Received: 14 June 2022 | Revised: 11 October 2022 | Accepted: 25 October 2022

DOI: 10.1111/and.14628

ORIGINAL ARTICLE

First International Journal of Andrology ANDROLOGIA WILEY

Recovery of hypothalamic–pituitary–gonadal function with low dose testosterone treatment in a male with congenital hypogonadotropic hypogonadism

Fernando Braca[1] | Juan C. Betancort[1] | Nuria Pérez-Martín[1] | Alvaro Cabrera Argany[2] | Mauro Boronat[1,3]

[1]Section of Endocrinology and Nutrition, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain

[2]Biochemistry Laboratory, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain

[3]University Institute for Biomedical and Health Research, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Correspondence
Fernando Braca, Section of Endocrinology and Nutrition, Hospital Universitario Insular de Gran Canaria, Avda. Marítima del Sur, S/N, 35016 Las Palmas de Gran Canaria, Las Palmas, Spain.
Email: fernando.braca@hotmail.com

Abstract

Congenital hypogonadotropic hypogonadism (CHH) is a rare disease caused by deficiency or action of gonadotropin-releasing hormone. While generally considered a long-life condition, CHH can be reversible in about 5%–20% of cases, but mechanisms of reversibility are unknown. We report the case of a male with CHH who began treatment with low dose (20 mg/day) transdermal testosterone to induce pubertal development at age 17. Following the start of treatment, he experienced testicular growth and his serum testosterone concentrations increased beyond the expectations in relation to the dose. Treatment was withdrawn, but this led to the reappearance of symptoms of hypogonadism and a drop in testosterone levels. Testosterone was again prescribed at the same dose and, for the subsequent years, he completed full puberty, including attainment of 20 cc testicular volume, mature secondary sexual characteristics, normal levels of testosterone and only partially arrested germinal function, as demonstrated by inhibin B levels and spermogram. Testosterone treatment was withdrawn three more times, but hypogonadism resumed on each occasion. This case suggests that low-dose testosterone treatment can induce reversal of CHH through the activation, albeit non-permanent, of the hypothalamic–pituitary–gonadal axis, indicating that testosterone administration might be a reliable therapeutic option for reverting GnRH deficiency.

KEYWORDS
congenital hypogonadotropic hypogonadism, constitutional delay of growth and puberty, reversal, testosterone

1 | INTRODUCTION

Puberty is the period of transition between childhood and adulthood during which primary and secondary sexual characteristics develop, leading to important psychological changes, complete reproductive capability, and sexual activity. This process begins with the activation of gonadotropin-releasing hormone (GnRH) secreting neurons in the hypothalamus, stimulating the pulsatile release of LH and FSH in the peripheral circulation, the secretion of sex steroids and the appearance of secondary sexual characteristics (Styne & Grumbach, 2011).

Congenital hypogonadotropic hypogonadism (CHH) is a syndrome defined by the inability to synthesize, secrete or respond to GnRH, which leads to absent or incomplete pubertal development, insufficient gonadotropins secretion, deficiency of sex steroids and infertility. CHH is a rare disorder which has an estimated incidence of around 1 in 4000 males, and affects 2–5 times more commonly men than women. It can be accompanied by other non-reproductive

manifestations. Defective sense of smell (Kallmann syndrome) is by far the most common, affecting approximately 50% of cases (Boehm et al., 2015; Young et al., 2019).

During recent years, complex oligogenic-environmental interactions have been identified to take part in the clinical course and to modify the phenotype of CHH (Boehm et al., 2015; Mitchell et al., 2011; Young et al., 2019). To date, more than two dozen different genes have been known to underlie CHH (Young et al., 2019) and their mutations are characterized by incomplete penetrance and variable expressivity.

