Case report

Hypogonadism in an opioid dependent man

Nnamdi Nkire, Michael Doran, John J O'Connor

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Abstract

We describe here the case of a 45-year-old man with a chronic history of heroin abuse who has received methadone maintenance therapy for 12 years. At admission, on this occasion, for stabilisation on methadone, he reported a two-year history of painful gynaecomastia and testicular atrophy. Investigations revealed abnormal sex hormone levels. Liver function tests, thyroid function tests, Brain (pituitary) MRI and viral screens were normal. Following assessment and abnormality in two morning total testosterone level measurements he was diagnosed with hypogonadism secondary to opioid use. Although he had a previous history of alcohol abuse, he was abstinent from alcohol use for five years at time of assessment. He was commenced on parenteral testosterone replacement with therapeutic benefit.

In light of the increased use of opioids, it is important to recognise and manage the endocrine complications of opioid use. The need for an empathic and adequate sexual history, physical examination and investigation is essential in patients who use opioids to ensure that cases of hormonal dysfunction are detected early and managed appropriately.

Key words: Endocrine; Hypogonadism; Opioids; Gynaecomastia; Testosterone.

Introduction

The hypothalamic-pituitary system regulates the secretion of gonadal hormones. Gonadotropin releasing hormone (GNRH) is produced by the hypothalamus. This acts on the pituitary, causing it to secrete leuteinising hormone (LH) and follicular stimulating hormone (FSH) which in turn acts on the gonads causing the release of sex hormones, testosterone or oestrogen. The sex hormones feed back to the hypothalamus and pituitary in a negative feedback system, to form a complete loop. The sex hormones facilitate and support normal sexual and reproductive growth/function.

External factors may also act on the hypothalamo-pituitary system to modulate its effects. These external factors include drugs, infections, trauma and radiation. Drugs such as opioids can have direct or indirect effects by binding to opioid receptors at any point in the pathway of the hypothalamo-pituitary-gonadal system, thereby causing disruption to the release of sex hormones.[1-6] The effects of opioids on the endocrine system of laboratory animals and humans have been demonstrated by various researchers.[7-9] They cause increased pituitary release of prolactin in preclinical studies, although this is generally not evident in clinical studies.[10] Some studies have reported that in heroin addicts, testosterone levels are decreased in males, with a decrease in LH and/or FSH consistent with central hypogonadism;[11] levels returned to normal within a month of cessation of heroin use.[12] The symptoms and signs of hypogonadism are widely documented and include loss of libido, impotence, infertility, depression, anxiety, loss of muscle mass and strength, fatigue, galactorrhoea, osteoporosis and fractures. Opioids may also cause decreased cortisol and growth hormone levels but appear to have no effect on the thyroid.

Case report

Mr X, a 45-year-old single mechanic, started smoking heroin at the age of 12 years. By age 16 years he had become opioid dependent. He denied any previous intravenous use of opioids. At age 20 years he was diagnosed with hepatitis C. He underwent treatment with interferon and ribavirin. During the same period he underwent detoxification for opioids. He reported that he had remained abstinent from opioid use until age 27 years when he relapsed into street heroin use. However, we were unable to confirm the veracity of this report as he had resided outside of Ireland at the time. At age 28 years he sought treatment at the Drug Treatment Centre Board for opioid use and was commenced on methadone maintenance therapy (MMT). His engagement with treatment was erratic at the outset but in recent times was more stable. However, he continued to use heroin sporadically.

Mr X had a history of heavy use of alcohol and met criteria for alcohol dependence in his 20s and 30s. However, for the past five years he has remained abstinent from alcohol use (as confirmed by regular supervised breathe alcohol tests) following a near fatal road traffic accident. He had experimented with cannabis and used cocaine recreationally in the past. He denied use of benzodiazepines. He was diagnosed with bronchiectasis three years ago. He attends a respiratory clinic at a tertiary hospital for regular reviews and continues management with good service engagement. He was prescribed no medication with an effect on the endocrine system.

He is the second of a sibship of five and currently lives with his mother. His sexual development was normal with no difficulties relating and interacting with the opposite sex. His first intimate relationship with a female was in his mid-teens. He had difficulties with reading and writing and left school at age 16 to train as a mechanic.

