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Case Report

Erectile Dysfunction in Man with Hyperprolactinemia, Obesity, and Genetic Abnormality 46XYinv(9)(p11q13)

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Abstract

The ability to have normal sexual function is a measure of overall health and well-being. Erectile dysfunction and loss of libido both have a negative impact on overall quality of life. The purpose of this study is to gain an understanding of the challenges that are associated with sexual function in men who have genetic abnormalities and find solutions to those challenges. A 32-year-old patient was examined for sperm analysis. Morning erections were uncommon. No history of measles or orchitis and puberty at age 15; no history of measles or orchitis. The physical examination revealed the subject's height to be 180 cm, weight to be 100 kg, and arm spread to be 186 cm. The waist measurement was 104 cm. Each testicle measured 4 cc and had a mushy consistency. The penis measured 8 cm. Analysis of sperm revealed azoospermia. The results of the cytogenetic analysis were 46XY inv(9)(p11q13), LH 11.92 mIU/ml, and FSH 30.29 mIU/ml. His hyperprolactinemia was measured at 25.89 ng/ml, estradiol at 16 pg/ml, and total testosterone at 2.33 ng/ml. HbA1c 5,9 %. The patient was treated 0.25 mg cabergoline and 2.5 mg letrozole. At least four morning erections occur each week after two months. He weighed 94 kg and had a 99 cm waist circumference. Both testicles were 5 cc in size. LH was 7.89 mIU/ml, FSH was 14.53 mIU/ml, prolactin was 15.00 ng/ml, estradiol was 10 pg/ml, and total testosterone was 1.69 ng/ml. The therapy is still in progress. The treatment of erectile dysfunction demands an interdisciplinary approach. The most important are risk factor management and healthy lifestyle. In this instance, medication has improved erectile function, hormonal equilibrium, and well-being. The objective of treating erectile dysfunction is not only sexual happiness but also an improvement in quality of life.

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1. Introduction

Erectile function is one of many symptoms that can cause problems for both the person experiencing it and the relationship with a partner. The causes of erectile problems can be caused by impaired vasculogenic, endocrinopathy, hormonal imbalance, neurogenic, trauma, iatrogenic and also due to psychological causes. Management of erectile dysfunction requires a comprehensive and multidisciplinary study of each of the risk factors.[1,2]

There are many factors that worsen the condition, obesity, diabetes and in rare cases hyperprolactinemia.[3,4] Although endocrinopathy is a rare cause of erectile dysfunction, it is necessary to evaluate prolactin as well. Obtaining serum testosterone and prolactin with or without thyroid hormone profile has been advised as a cost-effective screening to identify those cases.[4] Hyperprolactinemia leads to increased expression of tyrosine hydrosilase mRNA region in hypothalamus associated with erectile and sexual function.[5]

One third of men with obesity or type 2 diabetes have subnormal free testosteron concentration. Total testosteron serum were 25-32% lower in obese men in comparison to normal weight men and estradiol were 6% higher in obese men.[6] Obesity related comorbidities contribute to impairment of nitric oxide synthesis in vascular bed, reduced testosterone level, alter endothelial function and increase dyslipidemia.[7]

Genetic abnormality of pericentric inversion in chromosome 9 is common in 1-3 population. Despite being categorized as minor chromosomal arrangement, it has also been reported with various abnormality such as congenital genital malformation, mental retardation, undescensus testis, habitual abortus and cardiac defect and subfertility has also been reported.[8,9] This kind of inversion could cause silent or mild problem in some cases but it needs further investigation especially for the risk of chromosomal instability, congenital problem and certain cancers.[9]

2. Case

A patient who was 32 years old and was going to get married in the near future presented himself for a sperm analysis examination. Although the patient did not report any sexual issues at the beginning of the treatment, he did disclose that he had never been particularly interested in sexual matters since he was a young adult. As an adult, having a low libido may be the result of being overly preoccupied with professional responsibilities. Erections during the night and in the morning were an unusual occurrence. Patient went through puberty at the age of 15 and was currently in a relationship with a woman. He was also making plans to be married, which led him to believe that his libido was healthy at this point. There were no severe visual disturbances or visual field disturbances. EHS 2.

The results of the physical examination revealed that the individual's height was 180 centimeters, their weight was 100 kilograms, and their arm spread was 186 centimeters. 104 centimeters in circumference at the waist. The results of the other physical exams were within the usual range. The man's testicles measured 4 cc on each side, and their substance was described as being soft. The examination of his genitalia revealed this information. Penis measuring 8 centimeters in circumference when stretched. There were no serious issues with either the vision or the visual field. EHS 2. Sperm analysis showed azoospermia. Cytogenetic examination showed 46XY inv(9)(p11q13) and no Klinefelter syndrome was found.

Hormone examination results showed LH 11.92 mIU/ml, FSH 30.29 mIU/ml, prolactin 25.89 ng/ml, estradiol 16 pg/ml and total testosterone 2.33 ng/ml. HbA1c 5,9 %. Normal total testosterone level is 2,8-8,0 ng/ml. His testosterone was below normal level and it could be considered as hypogonadism.

