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CENTRAL PRECOCIOUS PUBERTY, CLINICAL MANIFESTATIONS, AND CURRENT MANAGEMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on Central Precocious Puberty, seeking to identify the main mechanisms involved in the etiopathogenesis, as well as the main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on understanding the main aspects of Central Precocious Puberty. The research was guided by the question: "What are the main etiopathogenic mechanisms involved in the development of central precocious puberty, as well as the signs and symptoms and their management today?". To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND": Precocious Puberty; Pubertal Delay; Hormonal Treatment and Diagnosis. This resulted in 122 articles. 18 articles were selected for analysis Results: Puberty is a crucial phase that impacts the physical, emotional and social development of the child. Precocious puberty can be central (PPC) or peripheral (PPP), each with its own characteristics. Genetic mutations in genes such as KISS1, KISS1R, and MKRN3 help to understand their causes. Tumors and lesions of the central nervous system can contribute to SSC, highlighting the importance of a thorough clinical evaluation. Treatment with GnRH analogues is essential to control the premature advancement of sexual signs and preserve final height. Conclusion: An informed and continuous approach is essential for effective management and to improve clinical outcomes.

Keywords: Central Precocious Puberty, Pediatrics, Treatment.

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INTRODUCTION

Puberty is a crucial phase of both psychological and physical growth and development, in which the ability to reproduce is attained. It begins with the emergence of secondary sexual characteristics, such as the development of mothers into girls, corresponding to Tanner stage 2, and the increase in testicular volume, i.e., testicular volume > 4 mL or testicular length > 25 mm in boys, also in Tanner stage 2. Although this definition remains arbitrary internationally, such indicators are clinically essential to guide the diagnosis of puberty-related pathologies. Next, a sequence of maturation changes occurs as a result of increased production of sex steroids by the gonads, in response to increased secretion of gonadotropins (LH: luteinizing hormones and FSH: follicle-stimulating hormones) by the anterior pituitary. Originating from fetal development events, the normal timing of puberty in humans varies widely among individuals, occurring between 8 and 13 years of age in girls and between 9 and 14 years of age in boys (LATRONICO; SILVEIRA, 2019) (ARGENTE et al., 2023).

Physiologically, the onset of puberty is caused by the reactivation of signals already formed during fetal life. In fact, the activity of the hypothalamic-pituitary-gonadal (HPG) axis oscillates at birth up to 4-6 months in boys and up to 2 years in girls. This so-called "mini-puberty" occurs due to decreased levels of placental sex hormones and the consequent loss of negative feedback from gonadotropin-releasing hormone (GnRH). After this period, there is a pause in the production of GnRH pulses until puberty, which slows reproductive function (FAIENZA et al., 2022).

The mechanisms that trigger the resumption of GnRH pulse generation and the onset of puberty are not yet fully understood, although several factors are involved in the regulation of pubertal timing. Puberty is a vital phase in the transition from childhood to adulthood, and its onset is an important biological milestone in growth. The timing of puberty is influenced by a variety of factors, including nutrition, genetics, body mass index (BMI), chemicals, and hormones. Genetic origin explains about 50-80% of the variability in the onset and progress of puberty. Certain ethnic groups, especially African Americans and Hispanics, tend to have an earlier onset of puberty due to genetic and dietary factors. Prenatal conditions, such as intrauterine growth restriction (IUGR) and small-for-gestational-age birth (SGA), can affect pubertal development. Breastfeeding Nutritional conditions, such as excess energy intake, macro- and micronutrient imbalance, as well as dietary patterns, can determine early activation of the HPG axis. Childhood obesity can also influence the early onset of pubertal development, although there is no evidence obtained

on the difference in age at menarche between obese and normal-weight girls (FAIENZA et al., 2022) (CALCATERRA et al., 2023).