***Nnamdi Nkire**, Senior Registrar at Our Lady's Hospital Navan, Ireland. Email: nnkire@yahoo.com
Michael Doran, Senior Registrar, **John J O'Connor**, Consultant Psychiatrist/Clinical Director, The Drug Treatment Centre Board, McCarthy Centre, 30-31 Pearse Street, Dublin 2, Ireland.
**Correspondence*

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In January 2009, his drug use destabilised and his urine tests remained consistently positive for opioids. He was admitted to an inpatient unit for stabilisation in March 2009. At time of assessment for admission, he was smoking one bag of heroin (€20 worth) daily, in addition to daily supervised dispensing of 80mg of methadone. At assessment he described bilateral painful swelling of his breast of two years duration, initially commencing in his left breast, which he first noticed while working. There was associated discharge on expression. The swelling of the right breast was noticed a week after the left. These symptoms were initially reported to his general practitioner, but were not investigated further as they were attributed to 'worry' and past alcohol misuse. According to Mr X, he subsequently failed to report his symptoms at the methadone clinic in the intervening period for fear of stigmatisation, despite being preoccupied with thoughts that he may have developed breast cancer.

Furthermore, he had slow re-growth of facial hair after shaving. He had previously shaved daily but at time of assessment, his frequency of shaving was once every fortnight without apparent re-growth of facial hair. He admitted decreased sexual drive with difficulties producing and maintaining penile erection. This resulted in relationship difficulties and subsequent separation from his long-term girlfriend, who had accused him of having an affair due to his sexual dysfunction and decreased libido. He has not been involved in any relationships for the past two years.

He reported his testes appearing to shrink in size over the past two years. He denied any associated headaches, blurred vision, vomiting, cardiac difficulties, bone pain or fractures. However, he was easily fatigued though he continued to work as a motor mechanic. There was no history of similar symptoms in other family members and he had no significant psychiatric difficulties.

On physical assessment, he presented as an obese man with effeminate stature, sparsely distributed facial hair growth, anicteric, acyanosed and no pallor or clubbing. He had bilateral gynaecomastia, with associated tenderness and expressed galactorrhoea. In addition, he had testicular atrophy.

The result of his initial investigations *(see Table 1)* included abnormal sex hormone levels including low serum total testosterone (two morning samples); brain (pituitary) MRI, ECG, and bone mineral studies indicated no abnormalities. His LFTs were normal and he tested negative for HIV and active hepatitis C infection, although he remained positive for HCV antibodies.

He was referred to and assessed by a consultant endocrinologist who diagnosed hypothalamic hypogonadism secondary to opioid use in the absence of a pituitary tumour or other causes for this diagnosis *(see Table 2)*.

Following a month of inpatient stabilisation (where he received counselling and education regarding the effects of opioids on the endocrine system), and a further period of stable urines as an outpatient totalling three months, Mr X was commenced on testosterone replacement therapy by intramuscular injection every three months with reported improvement in symptoms that included increased libido, erectile function and gradually decreasing gynaecomastia without full resolution and normalising hormone levels as at time of writing this report.

Table 1: Results of investigations

Hormones	Result	Reference range
Sex hormones		
FSH	0.9IU/L	1-12IU/L
Oestradiol	87pmol/L	73-173pmol/L
Prolactin	598.6pmol/L	112.4-567.9pmol/L
Testosterone	0.8nmol/L	10.3-34.5nmol/L
LH	Less than 0.2IU/L	1-9IU/L
Thyroid function test		
Free T4	8.6pmol/L	7-16pmol/L
Other tests		
Ferritin	224.7pmol/L	35.9-483.1pmol/L
Amylase	54IU/L	0-90IU/L
GGT	44IU/L	0-58IU/L

Table 2: Causes of central hypogonadism

- Idiopathic gonadotropin or gonadotropin releasing hormone deficiency
- Trauma
- Radiation
- Tumours
- Pituitary hypothalamic injury
- Drugs, eg. opioids, steroids

Discussion

Hypogonadism denotes a defect in the reproductive system that results from decreased functional activity of the gonads with retardation of growth of sexual development and secondary sex characteristics.[13] Hypogonadism can be primary, ie. defect inherent to the gonads or secondary, due to inhibition of FSH or LH by factors external to the gonads. It can also be classified as congenital or acquired. Clinicians distinguish primary from secondary hypogonadism by measuring gonadotropins (LH and FSH). In secondary hypogonadism, LH and/or FSH are normal or low (hypogonadotrophic hypogonadism), while in primary hypogonadism they are usually elevated, showing that the problem is testicular. The patient presented low LH and near normal FSH, which on further investigations and in the absence of other causes suggested hypogonadotrophic hypogonadism.

