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CASE REPORT

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Wolfram Syndrome with Variable Presentation: Case Series Experience from Royal Hospital, Oman

Nagla Nassor[1]*, Hanan Al-Zkawi [1], Mouza Al-Yahyai[2] and Shaima Al Madhani[3]

[1]National Diabetes and Endocrine Center, Royal Hospital, Oman

[2]National Diabetes and Endocrine Center, Oman

[3]Royal Hospital-Child Health Department, Oman

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Background

Wolfram syndrome (WS) is an extremely rare genetic disorder that can cause dysfunction of multiple organs and systems in the body. The symptoms of this syndrome typically include diabetes mellitus, optic atrophy leading to visual impairment, deafness, diabetes insipidus causing excessive thirst and urination, neurological signs such as seizures and muscle weakness, and other abnormalities such as urinary tract problems and psychiatric disorders. WS is caused by mutations in two genes, WFS1 and WFS2, which are responsible for the clinical features of the syndrome. Although the disease is usually inherited as an autosomal recessive, autosomal dominant mutations have also been identified as WS-related disorders.

The clinical presentation of WS can be highly variable and sometimes misleading, making it difficult to diagnose. In this report, we present a case series of genetically confirmed Wolfram syndrome patients with varying phenotypic presentations to increase awareness about this rare syndrome. By shedding light on the diverse symptoms and manifestations of WS, we hope to improve the diagnosis and management of this challenging disorder.

Case Presentation

Case 1

Currently a twelve-year-old Omani female child, at the age of 4 years, presented with episodes of symptomatic hypoglycemia (2.0-3.0 mmol/l). The critical sample was not sent as the hypoglycemia episodes were treated before collecting the critical sample. She was admitted for a challenged controlled fasting test. However, she didn't develop hypoglycemia, but the c-peptide and insulin levels were appropriate for fasting (151pmol/L and 20pmol/L, respectively). The other hormonal profile and metabolic workup were not confirmed as she didn't develop hypoglycemia during the test. At the age of six years, she was presented with gradual hyperglycemia, initially fasting hyperglycemia then post-prandial hyperglycemia. The investigations revealed high C-Peptide and insulin levels (2660pmol/L and 260.5pmol/L), negative autoantibodies (Anti GAD and Anti Islet Cell antibodies), normal Thyroid function test, negative thyroid peroxidase antibodies, and negative anti-tissue Transglutaminase antibodies for celiac disease. There is a positive family history of Type 2Diabètes Mellites (T2DM) in grandparents. The parents are consanguineous. The father of the child has a history of episodes of high blood glucose, mainly post-prandial, however, it is not constant, and not on medication or regular medical checkups. Examination of the child revealed a well-thriving child. The weight and height are between the 25th and 50th percentile. She has no dysmorphic features. There is no goiter and no evidence of autoimmune disease. The systemic examination was unremarkable. The Continuous Glucose Monitoring (CGM) showed a blood glucose range between 8-15mmol/l, with an occasional reach of 20mmol/l after the meal. The child started on subcutaneous insulin injection. She started with basal insulin initially as she had fasting hyperglycemia. With follow-up, she was noticed to have post-prandial hyperglycemia. Hence, she also started on a meal bolus subcutaneous insulin injection. During the follow up she was noticed to have persistent ketonuria without sickness or hyperglycemia. Initially was treated with intravenous fluid, however, later was advised to drink plenty of water. She has normal renal function, normal electrolytes, and no metabolic acidosis. The glycemic control during the follow-up was good as the glycated HB(HBA1c) was between 5.6-6.5%. The mother later requested for insulin pump which commenced at the age of 8 years. The child requires very minimal insulin doses, she takes it as basal with very occasional meal bolus. It was not understood why the child had very good glycemic control with minimal insulin doses, while children of this age and in our culture usually have suboptimal glycemic control, this is based on our experience. On the other hand, the mother has good adherence to dietary control and the child is thriving well. We investigated the accuracy of glycated hemoglobin (HbA1cC) and found that

Contact: Nagla Nassor, National Diabetes and Endocrine Center, Royal Hospital, Oman.

