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Transition of Care from Childhood to Adulthood: Congenital Hypogonadotropic Hypogonadism

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Abstract

Passage from childhood to adult life involves biological changes culminating in full reproductive capacity as well as psychosocial development. For patients with congenital hypogonadotropic hypogonadism (CHH), this can be an emotionally challenging time as their pubertal failure results in striking physical differences from their peers. CHH is difficult to differentiate from common disorders of puberty such as constitutional delay of growth and puberty. As such, delays in diagnosis are frequent, and it is a common source of stress and frustration for these adolescents. While effective treatments are available for inducing puberty and attaining fertility is possible in most cases, patients may find it difficult to cope with living with CHH. A critical issue for adolescents with CHH is the risk for being lost to follow-up during the transition from pediatric-centered care to adult care. This article will review the state of the art in diagnosis and treatment of patients with CHH with a particular focus on supporting an effective transition from pediatric-centered care to adult-oriented endocrine services. A synthesis of best practices is offered to help guide clinicians in supporting patients and families during this challenging period of care.

Puberty refers to the biological events and sexual maturation bridging childhood and adulthood that culminate in full reproductive capacity [1]. Adolescence is the complementary developmental process encompassing psychological changes and social reorientation as emerging adults begin taking on adult roles. These events are intertwined and directly related to hormonal changes in the hypothalamic-pituitary-gonadal (HPG) axis that are orchestrated by neuroendocrine hormones. Accordingly, for those young adults with disorders affecting the secretion or action of these critical

hormones (i.e., congenital hypogonadotropic hypogonadism, CHH), management should attend to both biological and psychosocial aspects [2–4]. This paper will provide an overview of pubertal development and the pathophysiology of CHH, challenges for diagnosis, approaches to treatment and specific aspects related to transitional care from a pediatric setting to adult care.

HPG Axis and Puberty

Puberty is triggered by the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from specialized hypothalamic neurons in the preoptic area. Notably, GnRH neurons originate outside of the central nervous system and migrate across the cribriform plate into the brain during early embryonic development [3]. Pulsatile GnRH secretion stimulates the gonadotropes of the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the peripheral circulation. In turn, these gonadotropins exert their effect on the gonads stimulating gametogenesis and sex steroid production. The axis is first activated in utero and during the initial 3–6 months of life (minipuberty) after which it remains suppressed until puberty [5]. The reactivation at puberty is regulated by a complex interplay of genetics and environmental factors [6], yet the precise trigger for the reactivation of the HPG axis remains unclear. Initially, sleep-entrained nocturnal GnRH pulses stimulate gonadotropin release [7], and subsequently these pulses extend throughout the day [3]. Rising gonadotropin and sex steroid levels are clinically manifested in the initial signs of pubertal development: testicular growth (≥4 mL) in boys and breast budding (Tanner II) in girls [8]. However, the variation between individuals is considerable with hallmark signs arriving between the age of 9 and 14 in boys and between 8 and 13 in girls [9, 10]. There is a significant hereditary component to pubertal timing as 50–75% of patients with delayed puberty have a family history [11]. Delayed onset of puberty is common (2%), and most cases are explained by constitutional delay of growth and puberty wherein puberty is eventually completed spontaneously [8]. Recently, large-scale genetic investigations have begun to elucidate this genetic contribution [12]. On the extreme end of this pubertal spectrum are patients with CHH who do not initiate/complete puberty spontaneously.

Challenges for Identifying CHH

CHH is caused by the deficient secretion or action of GnRH resulting in low (or inappropriately normal) serum gonadotropins and low sex steroids (hypogonadotropic hypogonadism) Clinically, CHH manifests as failure to initiate (or complete) puberty and infertility. CHH is challenging to diagnose as it is a diagnosis of exclusion. Careful history taking and physical examination with targeted evaluation can often elicit

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functional causes of hypogonadotropic hypogonadism (e.g., inflammatory disease, eating disorders). Similarly, serum hormone measurements identify hypergonadotropic hypogonadism resulting from primary gonadal failure (e.g., Klinefelter or Turner syndrome). There are some clues that point towards a CHH diagnosis such as history of micropenis with/without cryptorchidism (maldescended testes), hearing loss, impaired sense of smell (hyposmia, anosmia), synkinesia (involuntary mirror movements), renal agenesis, as well as midline and skeletal defect (cleft lip/palate, dental agenesis, digit anomalies) [3] (Fig. 1). Differentiating transient from permanent hypogonadotropic hypogonadism is challenging during early adolescence (14–16 years of age) as there is no definitive, widely available "gold standard" test that effectively dissects the two [13]. Typically serial follow-up visits can identify those who will not spontaneously start puberty. Further, there is no clear consensus regarding whether such cases should be treated with low-dose sex steroids in an attempt to "jump start" puberty or whether a more conservative watchful waiting approach is warranted. In the setting of delayed puberty, the decision to initiate treatment should be a shared decision between the clinician and patient based on the impact that the lack of pubertal development is having on the child [3, 8]. In light of these clinical challenges and uncertainties, most patients with CHH are diagnosed in their late teens to early twenties – a time when patients are vulnerable to gaps in care as they move from pediatric-oriented services to adult-centered care [2].

