CASE REPORT

Hypogonadotropic Hypogonadism and Gynaecomastia in the Young Adult: A Case Series

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Abstract We present three cases who presented to our Endocrinology OPD a few days apart with the common complaints of no or minimal development of secondary sexual characteristics. Although they had similar problems, investigations revealed a spectrum of different clinical, biochemical and genetic abnormalities. All the patients had otherwise normal anterior pituitary hormone secretion and sellar anatomy. One had a short Y chromosome, one was a Klinefelter syndrome and the other had no chromosomal abnormality. These findings along with absence of any detectable abnormality on pituitary imaging helped us diagnose these cases as Idiopathic hypogonadotropic hypogonadism. Treatment with testosterone showed marked improvement at 1 year follow up.

Keywords Male infertility · Hypogonadism · Endocrine system abnormalities · Gynaecomastia · Testosterone · Azoospermia

Introduction

Congenital hypogonadotropic hypogonadism (CHH) is divided into anosmic hypogonadotropic hypogonadism Kallmann syndrome (KS) and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic

hypogonadotropic hypogonadism). The incidence of CHH is approximately 1–10:100,000 live births, with approximately 2/3 caused by KS and 1/3 of cases by idiopathic hypogonadotropic hypogonadism [1]. Estimates based on civilian and military hospital series of male CHH, have given a prevalence of 1/4000–1/10,000 [2]. Idiopathic hypogonadotropic hypogonadism (IHH) is a selective failure of neuroendocrine components of the reproductive system in the absence of an anatomic or functional cause. IHH is sporadic or familial in occurrence, with the latter inherited in either X-linked or autosomal mode with a male to female ratio ranging from 4 to 5:1 [3].

Case 1

A 20 year old boy reported to endocrinologist for non development of secondary sexual characteristics and feminine voice (Fig. 1a). He weighed 40 kg. At presentation, his lab tests were as follows (reference range in parantheses): hemoglobin 13.71 gm/dl (13–18), total and differential count, urea, creatinine, uric acid and ferritin were within reference range. Fasting plasma glucose 114.1 mg % (70–110), thyroid stimulating hormone (TSH) 1.88 μ IU/ml (0.35–5.5), total thyroxine (TT4) 12.6 μ g/dl (5.01–12.45), total triiodothyronine (TT3) 1.14 ng/ml (0.6–1.61), total testosterone 28.16 ng/dl (241–827), prolactin 4.56 ng/ml (2.10–17.7). Repeat testing after 1 month showed total testosterone 38.39 ng/dl (241–827), luteinizing hormone (LH) 0.05 μ IU/ml (1.1–7), follicle stimulating hormone (FSH) 1.26 μ IU/ml (1.7–12), Prolactin 7.91 ng/ml (5–35), TSH 3.06 (μ IU/ml), dehydroepiandrosterone sulphate (DHEAS) 194.62 μ g/dl (34.5–568.9), total prostate specific antigen (PSA) 0.11 ng/ml (0–4). Chromosomal analysis showed normal 46 XY male karyotype. X-ray of hands showed no obvious abnormality.

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Fig. 1 Body habitus of the patients

Case 2

The parents of an 18 year old boy brought him to the endocrinologist concerned about his marked weight gain and marked enlargement of breasts.

No similar history could be found in the family. The only child, he is a student with no addiction. His parents reported that he had normal milestones. Father is a known diabetic. Patient was not known to be receiving any relevant treatment. At presentation, his weight was 78 kg and height 166 cm. He had a high-pitched voice, and physical examination showed absent facial, axillary and pubic hair. He had bilateral gynecomastia (Fig. 1b) and central obesity. X-ray of the left hand (Fig. 2) showed a bone age of 11 years. Ultrasonography of bilateral mammary region showed abnormal proliferation of fatty and fibroglandular tissue. Ultrasonography revealed right testis to be 14.8 cm × 13.5 cm × 10.5 cm and left testis to be 17.3 cm × 10.5 cm × 7.9 cm in dimension. Although both testes were small in size, they were normal in shape and echo texture with no focal lesion. Both epididymis were of normal size, shape and echo texture. There was no

Fig. 2 X-ray wrist joint in second case

fluid in scrotal sacs and no dilated vein on either side. MRI brain with particular reference to pituitary gland showed no obvious abnormality. There was no radiological evidence of spina bifida or intervertebral disc space narrowing.

