



Pituitary Magnetic Resonance Imaging in Patients with Isolated Hypogonadotrophic Hypogonadism: A Single Center Experience

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Abstract

Hypogonadism is a result of testicular/ovarian failure and/or insufficient pituitary stimulation. Various hypothalamo-pituitary abnormalities or lesions can contribute to hypogonadism. Benign or malign tumoural lesions of cellular or paracellular region, may lead to hypogonadism. Therefore, pituitary magnetic resonance imaging (MRI) is needed in patients with hypogonadism. In our study, we aimed to investigate our hypothalamo-pituitary MRI findings of hypogonadal patients. We evaluated 42 isolated hypogonadal patients followed in our clinic. These patients' pituitary MRI findings were analyzed retrospectively. 80.9 % of isolated hypogonadotrophic patients' were male, 19.1 % were female. Pituitary MRI findings of isolated hypogonadotrophic patients revealed that; 59.5% (n=25) were normal, 16.7 % (n=7) pituitary microadenoma, 11.9% (n=5) partial empty sella, 4.7% (n=2) pituitary macroadenoma, 2.4% empty sella (n=1), 2.4% (n=1) ectopic neuropituitary, and 2.4% (n=1) empty sella plus ectopic neuropituitary together. In half of the patients with isolated hypogonadotrophic hypogonadism, pituitary MRI findings may be normal. In these patients, if clinic and laboratory results are harmonious, to determine the diagnosis dynamic tests are required and appropriate therapy must be done, even if pituitary MRI is normal.

Keywords: Hypogonadism, magnetic resonance imaging, microadenoma, macroadenoma

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Introduction

Pulsatile secretion of gonadotropin releasing hormone (GnRH) by hypothalamic neurons is a crucial element of the reproductive cascade, initiating the release of pituitary gonadotropins, gonadal secretion of sex steroids, pubertal development, and gametogenesis. Impaired testicular function, i.e., hypogonadism, can result from a primary testicular/ovarian disorder (hypergonadotropic) or occur secondary to hypothalamic-pituitary dysfunction (hypogonadotropic). Hypogonadotropic hypogonadism (HH) is characterized by failure of gonadal function secondary to deficient gonadotropin secretion [1]. This condition is commonly seen in association with other pituitary hormone deficiency states caused by structural lesions of the hypothalamic-pituitary region. HH can be congenital or acquired. Congenital HH is divided into anosmic HH (Kallmann syndrome) and normosmic HH (idiopathic HH). Acquired HH can be caused by drugs, infiltrative or infectious pituitary lesions, hyperprolactinemia, encephalic trauma, pituitary/brain radiation, exhausting exercise, abusive alcohol or illicit drug intake, and systemic diseases such as hemochromatosis, sarcoidosis and histiocytosis X.

Male hypogonadism may manifest with testosterone deficiency, infertility, or both conditions. Low libido is a clinical hallmark of hypogonadism but erectile dysfunction (ED) is also commonly noted [2,3]. Symptoms of hypogonadism depend primarily on the age of the male patient at the time of development of the condition. Hypogonadism is often unrecognized before the age of puberty unless it is associated with growth retardation or other anatomic or endocrine abnormalities.

Female hypogonadotropic hypogonadism (World Health Organization group I anovulation) can lead to very low or undetectable serum gonadotrophin (LH and FSH) concentrations, manifested in anovulation, amenorrhoea and subsequent infertility [4,5]. Irrespective of the underlying aetiology, women with HH require both luteinizing hormone (LH) and follicular stimulating hormone (FSH) to restore normal ovarian function and override follicular growth arrest [4,6]. While FSH may be essential to induce follicular growth, a minimum amount of LH is also required for optimal growth. In these women, FSH alone was shown to induce a minor increase in oestradiol concentration, poor follicular luteinization and decreased oocyte fertilization rate [7,8].