Effects of CHH on Health and Well-Being

Clinically CHH is characterized by absent/incomplete puberty (and infertility) Both men and women with CHH lack the accelerated growth, change in body composition, skeletal maturation, and secondary sexual characteristics and sexual development due to their hypogonadism [1] (Fig. 1). These factors place both sexes at high risk for "silent" problems such as poor bone health (osteopenia/osteoporosis) [14] as well as the metabolic syndrome and type 2 diabetes in males [15]. Notably, a wide range of CHH-associated phenotypes have been reported. Further, the clinical spectrum of CHH ranges from relatively mild (i.e., partial pubertal development, fertile eunuch variant) to severe GnRH deficiency evidenced by a complete absence of puberty (with/without cryptorchidism, micropenis) to syndromic forms in which hypogonadotropic hypogonadism is part of a larger constellation of features (e.g., combined pituitary hormone deficiency, septo-optic dyplasia, CHARGE syndrome, Hartsfield syndrome, Lawrence-Moon-Biedl syndrome, Prader-Willi syndrome) [3].

While secondary sexual characteristics, sexual function, and libido are amenable to sex steroid replacement, there is evidence that psychological and psychosexual issues often persist long after patients are treated with full-adult replacement doses [16–18]. These data suggest that the availability of effective treatment to mitigate physical consequences of CHH does not necessarily ameliorate the psychological im-

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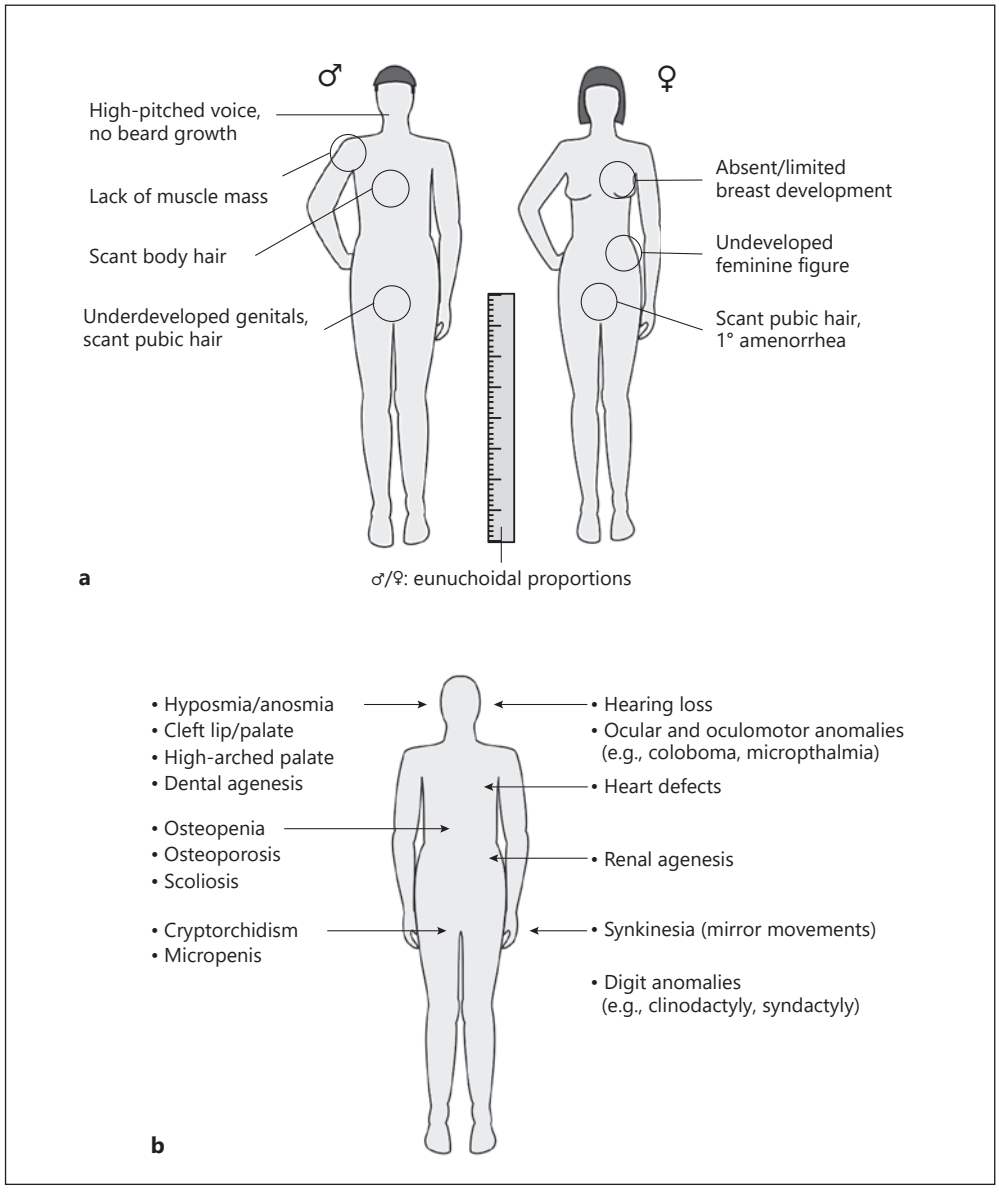

