Case Report

Unusual association of priapism with Wolfram syndrome

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ABSTRACT

Wolfram syndrome is an autosomal recessive disorder resulting from mutation of *WFS1* gene located on 4p16.1 and is characterized by diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy, and sensorineural deafness with features of neurodegeneration, renal anomalies, and primary gonadal atrophy. Priapism itself is a rare disease with isolated reports in association with type-2 DM due to change in coagulation status causing endothelial dysfunction and local vascular thrombosis leading to ischemic priapism. Here, we present a case of a 14-year-old male with type-1 DM and optic atrophy who was presented to us with two episodes of priapism. He was suspected to have Wolfram syndrome and his genetic evaluation for *WFS-1* gene confirmed the diagnosis. Our case suggests that priapism is an atypical association in patient with the Wolfram Syndrome due to hypercoagulability in type-1 DM which is rarely reported.

Key words: Diabetes insipidus, Diabetes mellitus, Optic atrophy, Priapism, Wolfram syndrome

Wolfram syndrome, also known as DIDMOAD (Diabetes Insipidus [DI] Diabetes Mellitus [DM] Optic Atrophy Deafness) syndrome is a rare autosomal recessive disorder due to biallelic pathogenic variants in *WFS1* gene located on 4p16.1 (OMIM 606201) [1]. *WFS1* is expressed in ß-cells of pancreas and neurons of the hippocampus, olfactory tubercle and the amygdala. The gene encodes for Wolframin, an 890 amino acid protein which locates to the endoplasmic reticulum and is a component of the stress response mechanism [2]. Wolfram syndrome is characterized by central DI, monogenic DM, optic atrophy, and sensorineural deafness with additional features of progressive neurodegeneration, depression, and primary gonadal atrophy in males. Its prevalence has been reported between 1 and 9 per million. DM is the first symptom with median age of presentation around 6 years, followed by optic atrophy at around 11 years and DI (reported in 2/3rd of patients) in 2nd decade of life [3,4]. Deafness is seen in 3/4th of the patients in 2nd decade, renal tract anomalies in half the patients in 3rd decade, neurological symptoms like ataxia and myoclonus in half the patients in 4th decade. Onset of DM before age of 15 years together with optic atrophy is highly suggestive of the Wolfram syndrome. Neurorespiratory death occurs by median age of 30 years [5].

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CASE REPORT

We present a 14-year-old male child born of a third-degree consanguineous marriage who was first presented to us at 4 years of age with complaints of recent onset of weight loss, polyuria, and polydipsia. He was detected to have type-1 DM during an acute presentation of abdominal pain and difficulty in breathing (diabetic ketoacidosis). At that time, his c-peptide was <0.1 ng/mL. The glutamic acid decarboxylase antibodies and tissue tissue transglutaminase were negative, the thyroid and renal function tests were within the reference range and Glycated hemoglobin was 13.6%. He was started on Insulin therapy at 1 U/kg for the same. At 8 years of age, he complained of reduced vision and was evaluated for a refractory error. His vision had deteriorated over the years, a progressive optic atrophy was diagnosed, and low vision aids were provided to him.

At 12 years of age, he had increased frequency of micturition and suffered from sleep disturbance (as he had to pass urine 10–12 times every night). Poor control of DM was ruled out as the cause of polyuria (HbA1c of 7.7%). He was evaluated for DI by measuring serum and urine osmolality. His baseline serum osmolality was 279 mOsm/kg and urine osmolality was 43 mOsm/kg which was suggestive of DI. After 4 h of water deprivation, his serum osmolality increased to 304 mOsm/kg and urine osmolality to 48 mOsm/kg which confirmed the diagnosis of DI. To identify if DI was of central

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or nephrogenic origin, desmopressin challenge test was performed by administering 10 mcg of desmopressin intranasally, after which serum osmolality was 275 mOsm/kg and urine osmolality increased to 202 mOsm/kg. The increase in urine osmolality by more than 50% was suggestive of central cause of DI and the patient was started on oral desmopressin 100 mcg every night.

He also suffered from an episode of priapism which lasted for about 10 hour and required a hospital admission. Similar episodes requiring hospital admission occurred on two more occasions in the following year. Other causes of priapism like sickle cell anemia and drugs implicated in priapism were ruled out.

On anthropometric assessment, his height was 152 cm (Z score: −0.97), weight was 51 kg (Z score: 0.24), and BMI was 22.07 kg/m^2 (Z score: 0.84). He was suspected to suffer from DIDMOAD syndrome and a genetic test for *WFS1* mutation was requested. His targeted gene sequencing showed a pathogenic variant in exon 8 of the *WFS1* gene, c.1300_1302del. A homozygous three base pair deletion in exon eight of the *WFS1* gene that results in the in-frame deletion of p.Val434del; was detected and hence genetically confirmed diagnosis of Wolfram syndrome was made.

The patient is currently on treatment with insulin for type-1 DM and tablet desmopressin 100 mcg at night for central DI. There have been no further episodes of priapism. He is being evaluated periodically for the development of deafness and neurological symptoms. The evaluation has not revealed any abnormal findings till date. His younger brother is also a known case of type-1 DM and is being monitored regularly for development of optic atrophy as features of Wolfram are likely to evolve in future.

DISCUSSION

Our patient has evolved symptoms of Wolfram syndrome in accordance to classically described sequence of symptoms. He first developed DM at 4-year of age (median age 6 years), followed by optic atrophy at 8-year age (median age 11 years) and lastly central DI at 14 years age (in 2nd decade). There have been multiple case reports on Wolfram syndrome describing its endocrinological, neurological, and renal tract complications. It is recommended that a patient must be evaluated regularly for deafness, renal tract anomalies such as incontinence and atony and neurological symptoms such as ataxia, myoclonus, nystagmus, hemiparesis, depression, and psychosis. However, priapism has not been described in any of these reports so far.

Priapism itself is a rare disease with incidence of 1.5/100,000 in men [6]. There have been isolated reports of priapism with type-2 DM and the cause hypothesized is the pro-thrombotic tendency due to increased fibrinogen, von Willebrand factor, and plasminogen activation inhibitor [7]. In our case, the cause of priapism may be attributed to hypercoagulability in type-1 DM [8]. The increase in procoagulant factors may cause endothelial dysfunction and local vascular thrombosis leading to ischemic priapism.

CONCLUSION

Wolfram syndrome should be suspected in a patient with onset of DM at age <15 years with optic atrophy and the patient should be carefully followed up for early diagnosis of associated disorders known to evolve as a part of the syndrome. Our case suggests that priapism is an atypical association in patient with the Wolfram Syndrome.

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