the patient has HbA/E hemoglobinopathy but not G6PD deficiency. We consulted with the hematology team and confirmed that HbA/E usually doesn't cause hemolysis. A fructose amine level test showed HbA1C accuracy, and CGM confirmed accurate glycemic control with almost 97% of blood glucose within target. The child has normal annual checkups for diabetic-related complications, including a retinal check of renal function, and microalbuminuria. The child has a genetic test as the diabetes presentation and progression suggestive of Maturity Onset Diabetes of Youth (MODY). It was reported as A heterozygous variant in the Wolfram Syndrome 1 (WFS1) gene. Mutation in this gene is associated with an autosomal dominant nonclassical WFS1 spectrum disorder. Further recommendation for this case is to screen for associated morbidities (optic atrophy, Diabetes Insipidus, deafness, and neurological assessment). The parents were counseled for the genetic test result of their child and further plans were discussed.

	At presentation BG: 5.0mmol/l	Controlled fasting BG: 4.2mmol/l	Before starting insulin therapy BG: 5.5mmol/l	On insulin at age of 7 years BG:4.0mmol/l	Off insulin at the age of 9 years BG: 5.5mmol/l	Last visit At 12 years BG:4.9mmol/l
C- peptide (260-1710)pmol/L	558	152	2660.0	193	1758	649.5
Insulin (18-260)pmol/L	63.6	20.4	462.5		515.3	86.6
HBA1C	5.3%		5.1%			5.3%
s. Na (136-145)mmol/l						139
s. Osmolality (275-295)mosm/kg						278
u. Osmolality mosm/kg						1017

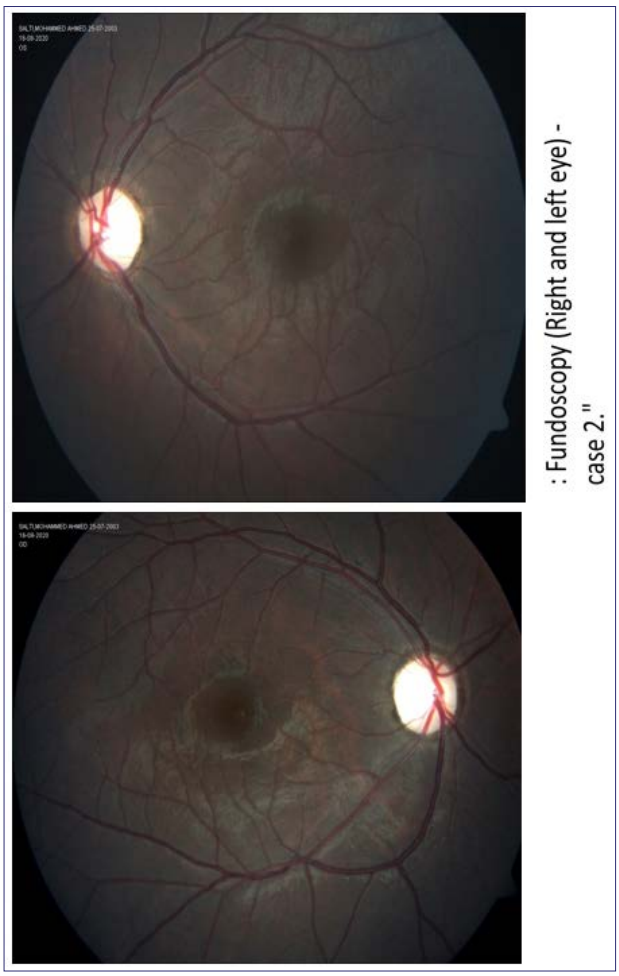
Table 1: Case -1 Biochemical Values:

Metabolic workup result: negative urine-reducing substance, normal ammonia, and lactate, normal CK, normal blood g.Metabolas, negative urine organic acid normal Gal-1-P uridyltransferase, normal Gal-1-P, normal fructose 1,6 bisphosphoatase).

These results rule out classical galactosemia, GALT variants, and a typical form of fructose bisphosphatase deficiency.