Fig. 1. Clinical signs of hypogonadism in young adults and observed CHH-associated phenotypes. **a** Clinical signs commonly seen in male and female young adults with hypogonadism. Eunuchoidal proportions refer to an abnormal upper:lower segment ratio or arm span exceeding height by >7 cm. **b** CHH-associated phenotypes occur as variable rates [3].

pact that many patients experience. Body image concerns, anxiety, depressive symptoms, and feelings of shame and isolation can significantly impair intimate relationships and quality of life for these patients. Thus, these less obvious psychological and emotional aspects warrant attention as part of a comprehensive approach to care.

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For newly diagnosed adolescents and young adults, the focus of treatment is on virilization and estrogenization, respectively [3, 19]. Low-dose testosterone treatment (i.e., injections) for young men and low-dose estradiol (i.e., ethinyl estradiol, 17β-estradiol) for young women have been the mainstay for inducing secondary sexual characteristics in adolescents with CHH. It can be very difficult for young adults to have a prepubertal child's body when their chronological peers are more advanced in terms of sexual development [16, 17]. These outward signs of puberty (i.e., deepening of the voice, beard growth, muscle mass in boys and breast development in girls) are obvious to peers, and patients commonly report experiences with teasing and bullying that is associated with heightened future psychological morbidity [20]. There is no set universal approach for inducing secondary sexual characteristics (virilization/estrogenization), yet several recent publications have delineated expert opinion and protocols on this matter [3, 8, 19]. Regardless of the dose schedule or regimen, it is important to provide adequate anticipatory guidance and psychological support to help young adults understand the rationale for the initial low dose and the gradual escalation (i.e., to maximize statural growth in both sexes and stimulate breast development in females). After breast development is sufficiently advanced on estrogen-only therapy, subsequent introduction of progestins will lead to monthly withdrawal bleeding (menses).

GnRH therapy and gonadotropins will also induce development of secondary sexual characteristics. In addition, these treatments will induce gonadal maturation and fertility. Pulsatile GnRH is effective for inducing puberty in patients with CHH [21] as are gonadotropins as an initial treatment approach for adolescents [22, 23; reviewed in 24]. A recent report posited that GnRH is superior to human chorionic gonadotropin (hCG) monotherapy for pubertal induction [25]. However, hCG monotherapy has suboptimal results in cases of absent puberty (testicular volume, TV, <4 mL), and the addition of FSH is required to improve outcomes [26]. Moreover, the emergence of sequential treatment (FSH alone prior to FSH and hCG) [27, 28] to maximize fertility in CHH men with a complete absence of puberty is a promising option that may extend benefits even in cases of cryptorchidism. However, the optimal treatment has yet to be determined and will likely require international multicenter trials given the rarity of these patients [3].

In contrast to testosterone replacement treatment for males with CHH, gonadotropin therapy (i.e., hCG ± FSH) stimulates testicular development, and there is some evidence that the physical changes with this therapeutic approach have additional benefits on patient quality of life measures [29]. Thus pulsatile GnRH or gonadotropin therapies, i.e., hCG monotherapy in cases of partial pubertal development (TV ≥4 mL) or sequential treatment in absent puberty (TV <4 mL), are viable options for adolescent males with CHH. Typically, such treatment is not given prior to the age of 16 unless there is a strong confidence of a CHH diagnosis (i.e., anosmia). The vast

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majority of delayed puberty cases are caused by constitutional delay of growth and puberty and do not require gonadotropin or GnRH therapy. However, fertility-inducing regimens using gonadotropins require frequent self-injection and extended courses of up to 2 years to develop fertility potential [26]. Therefore, maturity level and willingness to adhere to the autoinjection regime must be carefully evaluated. Depending on the health system, the costs associated with long-term gonadotropin treatment should also be considered and discussed with the families.

