CASE REPORT

Acquired Hypogonadotrophic Hypogonadism and Bipolar Disorder in a Middle-Aged Man: Unresolved and Perplexing Management Issues

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Abstract
A case of acquired hypogonadotropic hypogonadism (AHH) associated with bipolar disorder in a middle-aged man is presented and the unresolved and perplexing management issues are discussed. The area of care in endocrinology is immensely neglected and currently understudied. We hope to attract attention, focused care and perhaps research to look into the etiologic approach for managing such cases with this considerable amount of complexity, which endocrinologists and psychiatrists commonly encounter in their practice.

Key words: Acquired Hypogonadotrophic Hypogonadism; Bipolar disorder; Serum Inhibin B; Bone densitometry

Introduction

Gonadal function is a complex process involving intricate and properly timed relationships between the hypothalamus, the pituitary and the gonads. Systemic disorders are known to cause or are associated with gonadal dysfunction in both males and females (1).

Prevention and treatment of gonadal dysfunction require collaboration between the internist, andrologist, gynecologist and often the psychiatrist (1).

Psychiatric disorders cause alteration in the gonadal function, oligo- or amenorrhea is frequently seen in patients with various psychotic disorders, and is particularly common in schizophrenia (2,3).

This case report aims primarily to illustrate an area of care in endocrinology, which is immensely neglected and currently understudied.

We hope to draw attention, focus care and perhaps stimulate research to elucidate a rational approach for management of similar cases with this considerable amount of complexitywhich are encountered by both endocrinologists and psychiatrists in their respective practices.

Case Report

A 59-year-old man, who has worked previously as design engineer, was diagnosed having depression with bipolar disorder in November 2004. There was a background history of ethanol abuse. He has been followed up in the endocrinology clinic since December 2013, in response to a referral with tiredness, lethargy and erectile dysfunction.

He has unremarkable physical examination with normal secondary sexual characteristics, normal fundoscopy and visual fields. As he was initially found to have low am cortisol level of 95 nmol/l and biochemical picture consistent with secondary hypogonadism, other pituitary axes were tested in the programmed investigations unit and were with satisfactory results.

However, in the course of the investigation, an MRI of the pituitary revealed a 2 mm pituitary microadenoma. Further investigations revealed a normal short synacthen test and normal GH suppression <0.1 mcg/l following glucose load, serum IGF-1 readings were all normal, thyroid function tests, serum prolactin were also normal. Low testosterone, LH and FSH were all documented in May 2013 [serum testosterone 1.5 nmol (9-29), FSH < 1.0 U/L (2.0-12.0), LH <1.0 U/L (2.0-9.0) and PRL 234 mU/L (86-324)]. LHRH stimulation test and serum

Inhibin B level were not checked, eGFR was 80, rest of laboratory investigations were unremarkable.
Repeat pituitary MRI January 2015, though suboptimal study because of patient movement, showed no sellar or suprasellar lesions. His current treatment composed of testosterone gel 3 squirts (30 mg) daily, salmoterol, clenil inhalers, omeprazole, indapamide 2.5 mg, and psychotropic medications. The patient is cared for by his female partner, testosterone level, PSA and FBC monitoring was undertaken during endocrine clinic follow up visits, besides periodic bone densitometry.

Final diagnoses:
Bronchial asthma
Essential arterial hypertension
Isolated hypogonadotrophic hypogonadiam
Pituitary microadenoma (non functioning)

Discussion
There is a paucity of literature on the effect of systemic diseases in general, particularly the bi-directional effect of mental diseases on gonadal function in males.

Prolonged phases of hypoestrogenemia and lowered gonadotropins excretion were documented in psychiatric patients with amenorrhea, suggesting a central cause for their amenorrhea (4). In patients with depressive disorders low level of LH is commonly observed, in anorexia nervosa cases, lowered level of estrogen and gonadotropins is often noted and subnormal response to LHRH stimulation test (1).

