# Wolfram Syndrome: Report of Two New Cases

Khadija Diyane*, Ghizlane El Mghari and Nawal El Ansari

*Department of Endocrinology, Ibn Tofaïl Hospital. PCIM Laboratory, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Rue el Mostachfa, Gueliz, 40 000, Marrakech, Maroc*

**Abstract:** Wolfram Syndrome (WFS) is a rare autosomal recessive disease. It is a progressive neurodegenerative disorder in which patients present with diabetes mellitus, optic atrophy, diabetes insipidus, sensorineural deafness, urologic abnormalities and multiple neurological abnormalities.

This study reports two sisters with late diagnosed wolfram syndrome with diabetes insipidus, diabetes mellitus, optic atrophy, deafness and urological abnormalities.

The condition should be evaluated in a multidisciplinary attitude and specific tests are necessary to make a precise diagnosis of the syndrome.

**Keywords:** Wolfram syndrome, diabetes Mellitus, Optic Atrophy, diabetes insipidus.

## INTRODUCTION

Wolfram Syndrome (WFS) is a rare autosomal recessive disease. It is a progressive neurodegenerative disorder in which patients present with diabetes mellitus, optic atrophy, diabetes insipidus, sensorineural deafness, urologic abnormalities and multiple neurological abnormalities, like cerebellar ataxia, myoclonus, and psychiatric illness early in the fourth decade [1-2].

This study reports two cases of two sisters with wolfram syndrome, which was not diagnosed until late. We want through these observations to raise awareness of clinicians to think of this syndrome.

## CASE PRESENTATION

### Case Report 1

First case is an 18-year old female patient with diabetes since the age of 8 years, treated with insulin with rather poor control of her blood sugar. She was admitted to endocrinology service complaining several hypoglycemia put at the expense of errors of injections of insulin. She has suffered progressive visual deterioration since 11 years ago. On fundoscopic examination, bilateral optic atrophy was recognized, and there was no evidence of diabetic retinopathy (Figures **1**, **2**). She has a history of nocturia, high urine output (24 liter per day) and voiding difficulty. Renal sonography showed pelvicalyceal dilatation in both kidneys equal to hydronephrose grade IV with bladder enlargement secondary to high urine output.

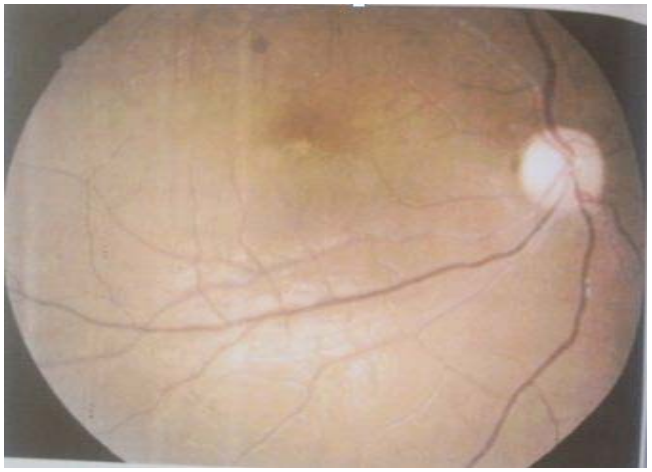

**Figure 1:** Photographic image of the patient right eye (Case report 1) showing optic atrophy without diabetic retinopathy.

