advancement of growth, which is mediated by EDC exposure. Therefore, the role of EDCs on female pubertal timing seems to be a minor one.

Study ID	Study Design	Objective	Population	Intervention/Exposure	Outcome	Notes
10	Cohort	Control environmental factors in Prader-Willi syndrome a rare genetic disorder	21	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	NA	Although rare patients with Prader-Willi syndrome exhibit hyperphagia and type 2 diabetes, there is evidence that GHrelin and Ghrelin may be involved in the pathogenesis of Prader-Willi syndrome.
11	Case study	Endocrine Activity in Girls with Signs of Precocious Puberty as Reported Relative to Endocrine Disrupting Chemicals A Pilot Study	4	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	NA	This study showed only a marginal correlation between EDC exposure and signs of PP. Therefore, it was not possible to confirm the interference of EDCs on HPG axis, nor their contribution to the occurrence of PP.
12	Case control	The effect of environmental factors on precocious puberty in children: a case-control study	75	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	months	findings suggest that environmental factors were associated with precocious puberty in children, particularly in girls.
13	Case-control	Genetic etiologies of central precocious puberty and the role of imprinting genes	NA	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	NA	genetic causes of CPP have been identified, including mutations in <i>KMT2D</i> , <i>KAT5B</i> , <i>MIR293</i> and <i>DLX5</i>
14	Case-control	Gender-related differences in etiology of idiopathic central precocious puberty	376	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	20 years	Overall, CPP was 3.5 times more common in boys compared to girls. The likelihood of sexual maturation/puberty associated with CPP is quite low in girls with an onset after six years of age and in boys with an onset after seven years of age.
15	Systematic review	MIR293 role in regulating pubertal onset: the role of an of functional studies	NA	GH, GHrelin, Ghrelin, Ghrelin, Ghrelin	NA	There are multiple ways through which MIR293 exerts its action on puberty onset timing.

Discussion

Physiology Of The Hpg Axis And Puberty

Hypothalamic network regulating the HPG axis

The correct operation of the gonads, pituitary gonadotropes, and the complicated hypothalamic neuronal network is required for the HPG axis to be intact Figure 1. This network's components work together to influence the neurosecretory activity of GnRH neurons [4]. GnRH-expressing neurons form outside the brain during embryonic development in the olfactory placode and travel through the forebrain along the olfactory axons. They eventually settle in a dispersed pattern across the hypothalamus, including the medial septum, the organum vasculosum of the lamina terminalis, and the rostral preoptic area. GnRH neurons are a small population of neurons, and their cell bodies are separated by a large distance. They do, however, extend long axonal projections that cluster together in the median eminence. The ability to generate and sustain a membrane potential within the axon, as well as the unusual nerve terminals with properties of both dendrites and axons (dubbed "dendrons"), are likely essential for producing synchronized covert bursts [5]. GnRH is eventually released into the pituitary portal circulation's neurovascular space to stimulate pituitary gonadotropes. GnRH pulses of adequate frequency and amplitude are required to activate the gonads and create sufficient gonadotrophin release.

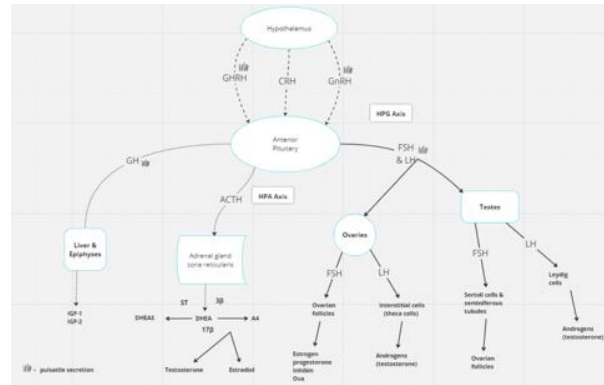


Figure 1. A schematic depiction of the normal physiology of Hypothalamic-pituitary-gonadal (HPG) axes.

