Wolfram syndrome: a case report.

Abstract: Wolfram syndrome is a rare autosomal recessive disorder characterized by juvenile-onset diabetes mellitus, optic atrophy, and neurodegeneration. Originally described by Wolfram and Wagener in 1938. We report the case of a 16 year old female patient with Wolfram Syndrom.

Key words : Genetic ; Optic atrophy ; Diabetes ; Adolescent; Deafness.

Introduction :

Wolfram Syndrome is a rare autosomal recessive disorder characterized by juvenile-onset diabetes mellitus, optic atrophy, and neurodegeneration. First described in 1938by Wolfram and Wagener, .(1) it is also known as DIDMOAD, reflecting its key features: Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness. The prevalence varies, estimated at 1/770,000 in the UK and 1/100,000 in North America (2;3). Despite its rarity, Wolfram Syndrome leads to significant morbidity and mortality due to the lack of effective treatments to stop or reverse disease progression.

Case studies :

We report the case of a 16-year-old female patient with no siblings; followed for diabetes since the age of 1 year on insulin; as well as a deafness detected at the age of 8 years which required a hearing aid; who consulted for progressive lost of vision for several years bilaterally.

Ophthalmological examination revealed visual acuity of 210 OD and 1/10 OG, with corrected myopia of -2.D OD and -3.5D OG.

Examination of the anterior segment was strictly normal. Fundus revealed bilateral optic atrophy, with no evidence of diabetic retinopathy.

Papillary OCT showed a fiber thickness of 47µm on the right and 51µm on the left. CV showed superior and inferior fascicular involvement.

On a general level, the patient presented with recurrent urinary tract infections secondary to a urinary tract anomaly; a cerebral CT scan returned normal.

Discussion :

Wolfram syndrome is a rare autosomal recessive disorder marked by juvenile-onset diabetes and neurodegeneration. Diagnosis follows the EURO-WABB criteria, with diabetes mellitus and optic atrophy as major diagnostic features.(4)

The diabetes in Wolfram syndrome is classified as Type 3H (genetic diabetes) and occurs in 98% of DIDMOAD cases, though in 20% of patients;it may not be the initial symptom.(5) Unlike type 1 diabetes, it is non-autoimmune, insulin-deficient, and not HLA-linked, with typically negative insulin antibodies.(2) However, many patients are initially misdiagnosed with type 1 diabetes and started on insulin therapy. The average age of onset is 6 years, and the condition is not prone to ketoacidosis (our case was detected at age 5).Interestingly, microvascular complications (retinopathy, neuropathy, nephropathy) are uncommon, even in adulthood—our patient showed no such signs. (2)Nonetheless, insulin therapy remains the standard treatment for glycemic control, as supported by previous case reports.

Optic atrophy represents the second most frequent clinical feature of Wolfram syndrome, affecting approximately 82% of patients. This condition manifests as a gradual, painless loss of vision in both eyes, typically beginning around 11 years of age. (5)While corrective lenses remain the primary therapeutic approach, additional ocular complications may develop, including cataracts (66.6% of cases), pigmentary retinopathy (30%), and diabetic retinopathy (20%) [6].

Wolfram syndrome presents with a constellation of endocrine, neurological, and sensory impairments. Central diabetes insipidus develops in approximately 38% of affected individuals, with a typical onset around 14 years of age.(5) Diagnostic confirmation in these cases requires serum arginine vasopressin (AVP) measurement and neuroimaging.

Sensorineural hearing loss represents another frequent complication, affecting nearly half of all cases (48%)(5) with a mean onset at 16 years(2). Notably, our patient manifested this feature unusually early at 8 years of age. Genitourinary involvement, particularly neurogenic bladder with pelvicalyceal system dilatation as seen in our 16-year-old patient, occurs in about 19% of cases.(5)

The complete DIDMOAD tetrad (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) appears variably in 14-58% of patients.(2;7) This diagnostic combination,

particularly when emerging in early adolescence, should prompt consideration of Wolfram syndrome.

The disease progression typically leads to neurological deterioration (cerebellar ataxia, peripheral neuropathy) by the third decade; psychiatric comorbidities including depression and psychotic features; endocrine dysfunction secondary to pituitary insufficiency.(2;8)

Wolfram syndrome results from mutations in the *WFS1* gene located on chromosome 4p16.1. The WFS1 protein plays a crucial role in cellular homeostasis by regulating the unfolded protein response (UPR) pathway. Deficient WFS1 function leads to ER stress, which subsequently causes endocrine dysfunction and progressive neurodegeneration [9,10].

