ERECTILE DYSFUNCTION WITH HYPOGONADISM SECONDARY TO POST-PITUITARY ADENOMECTOMY: ACASE REPORT AND MINI-REVIEW

Haris Cakrasana [1], Reny I'tishom [2], William William [1,3]

[1] Department of Andrology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General-Academic Hospital
[2] Department of Biomedical Science, Faculty of Medicine, Universitas Airlangga
[3] Department of Medical Biology, Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia

ABSTRACT

Erectile dysfunction is one of the symptoms that arise from several causative factors. Treatment of sexual dysfunction requires a comprehensive multi-disciplinary science of all the risk factors that cause it. In the case of post pituitary adenomectomy, intervention in the pituitary dramatically affects all the hormones produced by the pituitary. Hormone replacement therapy is required to maintain hormone levels within physiological limits. Sexual function is sometimes not a priority of therapy after surgery. Here, we present a A 58-year-old man with complaints of decreased erection after surgical removal of a pituitary macroadenoma.(History post-operation pan-hypopituitary and treated with thyroid, glucocorticoid replacement therapy. Internist consulting for testosterone replacement therapy and erectile dysfunction, and premature ejaculation. (IIEF-5) score 5 with severe ED, EHS score 1, PEDT score was 14 (Premature ejaculation), absence of NPT. Receiving some testosterone replacement therapy but not regularly and sometimes get PDE5 inhibitor. This case report concludes that erectile dysfunction caused by secondary hypogonadism, testosterone therapy, and PDE5 inhibitors had a better effect than a single therapy alone. Testosterone helps the formation of nitric oxide and PDE 5, which functions for the erection process.

Keywords: Erectile Dysfunction, Male Sexual Impotence, Hypogonadism, Panhypopituitarism, Pituitary Insufficiency

1. INTRODUCTION

The World Health Organization states that "Sexual health is fundamental to the physical and emotional health and well-being of individuals, couples and families, and communities and countries' social and economic development.".[1] From this definition, sexual health is vital to be maintained by every individual. However, the increasing public awareness of the health of sexual function makes more and more sexual health problems exposed in the community.

The most common sexual health problem is erectile dysfunction (ED) or impotence. ED is defined as an inability to achieve or maintain an erection sufficient for satisfactory sexual performance for a minimum of 6 consecutive months. [2] Prevalence of ED was 3-76.5% of men and related to age. [3] Erectile dysfunction may be a symptom of some pathologies and an "alarm" indication of the risk of cardiovascular disease. [4] ED is closely related to metabolic conditions like cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension. However, in rare cases, ED can also be caused by certain conditions, such as panhypopituitarism. This article will discuss a case of ED due to panhypopituitarism that occurred after a pituitary adenomectomy procedure.

2. CASE PRESENTATION

A 58-year-old male patient was consulted to the Andrology Outpatient Department of Internal Medicine with the chief complaint of a gradual decrease in erectile strength, especially after surgery. At this time, the strength of his erection can only be enlarged but not strong enough for vaginal penetration. The patient explained that this complaint began to appear after undergoing surgery to remove a pituitary adenoma six years ago. Initially, the patient complained of severe pain in the head accompanied by narrowed vision without any increase or decrease in libido. The patient was diagnosed with pituitary macroadenoma and planned for four pituitary adenomectomy in two years. Four years after surgery, the patient was diagnosed with panhypopituitarism and was taking methylprednisolone, calcium lactate, levothyroxine,

After the third operation, the patient started to feel decreased erection strength. He had sought treatment and was given Sildenafil on demand and a short-acting testosterone injection. Patients say the strength of the erection can increase again so that can penetrate the vagina during sexual intercourse. However, three months later, the patient felt his libido decreased, and the frequency of coitus reduced to once every two weeks from the previous two times per week. Due to difficulty maintaining an erection, ejaculation is also felt came faster for about 1 minute or less.

The patient has been married for 33 years and has three children. The patient said he was still sexually attracted to his wife. So far, there are no psychological problems with the wife, and the wife is always willing to have sexual intercourse. Assessment of erectile function using the International Index Erectile Function 5 (IIEF-5) questionnaire resulted in a score of 5, which is classified as severe erectile dysfunction. On further assessment using the Premature Ejaculation Diagnostic Tool (PEDT) and Partial Androgen Deficiency Score (PADAM) questionnaires, it was found that the patient had premature ejaculation and was positive for PADAM.

On physical examination, vital signs were found within normal limits. The patient's weight and height were 63 kg and 164 cm, with a BMI of 23.4 kg/m2 (overweight according to the Asia-Pacific classification). Examination of the external genitalia was within

normal limits, with a penis length of 10 cm and a penis diameter of 8 cm. The testicles were palpable within normal limits with a volume of 10ml/10ml and spongy consistency.