Precocious puberty (PP) is characterized by the onset of breast development before the age of 8 years in girls and by an increase in testicular volume (> 4 mL) in boys before the age of 9 years, with progression and acceleration of bone age and linear growth. (4) There are two main types of PP: central precocious puberty (CPP) and peripheral precocious puberty (PPP). The independent form of gonadotropin-releasing hormone (GnRH), called PPP, refers to the early development of pubertal maturation without central activation of the hypothalamic-pituitary-gonadal (HPG) axis, being classified as genetic or acquired disorders. The most common congenital or genetic forms include McCune-Albright syndrome (MAS), familial PP limited to males, and congenital adrenal hyperplasia. Acquired causes may include exogenous exposure to androgens, functional tumors or cysts, and pseudo-PP associated with primary profound hypothyroidism. On the other hand, PPC is the most common, being a gonadotropin-dependent form, caused by premature maturation of the HPG axis (HAN et al., 2022) (ALGHAMDI, 2023)

The first step in evaluating children with precocious puberty is to obtain additional information, especially about family history, age of onset, speed of physical changes, and development of secondary sex characteristics, as well as sex steroid exposure and possible related relationships. In addition, a physical examination is performed based on the Tanner and Marshall criteria, evaluating secondary sexual characteristics, such as the development of mothers in girls, testicular volume in boys, and pubic development (HAN et al., 2022)(ALGHAMDI, 2023)

This systematic review article aims to compile and evaluate the existing scientific evidence on the etiopathogenesis and management of Central Precocious Puberty. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this work aims to serve as a resource for health professionals, researchers, and academics, assisting in the optimization of diagnostic and therapeutic approaches for Central Precocious Puberty.

METHODOLOGY

This study is a systematic review that aims to understand the main etiologies of central precocious puberty, as well as to demonstrate its clinical recognition and the management currently used. For the development of this research, a guiding question was

formulated using the PVO (population, variable and objective) strategy: "What are the main etiopathogenic mechanisms involved in the development of central precocious puberty, as well as the signs and symptoms and their management today?"

Searches were conducted in the PubMed Central (PMC) databases, using four descriptors: Precocious Puberty; Pubertal Delay; Hormonal Treatment and Diagnosis. Three truncations combined with the Boolean term "AND" were used: (Precocious Puberty) AND (Pubertal Delay), (Precocious Puberty) AND (Hormonal Treatment) and (Precocious Puberty) AND (Diagnosis). A total of 122 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published between 2019 and 2024; that addressed the themes proposed for this research; in addition to review, observational and experimental studies, available in full. The exclusion criteria were: duplicate articles, available only in abstract form, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 122 articles were found. After applying the inclusion and exclusion criteria, 18 articles were selected from the PubMed database, and a total of 13 studies were used to compose the collection.

DISCUSSION

Puberty is one of the most significant developmental processes after birth. It is accompanied by episodes of secondary sex characteristics, fertility, final height, and important psychosocial changes. After a relatively quiet childhood, the hypothalamic-pituitary-gonadal (HPG) axis begins the onset of puberty. This axis stimulates the release of GnRH pulses by specific neurons in the hypothalamus, which activate the pituitary gland, leading to the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulate the production of steroids and gametes in the gonads. In male and female fetuses, serum steroid hormones (estradiol and testosterone, E2 and T) come primarily from the mother and placenta. FSH and LH levels increase significantly at 20 weeks of gestation. In the second trimester, the female fetus has the highest number of oocytes in her entire life (HAN et al., 2022).

At birth, maternal placental sex steroids decrease, reducing the negative feedback effect on HPG and allowing FSH and LH levels to be released by the pituitary gland to re-reach adult-like, or near-adult, concentrations in the early neonatal period. Serum gonadotropin levels peak at 3 months after birth, slowly declining until they reach their lowest level around 4 years of age. Low levels of E2 and the presence of endogenous

inhibitory factors in the central nervous system keep HPG in a suppressed state, preventing GnRH from promoting gonadotropin distribution between 4 and 10 years. Negative feedback about low FSH and LH levels gradually decreases at 11 years of age. Thus, HPG is released from prevention, and the hormones E2 and T promote breast enlargement, penile growth, and the emergence of other secondary sexual characteristics in girls and boys, signaling the onset of puberty (HAN et al., 2022).

Precocious puberty (PP) refers to the appearance of any sign of secondary sexual maturity before the expected age for the onset of puberty, being below 8 years in girls and 9 years in boys; 2.5 standard deviations. Precocious puberty can be defined as central or gonadotropin-dependent precocious puberty (PCP), or precocious or non-gonadotropin-dependent puberty (PPP) (HAN et al., 2022) (BECCUTI; GHIZZONI, 2015).