Hypogonadism has a higher prevalence amongst patients with type 2 diabetes, obesity, chronic obstructive lung disease and coronary heart disease.[14] Some authors report that opioid-induced androgen deficiency has become one of the most common causes of testosterone deficiency among men in many communities, yet this is frequently overlooked.[15] It is found in men who are prescribed long-acting opioid preparations on a chronic basis. A similar but less well-defined disorder has been reported in women.[16] Our patient was obese with a history of bronchiectasis and chronic opioid use. These factors may have contributed in his development of hypogonadism.

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The diagnosis of hypogonadism is an easy one in the presence of a history of decrease in libido, decrease in energy, impotence, infertility, change in menstrual function, loss of sexual hair, loss of muscle mass, depression/anxiety and decreased bone density with subsequent fractures, amongst other symptoms. These may occur over months to years in the presence of low levels of testosterone, commonly defined as total testosterone less than 8nmol/L (17) or < 300ng/dL in men.[18]

Whether these abnormalities are opioid-induced, or not, is a matter of excluding other possible causes of hypogonadism by appropriate history and investigation. Laboratory studies include total testosterone, free testosterone, oestradiol, LH, FSH. Serum ferritin measurement may help exclude haemochromatosis which is an important cause of hypogonadotrophic hypogonadism. Brain MRI examining the pituitary and surrounding structures may be helpful to rule out hypothalamo-pituitary tumours. Hypogonadism in men has been associated with an increased mortality[19] as it can lead to complications including fractures. It is necessary therefore to monitor bone mineral density in at-risk patients, as fractures can occur with no other symptoms of hypogonadism.

Note that fear of stigmatisation is an important component of the process of feminisation or masculinisation of clients with hypogonadism. Patients worry about how others will view them. This may lead to affective symptoms, including depression and anxiety. Mr X kept concerns about his testicular atrophy to himself, even in the face of an inherent fear that his enlarged breasts may have been due to malignancy. However he did not develop any clinically significant affective symptoms.

Management

Accurate diagnosis is of importance. This may require a specialist endocrinologist but there is a need for physicians prescribing opioids to be able to identify symptoms of hypogonadism. Diagnosis may be achieved through frequent reviews/assessments of patients prescribed opioids, specifically asking for and looking for symptoms of hypogonadism. It should be borne in mind that because of the stigma attached to feminisation or masculinisation, some patients may be reluctant to disclose symptoms to their doctors. These assessments should be done in an empathic and sensitive manner. Informing patients of the diagnosis and reassurance is a logical next step, as it puts the patients mind at rest and eases their concerns with the knowledge that the condition is treatable.

Following the confirmation of diagnosis, treatment options involve stopping opioids (if possible) or strategies that allow opioid rotation (eg. buprenorphine) or opioid dose reduction.[18] In addition, testosterone supplementation may be considered. This supplementation may be in the form of intramuscular injections, transdermal patches or gels. Prior to commencing testosterone supplementation the issue of continued abuse of opioids should be addressed with the patient.

It needs to be noted that treatment with androgens for this indication is still controversial and not universally accepted.[17] It is important to monitor prostatic specific antigen (PSA) and other clinical and laboratory tests when androgen supplementation is implemented. Side-effects associated with androgen supplementation in males include oligospermia, priapism, male pattern baldness, polycythaemia, sleep apnoea and misuse.

Androgen supplementation has the potential for stimulating the growth of the prostate gland leading to enlargement. However, studies have found no strong association between testosterone blood levels and prostatic neoplasm.[20] It is advised that patients must be monitored with digital examination of the prostate per rectum and annual PSA measurement. It is also advised that serum lipids are monitored even though there is no specific evidence linking testosterone supplementation and clinically significant lipid abnormalities.[18]

Conclusions

Hypogonadism in opioid-dependent individuals may be common. It poses a challenge in patient care as more patients are prescribed opioids for addiction and pain management; and indeed more over-the-counter analgesics have opioids as an essential ingredient. It is important that psychiatrists and other physicians are aware of this condition and are proactive in identifying and liaising with endocrinologists in its management. This will ensure that patient care is optimised and that patients are not stigmatised iatrogenically. Opioid-dependent patients diagnosed with hypogonadism should be commenced on appropriate treatment and should be monitored for potential risks and benefit of that treatment.

Declaration of interest: None.

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