Subsequently, laboratory tests were carried out with the results of TSH = 0.724 (0.3-4 mU/L), FT4 = 1.19 (0.7-2.1 ng/dL) , Cortisol: 0.63 (3.95-27.23 g/dL), Testosterone = 266.67 (300-1000 ng/dL), PSA = 0.33 (<3.5 ng/ml). Our patient was diagnosed with concomitant erectile dysfunction of premature ejaculation due to panhypopituitarism post-pituitary adenomectomy. The patient was then treated with Sildenafil on demand.

Two months after that, the complaint was still the same, unable to get an erection, EHS: 1 NPT;-, Testosterone = 217.95, PSA = 0.33 on therapy with Sildenafil on demand, Tadalafil daily, and short-acting testosterone injection. After that, the patient did not return to the andrology out clinic for one year and four months, and when he claimed to have received a testosterone injection, the patient forgot the time of the injection. When he arrived, the patient still complained of not being able to get an erection, EHS: 1, NPT:-, Testosterone: 327.9 ng/dL, treated with Sildenafil on demand, Tadalafil daily, and short-acting testosterone injection. Follow-up 3 months later, the patient got an erection, and EHS reached 2-3 with Sildenafil, NPT: - with Testosterone level = 546.54 ng/dL treated with Tadalafil daily and short-acting testosterone injection. Follow-up 2 months later, stronger erection with EHS 3, NPT: + with testosterone levels: 650 and treated with daily Tadalafil and short-acting testosterone injections. Follow-up for the next two months, maximum erection hardness, EHS: 4, NPT:+, testosterone level: 1132 ng/dL, treated with daily Tadalafil. Follow-up 1 month later, erectile hardness sometimes decreased EHS:3-4, NPT:+, testosterone levels: 549.62 ng/dL, treated with daily Tadalafil. Follow-up 1 month later, erectile hardness decreased EHS:3, NPT:+, testosterone level=724.74 ng/dL, treated with daily Tadalafil. Follow-up 1 month later, erectile hardness increased EHS: 4, NPT:+, testosterone levels=725.96 and treated with daily tadalafil. The patient could not be contacted and had never been to an andrology clinic again.

Table 1. Hormonal Profile

Testosterone Injection		**Start**				**Stop**			
TSH	0.724	0.292	1.009	1.61	0.742	0.494	0.822	1,482	0.889
Testosterone	266.67	327.9	546.54	524	650	1132	549.62	724.74	725.96
Cortisol	0.63	0.80	0.75	0.68	1.1	0.71	0.68	0.65	14.45
FT4	1.19	1.27	1.33	1.15	1.16	1.29	1.12	1.10	0.97

3. DISCUSSION

Erectile dysfunction (ED) is the inability to achieve or maintain an erection that lasts at least six months [2]. Erectile dysfunction can be caused by various causes, such as arteriogenic, neurogenic, psychological, and endocrinological. The hypothalamic-pituitary-gonadal axis (HPG axis) plays a vital role in erectile function. Impaired hormone secretion from the pituitary can interfere with the maximum erection. The pituitary is divided into two, namely the anterior and posterior areas. The anterior pituitary (adenohypophysis) secretes TSH, ACTH, gonadotropins (FSH and LH), GH, and prolactin, while the posterior segment (neurohypophysis) produces oxytocin and vasopressin. Some of these hormones have an essential role in the mechanism of erection.

Growth Hormone has a synergistic role with androgens, where testosterone secretion will affect GH production. GH will stimulate IGF1 [5]. GH also plays a role in maintaining erection strength by stimulating the effects of cyclic guanosine monophosphate (cGMP) on the corpus cavernosa smooth muscle [6]. In addition, GH/IGF-1 plays a role in regenerating NO by forming angiogenesis in blood vessels [7, 8]. ACTH plays a role in the production of dopamine and serotonin. Dopamine acts as a neurotransmitter in the MPOA and paraventricular nucleus to autonomic and somatic nerves in the lumbosacral area. Stimulation of an erection by stimulation of the central nervous system and spinal cord requires adequate dopamine levels. Meanwhile, serotonin plays a role in the spinal cord as a signaling mediator from sympathetic and parasympathetic that plays a role in the mechanism of erection [9]. ACTH also affects the production of melanocyte-stimulating hormone (MSH), which plays a role in erection, although the exact mechanism is still unknown. Subcutaneous injection of MSH analog (Melanotan II) gives erection effect in psychogenic ED patients [10]

Cortisol, along with Testosterone, works to maintain the function of nNOS in the penis to produce Nitric Oxide, which plays a role in erection [11]. In patients with Addison's disease, administration of the hormone cortisol can improve sexual function, especially erection. Cortisol replacement therapy such as mineral corticoid cannot be concluded will give the same result as the administration of the hormone cortisol [12]. TSH plays a role in producing thyroid, where the Thyroid can reduce the bioavailability of Testosterone by increasing levels of SHBG, which will bind to Testosterone, which will reduce Free Testosterone which has high bioavailability. The Thyroid also functions in the erection process, where a lack of Thyroid can cause a drastically decreased PDE1 and PDE-5 response [13]. Oxytocin acts on the supraoptic and paraventricular nuclei of the hypothalamus to induce autonomic nerves in the sacral [14]. Oxytocin plays a role in inducing early erection because the effect of oxytocin on the sacral preganglionic nerves to stimulate an erection is more potent than somatic stimulation [15].