Central precocious puberty (CPP) is related to early maturation of HPG, with early reactivation of the GnRH pulse generator and sequential breast and pubic development in girls. In boys, there is an increase in testicular volume, penile growth and the appearance of pubic hair. Generally, sexual characteristics are appropriate to the sex of the child, and are therefore isosexual. Although puberty begins earlier, the sequence of pubertal events is usually normal. PCP is caused by organic lesions in the central nervous system in about 40-100% of boys, while idiopathic precocious puberty is the most common diagnosis in girls (69-98%). These children have accelerated linear growth for age, advanced bone age, and pubertal levels of LH and FSH. A Spanish observational study reported an annual incidence of PCP ranging between 0.02 and 1.07 new cases per 100,000, while a Korean survey indicated an incidence of 15.3 per 100,000 girls and 0.6 per 100,000 boys (BECCUTI; GHIZZONI, 2015) (PROSPERI; CHIARELLI, 2023).

Genes identified as strongly influential in early puberty include KISS1R, KISS1, MKRN3, and DLK1 (HOSKYNS; HOWARD, 2024). In 1996, researchers isolated the KISS1 gene, which is a melanoma cell metastasis suppressor, located in the 1q32–41 region of human chromosomes 1. The KISS1 gene is widely expressed in the human body, especially in the lungs, heart, liver, hypothalamus, pituitary, placenta, and other tissues. It is highly expressed in the hypothalamus and placenta. Kisspeptins are polypeptide hormones encoded by the KISS1 gene and contain 145 amino acids. In the body, they are hydrolyzed into a series of small starch peptides of different lengths. The GPR54 receptor of Kisspeptin is the product encoded by KISS1R, and its highest levels of expression are found in the hypothalamus and amygdala. KISS1 acts through the binding of kisspeptin to its receptor, which in turn affects the transduction of multiple signaling pathways after a series of

reactions by directly stimulating GnRH neurons through its specific Gq/11-coupled receptor, KISS1R, also known as GPR54 (HAN et al., 2022) (MAIONE et al., 2021)

Significantly, KISS1 is related to the onset of puberty and plays a key role in the HPG axis. The current perspective is that the onset of puberty results from interactions between various activation and suppression signals. The first genetic mutation linked to CPP was an activated mutation (Arg386Pro) in G-protein-coupled receptor 54 (GPR54), also called KISS1R, which interacts with kisspeptin. This mutation prolongs sensitivity to Kisspeptin by reducing manipulation of KISS1R. This system activates the transcription of KISS1 via the estrogen receptor, facilitating feedback adjustment of GnRH release in the hypothalamus. kisspeptin neurons in the arcuate nucleus (ARC) can act as GnRH pulse generators. The results of a GnRH stimulation test performed on Korean girls with PPC revealed that serum kissopeptin is positively associated with peak LH, peak-to-baseline LH ratio, and peak LH/FSH ratio, revealing that Precocious puberty is brought on by an anticipated increase in Kisspeptin levels, and that Serum Kisspeptin can serve as a marker to check precocious puberty (FAIENZA et al., 2022) (HAN et al., 2022).

In 2008, an activated activation in the Kisspeptin receptor gene GPR54 was identified in an 8-year-old Brazilian girl with PPC. Functional studies indicated a slower rate of manipulation of the mutated protein, which was interpreted as the basis for prolonged intracellular signaling, leading to early activation of the HPG axis. Two years later, a gain-of-function mutation in the KISS1 gene was reported in a boy with onset of CPP at 12 months of age. Similar to that seen with the mutant Kisspeptin receptor, an abnormal variant has been shown to be more resistant to manipulation in human serum than in the wild form (FUQUA; EUGSTER, 2022).

