Global Journal of Reproductive Medicine
ISSN: 2575-8594

Juniper Publishers
key to the Researchers

Case Report
Volume 4 Issue 3 - April 2018
DOI: 10.19080/GJORM.2018.04.555636

Glob J Reprod Med

Wolfram Syndrome with Primary Gonadal Insufficiency

Serhat Özcelik[1], Mehmet Sariyadin[1], Suleyman Bas[1], Bünyamin Aydin[1], Sibel Temiz[2], Kenan Caglayan[2], Mehmet Celik[3], Muhammed Kizilgul[4]* and Hulya Iliksu Gözür

[1]*Haydarpaşa Training and Research Hospital, Endocrinology and Metabolism Section, Turkey*

[2]*Department of Endocrinology and Metabolism, Trakya University, Turkey*

[3]*Endocrinology and Metabolism Section, Kilis State Hospital, Turkey*

[4]*Department of Endocrinology and Metabolism, Marmara University, Turkey*

Submission: March 22, 2018; **Published:** April 18, 2018

***Corresponding author:** Muhammed Kizilgul, Department of Endocrinology and Metabolism, Marmara University, Istanbul, Turkey; Email: muhammedkzgl@gmail.com

Abstract

A 24-year old male patient admitted to our clinic with the complaints of mouth dryness, polyuria, and polydipsia. He was diagnosed with tip 1 Diabetes Mellitus (DM) at the age of seven and intensive insulin therapy was instituted subsequently. Despite the stable blood glucose levels, the daily liquid intake of the patient was 10 liters, and the urine output was 9.5 liters. The patient also had complaints of loss of libido, impotence, erectile and ejaculatory dysfunction in the last 6 months. The insulin therapy was given as insulin aspart 4-unit t.i.d and insulin detemir 12 unit per day. In the physical examination, bilateral gynecomastia was observed. In the hormonal panel; FSH: 45 U/L (N:1.5-12.7), LH:28.4 U/L (N:1.7-8.6), total testosterone: 3.83ng/ml (N:3-10ng/ml), free testosterone: 2.15pg/ml (N:12,00-30,00pg/ml). Bone mineral densitometry revealed low bone mass for chronologic age with the Z score of -2.3 SD. Spermiogram revealed azoospermia. Male karyotype 46, XY was confirmed in the cytogenetic studies. The fluid deprivation test was done and according to the test results the patient was diagnosed with diabetes insipidus. In the fundus examination, bilateral optic atrophy was found out. In the audiogram, the hearing loss with high-frequency sounds was considered to be associated with sensorineural deafness. As the treatment of primary hypogonadism, testosterone was given. As in our case, the patients diagnosed with WS requires long-term follow-up. With early diagnosis and appropriate hormone replacement the quality of patient's life and prognosis ameliorates

Keywords: Hypergonadotropic hypogonadism; Wolfram syndrome; Gynecomastia; Diabetes mellitus; Diabetes insipitus; Optic atrophy; Sensorineural deafness; Polyuria; Polydipsia; Insulin; Cortisol; Prolactin; Spermiogram; Microvascular; Odyogram; Fundus; Phenylpropionate; Mammoplasty; Neurologic abnormalities; Urinary tract abnormalities; Deafness;

Introduction

Wolfram syndrome is characterized by diabetes mellitus (DM), diabetes insipitus (DI), optic atrophy and sensorineural deafness [1]. The syndrome was first described by Wolfram and Waganer in 1938 [2]. The prevalence of the syndrome is 1/770.000 and it has an autosomal recessive inheritance pattern [3]. It is caused by a genetic defect in the short arm of the fourth chromosome [4]. DM is the first manifestation and optic atrophy also onsets in the first decade of life. The onsets of DI and sensorineural deafness are in the second decade, urinary tract abnormalities are in the third decade and neurologic abnormalities are in the fourth decade respectively. Hypogonadotrophic hypogonadism is a usual manifestation of the syndrome, however, as in our case, hypergonadotrophic hypogonadism can be rarely seen [5]. We are reporting a case of Wolfram syndrome with primary gonadal insufficiency.