CHH has been traditionally considered a permanent condition, and patients typically undergo lifelong treatment. However, since the first case described in 1975 (Rezvani et al., 1975), in the last three decades there have been numerous reports of individuals with CHH who spontaneously recovered reproductive endocrine function (Bauman, 1986; Finkelstein et al., 1989; Gianetti et al., 2010; Mao et al., 2015; Pitteloud et al., 2005; Quinton et al., 1999; Raivio et al., 2007; Ribeiro et al., 2007; Sidhoum et al., 2014). At present, no factors have been identified that permit identifying individuals with potentially reversible forms of CHH. It has been shown that replacement therapy with GnRH pulses (Delemarre-Van de Waal, 1993; Hoffman & Crowley Jr, 1982) or gonadotropins (Barrio et al., 1999) can normalize testicular function and achieve fertility, but there are no defined strategies to induce CHH reversal and restore endogenous GnRH secretion. In this regard, some previous cases have observed reversal of CHH in males who had received sex steroid treatment (Kulshreshtha et al., 2013; Rowe et al., 1983; Santhakumar et al., 2014), but a causal relationship between the two has not been established. The present report presents a case of CHH in which treatment with low-dose transdermal testosterone produced a non-permanent reactivation of the hypothalamic–pituitary–gonadal axis, which invariably relapsed with treatment withdrawal. Thus, this clinical experience strengthens the possibility that testosterone treatment, albeit at low doses, is a reliable therapy for reversing GnRH deficiency.

2 | CASE PRESENTATION

The patient was a 17-year-1-month-old boy who came for the first time to our Endocrinology Department in July 2007 because of delayed puberty.

There was no family history of delayed puberty, anosmia, infertility or other endocrine disorders. The boy had had a normal development during his childhood, although he had been diagnosed of Asperger's syndrome at age 13–14. He had no history of cryptorchidism or micropenis.

Physical examination showed incomplete secondary sexual characteristics, in a Tanner stage II (testicular volume 6 cc), and gynecomastia grade 2–3; weight was 100.2 kg, height 183 cm (BMI 29.9 kg/cm^2) and arm span 183 cm.

In the laboratory work-up, blood count was normal but biochemistry showed low serum levels of FSH and LH and total testosterone was in the peripubertal range, with normal prolactin, TSH, free T_4, DHEAs, SHBG and inhibin-B. Although not established cut-off points have been defined to distinguish between CHH and constitutional delay of growth and puberty, there was a poor response of LH to the stimulation with GnRH (Kauschansky et al., 2002). Complete results of hormonal assessment at first visit are shown in Table 1. Bone age was delayed 2–3 years (assessed with Greulich-Pyle atlas). Brain magnetic resonance imaging showed a normal-appearing pituitary gland, no space-occupying lesions in the hypothalamic–pituitary area, and normally developed olfactory grooves and bulbs. The patient was followed up and, in the absence of pubertal progression and the existence of indirect data contrary to constitutional delay of growth and puberty (tall stature, adrenarche, lack of family history), a diagnosis of CHH was established in March 2008 (17 years and 9 months). He was then prescribed a starting low dose testosterone 2% gel of 20 mg/day, lower than literature's recommended replacement adult dose (40–70 mg/day) (Bhasin et al., 2018), with the intention of promoting a progressive development of secondary sexual characteristics. This option has been suggested by other authors for initiating testosterone replacement therapy in adolescent patients (Rey & Grinspon, 2020).

TABLE 1 Sexual hormone levels at first visit

Hormone (units)	Result	Normal adult range (CV intra; imprecision/ CV inter[b])
Prolactin (μg/L)	6.7	2.6–13.1 (<10%/<10%)
TSH (mUI/L)	5.094	0.34–5.6 (<10%/<10%)
Free T_4 (ng/dl)	0.87	0.6–1.6 (<10%/<10%)
LH (luteinizing hormone) (U/L)	0.34	1.2–8.6 (<10%/<10%)
FSH (follicle-stimulating hormone) (U/L)	0.53	1.31–19.3 (<10%/ <10%)
Total testosterone (nmol/L)	1.28	4.37–19.5 (10%–20%/ <20%)
DHEAs (μmol/L)	5.91	1.15–25.9 (10%–20%/ <10%)
SHBG (sex hormone binding-globulin) (nmol/l)	20.40	12.00–75.00 (<7%/ <7%)
Inhibin B (ng/L)	140	80–300 (2.91%/2.15%)
GnRH test (100 μg i.v. bolus)		
LH (U/L) (0, 30, 60 and 120 min)	0.27, 2.75, 2.74, 2.02	(10%–20%/10%–20%)[a]
FSH (U/L) (0, 30, 60 and 120 min)	0.4, 0.94, 1.09, 1.09	(10%–20%/10%–20%)[a]
Alpha subunit (μg/L) (0, 30, 60 and 120 min)	<0.2, 0.2, 0.3, 0.2, <0.2	(10%–20%/10%–20%)[a]