A plethora of upstream signals and pathways drive the GnRH pulse generator (Figure 2). Among these, the discovery of kisspeptin is recognized as a watershed moment in reproductive neuroendocrinology. Kisspeptin neurons are found in distinct hypothalamic and extrahypothalamic locations (ARC, AVPV, and amygdala), and kisspeptin directly activates GnRH neurons via its corresponding Gq/11-coupled receptor, KISS1R (also known as GPR54) [6-8]. Kisspeptin neurons also mediate, either directly or indirectly, feedback on the HPG axis exerted by a variety of regulatory inputs such as sex hormones, prolactin, and leptin. The significant GnRH insufficiency reported in men and women with mutations in the genes encoding kisspeptin (*KISS1*) or its receptor, *KISS1R*, demonstrates the importance of kisspeptin in activating GnRH [9]. Rodent studies have verified kisspeptin's role in neurosecretory GnRH release.

Neurokinin B and its receptor, NK3R, have been identified as additional key GnRH activators in humans over the last decade [10]. The co-localization of neurokinin B, kisspeptin, and dynorphin A in the ARC implies the presence of *KNDy* neurons, a group of neurons capable of secreting multiple peptides. Despite compelling evidence in rodents and sheep, the presence of such a population in humans has yet to be proven [11]. GnRH neurons also receive input from glutamatergic and GABAergic neurons, as well as paracrine neuroactive substances emanating from neighboring neuroglia. Tanycytes are specialized glial cells that line the third ventricle and surround the GnRH axon terminals, and their roles appear to favor the synchronization of GnRH terminals to allow for pulsatile GnRH release [12]. Nitric oxide, which is generated by distinct neuronal populations, also aids in neuron-neuron and endothelium-glia communication and is implicated in neuroendocrine reproductive control [13]. This intricate neural network undergoes constant alterations, especially throughout puberty. Remodeling of GnRH fibers occurs in prepubertal rodents, with increasing spine/dendron density at numerous levels in the hypothalami of mice.

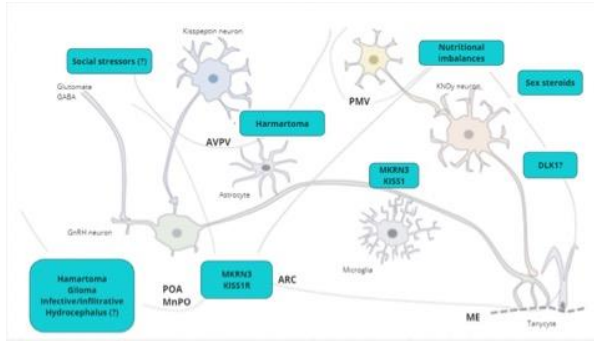


Figure 2. GnRH network in the hypothalamus and potential sites of CPP etiology action are shown schematically. This diagram shows the brain network that regulates GnRH neurons as well as possible regulator action sites and CPP-related illnesses. The main regulatory inputs known to interact with GnRH neurons both directly and indirectly are displayed.

Etiologies of Central Precocious Puberty

Isolated genetic forms of CPP

The discovery of mutations in the MKRN3 gene in people with familial CPP in 2013 was a watershed moment in the understanding of genetic CPP [14]. MKRN3 encodes makorin RING finger protein three, an intracellular protein containing zinc finger motif arrays that are highly conserved. While the MKRN3 protein has multiple putative activities, ubiquitination of substrates is a crucial potential activity [15]. MKRN3 is therefore expected to be involved in cellular processes such as protein degradation, protein-protein interactions, protein stability, and protein quality control. MKRN3 expression studies in rodents and primates indicated that it is abundantly expressed in important hypothalamic locations early in life and gradually diminishes over time, most notably immediately before puberty [16].