In cases of acquired hypogonadotropic hypogonadism (low testosterone/oestradiol with low-normal FSH and LH levels) not clearly attributable to a specific cause, pituitary imaging studies with MRI or computed tomography may be needed to evaluate for structural lesions in the hypothalamic- pituitary region. MRI generally provides better pituitary images, but bony changes in the sella may be better characterized by computed tomography. In general, MRI done with and without a contrast agent is recommended as the initial pituitary imaging study in patients requiring delineation of a pituitary pathologic condition. Although no published studies have clearly indicated a particular level of testosterone in the setting of hypogonadotropic hypogonadism that should prompt pituitary evaluation, a total testosterone concentration of 150-200 ng/dl or below has been considered a reasonable level at which to pursue pituitary imaging, even in the absence of other symptoms. Certainly other symptoms suggestive of pituitary disease necessitate appropriate further evaluation.

Pituitary imaging is often recommended when there is suspicion of pituitary contribution to hypogonadism. Some pituitary abnormalities may have significant health implications. Diagnosis is valuable since these may respond to treatment other than testosterone replacement therapy [9, 10]. However, it remains unclear who deserves magnetic resonance imaging (MRI) of the hypothalamic-pituitary region during evaluation of hypogonadism. Some have argued that the yield of clinically significant lesions is low whereas others fear missing a cancer or a treatable pituitary adenoma [11-13].

We reviewed our results with pituitary MRI in isolated hypogonadal male and female patients to see the frequency of radiologic abnormalities if we could identify them for treatment.

Materials and Methods

The study group consisted of 42 patients with hypogonadism evaluated between October 2005 and March 2011 who underwent MRI of the pituitary during evaluation of hypogonadism at Ankara Ataturk Education and Research Hospital. Indications for MRI were the presence of hypogonadism associated with increased levels of prolactin (PRL), subnormal levels of luteinizing hormone (LH) (hypogonadotropic hypogonadism). Clinically we used a value of less than 200 ng/dl to define men with markedly low total testosterone (TT). All men were symptomatic and had levels of TT and/or free testosterone (FT) less than the normal range. Serum levels of LH, FSH and PRL were obtained for all individuals. Men taking medications

known to decrease testosterone levels or interfere with the hypothalamic-pituitary axis were excluded from the study. For female patient hypogonadotropic hypogonadism was defined as serum estradiol levels below 20 pg/ml; and low LH and FSH level. Serum determinations of TT, FT, PRL, LH, FSH and estradiol were obtained during clinical hours, from 8:00 am to 5:00 pm. TT and FT were measured by radioimmunoassay. TT levels less than 300 ng/dl were defined as abnormal for this study. LH, FSH and PRL were determined by radioimmunoassay with normal values of 2-10 mIU/ml, 10-40 mIU/ml and 10-24 ng/ml, respectively.

MRI was performed before and after administration of intravenous gadolinium (gadolinium-diethylenetriamine pentaacetic acid, gadopentetate dimeglumine, Magnevist [Berlex, Montville, New Jersey]) injection. Special attention was directed to the hypothalamic pituitary region regarding normal size, configuration, intensity and pattern of enhancement. MRI results were based on written reports in the medical record. Student's t test, chi-square analysis and analysis of variance were used to assess the statistical differences between groups with $p < 0.05$ considered significant.

Results

Study group characteristics were separately defined according to gender. Study group included 34 (80.9%) male and 8 (19.1%) female patients. Mean age of group was 27.69 years with a range of 16 to 58 years. Characteristics and mean hormone values of male and female patients are shown in Table 1. The presenting complaints were retardation of secondary sex characteristics, growth retardation, infertility, osteoporosis and delayed puberty. 11 male patients had erectile dysfunction, 19 had ejaculation problems and 7 had gynecomastia. Pituitary MRI findings of isolated hypogonadotropic patients revealed that; 59.5% (n=25) were normal, 16.7 % (n=7) pituitary microadenoma, 11.9% (n=5) partial empty sella, 4.7% (n=2) pituitary macroadenoma, 2.4% empty sella (n=1), 2.4% (n=1) ectopic neuropituitary, and 2.4% (n=1) empty sella plus ectopic neuropituitary together. Microadenomas were found in 16.7% (n=7) of all patients with no function. Only one male patient had macroadenoma with mild hyperprolactinemia but he was asymptomatic. Other patient with macroadenoma was nonfunctional.