[a]Normal and pathological results for GnRH stimulation test have not been established.
[b]The first percentage is the intra-assay coefficient of variation and the second one is the imprecision, except for the Inhibin B which is the inter-assay coefficient of variation.

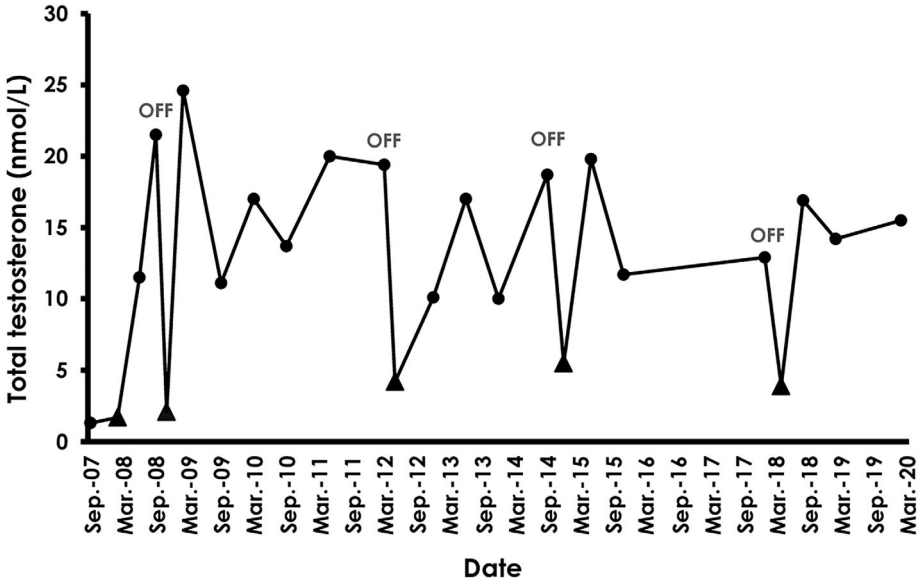

FIGURE 1 Serum levels of total testosterone through the follow-up period. The triangles indicate the dates when treatment with transdermal testosterone was prescribed, and the legends 'OFF' those when treatment was withdrawn.

3 | INVESTIGATIONS AND METHODS

Testicular volume was assessed with Prader orchidometer, bone age with Greulich and Pyle atlas. No objective quantitative methods were available, and smell function was evaluated exclusively through clinical history.

Laboratory evaluation was performed in the Biochemistry Laboratory of the Complejo Hospitalario Universitario Insular Materno-Infantil. Hormones were measured with chemiluminescence by using the Unicel DXI-800 analyzer (Beckman Coulter, CA, USA).

A stimulation test was performed with GnRH and LH, FSH and α-subunit were measured at 0, 30, 60 and 120 min after its administration; hormones were also assayed with chemiluminescence in the Unicel DXI-800 analyzer (Beckman Coulter, CA, USA).

4 | TREATMENT AND FOLLOW-UP

At his first review after starting testosterone treatment, in September 2008 (18 years and 2 months), the patient reported enhanced sexual behaviour and libido, and physical examination showed increased testicular volume (testicle volume 8–10 cc, Tanner stage III) and progression of secondary sexual characteristics, including Tanner stage IV of pubic hair, while serum concentrations of total testosterone were 21.5 nmol/L, a value that was estimated to be higher than expected for the doses of testosterone he was receiving. In view of these findings, it was considered the possibility that testosterone treatment had boosted pubertal development and the patient actually had a constitutional delay of growth and puberty. Therefore, testosterone treatment was interrupted. However, 2 months later, he complained of a marked decrease of libido and sexual function and total testosterone levels fell down to 2.1 nmol/L. So, the same dose of testosterone gel treatment was reintroduced and the patient was kept on follow-up.

