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Letters to the Editor

Adult-onset idiopathic hypogonadotropic hypogonadism: possible aetiology, clinical manifestations and management

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Dear Editor,

We are doctors from Peking Union Medical College Hospital, Beijing, China. Male idiopathic hypogonadotropic hypogonadism (IHH) is a congenital disease that manifests as small testes, a short penis and no pubertal development. Some patients exhibit cryptorchism and ambiguous genitalia [1]. IHH has been reported being caused by gene mutations in *KAL-1*, *FGFR1*, *GnRHR*, *GPR54*, and several other ligands and receptors [2]. For these patients, gonadotropins or testosterone is the primary choice of therapy. However, adult-onset IHH, defined as idiopathic isolated hypogonadotropic hypogonadism, is very rare, occurring in sexually mature men who have experienced full pubertal development, normal sexual activity and spermatogenesis [3]. The possible aetiology, clinical manifestations, management and prognosis in this disease are quite different from those of congenital IHH.

We describe two male patients who experienced full pubertal development had active sexual lives and had impregnated their wives before experiencing symptoms of decreased libido, erectile dysfunction (ED) and gynaecomastia. Laboratory tests showed significantly decreased gonadotropins and testosterone as well as impaired spermatogenesis, while the other adenohypophyseal hormones were unaffected. Patient 1 received a recombinant human chorionic gonadotropin (HCG) + recombinant human FSH (rhFSH) combination regimen for 6 months, and his sperm count increased to be within the normal range. Patient 2 received testosterone therapy, and his sexual capability was restored. The aetiology of this disease is presumed to be autoimmune-related, considering that only the thalamic–pituitary–testis axis is involved. Combined HCG and rhFSH therapy should be administered if the patient wants to regain spermatogenesis.

Patient 1 was a 30-year-old man who was referred to our hospital because of decreased libido, ED for 5 months, and gynaecomastia for 3 months. He had experienced normal pubertal development and had been married for 8 years. He had four to five sexual activities per week and had impregnated his wife eight times. He did not have fever, fatigue, rapid weight loss, or shedding of pubic and axillary hair. Physical examination found his blood pressure to be 120/80 mmHg. He had gynaecomastia at P4, according to the Tanner–Stage score system. His testes were 20/20 mL in volume, according to Prader orchidometry, and soft when palpated; his pubic hair was stage V and penis length was 8 cm. Laboratory analysis found his transaminase, creatine and other parameters were all within the normal range. Routine blood and urinary tests were negative. Luteinizing hormone (LH) level was 0.0 mIU mL^{-1} (normal range 1.1–11.2 mIU mL^{-1}), follicle-stimulating hormone (FSH) level was 0.1 mIU mL^{-1} (normal range 1.2–20.3 mIU mL^{-1}) and serum total testosterone was 25.7 ng dL^{-1} (normal range 358–1 217 ng dL^{-1}). Other laboratory data and the

results from the GnRHa (Triptorelin) stimulating test and the HCG stimulating test are shown in Tables 1–3. Serum anti-ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Scl-70, anti-J0-1, anti-SSA, anti-SSB and anti-rRNP were all negative. Sellar magnetic resonance image (MRI) found no abnormalities in the hypothalamus or pituitary gland. He was diagnosed as having adult-onset IHH based on clinical manifestations, laboratory data and his wife's multiple pregnancies. rhFSH 75 U i.m. b.i.w. (intramuscular injection twice per week) and HCG 4 000 U i.m. b.i.w. were administered. After 2 weeks, his testosterone level increased to 735 ng dL^{-1} and his erectile function was restored. His sperm count gradually increased to 36×10^6 mL^{-1} within 6 months.

Patient 2 was a 35-year-old man who complained of ED for 1 year and gynaecomastia for 3 months. He reported an uneventful puberty and had fathered a 5-year-old daughter. He had two to three sexual activities per week. One year earlier, he had intermittent diarrhoea for 1 month, from which he recovered without treatment. After that, his libido and erectile function deteriorated, and gynaecomastia had begun 3 months before the clinical examination. He reported a weight loss of 5 kg, but no fatigue, polydipsia or shedding of pubic hair. Physical examination showed that his height was 175 cm and weight was 60 kg. His testes were 15/15 mL in volume and soft when palpated. His pubic hair and gynaecomastia were both at P4 stage. Laboratory tests found normal liver and renal functions. His LH and FSH levels were 0 and 0.2 mIU mL^{-1}, respectively, with testosterone at 17.5 ng dL^{-1}. No abnormalities were found by sellar MRI. Serum anti-ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Scl-70, anti-J0-1, anti-SSA, anti-SSB and anti-rRNP were all negative. Other laboratory data and the results from the GnRHa (Triptorelin) stimulating test and the HCG stimulating test are shown in Tables 1–3. Since he did not want another child, he was administered testosterone undecylate as a 250-mg

Table 1. Main laboratory findings in two patients with adult-onset IHH.

