‘Why are my diabetes symptoms getting worse?’

During a routine follow-up visit, a 15-year-old male with type 1 diabetes has complained of decreased visual activity and worsening of his polydipsia and polyuria. His past medical history included being diagnosed for type 1 diabetes at the age of eight years and under poor control due to lack of parental supervision. His review of systems was negative for chest pain, claudication and headache. His family history included type 2 diabetes in his paternal grandmother who suffered a vision loss attributed to it.

His physical examination showed bilateral mild optic nerve atrophy. There was no thyromegaly. Tanner staging was 4. Laboratory testing showed haemoglobin A1c of 12.8% and negative urine microalbumin.

The possibility of diabetes complications affecting the eyes and kidneys was considered, although it was unlikely due to the relatively short duration of diabetes. Ophthalmology consultation confirmed the bilateral optic nerve atrophy without any diabetic retinopathy. This prompted consideration of Wolfram (DIDMOAD) syndrome that consists of diabetes insipidus, diabetes mellitus, optic nerve atrophy and deafness. Extensive laboratory work-up including water deprivation test confirmed the diagnosis of diabetes insipidus. The patient was started on DDAVP (desmopressin) therapy; his polydipsia and polyuria resolved. He started complying better with his diabetes care.

Genetic testing showed a mutation in the WFS1 gene confirming the diagnosis of Wolfram syndrome type 1. Auditory testing did not show any hearing deficit. The patient and family were sent for genetic counselling. The aetiology and prognosis of different organ involvement of the syndrome were explained, including blindness, deafness and urinary dysfunction as well as the usual prognosis of diabetes.

Discussion

Wolfram syndrome is an autosomal recessive neuro-endocrine degenerative disorder. The syndrome is also known as DIDMOAD as mentioned above.

The first and major aspect of Wolfram syndrome is a persistent hyperglycaemia that is insulin dependent in a young child most commonly diagnosed as type 1 diabetes. Other organ involvement may start occurring later and may present at different times in life. Optic nerve atrophy is often the next sign to appear after diabetes. Diabetes insipidus affects almost 70% of patients with this syndrome while deafness occurs in around 65%. Other conditions that may occur with this syndrome include hypogonadism, urinary tract problems and neuropsychiatric disorders. Many cases of Wolfram syndrome may remain misdiagnosed as type 1 diabetes mellitus. Some patients may be misdiagnosed with complications of diabetes due to renal and ophthalmic symptoms. Diabetes complications, however, are extremely rare in paediatric diabetes patients.

Genetically, there are two types of Wolfram syndrome. Type 1 is the most common type (90%) and is due to mutations in the WFS1 gene. This gene provides instructions for producing a protein called wolframin that is thought to regulate the amount of calcium in cells. Wolframin’s function is important to produce functional proinsulin. WFS1 gene mutations lead to the production of a wolframin protein that has reduced or absent function which triggers apoptosis of beta cells in the pancreas causing diabetes and in the optic nerve leading to blindness.

Wolfram syndrome type 2 is caused by another mutation in the CISD2 gene which causes the production of a defective protein in the mitochondria that leads to its death. When multiple organ involvement is seen in young patients with diabetes, certain syndromes should be considered including Wolfram syndrome or mitochondrial disorders.

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References