Dauber and colleagues revealed a big family with a complicated genetic rearrangement inside chromosome 14 in 2017 [17]. The first exon of DLK1, another maternally imprinted gene, was eliminated by a substantial deletion. This family's lineage confirmed maternal imprinting; individuals developed CPP only after they inherited the mutation from their fathers. Between the ages of 4.6 and 5.9 years, affected female children had thelarche. Bone age was advanced, and high basal and stimulated LH levels supported the diagnosis of CPP [17]. Female children responded positively to GnRH analogs and grew to a near-normal adult height.

Kisspeptin, the natural ligand of the kisspeptin receptor KISS1R, is encoded by KISS1 [18]. To date, only a few sporadic examples of KISS1 mutations have been reported in conjunction with CPP. Silveira and colleagues described two unusual KISS1 mutations in three unrelated children with CPP in 2010 [18]. The

heterozygous mutant P74S was found to be resistant to degradation, implying an enhanced protein half-life and, thus, more sustained activation of downstream signaling. The damaged youngster showed evidence of pubertal progression as early as 17 months of age.

In an adoptive girl with CPP, the R386P KISS1R (GPR54) mutant was discovered in a heterozygous state [19]. As with KISS1 mutations, pubertal signs were observed shortly after birth, indicating that kisspeptin system gain-of-function variants cause very early activation of the HPG axis and confirming that kisspeptin system control of the HPG axis is mediated by kisspeptin system from very early stages [19]. In response to kisspeptin activation, functional investigations of the variant receptor revealed a gain of function, with increased downstream signaling such as inositol phosphate synthesis and ERK phosphorylation.

Syndromic forms of CPP

CPP is found in a variety of uncommon disorders as well as solitary hereditary variants. Pallister- Hall syndrome is a rare syndrome distinguished by polydactyly and/or cutaneous syndactyly, midline abnormalities, and neurological symptoms. CPP is seen in patients who also have a hypothalamic hamartoma. If the diagnosis is suspected clinically (Figure 3), molecular genetic investigations can confirm it. Mutations in the GLI3 coding sequence are observed in the majority of cases, with autosomal dominant transmission. De novo mutations account for 25% of GLI3 mutations [20].

Cowden and Cowden-like syndromes are two cancer-predisposing illnesses caused by PTEN, SDHB-D, and KLLN gene abnormalities [21]. Beyond malignancies, the presence of several multisystemic hamartomas dominates the clinical picture. If these non-cancerous growths involve the skull base, infundibulum, or hypothalamus, they can produce CPP.

Temple syndrome is a relatively uncommon maternally imprinted condition characterized by intrauterine growth retardation, postnatal short height, truncal hypotonia, small hands, and minor facial dysmorphism. In the majority of cases, this condition is caused by a paternal deletion or maternal uniparental disomy of chromosome 14. CPP is one of the most common clinical symptoms, and isolated CPP has been linked to DLK1 mutations (described above). In the context of a contiguous gene syndrome, the development of additional clinical manifestations is most likely attributable to connected gene abnormalities [22].

CPP is also present in a small number of Prader-Willi syndrome (PWS) individuals. Clinically, a variable combination of morbid obesity, cognitive and behavioral dysfunction, and typical dysmorphisms is typical. PWS is linked to the imprinted region on chromosome 15q11, which contains MKRN3, among other genes. As a result, it is likely that only those with MKRN3 deletions or methylation abnormalities are related to CPP in PWS [23].

CNS lesions

CPP has been linked to a number of CNS lesions. The most distinctive are hypothalamic hamartomas, which are extremely rare tumors with an incidence of 1 in 500,000-1,000,000. They can appear sporadically or in conjunction with gelastic seizures and typical skeletal abnormalities, which are characteristics of the Pallister-Hall syndrome or other syndromes.

