IABJ. Volume 4 No 2 .December 2023
Available online at https://e-journal.unair.ac.id/iabj

e-ISSN: 2746-4474
DOI=10.20473/iabj.v4i2.50468

INDONESIAN ANDROLOGY AND BIOMEDICAL JOURNAL

Case Report

The Urgency of Karyotyping Examination in Male Infertility Patients with Primary Hypogonadism

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OPEN ACCESS

ARTICLE INFO

Received: October 10, 2023
Accepted: November 08, 2023
Published: December 05, 2023

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Keywords:
Karyotyping
Hypogonadism
Infertility

Abstract

Infertility is a failure to get pregnant after one year of sexual intercourse without using contraception. The causes of infertility, especially in men, are very complex, including the aging process, hormonal disorders, lifestyle, environment, metabolic disease, and genetic problems. One of the most difficult causes in male infertility is genetic problems.

In this case, a 35 year old man was reported with primary infertility and often experienced premature ejaculation and even anejaculation. Previously, the patient had repeatedly consulted about his condition at other fertility service centers. The conclusion obtained was that the patient had azoospermia with bilateral varicoceles and had been given hormone therapy but had not yet found a final diagnosis so the patient was still confused about what had happened to him. At the first visit the patient underwent a sperm analysis and the results were azoospermia. Then, based on the results of the history and physical examination, which indicated hypogonadism, a Y chromosome microdeletion examination was carried out, and a deletion was found in the AZFc region, which is a marker of infertility that causes spermatogenic failure. The examination was continued with karyotyping, the result was 47.XXY, consistent with the condition of Klinefelter syndrome.

Conclusion: Carry out a karyotyping examination if you find signs and symptoms that suggest primary hypogonadism in male infertility. This can be done to streamline the diagnostic approach time in patients with primary hypogonadism, especially those with infertility.

Cite this as: Lestari PDA, Pramesemara IGN, The Urgency of Karyotyping Examination in Male Infertility Patients with Primary Hypogonadism. *Indonesian Andrology and Biomedical Journal*. 2023 December 05;4(2):65 – 70. DOI: https://doi.org/10.20473/iabj.v4i2.50468.

1. Introduction

Infertility is a fairly complex problem. Infertility is a failure to get pregnant after one year of having sexual intercourse without using contraception.[1] Various causes of infertility from those that can be identified to those that cannot be found are the focus of attention for clinicians, especially doctors who work in their fields. One study showed that the average age of infertt5p5tility is around the age of 30.[2] Approximately 10% of married couples face difficulties in fertility with the male prevalence increasing 0.3% annually. This certainly creates a lot of psychological problems in married couples. According to the International Committee for Monitoring Assisted Reproductive Technology, World Health Organization (WHO), infertility is a disease of the reproductive system which is defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[3]

Infertility has a complex etiology. Factors of aging, lifestyle, environment, physio pathology such as genetics, testicular trauma, infection, to hormonal disturbances can be a cause of infertility in men.[4,5] Referring to hormonal disorders, infertility can occur due to deficiency of hormones, especially testosterone. It is well known that the hormone testosterone plays an important role in life, especially in sexual and reproductive functions.[6] Hormonal abnormalities such as testosterone deficiency in hypogonadism can be a major cause of infertility in men. Hypogonadism is a complex clinical syndrome consisting of symptoms and signs as well as evidence of biochemical lab results with testosterone deficiency. This is also related to aging, where as a person gets older, the hormone levels in the body also decrease.[5]

The diagnostic approach related to hypogonadism can actually be established by looking at the signs and symptoms found in the patient. If you find signs and symptoms that suggest primary hypogonadism with infertility in a patient, you can immediately proceed with a karyotyping examination to streamline the time to approach the diagnosis in primary hypogonadism patients, especially those with infertility. Various kinds of supporting examination devices have been developed and can be used as a doctor's effort in establishing a patient's diagnosis. As in the condition of primary hypogonadism with infertility, of course, you have to think about the effectiveness and efficiency of doctors in making a diagnosis, identifying causes, so that patients can be treated promptly and can determine the management and prognosis of the patient's condition in the future.[7]

2. Case

Mr. IGNAEK, a 35 year old man from Bali, came with his wife to the Andrology Polyclinic at the Kasih Ibu Hospital (KIH) Denpasar in January 2023 with the main complaint infertility. The patient has been married for approximately 3 years. In the anamnesis, other complaints conveyed were frequently experiencing premature ejaculation or even being unable to ejaculate during sexual intercourse. Because of this frequent condition, the patient rarely has sexual relations. The patient experienced this condition from the start of sexual intercourse. Regarding other risk factors obtained from the anamnesis results, namely that the patient has a history of often staying up late, stress, often cycling, smoking and using vape quite often, and drinking alcohol until he gets drunk. The patient also said that hair in the genital area stopped growing when he reached adolescence (11 – 12 years old).

