Case Report

DOI: 10.4274/tjem.2340

46, XX Sry(+) Male Sexual Differentiation Disorder with Metabolic Syndrome: A Case Report

Metabolik Sendromlu 46 XX Sry(+) Erkek Seksüel Differansiyasyon Bozukluğu: Olgu Sunumu

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Abstract

In disorders of sexual differentiation, sexual development may not be in accordance with chromosomal structure. 46,XX male syndrome is one of these kind of situations of which most of the patients are in normal male phenotype at birth. These patients are diagnosed while investigating for gynecomastia during puberty or infertility at older ages. One of the comorbidities of testosterone deficiency is metabolic syndrome. Recent studies have demonstrated a strong relationship between hypogonadism and metabolic syndrome. A 42-year-old male patient was admitted to our outpatient clinic with the complaint of gynecomastia. Based on laboratory tests results, he was diagnosed with hypergonadotropic hypogonadism accompanied by metabolic syndrome. Chromosomal analysis showed 46,XX SRY (+) genotype. *Turk Jem 2014; 1: 28-30*

Key words: Metabolic syndrome, hypogonadism, 46,XX SRY (+) male, gynecomastia

Özet

Seksüel diferansiyasyon bozukluklarında cinsiyet gelişimi kromozom yapısıyla uyum göstermemektedir. 46,XX Erkek sendromu da bu durumlardan birisi olup hastaların çoğu doğumda normal erkek fenotipindedir. Pubertal gelişim esnasında ya da daha sonraki dönemlerde bu bireyler jinekomasti veya infertilite nedeniyle araştırılmakta iken tanı almaktadırlar. Testosteron eksikliğine eşlik eden komorbid hastalıklardan birisi de metabolik sendromdur. Son yıllarda yapılan çalışmalar hipogonadizm ile metabolik sendrom arasında güçlü bir ilişki olduğunu göstermektedir. Kırk iki yaşında erkek olgumuz jinekomasti şikayetiyle polikliniğimize başvurup laboratuar tetkikleri sonucu hipergonadotropik hipogonadizm saptanan ve bu nedenle yapılan kromozom analizinde de 46,XX SRY (+) gözlenen, metabolik sendrom birlikteliği bulunan vakadır. *Turk Jem 2014; 1: 28-30*

Anahtar kelimeler: Metabolik sendrom, hipogonadizm, 46,XX SRY (+) erkek, jinekomasti

Introduction

Disorders of sexual differentiation (DSDs) are defined by gonadal and anatomical sexual development dissonant with chromosomal structure (1). Male XX syndrome, one of the DSDs (46, XX testicular DSD), was defined by La Chapelle et al. in 1964 (2). Male XX syndrome is a rare condition seen in 1:20.000-25.000 male birth (3). Patients has male phenotype although they have 46,XX karyotype (4,5,6).

46, XX male patients can be grouped as SRY (+) and SRY (-) (7,8). In SRY (+) individuals, there is often hypergonadotropic hypogonadism with small azoospermic testicles but normal male genitalia (3). In most of the patients, SRY gene is translocated to X chromosome during paternal meiosis (9). SRY (+) patients are diagnosed in adulthood while searching for gynecomastia and/or infertility (5). SRY (-) patients include two subgroups: ovotesticular DSD patients having both testicular and ovarian tissue, and testicular DSD patients having no ovarian but testicular tissue (5). SRY (-) patients are diagnosed by gynecomastia or ambiguous genital researches during childhood.

Metabolic syndrome is a condition that can be described by the presence of abdominal obesity, hyperglycemia, and accompanying risk factors, such as a low HDL cholesterol level, high triglyceride level and hypertension (10). Decrease in testosterone level leads an increase in glucose and triglyceride levels and decrease in HDL cholesterol level (11).

Case Report

A 42-year-old male patient was admitted to our endocrinology department with the complaint of gynecomastia on both sides. The patient has been married for 20 years with no child and his complaints were present since adolescence. He had a family history of intermarriage but no infertility or genetic disorder. Physical examination revealed: blood pressure: 140/90 mmHg, height: 159 cm, weight: 68 kg (BMI: 26.9 kg/m^2), fathom distance: 159 cm, heel-pubis distance: 90 cm, pubis-vertex distance: 69 cm, chest circumference: 97 cm, waist circumference: 96 cm, penis size: 5cm, as well as testicle atrophy and softness, and normal pubic hair.

