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Clinical "Red Flags" Differentiating Delayed Puberty From Enduring Hypogonadism

Andrew A. Dwyer, Yee-ming Chan

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A B S T R A C T

Delayed puberty affects between 2% and 3% of the population and is a common reason for seeking endocrine consultation. Evaluation involves ruling out pathologic functional conditions disrupting puberty. Adolescents with constitutional delay of puberty (CDP) will initiate puberty spontaneously, albeit later than peers. However, some individuals have congenital hypogonadotropic hypogonadism (CHH) and will neither initiate nor progress in pubertal development. No single gold standard test differentiates CDP from CHH, posing diagnostic challenges for clinicians. This report provides an overview of normal/disrupted puberty, highlights clinical "red flags" facilitating identification of CHH, and emphasizes comprehensive and interprofessional approaches to care.

Introduction

Puberty is a remarkable period in human development that culminates in full reproductive capacity. Puberty is accompanied by a wide range of physical changes, including development of secondary sex characteristics, acceleration of linear growth, alterations in body composition, and development of strength and peak bone mass. In parallel, significant cognitive, psychological, emotional, and social changes occur.[1] Importantly, disrupted puberty can have a significant impact on both physical and psychosocial well-being.[2-4]

The changes of puberty are triggered by the activation of the reproductive endocrine (hypothalamic-pituitary-gonadal) axis. The mechanisms regulating the onset of puberty are not fully understood. Diverse factors influence pubertal timing, including heredity (ie, genetics), nutrition, general physiologic and psychosocial health, and environmental cues, including endocrine-disrupting chemicals.[5]

The first physical sign of typical male pubertal onset is testicular enlargement (testicular volume of 4 mL), whereas breast budding (Tanner II breast development) is one of the earliest physical signs of typical female puberty. On average, girls begin puberty earlier than boys (Table 1).[6,7] Delayed puberty is statistically defined (ie, >2 SDs from the mean), and thus, 2% to 3% of adolescents will have delayed puberty. Some individuals presenting with delayed puberty will never initiate/complete puberty on their own, which is termed congenital hypogonadotropic hypogonadism (CHH). Notably, CHH is more common in boys than girls, and the precise incidence is unclear—estimates suggest CHH occurs in 1 in 10,000 to 48,000 individuals.[8,9]

Physiology of the Reproductive AXIS

The reproductive system is regulated by the hypothalamic-pituitary-gonadal axis. Specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone. Traditionally, gonadotropin-releasing hormone is considered to be the "pilot light" of reproduction, although research has identified upstream neuropeptides (eg, kisspeptin) that activate neurons that secrete gonadotropin-releasing hormone.[10] The pulsatile secretion of gonadotropin-releasing hormone into the network of blood vessels connecting the hypothalamus and pituitary stimulates the gonadotrope cells in the anterior pituitary to release gonadotropins (luteinizing hormone and follicle-stimulating hormone). Luteinizing hormone and follicle-stimulating hormone both enter the peripheral circulation to stimulate gonadal sex steroid production (ie, testosterone or estradiol) and gametogenesis (ie, spermatogenesis in boys, follicular development in girls). Sex steroids exert negative feedback at the hypothalamus and pituitary, inhibiting gonadotropin-releasing hormone pulse generation and pituitary release of gonadotropins. Importantly, luteinizing hormone, follicle-stimulating hormone, and sex steroids are all needed for normal spermatogenesis and ovulation.

The hypothalamic-pituitary-gonadal axis is active at different periods in the lifespan. In utero, the fetal axis becomes active around the start of the second trimester of gestation (Figure 1). Clinical signs in neonatal life can indicate absent/disrupted fetal hypothalamic-pituitary-gonadal activity and provide important clues to identifying abiding hypogonadism (CHH).[11]

After birth, there is a dip in activity of the axis; then the axis becomes active again and remains running during the first 3 to 12

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Table 1
Timing of Normal Puberty and Traditional Definition of Delayed Puberty

