Brief Communication

Atypical presentations of Wolframs syndrome

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ABSTRACT

Background: Wolfram syndrome is a rare hereditary or sporadic neurodegenerative disorder also known as DIDMOAD. The classically described presentation is of insulin-dependent diabetes, followed by optic atrophy, central diabetes insipidus, and sensory neural deafness. Also included are less well-described presentations of Wolframs syndrome. We here present three cases of atypical presentation of this syndrome. **Case 1:** A 15-year-old boy with insulin-dependent diabetes was presented for evaluation of depressive symptoms associated with suicidal tendency. Neuropsychiatric manifestations are described with Wolframs syndrome, and wolframin gene, in recessive inheritance, is associated with psychiatric illnesses without other manifestations of Wolframs syndrome. **Case 2:** A 17-year-old diabetic boy on insulin with good control of blood sugar presented for evaluation of delayed puberty. Central hypogonadism and other anterior pituitary hormone dysfunctions are the less publicized hormone dysfunctions in Wolframs syndrome. **Case 3:** A 23-year-old female who was on insulin for diabetes for the past 14 years, got admitted for evaluation of sudden loss of vision. This patient had developed a vitreous hemorrhage and, on evaluation, was found to have optic atrophy, sensory neural hearing loss, and diabetes insipidus, and presented differently from the gradual loss of vision described in Wolframs syndrome. **Conclusion:** Wolframs syndrome being a multisystem degenerative disorder can have myriad other manifestations than the classically described features. Neuropsychiatric manifestations, depression with suicidal risk, central hypogonadism, and secondary adrenal insufficiency are among the less well-described manifestations of this syndrome.

Key words: Diabetes, Wolfram's syndrome

Introduction

Rare genetic or sporadic forms of diabetes can present as insulin-dependent diabetes in children and can mimic type-1 diabetes. Very early onset of symptoms and associated features help in differentiating these forms of diabetes from type-1 diabetes.[1] One of the rare forms of diabetes is Wolfram syndrome, which is an inherited or sporadic neuro-degenerative disorder, presenting as insulin-dependent diabetes, diabetes insipidus, optic atrophy, and deafness (DIDMOAD). But there are less well-known manifestations of this syndrome, which includes neuropsychiatric manifestations, reproductive abnormalities, limited joint mobility, and cardiovascular and gastrointestinal autonomic neuropathy, any of which can be the presenting feature. We report here three cases of Wolfram syndrome with atypical presentation.

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Case 1. A 15-year-old diabetic boy was admitted in our hospital for evaluation of depressive symptoms. He was diagnosed to have diabetes at the age of 4 years and is on insulin. He had a history of decreased vision for the past 4 years and decreased hearing for the past 2 years. His blood glucose values were relatively under control until 6 months previously, but the last 2 HbA1c levels were above target. Examination revealed that he had a significant loss of vision with b/l optic atrophy, and audiometry revealed significant sensory neural hearing loss. The 24 hour urine output, urine osmolality, serum osmolality, and urine sodium levels were suggestive of diabetes insipidus and MRI of the brain was suggestive of central diabetes insipidus. Neuropsychiatric manifestations are described with Wolframs syndrome and are associated with recessively inherited wolframin gene, without other manifestations of Wolframs syndrome.

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Case 2. A 17-year-old diabetic boy was admitted in our hospital for evaluation of delayed puberty. He has insulin dependent diabetes since 10 years of age. He had a history of polyuria for past 2 years and decreased vision for the past 1 year. On examination, he was of a short stature, his pubic and axillary hairs were absent, and testicular volume was <4 ml. Fundus examination revealed b/l optic atrophy, and audiometry revealed significant sensory neural hearing loss. On evaluation of reason for delayed puberty, he was found to have low serum testosterone along with low FSH and LH. The 24 hour urine output, urine osmolality, serum osmolality, and urine sodium levels were suggestive of diabetes insipidus, and MRI brain showed absence of posterior pituitary bright spot. Central hypogonadism and other anterior pituitary hormone dysfunctions are the less known hormone dysfunctions in Wolframs syndrome.

Case 3. A 23-year-old female got admitted for evaluation of sudden loss of vision. She was diagnosed to have diabetes 14 years back and is regular on insulin. She had a history of decreased hearing for past 6 years. Her HbAIC levelwas well controlled . Fundus examination showed vitreous hemorrhage with optic atrophy and severe proliferative diabetic retinopathy. Audiometry revealed sensory neural hearing loss, and urine volume, urine osmolality, serum osmolality, and urine sodium levels were suggestive of diabetes insipidus. Brain MRI showed absent posterior pituitary, confirming Wolframs syndrome. This patient had developed a vitreous hemorrhage and, on evaluation, was found to have optic atrophy, sensory neural hearing loss, and diabetes insipidus, and he presented differently from the gradual loss of vision described in Wolframs syndrome.

Conclusion

Wolfram syndrome is a rare neurodegenerative disorder that may be sporadic or autosomal recessively inherited. First described in 1938 by Wolfram and Wagener, Wolfram syndrome manifests as a combination of young onset non-immune insulin-dependent diabetes mellitus and progressive optic atrophy in all patients with added diabetes insipidus and sensory neural deafness in 70% of the patients; hence, referred to as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) syndrome.[2]

This syndrome is due to the defective synthesis of wolframin (a 100-kd transmembrane protein encoded by WFS1, a gene located at 4p16.1.116), found in the endoplasmic reticulum and in the neuronal and neuroendocrine tissues. Wolframin induces ion channel activity with a resultant increase in intracellular calcium and it may play an important role in intracellular calcium homeostasis.[3]

Due to variable expression of the protein, the phenotype of the disease varies, with diabetes mellitus manifesting early, followed by optic atrophy in all patients. Other manifestations such as diabetes insipidus, deafness, neurological manifestations, and hormonal deficiencies (e.g., ACTH deficiency and growth hormone deficiency, and thiamine responsive sideroblastic anaemia) have variable penetrance.

Psychiatric manifestations of Wolfram syndrome occur less commonly and are less well documented. Upto 22% of patients can have psychiatric problems, based on different published series. The major manifestations include severe depression, suicidal risk, poor scholastic performance, temper tantrums, and adjustment disorder.[4] Moreover, heterozygous carriers of the gene for Wolfram syndrome, which constitutes about 1% of the general population, are at a higher risk of developing psychiatric illness and have 26-fold more chances of having a psychiatric hospitalization.

Signs of hypogonadism have also been found in association with Wolfram syndrome.[5] Hypogonadism in Wolfram syndrome has been attributed to hypothalamic dysfunction, and serum gonadotropin levels have been consistently low or normal.[5]

Refrences

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