CASE REPORT

Idiopathic hypogonadotropic hypogonadism in selective human gonadotropin deficiency in adult man: a case report

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Abstract. We report a rare case of idiopathic hypogonadotropic hypogonadism in an adult male (31-jear-old), who underwent an endocrinological examination because of erectile dysfunction and suspected infertility. Laboratory data showed isolated gonadotropin deficiency. Magnetic resonance imaging (MRI) of the hypothalamic-pituitary unit showed no tumoral expansions. The patient was tested with gonadotropin releasing hormone (Gn-RH) (100 μg as an i.v. bolus injection). No significant LH and FSH responses were observed. Idiopathic hypogonadotropic hypogonadism is usually caused by hypothalamic lesions, however, since Gn-RH was unable to stimulate LH and FSH secretions, we supposed that our patient was affected by defective gonadotropin secretion at pituitary level. (www.actabiomedica.it)

Key words: Hypogonadotropic hypogonadism, erectile dysfunction

Introduction

The aetiology of hypogonadotropic hypogonadism depends on various conditions. It may be caused by a selective gonadotropin deficiency or by concomitant lack of other pituitary hormones in the context of a more complex pathology. It could be congenital or late onset in the adult male, because of a known condition. The location of the damage could be at the hypophyseal or the hypothalamic level. Congenital hypogonadism presents isolated gonadotropin deficiency, mostly caused by a genetic abnormality associated with the KAL1 gene (1).

The acquired forms present multiple alterations of the hypophyseal function and are brought on by conditions such as inflammatory diseases, hypothalamus-pituitary expansive pathologies (adenomas), immune disorders. Chronic diseases, some psychiatric illnesses, important nutritional disorders, such as anorexia nervosa, could also determine a gonadal dysfunction (2).

In this study, we describe a case of idiopathic hypogonadism in the adult brought on by isolated pituitary gonadotropin deficiency.

Case report

A 31-year-old man, underwent an endocrinological examination because of suspected infertility, progressively decreasing libido and erectile dysfunction continued over a period of years. Statural growth was regular and puberty normal at age 13 years.

There was no history of cryptorchidism, pathological episodes, head trauma, or drug assumption.

Physical examination: normal body structure (height 175 cm; weight 78 kg). He was Tanner stage V and testis volume was 15 ml, estimated by Prader's orchidometer (normal range: 15-25 ml). No signs of varicocele or gynecomastia. Olfaction was normal. The prostate was normal on digital examination.

Laboratory analyses were all within the normal range: blood count, serum iron, ferritin, glucose, cholesterol, triglycerides, urea and creatinine, electrolytes, albumin, ALT, AST, γ-GT, total and direct bilirubin, urine analysis.

Tests for anti-nuclear, anti-DNA, anti-mitochondrion, anti-smooth muscle, anti-gastric mucosa, anti-thyroid, anti-hypophysis and anti-adrenal gland serum antibodies were negative.

Sperm count presented oligo-astheno-teratozoospermia.

The endocrine function of pituitary, thyroid, adrenals and gonads were evaluated in basal conditions and after stimulation with specific releasing hormones. The laboratory data presented normal basal levels of thyroid hormones, TSH, GH, IGF-1, PRL, ACTH and cortisol (Tab. 1). Serum concentrations of LH (0,1 mU/ml) and FSH (0,1 mU/ml) were undetectable, while testosterone levels (1 ng/ml) were significantly lower than the normal range (Tab. 1).

In order to study gonadotropin pituitary function, a repeated Gn-RH test (100 μg i.v.) in addition to HCG test (5000 UI i.m. for three days for the evaluation of testosterone secretion), was carried out. 100 μg Gn-RH was given i.v. once a day for 5 consecutive days before Gn-RH test. On day 1 and 7 Gn-RH was done. Blood samples for LH and FSH determination was collected at basal level (time 0) and 30 minutes after i.v. Gn-RH administration (Tab. 2).

The results showed lack of LH and FSH responses to Gn-RH stimulation (Tab. 2), while the stimulation test with HCG revealed testosterone levels at the lower limit of the normal range (Tab. 3). Thyroid and adrenal function, growth hormone (GH) – insulin-like growth factor (IGF-1) axis, and Prolactin secretion, evaluated in basal condition and after specific releasing hormones, were normal.

Table 1. Basal hormonal parameters

LH	<0.1 mIU/ml	
FSH	<0.1 mIU/ml	
Total Testosterone	1 ng/ml	
Estradiol	90 ng/ml	
Prolactin	8 ng/ml	
GH	1 ng/ml	
IGF-1	205 ng/ml	
TSH	1.35 μU/ml	
FT4	1.60 ng/ml	
FT3	1.0 pg/ml	
Free-urinary cortisol	35 μg/24h	
Aldosterone	116 pg/ml	
Plasma Renin Activity	1.35 ng/ml/h	
	h 08.00	h 24.00
Cortisol (μg/dl)	23.0	5.2
ACTH (pg/ml)	53.8	7.4

Table 2. Gn-RH test. 100 μg of Gn-RH was given i.v. once a day for 5 consecutive days before Gn-RH test. On days 1 and 7 the Gn-RH test was done

	Day 1		Day 7	
Time	0	30'	0	30'
LH (mIU/ml)	0.1	0.1	0.1	0.1
FSH (mIU/ml)	0.1	0.1	0.1	0.1

Table 2. Human Chorionic Gonadotropin (HCG) test (5.000 IU i.m. for 3 days)

Time	Basal	24 h	48 h	72 h	96 h
Total Testosterone (ng/ml)	1	1.85	1,9	2.7	4.8

The patient underwent radiological examination by pituitary Magnetic Resonance Imaging (MRI). The examination showed no expansive lesions. The DEXA bone mineral density examination was normal.