Case 2

The present report describes an Omani male who was diagnosed with type 1 diabetes mellitus (T1DM) at the age of five. The patient presented with symptoms of polyurea, weight loss, and hyperglycemia, as evidenced by a blood glucose level of 28.8mmol/l. Notably, the patient had negative autoantibody markers and no ketonuria or acidosis. The patient's parents were consanguineous and a family history of T2DM was reported in the patient's grandfather. He was examined and found to be well-thriving, with no dysmorphic features. However, a squint in the right eye was noted. The other systemic examination was unremarkable. After diagnosis, the patient was started on subcutaneous insulin injection with a basal and meal bolus regimen for T1DM. However, during follow-up, poor glycemic control was observed despite HbA1c ranging between 6.8-7.5%. He was screened for factors affecting HbA1c accuracy and was found to have glucose-6-phosphate dehydrogenase deficiency with a high fructose amine level, corresponding to HbA1c of 11-12%. At the age of 10, the patient was switched to an insulin pump and showed good compliance and response. At the age of 12, the patient was genetically tested for Wolfram syndrome (WFS) due to optic atrophy reported by an ophthalmologist. The genetic test revealed a homozygous variant in the WFS1 gene, which is associated with autosomal recessive WFS. The patient's parents were also tested and found to have a heterozygous variant in the WFS1 gene. Appropriate counseling was provided to the parents regarding the genetic test result. The patient was followed up regularly for over 10 years at the National Diabetes and Endocrine Center and had detailed screening for WFS-associated disorders. He had bilateral atrophied optic nerves and confirmed mild sensorineural hearing loss, which progressed to moderate in subsequent follow-up. However, the patient had no other neurological manifestations or diabetes insipidus (DI). The patient's visual acuity deteriorated during early adolescence at the age of 11 and progressed to complete blindness in the right eye by the age of 13. Annual screenings done at the age of 17 showed no retinopathy, nephropathy, or neurological manifestation. He is currently 18 years old and is under follow-up at the National Diabetes Center, adult Diabetic clinic, and other multi-specialty teams. However, long-term follow-up and monitoring for this case will be challenging.



: Fundoscopy (Right and left eye) - case 2."

Case 3

A ten-year-old Omani male child, was diagnosed with diabetes with negative anti-Islet antibodies and anti-GAD antibodies. He was presented with polyurea, hyperglycemia, and glycosylated hemoglobin was 8 %. Examination of the child revealed a well-thriving child. The weight and height are between the 25th and 50th percentile. There is no goiter. The system examination was unremarkable. The investigation revealed negative autoantibodies (Anti GAD and Anti islet cell antibodies), normal Thyroid function test (FT4 and TSH), negative thyroid peroxidase antibodies, and negative anti-tissue Transglutaminase antibodies for celiac disease. The child has mild valvular pulmonary stenosis under follow-up with the pediatric cardiology team. The parents are consanguineous, they have three healthy children. There is a positive family history of T2DM in both maternal and paternal grandfathers. Since the diagnosis the child has been running a mild course of hyperglycemia with correlating HBA1C for more than a year, hence it was thought with the evidence of negative antibodies that he might have one type of MODY. For which, whole exome sequencing (WES) was sent to him. With time his continuous Glucose Monitoring (CGM) showed a blood glucose range between 7-14mmol/l, and for that, he was started on a subcutaneous low dose of insulin injection (0.3-0.5u/kg/day), basal and meal bolus insulin regimen. Genetic testing revealed a homozygous variant was identified in the WFS1 gene. Pathogenic variants in this gene are associated with autosomal recessive Wolfram syndrome 1 mutation for wolfram syndrome. The parents were tested for the targeted WFS1 gene, and the results are still awaited. The parents were counseled about the genetic test result of their child and further plan was discussed. The child was screened for the associated morbidities. He has no clinical or biochemical evidence of diabetes insipidus (DI). He was referred for a hearing assessment to look for evidence of sensorineural deafness which was excluded. He also was referred to an ophthalmologist, who excluded optic atrophy.