Previously, the patient had consulted his complaints in another infertility clinic. The results of the patient's wife's examination in the form of abdominal ultrasound and transvaginal ultrasound, hormone examination, and hysterosalpingography stated that there were no significant abnormalities or within normal limits. The Andrologist previously advised the patient to have a semen analysis and the result was azoospermia and he was advised to do a scrotal ultrasound which showed the conclusion of grade II bilateral varicoceles and testicular size that was smaller than normal. The patient received a gonadotropin hormone injection once but there was no sign of change. The patient said he still did not understand or reach a conclusion about what was happening in his current condition. Therefore, patients come to visit the andrologist again to find out and consult about their complaints again.

Anthropometric examination (on January 2023) it was found that the patient's weight was 85 kg, height 164 centimeters, hand span 174 cm, abdominal circumference 100 cm. General

physical examination, head, thorax, abdomen, inguinal and upper and lower extremities were within normal limits. Signs of secondary sexual development were found to be signs of gynecomastia on the patient's breasts, there was no fluid coming out of the nipples. Only a little hair was found on the mustache, beard, axillae, chest and pubis/genital area.

In particular, the andrological examination at the first visit showed that the penis was not circumcised with the impression of a "small penis". The outer opening of the urethra is located in the correct position and no pus or blood comes out. Both testicles are in the scrotum in a normal position but with a very small volume < 4 cc / < 4 cc, hard consistency, and without any palpable pain.

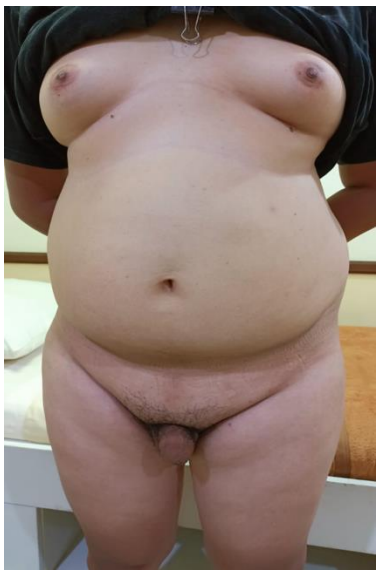

Figure 1. Eunuchoid Body Shape of A Patient With Gynecomastia and A Small Penis.

By palpation, both of pampiniform plexuses were enlarged showing bilateral grade 2 varicocele according to previous ultrasound results, no cystic masses were found, and the cremaster reflex response was normal. The epididymis were palpable in the normal shape of the head, corpus and cauda, with a springy consistency and a flat surface. Patients are also given an introduction to check the hormones LH, FSH, Testosterone, SA (as well as post ejaculation urine), karyotyping and genetics.

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Furthermore, the patient came back (March 2023) reported the results of blood hormonal laboratory tests with levels of Luteinizing Hormone (LH) 10.77 mIU/mL, Follicle Stimulating Hormone (FSH) 30.27 mIU/mL, and Testosterone 59.73 ng/dL. In the karyotyping results, an extra X chromosome was obtained, making it 47,XXY. This condition corresponds to Klinefelter syndrome. At the same time, the results of the Y chromosome microdeletion (YCMD) genetic examination found a deletion in the AZFc region *Sy-169*, *sY-159*, *RBM-2*, *DAZ-3*.

At the next patient's arrival (April 2023 – 3 months of drug therapy), the patient returned for another physical examination and the results obtained on andrological examination were as follows: tanner 3-4, right testicular volume 4 cc / left 3 cc high position with hard consistency length penis 10 cm, penis diameter 9 cm. There were significant changes after being given therapy, the patient also said that his penis was much bigger and longer after therapy. The patient also brought the results of previous examinations. Sperm analysis showed results with the conclusion of azoospermia and hypospermia (volume 0.4 ml). Post ejaculation urine only found bacteria and leukocytes.

Referring to the results of the anamnesis, patient history, physical examination and andrology, to the supporting examinations, the diagnosis can be made in the patient, namely primary infertility with Klinefelter syndrome. Patient are given an explanation about Klinefelter syndrome and given counseling about the therapy given which can only help patient maintain their quality of life in the future. Assisted reproductive technology in Indonesia does not seem to be able to help cases like the condition experienced by the patient. Patient are given a choice of solutions to adopt a child by a doctor.

3. Discussion

It was reported that a 35 year old man from Bali who was married had a main complaint of wanting

to have children. Another complaint that was submitted was often experiencing premature ejaculation or even being unable to ejaculate during sexual intercourse. The patient has consulted other andrologists for his complaints, but all he got were conclusions regarding sperm results with azoospermia and varicocele. The causes and diagnostic conclusions in patients are still unclear. So the patient came back to the andrologist to find out what happened to him.