Patient education and counseling during adolescence should include anticipatory guidance regarding the timing and onset of somatic changes brought on by sex steroid treatment (i.e., erections and nocturnal emissions in boys and breast development and menses in girls). There are data to suggest that discussions regarding intimate relationships and sexuality are not frequently raised with patients [17, 30]. These topics warrant attention, and time should be allotted for these sensitive yet weighty discussions. While fertility is likely not the most pressing priority of young adults with CHH, it is important to underscore that there are effective treatments for developing fertility. Approximately 75% of males with CHH are able develop sperm in the ejaculate [31–33] using fertility-inducing regimens, and females have a similar ovulation rate per cycle as normal women (with 25–30% attaining pregnancy per cycle) [34]. Additionally, emphasis should be given to the importance of adherence and ongoing endocrine care due to the fact that patients frequently report gaps and cracks in care [16]. Similarly, patients should be made aware that approximately 10–15% of patients undergo a reversal and recover function of the HPG axis [35]. Reversal is identified by sustained normal serum gonadotropin and sex steroid levels following treatment washout (or by spontaneous pregnancy in females). It is crucial that treatment washouts be done in the context of medical supervision to ensure that restarting hormonal therapy occurs in a timely manner for those patients who do not recover HPG axis function. Many patients may undergo genetic testing as part of their CHH evaluation. While genetic findings can contribute to making the diagnosis of CHH, there are more than 20 genes identified to date underlying CHH, and the genetic architecture can be complex including digenic and oligogenic forms [3]. Therefore, we recommend that families receive genetic counseling when considering testing and when receiving results [36]. For adolescents, it is also recommended that they be offered individual genetic counseling once they have reached legal independent age to facilitate their informed decision-making.

Transitional Care of Patients with CHH

The notion of transitional care from the pediatric setting to adult care has gained growing attention [37]. International guidelines and expert opinion underscore the importance of continuity of care for emerging adults with chronic conditions [38, 39]. This is particularly important as adolescents are vulnerable to experiencing gaps in care and lapses in adherence [40]. Transition can be an uncertain and challenging time for both

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Table 1. Synthesis of recommended best practices for transition of young adults with congenital hypogonadotropic hypogonadism (CHH)

Targets	Goals	Approaches	Comments
Promoting autonomy	↑ ability to navigate adult care ↑ participation in decision-making ↑ independence	Promote independent appointments "How to" fill prescriptions and make appointments Discuss educational/vocational concerns	Timing of transition is individual and may range between16 and 20 years based on development
Self-management	↑ self-efficacy ↑ adherence ↑ health status	Therapeutic education/coaching Behavioral therapy Motivational interviewing Shared decision-making, self-infection	A trusting, nonjudgmental therapeutic relationship is important
Coordinated care	↑ continuity of care ↓ uncertainty ↑ patient and family satisfaction	Engage receiving team/specific provider Provide a detailed summary report Telephone/web/SMS support Follow-up to ensure first appointment is kept	Try to make the first appointment easy to ensure first contact is made
Guiding and supporting patients/families	↑ patient and family satisfaction ↑ patient quality of life	Transition team/transition coordinator Joint consultations if possible Use checklists, readiness tools Address psychosexual concerns Offer links for peer-to-peer support	Planning should begin early and delineate roles to clarify expectations

Adapted from: Dwyer et al., 2015 [2]; Boehm et al., 2015 [3]; Vaks et al., 2016 [42]; Gleeson and Turner, 2012 [44]; Kapellen and Kiess, 2015 [46].

patients and their parents alike [41]. To date, there is no clear consensus on the most appropriate model of transitional care. However, there is growing agreement that transition is not a simple transfer between health care providers, and best practices guiding the transition process are emerging from the synthesis of systematic reviews and expert opinion (Table 1) [42–46]. Patients with chronic endocrine disorders have condition-specific needs during transition [30, 45], and patients with CHH often experience gaps and disjointed care as they pass from pediatric to adult settings [16].

