North Clin Istanb
doi: 10.14744/nci.2018.57625

Case Report ENDOCRINOLOGY
UNCORRECTED PROOF

46 XX male syndrome with hypogonadotrophic hypogonadism: A case report

Mehmet M Yalcin,[1] Cigdem Ozkan,[1] Mujde Akturk,[1] Ferda Emriye Percin,[2] Alev Altinova,[1] Ayhan Karakoc,[1] Goksun Ayvaz,[1] Nuri Cakir[1]

[1]Department of Endocrinology and Metabolism, Gazi University Faculty of Medicine, Ankara, Turkey

[2]Department of Medical Genetics, Gazi University Faculty of Medicine, Ankara, Turkey

ABSTRACT

We want to report a 46 XX Male Syndrome diagnosed after failure of gonadotropin therapy taken for hypogonadotropic hypogonadism due to a pituitary macro-adenoma. A 39-year-old man with a nonfunctioning pituitary macro-adenoma admitted to our clinic for vision loss and infertility. After pituitary surgery vision loss impoves while infertility still existed. Low testosteron levels without elevated gonadotropins was established suggesting hypogonadotropic hypogonadism due to the pituitary adenoma. Gonadotropin treatment was initiated. There were no response to treatment after 12 months. A karyotype analysis was ordered in order to investigate other causes of infertility. Karyotype analysis showed a 46 XX male syndrome which can explain the failure of the gonadotropin therapy. Testosterone therapy was started instead of gonadotropin therapy. The 46 XX male syndrome usually presents with hypergonadotrophic hypogonadism however in our case it presented with hypogonadotrophic hypogonadism due to pituitary mass not responding to gonadotropin therapy. It is important to keep in mind to obtain genetic analyse etc. in patients whose gonadotropin therapy failed, even if their gonadotropin levels are not elevated.

Keywords: Hypogonadism; infertility; 46 XX male.

Cite this article as: *Yalcin M. M., Ozkan C., Akturk M., Percin F. E., Altinova A., Karakoc A., Ayvaz G., Cakir N. 46 XX male syndrome with hypogonadotrophic hypogonadism: A case report. North Clin Istanb*

Infertility is defined as the inability of achieving pregnancy without contraception in a couple regularly intercourse for one year [1]. Infertility may occur due to male factors (30%), female factors (45%) or both (25%). Male factors can be categorized as sexual disorders, primary testicular defect in sperm production, endocrinopaties which affect spermatogenesis and defects in sperm transportation. According to Jungwirthet al, 10.1% of the infertile males have hypogonadism which can be defined as inability of testicles to produce testosterone [2]. Hypogonadism is divided into two categories according to gonadotropin levels. Hypergonadotrophic hypogonadism (primary hypogonadism) and hypogonadotrophic hypogonadism (secondary hypogonadism) Differantial diagnosis of hypogonadism is crucial for the treatment in fertility. Gonadotropin theraphy could achieve pregnancy in patients with hypogonadotrophic hypogonadism, which is different from hypergonadotrophic hypogonadism. It can be hard to diagnose or treat a patient with different causes of hypogonadism.

Here, we report a case with 46 XX male syndrome presented with a hypogonadotrophic hypogonadism due to coexisting non-functioning pituitary adenoma.

CASE REPORT

A 39 year-old man was referred to our clinic with a pituitary mass. He had right-sided vision loss which was occured suddenly. A pituitary adenoma of 45x28x40 mm size was detected while evaluation of vision loss.

Received: November 26, 2017 *Accepted:* April 12, 2018 *Online:* September 05, 2018

Correspondence: Dr. Mehmet M. YALCIN. Dr. Ersin Arslan Egitim ve Arastirma Hastanesi, Sahinbey, Gaziantep Turkey.
Phone: +90 505 525 25 48 e-mail: yalcin.muhittin@gmail.com

Table 1. Testosterone, FSH, LH, prolactin, estradiol levels, testicular volume and semen analysis before and after treatment

	Before the first operation	Before second operation	Before gonadotropin treatment	After 1 years of gonadotropin treatment
Total testosterone (ng/dL) (262–1593)	23.8	36.0	32.0	76.0
FSH (mIU/mL) (0.70–11.0)	6.5	4.6	4.1	5.5
LH (mIU/mL) (0.80–7.60)	1.97	1.50	1.71	1.64
Prolactin (mg/mL) (2.50–17.0)	14.0	12.4	7.7	18.7
Estradiol (pg/mL) (11–44)	NA	24	14	<10
Testicular volume	(-)	(-)	R: 1.6 mL R:1.4 mL	L: 1.4 mL L: 1.5 mL
Semen analysis	no sperm	no sperm	no sperm	no sperm

Normal ranges for analyses were given in the paranthesis. FSH: Follicle stimulating hormone; LH: Luteinizing hormone; NA: Not available.

