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CASE REPORT

Idiopathic hypogonadotropic hypogonadism reversal after testosterone replacement in a 34-year-old male

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SUMMARY

A 34-year-old male presented to the endocrinology clinic with the complaint of the absence of facial, axillary and pubic hairs. Further history revealed absent ejaculations and decreased early morning erections. The patient had no history of headaches, visual problems or anosmia. On physical examination, there were sparse facial, axillary and pubic hairs, bilateral gynaecomastia, stretch penile length of 5 cm and bilateral testicular volume of 10 mL. Laboratory investigations showed low luteinising hormone, follicular stimulating hormone and testosterone with normal prolactin and thyroid profile. MRI of the pituitary gland showed no evidence of pituitary microadenoma or macroadenoma. The patient was started on testosterone injections. After 9 months of testosterone replacement, the patient's testicular size increased to 20 mL bilaterally and his penile length increased to the mean adult size for his age with normal testosterone and luteinising hormone. He was, thus, advised to discontinue testosterone therapy.

BACKGROUND

Hypogonadotropic hypogonadism (HH) is a relatively uncommon disorder with prevalence ranging from 1 in 10 000 to 1 in 86 000 individuals and a male to female ratio of 1:5.^{1,2} Idiopathic HH is diagnosed in the presence of low testosterone and follicular stimulating hormone/luteinising hormone without any structural or functional abnormalities in the hypothalamic–pituitary–gonadal (HPG) axis. It is primarily due to a flaw in the secretion or action of gonadotropin-releasing hormone (GnRH) and is diagnosed when there is a failure of sexual maturation by 18 years of age.²

Typically, puberty is caused by the maturation of the HPG axis during which the pulsatile release of GnRH by the hypothalamus causes secretion of luteinising hormone and follicular stimulating hormone by the pituitary gland. In males, this causes the production of testosterone and the maturation of sperm.³ This results in the development of secondary sexual characteristics and attainment of fertility. Generally, puberty in boys starts around 11 years of age and is complete by the age of 16–17 years. Delayed puberty for boys is defined as the absence of testicular enlargement by an age 2–2.5 SD above the mean for a given population (usually 14 years of age).^{4,5}

Both congenital and acquired forms of HH are present with the latter caused by chemotherapy, radiation, damage to the pituitary gland/hypothalamus,

malnutrition and hyperprolactinaemia among other reasons. Treatment of this condition is paramount because it leads to a significantly decreased quality of life and problems such as reduced muscle mass, energy, libido, facial and pubic hair, small genitalia, failure of voice to deepen, infertility, etc. Furthermore, patients might also develop low self-esteem, depression and osteoporosis later in life because of low testosterone levels in the body.⁶

CASE PRESENTATION

A 34-year-old male with no known co-morbidities presented to the endocrine clinic with the complaints of scarce facial, axillary and pubic hairs. The prompting factor for the patient to seek medical advice was that he wanted to get married soon. Further history revealed absent ejaculations and decreased early morning erections. There was no current or prior history of headache, visual problems, decreased sense of smell, trauma or radiation exposure. The patient was not using any medication or hormone therapy and had a sedentary lifestyle. Past medical, surgical and family history was unremarkable.

On examination, the patient had a blood pressure of 116/70 mm Hg, pulse of 92 beats per minute, height of 172.5 cm and a weight of 68 kg. There were no facial hairs, sparse axillary and pubic hairs, bilateral gynaecomastia, stretch penile length of 5 cm and bilateral testicular volume of 10 mL. The rest of the physical examination was unremarkable. A diagnosis of hypogonadism was made and he was advised to have serum luteinising hormone, follicular stimulating hormone, testosterone (AM), prolactin, thyroid-stimulating hormone and free thyroxine tested.

INVESTIGATIONS

The laboratory reports of the patient showed luteinising hormone 2.60 mIU/mL (normal limit in males: 1.2–7.8), follicular stimulating hormone 1.50 mIU/mL (normal limit in males: 1.5–15.4), *ante meridiem* (AM) testosterone 55.99 ng/dL (normal limit in males: 249–836), prolactin 5.2 ng/mL (normal limit in males 2–18 ng/mL), thyroid stimulating hormone 1.03 uIU/mL (normal limit: 0.4–4.2) and free thyroxine 1.13 ng/dL (normal limit: 0.89–1.76).

After biochemical confirmation of HH, he was advised MRI of the pituitary gland which showed a normal pituitary fossa with no evidence of pituitary microadenoma or macroadenoma (figure 1).



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Figure 1 MRI of the pituitary gland showing no pituitary pathology. HPR, half-plane representation; LP, left posterior; MRI axis: RA, right anterior.

The patient was subsequently started on testosterone injections. Table 1 shows the initial laboratory investigations of our patient.

DIFFERENTIAL DIAGNOSIS

Hypogonadotropic hypogonadism.

TREATMENT

The patient was started on testosterone injection 250 mg once every 4 weeks which was later decreased to 250 mg once every 6 weeks. At that time, the plan was to start the patient on pulsatile GnRH therapy once he got married in order to restore fertility.

OUTCOME AND FOLLOW-UP

At 3 months on follow-up, the morning testosterone peak level of the patient reached 643.3 ng/dL with trough level of 163.3 ng/dL. After 9 months of testosterone replacement, the patient’s testicular size increased to 20 mL bilaterally and his penis length increased to the mean adult size for his age. He became well virilised. Considering the sexual maturation on clinical examination, patient was advised to hold testosterone replacement and his testosterone and luteinising hormone levels were rechecked after 2 months to see whether the hypothalamic–gonadal axis had recovered. His testosterone levels off replacement were 433.8 ng/dL with a luteinising hormone level of 3.30 mIU/mL (1.2–7.8). The patient was, therefore, advised to stop testosterone. Table 2 shows the follow-up laboratory investigations of our patient.