In patients with schizophrenia, a major part of the pathogenesis is hypothetically related to the excess of functional dopamine activity. Prolactin has been used as a marker for disordered dopamine function in a number of neurologic disorders (1). Morning serum prolactin levels were studied in newly hospitalized, unmedicated schizophrenic patients (5). No differences were found in prolactin levels in these schizophrenic patients compared to normal (non-hospitalized) controls (5). Slightly less suppression of prolactin after apomorphine was shown in schizophrenic patients compared with controls and there was no significant difference in the effect of L-dopa or prolactin levels in either group. The poor prolactin response seen in chronic schizophrenic patients given apomorphine is consistent with similar inadequate hGH response seen with this drug. (6)

Depressive disorders are commoner in women than in men, there is data linking gonadal disturbance to depression, but only few studies reflecting the status of the hypothalamic-pituitary-gonadal axis in depressed patients (7). Plasma LH levels have been found to be reduced in postmenopausal depressed women compared with controls (8). Klaiber et al. identified in a highly selective group of depressed women who showed estrogen resistance (i.e. estrogen in their case caused less inhibition of monoamine oxidase than did in controls), that they exhibited a favorable antidepressant response when given large doses of estrogen (9). Another group showed no advantage in adding estrogen to the treatment of women with unipolar depression (10). The depression occasionally associated with oral contraceptive pills may be due to estrogen enhancing the capacity for conversion of tryptophan to nicotinic acid ribonucleotide, which may lead to suppression of the alternative metabolic pathway that produces 5-hydroxytryptamine.

Depression has been linked to the development of the galactorrhea-amenorrhea syndrome commonly seen on endocrinology consults (11)

Testosterone treatment can improve symptoms in hypogonadal men with depression. It is also known to induce aggressive behavior hypomania and even mania. When patients with bipolar disorder and hypogonadism present with manic symptoms it is particularly difficult to decide whether testosterone should be discontinued or not during manic phase of the illness (12). This can be difficult management decision, because it is almost impossible to determine whether the patient's manic symptoms are caused by fluctuating levels of testosterone or not. When treating hypogonadal patients with bipolar disorder, which could be potentially, be worsened by testosterone, it would be sensible to prefer daily forms of testosterone, such as gel and patches, as opposed to long acting intramuscular preparations (12).
Osteoporosis occurs in common psychiatric conditions and causes significant morbidity. Many neuroleptic medications can cause hyperprolactinemia, which can then potentially be associated with bone loss. Few reviews have thus far addressed this issue. Misra et al. consolidated information from studies that examined effects of psychiatric conditions and their treatment on bone metabolism (13). Owing to the fact that, significant morbidity is associated with low bone density and many psychiatric conditions may have a negative impact on bone metabolism, bone density evaluation should be considered an integral component of chronic medical care of these disorders, and risk factors should be identified and addressed (13).

Men with AHH have less stamina, decreased libido, erectile dysfunction and strength, and a worsened sense of well being leading to degraded quality of life. The physical examination is usually normal if hypogonadism is of recent onset. Diminished facial, body hair and muscle mass, fine facial wrinkles, gynecomastia, and hypotrophic testes are observed in long-standing and complete AHH. Spermatogenesis is impaired and the volume of ejaculate is decreased only when gonadotropins and testosterone levels are very low. Men with AHH may have normal or low serum LH and FSH concentrations, but normal gonadotropin values are inappropriate when associated with low serum testosterone. In the majority of AHH patients, serum inhibin B is "normal". The decrease of this sertolian hormone indicates a long-standing and severe gonadotropin deficiency. Symptoms, usually associated with significant testosterone deficiency in men with AHH, improve with testosterone replacement therapy (14)

Testosterone therapy is also known to occasionally induce aggressive behavior hypomania and even mania. The psychiatric adverse effects of testosterone are hugely overstated, particularly in reports related to eugonadal men who abuse it (e.g. androgenic anabolic steroid) at relatively high doses.

There are no data to suggest that physiological testosterone replacement in a hypogonadal man carries any risk of aggressive, or risk-taking behavior. There is, however, good evidence that untreated hypogonadism is associated with emotional lability. So if serum LH, FSH and testosterone are found to be low in a (previously

eugonadal) man with acute mania, the reason for not giving testosterone is that his endogenous HPG axis might well recover once he has been psychiatrically stabilized.

Caronia et al. found rare variants in genes associated with idiopathic hypogonadotrophic hypogonadism are found in women with hypothalamic amenorrhea, suggesting that these mutations may contribute to the variable susceptibility of women to the functional changes in GnRH secretion that characterize those cases with hypothalamic amenorrhea (15).

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