WOLFRAM SYNDROME PRESENTING AS DIABETIC KETO ACIDOSIS- A CASE REPORT

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HOW TO CITE THIS ARTICLE: Jayaprakash S, Majumdar SS, Singh H, et al. Wolfram syndrome presenting as diabetic keto acidosis- a case report. J. Evid. Based Med. Healthc. 2018; 5(12), 1106-1108. DOI: 10.18410/jebmh/2018/229

PRESENTATION OF THE CASE

Wolfram syndrome, named after the physician D J Wolfram is a rare inherited neurodegenerative disorder. It is characterised by diabetes insipidus, juvenile-onset insulin dependent diabetes mellitus, optic atrophy, and deafness, and hence is also known as DIDMOAD syndrome.[1] Prevalence rates among the general population vary from 1 in 100,000 in North America to 1 in 770,000 in UK.[2,3] The syndrome is caused by a defect in wolframin protein, a 100 kDa transmembrane protein localizing in the Endoplasmic Reticulum encoded by the WFS1 gene located in Chromosome 4p16.1. The protein is involved in the regulation of ER stress and calcium homeostasis and is found in abundance in pancreas, brain, heart and muscle.[2] Two modes of inheritance of Wolfram syndrome have been documented, Autosomal recessive and Mitochondrial.[4]

The natural history of Wolfram syndrome begins with Diabetes mellitus at a median age of 6 years and progressive optic atrophy at a median age of 11 years, followed by central diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade and multiple neurological abnormalities early in the fourth decade of life. Diabetes mellitus and optic atrophy are reported in all cases, but the expression of other features of the syndrome are variable.[5,6] Wolfram syndrome patients rarely present with ketoacidosis as they usually maintain a significant level of C-peptide in the blood. Here we report one such rare case.

A 23-year-old male presented to the emergency room with complaints of pain abdomen and altered sensorium. He had no history of fever, headache, vomiting, convulsions or trauma. His past history revealed that he had been on treatment from alternate system of medicine for complaints of polyuria and polydipsia for the past nine years. He has also had progressive loss of vision for 4 years due to which his schooling was discontinued. He denied any history of deafness. Born to parents from a non-consanguineous marriage, he attained his developmental milestones as per age with normal secondary sexual characteristics. Anthropometrically his height was 154 cm, weight was 48 kg and BMI 20.23 kg/m^2. Per abdomen there was tenderness in the right iliac fossa.

Ophthalmic examination revealed bilateral horizontal nystagmus with exotropia of Left eye. Visual acuity was 1/60 bilaterally. On fundoscopy, there was bilateral optic atrophy (Fig 1) but no evidence of diabetic retinopathy. Pure tone audiometry showed a sensorineural deafness pattern.

DIFFERENTIAL DIAGNOSIS

1. Type 1 diabetes mellitus with diabetic ketoacidosis precipitated by acute appendicitis.
2. Wolfram syndrome (type 1 diabetes mellitus and optic atrophy) presenting as diabetic ketoacidosis.

CLINICAL DIAGNOSIS

Young male with optic atrophy and type 1 diabetes presenting as diabetic ketoacidosis, we thought of clinical diagnosis of wolfram syndrome.

PATHOLOGICAL DISCUSSION

Wolfram syndrome was first described in 1938 by Wolfram and Wagner as a hereditary syndrome characterised by diabetes mellitus and optic atrophy acquired in early life. Subsequent reports added diabetes insipidus and deafness to the syndrome, which develop in approximately 73% and 62% of the cases respectively.[3,7]

The minimum criteria for diagnosis are juvenile onset diabetes and optic atrophy. However, patients also present with additional complications and hence the acronym DIDMOAD (Diabetes insipidus, Diabetes mellitus, Optic atrophy and Deafness) is used. The diagnostic criteria for Wolfram syndrome is shown in table 1.[8]

The pathogenesis of the disease remains unknown, but genetic linkage studies suggest mutations of the WFS1 genes responsible for the symptoms in 90% of the cases meeting specific diagnostic criteria. This gene is located on the short arm of chromosome 4 (4p16). The WFS1 gene encodes an 890 amino-acid called wolframin, a putative multispanning membrane glycoprotein of the endoplasmic reticulum.

Our case report is rare in the sense that only 3 percent of wolfram syndrome present as diabetic ketoacidosis. Even though symptoms of diabetes were present much before, it was not diagnosed earlier. While the mean age of diagnosis is 6-15 years, our patient was diagnosed only at 23 years of age. Pure tone audiometry was suggestive of sensory neural hearing loss. We also noted the absence of central Diabetes

Financial or Other, Competing Interest: None.
Submission 26-02-2018, Peer Review 03-03-2018,
Acceptance 12-03-2018, Published 19-03-2018.
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DOI: 10.18410/jebmh/2018/229

insipidus in our case. Imaging findings were optic atrophy, partial empty sella. GAD 65 antibody was negative indicating the non-immune nature of diabetes. Juvenile onset diabetes mellitus, optic atrophy and sensory neural deafness clinches to the diagnosis of Wolfram syndrome. Genetic studies can confirm the diagnosis. Early diagnosis and proper management can improve the quality of life and prevent the complications and provide opportunity for genetic counselling also.