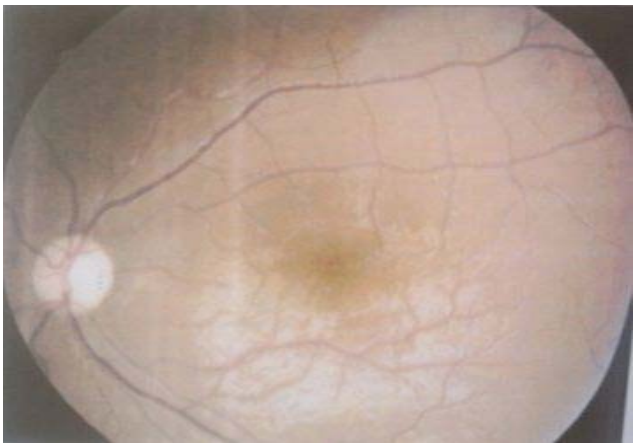

**Figure 2:** Photographic image of the patient left eye (Case report 1) showing the same aspect.

Accordingly wolfram was suspected. Diabetes insipidus was diagnosed in front of the high urine output and after starting desmopressine, urine output decreased and voiding difficulty improved. Audiometry showed

*Address correspondence to this author at the Lotissement Bennani Smires Azli Sud, Marrakech, Maroc; Tel: +212661070598;
E-mail: khadijadiyane@gmail.com, Khadija.diyane@hotmail.fr

E-ISSN: 2310-9971/14 

bilateral high frequency sensorineural hearing loss. Renal function, hepatic function, thyroid function and other blood test were normal. Metabolically, she had poor glycemic control with a mean HbA1c of 9%. The patient was treated with premix insulin at breakfast and dinner, and rapid insulin at lunch. There was a family history of similar conditions among her sister that we convened.

**Case Report 2**

First case has a 20-year old sister. She was diagnosed with diabetes at the age of 6 years and has been receiving insulin since then. She has had nocturia and polyuria (7 liter per day). Her visual acuity reduced on both sides. On fundoscopic examination, she has bilateral optic atrophy without diabetic retinopathy. Renal sonography showed pelvicalyceal dilatation in both kidneys equal to hydronephrose grade III with bladder enlargement. Subsequently wolfram was diagnosed for her and desmopressing started. Audiogram was normal. Renal and hepatic function, thyroid function and other blood tests were normal. However she had a poor glycemic control with a mean HbA1c of 10%. The patient was also treated by premix insulin at breakfast and dinner, and rapid insulin at lunch genetic study is underway for both cases.

## DISCUSSION

Wolfram syndrome (WFS) is a rare (1/770,000) autosomal recessive genetic disease [3]. However, much is known about the mechanisms underlying these effects. The causative gene (WFS1) was identified in 1998, and a number of loss-of-function mutations have been described [4]. The gene WFS1 encodes an endoplasmic reticulum membrane embedded protein nominated *wolframin* [5], and that mutant forms of the WSF1 protein is driving to endoplasmic reticulum stress apoptosis [6]. This process kills insulin producing pancreatic b-cells, leading to diabetes mellitus. WFS1 is also expressed throughout the brain, and cell death *via* endoplasmic reticulum stress is thought to underlie neurodegeneration in WFS.

Wolfram has an autosomal recessive mode of transmission. Although WFS with transmission dominant autosomal were described [7-8].

The minimum criteria for the diagnosis of Wolfram syndrome are the presence of diabetes mellitus and optic atrophy, declaring usually before the age of 15 years. Patients with wolfram present progressive ophthalmologic symptoms that usually occur after diabetes mellitus. Besides optic atrophy, decline visual acuity and color vision are the other ophthalmological findings in wolfram syndrome. Diabetic retinopathy in turn, it is rarely observed.

Our two patients had first type 1 diabetes in eight years for the one and in six years for the other one, which is consistent with the literature. A low visual acuteness was appeared in adolescence allowing the diagnosis of optical atrophy and secondary the diagnosis of syndrome of Wolfram. Both patients have a urologic signs, with a deafness of perception to the youngest.

Neurological disorders are many and varied, in particular to type of apnea of central origin and collapse of the superior air traffics at the origin of respiratory distress syndromes causes of certain deaths. The magnetic resonance imaging (MRI) highlights of brain atrophy images, in particular pontic and mesencephalic [9].

