A Case of Persistent Polyuria in an Insulin-Dependent Child With Diabetes

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Presentation

A 10-year-old girl presented with complaints of polyuria, polydipsia, intermittent abdominal pain, and poor growth. She was diagnosed with diabetes at the age of 6 years and had been taking insulin ever since. She had been hospitalized previously with diabetic ketoacidosis (DKA). There was no history of parental consanguinity or similar illness in her sibling or other family members.

On evaluation, she had severe short stature (height 110 cm, <5th percentile), low body weight (15 kg, <5th percentile), and prepubertal sexual development. She had a fasting plasma glucose of 185 mg/dL, postprandial plasma glucose of 250 mg/dL, and A1C of 10.2%. Liver function, renal function, and serum electrolytes were normal.

Euglycemic status was achieved with insulin therapy. Ultrasonography of the abdomen and pelvis showed bilateral, moderate hydroureteronephrosis, with the ureter dilated up to the distal end (Figure 1). Urodynamic studies were consistent with neurogenic bladder.

During insulin therapy, she had two episodes of hypoglycemia (blood glucose <40 mg/dL) but was completely asymptomatic. Despite achieving euglycemia, her osmotic symptoms and urine output (4.2 L/day) did not improve. Baseline urine specific gravity and osmolality measurements were low. The possibility of diabetes insipidus was raised, and a formal water deprivation test (WDT) was done. WDT and positive response to desmopressin confirmed the diagnosis of central diabetes insipidus.

The patient's parents provided history of the child having poor vision. Ophthalmological evaluation revealed visual acuity of 3/60 (left eye) and 5/60 (right eye). Fundoscopy showed bilateral primary optic atrophy (Figure 2).

Based on these findings, a diagnosis of Wolfram syndrome was made. The optic atrophy and diabetes insipidus were crucial clinical markers prompting us to look for Wolfram syndrome. MRI of the pituitary and brain revealed nonvisualization of a posterior pituitary bright spot and normal anterior pituitary (Figure 3). Pure tone audiometry showed bilateral sensorineural hearing loss. Lack of an appropriate facility precluded genetics studies.

After achieving euglycemia and improvement in other clinical parameters, the patient was discharged with an optimized insulin regimen and desmopressin spray for inhalation. Her parents were educated about intermittent self-catheterization for neurogenic bladder management.

Questions

1. What is Wolfram syndrome?
2. What is its pathological basis?
3. When should a clinician suspect Wolfram syndrome?
4. How is Wolfram syndrome different from classical type 1 diabetes?
5. What are other monogenic forms of diabetes?

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Commentary

Wolfram and Wagener gave the first description of Wolfram syndrome in 1938. They described a family in which four siblings developed bilateral optic atrophy and diabetes mellitus, followed by deafness, incontinence, and ataxia (1). DIDMOAD is the acronym for the classical and cardinal signs of the disease, which include diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (2). Wolfram syndrome is a rare, progressive, neurodegenerative disorder. Patients present with nonautoimmune and non-HLA–linked diabetes mellitus associated with optic atrophy in the first decade of life. Diabetes insipidus and sensorineural deafness follow in the second decade, renal tract abnormalities early in the third decade, and multiple neurological abnormalities such as cerebellar ataxia, myoclonus, and psychiatric illness early in the fourth decade (3). The incidence is estimated to be 1/770,000 live births (4). The prevalence, severity, and age of onset of the various manifestations of this syndrome have not been consistently reported (5).

The basic genetic defect results from a mutation in the *WFS1* gene, located on chromosome 4p16.1, which encodes the protein wolframin (3,6). Recently, Wolfram syndrome 2 has been described and is caused by mutation in the *CISD2* gene on chromosome 4q22-q24, which encodes the protein ERIS (endoplasmic reticulum [ER] intermembrane small protein) (7).

Wolframin is a transmembrane glycoprotein localized in the ER. This protein has been characterized as part of the unfolded protein response, which is a cellular stress response induced by the accumulations of unfolded proteins within the ER lumen. This response is a key factor in maintaining cellular homeostasis. Loss of this function by alteration of the *WFS1* gene is thought to result in chronic ER stress, leading to apoptosis in pancreatic β-cells, neuroendocrine cells, and neuronal cells. Together, these processes result in a progressive decline of endocrine and neuroendocrine function (8). Since the discovery of the association between the *WFS1* gene and Wolfram syndrome, more than 150 mutations have been identified in Wolfram syndrome patients (9).

Wolfram syndrome has a distinctly different clinical trajectory from that of type 1 diabetes. Patients with the syndrome have a lower incidence of DKA at diagnosis, much lower insulin requirements in the first several years after diagnosis, rare microvascular complications, and nonautoimmune diabetes, as compared to those with type 1 diabetes (10,11). The average age of diabetes onset in Wolfram syndrome has been reported to be younger than that in type 1 diabetes (4).