On the hypogonadal axis, FSH production affects Sertoli cells to help the process of spermatogenesis, while LH will influence Leydig cells to produce testosterone. Testosterone has several essential roles in adults, such as increasing libido, muscle mass growth, erythropoietin formation, and erectile function of the penis. Testosterone will help increase the production of Nitric Oxide, which plays a role in erection. Although slow-growing and benign, Pituitary adenomas can cause problems with the HPG axis [16]. Most pituitary adenomas are macroadenomas, and more than 50% of patients have increased prolactin production, while others are non-functional [17, 18]. Several symptoms that can appear include headaches, visual disturbances, and hyperproduction or hypoproduction of pituitary hormones. As found in our case, visual disturbances are an effect of compression of the optic chiasm. An enlarged tumor can also press on other brain parts and cause headaches [19].

Management of pituitary macroadenoma is surgery, plus medical and radiation therapy. Transsphenoidal surgery is the first-line therapy for functional and non-functional pituitary adenomas [20, 21]. One common effect of surgery is hypopituitarism. In this case, the patient underwent transsphenoidal surgery, and panhypopituitarism occurred. The evaluation of this case is the evaluation of the

thyroid axis, ACTH axis, growth hormone axis, and gonadal axis [22]. In this case, the priority axis is the thyroid, ACTH, and the gonadal axis.

In this case, the pituitary function is still secreting hormones but not enough for body functions, so appropriate therapy is given for the impaired function such as thyroid gave levothyroxine, ACTH cortisol levels are monitored with mineralocorticoids administration. Meanwhile, the gonadal axis is given with testosterone hormone replacement therapy. Axis growth hormone was not examined because of budget constraints in the examination and therapy carried out. In table 1, it can be seen that the testosterone hormone profile is very influential in the clinical patient, where low testosterone levels cause severe erectile dysfunction symptoms in patients, and after giving testosterone replacement therapy and testosterone levels have increased, these complaints begin to be resolved. Another concern is that increased cortisol can affect the patient's erection, where increased cortisol levels can provide improved erectile quality at testosterone levels which are almost the same as 725.96 and 724.724. In this case, single therapy with a PDE-5 inhibitor at low testosterone did not give significant results. There is a correlation between erection and the testosterone hormone.

Psychogenic stimulation of the central nervous system controls the sympathetic and parasympathetic systems of the penis. Sensory stimulation of the penis initiates or maintains the erectile reflex. Parasympathetic induce the release of acetylcholine (ACTH) into endothelial cells. Endothelial cells release endothelial Nitric oxide (e-NOS) from L-Arginine and Oxygen (O2). NOS induces Guanylyl cyclase to convert GTP to cGMP. In addition to having other mechanisms in smooth muscle, activation of G protein induces Adenylyl cyclase to convert ATP to cAMP. cGMP or cAMP induces specific protein kinases to open potassium channels and induce relaxation of trabecular smooth muscle, dilating the corkscrew arteries of the penis, resulting in entrapped blood and compressed venules [23]. PDE5 inhibitors prevent cGMP from converting to 5 GMP. Other PDE 2,3,4 inhibitors prevent cAMP from converting to 5AMP leading to relaxation of penile smooth muscle arterioles.

First-line therapy for ED is a PDE 5 inhibitor, but 23-50% does not fully respond to this therapy, particularly when the testosterone with testosterone levels <340 ng/dL. After therapy with testosterone and PDE 5 inhibitors for 1-3 months had better progress [23]. Normal physiological serum testosterone 450-600 ng/dL. Indications for testosterone replacement therapy are serum testosterone levels <350ng/dl [24]. Testosterone plays a role in increasing the release of the NOS gene to produce Nitric oxide; besides that, testosterone increases the production of PDE5, which is the effect of increasing NO [22]. In the Tirabassi study, patients with postoperative transsphenoidal hypopituitary-hypogonadism who received testosterone replacement therapy increased IGF1 and improved erection due to a suspected shortening of the Androgen receptor CAG gene [25].

4. CONCLUSION

Erectile dysfunction is a disorder that is not life-threatening but can impair the quality of life. The causes of ED are multifactorial, ranging from vascular, neurological, psychological, and hormonal. First-line therapy for ED is PDE 5 inhibitors, but not all cases of ED can be resolved with PDE 5 inhibitors. In cases of secondary hypogonadism caused by a postoperative pituitary macroadenoma, the pituitary gland cannot produce enough hormones and requires hormone replacement therapy. Testosterone induces the production of Nitric Oxide and PDE 5. Combination therapy of PDE5 and Testosterone inhibitors can give better results in patients with erectile dysfunction. An increase in cortisol levels to normal also affects better erection quality.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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