Variable	Boys (TV ≥4 mL)	Girls (Tanner II breasts)
Normal timing		
Non-Hispanic White, y	11.46 ± 1.97	9.96 ± 1.82
Black/African-American, y	11.75 ± 1.83	8.87 ± 1.93
Hispanic/Latino, y	11.29 ± 1.83	Not reported
Delayed puberty	TV<4 mL at 13.5-14 y	Tanner I at 12-13 y

TV = testicular volume.

months of life (termed "minipuberty"). Serum gonadotropin and sex steroid levels during minipuberty approximate those of mid-puberty; yet, infants do not develop secondary sex characteristics or undergo sexual maturation. The neonatal window of hypothalamic-pituitary-gonadal axis activity is thought to contribute to development of the sexual organs and gonads and priming the reproductive axis for future fertility.[12,13]

The axis becomes relatively quiescent during childhood. Accordingly, childhood is biochemically characterized by low serum gonadotropins (luteinizing hormone/follicle-stimulating hormone) and sex steroid (testosterone/estradiol) levels. At the end of the childhood period, the reawakening of the axis signals the onset of puberty and is clinically characterized by testicular enlargement in boys and breast budding in girls.

Clinical Presentation and Causes of Delayed Puberty

The classic presentation of delayed puberty includes diminished height compared with peers (due to lack of pubertal growth acceleration) and lack of development of secondary sex characteristics; that is, no testicular enlargement (<4 mL) in boys by age 13.5 to 14 years or lack of breast development (Tanner I breasts) in girls by age 12 to 13 years. Most adolescents will spontaneously initiate puberty on their own, without intervention, and are classified as having constitutional delay of puberty (CDP). CDP appears to be more common in boys than in girls, although this may be partly due to referral bias.

Other etiologies of delayed pubertal onset may be functional hypogonadotropic hypogonadism, primary hypogonadism (ie, gonadal insufficiency with elevated serum gonadotropin levels [hypergonadotropic hypogonadism]) or secondary hypogonadism (ie, central hypothalamic/pituitary defect resulting in low serum gonadotropin levels) (Table 2). Self-limited CDP is the most common cause of pubertal delay in both sexes. Indeed, a recent study of adolescents presenting for evaluation of delayed puberty identified CDP as the most frequent cause (70% in boys and 32% in girls), followed by functional causes (16% and 29%), gonadal insufficiency (2% and 18%), endocrine conditions suppressing the hypothalamic-pituitary-gonadal axis (4.8% and 8.0%), abiding hypogonadism/CHH (3.2% and 5.3%), and congenital and/or anatomic lesions impairing pituitary function (1.9% and 3.3%).[14]

Evaluation: Differentiating CDP AND CHH

CDP and CHH are both diagnoses of exclusion. Thus, understanding the different potential causes of pubertal delay is crucial for evaluation. Past medical history and family history are perhaps the most useful tools in evaluating adolescents presenting with pubertal delay (Table 3).[5,8,9,15] History and review of systems can elicit functional and iatrogenic underlying causes of pubertal delay, including chronic medical conditions (eg, thyroid disease), disordered eating, energy deficit (eg, competitive athletics, particularly distance running, gymnastics, figure skating, and dance), as well as exposures (eg, chemotherapy/radiotherapy) and medications (eg, glucocorticoids). Of particular note, the suspicion of CHH is heightened in the presence of key "red flags," including congenital anosmia (suggesting Kallmann syndrome) and signs indicative of absence of prenatal reproductive endocrine activity (ie, cryptorchidism and/or micropenis in boys).[12]

Evaluation of undescended testes and/or micropenis includes ultrasound and hormonal profiling (ie, sex steroids, gonadotropins, inhibin B, and anti-Müllerian hormone/Müllerian-inhibiting substance) and appropriate referral for treatment (ie, urology, endocrinology). If the individual also has hypospadias, additional testing for potential differences of sex development should be performed, including karyotype/microarray to assess for chromosomal anomalies and 17-hydroxyprogesterone and possibly other adrenal hormone precursors to screen for congenital adrenal hyperplasia.

Heredity (ie, genetics) plays a significant role in pubertal timing. Thus, documenting a detailed, 3-generation family history with a focus on family history of CDP is an essential component of evaluating delayed pubertal onset.[16] Clinicians should calculate mid-parental target height (mean of the parents' heights, plus 6.5 cm [boys] or −6.5 cm [girls]) and record the adolescent's current height on the growth chart to visualize trends in growth relative midparental target height. Markedly delayed growth (<3 cm/y) and low body mass index may point to a functional etiology.

