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Case Report

Wolfram Syndrome 1 in Two Brothers Treated with Insulin Pump

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ABSTRACT

Background/Objective: Wolfram syndrome (WS) is a rare genetic disorder, in which patients develop early-onset diabetes mellitus (DM), optic nerve atrophy, and neurodegeneration, which has no specific treatment available. Here, we report 2 brothers treated with an insulin pump to manage the alterations of the glycemic levels due to the DM.
Case Report: We present the case of 2 siblings diagnosed with Wolfram syndrome 1, they presented with typical endocrinological and neurodegenerative early manifestations, one brother was treated with a sensor-augmented insulin infusion system, and the other with an insulin pump. Both reached a better metabolic state and had improved quality of life.
Discussion: The management of WS is still a challenge; however, the use of a sensor-augmented insulin infusion system and the information that it provides may offer better care to patients who require frequent monitoring and adjustments in their treatment. It has been reported that the neurodegenerative progression of WS is also associated with high glucose peaks; therefore, it is necessary to control it, even when it is hard due to the difficult-to-manage DM. There is only 1 previous case report of WS with insulin pump that describes the benefits of continuous subcutaneous insulin infusion and tight metabolic control during pregnancy.
Conclusion: The use of insulin pumps may be an effective treatment for DM in WS patients, mainly in terms of improving the prognosis of difficult-to-manage DM.

Introduction

Wolfram Syndrome (WS) or Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness is a rare autosomal recessive disorder characterized by the presence of diabetes insipidus, early-onset diabetes mellitus (DM), optic atrophy (OA), deafness, urological dysfunction, and neurodegeneration.[1,2] WS has an estimated prevalence of 1 in 770,000 people in the United Kingdom and is more common in areas with higher rates of consanguinity.[2,3]

Among the disease-causing genetic variants, those affecting the WFS1 gene are particularly noteworthy. The WFS1 gene encodes for a transmembrane protein located in the endoplasmic reticulum (ER) and exhibits significant expression in brain tissue, pancreatic β-cells, heart, lung, and placenta. Pathogenic variants in WFS1 are responsible for the classic form of Wolfram syndrome, commonly referred to as WFS1.[2,4] The genetic variants in WFS1 lead to the accumulation and response of unfolded proteins in the ER, which induces stress, and when it chronifies along with physiologic or pathologic processes, it stimulates cell apoptosis.[4,5] Thus, the pancreatic and neuronal cells are affected, which explains the appearance of DM and neurodegeneration.[4,5] As a marker of progression, DM has garnered particular interest because it is the earliest feature to be recognized and consequently controlled; it is remarkable due to the strong correlation between metabolic control of DM, the number of associated symptoms, and the progression of neurodegenerative diseases.[5,6]

Despite the poor prognosis of WS, with premature deaths occurring in the fourth decade of life, an early diagnosis is crucial to ensure that patients receive the appropriate care and multidisciplinary management, especially in terms of avoiding the metabolic imbalance associated with DM.[1,2,4] Here, we present the case of 2

Abbreviations: CGM, continuous glucose monitoring; DM, diabetes mellitus; ER, endoplasmic reticulum; HbA1c, Hemoglobin A1c; MDI, multiple daily injections; OA, optic atrophy; SIIS, sensor-augmented insulin infusion system; WS, Wolfram syndrome.

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siblings with WFS1, who were treated with an insulin pump to control DM and stabilize their metabolic state. Our institution has approved the use of this case report and informed consent has been obtained from the patients.