The patient was treated with cabergoline 0.25 mg 3 times a week and letrozole 2.5 mg once a day for 2 months. After two months have passed, there is an increase in sexual arousal, morning erections occur at least 4 days a week, erections begin to improve. weight 94 kg, arm span 186 cm. waist circumference 99 cm. Other physical examinations were within normal limits. One of the result of physycal examination can be seen in Figure 1. Examination of the genitalia showed testicle size of 5 cc right and 5 cc left with soft consistency. EHS 3.

Recent investigations showed LH 7.89 mIU/ml, FSH 14.53 mIU/ml, prolactin 15.00 ng/ml, estradiol 10 pg/ml and total testosterone 1.69 ng/ml. Comparison of hormonal examination can be seen in Table 1. Until now, evaluation and treatment is still ongoing. For the next visit, we suggest metformin, phosphodiesterase 5 inhibitor, and hormonal therapy using gonadotropin. Our patient has also visit nutrition specialist and do nutrigenomic test to ensure that he had a good nutrition that will support his well being.

Table 1. Hormonal Examination and Monitoring

Hormone (Normal Value)	July 2022	September 2022
LH (0,57-12,07 mIU/ml)	11,92	7,89
FSH (0,95-11,95mIU/ml)	30,29	14,53
Prolactine (4,04-15,02ng/ml)	25,89	15,00
Estradiol (11-44pg/ml)	16	10
Total testosterone (2,8-8,0 ng/ml)	2,33	1,69

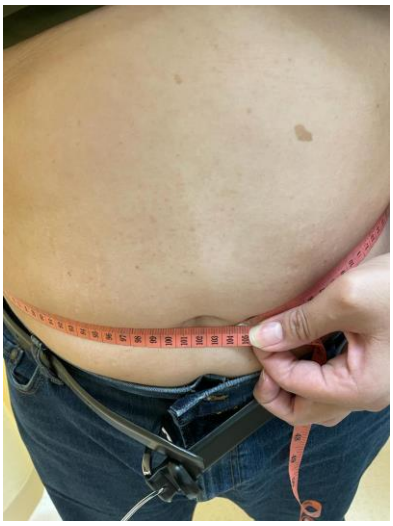

Figure 1. Waist Circumference

3. Discussion

At the beginning, our patientbcame to the clinic to check his fertility status. We suggested him to undergo sperm analysis. The result was azoospermia. Then we continued to physical examination and it revealed that he was obese and his testicules volume were below normal. Later we knew that the libido and erection were not good either. We went to further step and did the hormonal examination. The result can be sees in table 1. Also we asked him to undergo karyotyping because we suspected it was Klinefelter. However we got the result 46 XY inv(9)(p11q13).
In this case, there are several things that cause erectile dysfunction and infertility:
1. Hypogonadism
2. Hyperprolactin
3. Obesity
4. Genetic disorders

This is a unique case because patient did not pay attention to his erection and libido as well. He always been in a relationship and never try sexual activity at all. Now he want to get married and the main reason to go to the clinic is the fertility awareness. He became fully aware about his weak erection when we showed Erection Hardness Score tools.[10,11] There is another tools to evaluate quality of erection by using International Index of Erectile Function (IIEF) but in this case it was hard to perform since our patient has not engage in any sexual activity at all.[12]

Erectile dysfunction is the inability to achieve and maintain an erection and it last for at least 6 months. Erectile dysfunction can be caused by various problems such as arteriogenic, neurogenic, psychological and endocrine.[13] And in this case, the main cause of erectile dysfunction is strongly because of endocrine problems or hypogonadism.

Male hypogonadism is a clinical syndrome characterized by impaired testicular function with reduced or absent spermatogenesis and testosterine secretion. It is cause by diseases at the level of hypothalamus or pituitary gland or an intrinsic defect of the testes themselves.[14] Our patients was below normal level and he also showed clinical symptoms so that he was included in hypogonadism and he has high LH and FSH, it was strongly suspected that this is primary hypogonadism or testicular failure. It is not clear why do this happened because there was no history of mumps or orchitis or even gonadotoxic medication. Therefore we need to seek other possibilities. During treatment, our patient showed a positive and enthusiastic attitude and sometimes go to far with the diet causing sudden changes which can also affect testosteron.