Currently, there is no gold standard test to differentiate CDP from CHH.[17] Biochemically, CDP and CHH exhibit similar reproductive hormonal profiles, including low serum luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol. Thus, such measures are often not clinically useful for differentiating the conditions. Some have proposed serum inhibin B or dynamic gonadotropin-releasing hormone stimulation testing as diagnostic tools.[8,9] However, there is significant overlap in CDP and CHH, resulting in insufficient specificity to accurately discriminate the conditions.[18]

Follicle-stimulating hormone−stimulated inhibin B has recently been proposed as a more accurate predictor than inhibin B at baseline.[19] Additionally, work has examined the utility of kisspeptin stimulation to differentiate CDP and CHH.[20] Kisspeptin is an upstream neuropeptide that stimulates hypothalamic release of gonadotropin-releasing hormone. Accordingly, kisspeptin could be used to probe the integrity of the reproductive endocrine axis and differentiate CDP and CHH. A recent longitudinal study used kisspeptin testing in 16 adolescents presenting with delayed pubertal onset.[20] Although kisspeptin is currently only used in the research setting, initial results are promising; however, further work is needed establish this as a robust diagnostic test.

Because timing of pubertal onset is strongly influenced by genetics, investigators have sought to identify genes that could facilitate the diagnostic process. In terms of CDP, genome-wide association studies have identified nearly 400 independent loci at genome-wide significance that affect pubertal timing.[21] However,

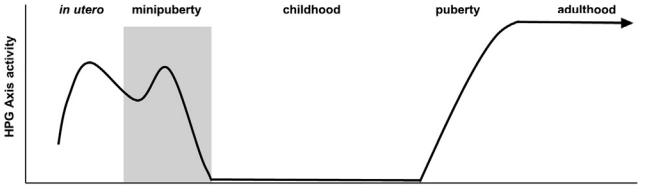

Figure 1. Activity of the reproductive axis across the lifespan. Minipuberty (shaded) represents a brief 6-month window of activity during neonatal life to identify abiding hypogonadism (ie, congenital hypogonadotropic hypogonadism). *HPG = hypothalamic-pituitary-gonadal axis.*

Table 2
Other Causes of Delayed Pubertal Onset

Etiology	Examples
Functional hypogonadism (↓LH/FSH, ↓T/E2)	Disordered eating/energy deficit (eg, anorexia nervosa, bulimia, intense exercise), malnutrition/malabsorption (eg, celiac disease), chronic diseases
Primary hypogonadism (↑LH/FSH, ↓T/E2)	Sex-chromosome aneuploidies (eg, Klinefelter syndrome, Turner syndrome), iatrogenic (postchemotherapy/radiotherapy)
Secondary hypogonadism (↓LH/FSH, ↓T/E2)	Congenital hypogonadotropic hypogonadism, Kallmann syndrome, combined pituitary hormone deficiency, CHARGE syndrome, septo-optic dysplasia

CHARGE = Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital abnormality, and Ear abnormality; E2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; T = testosterone.

the genetics of CDP are still being determined, and no genetic tests are currently available.

In contrast, genetic testing may be a useful addition to a diagnostic workup when CHH is suspected in the setting of clinical red flags—particularly anosmia and an X-linked inheritance pattern suggesting a pathogenic variant in anosmin 1 (*ANOS1*). To date, >60 genes have been found to underlie CHH, accounting for about half of all cases.[10] However, the lack of a genetic finding does not rule out a diagnosis of CHH. Further, there is considerable variability associated with genetic mutations in CHH genes, and the same mutation may manifest as CHH in some individuals and CDP in others. Thus, although the presence of a genetic mutation may increase suspicion for CHH, it does not definitively establish a diagnosis. Widespread genetic testing may not provide a definitive diagnostic answer, but it can be used in a targeted manner when CHH is clinically suspected (ie, red flags suggesting *ANOS1*).[22] Importantly, all patients should receive pretest genetic counseling to support high-quality testing decisions that are informed and aligned with values and preferences.[23]