Wolfram syndrome patients usually die from central respiratory failure as a result of brain stem atrophy in their third or fourth decade (3). Multiple endocrine disorders such as hypogonadism, hypothyroidism, and growth failure are also associated with Wolfram syndrome.

The neurological damage associated with the impaired unfolded protein response underlying Wolfram syndrome is believed to cause impairment in the body's ability to recognize low blood glucose levels associated with insulin treatment. The prevalence of severe hypoglycemic episodes in patients with Wolfram syndrome is significantly higher than in those with type 1 diabetes (8,11). Chronic oxidative stress induced by chronic hyperglycemia exacerbates ER stress and possibly enhances the neurodegenerative process inherent in the disease (11).

Monogenic forms of diabetes occur as a result of mutation in a single gene, which is both necessary and sufficient to cause the disease (12,13). The monogenic forms of diabetes usually are diagnosed in younger patients, often in the first two to three decades of life (13). Depending on the clinical presentation, they can be confused with either type 1 or type 2 diabetes (12). Wolfram syndrome is one form of monogenic diabetes. MODY

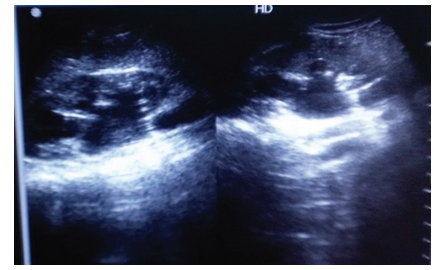

FIGURE 1. Ultrasound scan photograph showing moderate hydroureteronephrosis with ureteric dilation up to distal end.

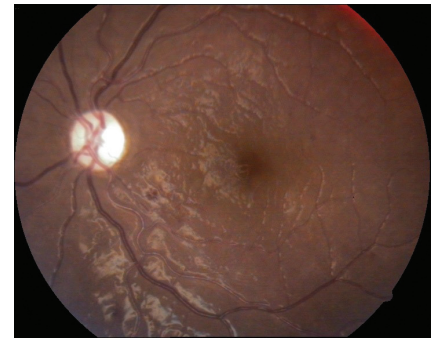

FIGURE 2. Fundus photograph showing primary optic atrophy.

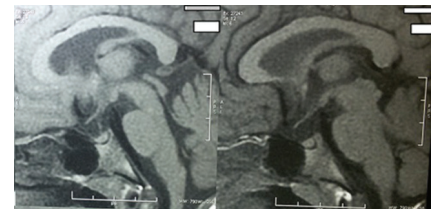

FIGURE 3. MRI of pituitary region showing absence of posterior pituitary bright spot.

(maturity-onset diabetes of the young) is a genetically and clinically heterogeneous group of disorders characterized by nonketotic diabetes mellitus; an autosomal dominant mode of inheritance; onset usually before 25 years of age and often in childhood or adolescence; and a primary defect in pancreatic β-cell function (13). Neonatal diabetes mellitus (NDM) usually manifests before 6 months of age. Patients with NDM present with marked hyperglycemia with or without ketoacidosis (13). NDM can be either transient or permanent. Transient NDM usually resolves at 6–12 months of life but often recurs later. Table 1 describes various clini-

TABLE 1. Forms of Monogenic Diabetes With Their Associated Mutations, Clinical Findings, and Management (12,13)