During the following 3 years, he completed his pubertal development, achieving a Tanner Stage IV at 20 years and 2 months and Tanner stage V (testicular volume 20 cc) at 20 years and 11 months. His final height was 191 cm. Through this time, testosterone levels remained at normal adult male values (Figure 1).

In March 2012 (21 years and 8 months) a second trial was performed to stop testosterone treatment. Total testosterone levels dropped again to 4.2 nmol/L 3 months after the withdrawal and the patient complained of fatigue, concentrating trouble and decreased libido, so that the treatment was resumed again. For the subsequent years, he continued on the same dose of transdermal testosterone (20 mg/day). A slight trend of increased LH levels was observed throughout this period in successive laboratory tests (Figure 2), although gonadotropin levels remained low through the entire follow-up. Testosterone was stopped twice more (in September 2014 and in January 2018, at 24 and 28 years, respectively) (Figure 1), but marked decline of testosterone concentrations was observed again on both occasions. So, treatment was continued until his last appointment, achieving normal levels of testosterone, normal libido and overall well-being. Behavioural changes attributable to testosterone treatment were not observed. On the last visit in March 2020 (29 years), total testosterone level was normal (15.5 nmol/L), LH was 1.18 U/L and FSH 0.54 U/L. After that, the patient lost follow-up.

Spermogram was obtained in February 2014, at 23 years and 7 months, and showed oligozoospermia (sperm concentration 4.0 million/ml and total sperm number 24 million per ejaculate) with total motility in range (50%). Inhibin B levels ranged between 63 and 386 ng/L, with a growing trend after the start of treatment.

The patient was screened for genetic mutations in several genes related to normosmic CHH, namely *GNRHR*, *GNRH1*, *KISS1R*, *TACR3* and *TAC3*, but no pathogenic mutations were found.

5 | DISCUSSION

Reversal of CHH is an interesting phenomenon that has been well documented in the past. In a small prospective study (Raivio et al.,