Pituitary MRI findings of male patients' revealed that; 21 patients were normal, 5 patients' had microadenomas; 2 patients' had macroadenomas, 4 patients' had partial empty sella, 1

patient had ectopic neuropituitary and 1 patient had empty sella plus ectopic neuropituitary together (Figure 1,2,3). Pituitary MRI findings of female patients' revealed that; 4 patients' were normal, 2 patients' had microadenomas, 1 patient had empty sella and 1 patient had partial empty sella (Table 2).

Table 1. Patient characteristics

	Gender	Gender
	Male (n=34)	Female (n=8)
	Mean±SD (range)	Mean±SD (range)
Age	28.6±9.39 (16-58)	22.29±4.71 (17-29)
Total testosterone	99.31±86.3 (13-285)	-
Free testosterone	4.17±3.83 (1-20)	-
LH	4.76±8.67 (0-35)	1.86±2.67 (0-7)
FSH	12.45±28.64 (0-147)	2.14±2.47 (0-6)
Prolactin	11.26±9.58 (0-40)	5.29±1.25 (4-8)
Estradiol	-	24.43±19.34 (13-68)

Table 2. Patient characteristics based on magnetic resonance imaging findings

MRI findings n(%)	Male n:34 (% 80.9)	Female n:8 (% 19.1)
Normal n=25(%59.5)	21	4
Microadenomas n=7 (16.7)	5	2
Macroadenomas n=2 (%4.7)	2	-
Empty sella n=1 (%2.4)	-	1
Partial empty sella n=5(%11.9)	4	1
Ectopic neuropituitary n=1(%2.4)	1	-
Empty sella ve ectopic neuropiuitary n=1(%2.4)	1	-

All microadenomas and macroadenomas found on pituitary MRI were non-functional. One patient with macroadenoma underwent surgery and was found histopathologically as null cell adenoma. Other patient refused surgery.

