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Wolfram Syndrome: Case Report

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Abstract

Wolfram syndrome is a condition characterised by juvenile onset of diabetes mellitus, diabetes insipidus, optic atrophy and deafness also known as DIDMOAD. Wolfram syndrome is rare autosomal recessive disorder caused by mutations in WFS1gene, a gene involved in endoplasmic reticulum and mitochondrial function. Patient presents with diabetes mellitus followed by optic atrophy in 1st decade, cranial diabetes insipidus and sensorineural deafness in the 2nd decade, dilated renal outflow tracts as early as in the 3rd decade and various neurological abnormalities in the early 4th decade. Other abnormalities include primary gonadal atrophy. Patients eventually develops the all complications of neurodegenerative disorder. The pathogenesis is unknown but the prevalence is 1 in 770,000. Death occurs prematurely often from respiratory failure associated with brain stem atrophy. We describe a case with early onset insulin dependent diabetes mellitus and optic atrophy together should be evaluated with respect to wolfram syndrome and present with persistent polyuria or neurogenic bladder despite good glycaemic control and secondary urological abnormalities. Recognizing and timely management of this condition will help to improve the quality of life in the patient.

Keywords: Wolfram syndrome, polyuria, secondary urological abnormalities, diabetes mellitus, diabetes insipidus, optic atropy, deafness, DIDMOAD.

Introduction

Wolfram syndrome, also known as Diabetes Insipidus, Diabetes Mellitus, Optic atrophy and Deafness (DIDMOAD), is an autosomal recessive neurodegenerative disease of very rare occurrence [1]. The prevalence of WS has been estimated between 1 in 770,000 in United Kingdom and 1 in 100,000 in North America [1]. This entity was first described in 1938 by Wolfram and Wagner [4]. It is a progressive neurodegenerative disorder, in which patients present with non-autoimmune and non HLA linked diabetes mellitus associated with optic atrophy (87%) in the first decade; followed by diabetes insipidus (42%) and sensorineural deafness (48%) in the second decade; thereafter renal tract abnormalities early in the third decade, and various neurological abnormalities, like cerebral ataxia, myoclonus early in the fourth decade. early in the third decade, and various neurological abnormalities ,like cerebral ataxia , myoclonus early in the fourth decade .

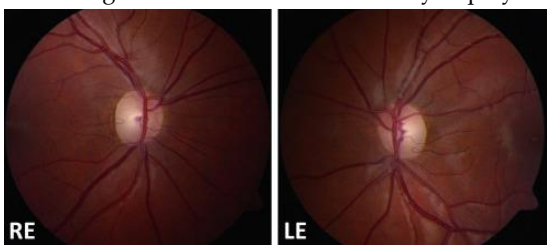
Early onset of diabetes mellitus and optic atrophy are usually the first manifestations of syndrome and presenting typically in childhood [1]. Additional morbidities include hypogonadism, infertility, hypopituitarism, peripheral neuropathy, dementia, psychiatric illness [5]. Previously hypothesized to be a mitochondrial disorder, it is now known that classical WS is the result of autosomal recessive mutations affecting the WFS1 gene, which is implicated in endoplasmic reticulum function(6). Wolfram syndrome is caused by a pathogenic variation in the WFS1 gene (chromosome), which encodes wolframin, a transmembrane protein found in the endoplasmic reticulum [2]. The best available diagnostic criteria are juvenile onset diabetes mellitus and optic atrophy, but there is no definite

treatment for the disease, although research focuses on regenerative and gene therapy [3].

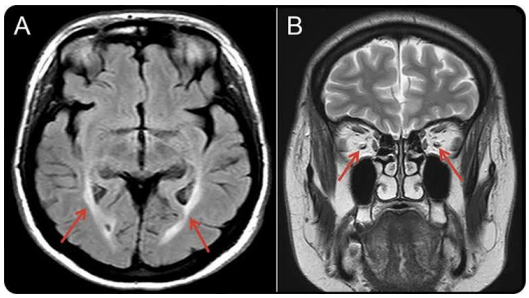
We report a case of two siblings with wolfram syndrome documented by genetic analysis of the WFS1 gene.

Case Report

Two siblings, aged 20 years old (female) and 25 years old (male), were presented with a complaint of pain in the abdomen and occasional episodes of the postural dizziness respectively. Past history revealed that both siblings suffered from type1 diabetes mellitus, manifested at 6 and 7 years of age, respectively. They were started insulin therapy and at 10 years of age both developed optic atrophy and subsequently developed diabetes insipidus at the median age of 16. There was also history of polyuria and polydipsia over the last 8 years and there is no history of consenguity, diabetes mellitus, diabetes insipidus or a neurological disorders. On neurological examination, cooperation was limited because of marked blindness and deafness. Female patient has developed dysarthriatic speech, her judgement and memory impaired and has developed scoliosis and epilepsy. There is no evidence of diabetic retinopathy. Laboratory findings were within normal limits, random blood sugar levels was 300mg/dl and 600mg/dl respectively. Urine culture showed a urinary tract infection with burning micturition. An indwelling catheter was used to control incontinence resulting from bladder atony. Ultra sound of renal tract and urodynamic studies are helpful to diagnosis the renal tract dilation and neuropathy bladder.



