REVIEW

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Central precocious puberty as a prelude of gonad dysplasia

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ABSTRACT
There is increasing evidence that patients with gonad dysplasia, as characterized by absent or incomplete puberty, can also exhibit central precocious puberty (CPP). Herein, we review the reported cases that manifest with both gonad dysplasia and CPP. Further, we examine the hypothesis that these patients exhibit a normal hypothalamic-pituitary-gonadal axis, hypogonadism, and the presence of residual gonadal function, and that the onset of disease is related to early initiation of the hypothalamic-pituitary-gonadal axis. Thus, we suggest that CPP is a prelude of some partial hypogonadism.

KEYWORDS
Gonad dysplasia, Central precocious puberty, Turner syndrome, Klinefelter syndrome

Introduction

Gonadotropin-releasing hormone (GnRH) secretion is active in utero during the second half of pregnancy and in infancy (mini puberty), and then becomes quiescent in children because of an inhibitory 'brake' until the onset of puberty. At puberty, reactivation of pulsatile GnRH secretion leads to an increase in secretion of gonadotropins, which in turn activates the production of gonadal sex steroids. The GnRH brake was originally believed to be centrally controlled and independent of ovarian or testicular action. However, recent studies have shown U-shaped gonadotrophin levels in normal males from birth to puberty, and the same pattern with considerably greater levels in anorchid boys, indicating some contribution of the gonads to negative feedback of gonadotrophins in childhood.[1] An intact hypothalamic-pituitary-gonadal axis (HPGA) is essential to normal puberty. There is increasing evidence that gonad dysplasia patients, characterized by absent or incomplete puberty, can also exhibit central precocious puberty (CPP). This, which is caused by premature reactivation of the HPGA, and is usually defined by development of secondary sexual characteristics before the age of 8 years in girls and 9 in boys. Herein, we review the reported cases manifesting with both gonad dysplasia and CPP to examine the mechanisms underlying the occurrence of these two entirely different phenomenon. To this end, we searched the literature using the key words 'precocious puberty', 'gonad dysplasia', 'Turner syndrome', 'Klinefelter syndrome', 'adrenal hypoplasia congenita', 'polycystic ovary syndrome', and 'Prader-Willi syndrome' in MEDLINE, PUBMED, EMBASE, and CNKI up to November, 2017.

Klinefelter Syndrome

Klinefelter syndrome (KFS) is a type of male primary hypogonadism involving an increased extra X chromosome, and is mainly characterized by testicular dysplasia, azoospermia, and infertility. KFS accounts for approximately 3.1% of cases of male infertility, and

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is the most common form of male gonad dysfunction, occurring in approximately 1 in 550 live births. According to the chromosome karyotype, KFS can be divided into the classical form (e.g., 47, XXY, accounting for 83.4% of cases), the 47 mosaic form (e.g., 47, XXY/46, XY; 47, XXY/46, XX; 47, XXY/46, XY/45, XO; accounting for approximately 10% of cases), and other rare karyotypes (e.g., 48, XXXY; 48, XXYY; 49, XXXXY).[2] KFS patients typically exhibit incomplete pubertal development, whereas a combination with CPP is very rare. We found nine studies on precocious puberty,[3-12] four studies on endocrine tumors of human chronic gonadotropins ectopic secretion, including three cases of 47, XXY and one case of 48, XXYY,[4-8] and five non-mosaic cases of KFS combined with central sexual precocity. The main observations in KFS patients with CPP are: (1) an X chromosome dose compensation effect; (2) the X chromosome shows abnormal expression of particular genes; and (3) abnormal expression of the androgen receptor. However, we do not believe that these three factors can explain the clinical combination of KFS and CPP. Importantly, both the central GnRH pulse generator and the gonad itself can contribute to the onset of puberty. Thus, in KFS patients, gonad dysplasia may decrease the negative feedback of gonadotrophins, leading to earlier activation of the HPGA.

