Complete reversal of adult-onset isolated hypogonadotropic hypogonadism with clomiphene citrate

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Objective: Inhibition of pituitary gonadotropin secretion in men by T is principally mediated by aromatization to estrogen (E), which inhibits hypothalamic secretion of GnRH. We hypothesized that adult-onset isolated hypogonadotropic hypogonadism (IHH) might result from an altered central set-point for E-mediated negative feedback.

Design and Setting: Longitudinal clinical investigation unit-based evaluation of the clinical and biochemical response to E-receptor blockade.

Patient(s): A 31-year-old man presenting with an 18-month history of sexual dysfunction resulting from severe adult-onset IHH (LH 1.7 U/L, FSH 2.0 U/L, T 3.5 nmol/L).

Intervention(s): Initial therapy with 50 mg of clomiphene citrate (CC) three times a day for 7 days, with overnight LH pulse profiling and 9 AM T levels evaluated at baseline and on completion. A 2-month washout period, followed by low-dose maintenance therapy (25–50 mg/d) for 4 months.

Main Outcome Measure(s): Baseline and stimulated T levels and LH pulsatility; effect on sexual function.

Result(s): Clomiphene therapy resulted in complete normalization of pulsatile gonadotropin secretion, serum T level, and sexual function.

Conclusion(s): Isolated hypogonadotropic hypogonadism may result from an acquired defect of enhanced hypothalamic sensitivity to E-mediated negative feedback. Whereas direct T replacement therapy can further suppress endogenous gonadotropin secretion, treating IHH men with gonadotropins can stimulate endogenous T secretion and enhance fertility potential. On theoretical grounds, reversal of gonadotropin deficiency with CC might be expected to have a similar biological effect. (Fertil Steril® 2006;86:1513.e5–9. ©2006 by American Society for Reproductive Medicine.)

Key Words: Hypogonadotropic hypogonadism, testosterone, estradiol, inhibin, clomiphene citrate, hypothalamus, GnRH

Isolated hypogonadotropic hypogonadism (IHH) is defined biochemically by low serum levels of gonadal steroids with low or inappropriately "normal" gonadotropins, without wider anterior pituitary dysfunction. This is termed Kallmann syndrome in the approximately 50% of cases with associated anosmia. Isolated hypogonadotropic hypogonadism is classically congenital in origin; therefore, patients usually present with pubertal delay or primary amenorrhea, and at least four genetic causes have been identified to date. In practice, the term IHH excludes patients with likely secondary etiologies, such as structural lesions of the hypothalamus-pituitary region or systemic illness.

Organic IHH needs to be distinguished from the functional suppression of the gonadotropic axis that is commonly observed in both acute and chronic illness, in proportion to disease severity. The latter is completely reversible with treatment or remission of the underlying condition. Whether this physiological response to systemic illness is adaptive or maladaptive has not been adequately tested, and the clinical decision whether to institute replacement therapy in cases of equal severity varies in practice according to the context and the evidence base. Women with weight-related hypothalamic amenorrhea are usually given estrogen (E) replacement, whereas high dependency unit/intensive therapy unit-based patients with prolonged critical illness are not usually offered treatment.

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MATERIALS AND METHODS

Clinical Features of Presenting Case

A 31-year-old office administrator presented to a primary care-based sexual dysfunction clinic with an 18-month history of reduced libido and severe erectile dysfunction. Initial investigations confirmed hypogonadism (serum levels of T 3.5 nmol/L, LH 1.7 U/L, and FSH 2.0 U/L), and he was referred for an endocrine opinion. He recalled a normal puberty, consonant with his peers, and had conceived a

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TABLE 1

09:00 Baseline anterior pituitary function.

Cortisol: 601 nmol/L (normal range: 190–650 nmol/L); 26 nmol/L at 17:00
PRL: 275 U/L (normal range: <450 U/L)
Free T_4: 15 pmol/L (normal range: 11–23 pmol/L)
tT3: 2.9 nmol/L (normal range: 0.9–2.9 nmol/L)
TSH: 1.26 mU/L (normal range: 0.3–4.7 mU/L)
IGF-1: 10 nmol/L (consistent with age, sex, and body mass index)
Normal blood count, ferritin, electrolytes, liver enzymes, glucose, HbA_{1c}.
GH pulsatile secretion preserved.
MRI scan: normal brain and pituitary

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daughter by his previous partner 5 years before. There was no history of exposure to anabolic or sex steroids, and his partner confirmed the absence of any symptoms of sleep apnea. Although physically reasonably active, he was not a gym attender. He had sustained a comminuted femoral fracture in a road traffic accident 7 years before (which had not involved any head trauma), and this had required several operative interventions.