Fundus photography of a patient with wolfram syndrome



MRI of brain findings of patients with wolfram syndrome

Discussion

Wolfram syndrome is a neurodegenerative diseases, incidence is about 1 in 770,000 [7]. Early onset of insulin dependent diabetes mellitus and optic atrophy are the basic features of the syndrome [8]. Patients present with diabetes mellitus associated by optic atrophy in the first decade, sensorineural deafness and diabetes insipidus in the second decade, dilated renal outflow tracts in the early third decade and multiple neurological abnormalities early in the fourth decade [9].

Diabetes mellitus is a non-autoimmune, non-HLA linked, insulin deficient and progressive optic atrophy with reduced visual acuity and loss of discrimination of light and dark .Both pupils were fixed and dilated. On funduscopic examination bilateral optic atrophy was detected. Electrophysiological studies suggest that the site of pathology is the optic nerve (10). The cranial nature of diabetes insipidus occurs about three quarters of patients at the median of 14 years and response to vasopressin treatment and MRI scan showed loss of signal from hypothalamus and pituitary gland (11). Sensorineural deafness develops at the median age of 16 years with requiring a hearing aid for high frequency loss. Renal outflow tract are dilated at median age of 20 years with a urinary frequency, incontinence and recurrent infections (11). This appears to be a functional obstructions with bladder atony.

Table 01: clinical features of wolfram syndrome

Features	% Frequency	Findings in current case report
Type 1 diabetes mellitus	95-98	Present diagnosed 4 years back
Optic atrophy	82	Bilateral optic atrophy with mild non proliferative diabetic retinopathy with bilateral subcapsular cataract
Sensorineural deafness	48	Left sided mild sensorineural hearing loss
Central Diabetes insipidus	70	Present
Urinary tract abnormalities	60-70	Grade 3 hydroureteronephrosis with neurogenic bladder
Neurological manifestation (cerebellar ataxia, peripheral neuropathy, dementia	53	Present
Psychiatric illness	39	Present
Endocrine abnormalities	-	Present
Autonomic disturbance	-	Present

Other features include reduced limb reflux, ataxia, dysarthria, central apnoea, loss of taste, smell, and hemiparesis [12]. In a separate study severe psychiatric symptoms of depression, psychosis and other endocrinological abnormalities such as diabetes insipidus are present in approximately 38%, include primary gonadal atrophy in males and menstrual irregularities and delayed menarche in females and growth hormone deficiency also been reported [12]. Median age at death is 30 years, the causes include (25-49 years) central respiratory failure, renal failure, secondary to infections.

Pathogenesis

In wolfram syndrome, wolframin is a protein located on endoplasmic reticulum, it is responsible for 2 types of WFS1 gene, WFS2 gene. WFS1 gene maps on chromosome 4p whose gene product is the transmembrane glycoprotein. The WFS1 gene is present in a variety of tissues, heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. The main function of wolframin is to maintain homeostasis in endoplasmic reticulum and responsible for folding of secretory protein including insulin. Missense mutations in WFS1 gene carries a disruption in homeostasis of endoplasmic reticulum with increase in unfolded protein which is responsible for endoplasmic reticulum stress which results in cell apoptosis [13]. In WS functional protein WFS1 gene deficiency alters inositol triphosphate receptor (ip3) mediated endoplasmic reticulum calcium release which disrupts the cytoplasmic calcium homeostasis. In mitochondria of cytosol presenting acalpain-2 in inactive state, when the calcium levels overloaded in mitochondria, it gets activated and cause apoptosis of beta-cells of pancreas [14]. In neurons there is a disruption of cytoplasmic calcium homeostasis and also dysregulation mitochondrial dynamics and ATP levels which binders the neuronal development survival [15]. Endoplasmic reticulum transmembrane proteins sense the stress and activate the unfolded protein response (UPR) leads to toxicity of cell which promotes cellular apoptosis [16].

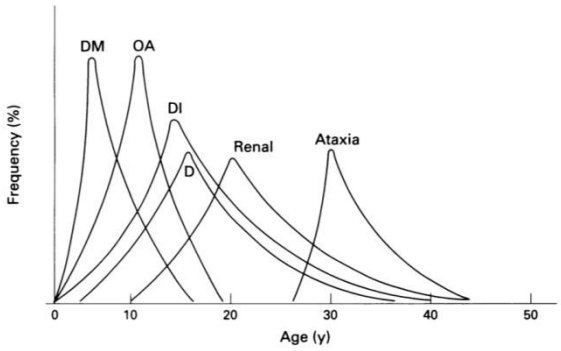


Figure 01: Natural history of wolfram syndrome

Conclusion

In summary, diabetes mellitus and optic atrophy are the initial and essential features of wolfram followed by developed deafness, diabetes insipidus, urinary tract abnormality. It is known case of diabetes mellitus and present with persistent polyuria and neurogenic bladder and despite good glycaemic control, suspicion of wolfram syndrome and further evaluation regarding the same must be done. In these case rehabilitation to a normal social life if possible with good follow up and treatment. Recognizing and timely management of this condition will help to improve the quality of life in the patient.

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