Turner syndrome

Turner syndrome (TS) is the most common chromosomal aneuploidy, affecting 1 in every 2000 girls, and is characterized by short stature and gonadal dysgenesis in females who lack all or part of one X chromosome.[13] Because of the high variability, approximately 30% of TS girls belong to the mosaic karyotype. Short stature, gonadal dysgenesis, and congenital malformations are the main clinical features of TS. Absent pubertal development and primary amenorrhea occurs in most individuals with TS. Although 30% of TS girls have natural puberty, only half of those complete puberty with menarche, and spontaneous pregnancies are rare (approximately 2%–5%).[14] Only 10 cases of precocious puberty have been reported, mainly in girls with mosaic TS or X structural abnormalities (one 45, XO case).[15-19] As TS girls with normal fertility and premature amenorrhea are more likely to exhibit a complex mosaic karyotype, researchers also suggest that this mosaic is related to an imbalanced haploid dose compensation effect of the X chromosome in some somatic cells. However, the so-called dose compensation only explains the acquisition of part of the ovarian dsyfunction.[18] The karyotype of TS patients with precocity is mainly characterized by mosaicism, suggesting incomplete gonadal dysgenesis of the ovary. The differing degrees of residual ovarian function can present as different degrees of puberty, menstrual cycling, and fertility, and some patients display premature ovarian failure in adulthood. However, there remains no clear explanation for the pathogenetic mechanism for CPP in TS.

Triple X syndrome is also a common sex chromosome aneuploidy, with an incidence of 1 in 1000 female births.[20] Triple X syndrome patients commonly exhibit premature ovarian failure, mild mental retardation, minor physical abnormalities, and delayed motor and speech development.[21] In a study examining the hypothalamus-hypophysis-gonad axis in a cohort of children and adolescents with triple X syndrome, these patients showed premature activation of the GnRH pulse generator, and an increase in basal and peak luteinizing hormone (LH), and follicle-stimulating hormone (FSH), a reduction in estradiol and inhibin levels, and ovarian volume, indicating reduced gonad function. These cross-sectional data also suggest that puberty may occur earlier in these patients than in the general population.[22] Both of these chromosomal aneuploidies have common features, including decreased ovarian function, with increased levels of gonadotropins to compensate for blunted ovarian function, to the extent that they manifest as CPP, but eventually progress to premature ovarian failure.

Adrenal hypoplasia congenita

Adrenal hypoplasia congenita (AHC) is caused by an X-linked NR0B1(Nuclear Receptor Subfamily 0 Group B Member 1) gene mutation, and presents with adrenal insufficiency accompanied by gonad disorder. AHC is classically known to cause hypogonadotropic hypogonadism, as NR0B1 mutations likely impair gonadotropin production by acting at both the hypothalamic and pituitary levels.[23] However, the onset of puberty can be variable, from arrest of absent puberty to precocious puberty (PP).[24-30] The reported cases of PP present with extended mini-puberty or temporary PP, and then progress to hypogonadotropic hypogonadism (HH). Reported cases include CPP and gonadotropin-independent PP. Katsumata et al[27] reported the first association of AHC with presumed CPP. In that study, the patient developed public hair at 6 months of age, and his mean testicular volume had increased to 3.5 mL at 1 year and 3 months old. The patient was presumed to have CPP based on the increased urinary excretion of gonadotropins and testosterone, and was treated with cyproterone acetate until 13 years old. Interestingly, after cessation of treatment, the patient developed inadequate secondary sexual characteristics, and was diagnosed with HH. Other studies reported that AHC combined with CPP cases all responded to Gonadotrophin releasing hormone agonist (GnRHa) therapy, and that patients with a longer follow-up period eventually develop HH, indicating that HH is the entity. The exact mechanism and natural history of this phenomenon remains unclear. Loke et al[24] speculated that DAX-1 is not the only regulator of puberty in AHC, and that several other transcription factors that regulate puberty

may be involved in a network cascade of transcription factors that are intricately related and exquisitely timed. More recently, the stem cell model has been suggested.[23,31] In one study, detailed analysis of adrenal function in aging Dax1/Nrob1-deletion mice demonstrated a key role of DAX-1 in regulating stem cell development. DAX-1 is expressed in a population of progenitor stem cells, where it represses differentiation to allow expansion of the cell pool. In the absence of DAX-1, the progenitor cells can prematurely differentiate into steroidogenic cells before expansion of cell number. However, this process leads to reduced numbers of steroidogenic cells rather than cells related to PP. This model may partially account for the early hyperfunction of the gonad, followed by decline in function as the pool of cells available for regeneration is depleted. Further research in this field may help elucidate the definite mechanism. Nevertheless, excessive activation of the HPGA in early period is likely to contribute to precocious puberty.