Monogenic Forms of Diabetes	Genetic Locus of Mutation	Important Diagnostic Findings	Treatment Modality
MODY (maturity-onset diabetes of the young)			
MODY 1	HNF4A	Increased birth weight/macrosomia	Sensitive to sulfonylurea Treatment; may progress to require insulin
MODY 2	GCK	Mild fasting hyperglycemia	Usually not required except in pregnancy (may require insulin)
MODY 3	HNF1A	Low renal glucose threshold (glycosuria), raised HDL cholesterol, increased cardiovascular risk	Sensitive to sulfonylurea Treatment; may progress to require insulin
MODY 4	IPF1	Early- to late-onset diabetes (heterozygous form), pancreatic agenesis (homozygous)	
MODY 5	HNF1B	Renal cystic disease, genitourinary anomaly, pancreatic atrophy	
MODY 6	NEUROD1	None	
NDM (neonatal diabetes mellitus)			
Transient NDM (TNDM)	UDP6 (most common)	Macroglossia and umbilical hernia	Insulin
	K_{ATP} channel (ABCC8 and KCNJ11)	Developmental delay and epilepsy	Sulfonylureas (high dose)
Permanent NDM (PNDM)	K_{ATP} channel (ABCC8 and KCNJ11)	Developmental delay and epilepsy	Sulfonylureas (high dose)
	INS	None	Insulin
Wolcott-Rallison syndrome	EIF-2Ak3	Spondylo-epiphyseal dysplasia, renal and acute hepatic failure, developmental delay	Insulin
Lipoatrophic diabetes			
Koberling-Dunnigan syndrome	LMNA	Face-sparing partial lipoatrophy	Insulin/leptin
Berardinelli-Seip syndrome	AGPAT2 or seipin gene product	Congenital generalized lipoatrophy	Insulin/leptin
Diabetes with extra pancreatic features			
RCAD syndrome	HNF1B	Renal cysts, exocrine pancreatic deficiency, genitourinary abnormalities	Insulin
Wolfram syndrome	WFS1	Optic atrophy, diabetes insipidus, deafness, renal tract and neurological abnormalities	Insulin
MIDD	Mitochondrial m.3243A>G mutation	Neurosensory deafness, maternal diabetes or deafness, short stature, pigmentary retinopathy	Oral sulfonylurea initially, but rapid insulin requirement
TRMA syndrome	SLC19A2	Megaloblastic anemia, deafness, cardiac and neurological abnormalities	Thiamine and/or sulfonylurea and/or early insulin
Insulin resistance syndrome			
Type A insulin resistance	Insulin receptor	Hyperandrogenism, acanthosis nigricans, insulin resistance (HAIR-AN)	Metformin, thiazolidinediones, insulin

TABLE CONTINUED ON P. 112 →

TABLE 1. Forms of Monogenic Diabetes With Their Associated Mutations, Clinical Findings, and Management (12,13) *continued from p. 111*

Monogenic Forms of Diabetes	Genetic Locus of Mutation	Important Diagnostic Findings	Treatment Modality
Insulin resistance syndrome continued from p. 111			
Leprechaunism (Donohue syndrome)	Insulin receptor	IUGR, fasting hypoglycemia, lipoatrophy, and death in infancy	Insulin (high doses)
Rabson-Mendenhall syndrome	Insulin receptor	Short stature, protuberant abdomen, and abnormalities of teeth and nails; coarse senile facies; paradoxical fasting hypoglycemia	Insulin (high doses)

ABCC8, ATB-binding cassette subfamily C; AGPAT2, 1-acyl-sn-glycerol-3-phosphate acyltransferase-2; GCK, glucokinase; EIF-2Ak3, eukaryotic translation initiation factor 2-alpha kinase 3; HAIR-AN, hyperandrogenism, insulin resistance, and acanthosis nigricans; HNF, hepatocyte nuclear factor; INS, insulin gene; IPF, insulin promoter factor; IUGR, intrauterine growth retardation; K_{ATP} channel, adenosine triphosphate-sensitive potassium channel (ABCC8 and KCNJ11); KCNJ11, potassium inwardly rectifying channel, subfamily J, member 11 gene; LMNA, lamin A/C; MIDD, maternally inherited diabetes and deafness; mitochondrial m.3243A>G mutation, heteroplasmic G to A substitution of the mitochondrial DNA at nucleotide pair 3243 in one of the two tRNA(Leu) genes; NeuroD1, neurogenic differentiation 1; RCAD, renal cysts and diabetes; SLC19A2, solute carrier family 19, member 2 gene; UDP6, uniparental disomy 6 chromosome (6q24) abnormality; TRMA, thiamine responsive megaloblastic anemia; WFS1, Wolfram syndrome 1 (wolframin).

cally important monogenic forms of diabetes (12,13). The association of diabetes mellitus with optic atrophy also occurs in Friedreich's ataxia, Refsum's disease, Alstrom syndrome, Lawrence-Moon syndrome, and Kearn-Sayre syndrome. However, these diseases can be excluded because of their distinct features.

Our patient presented with a relatively severe phenotype featuring diabetes mellitus, diabetes insipidus, optic atrophy, severe urological abnormalities, hearing loss, and growth failure evident at 10 years of age. She suffered from significant hypoglycemia unawareness, which posed a challenge to offering a more intensive blood glucose control regimen.

Clinical Pearls

- Early distinction of Wolfram syndrome from type 1 diabetes is crucial. Hence, all clinicians caring for children with diabetes should be aware of this entity.
- The presence of optic atrophy, polyuria despite optimal glycemic control, or unexplained sensorineural hearing loss should alert providers to explore the possibility of Wolfram syndrome.
- Wolfram syndrome patients suffer from significant hypoglycemia unawareness, and this should be kept in mind when prescribing insulin therapy.
- A multidisciplinary team effort is needed to manage this rare and difficult-to-treat disease.

Acknowledgment

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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