In the history of the patient, complaints were found, such as the patient felt that his testicles were small, hair in the genital area stopped growing when he was about to enter his teens (11 – 12 years old), often had difficulty reaching ejaculation, and had difficulty concentrating. On physical examination, eunuchoid impressions were found that the span of the arms exceeds height, the pelvis is wide, gynecomastia, the penis is not circumcised with the impression of "small penis" and the testicles are in the scrotum in a normal position but with very small volumes both <4cc / <4cc. The patient's history and physical examination suggest hypogonadism.[8]

In the supporting examination, the results of blood hormonal laboratory examinations were reported which showed Luteinizing Hormone (LH) levels of 10.77 mIU/mL, Follicle Stimulating Hormone (FSH) 30.27 mIU/mL, and Testosterone 59.73 ng/dL. The patient's condition is in accordance with the theory which states that in Klinefelter syndrome LH and FSH levels in Klinefelter Syndrome are usually found to be higher than the normal reference.[9] Other hormone levels such as E2, Prolactin, SHBG, inhibin B are still within normal limits. However, Testosterone levels will certainly be very low.[10]

Based on the SA results which showed azoospermia, this patient also underwent a genetic examination for microdeletion of the Y chromosome and found a deletion in the AZFc region Sy-169, sY-159, RBM-2, DAZ-3 which is a marker of infertility. Y chromosome microdeletion examination is carried out to find out which AZF gene is located on the Y chromosome which is deleted in the condition of azoospermia. Deletions were also found in the DAZ region where the DAZ gene in the AZF gene was also reported to frequently experience deletions. This causes a decrease in the production of mature sperm. The patient was referred for karyotyping and sperm analysis after 3 months of therapy and post-ejaculation urine. The results of karyotyping showed a total number of chromosomes of 47 with an extra X chromosome. In accordance with theory, this condition led to the diagnosis of Klinefelter Syndrome.[11, 12]

Hypogonadism is a complex clinical syndrome which consists of symptoms and signs as well as low testosterone hormone examination results. [5] As is known, testosterone is a hormone that has an important function in a person's sexual development, cognitive development and quality of life. Symptoms of hypogonadism or testosterone deficiency conditions include fatigue, decreased sex drive, erectile dysfunction, mood changes, difficulty concentrating, loss of muscle mass, decreased bone density, gynecomastia in men, and infertility. Hypogonadism can be confirmed if the patient has symptoms of hypogonadism, a family history of symptoms of hypogonadism, decreased testosterone levels, or if the patient has had an infection, trauma, or medical therapy related to hormonal changes.[7]

Hypogonadism is classified into 2, namely primary and secondary. Primary hypogonadism is usually caused by genetic disorders (such as Klinefelter syndrome, X chromosome abnormalities, Sertoli-cell only syndrome), infections such as orchitis, or testicular trauma and other abnormalities of the testicles. In secondary hypogonadism there is a problem with the hypothalamus which cannot stimulate the formation of hormones but the testicles are normal. Even though there are no abnormalities found in the testicles, the testosterone hormone still decreases because there is no stimulation of hormone formation due to problems with the hypothalamus. Causes of secondary hypogonadism include Kallman's syndrome, panhypopituirarism, congenital hypogonadotropic hypogonadism, and poor nutritional status.[13]

Because we know the signs and symptoms of hypogonadism that lead to conditions that cause primary hypogonadism, to make the diagnostic approach more efficient, it's a good idea to immediately carry out a karyotyping check. [12] Moreover, in patients we can exclude the possibility of infection or trauma to the testicles. An earlier karyotyping examination can be carried out to find out the cause of primary hypogonadism, especially with infertility. If the diagnosis has been

established, then the appropriateness of therapy and management of patients with primary hypogonadism with infertility can be handled more quickly. The YCMD examination should also be carried out considering the high prevalence of microdeletions in oligospermia and azoospermia patients. This will also make it easier for doctors to plan future treatment of patients related to infertility.[15]

4. Conclusion

It can be concluded that if anamnesis, physical examination is found in a patient, accompanied by a decrease in the hormone testosterone which leads to signs and symptoms of hypogonadism, then the first thing to do is to focus on determining patients with primary hypogonadism with infertility according to these typical signs and symptoms. Genetic examination can be carried out after establishing a diagnosis because in this case report, signs and symptoms of primary hypogonadism were found by ruling out the possibility of testicular infection/trauma, then a karyotype and YCMD examination can be carried out to streamline time and costs in diagnosing. The sooner the diagnosis is established, the sooner we can find the right treatment for the patient, especially in primary hypogonadism with infertility.

Author's Contribution

All authors have contributed to the final manuscript.

Acknowledgment

We thank the patient for his cooperation and permission to publish this case and photos. This work was supported by Andrology Polyclinic, Kasih Ibu Hospital, Denpasar Bali and Department of Andrology and Sexology, Faculty of Medicine, Udayana University, Denpasar Bali

Conflict Of Interest

The authors declare that there are no conflicts of interest regarding this article.

Funding Information

The authors does not received any specific funding for this research.

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