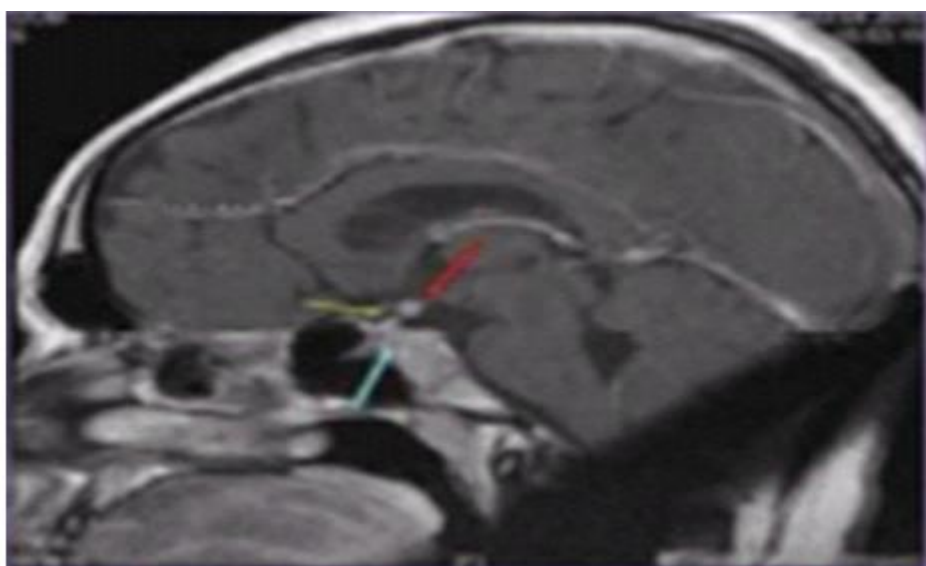


Figure 1. Ectopic Neurohypophysis



Figure 2. Partial Empty Sella



Figure 3. Partial Empty sella and Ectopic Neurohypophysis

Discussion

The hormonal regulation of testicular and ovarian function is exerted by LH and FSH synthesized and secreted by the pituitary gland under hypothalamic control via gonadotropin-releasing hormone. The testes, ovaries and the hypothalamic-pituitary system communicate through a feedback system of steroid and protein hormones [14]. Testosterone has a central role in this complex system and is well recognized for its important actions in the male body regarding hair growth, bone metabolism, muscle mass, secondary sexual characteristics, libido, sexual function and spermatogenesis [15,16].

In the female, estradiol acts as a growth hormone for tissue of the reproductive organs, supporting the lining of the vagina, the cervical glands, the endometrium, and the lining of the fallopian tubes. It enhances growth of the myometrium. Estradiol appears necessary to maintain oocytes in the ovary. During the menstrual cycle, estradiol produced by the growing follicle triggers, via a positive feedback system, the hypothalamic-pituitary events that lead to the luteinizing hormone surge, inducing ovulation. In the luteal phase, estradiol, in

conjunction with progesterone, prepares the endometrium for implantation. The development of secondary sex characteristics in women is driven by estrogens, to be specific, estradiol.

Low testosterone can be caused by testicular failure and/or inadequate pituitary stimulation of the testes via LH [17]. A number of pituitary abnormalities are known to result in hypogonadism. First admission of patients with isolated hypogonadotrophic hypogonadism is generally to urology clinics. And they are being administered replacement therapy.

Sellar and parasellar tumors can be associated with hyperprolactinemia, hypogonadism and other endocrine manifestations [15,18,19]. The most common sellar tumors are pituitary adenomas. Autopsy studies reveal pituitary adenomas in approximately 27% of men and women. They are also identified incidentally in 10% to 20% of imaging scans of the sellar area [20]. Most adenomas are silent and undiagnosed unless they cause significant clinical symptoms, usually on an endocrine basis. Prolactinomas are the most common pituitary tumors and are divided into micro (less than 10 mm) and macroadenomas (greater than 10 mm), with larger tumors more commonly associated with clinical manifestations [20,21].

Other sellar and parasellar tumors include craniopharyngiomas (accounting for up to 30% of pituitary tumors), Rathke's cleft cyst, chordoma, germ cell tumors, tumors of the infundibulum and neurohypophysis, gangliocytomas, and primary and metastatic pituitary carcinoma. These may or may not be associated with hypogonadism [18,19,22,23]. Craniopharyngiomas account for 1.2% to 3% of intracranial tumors, and have been associated with endocrine abnormalities in 52% to 85% of cases and impotence in 42% [19,24]. The possibility of missing a sellar or parasellar tumor is a major concern of clinicians during the evaluation of male hypogonadism. Fortunately these tumors are rare and usually associated with headaches, visual disturbances, cranial nerve involvement or other endocrine manifestations such as hypothyroidism, diabetes insipidus, hypo or hyperthermia and acromegaly [15,23]. We didnt seen craniopharyngiomas, Rathke's cleft cyst, chordoma, germ cell tumors, tumors of the infundibulum and neurohypophysis, gangliocytomas, and primary and metastatic pituitary carcinoma among our patients.

Another condition commonly observed is the empty sella syndrome, sometimes called the partially empty sella syndrome, which is believed to be due to the absence of the dura during formation of the sellar diaphragm, with progressive invagination of subarachnoid space into

the sella and compression of the pituitary gland against the sella floor. Mild pituitary dysfunction with blunted stimulation test results is common, but clinically significant hypopituitarism is rare [13].