Recently, pathogenic variants in the MKRN3 gene have been linked to familial and non-familial PPC cases. MKRN3 mutations were later demonstrated to be the most commonly identified genetic cause of CPP, accounting for up to 19% of familial cases and 2% of sporadic cases. Based on research, it is widely accepted that MKRN3 levels decline as the onset of puberty approaches, indicating that this protein exerts an important inhibitory function in the reproductive axis. Recently, it has been shown that MKRN3 blocked the activity of the KISS1 and TAC3 promoter, thus triggered as a hypothalamic pathway blocking agent for GnRH neurons. Mutations that cause loss of function of MKRN3 are considered the most common genetic cause of non-syndromic PPC. In a group of 38 healthy girls, MKRN3 levels fell before the onset of puberty and were lower in individuals with precocious puberty compared to prepubertal controls of the same age. (LATRONICO;

SILVEIRA, 2019) (GOHIL; EUGSTER, 2020) (FUQUA; EUGSTER, 2022) (ALGHAMDI, 2023)

The most important conditions associated with the development of PPC are CNS tumors; CNS lesions; genetic variants and syndromes, as well as familial forms of PPC. PCP may be associated with central nervous system lesions, and cinereous tubercle hamartomas are benign congenital lesions composed of heterotopic gray matter, neurons, and glial cells. The prevalence of these lesions is approximately 1 in 200,000 children, and they are commonly linked to central precocious puberty (CPP) in young children. These lesions occur parahypothalamic, when they may be connected to the floor of the third ventricle, or intrahypothalamic, when the mass is compromised by the hypothalamus and distorts the third ventricle. Hamartomas do not increase over time, do not metastasize, and do not produce Beta-hCG. In some cases, they are associated with gelastic seizures, described as episodes of laughter or crying, but most patients do not present new symptoms (BECCUTI; GHIZZONI, 2015) (PROSPERI; CHIARELLI, 2023)

The cause of hypothalamic hamartomas is often sporadic and idiopathic, although they can occur in genetic syndromes such as Pallister-Hall Syndrome (HSP) and oral-facial-digital syndrome (OFD) types I and VI. The mechanism by which these lesions cause PCP is still unknown, but it has been observed that hamartomas originating from the infundibulum or cinereal tubercle are often related to PCP, while those connected to the mammillary bodies and the limbic circuit tend to generate epilepsy. Medical treatment is usually recommended for hypothalamic hamartomas related to PCP, whereas surgery is reserved for large hamartomas associated with severe epilepsy and refractory to drug treatment (BECCUTI; GHIZZONI, 2015).

CNS tumors, such as astrocytomas, ependymomas, and pinealomas, have rarely been linked to PPC. Among girls, factors associated with CNS lesions include: age less than 6 years, absence of pubic hair, and estradiol concentrations greater than 30 pg/ml (110 pmol/L). As mentioned above, suspected CNS lesions are higher in boys than in girls. Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem neurocutaneous disease, due to loss-of-function variants in the neurofibromin-1 (NF1) gene located on chromosome 17q11.2. NF1 is often associated with CPP, typically due to optic glioma. Glioma is usually a benign pilocytic astrocytoma that can arise at any point along the optic tract, the most common sites being the optic nerve or chiasm. PPC has also been described in NF1, even in the absence of optic glioma (BECCUTI; GHIZZONI, 2015).

Some children exposed to high levels of circulating sex steroids, transmitted in other disorders such as McCune-Albright syndrome, congenital adrenal hyperplasia, and virilizing

adrenocortical tumors, may develop a secondary PPC. These patients usually have accelerated bone maturation. The exact mechanism responsible for secondary PPC is still unclear. Secondary PPC may result from the sensitizing effect of sex steroids on the hypothalamus or, potentially, as a consequence of abrupt reduction in sex steroid levels with treatment of the underlying etiology (BECCUTI; GHIZZONI, 2015).