In laboratory tests, blood glucose was 132 mg/dL (74-106), creatinin - 0.81 mg/dL (0.84-1.25), - ALT - 41 U/L (0-45), total

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testosterone - 0.64 ng/ml (1.75-7.81), prolactin - 19.6 ng/ml (2.64-26.72), LH - 30.6 mIU/ml (1.24-103.3), FSH - 56.03 mIU/ml (1.27-22.51), estradiol - 65 pg/ml (20-47), TSH - 1.8 uIU/ml (0.34-5.6), PSA - 0.39 ng/ml (0-4), beta-HCG - 2.21 mIU/ml (0-5), total cholesterol - 227 mg/dL (110-200), LDL cholesterol - 167 mg/dL (100-130), HDL cholesterol - 45 mg/dL (35-95), and triglyceride was 77 mg/dL (50-150). In addition, azoospermia was found in spermiogram.

In breast ultrasound, the right mammary tissue was found to be 3 cm, left one 4 cm in thickness with gynecomastia in left retroareolar area. Scrotal ultrasound showed the right testicle 8x7x13 mm, the left testicle 9x5x10 mm in size with heterogeneity and atrophy. In abdominal ultrasound, no uterus or over was observed. However, abdominal magnetic resonance imaging was performed for investigating rudimentary organs. On MRI, testicles were found to be atrophic and filled with liquid. No structure was observed related with Mullerian duct. No testicle biopsy was performed because of testicle atrophy.

Karyotype was searched by cytogenetic tests of peripheral blood. Karyotype was shown as 46, XX by G-banded chromosome analysis. DNA isolation from peripheral blood showed SRY(SY14) positivity in molecular diagnosis. As patient had male phenotype with 46, XX karyotype, SRY translocation on X chromosome was thought (Figure 1).

Diabetes mellitus (DM) was diagnosed based the second measurements of blood glucose (129 mg/dL) and HBA1c (7.46%). 2 gr/day metformin and 10 mg/day atorvastatin was given with life style changes. Testosterone transdermal gel was prescribed for the treatment of hypogonadism. In bone mineral density measurements done in our center, the results were: T score: -0.90, Z score: 0.10 at the femural neck of the left side, and T score: -0.91 and Z score: -0.76 at antero-posterior L2-L4.

Discussion

Terms, such as intersex, hermaphroditism, pseudohermaphroditism, used for defining disorders of sexual development were re-classified under the name of Disorder of Sex Development in 2005 (1).

SRY gene is the crucial gene found on Y chromosome and defines testicle development. SRY gene provides differentiation of gonads into testes. There are two types of well-defined sexual transformation: 46, XX male (having bilateral testicle and male phenotype) and 46, XY female (bilateral streak gonad and female phenotype despite the presence of Y chromosome). 46, XX male syndrome was defined by De La Chapelle in 1964. The frequency 46 XX males is 1:20.000 live births. This syndrome accounts for of 2% of cases of male infertility (3). 85% of patients have normal phenotype at birth. They are diagnosed while being investigated for hypogonadism, gynecomastia or infertility (12). Our patient was diagnosed during the investigations for his complaint of gynecomastia.

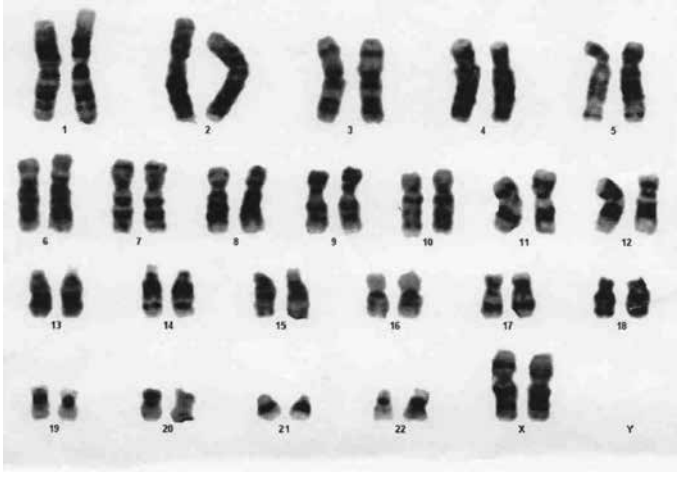

Figure 1. 46, XX SRY(+) male chromosome form

Testicular DSD occur by translocation between X and Y chromosomes during paternal gametogenesis (5,13). As a result of translocation, SRY gene passes through X chromosome and males become with XX chromosome. In our patient SRY (SY14) zone translocated on X chromosome.

Males with testicular DSD can be divided into 3 groups: The 1st group is the classical group characterized by male phenotype. The 2nd is the "ambiguous genital" group and the 3rd one is the "real hermaphrodites" (5). Our case belongs to the first group.

In 90% of patients of the first group, like in our case, SRY gene which belongs to Y chromosome exists on the short arm of paternal X chromosome. Azoospermia is frequently seen most probably due to the absence of AZF gene zone from Y chromosome (6). On long arm of Y chromosome, at least 3 zones were known (AZFa, AZFb and AZFc) which takes part in spermatogenesis. DAZ (Deleted in Azoospremia) gene groups take place on distal of AZFc on the 6th site of Y chromosome (14). In our case, DAZ(SY254) zone was analyzed on molecular basis and was found to be (-).