Discontinuity of care can have marked effects on both health and quality of life for young adults with CHH. Poor adherence or gaps in sex steroid treatment can result in diminished sexual function, decreased energy levels [47], and impaired bone health [14]. Further, lapses in treatment as short as 2 weeks can result in increased fasting insulin levels [48] placing patients at a potentially higher risk for metabolic problems [15]. Structured transition programs for patients with CHH have been proposed as a means to ameliorate these problems [2] and have been effective in other chronic conditions [43]. There is consensus among European experts in the field that a structured approach (e.g., joint consultations, dedicated transition team) is preferable [3] yet financing can often be challenging [44]. Recently, a systematic review was conducted to develop a transition framework for young adults with chronic conditions to facili-

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tate effective transition [42]. A number of key elements can contribute to an effective, purposeful, planned passage of young adults from child-centered care to an adult-oriented environment. Important factors include promoting independence and autonomy, cultivating self-management to promote adherence to treatment (including offering to teach self-injection techniques), coordinating care (either supporting or guiding patients and families during transition). Based on the available evidence and expert opinion, we have synthesized key elements and recommended practices for transitional care of adolescents with CHH that may be used to develop priorities for resource-limited settings (Table 1).

Challenges and Future Directions

Presently, diagnosing CHH is challenging as there is no "gold standard" test widely available and able to rapidly and easily discriminate CHH from simple delayed puberty. Thus, there is an opportunity to identify novel biomarkers and new approaches to diagnosis that may help ease this challenge. Indeed, the process of excluding potential causes of failed/stalled puberty can be lengthy involving multiple visits, tests, and imaging studies. This can sometimes be a source of frustration for patients and families. Further, there is mounting evidence supporting the notion that earlier diagnosis and initiation of treatment is important for alleviating some of the psychological impact of CHH [2, 3, 16]. As access to next-generation sequencing technologies increases in parallel with falling costs, exome/genome sequencing may hold promise for enhancing early identification of CHH. Yet, the technological advances in genetics also bring additional challenges for care in terms of genetic literacy of patients and families and how clinicians can help patients make informed decisions and communicate the risk to family members regarding heritable conditions such as CHH. This poses a significant challenge given the sometimes complex genetic architecture of CHH (i.e., digenicity, oligogenicity) and the incomplete penetrance/variable expressivity observed in CHH pedigrees [3].

While effective treatments are available for CHH, more work is needed to clarify the optimal approach for young adults. For example, it remains unclear whether there is a time window to achieve optimal effects for future fertility potential [3, 24]. Thus, additional studies – likely in the form of international randomized multicenter trials – are needed to identify the optimal regimen for pubertal induction and for attaining the maximal fertility potential among these patients. Similarly clear clinical guidance is lacking regarding psychosexual development issues in CHH patients. This has been identified as an area of need that warrants attention and referral to specialists (e.g., psychologists, sex therapists) as needed [16, 17, 30]. The notion that CHH is reversible in 10–15% of cases also merits discussion, and it seems appropriate that periodic supervised treatment washouts be conducted to assess for HPG axis recovery [3, 35]. To date, there are no clear predictors or genetic signatures that will indicate who will have reversible hypogonadism but we anticipate that additional investigation may shed light onto this clinical phenomenon.

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Table 2. Key points for young adults with congenital hypogonadotropic hypogonadism (CHH)

Early diagnosis can help ameliorate some of the psychosocial aspects of CHH
Focus on developing lifelong management skills
– Ask about medication adherence
– Help patients understand the consequences of gaps in treatment
Discuss intimacy and psychosexual concerns
Provide resources for online peer-to-peer support
In the absence of a structured transition process:
– Provide a referral to a specific adult-oriented endocrine provider
– Provide a comprehensive summary report to receiving team
– Follow up to make sure that initial consultation has been completed
Affirm that fertility is possible in the vast majority of cases
Evaluate reversal in supervised "wash-out" periods every 2–3 years

Conclusions

Transitional care for young adults with chronic conditions poses challenges for maintaining continuity of care and fostering individual health and well-being. Elements for successful transition include close collaboration between pediatric and adult service providers combined with effective communication with adolescents and their families (Table 1). This process should be patient-centered taking into consideration the patient's condition-specific needs, emotional development and readiness for transition in terms of self-care and psychological coping (Table 2). Further studies are needed to enhance diagnosis and treatment of young adults with CHH and to explore the long-term health consequences of hypogonadism in adolescence. Additionally, more work is needed to test specific transition models and to develop evidence-based disorder-specific guidelines for transitional care in endocrinology.

Case History

Presentation and History

A white European adolescent male (15 years and 10 months old) presented for pediatric endocrine consultation for evaluation of absent spontaneous pubertal development. He was otherwise healthy, had a normal body mass index (22.1) and had steady linear growth without growth spurt (165.2 cm). His past medical history was significant for bilateral cryptorchidism for which he had undergone orchiopexy at the ages of 4 and 7, respectively. The family history is notable for delayed puberty in both parents (Fig. 2). The mother had had late menarche at the age of 16, and the father reported being a "late bloomer" stating that he continued to grow until the age of 20 and began shaving much later than his peers. The proband's 14-year-old sister had yet to have menarche.