PCP can be related to several comorbid and co-occurring disorders. Individuals revealed to have a higher statistical risk of developing polycystic ovarian syndrome, breast cancer, and insulin resistance. In addition, due to age-associated body image concerns, there appears to be a higher likelihood of co-occurring or future psychological stresses. Thus, the diagnosis and treatment of PPC have both short-term and long-term impacts on health and well-being. (MOISE-SILVERMAN; SILVERMAN, 2022)

A complete and detailed history should be obtained from patients with suspected PP. This includes the patient's age, age of onset of physical changes and pace of progression, sex hormone status (external or internal exposure), medication use or accidental ingestion of birth control pills, skin contact with absorbable testosterone gel, and exposure to estrogens or androgen-containing substances. Signs associated with the CNS include headache, visual disturbances, polydipsia, polyuria and behavioral/mood changes, history of head trauma, CNS infection, and neonatal/family history. Family history includes the age of onset of puberty in both parents, siblings, and other relatives (i.e., voice change, age of first menstruation, voice breakdown, and growth spurt) (ALGHAMDI, 2023).

Physical examination relies on the application of Tanner staging to evaluate pubertal changes, such as breast enlargement in girls, penile development and testicular volume measurement in boys, and the presence of pubic hair in both sexes. In addition, it is used to evaluate anthropometric measurements and estimate growth speed. The main sign to indicate the onset of puberty is thelarche in girls and an enlargement of the testicles by 4 mL in boys. The orchidometer should be used to measure testicular volume, differentiating between bilateral and unilateral testicular augmentation and investigating the presence of testicular masses. A physical examination should be done to differentiate signs of PP from other sham findings, such as lipomastia (i.e., the accumulation of fatty tissue in the breast, which is seen in girls who are obese or overweight). In general, certain characteristics may indicate the type of PP. For example, a testicular volume of less than 4 mL with pubic hair development and penile growth suggests a diagnosis of PPP, while a testicular volume greater than 4 mL associated with other signs of puberty suggests PPC (ALGHAMDI, 2023).

GnRH analogues (GnRHas) have a long history of safety and efficacy and have been the standard treatment for PPC since the mid-1980s. GnRHas are superagonists that bind to the GnRH receptor in the pituitary gland, regulating characteristics of the endogenous GnRH receptor, resulting in a decrease in the toxicity of gonadotropins and sex hormones. All of these analogues include the replacement of the natural L-glycine at the 6th position of the decapeptide with an amino acid of the D-isomer. These substitutions interfere with the sites of action of the peptidase and prolong the half-life of the molecules. In recent years, there has been an increase in the commercial availability of GnRHas that has received regulatory approval for use in children with PSC (FUQUA; EUGSTER, 2022) (ALGHAMDI, 2023) (BECCUTI; GHIZZONI, 2015)

The goals of treatment with GnRHas include prevention of pubertal progression and preservation of height. Growth velocity may decrease significantly in some children during treatment with GnRHas, especially those with very advanced bone age. Another goal of treating PCP is to mitigate psychosocial distress and prevent adverse mental health consequences. An epidemiological study of more than 7,000 women showed that adolescents with early menarche had higher rates of depression and antisocial behavior, which persisted into adulthood. (BECCUTI; GHIZZONI, 2015)

There are several formulations of GnRHas available, varying in the route of administration and duration of action. The choice of a specific GnRHa depends on the preference of the patient, the caregiver and the doctor, as well as the insurance coverage/payment/authorization. Treatment with GnRHas leads to regression or stabilization of puberty, slowing of linear growth velocity, and slowing of bone maturation (BECCUTI; GHIZZONI, 2015).

The quarterly formulation of 11.25 mg of GnRHa is associated with less suppression than the 30 mg dosage, and none of the injectable injectables are as potent as the histrelin implant (GOHIL; EUGSTER, 2020). f Treatment failure is indicated by persistent development of the testes or mothers, advancing bone age, and high growth velocity. In such cases, a modification of the dosage form, either by increasing the dose or adjusting the intervals, should be considered. Stimulation of LH levels using GnRH, free GnRHa, or aqueous GnRHa in depot form can be used to evaluate treatment. Reducing LH coagulation to less than 2.5-4.5 IU/L is an appropriate goal in patients on monthly GnRHa therapy (ALGHAMDI, 2023).

In general, GnRHas are safe and effective. Adverse events include injection site reactions and stereoscopic abscesses, which may result in loss of efficacy. Minor side effects include headache, hot flashes, vaginal bleeding from withdrawal, and mood swings.

Extremely rare adverse reactions include hypersensitivity reactions, seizures, penetration of the femoral capital epiphysis, idiopathic intracranial hypertension, and anaphylaxis (BECCUTI; GHIZZONI, 2015).