Hormonal analyses showed hypogonadotrophic hypogonadism without any excess or deficient hormone levels as shown in Table 1. A transcranial pituitary adenomectomy was performed. Pathology of the surgical specimen was considered as an adenoma which had no immunstaining with TSH, ACTH, GH and prolactin. After the operation, his vision loss improved.

When he readmitted to our clinic, he was suffering from loss of libido, infertility, headaches and relapsing of vision loss on the right side which started four years after pituitary operation. He had no child. His height and weight were 161 cm and 71 kg with a body mass index of 27.4 kg/m^2. His physical examination was normal, except bilateral gynecomastia and small testicles. Hormonal analyses showed hypogonadotrophic hypogonadism as shown in Table 1. MRI of the pituitary gland revealed a 37x32x28 mm residual pituitary mass. Second pituitary adenomectomy was performed, but there was still residual pituitary mass of 24x25x20 mm after the second operation (Figure 1). Histopathology of the speciment revealed pituitary adenoma without immunostaining for TSH, ACTH, GH and prolactin. Although the patient had no headaches and vision problems after the operation, he was still suffering from loss of libido and infertility. According to his laboratory results, hypogonadotropic hypogonadism was still existed and there was not any disturbance of other pituitary hormones (Table 1). Ultrasonography of testicles revealed that both testicles were small as shown in Table 1. His semen analysis showed no sperm since patient and his wife desired to have a child. Initially human chorionic gonadotropin (hCG) (1500 units, three days in a week) treatment was started. After three months, as testicular volume was still too small and no improvement on testosterone levels, hCG dose increased into 3000 units, three days in a week and human menopausal gonadotropin (hMG) 75 mcg three days in a week added to hCG treatment. Then, HMG treatment was increased up to 150 mcg three days in a week while he was on hCG (3000 units, three days in a week). After 12 months, because of no improvement on both testosterone

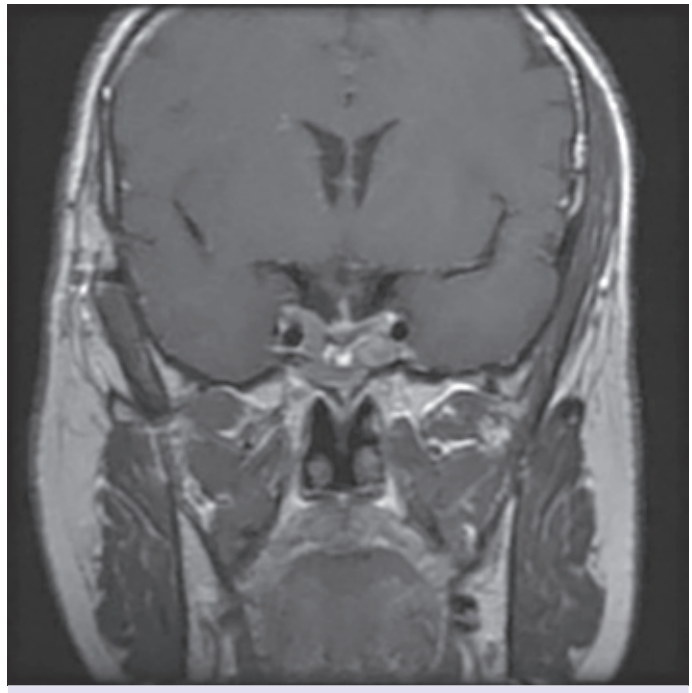

Figure 1. Pituitary MRI image after second operation.

levels, sperm production and testicular size, we performed a chromosomal analysis to investigate other causes of infertility. As a result of the analysis, GTG banding procedure were performed on metaphase chromosomes obtained from peripheral blood lymphocytes of the patient. The karyotype 46,XX was observed on 100 metaphases in order to exclude mosaiciszm and chimerism. Diagnostic testing of deletions of the sex-determining region Y (SRY), ZFY genes and AZF region located on the long arm of the Y chromosome, was performed by Real time PCR amplification. The set of PCR primers that was used in multiplex PCRs for the diagnosis of microdeletion of these regions included: sY14 (SRY), ZFX/ZFY, sY84, sY86, sY127, sY134, sY254, and sY255. Molecular analysis revealed ZFY and SRY genes were intact, but AZF region was deleted. Therefore, SRY-positive 46, XX male sex reversal was diagnosed.

Since no treatment could induce spermatogenesis in 46 XX males, testosterone therapy was started instead of gonadotropin therapy. A genetic consultation and alternative ways of having a child (adoption etc) recommended to the couple. Also, we advised the couple to take a psycological support if they need.

DISCUSSION

We presented an infertile patient with hypogonadotropic hypogonadism due to a pituitary adenoma in whom fertility treatment with hCG and hMG failed. Underlying 46 XX male syndrome was diagnosed after chromosomal analysis.