Table 1 Initial laboratory investigations of the patient

Investigation	Value	Normal limit
Luteinising hormone (mIU/mL)	2.60	1.2–7.8
Follicular stimulating hormone (mIU/mL)	1.50	1.5–15.4
Testosterone (AM) (ng/dL)	55.99	249–836
Prolactin (ng/dL)	5.2	2–18
Thyroid-stimulating hormone (uIU/mL)	1.03	0.4–4.2
Free thyroxine (ng/dL)	1.13	0.89–1.76

Table 2 Follow-up laboratory investigations of the patient

Investigation	Value	Normal limit
Luteinising hormone (mIU/mL)	3.30	1.2–7.8
Testosterone (AM) (ng/dL) (on replacement)	643.3	249–836
Testosterone (AM) (ng/dL) (off replacement)	433.8	249–836

AM, ante meridiem.

DISCUSSION

Multiple factors may have been involved in causing the patient’s hypogonadism; however, a detailed history and examination failed to suggest alternative reasons for it. Our patient presented at the age of 34 years which is quite unusual; however, Sumko *et al*⁷ described a similar case of a 27-year-old man who was found to have microphallus, undescended testes and scarce pubic hair, whereas Zhang *et al*⁸ reported a 34-year-old male with osteoporosis, diabetes mellitus and metabolic syndrome. Both of these patients were discovered to have idiopathic HH while being evaluated for another disease. This hesitancy to seek medical care regarding delayed puberty may be because of the social stigma associated with sexual disorders; therefore, a lot of the cases might go unreported and present at a relatively advanced age. Our patient was 34 years old at presentation; therefore, the possibility of constitutionally delayed puberty was remote. However, at younger ages, it may be difficult to distinguish between constitutionally delayed puberty and HH. Two clinical features that might help to differentiate between the two are undescended testes and micropenis, which are more frequently found in HH.⁷

Failure of pulsatile GnRH secretion may be due to mutations in a number of genes such as PROK-2, FGFR1, etc. Furthermore, a protein, prokineticin-1, is involved in olfactory bulb development and release of GnRH. Mutations in this protein can also cause idiopathic HH which may be normosmic or anosmic (Kallmans syndrome).⁷ Although many genes have been linked with idiopathic hypogonadotropic hypogonadism (IHH), the majority of cases are due to genetic mutations which are yet unidentified.

Treatment of this disorder mainly depends on the desire for fertility. Androgen replacement alone can be used to reverse the problems associated with hypogonadism and is considerably less expensive than the other options available. Furthermore, our patient did not desire fertility at the time of presentation and considering the cost this was the best choice for him. However, pulsatile GnRH therapy and gonadotropins are better suited for patients who wish to become fertile because in addition to treating the low testosterone state they also stimulate spermatogenesis.⁶

Previously, treatment was thought to be lifelong; however, Raivio *et al*² described 15 patients who had sustained reversal of HH on discontinuation of therapy. Reversals occurred in five men treated with testosterone alone, three men treated with pulsatile GnRH therapy only and seven men who received a mixed regimen, including testosterone, gonadotropins or GnRH. Although the mechanism of reversal is unclear, the researchers speculated that because sex steroids were the only common medication given to all the patients with reversal, they somehow modify the hypothalamic neurons responsible for producing GnRH. This might lead to reversal of HH and initiation of spermatogenesis. After the administration of testosterone, our patient’s HPG axis recovered with

subsequent sexual maturation on clinical examination; therefore, he was advised to stop testosterone injections.

Learning points

- ▶ Hypogonadism has significant psychosocial and health-related effects which are easily treatable if this condition is caught early.
- ▶ Treatment depends on the desire for fertility and can be via testosterone replacement, pulsatile gonadotropin-releasing hormone therapy or gonadotropins.
- ▶ In a patient with hypogonadotropic hypogonadism being treated with testosterone, treatment should be temporarily discontinued after sexual maturation has occurred because a minority of cases may have achieved reversal.

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REFERENCES

- 1 Silveira LF, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2013;98:1781–8.
- 2 Raivio T, Falardeau J, Dwyer A, et al. Reversal of idiopathic hypogonadotropic hypogonadism. *N Engl J Med* 2007;357:863–73.
- 3 Medlineplus. Hypogonadotropic hypogonadism. 2016. <https://medlineplus.gov/ency/article/000390.htm>
- 4 Delayed puberty — NEJM. *New England Journal of Medicine* 2016. <http://www.nejm.org/doi/full/10.1056/nejmcp11092908>
- 5 Fraietta R, Zylberstein DS, Esteves SC, et al. Hypogonadotropic hypogonadism revisited. *Clinics* 2013;68(S1):81–8.
- 6 AACE Guidelines. American Association of clinical endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract* 2002;8:455.
- 7 Sumko D, Weis SE, Wong L. Congenital idiopathic hypogonadotropic hypogonadism: a case report. *Journal of Clinical Case Reports* 2014;4:371.
- 8 Zhang MN, Su B, Qian CH, et al. An idiopathic hypogonadotropic hypogonadism patient with metabolic disorder and diabetes: case report. *Asian J Androl* 2015;17:341.

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