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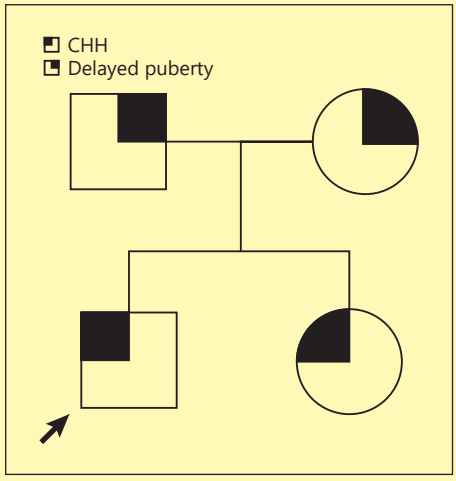

Fig. 2. Family pedigree. The proband (arrow) was born with bilateral cryptorchidism and underwent orchiopexy at the ages of 4 and again 7. He presented at the age of 17 with absent puberty. Both parents had a history of delayed puberty. The mother had menarche at the age of 16 and reported being a "late bloomer" with growth spurt and shaving starting much later compared to peers. At the age of 17, the proband's sister presented for evaluation of primary amenorrhea.

Evaluation: What Is Causing the Lack of Pubertal Development?

The physical examination was unremarkable but for his lack of pubertal development and absent virilization. He had Tanner III pubic hair, prepubertal testes (2 mL) and bilateral scars from his past orchiopexy procedures. Hormonal profiling revealed hypogonadotropic hypogonadism with undetectable gonadotropins (LH <0.5 IU/mL, FSH <0.4 IU/mL) and low serum testosterone (0.4 nmol/L) with low serum inhibin B levels at 62 pg/mL. Thyroid function studies (thyroid-stimulating hormone, free thyroxine) and insulin-like growth factor I levels were within normal limits as were his response to adrenocorticotropin. Cranial MRI revealed normal pituitary imaging. Formal smell testing (Sniffin Stix^{TM}) confirmed normal olfactory function (14/16, 95th percentile for age). Given the family history of constitutional delay of growth and puberty, the challenge was to differentiate self-limited delayed puberty from CHH. In an attempt to differentiate these 2 possibilities, an LH-releasing hormone test was performed (Relefact^{TM} 0.1 mg i.v.) with blood sampling over 2 h. Stimulation testing revealed a modest LH response (<0.5 IU/L at baseline rising to a peak of 2.4 IU/L) and thus was not able to determine the diagnosis [3, 13].

The patient who was 15 years 10 months old presented with delayed puberty; he had prepubertal testes and absent growth spurt, a history of bilateral cryptorchidism, isolated hypogonadotropic hypogonadism with poor response to the GnRH test and low serum inhibin B levels. At this time, the diagnosis of a congenital form of GnRH deficiency is increasingly likely, as the patient is almost 16 years old and his TV is >4 SD from the norm [49]. The patient was keen to start treatment to induce secondary sexual characteristics in order to appear more in line with his peers. As such, we discussed low-dose testosterone replacement to advance his development and determine whether spontaneous pubertal onset could be initiated with exogenous testosterone.

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Treatment 1: Can Puberty Be Triggered?

We discussed the treatment plan involving low-dose testosterone (50 mg) administered monthly via intramuscular (IM) injection for 3 months then increased to 100 mg IM for 3 more months. In order to set realistic expectations for his response to treatment, we discussed that the low doses were necessary to avoid prematurely fusing his epiphyses, thus enabling him to complete his growth and attain his maximal height. Further, we noted that the outward signs (i.e., beard growth and deepening of the voice) would not occur immediately. The plan was to conduct a 6-month course of treatment followed by a pause to re-evaluate serum testosterone and gonadotropin levels after 2 months off treatment to determine whether puberty had been initiated following exogenous testosterone therapy. He tolerated the injections well and after 2 months off treatment, he showed no evidence of spontaneous puberty. At the age of 16.5, his TV remained prepubertal with serum testosterone levels frankly hypogonadal in the setting of undetectable serum gonadotropins. With the history of bilateral cryptorchidism, he was diagnosed with normosmic CHH.