For the past 2 years, he had been receiving a stable and successful drug regime for chronic pain in his left leg under specialist supervision, comprising 1 g of paracetamol twice a day, 15 mg of methadone three times a day, 7.5 mg of zopiclone, 100 mg of sertraline, and 15 mg of lansoprazole daily. Although obese (height, 1.9 m; body mass index, 38 kg/m^2), he appeared systemically well, normotensive (blood pressure 135/86 mm Hg) and was externally normally virilized (G(enitalia) stage 5, P(ubic hair) stage 5, A(xillary hair) stage 3, testes 25 mL) with intact olfaction and mild bilateral fatty gynecomastia.

Laboratory Assays

Serum gonadotropin concentrations were measured using automated two-site chemiluminometric immunoassays, using mouse monoclonal capture antibodies immobilized to paramagnetic beads, and acridinium ester-labeled polyclonal signal antibodies (Advia Centaur System, Bayer Diagnostics, Newcastle-upon-Tyne, United Kingdom); the sensitivity is 0.07 IU/L for FSH and 0.3 IU/L for LH. The E_2 and T concentrations were measured using direct competitive chemiluminescent immunoassays (Advia Centaur System); the sensitivity is 37 pmol/L for E_2 and 0.35 nmol/L for T. The SHBG was measured by a two-site immunoradiometric assay (SHBG IRMA kit, Orion Diagnostica, Turku, Finland). Free T was estimated using a mass action formula incorporating T and SHBG values (1). Inhibin concentrations were measured using a one-step two-site ELISA (Inhibin EASIA kit, Biosource Europe SA, Nivelles, Belgium).

Management Plan

Initial investigations confirmed IHH, with the clinical history and features indicating adult-onset disease (Tables 1 and 2). Possible secondary causes of gonadotropin deficiency included chronic pain, obesity, and opioids, although his overall state of well-being was strikingly discordant with the severity of hypogonadism (2). It is conceivable that adult-onset IHH could arise through an altered hypothalamic "gonadostat" set-point, leading to enhanced negative feedback sensitivity to sex steroids, with recent data underscoring the importance of aromatization to E_2 to the biological actions of T in men, including modulation of gonadotropin secretion. To ascertain whether his reproductive axis was suppressed through

TABLE 2

Baseline and CC-induced changes in endocrine biochemistry.

		CC treatment				
Analyte (normal range)	Baseline (9 AM level)	50 mg three times per day for 1 wk	Washout (3 wk)	Washout (8 wk)	25 mg/d for 9 wk	50 mg/d for 11 wk
LH (3–13 U/L)	<1.0	3.0	4.1	<1.0	3.9	7.7
FSH (1.3–9.2 U/L)	<1.0	2.6	3.4	1.1	3.5	6.8
E_2 (<150 pmol/L)	75.0	197.0	125.0	80.0	110.0	177.0
T (9–25 nmol/L)	3.6	13.4	17.9	3.7	11.2	19.0
SHBG (13–71 nmol/L)	16.0	29.0	24.0	24.0	25.0	21.0
Free T (215–760 pmol/L)	96.0	295.0	453.0	82.0	262.0	516.0
Inhibin (0.6–2.5 kU/L)	<0.5	–	1.2	1.0	1.3	–

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an E_2-mediated effect, the patient was treated with clomiphene citrate (CC, 50 mg three times daily for 7 days).

Clomiphene is a long-established selective estrogen receptor modulator (SERM) with predominant antagonist activity at the hypothalamus and pituitary estrogen receptor (ER), being a 62:38 mixture of enclomiphene (*trans*-isomer, E_2 antagonist) and zuclomiphene (*cis*-isomer, mixed E_2 agonist). After a single oral dose steady-state plasma levels are achieved for 2–14 days, with a cumulative effect of repeated doses resulting in biological action potentially lasting for 1–2 months after cessation of intake (3). Throughout the period of this study, his other medications remained unchanged.