Hypergonadotrophic hypogonadism can be defined as elevated gonadotropin levels in a male with hypogonadism. Testicular diseases should be investigated for the etiology of hypergonadotropic hypogonadism.

Gonadotropin treatment is considered for sperm induction in males with hypogonadotropic hypogonadism. Although hypogonadotropic hypogonadism is the cause of only 2–3 % of male infertillity, fertility and sperm production can be achieved with gonadotropin treatment only in this group [3]. Congenital factors such as Kallmann syndrome and idiopathic hypogonadotropic hypogonadism or acquired forms such as hypothalamopituitary tumors, granulamatous diseases, empty sella syndrome, obesity, the use of anabolic steroids can cause hypogonadotropic hypogonadism. Non-functioning pituitary adenomas may lead to hypogonadotrophic hypogonadism, because of mass effect of the adenoma or complication of pituitary surgery. After removing the adenoma -the underlying cause of hypogonadism-, fertility can be achieved spontaneously in some cases. In patients with a persistant hypogonadism despite surgical treatment, fertility can be achieved by gonadotropin treatment (human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG)). hCG treatment can induce sperm production by increasing intratesticular testosterone levels [3, 4]. hMG can be added to hCG therapy, if adequate sperm production could not achieved after 3–6 months therapy with hCG [5–9]. Pregnancy has been shown to be achieved in 40–53% of patients with gonadotropin replacement theraphy in 24–36 months [5, 4]. If there is no improvement in fertility despite using gonadotropin treatment, the clinician should investigate for other diseases which lead to male infertility etiologies.

According to the algoritm for infertile men published by Anawalt et al., a chromosomal analysis recommended if the gonadotropin treatment fails in a man with hypogonadotropic hypogonadism [5]. Actually, genetic analysis is recommended for patients with hypergonadotrophic hypogonadism, while it is not routine investigation for a patient with hypogonadotrophic hypogonadism [10, 5]. Prevalence of chromosomal abnormalities in infertile men has been reported as 3–19% in different studies [11]. Although Klinefelter Syndrome is the most frequent genetic disorder causing infertility, 46 XX male syndrome can be found 0.3% of infertil men who ordered for chromosomal analysis [12].

Sex reversal syndromes consist of 46 XY females and 46 XX males [13]. 46 XX male syndrome is a rare disorder, it was first described by De la Chapelle et al. in 1964 [14]. It can be seen in 1 of 20000–25000 births [15]. It is characterized by a male fenotype with a 46 XX karyotype. 46 XX male syndrome is divided to sex-determining region Y (SRY)+ (80%) and SRY – (20%) according to presence of SRY region on X chromosome. SRY - 46 XX males often have genital anomalies and loss of masculinisation as they almost always diagnosed at early childhood [16]. SRY + 46 XX males often have normal puberty, while some of them have chriptorchidism [16]. They often diagnosed while evaluating for infertility or gynecomastia in early adulthood. They have normal secondary sexual characters, but they do not produce sperm. Eleveted gonadotropin levels often determined while testosteron levels can be low, normal or even high [16]. None of the infertility treatments induce sperm production.

In our case, FSH level was inappropriately in normal range, while LH level was low. In hypogonadotropic hypogonadism, gonadotropin levels can not be elevated despite low testosterone levels. However, FSH levels which was in normal range in our case could be related with 46 XX male syndrome, because highly elevated FSH levels was reported in case reports with 46 XX Male Syndrome [17–22]. Also, FSH levels were almost always higher than other causes effecting Y chromosome according to the literature [20].

We suggest that if gonadotropin therapy fail to provide sufficient amount of testesteron level and/or amunt of sperm, which are needed to get fertility, in a man with hypogonadotropic hypogonadism, other diseases which cause to infertility such as 46 XX male syndrome should be investigated with genetic analysis. Early diagnose for 46 XX male syndrome may be usefull for providing early genetic consultation, to prevent unnecessary using painful and expensive gonadotrophin therapy, contributing to early initiation of adoption process.

We report a case of 46 XX male syndrome with inappropriately normal FSH, low LH levels,in spite of there was too low testesterone levels. He was diagnosed after failure of gonadotropin therapy for hypogonadism with low levels of gonadotropins, because of pituitary adenoma. Presence of pituitary adenoma was a confounding factor and delayed the diagnosis in our case. It is important to keep in mind to obtain genetic analyse etc. in patients whose gonadotropin therapy failed, even if their gonadotropin levels are not elevated. To the best of our knowledge, it is the first case of 46 XX male syndrome presented with hypogonadotropic hypogonadism due to pituitary adenoma in adults.