At the age of 17, he was transitioned to the adult endocrine team via a joint initial consultation with both the pediatric and adult endocrinologists. At the initial consultation the various treatment options were discussed for inducing secondary sex characteristics [2, 3, 19]. The relative pros and cons for each option were discussed in terms of his individual situation. We presented the possibility to continue the monthly testosterone injections, longeracting formulations such as testosterone undecanoate (Nebido^{TM}) that only require an injection every 12 weeks or so, and gonadotropin therapy that would stimulate testicular development, endogenous testosterone production and possibly fertility [24, 50]. He opted to pursue gonadotropin therapy as he considered testicular growth an important factor in his decision. Given his diagnosis, we discussed genetic testing with the family as well as evaluating the sister as she was now 15 years old and had not had menarche.

Treatment 2: Can Testicular Growth and Fertility Be Developed?

Attention was given to discussing the predictors of outcome for fertility-inducing treatments. In particular, patients with a history of maldescended testes (cryptorchidism), prepubertal testes (<4 mL) and low serum inhibin B (<60 pg/mL) have poorer outcomes [31]. Given his history of such negative predictors, we discussed that up to 2 years of treatment would be needed to stimulate testicular growth and develop fertility, and that we recommended a specialized approach to maximize his potential to develop fertility [26]. Low serum inhibin B levels in prepubertal testes reflect a limited population of immature Sertoli cells; thus, a sequential treatment approach involving pretreatment with FSH only is intended to act as a proliferative phase for increasing the numbers of immature

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Sertoli cells and spermatogonia (the stem cells of germinal cells) prior to maturation (i.e., induced by the addition of hCG) [27, 28, 51].

He started sequential treatment with a 2-month pretreatment with rFSH (Gonal-F 75 IU) daily via subcutaneous injection. This rapidly normalized serum FSH (4.3 IU/L at 1 month) and was paralleled by a corresponding rise in inhibin B into the normal range (Fig. 3). After 2 months of rFSH treatment, TV had increased to 4 mL. Combined rFSH + hCG was started (rFSH 75 IU + hCG 500 IU 3 times weekly), and within 2 months his testosterone levels increased to 7.2 nmol/L (trough level prior to injection). hCG was further increased to 1,000 IU 3 times weekly with normalization of serum testosterone levels 1 month later. He became progressively virilized and reported an improved sense of well-being. Notably, he appeared significantly more confident and was much more at ease with eye contact and interactions with the care team. Sperm was first observed in his ejaculate after 12 months of treatment (0.1×10^6/mL). His TV continued to grow reaching 11 mL at 24 months of combined gonadotropin treatment with a maximal sperm count of 2.0×10^6/mL. Thus, the fertility potential was achieved despite the negative predictors at the outset of treatment.

Follow-Up and Other Transitional Care Issues

At the initial transitional care consultation jointly held with the pediatric and adult endocrinologists, the family agreed to have genetic testing for mutations in known CHH genes and to have the sister's primary amenorrhea evaluated. The patient and his sister harbor the same homozygous stop codon in tachykinin receptor 3 (*TAC3R*) p.Trp275* inherited from their heterozygous parents (Fig. 2). Mutations in *TAC3R* have previously been demonstrated to underlie normosmic CHH [52–55]. Further, some CHH patients harboring mutations in *TACR3* do undergo spontaneous reversal [53]. So the patient is being followed closely with periodic withdrawal of treatment for reversal [35]. Additionally, the sister underwent clinical and biochemical evaluation, and in light of the genetic studies, she was also diagnosed with normosmic CHH, and low-dose estrogen therapy was initiated.

Near the end of the 2-year pubertal induction with sequential gonadotropin therapy, the patient decided to enter the military service. However, he expressed concern about having to manage the gonadotropin therapy while living in the barracks. Specifically, he was worried about having to store, mix, and inject several times a week and the possible questions that might arise from his military peers. Accordingly, we scheduled a follow-up visit to specifically revisit treatment options. He expressed his satisfaction with the clinical response (i.e., increased TV) and was somewhat concerned that this would diminish if he switched to testosterone replacement. After discussion, the patient decided that the privacy attained by self-injecting testosterone monthly (vs. mixing medication and injecting 3×/week) outweighed his concerns of diminished testicular size.