Sequelae of CDP AND CHH

Most studies on adult outcomes of CDP have been in small series with varying study criteria and different outcome measures. Although CDP is largely believed to be a benign developmental variant with no long-term consequences, several studies suggest CDP may in fact have both harmful and protective effects on a variety of adult health outcomes. A history of CDP appears to be protective for breast and endometrial cancer in women and for testicular cancer in men.[2] In contrast, some studies (but not others) have shown compromised height and bone mineral density in adults with a history of CDP.[2] Mounting evidence suggests that later age at menarche is associated with increased risk for cardiovascular (ie, hypertension, coronary artery disease, angina, myocardial infarction) but decreased risk for metabolic disease (ie, metabolic syndrome, type 2 diabetes).[24] Although CDP represents a delay in reaching reproductive capacity, data on fertility outcomes are scant.[25]

Little is known about the extent of psychosocial distress and neuropsychological aspects of CDP. A recent synthesis of the existing literature noted that CDP may negatively affect educational attainment and psychosocial functioning in adulthood.[24] Some studies have observed associations between CDP and decreased self-esteem and body image; yet, these observations appear to be partly mediated by race and ethnicity. There is no clear evidence supporting lasting psychosocial consequences in females with a history of CDP. However, CDP in males is associated with greater internalizing of symptoms (ie, anxiety, depression) and substance use in adolescence as well as adulthood.[24] Further work is needed to clarify the extent to which the psychosocial distress of CDP in adolescence has lasting, persistent effects in adult life.

The abiding hypogonadism of CHH can have significant effects on metabolic health (ie, metabolic syndrome, type 2 diabetes),[26] bone health (ie, osteopenia, osteoporosis),[8,9] and sexual function.[4] Thus, long-term adherence to hormone replacement (to normalize serum sex steroid levels) is essential to mitigate these risks. All patients should have a baseline bone density measurement (with dual-energy X-ray absorptiometry) with serial, long-term monitoring to assess fracture risk.

CHH does not shorten life expectancy, but it can be a profoundly life-altering condition in terms of psychological well-being.[3,4] Patients with CHH often struggle with lasting feelings of shame, isolation, low self-esteem, and altered body image well into adulthood—effects that can persist despite long-term sex steroid treatment.[3,4] As a diagnosis of exclusion, CHH is challenging to diagnose, and most patients are not diagnosed until very late in adolescence (or early adulthood).[3] Such a “diagnostic odyssey” is common among rare diseases with significant impact on well-being. In CHH, young adults are essentially trapped in a prepubertal body, resulting in significant psychosexual issues.[4]

Table 3
Potential Findings on History/Physical Examination and Related Etiologies

History (Hx) & Physical Examination (PE) Findings	Potential Etiology
Hx: Food restriction, excessive exercise PE: ↓Weight for height, dental erosions	Excessive exercise, disordered eating (eg, anorexia nervosa, bulimia)
Hx: Abdominal pain, constipation, diarrhea, hematochezia PE: ↓Weight for height, pallor, abdominal distension	Malabsorption/malnutrition (eg, celiac disease, inflammatory bowel disease)
Hx: Chemotherapy, radiatotherapy, testicular trauma	Iatrogenic/acquired hypogonadism
Hx: Intellectual disability, seizures, midline defects PE: Midline defects, dysmorphic features, severe short stature	Syndromic hypogonadism (eg, CHARGE syndrome, septo-optic dysplasia, multiple pituitary hormone deficiency)
Hx: Headaches, visual changes, seizures PE: Visual field and neurologic abnormalities	Central nervous system tumor
Hx: Anosmia/hyposmia, cryptorchidism, micropenis PE: Small testicular size, synkinesia (mirror movements)	CHH/Kallmann syndrome
Hx: Family history of delayed puberty	CDP (possibly CHH)

CDP = constitutional delay of puberty; CHARGE = Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital abnormality, and Ear abnormality; CHH = congenital hypogonadotropic hypogonadism.