Case Report

Case 1

A 25-year-old Colombian man, whose parents are cousins, was diagnosed with DM at the age of 3 years. Subsequently, he developed bilateral OA and neurosensory hearing loss. The patient's diagnosis of WS was genetically confirmed at the age of 17 years, and biallelic compound heterozygous variants WFS1 c.315+1G>A and c.589G>A, were identified. The first variant had not been previously reported in patients with WS and was considered a likely pathogenic variant. The second variant was reported as a variant of uncertain significance in the VarSome database. In 2016, at the age of 19 years, the patient was diagnosed with peripheral neuropathy in the lower limbs related to DM. In April 2018, he had a blood glucose level of 279 mg/dL, a hemoglobin A1c (HbA1c) level of 9.7% (83 mmol/mol), and wide glycemic variability. Eight months later, the studies showed blood glucose level of 300 mg/dL, and HbA1c of 10.2% (88 mmol/mol). In August 2019 he discontinued Insulin glargine 30 units per day and Insulin glulisine 25 to 30 units per day and was referred for start on sensor-augmented insulin infusion system (SIIS) with a weight of 48.5 kg, blood glucose level of 340 mg/dL, and HbA1c level of 10.4% (90 mmol/mol). The SIIS consists of a continuous glucose monitoring (CGM) system (Guardian Sensor 3; Medtronic), Quick set Minimed infusion system (Medtronic) (6 mm), a 3 ml reservoir, and IV3000 dressings to protect the sensor. After 2 years of starting SIIS, the patient weighed 50 kg and had a blood glucose level of 126 mg/dL and HbA1c of 7.4% (57 mmol/mol). In August 2022 and January 2023, he had an HbA1c of 8.3% (67 mmol/mol) (Table 1).

Case 2

The second case was of a 22-year-old Colombian man, the brother of the first patient. DM was diagnosed at the age of 3 years, and the patient similarly developed OA and deafness in the next years, receiving a diagnosis of WS in 2014. The genetic study revealed biallelic compound heterozygous variants, WFS1 c.315+1G>A and c.589G>A. This patient was diagnosed with diabetes insipidus, primary hypothyroidism, asthma, and dermatitis. In 2019, the patient discontinued insulin degludec 32U once a day and insulin glulisine 10 units with each meal, and he was prescribed an insulin pump with insulin aspart, with a weight of 50 kg, a blood glucose level of 418 mg/dL and an HbA1c of 13% (119 mmol/mol).

After starting the insulin pump, blood glucose levels were maintained <180 mg/dL from 2019 to 2022, and in 2023, it increased to 211 mg/dL. However, HbA1c had a more variable behavior, fluctuating from 7.5% (58 mmol/mol) in 2020, 7.3% (56 mmol/mol) in 2021, 9.5% (80 mmol/mol) in 2022, and 8.5% (69 mmol/mol) in 2023; he also weighed 51 kg this year (Table 2).

Table 1
Blood Glucose and Hemoglobin A1c Levels of the First Patient Over a Period of 6 Years

	Year				
	2018	2019[a]	2021	2022	2023
Blood Glucose Levels (mg/dL)	300	340	126	—	—
HbA1c (%)	10.2	10.4	7.4	8.3	8.3

Abbreviation: HbA1c = Hemoglobin A1c.
— The values of blood glucose levels in 2022 and 2023 are unknown.
[a] This year the SIIS was started.

Highlights

- Wolfram syndrome (WS) is a poor prognosis disease; its treatment is based on metabolic control of diabetes mellitus.
- Insulin pump is a good option to control dysregulated diabetes mellitus.
- Hemoglobin A1c and time-in-range values are better controlled with a sensor-augmented insulin infusion system than other types of therapies.
- Using an insulin pump can generate a positive impact on the lifestyle of WS patients.

Clinical Relevance

We present 2 siblings with Wolfram syndrome (WS) treated with insulin pump and sensor-augmented insulin infusion system therapies. This approach has been shown to be effective in the improvement of some important metabolic variables like time-in-range and hemoglobin A1c, as well as in these patients' lifestyles. This is important due to the lack of information about the treatment approach of WS.

