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Wolfram syndrome in early adulthood: A Case Report

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Abstract

Wolfram Syndrome is autosomal recessive characterized by juvenile diabetes mellitus, optic atrophy and neurodegeneration. It was reported in 1938 by Wolfram and Wagener in four out of eight siblings who has diabetes and optic atrophy. The acronym DIDMOAD comprises of most common findings of the syndrome: Diabetes insipidus, diabetes mellitus, optic atrophy and deafness. Although a rare disease, it is associated with significant morbidity and mortality due to lack of effective treatment to halt, delay or reverse the progression of disease. The present study aims to report the case of an adolescent, 17 yaers old, born in Algeria with diabetes mellitus in the context of Wolfram syndrome. Moreover, we adress the need for interaction between different child health specialists to minimize the suffering experienced by patients with the disease and their families.

KeyWords: Walfram, optic atrophy, diabetes millitus, neurodegeneration.

* Introduction

Wolfram Syndrome is autosomal recessive characterized by juvenile diabetes mellitus, optic atrophy and neurodegeneration. It was reported in 1938 by Wolfram and Wagener in four out of eight siblings who has diabetes and optic atrophy [1]. The acronym DIDMOAD comprises of most common findings of the syndrome: Diabetes insipidus, diabetes mellitus, optic atrophy and deafness. The prevalence has been estimated to be 1/770,000 in the UK

and 1/100,000 in the North American population [2,3], 1/805,000 in India [4].In Algeria , no statistical data has been established in this sense.

Although a rare disease, it is associated with significant morbidity and mortality due to lack of effective treatment to halt, delay or reverse the progression of disease.

We present the only case of Wolfram Syndrome followed at our level, presented to medical OPD with diabetes millitus and sensorineural hearing loss.

*** Case Presentation**

S.A, a 17-year-old teen born in Tlemcen in western Algeria, to a couple consanguineous (first cousins) , presented with type 1 diabetes from the age of 4, the patient undergoes insulinic therapy.the glycemia has been compensated.

He develloped progressive bilateral visual diminution for seven years of age and progressive bilateral hearing impairment for 10 years of age.

Ophtalmological examination revealed visual acuity of 1/10 on the right and 0,5/10 on the left. The anterior segment examination was normal, and bilateral optic atrophy was found on fundoscopy(figure1). Optical coherence tomography (OCT) revealed decreased retinal fiber layer thickness (figure2)

Magnetic resonance imaging (RMI) demonstrated optic atrophy from the optic chiasm to the optic tract but did not show any causative lesion (figure3)

Pure tone audiometry revealed bilateral sensorineural hearing loss.

Renal function and diuresis were also preserved. The patient had a BMI of 21.5 kg/m2, an HbA1c rate of 10.8% Since 2022, the patient has been under the care of psychiatric services for depression and aggressive behavior, sleep disorders, and anxiety, for which he is receiving medication.

Given the consanguinity and the association of diabetes, optic atrophy, and hearing loss, the diagnosis of Wolfram syndrome was considered.

Unfortunately, the family declined genetic testing.