RESULTS

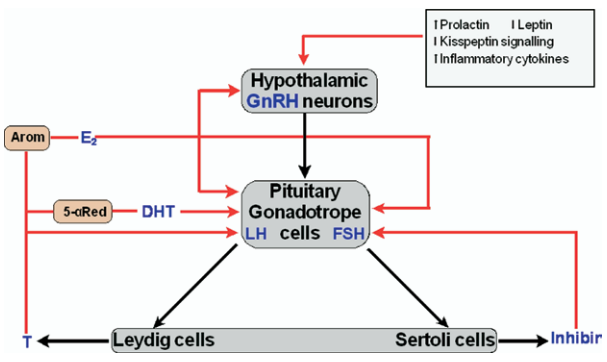
Libido and sexual function normalized during the week of high-dose CC therapy and this clinical improvement persisted for 4–5 weeks after the end of therapy. He was able to engage in full penetrative intercourse and achieve orgasm with ejaculation. Although he experienced unpleasant hot flashes within 1–2 days of starting CC, these resolved entirely within 2 weeks of stopping treatment.

There was a near-doubling of overnight LH pulse frequency (mean interpulse interval falling from 170–110 minutes), with a markedly greater pulse amplitude consistent with normalization of GnRH pulse-generator activity (Fig. 1). Serum levels of total T and calculated free T normalized and remained for ≥3 weeks, returning to baseline by 8 weeks after the end of treatment (Table 2). No significant changes in testicular volume were recorded, and the patient declined to provide serial semen samples, although serum inhibin levels did normalize.

He subsequently chose to take low-dose daily oral CC as an alternative option to direct androgen replacement or gonadotropin therapy. Clinical and biochemical improvements were maintained in a dose-dependent manner for a 20-week period (Table 2) and, unlike his experience with short-term, high-dose CC, hot flashes remained within tolerable limits.

FIGURE 1

The male hypothalamic-pituitary-testicular axis. *Black arrows* indicate stimuli to secretion and *red arrows* represent feedback inhibition of secretion.



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DISCUSSION

Baseline investigations confirmed IHH, with the history and clinical features indicating adult-onset disease. Idiopathic adult-onset IHH is essentially a diagnosis of exclusion; most individuals diagnosed with gonadotropin deficiency in adult life are either late presenting classic IHH or are likely to harbor a defined secondary cause (4–6). Although obesity and chronic opioid use represented possible secondary causes in this case, the striking degree of gonadotropin suppression was more typical of critical illness and thus appeared discordant with our clinical appreciation of his overall health and well-being.

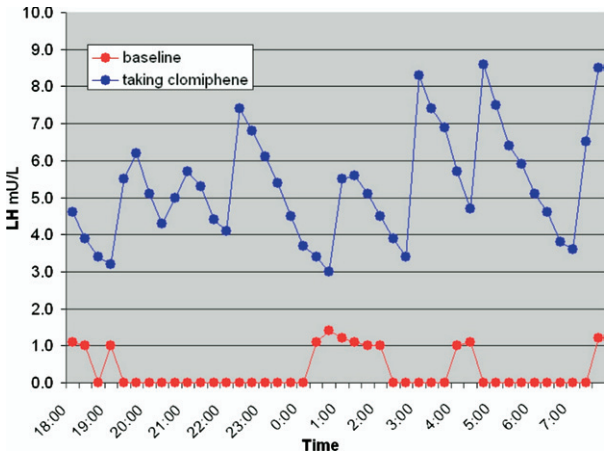
Obesity-associated gonadotropin deficiency tends not to be biochemically severe, and moderate doses of oral opioids do not significantly affect hypothalamic-pituitary-testicular function (7, 8). Almost all the data for opioid-induced gonadotropin deficiency derive from individuals with cancer pain or opioid addiction (both situations where the underlying chronic disease burden is high), or who were receiving opioids intrathecally (9–12). We therefore leave open the issue of whether this individual harbored a compelling secondary cause of IHH. However, his complete clinical and biochemical response to CC did contrast with individuals with classic idiopathic IHH, who are known to be entirely unresponsive to CC, and for whom spermatogenesis induction is necessarily only achievable with gonadotropin therapy or pulsatile GnRH (13).

