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Case Report

Reversal of Idiopathic hypogonadotropic hypogonadism triggered by testosterone therapy

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A 21-year-old male presented to us with delayed development of secondary sexual characteristics. Based on examination and investigations, a diagnosis of idiopathic hypogonadotropic hypogonadism was made and the patient was started on testosterone therapy. After around a year of therapy the patient had an increase in bilateral testicular volume with increased serum luteinizing hormone (LH) values. The patient was advised to stop treatment. On follow-up there was persistence of increase in LH values with maintenance of normal serum testosterone values. Thus the case highlights the importance of regular follow-up in cases of idiopathic hypogonadotropic hypogonadism to watch for reversal.

Key words: Puberty, hypogonadism, reversal.

INTRODUCTION

Idiopathic hypogonadotropic hypogonadism (IHH) is a disorder characterized by secondary hypogonadism frequently associated with anosmia (Fraietta et al., 2013). It is caused by a congenital defect in the secretion or action of gonadotropin-releasing hormone (GnRH) (Seminara et al., 1998). It is often difficult to differentiate this condition from the more common condition constitutional delay in growth and puberty (CDGP). IHH was previously thought to be a permanent condition requiring lifelong therapy. Recent studies have reported a sustained reversal of IHH after discontinuation of treatment in few cases (Raivio et al., 2007; Kulshreshtha et al., 2013). We present a similar case of a male patient on testosterone therapy with reversal of IHH.

Case presentation

A 21-year-old male presented in March, 2014 with poorly developed secondary sexual characteristics and bilateral breast enlargement. He was born of a non-consanguineous marriage and his prenatal and birth history was uneventful. There was no history suggestive of any developmental delay during childhood and his academic performance was fair. The patient did not give any history suggestive of hyposmia or anosmia. There was no family history of delayed puberty on examination, the patient was found to have a height above the 75th centile (171.5 cm), which was well above his mid parental height (160 cm). His arm-span was 177 cm and his upper segment to lower segment ratio was 0.87. He weighed 100 kg and his BMI was 33.9 kg/m^2. He had absence of facial hair with a pubertal stage of P2. Axillary hair was present. His stretched penile length was 4 cm and his right and left testicular volumes were 3 and 4 cc respectively. He had bilateral gynaecomastia. Olfactorytesting did not reveal any disturbances.

The basal 8:00 AM serum testosterone was <10 ng/dl

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Table 1. Results of 0.1 mg triptorelin stimulation test at presentation.

Parameter	LH (mIU/ml)	FSH(mIU/ml)
Basal	0.53	0.26
60 min	5.06	0.96
120 min	4.17	1.34
180 min	4.11	1.32

LH: Luteinizing hormone, FSH: Follicular stimulating hormone.

(Normal adult: 280 to 1100 ng/dl) and basal serum LH and FSH values were 0.33 mIU/ml (Normal adult: 1.24 to 8.62 mIU/ml) and 0.23 mIU/ml (Normal adult: 1.27 to 19.26 mIU/ml) respectively. Gonadotropin stimulation test was done using 0.1 mg of subcutaneous Triptorelin and the results are shown in Table 1. Peak LH stimulatory value of < 6 mIU/ml was taken to be suggestive of IHH. Other pituitary hormones were found to be within the normal range (TSH - 2.3 mIU/l [Normal adult: 0.4 to 4.2 mIU/L] , Prolactin - 6.35 ng/ml [Normal adult: 3 to 18 ng/ml], Basal 8:00 Am Cortisol – 23 µg/dl [Normal adult: 10 to 25 µg/dl]). MRI of brain and pituitary region did not reveal any obvious pituitary or hypothalamic abnormality and there was no evidence of olfactory bulb agenesis. A diagnosis of idiopathic hypogonadotropic hypogonadism was made and the patient was started on injectable depot testosterone preparation. Patient was followed up regularly at three monthly intervals. There was no increase in height during the course of treatment.

In December, 2015 the patient had come to us for follow up. On examination, his right and left testicular volumes were 8 and 10 cc respectively. His basal 8:00 AM serum testosterone was 314.08 ng/dl. Patient was advised to withhold the testosterone depot injection, which was due at that time, and to review after three months with relevant blood tests.

On follow up, after three months, the patient was found to have a serum testosterone of 320 ng/dl and a basal LH of 5 mIU/ml. There was good development of facial hair with right and left testicular volumes of 8 and 10 cc respectively. The patient was advised for follow-up after 3 months.

DISCUSSION

The above case is an example of reversal of Idiopathic hypogonadotropic hypogonadism triggered by administration of testosterone. The diagnosis of hypogonadotropic hypogonadism was made based on low LH and FSH levels in the background of a low testosterone level. Other causes of hypogonadism were evaluated for and ruled out. The enlargement of testicular volume and the increase in LH and FSH levels on follow up were indicative of recovery of gonadotropic axis. Maintenance of normal serum testosterone levels 3 months after discontinuation also supports the same. This return of functioning of the axis is what makes this case unique as most of the cases of IHH present with a permanent loss of gonadotropic axis.

Recent studies have reported that reversal of IHH had been seen in around 10 to 15% of patients (Raivio et al., 2007; Kulshreshtha et al., 2013; Mao et al., 2015; Root, 2010; Tommiska et al., 2013). The exact cause for this reversal is not known but previous studies have shown a role of androgen exposure as a common factor for reversal. The androgen exposure can either be due to exogenous testosterone or via endogenous testosterone production stimulated by HCG/GnRH. It has been known that sex steroids can influence neuronal generation (MacLusky et al., 2006). The increased androgen levels have been proposed to stimulate GnRH cells and regeneration of GnRH neurons by taking advantage of the plasticity of GnRH neurons.

Another feature seen in previous studies is a relapse of hypogonadism in those who have achieved reversal (Sidhoum et al., 2014). This is indicative of the susceptibility of the gonadotropic axis to insult. The above patient will have to be followed up regularly to check for any relapse. Thus this case reiterates the importance of constant surveillance of patients with hypogonadotropic hypogonadism on therapy, to look for possibility of reversal of axis.

Conclusion

Although IHH often requires life long treatment, reversal of the condition can be seen. Regular surveillance should be done to assess functioning of gonadotropin axis. Increase in testicular size on testosterone treatment is a clue for reversal of condition. Hormonal treatment can be temporarily withdrawn to assess for reversal of IHH.

Conflict of Interests

The authors have not declared any conflict of interests.

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