Hamartomas are non-cancerous overgrowth lesions that are frequently formed of myelinated axons, fibrillary gliosis, and clusters of several tissue subtypes. It is unclear how hypothalamic hamartomas specifically activate GnRH neurons. According to some research, they may stimulate neighboring glial cells (and, in turn, GnRH) via TGF [24]. Older pathological specimen descriptions revealed the presence of GnRH immunoreactivity within the tumor, providing indirect evidence for direct GnRH synthesis. Depending on the age, intensity, and duration of further clinical manifestations and the anatomical location of the lesion, a multimodal therapeutic approach, including medical treatment and/or neurosurgery/radiation therapy, is recommended [25].

Gliomas, particularly those in the tuber cinereum or optic pathways (whether solitary or coupled with NF-1), are another CNS lesion linked to CPP. It has been found that gliomatous cells express the GnRH receptor but not the ligand. It is unclear how this tumor subtype could activate the HPG axis. Only optic pathway or hypothalamic tumors were related to CPP in clinical investigations, including individuals with gliomas, such as those with NF-1. Taken together, these findings show that dysregulation of the HPG axis is caused by the tumor's location rather than its nature [26].

CPP has also been linked to rarer intracranial tumors, non-tumorous lesions, and other CNS illnesses. CPP has been linked to pineal cysts, meningomyelocele, hydrocephalus, and infiltrative, viral, radiation-induced, and cerebrovascular encephalopathies in children. The processes by which lesions that do not involve the hypothalamus might cause CPP to warrant additional exploration.

Etiology	Mechanism
Genetic (isolated CPP)	
<i>MKRN3</i> loss-of-function mutations	Release of HPG axis inhib
<i>DLK1</i> loss-of-function mutations	Unknown
<i>KISS1</i> gain-of-function mutations	Stimulation of the HPG ax
<i>KISS1R</i> (former <i>GPR54</i>) gain-of-function mutations	Stimulation of the HPG ax
Syndromic	
Type 1 neurofibromatosis	Optic pathway glioma
Temple syndrome	<i>DLK1</i> -related
Prader-Willi syndrome	<i>MKRN3</i> -related
Pallister-Hall syndrome	Hamartoma
Tuberous sclerosis (Bourneville disease)	Hamartoma
Cowden syndrome	Hamartoma
Cowden-like diseases	Hamartoma
Cohen syndrome	Hamartoma

Table 1. Summary of Etiologies of Isolated CPP and Syndromic CPP.

Social stressors and nutritional imbalances

One of the most generally established risk factors for CPP is adoption. Soriano-Guillen and colleagues calculated a 25 percent relative risk of developing CPP in females and 36 percent in male children. The mechanism behind the causal link between adoption and CPP is currently unknown. There is currently debate over the impact of emotional and environmental factors. A probable trigger among the latter is an early-life nutritional insufficiency followed by increasing obesity following adoption [27, 28].

The relationship between childhood obesity and pubertal advancement is now being discussed. Among the biochemical indicators associated with obesity, leptin appears to be the most likely candidate as a mediator of pubertal advancement because it is generally acknowledged as a permissive regulator of kisspeptin and hence GnRH. PACAP is a neuromodulator that is expressed in a subset of neurons in the ventral pre-mammillary nucleus of the hypothalamus. It is thought to respond to leptin stimulation and to play a role in the activation of kisspeptin neurons in the arcuate and AVPV nuclei [29]. Other central metabolic mediators, such as melanocortin, - MSH, and peripheral cues, such as ghrelin and insulin, may influence GnRH and puberty start directly or indirectly. Observational research on the relationship between BMI and age at menarche has proved ambiguous. A recent study indicated that female children with obesity had a higher rate of early puberty, but there was no difference in the

age of menarche between female children with normal weight and those with obesity [30, 31].

Endocrine disruptors and hormone exposure

Exposure to sex steroids or substances with estrogenic action has also been linked to an increase in the age at menarche. Childhood exposure to dichlorodiphenyltrichloroethane (DDT) and other chemicals with estrogenic characteristics has been linked to puberty advancement. Several studies suggest that endocrine-disrupting chemicals (EDCs) may impact pubertal timing, most likely through estrogen-like actions, especially during a critical developmental window. Nonetheless, the evidence is still ambiguous that these chemicals produce CPP or cause alterations in pubertal timing [32].