Testosterone is metabolized through two principal pathways in both peripheral tissues and the central nervous system: by 5α-reductase to dihydrotestosterone (DHT), a more potent androgen receptor (AR) ligand, and by aromatase to E_2. Testosterone itself has a critical role in embryonic sex determination, with DHT then acting on Wolffian duct-derived structures to promote external virilization of the fetus. However, many of the apparent biological effects of T ex utero are mediated by E_2, evidenced by the phenotypes exhibited by men harboring defects of the aromatase and estrogen receptor (ER) genes (14).

Clinical studies of normal male subjects using infusions of T, E_2, and DHT originally revealed that about two-thirds of androgen-mediated inhibition of gonadotropin secretion in humans was attributable to aromatization to E_2, with a direct effect of T or DHT contributing the remaining one-third. Significantly, cotreatment with CC blocked the suppressive action of T, E_2, and DHT on baseline and stimulated gonadotropin secretion (15). More recently studies using aromatase inhibition in normal men have established that the direct central negative feedback effect of androgens is limited to inhibition of pituitary LH secretion. Aromatization to

FIGURE 2

LH pulsatility at baseline (*red line*) and after 1 week of treatment with 50 mg of clomiphene citrate twice a day (*blue lettering*).



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E_2 acts at the pituitary level, to directly inhibit both LH and FSH secretion, and is the sole mediator of sex steroid-mediated feedback inhibition of hypothalamic GnRH secretion (16, 17). Inhibin contributes additionally to direct inhibition of pituitary FSH secretion (Fig. 2).

Aromatase inhibitors have been found to reverse gonadotropin deficiency in men with morbid obesity and premature ejaculation (18, 19). The gonadotropin deficiency of male obesity partly resides in enhanced adipose tissue-mediated aromatization of T to E_2. However, a reduction in serum E_2 levels through aromatase inhibition could have an undesired adverse effect on bone density. Hence, the theoretical advantage of using a SERM such as CC, which has a known beneficial effect on bone density in hypogonadism (20).

Clomiphene was traditionally used to treat nonobstructive oligospermia, although the evidence for efficacy was never strong and with the increasing availability of assisted fertilization techniques, its use for this indication has been tailing off. However, a recent multicenter study has shown more encouraging results (21). In addition, there is already a small literature on CC in male adult-onset IHH. Burge et al. (22) reported complete reversal of severe IHH for 5 months in an osteoporotic male endurance runner with 50–100 mg/d of CC.

More recently, Guay et al. (23) studied the therapeutic response to 50 mg of CC three times a week for 4 months in an impressive number of men (100+) with borderline IHH and a variety of chronic diseases. However, they focused on recovery of sexual function as the primary outcome and, although a biochemical response was seen in all patients, the study group was relatively heterogeneous—baseline free T levels were borderline rather than frankly low, and LH pulsatility was not examined. The case reported here therefore adds significantly to the body of evidence for enhanced E_2 feedback sensitivity in adult-onset IHH and supports the therapeutic use of CC citrate in selected individuals.

In conclusion, adult-onset hypogonadotropic hypogonadism is rarely idiopathic and should be fully investigated to identify secondary causes and to exclude wider anterior pituitary dysfunction. Serum T normal ranges are derived from data on healthy, rested young men sampled at 9 AM. An apparently subnormal T level may be physiologic in relation to an afternoon venipuncture or to concurrently low levels of SHBG.

The male reproductive axis in both health and disease is sensitive to alterations in T to E_2 metabolism and to modulation of ER binding by SERMs. There are presently no adequate prospective studies addressing the long-term role of androgen replacement in men with functional IHH secondary to systemic disease. However, in selected individuals with adult-onset IHH, long-term therapy with CC may represent a viable alternative to conventional androgen replacement or to gonadotropin therapy.

Significant advantages of CC in responsive individuals include convenience (a single daily tablet) and overall restoration of the hypothalamic-pituitary-testicular axis. Although seminal fluid analysis was not performed in the individual presented here, normalization of serum inhibin levels from an undetectable baseline did suggest recovery of Sertoli cell function accompanying the reversal of IHH. The therapeutic potential of CC has not escaped the pharmaceutical industry and clinical trials of enclomiphene (*trans*-isomer) have already been undertaken in primates and humans with encouraging results (24).

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