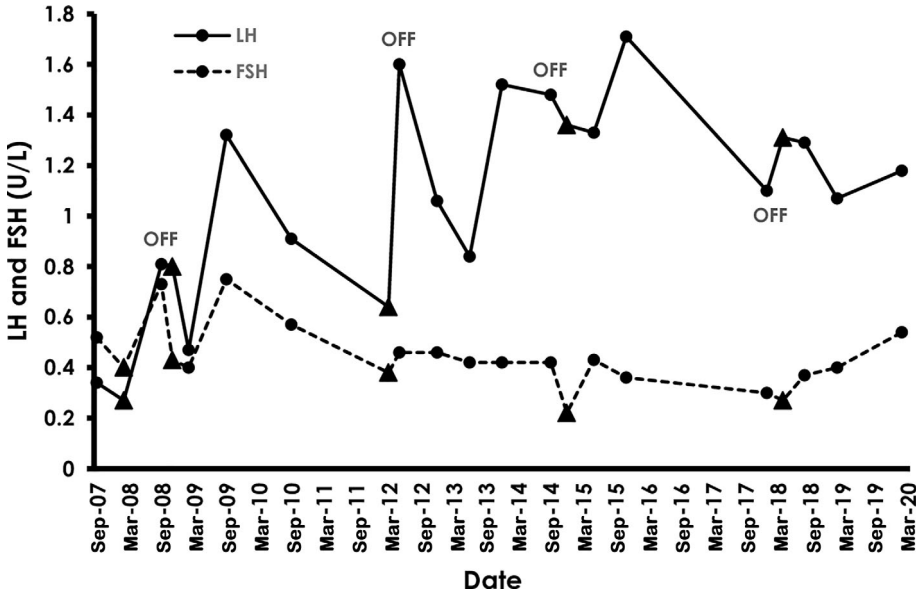

FIGURE 2 Serum levels of gonadotropins through the follow-up period

2007), 5 cases of reversal were identified among 50 men with CHH who were followed for 39 months. In retrospective analyses of large series of patients, the incidence of reversal has ranged from 5% to 22% (Mao et al., 2015; Sidhoum et al., 2014). The criteria for reversal have varied among different studies, but, in all cases, patients have uniformly demonstrated a dramatic improvement in their reproductive endocrine function, including normalization of circulating sex steroids, spontaneous increases in testicular volume, and paternity/maternity without the use of medications. On the other hand, reversal can be followed by relapse, for example under unfavourable environmental conditions (Dwyer et al., 2016; Sidhoum et al., 2014). Relapse has been defined as a decrease to hypogonadal sex-steroid levels (serum testosterone level <3.46 nmol/L in men or serum estradiol <73.4 pmol/L in women) (Sidhoum et al., 2014). Mechanisms of reversal are not clear yet. No phenotypic or genetic characteristics have been found to definitely distinguish patients with reversible CHH from those with permanent forms. One study found that reversible cases show higher basal and stimulated LH levels and larger baseline testicle size (Mao et al., 2015), but reversal can occur even in patients with severe GnRH deficiency (for example in males with micropenis or cryptorchidism), as well as in patients with Kallmann syndrome (Mao et al., 2015; Quinton et al., 1999; Raivio et al., 2007; Sidhoum et al., 2014). Some authors have suggested on several occasions that normalization of circulating levels of sex steroids, either by replacement with testosterone, gonadotropins or GnRH pulses, is the only common denominator of patients with CHH who experience a reversal of the disease (Dwyer et al., 2016; Raivio et al., 2007; Young et al., 2019), proposing that sex steroids could promote the activation of genes implicated in the functioning of GnRH neurons.

In this regard, several reports have called attention to CHH reversal in patients receiving sex steroids treatment (Kulshreshtha et al., 2013; Rowe et al., 1983; Santhakumar et al., 2014). However, in all cases reversal was detected after a prolonged period of hormonal replacement therapy, often as an incidental finding, and withdrawal of treatment did not lead to a relapse of hypogonadism, so it is difficult to establish a causal relationship between testosterone treatment and recovery of the hypothalamic–pituitary–gonadal axis. In the present case, spontaneous pubertal development was detected at the first evaluation after the initiation of hormone replacement therapy and a relapse of gonadal hypofunction was noted after each attempt to discontinue testosterone treatment. Thus, chronic low-dose testosterone therapy was intentionally maintained to promote the progression of endogenous puberty.

The findings in this case reinforce the suggestion that CHH reversal might be related to the neuronal GnRH network plasticity, following androgen treatment (Raivio et al., 2007). Although it is well known that sex steroids exert feedback effects regulating the GnRH pulse pattern, GnRH neurons do not express androgen receptors (Huang & Harlan, 1993). Genes involving kisspeptin function, a potent stimulator of GnRH secretion (de Roux et al., 2003), could be more plausible candidates as sex steroid targets. In fact, some reports have found that patients with reversible CHH characteristically show responsiveness to the administration of exogenous kisspeptin (Lippincott et al., 2016). The vast majority of kisspeptin neurons, often called KNDy neurons, as they produce kisspeptin, neurokinin B, and dynorphin, also express sex steroid receptors, and it has been demonstrated that their activity is modulated by steroid feed-back in male murine models (Ruka et al., 2016; Vanacker et al., 2017). Although androgen and oestrogen exposure mainly downregulate kisspeptin gene expression, the association between kisspeptin and sex steroids is more than a simple, unidirectional relationship. Estradiol is capable of augmenting kisspeptin signalling in the anteroventral periventricular nucleus of female mice, probably eliciting the positive feedback responsible for the increase of LH production preceding ovulation (Smith et al., 2005). In addition, progesterone and androgens can also play complementary modulating roles in the generation of LH surges (Gal et al., 2016;

Walters et al., 2018). This bidirectional relationship between sex steroids and kisspeptin could also exist in males (Kim et al., 2011).