Case Report

A 24- year old male patient admitted to our clinic with the complaints of mouth dryness, polyuria and polydipsia. The onset of polyuria, polydipsia, and blurred vision was at the age of six. He was diagnosed with tip 1 DM at the age of seven and intensive insulin therapy was instituted subsequently. His polyuria and polydipsia complaints continued even at the times when his blood glucose levels were at normal values. It was noticed that despite the stable blood glucose levels, the daily liquid intake of the patient was 10 liter/day, and the urine output was 9.5 liters/day. The visual complaints of the patient were thought to be related to myopia and diabetic retinopathy. It was found out that the patient had complaints of loss of libido, impotence, erectile and ejaculatory dysfunction in the last 6 months. The insulin therapy given was as insulin as part 4 unit tid and insulin

detemir 12 unit per day. In the physical examination bilateral grade, 3 gynecomastia was observed in the breasts [6].

The blood pressure was 110/80 mm-Hg, pulse was 86 beat/min and rhythmic. In the laboratuary studies glucose: 185mg/dl, BUN: 14mg/dl, creatinine: 0.7mg/dl, Na: 138mEq/L, K: 4.2mEq/L, Cl: 108mEq/L, Ca: 9.7mg/dl, P:4.6mg/dl, albumine: 4.3gr/dl, ALT: 15U/L, AST: 15U/L, cholesterol: 185mg/dl, trigliserid: 45mg/dl, HDL-K: 57mg/dl, LDL-K: 133 mg/dl, HBA1C: 8.1%, urine density: 1003. In the hormonal panel; FSH: 45U/L (N: 1.5-12.7), LH: 28.4U/L (N: 1.7-8.6), total testosterone: 3.83ng/ml (N: 3-10ng/ml), free testosterone: 2.15pg/ml (N: 12,00-30,00pg/ml). Serum GH, ACTH, cortisol, TSH, free T3, free T4, prolactin levels were normal. In the radiographic studies; bilateral gynecomastia was present in the breast ultrasonography. In the scrotal ultrasonography, bilateral testicles were in the scrotum and the sizes were normal. Urinary tract ultrasonography was reported as normal. In the hypophysis MRI, gland dimensions were normal and there were neither adenoma nor cystic lesions. In the bone mineral densitometry, the Z scores were -2.3 SD and revealed low bone mass for chronologic age. Spermiogram was reported as azoospermia. In the cytogenetic studies male karyotype 46, XY was confirmed.

The patient was admitted to the hospital. The fluid deprivation test was done and according to the test results the patient was diagnosed with diabetes insipitus. Desmopressin therapy was started as 1 nasal puff bid per day. With the intensive insulin therapy, the blood glucose levels were regulated. There were no diabetic macro or microvascular complications. Because the patient had the diagnosis of diabetes mellitus and diabetes insipitus together, he was searched for Wolfram syndrome. In the fundus examination, bilateral optic atrophy was found out. In the odyogram, the hearing loss with high-frequency sounds was considered to be associated with sensorineural deafness. According to clinical symptoms and laboratory findings, the patient was diagnosed with hypergonadotropic hypogonadism. As the treatment of primary hypogonadism testosterone propionate, phenylpropionate 250mg intramuscular once per three weeks was given. Because of the minimal regression of bilateral gynecomastia with testosterone therapy, the patient was consulted with plastic and reconstructive surgery. Mammoplasty, gland excision and liposuction according to clinical findings but the genetic analysis was negative.

Discussion

Wolfram syndrome is a very rare disease characterized by diabetes insipitus, diabetes mellitus, optic atrophy and sensorineural hearing loss [3]. The prevalence of the syndrome is 1/770.000. The prevalence in our country is not exactly documented, but it is estimated to be lower. In general, almost in all cases DM and optic atrophy are present. The frequency of DI is 10-83% and the frequency of sensorineural hearing loss is 51-83%. The first manifestation of Wolfram syndrome is diabetes mellitus, and the other manifestations are optic atrophy, diabetes insipitus, deafness, urinary tract abnormalities and neurologic abnormalities respectively. In our case, the first clinical manifestation is also diabetes mellitus. And the following manifestations are diabetes insipitus and optic atrophy.