Anorchidism

In 2012, Grinspon et al[1] examined the HPGA in 35 cases of anorchidism (patients with absolute maldeveloped testis) and 29 cases of cryptorchism in children compared with normal boys, and found that anorchidism children exhibited increased hypophyseal hormone levels (predominately FSH) from birth to pubertas. In that study, only 30% of anorchidism cases exhibited a silent period of LH and FSH, while the period with FSH < 5 IU/L was also very short (shortening of the silent period). Further, for most of the age phase, the levels of the pituitary gonadotropic hormones LH and FSH were in a hyperactivity state. By contrast, in the cryptorchism children the pubertal LH and FSH levels were similar to those of normal boys. These data suggest that cases with primary hypogonadodism hypogonadism can exhibit excessive and long-lasting activation of the HPGA during childhood. These findings support our explanation for some primary hypogonadodism hypogonadism combined with CPP, such as in KFS and TS patients. Further, these data suggest that the defective testes must have insufficient inhibitory activity for HPG, and that the testes can provide inhibitory feedback activity during childhood.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women, with a prevalence between 5%–15%, depending on the diagnostic criteria applied.[32,33] PCOS patients show 10%–12% of chromosomal abnormalities, in which 94% are X-chromosome structure abnormalities or number abnormities (e.g. 45, XO; 47, XXX; 45, XO/46 XY). These patients also show eventual premature ovarian failure, but present with insufficiency of residual function when they are young or during the early stages of the disease. Further, FSH levels increase to > 25 U/L, indicating that the HPGA is in an activated state.[34] A number of studies have also examined the occurrence of PCOS following CPP.[35-37] For example, Petrus et al described a girl with precocious puberty treated with medroxyprogesterone acetate at 4 years of age, who later presented with PCOS,[37] while the same group later reported 13 adolescents with a history of CPP who developed to PCOS.[35] There is also definitive evidence that patients with CPP are prone to developing PCOS, and atypical sexual precocity in early childhood was identified as an independent prepubertal risk factor for PCOS.[38] Interestingly, the original evidence that GnRHa treatment can cause PCOS in CPP patients was recently disproven. Indeed, in a large group of GnRHa-treated and untreated former CPP women (25–56 years of age), Lazar et al[39] found that the relative risk for developing PCOS was two-fold higher in untreated subjects, suggesting that pubertal suppression itself may reduce the risk of PCOS. Overall, these studies suggest that excessive HPGA activation may be a common mechanism underlying CPP and PCOS. Premature activation of GnRH neurons following predominant LH secretion in CPP may also persist in some cases, which may further stimulate the development of hyperandrogenism and anovulation, leading to PCOS.

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex multisystem disorder caused by a lack of expression of paternally-active genes in the PWS-critical region on chromosome 15.[40] PWS occurs in approximately 1 of 15 000–25 000 live births,[41] and is characterized by muscular hypotonia, insatiable hunger, obesity, small hands and feet, developmental delay, hypogonadism, and altered body composition. Hypogonadism is a major and prominent feature of PWS, which is widely believed to be hypogonadotropic and associated with hypothalamic-pituitary dysfunction. Recent studies have also reported that variable combinations of primary gonad defect and hypothalamic-pituitary dysfunction contribute to the hypogonadism in PWS patients.[42-44] Most patients with PWS exhibit delayed or incomplete pubertal development.[45] Moreover, 14 cases of CPP have been described in PWS,[46-52] with evidence of HPGA activation and advanced skeletal maturation. With respect to the etiology of CPP, there is evidence of a variety of brain lesions, including an empty sella and ischemic brain injury, which were suggested to cause the premature HPGA activation and idiopathic CPP.[53] However, we do not agree with this explanation, but rather prefer the hypothesis that the reduced expression of inhibitors (e.g., inhibin-B and/ or Anti Müllerian Hormone) resulting from the primary gonad defect (dysgenesis/ agenesis) may cause loss of the HPGA 'break' in childhood and premature activation of the GnRH pulse generator, which in turn stimulates the gonad that secret sex hormones.

In summary, patients with gonad dysgenesis diseases combined with CPP, whatever the causes (e.g., TS, AHC, anorchidism, PCOS, or PWS), share similar features, including (1) impairment of the gonad cells (e.g., gonadal dysgenesis), (2) sufficient residual function and remnants to secret sex hormones, and (3) normal GnRH levels and normal pituitary function, all of which result in premature activation of the HPGA. These three conditions are necessary, and when combined together, contribute to CPP in gonadal dysgenesis patients. Thus, these data suggest that CPP may be a prelude to partial hypogonadism, and that treatment of CPP with GnRHa may protect the gonads from premature failure.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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