Items	Patient 1	Patient 2	Normal range
FSH (mIU mL^{-1})	0.1	0.2	1.4–10.5
LH (mIU mL^{-1})	0	0	1.1–11.2
Estradiol (pg mL^{-1})	4.2	3.2	19.9–47.9
Testosterone (ng dL^{-1})	25.7	17.5	358–1 217
ESR (mm h^{-1})	6.0	8.0	0–20
Sperm count (10^6 mL^{-1})	0.0	0.6	20–60
Seminal volume (mL^{-1})	1.2	1.4	2–6
ACTH (8:00 am) (pg mL^{-1})	23.6	51.0	0–46
Cortisol (8:00 am) (μg dL^{-1})	26.8	24.0	4.0–22.3
24 UFC (μg)	51.6	ND	12.3–103.5
Free triiodothyronine (pg mL^{-1})	2.8	2.4	1.8–4.1
Free thyroxin (ng dL^{-1})	0.87	0.85	0.81–1.89
Thyrotropin (μIU mL^{-1})	4.0	3.34	0.38–4.34
Insulin-like growth factor-1 (ng mL^{-1})	123.0	66.0	117–329
Prolactin (ng mL^{-1})	16.2	7.1	2.1–11.8

Abbreviations: ACTH, adrenocorticotropin hormone; ESR, erythrocyte sedimentation rate; FSH, follicular stimulating hormone; IHH, idiopathic hypogonadotropic hypogonadism; LH, luteinizing hormone; ND, not done; 24 UFC, 24-h urine free cortisol.

Table 2. GnRHa stimulating tests (Triptorelin, 100 μg i.m. s.t.) in two male patients with adult-onset IHH.

	LH (mIU mL^{-1})		FSH (mIU mL^{-1})	
	0 min	60 min	0 min	60 min
Patient 1	0.1	0.3	0.0	0.4
Patient 2	0.0	0.6	0.2	0.8
Normal range	1.1–11.2	12–42	1.4–10.5	8.2–20.8

Abbreviation: IHH, idiopathic hypogonadotropic hypogonadism

Table 3. HCG stimulating tests (HCG 4000 U i.m. b.i.w. × 4 times) in two patients with adult-onset IHH.

	Serum total testosterone (ng dL^{-1})				
	Day 0	Day 3	Day 7	Day 10	Day 14
Patient 1	34	88	245	352	388
Patient 2	28	176	305	332	458
Normal range	–	–	–	–	358–1 217

Abbreviation: IHH, idiopathic hypogonadotropic hypogonadism

intramuscular injection each month. Improvement in libido and erectile function was achieved after therapy.

These two cases present some features that are rarely seen in clinical practice: (1) both patients were sexually mature men who had experienced normal pubertal development, sexual activities and spermatogenesis; (2) No other causative conditions were found to explain their ED and gynaecomastia; (3) Physical examination revealed an adult-sized penis and a testis volume of 15–20 mL; (4) Laboratory findings showed significantly reduced levels of gonadotropins and testosterone, while other hormones from anterior and posterior pituitary glands were not impaired. No abnormalities were found in their sellar MRIs. These clinical features led to a diagnosis of adult-onset IHH.

Hypogonadotropic hypogonadism in men is not an uncommon disease and can usually be classified into two categories representing congenital and acquired forms. The incidence of congenital IHH is about 0.025% [4]. Gene mutations in *KAL-1*, *FGFR1*, *GnRHR* and *GPR54* can lead to congenital IHH, which manifests as delayed or no puberty, short penis or ambiguous genitalia, and small testes or cryptorchism [1, 2]. Individuals from a family with a common *KAL-1* gene mutation reportedly demonstrated varied phenotypes, from IHH to delayed puberty to reversal of hypothalamic–pituitary–testis axis function [5]. However, adult-onset IHH caused by the above gene mutations has not been reported. Another type of congenital IHH is caused by *DAX-1* gene mutations. Such patients inevitably have symptoms of severe primary adrenal insufficiency, which differs greatly from the symptoms of our patients [6].