In the end, the patient was subjected to psychiatric appraisal to verify the presence of an anxious-depressive state; this turned out to be negative.

Based on instrumental data, endocrine function data, as well as the negativity in anti-hypophysis antibody search, a diagnosis of adult idiopathic hypogonadotropic hypogonadism was made, caused by isolated gonadotropin deficit.

The patient, therefore, began substitutive treatment with testosterone gel (50 mg/die).

Discussion

The case presents some aspects which are rarely encountered in clinical practice.

It's a case of acquired hypogonadism in the adult, caused by isolated gonadotropin deficit. The conditions usually responsible for hypogonadotropic hypogonadism are represented by flogistic or infiltrative processes that affect the hypophyseal-hypothalamus region and are especially represented by hypophyseal adenoma, neoplastic metastasis, granulomathosys pathologies as well as histiocytosis X, lymphocitary hypophysitis, detection of haemochromatosis, vascular pathologies (2). Our patient presented no alterations in the main laboratory test values that could suggest a flogistic-immunologic or granulomatosus process in progress or past, nor anomalies in the structure of the

hypothalamus-hypophyseal region by MRI. Thus, a case of idiopathic hypogonadism was diagnosed. Damage at hypophyseal level was confirmed by repeated stimulations carried out in order to estimate gonadotropin secretions. Another possible cause could be haemochromathosis, but this pathology was ruled out because of the presence of normal ferritin levels and the absence of familiarity (3).

Acute diseases, accidental trauma, alterations in nutritional status with significant loss of weight and the presence of depression can also be considered responsible for the alteration in gonadotropins synthesis and release, and this condition may be observed in female hypothalamic amenorrhoea (4). However, the anamnesis and the response of normal ACTH and cortisol to the stimulation with CRH, have allowed us to rule out these etiologies (5).

Some idiopathic cases of hypogonadism, in the adult, are caused by genetic factors involved in the gonadal function or by autoimmunity phenomena (1, 6, 7). The mutation of the DAX-1 gene is the main cause of congenital adrenal hypoplasia. A subgroup of subjects, with mutation in DAX-1, present late insurgence hypogonadotropic hypogonadism associated with several adrenal deficiency cases (6). In this condition, it is still not clear if the pathogenesis of the hypogonadism is hypothalamic or hypophyseal (8).

The literature has also described an anomaly in the gene which codifies for the Gn-RH receptor, with subsequent hypogonadotropic hypogonadism (9).

In the case described, to subject the patient to a genetic study seemed unnecessary, because he presented no adrenal function anomalies, nor positive familiarity.

Several possible autoimmune diseases have been considered. The lack of positivity for auto-antibody titration and, in particular, for anti-pituitary antibodies, has allowed us to rule out an autoimmune pathogenesis.

The clinical condition of hypogonadism, identified as idiopathic, has also been described as such by other authors (10), after silent anamnesis for the pathology, absence of demonstrable lesions with MRI, low testosterone and gonadotropin levels and no response to stimulation with Gn-RH.

On the other hand, several similar cases have been described but with a sensitivity to pulsatile administration of Gn-RH, with improvement in the sexual function, libido and fertility.

In these cases, the disease is at hypothalamic level because, after the pulsatile administration of Gn-RH, LH and FSH responses are positive.

Based on the data we have, the case we have presented has been diagnosed as idiopathic hypogonadotropic hypogonadism, in selective hypophyseal deficit.

The replacement therapy with testosterone was chosen because the patient, not married, does not want children. The problem of fertility therefore will arise in the future. Treatment with Gn-RH or gonadotrophin may encourage the resumption of fertility in a substantial number of patients, despite the parameters of sperm counts can remain altered. Replacement treatment with gonadotropin represent the rational and is the only accepted and effective (11). The treatment includes the use of human chorionic gonadotropin (HCG), a luteinizing hormone (LH) analog and human menopausal gonadotropin (HMG) which mimics LH and FSH, or purified FSH. Recombinant human FSH (rFSH) and HCG have replaced their counterparts purified as standard treatment for hormone replacement treatment because they are cheaper and more pure. Nevertheless, they showed equal effectiveness in increasing the sperm counts improving mobility, morphology and pregnancy outcomes (12). Pulsatile Gn-RH can be used to start a normal physiological function as in the tertiary hypogonadotropic hypogonadism (Kallman syndrome). Its use is not often because administration of this drug requires a portable minipump and then it is an expensive drug (13).

In order to better describe the pathogenetic mechanism of these rare cases, further more through immunological and biomolecular research will be necessary in the future, supported by the use of more sophisticated technology.

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