While no definitive cure currently exists for Wolfram syndrome, several therapeutic approaches are under investigation. These include drug repurposing strategies, gene therapy interventions, and novel compounds targeting ER stress pathways [11]. Current research efforts focus on developing treatments to modify disease progression and alleviate symptoms.

Conclusion :

In summary, Wolfram syndrome is a rare but severe neurodegenerative disorder characterized by multisystem involvement. Early clinical suspicion is crucial, particularly in adolescents presenting with juvenile-onset diabetes mellitus and optic atrophy. Given the complex nature of the disease, a coordinated multidisciplinary approach is essential for comprehensive management of its diverse manifestations, prevention of complications, and optimization of patient rehabilitation and quality of life.

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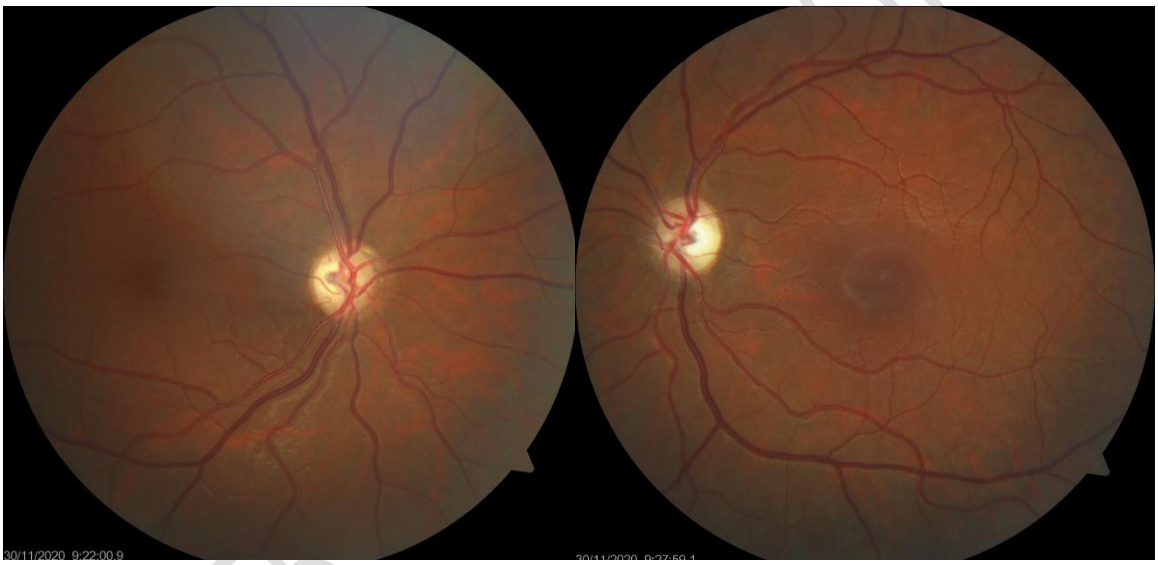

Figure 1 :Fundus revealed bilateral optic atrophy

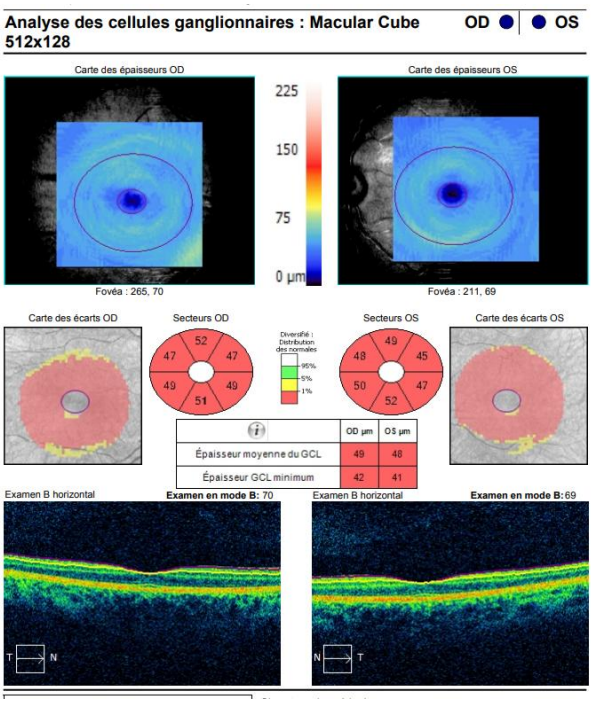

Figure 2 :OCT scanning .