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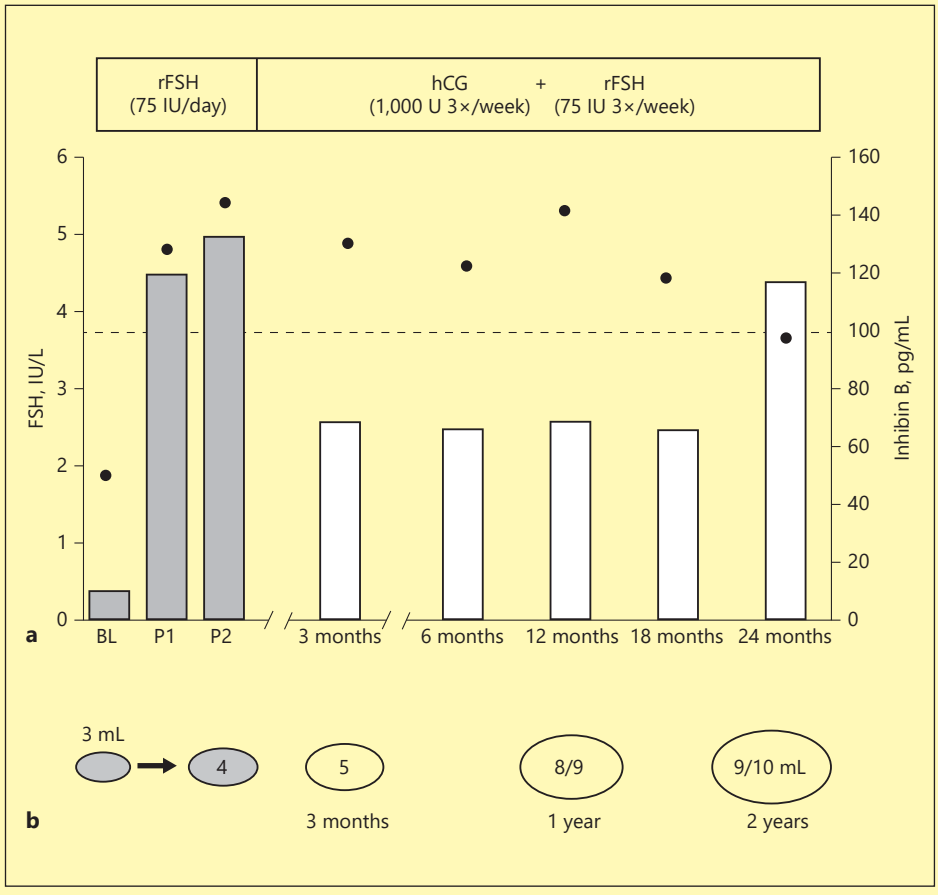

Fig. 3. Response to sequential gonadotropin treatment. **a** The sequential treatment consisted of a 2-month pretreatment (gray) with recombinant FSH alone (75 IU daily via subcutaneous injection) followed by combined gonadotropin therapy (hCG 1,000 U + rFSH 75 IU via subcutaneous injection 3 times per week for 24 months). The graph depicts serum trough FSH levels (bars) and inhibin B levels (circles). The dashed line represents the lower end of the normal range for inhibin B. BL, baseline; P1, P2, pretreatment 1 and 2. **b** Changes in testicular volume (TV) thoughout treatment. After rFSH pretreatment, TV increased from 3 to 4 mL bilaterally. Following 2 years of combined treatment, TV reached 10 mL bilaterally. Sperm was first observed in the ejaculate at 12 months (0.1×10^6/mL), increased to 1×10^6/mL at 18 months and 2×10^6/mL at 24 months.

We also discussed some uncertainty about redeveloping sperm if he later decided to restart gonadotropin therapy [32, 56]. Based on this, he opted to cryopreserve sperm before transitioning to testosterone replacement. After a sufficient number of straws had been attained and frozen, we arranged a dedicated follow-up visit with the endocrine nurse to teach the intramuscular autoinjection technique. He effectively demonstrated the technique and gave

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himself the initial testosterone injection. We underscored the importance of adherence to treatment and he began self-managing his testosterone replacement (Testoviron 250 mg IM every 4 weeks). Importantly, serial monitoring of his testosterone levels did not indicate any problems with ongoing adherence as testosterone levels were maintained in the normal range. Bone mineral density revealed normal scores for the lumbar spine (T score = –0.8) and osteopenia in the hip (T score = –1.2). The patient returns for biannual visits for ongoing monitoring.

Conclusion

Herein we report the case of a young adult male with a severe familial form of GnRH deficiency (cryptorchidism and absent puberty) who responded well to a sequential treatment strategy (FSH alone followed by FSH + hCG) to induce spermatogenesis. This case also demonstrates how a coordinated transition was made between the pediatric and adult care settings as well as how patient engagement and shared decision-making can contribute to a patient-centered care [57] that supports adherence to treatment and effective self-management for a chronic condition such as CHH.

Key Learning Points

1. There is no simple, effective way to differentiate constitutional delay of growth and puberty from CHH in 14- to 16-year-old adolescents.
2. Gonadotropin therapy can be effectively used to induce pubertal development in adolescents with CHH.
3. Fertility potential may be developed even in severe cases of GnRH deficiency with bilateral cryptorchidism.
4. Patient engagement and fostering shared decision-making with young adults are part of a patient-centered approach for the long-term management of CHH.

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