Discussion

The management of WS remains a challenge, as the progression of neurodegeneration is the primary cause of death in patients with the disease, and despite considerable efforts to improve and expand treatment options, the most effective interventions are those related to the metabolic control of diabetes.[2,6] A correlation has been registered between postprandial hyperglycemic peaks and the progression of the neurodegenerative course, in addition to glucose toxicity being considered an accelerating factor in the progression of the disease, besides the tissue and neuronal damage characteristic of high and sustained ER stress levels.[2,6,7] To avoid complications associated with either hypoglycemia or hyperglycemia, insulin therapy remains the first-line treatment for difficult-to-control DM; however, the method of insulin delivery has generated significant debate among health care providers.[8-11]

Blood glucose monitoring and CGM are essential tools for evaluating therapy and detecting incipient hypoglycemia.[12] Blood glucose monitoring is particularly useful for individuals treated with insulin to control and prevent both hypoglycemia and hyperglycemia.[8,12] Regular use of CGM in combination with insulin pumps for the configuration of SIIS has been shown to decrease HbA1c levels and hypoglycemic episodes, improve the glucose time-in-range (TIR), and provide psychosocial benefits.[8,12] Additionally, CGM allows the creation of an ambulatory

Table 2
Blood Glucose and Hemoglobin A1c Levels of the Second Patient Over a Period of 5 Years

	Year				
	2019[a]	2020	2021	2022	2023
Blood Glucose Levels (mg/dL)	418	122	173	172	211
HbA1c (%)	13	7.5	7.3	9.5	8.5

Abbreviation: HbA1c = Hemoglobin A1c.
[a] This year the insulin pump was started.

glucose profile and provides ongoing data on TIR, time above the range, time below the range, and glycemic variability, which is especially useful with patients who require frequent monitoring and adjustments to their treatment,[8-10,12] such as those with WS who usually develop difficult-to-treat DM. In the first presented case, a TIR of 75% was achieved, and in both cases, blood glucose levels, HbA1c, and weight were mostly within the expected range, indicating good metabolic control of the disease.

There is only 1 previous case report of WS and insulin pump in 2011 that described the first case in India of a successful pregnancy in a WS patient; the authors described the benefits of continuous subcutaneous insulin infusion and tight metabolic control in the prevention of abortions and fetal malformations in DM associated with pregnancy and WS.[13] In our patients, despite having the same genetic variant, due to individual characteristics, the first patient was treated with SIIS, and the second with an insulin pump only. It is important to consider that treatment with an insulin pump has some benefits related to the patient's adherence; however, individuals with neurodegeneration can report some difficulties, like in our WS patients who have had poor adherence to treatment, specifically in the daily use and care of the device.

In contrast to other exogenous insulin therapies, SIIS has undergone several improvements in recent years and has been found to be more effective in reducing HbA1c levels and severe hypoglycemia than other therapies, such as multiple daily injections (MDI),[8-10] which was used by our patients before starting with the insulin pump. A systematic review of 11 cost-effectiveness articles on SIIS versus MDI in 8 countries showed that although SIIS is approximately 1.4 times more expensive than MDI, this cost is partially offset by savings resulting from the reduction of complications from DM due to better metabolic control.[11] Additionally, there is an improvement in patient satisfaction and quality of life, as well as a reduction in the risk of diabetic ketoacidosis, retinopathy, and peripheral neuropathy in difficult-to-manage DM cases.[8,9]

Our findings suggest that both the use of insulin pumps and SIIS can effectively improve glycemic variability, prevent hypoglycemia, and enhance the quality of life in patients with WS. HbA1c and TIR values were better controlled in our patients compared with other previously used methods of insulin delivery, such as MDI. More studies are needed to confirm these findings and investigate the long-term outcomes of this treatment approach.

Disclosure

The authors have no multiplicity of interest to disclose.

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Author Contributions

M.C.G., A.A.G., J.D.S., and A.R.G. designed the presentation of case report research; J.D.S. and A.R.G. evaluated patient care; M.C.G. and A.A.G. wrote the manuscript; M.C.G., A.A.G., J.D.S., and A.R.G. revised the final manuscript.

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