Acquired hypogonadotropic hypogonadism can be caused by various clinical conditions: (1) pituitary adenomas, brain tumours, inflammatory diseases and traumas may directly disturb the hypothalamus and pituitary gland functions. Such pathologies always lead to multiple hormone deficiency from the anterior pituitary gland and sometimes even central diabetes insipidus. The human growth hormone is the most vulnerable of all adenohypophyseal hormones, while isolated gonadotropin deficiency is rarely seen. In our patients, local tumours, inflammatory diseases and traumas can be excluded because of normal secretion of other pituitary hormones, normal MRIs and no history of head trauma. (2) Testosterone levels are influenced by various diseases. Both acute stress and chronic systemic conditions such as malignancies, malnutrition, haemachromatosis and chronic obstructive pulmonary diseases can significantly reduce the levels of gonadotropins and testosterone [7, 8]. Some female patients with anorexia nervosa or extreme weight loss will present hypothalamic amenorrhea. However, these pathologies can be readily excluded for our patients on the basis of medical history, laboratory examination and normal ferritin levels. (3) Excessive exercise, alcoholism, major depression and other psychiatric diseases can lead to hypogonadotropic hypogonadism, but no signs of these conditions were found in our patients.

Adult-onset IHH was first reported by Nachtigall *et al.* [3] in 1997, who gave a detailed description of ten cases. Since then, only 10 more cases have been reported [9], including two patients from Japan [10, 11]. The underlying mechanism has not yet been elucidated because of the rarity of this disease and lack of pathological and immunohistochemical information from hypothalamic or pituitary tissues. Most clinical studies have found that administration of pulsive GnRH therapy can restore gonadotropin secretion and spermatogenesis, suggesting that GnRH neurons in the hypothalamus were impaired [3, 10]. However, recent evidence from two cases determined that pituitary gonadotrophs were impaired because no increase of gonadotropins was evoked by pulsive GnRH stimulation [9, 11]. As for our patients, the extremely low levels of gonadotropins and testosterone, which could not be stimulated by GnRHa, indicate severe and specifically damaged pituitary gonadotrophs. Our speculation that this disease might be caused by an autoimmune disease is based on the following points: (1) This disease seems to exclusively attack hypothalamic GnRH neurons and pituitary gonadotrophs, while other cells in the hypothalamus and pituitary gland are wholly spared. The damaged cells comprise a highly specific population, and such phenomena are not uncommon in autoimmune diseases. (2) Basic research aiming to investigate the relationship between IHH and pituitary antibodies found that some Ig antibodies were specifically accumulated in gonadotrophs [12]. We tested many possible autoimmune antibodies in our patients, but all proved negative. (3) No abnormalities were found in sellar MRI. (4) The trend toward low incidence of autoimmune diseases in men correlates with the rarity of this disease. (5) Isolated adrenocorticotropin deficiency, a very similar type of disease to adult-onset IHH, was recently confirmed to be caused by specific autoimmune antibodies [13]. (6) In patient 2, intermittent diarrhoea before ED may have increased the chance of developing an autoimmune

disease. However, we still lack firm evidence to confirm our speculation. Direct information from serum-specific antibodies and immunohistochemical studies in the hypothalamus and pituitary tissues should be collected in the future.

Women with menorrhoeal disturbances are more likely to approach doctors for medical help than men with adult-onset IHH who seldom consult with doctors because of a lack of obvious and critical symptoms. This tendency may result in underestimation of the incidence of male adult-onset IHH. In this regard, recognition of this disease in a population with ED would be appropriate because this is a treatable clinical condition.

The choice of therapy depends on the fertility requirements of the patients. Pulsive GnRH or gonadotropins are optimal choices for patients who wish to restore their reproductive capacity. The chances of restoring spermatogenesis are much higher in adult-onset IHH patients than in congenital IHH patients, as the Sertoli and Leydig cells of the former, but not the latter, have fully proliferated and developed [3]. Testosterone replacement is another convenient therapy if the patients have no requirement for spermatogenesis. One of our patients received a combination of HCG and rhFSH that resulted in spermatogenesis within 6 months.

In conclusion, adult-onset IHH patients may present symptoms of ED and gynaecomastia with isolated deficits in the hypothalamus–pituitary–testis axis. Although the underlying mechanisms are not clear, they might involve autoimmune antibodies specifically targeted to GnRH neurons or gonadotrophs. Gonadotropins should be considered as a clinically significant alternative therapy because spermatogenesis can be restored in most patients with adult-onset IHH.

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