Theoretically, variations in the amount of GnRH neurons effectively reaching the hypothalamus and establishing adequate connections could explain the broad spectrum of clinical manifestations of GnRH deficiency. This clinical spectrum has been suggested to be correlated to the range of responsiveness to kisspeptin, and encompasses from delayed puberty to severe permanent CHH (Pitteloud et al., 2005). Perhaps this report shows one new clinical variant which would lie between completely reversible forms of CHH, and permanent CHH. It might be hypothesized that, in the present case, only a relatively small number of GnRH neurons are properly positioned in the hypothalamus and functionally viable, making necessary a prolonged stimulation with exogenous androgens to restore and maintain hypothalamic function.

6 | CONCLUSIONS

In conclusion, this case brings a new perspective on the treatment of males with CHH and suggests that, before starting a substitute dose of testosterone, a short trial with low doses of testosterone could be tried with the goal of restoring the functionality of the hypothalamic–pituitary–gonadal axis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

Barrio, R., de Luis, D., Alonso, M., Lamas, A., & Moreno, J. C. (1999). Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. *Fertility and Sterility*, *71*(2), 244–248. https://doi.org/10.1016/s0015-0282(98)00450-6

Bauman, A. (1986). Markedly delayed puberty or Kallmann's syndrome variant. *Journal of Andrology*, *7*(4), 224–227. https://doi.org/10.1002/j.1939-4640.1986.tb00918.x

Bhasin, S., Brito, J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., & Yialamas, M. A. (2018). Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*, *103*(5), 1715–1744. https://doi.org/10.1210/jc.2018-00229

Boehm, U., Bouloux, P. M., Dattani, M. T., de Roux, N., Dodé, C., Dunkel, L., Dwyer, A. A., Giacobini, P., Hardelin, J. P., Juul, A., Maghnie, M., Pitteloud, N., Prevot, V., Raivio, T., Tena-Sempere, M., Quinton, R., & Young, J. (2015). Expert consensus document: European consensus statement on congenital hypogonadotropic hypogonadism—Pathogenesis, diagnosis and treatment. *Nature Reviews. Endocrinology*, *11*(9), 547–564. https://doi.org/10.1038/nrendo.2015.112

de Roux, N., Genin, E., Carel, J. C., Matsuda, F., Chaussain, J. L., & Milgrom, E. (2003). Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(19), 10972–10976. https://doi.org/10.1073/pnas.1834399100

Delemarre-Van de Waal, H. A. (1993). Induction of testicular growth and spermatogenesis by pulsatile, intravenous administration of gonadotrophin-releasing hormone in patients with hypogonadotrophic hypogonadism. *Clinical Endocrinology*, *38*(5), 473–480. https://doi.org/10.1111/j.1365-2265.1993.tb00342.x

Dwyer, A. A., Raivio, T., & Pitteloud, N. (2016). Management of endocrine disease: Reversible hypogonadotropic hypogonadism. *European Journal of Endocrinology*, *174*(6), R267–R274. https://doi.org/10.1530/EJE-15-1033

Finkelstein, J. S., Spratt, D. I., O'Dea, L. S., Whitcomb, R. W., Klibanski, A., Schoenfeld, D. A., & Crowley, W. F., Jr. (1989). Pulsatile gonadotropin secretion after discontinuation of long term gonadotropin-releasing hormone (GnRH) administration in a subset of GnRH-deficient men. *The Journal of Clinical Endocrinology and Metabolism*, *69*(2), 377–385. https://doi.org/10.1210/jcem-69-2-377

Gal, A., Lin, P. C., Cacioppo, J. A., Hannon, P. R., Mahoney, M. M., Wolfe, A., Fernandez-Valdivia, R., Lydon, J. P., Elias, C. F., & Ko, C. (2016). Loss of fertility in the absence of progesterone receptor expression in kisspeptin neurons of female mice. *PLoS One*, *11*(7), e0159534. https://doi.org/10.1371/journal.pone.0159534