Chronic exposure to endogenous gonadal or adrenal hormones, in addition to initiating peripheral puberty, may also promote central HPG axis activation. As a result, children with congenital adrenal hyperplasia, McCune-Albright syndrome, or autonomous ovarian/testicular steroid secretion in infancy, such as by a steroid-producing adrenal or gonadal tumor, are all at risk of premature HPG axis activation [33].

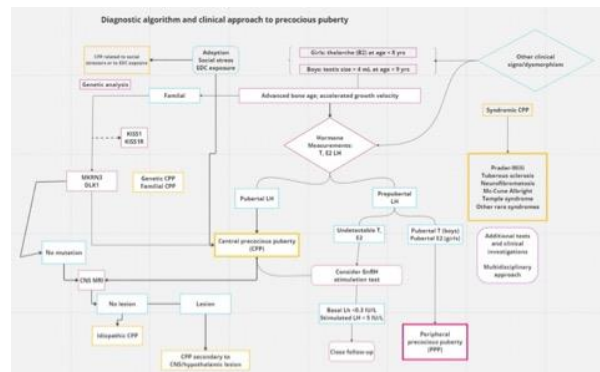


Figure 3. A technique to evaluating premature puberty using a diagnostic algorithm.

Precocious puberty must be looked into in female children who exhibit thelarche (i.e., B2 breast growth) before the age of eight or in male children whose testicles are larger than 3 mL (or >2.5 cm in length). To confirm the clinical suspicion, growth velocity, and bone age need to be carefully analyzed. Genetic testing is suitable for familial forms (first- or second-degree relatives). When a harmful mutation is found in one of the known CPP-related genes, genetic CPP can be diagnosed, necessitating a wider familial screening. The gonadotrophin and luteinizing hormone (LH), as well as the sex steroids total testosterone (T) in male children and total estradiol (E2) in female children, are all measured as hormones. The diagnosis of CPP is confirmed by pubertal LH levels. Prepubertal LH values indicate peripheral premature puberty when sex steroid hormone levels are high; if sex steroid hormone levels are low and clinical concern remains, further LH

measurements or a GnRH stimulation test are recommended. In this situation, baseline LH >0.3 IU/L or GnRH-stimulated LH >5 IU/L are consistent with CPP. The diagnosis of CPP owing to social stressors may be established in cases of adoption or obvious social pressures. It is recommended to perform a brain/hypothalamic MRI, especially if no known gene alterations are discovered or if additional neurological symptoms exist. CPP is classified as idiopathic if no lesion is visible on an MRI and no mutation is discovered in any of the known CPP genes. The presence of dysmorphic traits and additional clinical signs points to a syndromic origin. A multidisciplinary approach and further tests or studies may be required in addition to CPP diagnosis and therapy. EDCs, or endocrine-disrupting substances, affect the central nervous system.

Conclusion

This analysis focuses on irregularities in hypothalamic regulatory processes, specifically the HPG axis, leading to CPP. We examine diagnosing puberty, emphasizing the causes of CPP. Recent mutations in MKRN3 and DLK1 have changed how we approach CPP, with broader genetic implications. We also explore syndromic disorders and CNS lesions linked to CPP. It's vital to address these conditions comprehensively to prevent physical, psychosocial, and medical consequences. We propose a comprehensive clinical approach for evaluation, including genital exams, growth charts, and specialized testing. Recognizing CPP in syndromic cases is critical, often requiring in-depth, multidisciplinary investigation.

Additional details

Conflicts of interest: According to the ICMJE universal disclosure form, all authors disclose the following: Payment and service details: The submitted work has not received any financial support from any organizations, according to the authors. Relationships with groups that might be interested in the submitted work: All authors have stated that they have no present or previous three-year financial relationships with any such organizations. The submitted work has not been influenced by any outside relationships or activities, according to all authors.

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