Other rather frequent manifestations can be associated with the cardinal signs, in particular the urinary manifestations which are a part of neurodegenerative signs, to type of sphincter dyssynergia and bladder dysfunction [2-10]. The insipidus diabetes is diagnosed in the second or third decade. He could be due to anomalies of the posterior lobe of the pituitary gland or to atrophy of the hypothalamus [11]. Finally, certain rare signs were described as a primary hypogonadism or a disorders of secretion of growth hormone [10].

The most common causes of mortality and morbidity are due to the neuropsychiatric symptoms and to the urologic complications (infections, renal insufficiencies) [11, 12]. The average age of the death is from 30 to 35 years on average [11].

## CONCLUSION

Generally cases having diabetes mellitus and optic atrophy need to be evaluated with respect to Wolfram. The condition should be evaluated in a multidisciplinary attitude and specific tests are necessary to make a diagnosis of the syndrome. Therapeutic progress could be a result from a better knowledge of the determinism of this affection.

## REFERENCES

[1] Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc 1938; 4: 715-8.

[2] Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 1995; 346: 1458-63. http://dx.doi.org/10.1016/S0140-6736(95)92473-6

[3] Barrett TG, Bundey SE, Fielder AR, Good PA. Optic atrophy in Wolfram (DIDMOAD) syndrome. Eye 1997; 11: 882-8. http://dx.doi.org/10.1038/eye.1997.226

[4] Rigoli L, Lombardo F, Di Bella C. Wolfram syndrome and WFS1 gene. Clin Genet 2011; 79: 103-17. http://dx.doi.org/10.1111/j.1399-0004.2010.01522.x

[5] Fonseca SG, Ishigaki S, Oslowski CM, Lu S, Lipson KL, *et al.* Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. J Clin Invest 2010; 120: 744-55. http://dx.doi.org/10.1172/JCI39678

[6] Ishihara H, Takeda S, Tamura A, *et al.* Disruption of the WFS1 gene in mice causes progressive beta-cell loss and impaired stimulus-secretion coupling in insulin secretion. Hum Mol Genet 2004; 13: 1159-70. http://dx.doi.org/10.1093/hmg/ddh125

[7] Seyhmus A, Ugur K, Ihsan C, Kaan U, Hasan K. Wolfram Syndrome: Case Report and Review of the Literature. Compr Ther 2007; 33: 18-20. http://dx.doi.org/10.1007/s12019-007-0007-z

[8] Prundean A, Barth M, Paquis-Flucklinger V, *et al.* Nouvelle mutation du gène WFS1 responsable du syndrome de Wolfram atypique de transmission autosomique dominante. Revue Neurologique 2012; 168: A1-A55. http://dx.doi.org/10.1016/j.neurol.2012.01.041

[9] Scolding NJ, Kellar-Wood HF, Schaw C, Shneerson JM, Antoun N. Wolfram syndrome: hereditary diabetes mellitus with brainstem and optic atrophy. Ann Neurol 1996; 39: 352-60. http://dx.doi.org/10.1002/ana.410390312

[10] Kumar S. Wolfram syndrome: important implications for pediatricians and pediatric endocrinologists. Pediatr Diabetes 2009; 11: 28-37. http://dx.doi.org/10.1111/j.1399-5448.2009.00518.x

[11] Kinsley BT, Swift M, Dumont RH, Swift RG. Morbidity and mortality in the Wolfram syndrome. Diabetes Care 1995; 18: 1566-70. http://dx.doi.org/10.2337/diacare.18.12.1566

[12] Collier DA, Barrett TG, Curtis D, *et al.* Linkage of Wolfram syndrome to chromosome 4p16.1 and evidence for heterogeneity. Am J Hum Genet 1996; 59: 855-63.

Received on 26-03-2014 Accepted on 25-11-2014 Published on 30-11-2014

DOI: http://dx.doi.org/10.12970/2310-9971.2014.02.03.2