Case 4

A ten-year-old Omani female, who was diagnosed with diabetes at the age of 2 years old with a history of polyurea and polydipsia and found to have severe DKA, with A1C of 11% and negative anti-Islet cell antibodies and anti-GAD antibodies. The child also has global developmental delay, autism, and seizure disorder and she is following up with a pediatric neurologist. She also had a small PDA which closed spontaneously. The parents are consanguineous. Two siblings of the patient have the same neurological issue, but not diabetes. The child's examination followed. that both weight and height are below the 3rd percentile for her age and gender. She has profound neurological disabilities. The investigations showed negative autoantibodies with normal thyroid function tests. CT head showed brain atrophy. The child is on a multi-daily dose of insulin with glargine and regular insulin. She is on regular follow-ups with us, and her metabolic control is suboptimal. She is also on follow-up with pediatric neurology and a genetic specialist. She and her two siblings have the same neurological problems, hence an autosomal recessive inheritance was suspected, for which a genetic study was done. Surprisingly genetic testing has revealed two different genes PGAP1gene which is responsible for the profound neurological symptoms and developmental delay and a homozygous likely pathoogenic variant in the WFS1 gene. The information presented is of utmost importance in developing effective treatment plans for individuals suffering from the aforementioned condition along with other comorbidities linked to the coexisting gene that is responsible for the profound encephalopathic state.

	Optic atrophy	Hearing assessment	Diabetes insipidus	Genetic test	MRI/CT
Case 1	Not Present	Not Present	Not present	Heterozygous variant in the WFS1 gene. Autosomal dominant nonclassical WFS1 spectrum disorder.	Not done
Case 2	Present	sensorineural hearing loss	Not present	Homozygous variant in the WFS1 gene. Autosomal recessive Wolfram syndrome 1	Absent bright spot of neurophysis and atrophic optic nerve
Case 3	Not Present	Not Present	Not present	Homozygous variant in the WFS1 gene. Autosomal recessive Wolfram syndrome 1.	Not done
Case 4	Not Present	Left ear hearing loss	Present	Homozygous likely pathogenic variant in the WFS1 gene. Autosomal recessive Wolfram syndrome 1.	Brain atrophy

Table 2: Summary of the clinical presentation and genetics results for the case 1-4

Discussion

Wolfram syndrome is a rare genetic disease with an estimated prevalence of about 1 in 160,000–770,000. However, it has a higher rate in Arab countries due to consanguinity. Although there is a high prevalence of consanguineous marriages in the Middle East and North Africa, only a few cases of Wolfram syndrome have been reported from these regions. It is therefore reasonable to assume that the condition is under-reported in this part of the world. In Lebanon, it is thought to be responsible for up to 5.5% of the cases of juvenile-onset diabetes. There are two genes identified in Wolfram syndrome: WFS1 (4p16.1) and CISD2 (WFS2)(4q24). Mutations in the WFS1 gene are responsible for more than 90% of Wolfram Syndrome type 1 (WS1) cases. The majority of mutations in these genes have an autosomal recessive mode of transmission, but autosomal dominant mutations have also been described in association with WS-like disease. The WFS1 gene produces wolframine found in the ER, which regulates calcium and unfolded protein response. CISD2 gene produces ERIS, a small protein that maintains ER and mitochondria membrane integrity, and facilitates communication between these two compartments. WFS1 gene mutation leads to reduced or absent function of wolframin protein. This leads to unregulated calcium levels in cells and dysfunction of the endoplasmic reticulum, which causes cell death. The death of cells in various body systems results in diabetes, optic nerve atrophy, hearing loss, and neurodegeneration. The nonclassical WFS1 spectrum is a milder form of autosomal dominant disorder, which generally has a later onset and a wider range of symptoms than classic Wolfram syndrome. Typically, diabetes mellitus is the usual presentation of WFS. However, there have been no records of hypoglycemia associated with hyperinsulinism as an initial presentation. Considering that beta cell apoptosis is a known characteristic of the disease, insulin deficiency and hyperglycemia are expected features.

Conclusion

Wolfram Syndrome is a rare genetic syndrome with progressive neurological deterioration. Therefore, genetic testing to identify mutations is crucial in the clinical management of the syndrome. The implications of this study can have far-reaching effects on the management of the condition and related comorbidities. Therefore, it is imperative that this information be taken into account in the development of treatment protocols for the affected individuals with this rare syndrome [1-13].

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