Screening studies of the general population reveal that the prevalence of the empty sella syndrome is approximately 4% [11,13,23]. Studies of men and women with this condition revealed hyperprolactinemia in 32%, hypothyroidism in 9.6%, secondary adrenocortical failure in 5.7%, deficiency of growth hormone in 25.5% and hypogonadism in 28.7% of men. In contrast 59.6% of individuals presented with no identifiable endocrine abnormalities [11,13]. Other authors such as Neelon et al did not find any significant hormonal abnormalities in men with partially empty sella [25]. In our series we identified empty sella only in one female patient without hyperprolactinemia. She was euthyroid with thyroid nodules that biopsy was revealed malignancy.

In general MRI is the preferred imaging modality to investigate pituitary dysfunction due to its superiority over computerized tomography for the definition of soft tissues, optic chiasm and vasculature. It also avoids exposure to radiation [15]. The sensitivity and predictive value of imaging studies have a direct relationship to the size of the abnormality [23].

The prevalence of neuroanatomic abnormalities in men with hypogonadism is not yet well-defined in the literature. Citron et al reviewed imaging (MRI and computerized tomography) studies in 164 men 27 to 79 years old with ED and secondary hypogonadism who had normal PRL levels [13]. They found 27 men (16.6%) with hypothalamic-pituitary abnormalities including empty sella in 6.7%, pituitary microadenomas in 6%, and pituitary macroadenomas in 4% and hypothalamic lesions in 1.2%. They also found that a lower level of serum TT indicated a higher risk for hypothalamic or pituitary imaging abnormalities. Individuals with an empty sella, even when it appeared complete, did not differ endocrinologically from those with normal pituitary images.

Our study of isolated hypogonadotrophic hypogonadal patients revealed pituitary abnormalities in 40.4% (n=17). In 25 patients we found normal pituitary imagings. No hypothalamic abnormalities were noted. Microadenomas were found in 16.7% (n=7) of all patients with no function. Only one male patient had macroadenoma with mild

hyperprolactinemia but he was asymptomatic. Other patient with macroadenoma was nonfunctional.

We specifically evaluated the value of obtaining an MRI in 3 situations where it has been historically used in clinical practice, including our own. The rationale for obtaining MRI in men with markedly low TT in association with normal PRL and LH is to rule out the presence of a nonsecreting mass that fails to suppress gonadotropin levels completely. Although we are unaware of literature defining this population clinically we have used less than 200 ng/dl TT as a trigger for obtaining MRI.

We also evaluated women presenting with amenorrhoea. All had hypogonadotropic hypogonadism. Of the 8 women 2 demonstrated a pituitary microadenoma an MRI with normal prolactine levels; 1 patient demonstrated empty sella and 1 patient demonstrated partial empty sella.

The limitations of this study include the absence of a control group, limited study population size and the fact that it is a retrospective analysis. However, these data do represent a picture of the yield of MRI in clinical practice.

Conflict of Interest

All authors declare that there is no conflict of interest.

Acknowledgement

I declare that ethical approval was received from local ethical committee.

References

1. Seminara SB, Hayes FJ, Crowley WF Jr. Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. *Endocr Rev.* 1998;19(5):521-39.
2. Govier FE, McClure RD, Kramer-Levien D. Endocrine screening for sexual dysfunction using free testosterone determinations. *J Urol.* 1996;156(2 Pt 1):405-8.
3. Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost- effective strategy. *J Urol.* 1997;158(5):1764-7.

