46 XX male syndrome with hypogonadotrophic hypogonadism: A case report

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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 improves while infertility still existed. Low testosterone 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.


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) Differential diagnosis of hypogonadism is crucial for the treatment in fertility. Gonadotropin therapy 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.
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 immunostaining 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/m². 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 specimen 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, hypogonadotrophic 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

<table>
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<tr>
<th>Table 1. Testosterone, FSH, LH, prolactin, estradiol levels, testicular volume and semen analysis before and after treatment</th>
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<tr>
<td>Before the first operation</td>
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<tr>
<td>Total testosterone (ng/dL) (262–1593)</td>
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<tr>
<td>FSH (mIU/mL) (0.70–11.0)</td>
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<tr>
<td>LH (mIU/mL) (0.80–7.60)</td>
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<tr>
<td>Prolactin (mg/mL) (2.50–17.0)</td>
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<td>Estradiol (pg/mL) (11–44)</td>
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<td>Testicular volume</td>
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<td>Semen analysis</td>
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Normal ranges for analyses were given in the paranthesis. FSH: Follicle stimulating hormone; LH: Luteinizing hormone; NA: Not available.

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 mosaicism 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 psychological 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.

Hypergonadotropic 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 infertility, 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 hypothalamic-opituitary tumors, granulomatous diseases, empty sella syndrome, obesity, the use of anabolic steroids can cause hypogonadotropic hypogonadism. Non-functioning pituitary adenomas may lead to hypogonadotropic 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 therapy 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 algorithm 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 hypergonadotropic 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 infertile 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 phenotype 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 chiportochism [16]. They often diagnosed while evaluating for infertility or gynecomasia in early adulthood. They have normal secondary sexual characters, but they do not produce sperm. Elevated 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 normal in 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 amount 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 useful 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 testosterone 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.

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

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