Blood tests revealed the following result (reference ranges in parantheses). Fasting plasma glucose 103 mg/dl (70–110), post prandial plasma glucose 120 mg/dl (70–140), LH 0.1 mIU/ml (1.1–7), follicle stimulating hormone 0.98 mIU/ml (1.7–12), LH/FSH ratio 0.10 (<3), 17 beta estradiol 14.60 pg/ml (7.6–43), DHEAS 0.58 µg/ml (0.59–2.96), total testosterone 0.42 ng/ml (1.66–8.77), free testosterone 2.8 pg/ml (3.84–34.17), Inhibin B 16 pg/mL (<399). Serum electrolyte and ferritin levels were within reference range. Total testosterone after 1 week was 0.56 ng/ml (1.66–8.77) and free testosterone 2.6 pg/ml (3.84–34.17). The patient had normal pituitary function, including normal thyroid-stimulating hormone 2.59 µIU/ml (0.25–5), free T4 1.20 ng/l (0.8–1.8), cortisol 14.60 mcg/dl A.M (6.2–19.4), and prolactin 5.82 ng/ml (5–35). Serum fasting insulin was 13.5 µIU/ml (2.6–24.9).

Chromosomal analysis of peripheral blood was advised due to presence of small bilateral testes and absence of secondary sexual characters. 72 h stimulated cultures were put up with appropriate mitotic agents. A 46 XY male karyotype was observed with G and Q banded metaphases, with presence of small Y chromosome at 450-band resolution (Fig. 3). Decrease in length of heterochromatin of Y chromosome required Y microdeletion studies by molecular techniques. But the test along with androgen receptor gene analysis could not be performed due to financial constraints. We also had to rule out Idiopathic causes and delayed puberty. We ruled out IHH secondary to DAX1 gene mutations since such patients typically present with early-onset adrenocortical insufficiency and may have hyponatremia and hyperkalemia before specific treatment is begun. Prolactin and cortisol levels were within reference range. Hormone replacement therapy with

Fig. 3 Short Y chromosome (marked by arrow)

testosterone to stimulate the development of secondary sexual characteristics was offered.

Case 3

Parents of a 21 year old, 97.8 kg, 1.78 meter tall male consulted the endocrinologist for his lack of facial, chest or axillary hair. On examination, his heart rate was found to be 70/min and blood pressure 120/70 mm Hg. Virilization and tanner stage 1 bilateral gynaecomastia was also observed (Fig. 1c). The laboratory investigations were as follows: hemoglobin 12.5 g % (13–18), WBC 6400 (5–11,000/cmm), ESR was 20 mm (1st h), platelet count 2.10 lacs/cumm (1.5–3.5), red blood cells 4.3 million/cmm (4.5–6.2), MCV 97.6 cubic micron (82–98), MCH 29 pg (26–34), MCHC 29.7 % (32–36), Neutrophil 42 % (60–70), lymphocyte 50 % (20–30), eosinophil 7 % (0–5), monocytes 1 % (0–4), basophil 0 % (0–1), fasting plasma glucose 88 mg/dl (70–110), urea 20.7 mg/dl (10–45), creatinine 0.9 mg % (0.7–1.5), total bilirubin 0.6 mg % (up to 1), alanine transaminase 40 U/L (<41), aspartate transaminase 26 U/L (<35), alkaline phosphatase 71 U/L (40–129), total protein 7.2 g/dl (6–8.3), albumin 4.1 g/dl (3.2–5), total T3 126 ng/dl (60–200), total T4 8.2 µg/dl (4.5–12), TSH 3.56 µIU/ml (0.2–5.5), free T3 2.51 pg/ml (1.7–4.2), free T4 1.02 ng/dl (0.7–1.8), anti thyroid peroxidase 5.43 U/ml (<35), cholesterol 172 mg % (125–200), testosterone 119.28 ng/dl (241–827), free testosterone 4.24 pg/ml (8.80–27), % free testosterone 0.36 % (0.18–0.68), DHEAS 0.68 µg/ml (3.45–56.89), LH 23.98 µIU/ml (1.5–9.3), follicle stimulating hormone 29.59 µIU/ml (1.4–18.1), prolactin 5.93 ng/ml (2.1–17.7). LH, FSH and PRL were done with three sera pooled together. Repeat testing of total testosterone gave a value of 1.32 ng/ml (1.75–7.81) and free testosterone 3.98 pg/ml (4–30).

USG revealed bilateral small sized testes (right 20 × 12 mm and left 20 × 13 mm) with heterogenous echo texture and few small right sided epididymal cysts. Chromosomal analysis of peripheral blood at 450–550 banding resolution by GTG banding technique (G bands by trypsin and giemsa revealed 47 XXY karyotype. The extra X chromosome was consistent with Klinefelter syndrome).

The first two cases had remarkably low LH and lower than normal FSH levels. Low blood testosterone levels and low pituitary hormone levels confirmed the IHH diagnosis. IHH patients have no detectable abnormality on pituitary imaging. Hemochromatosis, the disease most likely to cause acquired isolated gonadotropin deficiency in relatively young men, was ruled out by the presence of normal serum ferritin concentrations.