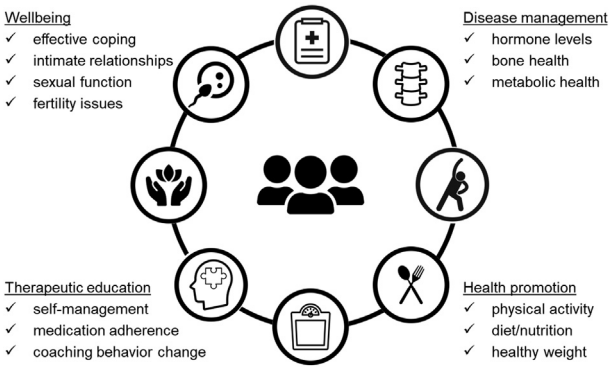

Figure 2. Elements of comprehensive care for congenital hypogonadotropic hypogonadism.

Psychosocial assessment is warranted, with appropriate referrals for professional support, and patients should receive resources for peer-to-peer patient support groups. Attention to red flags can lead to earlier diagnosis, enabling timely initiation of treatment that may mitigate psychosocial sequelae and improve health-related quality of life.[3]

Treatment and Interprofessional Aspects of Care

Even though CDP is self-limited, recent data indicate that some children with CDP wait years after the initial consultation for puberty to begin.[14] The decision to initiate treatment (ie, low-dose sex steroids)[5,27] depends on the psychosocial burden on the individual. Despite being a common condition, there are currently no clinical guidelines for managing CDP,[28] only expert opinion on the differential diagnosis of delayed puberty.[29] Psychosocial distress is the most frequent reason for initiating sex steroid treatment.[5] Thoughtful assessment of anxiety and depressive symptoms is warranted, because bullying is a significant risk factor for suicide and self-harm.[30] Psychologists, psychiatrists, social workers, counselors, and educators (in cases of bullying) may need to be involved in comprehensive approaches to CDP care.

Nurse practitioners (NP) should be prepared to refer patients/families on for specialized care, because hormonal treatment of CDP is optimally managed by a pediatric endocrinologist. There is significant variability in the clinical management of CDP. A 2020 study revealed that providers are more hesitant to treat girls (compared with boys) and cite different reasons for proposing treatment.[28] Whether the observed discrepancies in treatment are related to biologic differences or implicit sex-based biases is unclear.

The decision to treat is based on shared decision making between clinicians and the patient/family, including a frank discussion of benefits/potential risks. It is crucial to provide anticipatory guidance that developing secondary sexual characteristics is a gradual process, as sex steroids are initiated at a low doses to avoid premature closure of the epiphyses and maximize adult height and, in girls, optimal breast development.[27] Close monitoring is warranted with follow-up every 4 to 6 months. In many cases, endogenous puberty will start during (or shortly after) a 6-month course of treatment, but extended treatment may be appropriate for some individuals, and further evaluation for other causes of delayed puberty (eg, CHH) may be warranted.

When CHH is suspected, referral for endocrine consultation is needed to confirm the diagnosis. In contrast to CDP, sex steroid therapy is always indicated for adolescents/young adults with abiding hypogonadism,[31] and a recent clinical practice guideline has been published delineating specific regimens and protocols for sex hormone therapy.[32] After hormone therapy is initiated, primary care NPs play an essential role in monitoring treatment, assessing long-term adherence, and providing ongoing anticipatory guidance and psychosocial support.[33] Patients need to understand that sex steroids will induce secondary sex characteristics but will not induce fertility.

Notably, CHH is a treatable form of infertility, as ~80% of individuals can develop fertility with appropriate therapy.[34] Fertility-inducing treatments include gonadotropin therapy or pulsatile gonadotropin-releasing hormone administration via microinfusion pump[35] and are best managed by specialists with experience using these treatment modalities.[8,9]

It is worthwhile to note that one cannot assume that overall well-being will necessarily improve with treatment initiation. Patients with CHH often have impaired health-related quality of life[3] and psychosexual effects despite long-term treatment.[4]

Key Points About Constitutional Delay of Puberty and Congenital Hypogonadotropic Hypogonadism

Diagnosis

- Constitutional delay of puberty (CDP) is common, affecting 2% to 3% of adolescents.
- Careful history and review of systems provide critical information on the potential underlying etiology of pubertal delay.
- Red flags, including anosmia (in girls and boys) and cryptorchidism and micropenis (in boys) can point to abiding hypogonadism (ie, congenital hypogonadotropic hypogonadism [CHH]).
- CDP and CHH are both diagnoses of exclusion, and no gold standard test is currently available to differentiate the two.