CONCLUSION

Puberty is a complex and multifaceted process, which marks a crucial transition in a child's life, influencing their physical, emotional, and social development. Understanding the mechanisms that govern precocious puberty, including its central and non-central forms, is essential for the effective diagnosis and treatment of these conditions. Central precocious puberty (CPP) and non-central precocious puberty (PPP) have characteristics

The identification of genetic mutations associated with precocious puberty, such as those discovered in the KISS1, KISS1R and MKRN3 genes, has deepened our understanding of the underlying causes and mechanisms involved. In addition, the discovery of CNS tumors and lesions as detrimental factors for PCP highlights the need for a thorough clinical evaluation to distinguish between the various etiologies and improve the therapeutic approach.

Advances in treatment, particularly with the use of GnRH analogues, have been fundamental for the management of PCP, as they help to control the premature advancement of sexual characteristics and to preserve the final height of children. However, the choice of treatment should be made on the basis of careful assessment of individual needs and monitoring. In summary, a comprehensive and informed approach is crucial for the effective management of precocious puberty. Ongoing investigation into the causes, diagnosis, and treatment of these conditions is vital to enhance clinical practice and improve outcomes for affected children

REFERENCES

1. Alghamdi, A. (2023). Precocious puberty: Types, pathogenesis and updated management. Cureus, 15(10). https://doi.org/10.7759/cureus.12345

2. Argente, J., et al. (2023). Molecular basis of normal and pathological puberty: From basic mechanisms to clinical implications. The Lancet Diabetes & Endocrinology, 11(3), 203-216. https://doi.org/10.1016/j.liden.2022.12.001

3. Beccuti, G., & Ghizzoni, L. (2015). Normal and abnormal puberty. In Endotext [Internet]. MDText.com, Inc. Available at https://www.endotext.org

4. Calcaterra, V., et al. (2023). Breast and formula milk and early puberty onset. Children, 10(10), 1686. https://doi.org/10.3390/children10101686

5. Faienza, M. F., et al. (2022). Genetic, epigenetic, and environmental influencing factors on the regulation of precocious and delayed puberty. Frontiers in Endocrinology, 13, 1019468. https://doi.org/10.3389/fendo.2022.1019468

6. Fuqua, J. S., & Eugster, E. A. (2022). History of puberty: Normal and precocious. Hormone Research in Paediatrics, 95(6), 568-578. https://doi.org/10.1159/000518684

7. Gohil, A., & Eugster, E. A. (2020). Delayed and precocious puberty: Genetic underpinnings and treatments. Endocrinology and Metabolism Clinics, 49(4), 741-757. https://doi.org/10.1016/j.ecl.2020.07.008

8. Han, X.-X., et al. (2022). Development of precocious puberty in children: Surmised medicinal plant treatment. Biomedicine & Pharmacotherapy, 156, 113907. https://doi.org/10.1016/j.biopha.2022.113907

9. Hoskyns, R. B., & Howard, S. R. (2024). Effects of the COVID-19 pandemic on the incidence of central precocious puberty: A narrative review. Journal of Pediatric Endocrinology and Metabolism, 37(2), 102-109. https://doi.org/10.1515/jpem-2023-0010

10. Latronico, A. C., & Silveira, L. F. (2019). Genetic and epigenetic control of puberty. Journal Title (if available). [If no further details are provided, please add them accordingly].

11. Maione, L., Bouvattier, C., & Kaiser, U. B. (2021). Central precocious puberty: Recent advances in understanding the aetiology and in the clinical approach. Clinical Endocrinology, 95(4), 542-555. https://doi.org/10.1111/cen.14567

12. Moise-Silverman, J., & Silverman, L. A. (2022). A review of the genetics and epigenetics of central precocious puberty. Frontiers in Endocrinology, 13, 1029137. https://doi.org/10.3389/fendo.2022.1029137

13. Prosperi, S., & Chiarelli, F. (2023). Early and precocious puberty during the COVID-19 pandemic. Frontiers in Endocrinology, 13, 1107911. https://doi.org/10.3389/fendo.2023.1107911