All three cases were treated with Sustanon 250 mg (Sustanon 250 is a trade name for an oil-based injectable blend of four esterized testosterone compounds- 30 mg

testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate) once every 3 weeks to continue. At follow up after 1 year all three had developed muscle strength, were feeling better and exhibited a positive attitude.

Discussion

In IHH patients, several defects have been described in genes which encode for proteins with biological function in the gonadotropic axis, such as the gonadotropin releasing hormone (GnRH) receptor and the beta sub-units of LH and FSH [4]. Loss-of-function of GPR54 (G-protein-coupled receptor involved in the dynamic regulation of the gonadotropic axis) results in idiopathic hypogonadotropic hypogonadism. Fibroblast growth factor receptor1 (FGFR1) (involved in the development of the olfactory bulb) inactivation is described in autosomal KS.

The clinical characteristics of hypogonadotropic hypogonadism are androgen deficiency and a lack/delay/stop of pubertal sexual maturation. The anatomical causes of acquired hypogonadotropic hypogonadism encompass a large range of disorders, including infiltrative processes and space occupying lesions such as hemochromatosis, pituitary adenomas and other tumors, granulomatous disease, and lymphocytic hypophysitis [5]. All our cases had serum human chorionic gonadotropins (hCGs), prolactin, iron, ferritin and estradiol within reference range. There was no radiological evidence of spina bifida, intervertebral disc space narrowing, pituitary gland or adrenal abnormality.

All three of our cases were euglycemic, euthyroid non azotemic young males presenting to endocrinology department, a few days apart, for the same complaints of lack of appearance of facial hair and secondary sex characters. All the patients were accompanied by anxious parents seeking treatment and raising questions as to the risk of transmitting the condition to their offspring. Hypogonadism was confirmed by low total testosterone and low free testosterone. All were born out of nonconsanguineous marriage with male external genitalia. The absence of mullerian derivatives excluded a severe form of testicular dysgenesis or true hermaphroditism, the low testosterone level excluded incomplete androgen resistance (in which testosterone is elevated) and 5α-reductase deficiency (normal testosterone level).

Y-chromosome microdeletions represent a genetic abnormality affecting 10 % of men with nonobstructive azoospermia [6]. They are classified as azoospermia factor (AZF) regions AZFa, AZFb, AZFbc, and AZFc. Some chromosomal aberrations are also seen outside the AZF

regions involving PAR genes, several of which are associated with psychiatric and medical disorders [7]. However gene mutation studies and testosterone receptor studies could not be done in our cases due to financial constraints.

Suspicion for primary hypogonadism is warranted in any adolescent with persistent pubertal gynaecomastia. Gynaecomastia reflects an increased estrogen/androgen ratio, as estrogen synthesis still occurs by aromatization of residual adrenal and gonadal androgens.

Laboratory examination should aim at identifying the causes of hypogonadism, which could be due to systemic diseases, other endocrine abnormalities or intracranial lesions like craniopharyngioma. Serum luteinizing hormone, follicle-stimulating hormone and serum (total or free) testosterone (in males)/estradiol levels (in females) are low. Screening for serum prolactin, TSH and ferritin levels to rule out hemochromatosis is important and will be essentially normal. Imaging studies especially of the brain is essential to rule out intracranial lesion of the pituitary and hypothalamus.

While testosterone treatment is known to effectively induce virilization, including penile growth, pubic and male hair and beard growth, change of voice, libido, and pubertal growth spurt, testicular volume remains small, lacking spermatogenesis [8]. A significant increase in inhibin B, free testosterone, and total testosterone levels have been noticed 72 h after human chorionic gonadotropin (hCG) injection, in IHH patients [9]. hCG has a stimulatory effect on testicular steroidogenesis and penile growth [10]. Dickson et al. who have described the algorithm for diagnosis of gynaecomastia, mention that one-half of men with Klinefelter syndrome have gynaecomastia [11]. Surgery may be considered as treatment for gynaecomastia of long duration.

In addition to monitoring testosterone levels periodically, prostate screening by digital rectal examination and prostate specific antigen determinations at periodic intervals when the patient is on therapy should be carried out. Hemoglobin and hematocrit levels should also be checked periodically.

The clinical recognition of this syndrome is important, since it represents one of the few treatable forms of male infertility. [12]. The precise diagnosis facilitates appropriate treatment and counselling in affected patients. Established treatment procedures for hormone therapy can

improve quality of life and fertility, as shown in our case series. However, more prospective randomized controlled trials with long-term follow-up are required in future.

Conflict of interest None declared.

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