Metabolic syndrome diagnostic criteria is defined in IDF (International Diabetes Foundation)-2005 as the presence of waist circumference in male ≥94 cm, in female ≥80 cm (abdominal obesity) accompanied by at least 2 of the below mentioned conditions: triglyceride level ≥150 mg/dl; HDL (male <40 mg/dl, female <50 mg/dl), blood pressure ≥130/85 mmHg, fasting blood glucose ≥100 mg/dl or the presence of type2 DM (15). In our case, waist circumference was 96 cm, blood pressure was 140/90 mmHg and type 2 DM was present.

Among conditions accompanying low testosterone level; metabolic syndrome, DM, dyslipidemia, cardiovascular disorders and osteoporosis can be listed. There are several studies demonstrating the strong relationship between hypogonadism and metabolic syndrome (16). In our case, hypogonadism was accompanied by metabolic syndrome, DM and dyslipidemia. In bone mineral density evaluation, osteoporosis was not observed. Treadmill measurement and myocardial perfusion scintigraphy were performed due to ischemic changes in resting ECG. The results were within normal range.

Ucan reported a male patient with 46, XX karyotype who was normotensive and normoglisemic, however, our patient had central obesity, hypertension and type 2 DM that accompanied hypogonadism (17).

These patients are diagnosed by clinical signs, endocrine and cytogenetic tests as it happened with our patient. In 46, XX

testicular DSD, individuals have male genitals and, commonly, azoospermia. Mullerian structures do not exist. Patients are admitted to hospital due to small testicle, gynecomastia and infertility after puberty. In our case, normal pubic hair and small and soft testicles were observed. Hypospadias or cryptorchidism was not present. Individuals with 46,XX testicular DSD have hypergonadotropic hypogonadism due to testicular insufficiency. Treatment aim is to improve low level of testosterone and fix the consequences. Hormonal or surgical approach may be necessary for gynecomastia. In our case, no surgery was needed for the treatment of gynecomastia. Surgery may be necessary in case of hypospadias or cryptorchidism; sometimes reconstructive surgery may be needed for outer genitals or even sex reassignment surgery may be necessary. In our case, no surgery was needed. However, psychological support may be necessary for patients and for families.

Conclusion

Adolescents and adult males with hypergonadotropic hypogonadism should be investigated and evaluated for chromosomal anomalies, although having normal male phenotype when admitted to hospital because of gynecomastia or infertility. Besides, patients should be investigated for comorbid diseases.

References

1. Lee PA1, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics 2006;118:e488-500.
2. Delachapelle A ,Delachapelle A, Hortlnlg H, Nıemı M, Wennstroem J. Xx Sex Chromosomes in a Human Male. First Case. Acta Med Scand 1964;175:SUPPL 412:25-8.
3. de la Chapelle A. The etiology of maleness in XX men. Hum Genet 1981:58:105-16.
4. Ergun-Longmire B, Vinci G, Alonso L, Matthew S, et al., Clinical, hormonal and cytogenetic evaluation of 46, XX males and review of the literature. J Pediatr Endocrinol Metab. 2005;18:739-48.
5. 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.
6. Vorona E, Zitzmann M, Gromoll J, Schüring AN, Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. J Clin Endocrinol Metab 2007;92:3458-65.
7. Kim JW, Bak CW, Chin MU, Cha DH, Yoon TK, Shim SH. SRY-negative 46,XX infertile male with Leydig cell hyperplasia: clinical, cytogenetic, and molecular analysis and review of the literature. Fertil Steril 2010;94:753.e5-9.
8. 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.
9. Fechner PY, Marcantonio SM, Jaswaney V, et al. The role of the sex-determining region Y gene in the etiology of 46,XX maleness. J Clin Endocrinol Metab 1993;76:690-5.
10. Wubben DP, Adams AK. Metabolic syndrome: what's in a name? WMJ 2006;105:17-20.
11. Laaksonen DE1, Niskanen L, Punnonen K, et al. Testosterone and sex hormone–binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036-41.
12. Zenteno-Ruiz JC, Kofman-Alfaro S, Méndez JP. 46,XX sex reversal. Arch Med Res 2001;32:559-66.
13. Ferguson-Smith MA. XY chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. Lancet 1966;2:475-6.
14. Pryor JL, Kent-First M, Muallem A, et al.Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997;336:534-9.
15. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005;366:1059-62.
16. Makhsida N, Shah J, Yan G, Fisch H, Shabsigh R. Hypogonadism and metabolic syndrome: implications for testosterone therapy. J Urol 2005;174:827-34.
17. Uçan B, Özbek M, Topaloğlu O, et al., 46, XX Erkek Sendromu. Turk Jem 2013;17:46-8.