Treatment

- The decision to treat CDP with short-term sex steroid therapy is primarily based on psychosocial distress and should be done in the context of shared decision making.
- Effective treatments are available for CHH. Individuals with CHH should always be treated. Sex steroids do not induce fertility; specialized treatment by specialists (ie, gonadotropin therapy, pulsatile gonadotropin-releasing hormone) can induce fertility in ~80% of cases.
- Adherence to treatment should be assessed at each clinical encounter.

Interprofessional Care

- CDP and CHH can both have significant impact on psychosocial well-being and psychosexual development.
- Individuals should be assessed for psychological distress, anxiety, depression, and victimization/bullying with appropriate intervention, support, and referrals if needed. Individuals with CHH should be provided with information on peer-to-peer support groups.
- Comprehensive care implicates primary care, endocrinology (pediatric/adult), mental health providers (counseling, social work, psychology, psychiatry), genetic counselors/geneticists, as well as educators (ie, schools).
- Structured transition from pediatric to adult-oriented care provides continuity and facilitates improved health and well-being outcomes.

Comprehensive, holistic CHH care includes attention to disease management, health promotion, well-being, and self-management (Figure 2).

Transition for Pediatric to Adult-Oriented Care

Transitional care is a key aspect of coordinated care for adolescents/young adults with endocrine conditions. Transition is not a singular event; rather, it is a structured process enabling clients to smoothly move from pediatric to adult-oriented care, thereby ensuring continuity of care and enhanced health and well-being outcomes.[1] Endocrine providers need strong interpersonal and communication skills as well as the ability to work in teams to effectively help patients and families navigate transition in a complex health care ecosystem. Because the diagnosis of CHH is typically made in late adolescence, transition is critical for mitigating gaps in care and poor adherence.[36]

Transitional care relates to both providers/health systems and patients/families. From the health system perspective, effective pediatric-adult provider communication is needed to delineate roles/responsibilities while timely transfer of records and assessing the adolescent's readiness for transition can help ensure a smooth handoff and continuity of care. For the patient and family, anticipatory guidance is needed to set expectations for parents/guardians regarding the need to cultivate the patient's autonomy. For the adolescent, particular emphasis and priority is given to encouraging active coping and providing emotional support. In parallel, therapeutic education and coaching is needed to help adolescents understand their condition and develop essential self-management skills.[1,36]

Summary

This review provides an up-to-date synthesis of the literature highlighting key points to help clinicians understand and differentiate CDP and CHH (Inset Box). Delayed pubertal onset is a common reason for presenting for endocrine consultation, and evaluation involves ruling out multiple potential causes. Notably, CDP is common, and most adolescents are monitored using a watchful waiting approach. Most adolescents will spontaneously initiate puberty, but some have CHH and will never initiate puberty on their own. In such cases, the watchful waiting approach contributes to delays in starting necessary treatment that can amplify the negative psychosocial sequelae of CHH.[3,4]

Although no single gold standard test differentiates CDP from CHH, certain clinical red flags can facilitate identification of CHH, timely initiation of treatment, and improved outcomes. Importantly, CDP and CHH both have psychosocial implications. Clinicians should be mindful that although these conditions are not life-threatening, they can be significantly life-altering. A holistic approach to care includes attention to both physical and psychological well-being. Comprehensive endocrine care demands an interprofessional approach in which NPs can play an essential role.

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Both authors are at Massachusetts General Hospital, Harvard Center for Reproductive Medicine, Boston. Andrew A. Dwyer, PhD, FNP-BC, is also an associate professor at the William F. Connell School of Nursing, Boston, College, Chestnut Hill, MA, and can be contacted at andrew.dwyer@bc.edu. Yee-ming Chan, MD, PhD, is also with the Division of Endocrinology, Department of Pediatrics, Boston Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, MA.

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