Diabetes mellitus is the first manifestation of Wolfram syndrome and onsets in the first decade of life. In all the cases reported, diabetes mellitus is present and together with optic atrophy diabetes mellitus is essential for the diagnosis [2,7]. Diabetes mellitus is caused by lack of insulin due to pancreatic beta cell dysfunction and is not related to autoimmunity [8]. The insulin requirement is generally low. In our case with an insulin dosage of 24 unit per day, the glucose regulation is achieved. Also, the chronic complications of diabetes are less common in these cases. Especially diabetic retinopathy is infrequent and its progression is slower. Actually, in our case, despite the onset of diabetes mellitus was 18 years ago, neither diabetic retinopathy nor the other chronic complications were not present.

The optic atrophy in WS is usually bilateral and progressive. The onset of the optic atrophy is about the ages 11-13 in average, in our case optic atrophy was diagnosed about 24 years old but the findings had started in the former years. Sensorineural hearing loss onsets in the second decade. Also in our case hearing loss of high-frequency sounds was found out in the odyogram [9]. In tip 1 DM patients in whom there are findings that can be associated with Wolfram syndrome, it is important to make the differential diagnosis of Wolfram syndrome for early diagnosis and appropriate therapy. Thus, as in our case, assuming the complaints of polyuria and polydipsia to diabetes mellitus and its complications delayed the diagnosis. Hypergonadotrophic hypogonadism is manifested in 18-50% of the patients. In a case serial reported in Turkey, puberty tarda was manifested in two cases. In our case hypergonadotrophic hypogonadism was present. As in our case, the hypogonadism present in WS onsets in the third decade of life. There were no operation, trauma, infection or cytogenetic defect history that could be related with hypergonadotrophic hypogonadism. With the findings, no seconder reason was detected that could cause hypogonadism. So hypergonadotrophic hypogonadism was accepted as a component of WS. In the patient grade, 3 gynecomastia associated with gonadal insufficiency was detected.

Conclusion

As in our case, the patients diagnosed with WS requires long-term follow-up. With early diagnosis and appropriate hormone replacement the quality of patient's life and prognosis ameliorates.

References

1. Hardy C, Khanim F, Torres R (1999) Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. Am J Hum Genet 65(5): 1279-90.

2. Ökten A, Gedik Y, Demirci A, Mocan H, Erduran E, et al. (1995) Various clinical aspects of DIDMOAD (Wolfram) syndrome. The Turkish J of Ped 37(3): 235-240.

How to cite this article: Serhat Özcelik, Mehmet Sariyadin, Suleyman Bas, Bünyamin Aydin, Muhammed Kizilgul, et al. Wolfram Syndrome with Primary Gonadal Insufficiency. Glob J Reprod Med. 2018; 4(3): 555636. DOI: 10.19080/GJORM.2018.04.555636

3. Boutzios G, Livadas S, Marinakis E (2011) Endocrine and metabolic aspects of the Wolfram syndrome. Endocrine 40(1): 10-13.

4. Barrett TG, Bundey SE (1997) (DIDMOAD) syndrome. J Med Genet 34(10): 838-841.

5. Sahin M, Oguz A, Yilmaz S, Inanc E, Ozdemir M, et al. (2014) Wolfram syndrome with hypergonadotropic hypogonadism. Endocrine Abstracts 35: 638.

6. Bahçeci M, Tuzcu A, Bayan K, Çelik M (2002) A Case of Wolfram Syndrome. Turkish J Endocrinology and Metabolism 3:133-5

7. Kamel AJ, Nadim JA, Mohammed EK, Mohammed EZ, Hatem ES, et al. (2002) Wolfram syndrome: Identification of a Phenotypic and Genotypic Variant From Jordan. Am J Med Genet 115(1): 61-65.

8. Jayne AL, Lynne AR, Christopher R, Timothy GB (2003) Wolfram Syndrome. Reviews End Met Dis 4: 53-59.

9. Garcia Luna PP, Villechenous E, Leal Cerro A (1988) Contrasting features of insulin dependent diabetes mellitus associated with neuroectodermal defects and classical insulin dependent diabetes mellitus. Acta Paediatr Scand 77(3): 413-418.

DOI: 10.19080/GJORM.2018.04.555636

How to cite this article: Serhat Özcelik, Mehmet Sariyadin, Suleyman Bas, Bünyamin Aydin, Muhammed Kizilgul, et al. Wolfram Syndrome with Primary Gonadal Insufficiency. Glob J Reprod Med. 2018; 4(3): 555636. DOI: 10.19080/GJORM.2018.04.555636