The role of the hypothalamic-pituitary axis plays an important role in maintaining erectile function. The pituitary consists of two parts, namely the anterior pituitary and the posterior pituitary. The anterior pituitary produces thyroid stimulating hormone, growth hormone, gonadotropins, prolactin and the posterior pituitary produces oxytocin and vasopressin. All of these hormones work in synergism to support sexual function.[15]

Hyperprolactinemia is actually a rare case but needs attention because if it occurs then sexual function can be very disturbed. Hyperprolactinemia can interfere with the hypothalamic-pituitary-gonadal axis and disrupt the secretion of gonadotropins, resulting in decreased testosterone production and decreased sexual function. Hyperprolactinemia leads to increased expression of tyrosine hydrosilase mRNA region in hypothalamus associated with erectile and sexual function.[5] If hyperprolactinemia is treated then if testosterone levels return to normal then erectile function will usually gradually

improve, but if not, we need to look for other causes of erectile dysfunction. Management of hyperprolactinemia is by evaluating the cause of this hyperprolactinemia, which can be caused by drugs such as amitriptyline, amphetamines, cimetidine, dopamine antagonists, estrogens, levodopa, opiates, morphine, phenothiazide, metoclopramide and chlorpromazine. If there is no history of taking the drug, it is necessary to evaluate the prolactin level. If it reaches a very high level beyond the maximum level then a head MRI is recommended. In addition, hyperprolactin can be treated with dopamine agonists such as bromocriptine and cabergoline because dopamine from the hypothalamus inhibits the secretion of the hormone prolactin from the anterior pituitary by releasing Prolactin inhibitory factor (PIF).[16] Bromocriptine normalizes prolactin and decreases tumor size in 80-90 % cases of microadenoma but it has unpleasant adverse effect such as nausea, headache and fatique, The more sensitive dopamin receptor agonist, cabergoline is more effective and better tolerate. It was the reason why we choose cabergoline as therapy for this patient.[17] A case report in 2015 reported about a patient that have hyperprolactinemia caused by adenoma and did not recover erectile function.[5] Due to this fact, we thought we have to pay attention to another risk factor of erectile dysfunction and not rely on cabergoline only.

Obesity has now become a worldwide concern because of its increasing prevalence and the various metabolic problems it causes. Erectile dysfunction is one that can be triggered by obesity. Men with central obesity have a predisposition to erectile dysfunction. Increased free fatty acids cause lipotoxicity and oxidative stress that causes inflammation in the hypothalamus, disruption of the hypothalamic-pituitary gonad axis and decreased testosterone. In addition, the conversion of testosterone to estradiol causes a decrease in testosterone levels and endothelial dysfunction causes an erection that is not optimal due to a decrease in nitric oxide and blockage of blood vessels. Metformin has been shown to improve leptin resistance, reduce oxidative stress, inflammatory response, body weight and improve erectile dysfunction. Administration of metformin and phosphodiesterase 5 inhibitors improve erectile function in patient with erectile dysfunction and reduce the refractory response to penile vasodilators.[18]

Obesity is associated with inappropriately low luteinizing hormone (LH) and follicle stimulating hormone (FSH).[3] Unlike this statement, our patient has higher LH and FSH without any history of mumps orchitis and it still not clear what causes the high level oh LH and FSH. Another sourced mentioned that FSH and LH were a slight tendency higher in obese.[6] Chlomiphene (estrogen antagonist) and aromatase inhibitor which decrease estradiol concentration have been shown to increase testosterone concentration in obese men with low testosterone.[3]

Individuals who are carriers of a genetic disorder may appear normal but may also have an increased risk of genetic problems in their offspring. Although the pericentric inversion of chromosome 9 inversion (9) p11q13 is categorized as normal variation, there can be progeny imbalance that varies from 1-10%. This disorder also does not necessarily interfere with spermatogenesis and cause azoospermia but is very likely to cause recurrent miscarriage, implantation failure and/or subfertility.[9] Another case report , women 27 years old 5 years marriage. All was well until they found that there was 46 XX inv (9) (p11q13) while they were checking the causes.[19]

In Morocco, in a study of total 170 couples with reproductive disorder, Pericentric reversal of chromosom 9 were detected 3,5% of all couples.[20] A study of 2988 adult patients, 67 inv (9) cases were found and among them only 5 did not show any clinical feature and the remaining 62 adult exhibited different clinical features include infertility, azoospermia, bad obstetric history ang spontaneous abortion.[21] Although most expert considered this kind of inversion as normal variable, there still possibilities they carry another clinical problem especially in reproductive.

The history of patient's childhood is not clear, so we did not know exactly whether there was alteration of genital development, micropenis or obesity in childhood but the in the initial examination, patient considered puberty was normal and there was no history of mumps and orchitis. So that management is focused on managing a healthy lifestyle, weight loss, managing hyperprolactinemia and maintaining hormone balance. The treatment must be tailored suited to patient and precision medicine might have a great role in this patient.

4. Conclusion

Person with kromosomal disorder might have clinical problem and we have to see and manage every risk factor possible. Management of erectile dysfunction can not only be seen from one side but also requires a holistic and multidisciplinary approach. Risk factors that can cause erectile dysfunction problems must be assessed and controlled one by one. The purpose of the management of erectile dysfunction is not only for

sexual satisfaction but also to improve fertility and improve quality of life.

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Authors' Contributions

All authors have contributed to the final manuscript. The contribution each author as follow: collected the data, drafted the manuscript, devised the main conseptual ideas and critical revision of the manuscript. All authors discussed the result and contributed to the final manuscript..

Conflict of Interest

The authors state there is no conflict of interest.

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