Authorship contributions: All the authors participated in the clinical follow-up of the patient, F. E. P.; performed the genetic analysis including karyotype analysis and PCR analysis, M. M. Y., M. A. and A. A. wrote the manuscript, M. M. Y. and M. A. edited the manuscript.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. Hum Reprod 2005;20:1144-7. doi:10.1093/humrep/deh870.
2. Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G et al. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol 2012;62:324-32. doi:10.1016/j.eururo.2012.04.048.
3. Roth MY, Page ST, Lin K, Anawalt BD, Matsumoto AM, Snyder CN et al. Dose-dependent increase in intratesticular testosterone by very low-dose human chorionic gonadotropin in normal men with experimental gonadotropin deficiency. J Clin Endocrinol Metab 2010;95:3806-13. doi:10.1210/jc.2010-0360.
4. Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. J Clin Endocrinol Metab 2005;90:2595-602. doi:10.1210/jc.2004-0802.
5. Anawalt BD. Approach to male infertility and induction of spermatogenesis. J Clin Endocrinol Metab 2013;98(9):3532-42. doi:10.1210/jc.2012-2400.
6. Fraietta R, Zylberstejn DS, Esteves SC. Hypogonadotropic hypogonadism revisited. Clinics (Sao Paulo) 2013;68 Suppl 1:81-8.
7. Zacharin M, Sabin MA, Nair VV, Dabadghao P. Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis. Fertil Steril 2012;98:836-42. doi:10.1016/j.fertnstert.2012.06.022.
8. Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. Fertil Steril 1999;71:244-8.
9. Oldereid NB, Abyholm T, Tanbo TG. Spermatogenesis and fertility outcome in male hypogonadotrophic hypogonadism. Hum Fertil (Camb) 2010;13:83-9. doi:10.3109/14647271003639723.
10. Layman LC. Hypogonadotropic hypogonadism. Endocrinol Metab Clin North Am 2007;36:283-96. doi:10.1016/j.ecl.2007.03.010.
11. Martin RH. Cytogenetic determinants of male fertility. Hum Reprod Update 2008;14:379-90. doi:10.1093/humupd/dmn017.
12. Hofherr SE, Wiktor AE, Kipp BR, Dawson DB, Van Dyke DL. Clinical diagnostic testing for the cytogenetic and molecular causes of male infertility: the Mayo Clinic experience. Assist Reprod Genet 2011;28:1091-8. doi:10.1007/s10815-011-9633-6.
13. Wang T, Liu JH, Yang J, Chen J, Ye ZQ. 46, XX male sex reversal syndrome: a case report and review of the genetic basis. Andrologia 2009;41:59-62. doi:10.1111/j.1439-0272.2008.00889.x.
14. de la Chapelle A. The etiology of maleness in XX men. Hum Genet 1981;58:105-16.
15. Rajender S, Rajani V, Gupta NJ, Chakravarty B, Singh L, Thangaraj K. SRY-negative 46,XX male with normal genitals, complete masculinization and infertility. Mol Hum Reprod 2006;12:341-6. doi:10.1093/molehr/gal030.
16. Fruhmesser A, Kotzot D. Chromosomal variants in klinefelter syndrome. Sex Dev 2011;5:109-23. doi:10.1159/000327324.
17. Gunes S, Asci R, Okten G, Atac F, Onat OE, Ogur G et al. Two males with SRY-positive 46,XX testicular disorder of sex development. Syst Biol Reprod Med 2013;59:42-7. doi:10.3109/19396368.2012.73162.
18. Agrawala RK, Choudhury AK, Mohanty BK, Baliarsinha AK. All males do not have 46 xy karyotype: A rare case report. Indian J Endocrinol Metab 2013;17:271-3. doi:10.4103/2230-8210.119603.
19. Anik A, Catli G, Abaci A, Bober E. 46,XX male disorder of sexual de-

velopment:a case report. J Clin Res Pediatr Endocrinol 2013;5:258-60. doi:10.4274/Jcrpe.1098.

20. Chiang HS, Wu YN, Wu CC, Hwang JL. Cytogenic and molecular analyses of 46,XX male syndrome with clinical comparison to other groups with testicular azoospermia of genetic origin. J Formos Med Assoc 2013;112:72-8. doi:10.1016/j.jfma.2012.02.009.
21. Gao X, Chen G, Huang J, Bai Q, Zhao N, Shao M et al. Clinical, cytogenetic, and molecular analysis with 46,XX male sex reversal syndrome: case reports. J Assist Reprod Genet 2013;30:431-5. doi:10.1007/s10815-013-9939-7.
22. Jain M, V V, Chaudhary I, Halder A. The Sertoli Cell Only Syndrome and Glaucoma in a Sex - Determining Region Y (SRY) Positive XX Infertile Male. J Clin Diagn Res 2013;7:1457-9. doi:10.7860/JCDR/2013/5186.3169.