

Wolfram syndrome Q&A

Q: What is Wolfram syndrome?

A: Wolfram syndrome is a genetic form of diabetes mellitus. In addition to diabetes mellitus, most patients suffer from optic nerve atrophy and neurodegeneration, especially brain stem and cerebellar atrophy.

Q: What is diabetes mellitus?

A: Diabetes mellitus is a group of disorders characterized by hyperglycemia (high blood sugar levels). This is due to either an absolute deficiency of insulin, as occurs in type 1 diabetes and Wolfram syndrome, or a relative deficiency of insulin, as occurs in type 2 diabetes.

Q: What is diabetes insipidus?

A: Diabetes insipidus is one of the common symptoms in patients with Wolfram syndrome. It is defined as the passage of large volumes of dilute urine. It has the 2 major forms, and patients with Wolfram have the central diabetes insipidus.

1. Central (neurogenic, pituitary, or neurohypophyseal): characterized by decreased secretion of antidiuretic hormone called vasopressin.
2. Nephrogenic: characterized by decreased ability to concentrate urine because of resistance to vasopressin action in the kidney.

Q: What is optic atrophy? Is it different from retinopathy? Is there any treatment?

A: The mechanisms of vision impairment in Wolfram syndrome and type 1 diabetes are different. In short, the vision impairment in type 1 diabetes is a problem in small blood vessels supplying nutrition to the eyes. It is caused by high blood sugar levels and called retinopathy.

The vision impairment in Wolfram syndrome is a problem in neuronal cells in the eyes transferring the electrical signal produced in the eye to the brain. It is caused by neuronal cell death and called optic atrophy.

There is currently no treatment for optic atrophy. One of the major neuronal cells in the eyes declining in Wolfram syndrome are “retinal ganglion cells” which transmit electrical signals to the brain. If we can make these cells and transplant them to Wolfram patients, we can possibly treat blindness or improve eyesight. To accomplish this, we need a source for new retinal ganglion cells. I believe that induced pluripotent stem cells (iPSCs) is the source for the new retinal ganglion cells.

Q: “Is there any relationship between diabetes and optic nerve atrophy?”

A: This question implies a few different things. Here are my answers.

1. Type 1 Diabetes

I believe that there is no direct relationship between type 1 diabetes and optic atrophy. Type 1 diabetes is an autoimmune disease. Our immune cells attack antigens highly expressed in pancreatic β cells in type 1 diabetes. These autoimmune cells usually do not attack optic nerve although patients with type 1 diabetes are susceptible to other autoimmune diseases. As I mentioned in my previous blog, patients with type 1 diabetes may develop retinopathy if their blood sugar levels are not properly controlled.

2. Wolfram syndrome

In Wolfram syndrome, there is probably a direct relationship between diabetes and optic nerve atrophy. Both pancreatic β cells and optic nerve are susceptible to endoplasmic reticulum dysfunction. So β cell death and death of retinal ganglion cells have the same etiology, i.e. ER dysfunction.

3. Do all patients with Wolfram syndrome have diabetes and optic nerve atrophy?

The answer is, “No.” In most cases, diabetes is the first manifestation of Wolfram syndrome, followed by optic atrophy. However, there are some patients who develop optic atrophy first and don’t develop diabetes for a long period of time. I know one patient with Wolfram whose diabetes was diagnosed at 40 years old. I don’t know why, but it seems like these patients tend to have milder symptoms.

Q: What can you do to improve “neurogenic bladder” ?

A: Many patients with Wolfram syndrome experience neurogenic bladder. I always recommend that a patient consult with an urologist if he/she has a problem in urination. Here are my thoughts.

1. What is neurogenic bladder?

Our urination is regulated by two types of muscles in the bladder. These are the detrusor muscle and sphincter muscle. When we urinate, the detrusor muscle pushes out the urine and the sphincter muscle relaxes to open up the way out. These muscles are controlled by a part of the brain and neuronal cells connected to the bladder. Neurogenic bladder is a term applied to dysfunction of the bladder due to dysfunction of a part of brain and neuronal cells. In short, this is a problem in neuronal cells.

2. What can you do?

I always recommend that a patient see a urologist to determine the status of neurogenic bladder and get advice.

3. Our progress

As I mentioned in my previous blog, our recent progress strongly suggests that neuronal cell dysfunction in Wolfram syndrome is caused by dysregulation of cellular calcium homeostasis. We are developing a treatment to manipulate the calcium homeostasis in patients' cells using a drug, and making significant progress. I hope that my strategy will work out.

Q: What are electrolytes and sodium?

A: Electrolytes are “salts” in our blood and cellular fluids. The difference between the concentrations of these salts inside and outside the cells regulates the contraction of muscle cells and the signal transduction in brain cells (neurons). Sodium is the major salt outside the cells. The reference range for serum sodium is 135-145 mmol/L.

It seems like some patients with Wolfram syndrome experience “low sodium.” Our body regulates sodium levels by balancing water in the body with use of antidiuretic hormone. DDAVP is often prescribed for patients with Wolfram syndrome because they tend to produce less antidiuretic hormone and produce excess amount of urine. DDAVP is a synthetic antidiuretic hormone, regulates the body's retention of water, and decreases the volume of urine. The challenge for Wolfram patients is that they tend to have bladder problems and may need to go to bathroom often. This is not because of the excess production of urine, but they may increase the dose of DDAVP, which increases the body's retention of water and may lead to low sodium levels. As our colleague Dr. Marshall recommends, Wolfram patients should consult with their endocrinologists if they feel their serum sodium levels are low.

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In addition, serum sodium levels may not be reliable when patients have poor renal functions or have severe hyperglycemia.

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