Major Criteria	Minor Criteria	Minimum Required
1. Diabetes mellitus <16 yrs.	1. Diabetes insipidus.	2 Major
2. Optic atrophy <16 yrs.	2. Diabetes mellitus>16 yrs.	or
	3. Optic atrophy>16 yrs.	1 Major Plus
	4. Sensory neural deafness	2 Minor
	5. Neurological signs (ataxia, epilepsy, neuropathy, cognitive impairment)	
	6. Renal tract abnormalities	
	7. 1 loss of function mutation in WFS1/CISD2-AND/ OR family history of Wolfram syndrome	

Table 1. The Diagnostic Criteria For Wolfram Syndrome

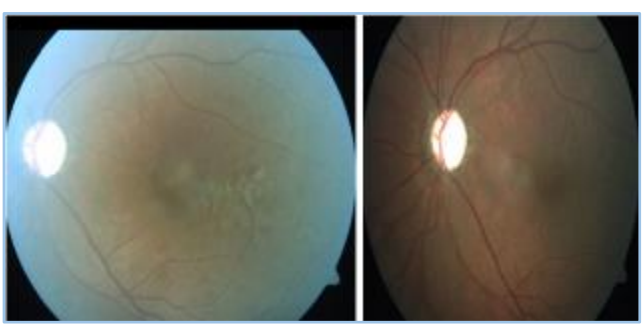

Figure 1. Fundoscopy Showing Optic Atrophy

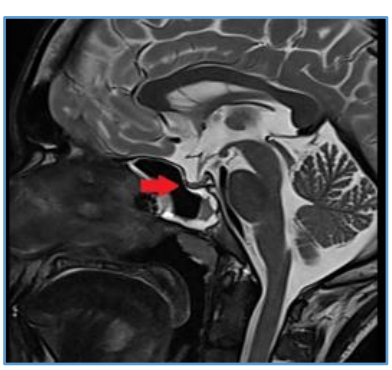

Figure 2. MRI Brain Showing Partial Empty Sella

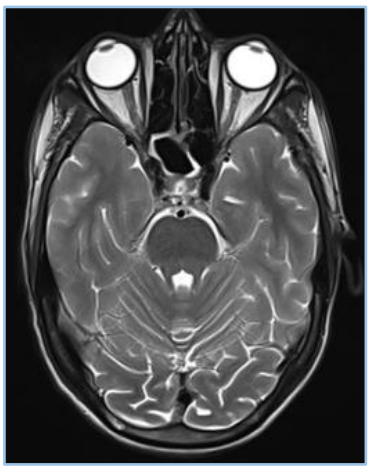

Figure 3. MRI Brain Showing Bilateral Optic Atrophy, Left>Right

DISCUSSION OF THE MANAGEMENT

His investigations revealed normal Renal, Hepatic and Thyroid parameters. Water deprivation test, ECHO cardiography and USG KUB was also normal. His blood sugars were high (416 mg/dl), urinary ketones positive and blood gas analysis revealed high anion gap metabolic acidosis. USG abdomen showed acute on chronic appendicitis. GAD 65 antibodies were negative. MRI brain discovered diffuse atrophy of bilateral optic nerves, retrobulbar, intra-canalicular, retrocanalicular segments and optic chiasma with a partial empty sella. (Fig. 2 & 3)

Ophthalmologic consultation was taken which revealed nystagmus both eyes, with exotropia (Lt). On fundoscopic examination bilateral optic atrophy was seen with no evidence of diabetic retinopathy. His urine osmolality, serum osmolality, urine sodium and water deprivation test were normal. USG KUB did not reveal any urogenital abnormalities. His pure tone audiometry revealed sensorineural hearing loss. His GAD 65 antibodies were negative. He was managed as a case of Type 1 DM with diabetic keto acidosis precipitated by acute appendicitis. He was started on insulin infusion, intravenous fluids, broad spectrum antibiotics. He had hypokalaemia on Second day of admission, managed with potassium supplements. For acute appendicitis surgical consultation was taken and planned for interval appendicectomy after glycaemic control. He was put on basal, bolus regimen of insulin after 72 hrs and discharged with the advice of regular follow up.

FINAL DIAGNOSIS

23-year-old male with optic atrophy, sensorineural hearing loss and Type 1 diabetes presenting as keto acidosis, the final diagnosis was Wolfram syndrome.

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