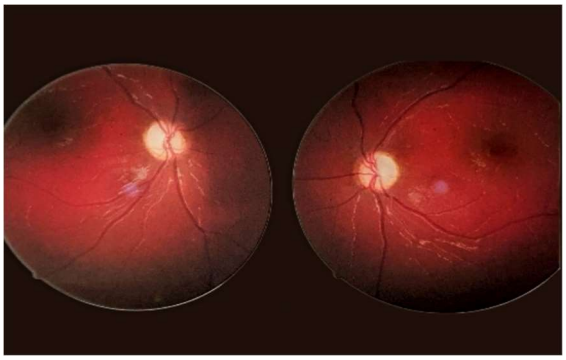

Figure 1: Fundoscopy showing bilateral optic atrophy

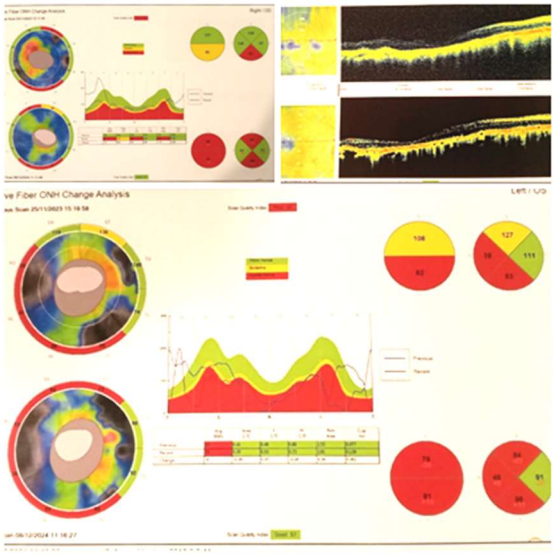

Figure 2: Decrease in the retinal fiber layer demonstrated by OCT

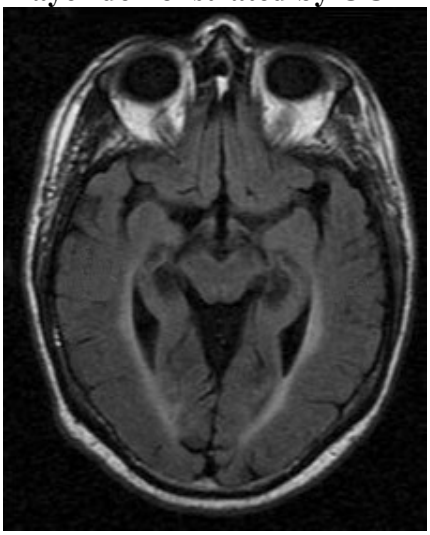

Figure 3: RMI showing bilateral optic atrophy

* Discussion

Wolfram syndrome is a rare autosomal recessive genetic disorder characterized by juvenile-onset diabetes and neurodegeneration. It is autosomal recessive. It usually involves multisystem diseases including diabetes insipidus (DI), diabetes mellitus (DM), visual atrophy (OA), and deafness (D); therefore, it is also known as DIDMOAD. Some patients present with growth retardation, hydronephrosis, or hypothyroidism.

sleep disturbances, and neurological symptoms [5]

The diagnosis was based on EURO. The WABB diagnostic criteria consist of major criteria such as diabetes mellitus and optic atrophy [8].

The clinical course of WS is characterized by different symptoms in chronological order, with non-immune insulin-independent diabetes mellitus generally starting at the age of 6 years, optic atrophy occurring at around 11 years, diabetes insipidus usually occurring at around 14 years, and sensorineural deafness gradually developing during late puberty [6].

Diabetes mellitus in Wolfram syndrome is classified as a type 3H diabetes associated with other genetic disorders. It is present in 98% cases of DIDMOAD;, however may not be the first presenting eature in 20% cases [7]. It is non-autoimmune, insulin-deficient, and non-HLA-linked [2]. Tests for insulin antibodies are usually negative. However, most patients are misdiagnosed with type 1 diabetes at the onset and are started on insulin therapy. The mean age of onset is 6 years of age [2]. It is not prone to, and is started on, insulin therapy. The mean age at onset was 6 years [2].

However, it is not prone to ketoacidosis.

In our case, it was detected at 5 years of age. Surprising and microvascular complications are not commonly observed even in adulthood [2]. Our patient showed no evidence of diabetic neuropathy, retinopathy, or nephropathy.

Optic atrophy is second most common feature of Wolfram syndrome, occurring in 82% cases.

It presents as painless progressive bilateral diminution of vision. The mean age of onset was 11 years [8]. In our case, the onset occurred at five years of age. Te treatment is usually based on corrective lenses. Other ophthalmic features like cataract, pigmentary retinopathy, and diabetic retinopathy, occur in 66.6%, 30%, and 20% cases, respectively [9].

Urinary tract anomalies may present at 12 to 20 years of age in approximately 19% cases [8]. Central Diabetes insipidus is seen in 38 % cases of Wolfram syndrome [6]. The mean age of onset was 14 years [8]. In the present case, it was detected at 22 years of age. Water deprivation tests are difficult to perform in view of the underlying diabetes mellitus. Serum AVP levels and brain MRI help to confirm the diagnosis in cases of polyuria.

Sensorineural hearing loss was observed in 48% cases [8]. The mean age of onset is 16 years of age [2]. Our patient had sensorineural hearing loss over the past 10 years, which occurred earlier than previously reported.

All four components of DIDMOAD- diabetes mellitus, Diabetes Insipidus, Optic Atrophy and Sensorineural Hearing Loss– were seen 14% to58% [2,10]. Wolfram syndrome is suspected in patients with diabetes mellitus and optic atrophy in early adolescence.

Neurological manifestations, such as cerebellar ataxia, central apnea, anosmia, and peripheral neuropathy, may occur at a median age of 30 years. Psychiatric disorders, such as anxiety, depression, and psychosis, may be observed in patients with Wolfram Syndrome. Gastrointestinal manifestations, such as peptic ulcers, diarrhea, or constipation, may also be present in some cases. Hyponatremia and hypogonadism due to pituitary insufficiency have been reported [2,10]. The cause of mortality is usually central respiratory failure due to brain stem atrophy and renal failure due to infection [2].

Wolfram syndrome is a manifestation of the WFS1 gene, located on chromosome 4p16.1. The

Te WFS 1 protein is located in the Endoplasmic Reticulum (ER) and functions to maintain homeostasis via Unfolded Protein Response (UPR) pathways. In cases of defective WFS1, ER stress leads to endocrine dysfunction and neuronal degeneration [11,12]. There is currently no cure for Wolfram syndrome, and several studies have been conducted on drug repurposing, gene therapy, and agents targeting ER stress [13].

In conclusion, Wolfram syndrome should be considered in patients with juvenile-onset diebetes millitus and hearing loss. This should be suspected early in adolescents with juvenile diabetes and optic atrophy. Therefore, a multidisciplinary approach is vital for such patients. Managing the manifestations, complications, and rehabilitation of patients with the disease is necessary.

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