Gianetti, E., Tusset, C., Noel, S. D., Au, M. G., Dwyer, A. A., Hughes, V. A., Abreu, A. P., Carroll, J., Trarbach, E., Silveira, L. F., Costa, E. M., de Mendonça, B. B., de Castro, M., Lofrano, A., Hall, J. E., Bolu, E., Ozata, M., Quinton, R., Amory, J. K., … Seminara, S. B. (2010). TAC3/-TACR3 mutations reveal preferential activation of gonadotropin-releasing hormone release by neurokinin B in neonatal life followed by reversal in adulthood. *The Journal of Clinical Endocrinology and Metabolism*, *95*(6), 2857–2867. https://doi.org/10.1210/jc.2009-2320

Hoffman, A. R., & Crowley, W. F., Jr. (1982). Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. *The New England Journal of Medicine*, *307*(20), 1237–1241. https://doi.org/10.1056/NEJM198211113072003

Huang, X., & Harlan, R. E. (1993). Absence of androgen receptors in LHRH immunoreactive neurons. *Brain Research*, *624*(1–2), 309–311. https://doi.org/10.1016/0006-8993(93)90094-4

Kauschansky, A., Dickerman, Z., Phillip, M., Weintrob, N., & Strich, D. (2002). Use of GnRH agonist and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. *Clinical Endocrinology*, *56*(5), 603–607. https://doi.org/10.1046/j.1365-2265.2002.01520.x

Kim, J., Semaan, S. J., Clifton, D. K., Steiner, R. A., Dhamija, S., & Kauffman, A. S. (2011). Regulation of Kiss1 expression by sex steroids in the amygdala of the rat and mouse. *Endocrinology*, *152*(5), 2020–2030. https://doi.org/10.1210/en.2010-1498

Kulshreshtha, B., Khadgawat, R., Gupta, N., & Ammini, A. (2013). Progression of puberty after initiation of androgen therapy in patients with idiopathic hypogonadotropic hypogonadism. *Indian Journal of Endocrinology and Metabolism*, *17*(5), 851–854. https://doi.org/10.4103/2230-8210.117245

Lippincott, M. F., Chan, Y. M., Delaney, A., Rivera-Morales, D., Butler, J. P., & Seminara, S. B. (2016). Kisspeptin responsiveness signals emergence of reproductive endocrine activity: Implications for human puberty. *The Journal of Clinical Endocrinology and Metabolism*, *101*(8), 3061–3069. https://doi.org/10.1210/jc.2016-1545

Mao, J. F., Xu, H. L., Duan, J., Chen, R. R., Li, L., Li, B., Nie, M., Min, L., Zhang, H. B., & Wu, X. Y. (2015). Reversal of idiopathic hypogonadotropic hypogonadism: A cohort study in Chinese patients. *Asian Journal of Andrology*, *17*(3), 497–502. https://doi.org/10.4103/1008-682X.145072

Mitchell, A. L., Dwyer, A., Pitteloud, N., & Quinton, R. (2011). Genetic basis and variable phenotypic expression of Kallmann syndrome: Towards a unifying theory. *Trends in Endocrinology and Metabolism: TEM*, *22*(7), 249–258. https://doi.org/10.1016/j.tem.2011.03.002

Pitteloud, N., Acierno, J. S., Jr., Meysing, A. U., Dwyer, A. A., Hayes, F. J., & Crowley, W. F., Jr. (2005). Reversible Kallmann syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the fibroblast growth factor receptor 1 gene. *The Journal of Clinical Endocrinology and Metabolism*, *90*(3), 1317–1322. https://doi.org/10.1210/jc.2004-1361

Quinton, R., Cheow, H. K., Tymms, D. J., Bouloux, P. M., Wu, F. C., & Jacobs, H. S. (1999). Kallmann's syndrome: Is it always for life? *Clinical Endocrinology*, *50*(4), 481–485. https://doi.org/10.1046/j.1365-2265.1999.00708.x

Raivio, T., Falardeau, J., Dwyer, A., Quinton, R., Hayes, F. J., Hughes, V. A., Cole, L. W., Pearce, S. H., Lee, H., Boepple, P., Crowley, W. F., Jr., & Pitteloud, N. (2007). Reversal of idiopathic hypogonadotropic hypogonadism. *The New England Journal of Medicine*, *357*(9), 863–873. https://doi.org/10.1056/NEJMoa066494

Rey, R. A., & Grinspon, R. P. (2020). Androgen treatment in adolescent males with hypogonadism. *American Journal of Men's Health*, *14*(3), 1557988320922443. https://doi.org/10.1177/1557988320922443

Rezvani, I., DiGeorge, A. M., Rutano, J., & Snyder, P. J. (1975). Delayed puberty and anosmia; coincidence or Kallmann variant? [Abstract]. *Pediatric Research*, *9*, 224.