4. Gibreel A, Bhattacharya S. Recombinant follitropin alfa/lutropin alfa in fertility treatment. *Biologics*. 2010;4(4):5-17.
5. Krause BT, Ohlinger R, Haase A. Lutropin alpha, recombinant human luteinizing hormone, for the stimulation of follicular development in profoundly LH-deficient hypogonadotropic hypogonadal women: a review. *Biologics*. 2009;3:337-47.
6. Howles CM. Role of LH and FSH in ovarian function. *Mol Cell Endocrinol*. 2000;161(1-2):25-30.
7. Schoot DC, Harlin J, Shoham Z, Mannaerts BM, Lahlou N, Bouchard P, Bennink HJ, Fauser BC. Recombinant human follicle-stimulating hormone and ovarian response in gonadotrophin-deficient women. *Hum Reprod*. 1994;9(7):1237-42.
8. Shoham Z, Smith H, Yeko T, O'Brien F, Hemsey G, O'Dea L. Recombinant LH (lutropin alfa) for the treatment of hypogonadotrophic women with profound LH deficiency: a randomized, double-blind, placebo-controlled, proof-of-efficacy study. *Clin Endocrinol (Oxf)*. 2008;69(3):471-8.
9. Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Morley PM, Stauber PM, Vellas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*. 1997;46(4):410-3.
10. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86(2):724-31.
11. Bunch TJ, Abraham D, Wang S, Meikle AW. Pituitary radiographic abnormalities and clinical correlates of hypogonadism in elderly males presenting with erectile dysfunction. *Aging Male*. 2002;5(1):38-46.
12. Quinton R, Beirne P, Bouloux PM, Stanhope RG, Conway GS. Routine neuroimaging in classical isolated gonadotrophin deficiency is of limited clinical value. *Clin Endocrinol*. 2001;54(1):127-9.
13. Citron JT, Ettinger B, Rubinoff H, Ettinger VM, Minkoff J, Hom F, Kan P, Alloo R. Prevalence of hypothalamic-pituitary imaging abnormalities in impotent men with secondary hypogonadism. *J Urol*. 1996;155(2):529-33.
14. Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation and treatment. *Endocr Rev*. 2001;22(3):342-88.
15. Segraves RT. Effects pf psychotropic drugs on human erection and ejaculation. *Arch Gen Psychiatry*. 1989;46(3):275-84.
16. Groves MD, Lewin VA. Neoplastic disorders; neoplasms. In: Ewans RW, Baskin DS, Yatsu FM, eds, *Prognosis of Neurological Disorders*. New York: Oxford University Press. 2000:429-457.
17. Lue TF. Erectile dysfunction. *N Engl J Med*. 2000;342(24):1802-13.
18. Malarkey WB. Prolactinomas. In: Mazzaferri EL, Samaan NA, eds, *Endocrine Tumors*. Boston: Blackwell Scientific Publications. 1993:124-135.

19. Crotty TB, Scheithauer BW, Young WF Jr, Davis DH, Shaw EG, Miller GM, Burger PC. Papillary craniopharyngioma: a clinicopathological study of 48 cases. *J Neurosurg.* 1995;83(2):206-14.
20. Young WF Jr, Scheithauer BW, Kovacs KT, Horvath E, Davis DH, Randall RV. Gonadotroph adenoma of pituitary gland: a clinicopathologic analysis of 100 cases. *Mayo Clin Proc.* 1996;71(7):649-56.
21. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *N Engl J Med.* 1981;304(3):156-8.
22. Mountcastle RB, Roof BS, Mayfield RK, Mordes DB, Sagel J, Biggs PJ, Rawe SE. Pituitary adenocarcinoma in an acromegalic patient: response to bromocriptine and pituitary testing: a review of the literature on 36 cases of the pituitary carcinoma. *Am J Med Sci.* 1989;298(2):109-18.
23. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med.* 1994;120(10):817-20.
24. Adamson TE, Wiestler OD, Kleihues P, Yaşargil MG. Correlation of clinical and pathological features in surgically treated craniopharyngiomas. *J Neurosurg.* 1990;73(1):12-7.
25. Neelon FA, Goree JA, Lebovitz HE. The primary empty sella: clinical and radiographic characteristics and endocrine function. *Medicine (Baltimore).* 1973;52(1):73-92.