Ribeiro, R. S., Vieira, T. C., & Abucham, J. (2007). Reversible Kallmann syndrome: Report of the first case with a KAL1 mutation and literature review. *European Journal of Endocrinology*, *156*(3), 285–290. https://doi.org/10.1530/eje.1.02342

Rowe, R. C., Schroeder, M. L., & Faiman, C. (1983). Testosterone-induced fertility in a patient with previously untreated Kallmann's syndrome. *Fertility and Sterility*, *40*(3), 400–401. https://doi.org/10.1016/s0015-0282(16)47310-3

Ruka, K. A., Burger, L. L., & Moenter, S. M. (2016). Both estrogen and androgen modify the response to activation of neurokinin-3 and κ-opioid receptors in arcuate kisspeptin neurons from male mice. *Endocrinology*, *157*(2), 752–763. https://doi.org/10.1210/en.2015-1688

Santhakumar, A., Balasubramanian, R., Miller, M., & Quinton, R. (2014). Reversal of isolated hypogonadotropic hypogonadism: Long-term integrity of hypothalamo-pituitary-testicular axis in two men is dependent on intermittent androgen exposure. *Clinical Endocrinology*, *81*(3), 473–476. https://doi.org/10.1111/cen.12347

Sidhoum, V. F., Chan, Y. M., Lippincott, M. F., Balasubramanian, R., Quinton, R., Plummer, L., Dwyer, A., Pitteloud, N., Hayes, F. J., Hall, J. E., Martin, K. A., Boepple, P. A., & Seminara, S. B. (2014). Reversal and relapse of hypogonadotropic hypogonadism: Resilience and fragility of the reproductive neuroendocrine system. *The Journal of Clinical Endocrinology and Metabolism*, *99*(3), 861–870. https://doi.org/10.1210/jc.2013-2809

Smith, J. T., Cunningham, M. J., Rissman, E. F., Clifton, D. K., & Steiner, R. A. (2005). Regulation of Kiss1 gene expression in the brain of the female mouse. *Endocrinology*, *146*(9), 3686–3692. https://doi.org/10.1210/en.2005-0488

Styne, D. M., & Grumbach, M. M. (2011). *Puberty: Ontogeny, neuroendocrinology, physiology, and disorders: Williams textbook of endocrinology* (12th ed.). Elsevier Saunders.

Vanacker, C., Moya, M. R., DeFazio, R. A., Johnson, M. L., & Moenter, S. M. (2017). Long-term recordings of arcuate nucleus kisspeptin neurons reveal patterned activity that is modulated by gonadal steroids in male mice. *Endocrinology*, *158*(10), 3553–3564. https://doi.org/10.1210/en.2017-00382

Walters, K. A., Edwards, M. C., Tesic, D., Caldwell, A., Jimenez, M., Smith, J. T., & Handelsman, D. J. (2018). The role of central androgen receptor actions in regulating the hypothalamic-pituitary-ovarian axis. *Neuroendocrinology*, *106*(4), 389–400. https://doi.org/10.1159/000487762

Young, J., Xu, C., Papadakis, G. E., Acierno, J. S., Maione, L., Hietamäki, J., Raivio, T., & Pitteloud, N. (2019). Clinical management of congenital hypogonadotropic hypogonadism. *Endocrine Reviews*, *40*(2), 669–710. https://doi.org/10.1210/er.2018-00116

How to cite this article: Braca, F., Betancort, J. C., Pérez-Martín, N., Cabrera Argany, A., & Boronat, M. (2022). Recovery of hypothalamic–pituitary–gonadal function with low dose testosterone treatment in a male with congenital hypogonadotropic hypogonadism. *Andrologia*, *54*(11), e14628. https://doi.org/10.1111/and.14628