

Wolfram Syndrome (DIDMOAD)

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The acronym DIDMOAD summarizes the most frequent findings: Diabetes insipidus (DI), juvenile insulin-dependent diabetes mellitus (DM), progressive optic atrophy (OA) and sensory neural deafness (D). The diagnosis of WFS is clinical and should be suspected in any child who develops DM and OA.

Introduction

The first description of Wolfram syndrome (WFS) is attributed to the physician DJ Wolfram, who reported four cases in 1938. The acronym DIDMOAD summarizes the most frequent findings: Diabetes insipidus (DI), juvenile insulin dependent diabetes mellitus (DM), progressive optic atrophy (OA) and sensory neural deafness (D). The diagnosis of WFS is clinical and should be suspected in any child who develops DM and OA. However DI, sensory neural deafness, urinary tract atony,¹ ataxia, neuropathy,² reproductive and psychiatric,³ abnormalities, limited joint mobility,⁴ cardiovascular⁵ and gastrointestinal anomalies, as well as some types of endocrine dysfunction⁶ are seen associated in majority of patients.

WFS is a rare, neurodegenerative genetic disorder with prevalence estimate of one in 100,000 children⁷ based on an observation of the prevalence of OA and DM. Parental consanguinity has been noted and an estimated one in 350 people carry the genes of WFS.

Causes

WFS is believed to be caused by both mitochondrial and nuclear gene dysfunction. The mutant genes responsible for WFS include WFS1 gene in chromosome 4P16.1 (A.R.) WFS2 gene in chromosome 4Q22-Q24 (A.R.) and mitochondrial genes.

WFS1 gene mutations is the most common cause of WFS. Usually the mutant gene is on the short arm

of 4th chromosome 4P16.1 (WFS1 gene)⁸ that normally encode for the structural properties and function of mitochondria, and also provide instruction for making an 100 kDa tetrameric H sensitive glycoprotein called wolframin.

Wolframin is a 890 amino acid transmembrane protein (also found in endoplasmic reticulum) located throughout the body, having strong activity in heart, brain, pancreas, liver, kidney, skeletal muscle and inner ear.

There are more than 100 mutations identified so far, that could cause WFS. Some mutations delete or insert DNA from WFS gene. As a result no or little wolframin is present in cells. Other mutations replace amino acids that make wolframin, with incorrect amino acid. As a result the wolframin activity is reduced dramatically. Alterations of 3 dimensional shape of the protein due to mutations could be the probable cause of decreased activity.

Researchers suggest that the loss of wolframin that is essential for neuron survival leads to neurodegeneration and its features in central nervous system. Apart from neurodegeneration it also disrupts production of insulin from proinsulin and there by leads to poor glucose control and DM. It is also evidenced that altered wolframin disturbs the levels of calcium ions or other charged particles that are essential for hearing.

Clinical manifestations and management

The clinical course of WFS varies, and the reasons for this are only slowly emerging.

Diabetes mellitus: DM manifests at a median age of 6 years (range 1 month to 26 years), often

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Distinctive Features of Various Gene Dysfunctions		
Autosomal recessive		Mitochondrial
1) WFS1	2) WFS2	3) Mitochondrial
Defective gene is linked to 4P16.1	Defective gene is linked to 4Q22-Q24	Abnormalities in DNA of the mitochondria
Should inherit genes from both parents	Should inherit genes from both parents	Inheritance is exclusively mother to child
Those who carry defective gene from single parent only will be at high risk of psychiatric abnormalities and adult onset diabetes but not WFS		—
Classical features of WFS are seen with age	Diabetes insipidus may be mild or absent. High incidence of peptic ulcer disease is seen	All features of DIDMOAD are seen but comparatively late in onset

without ketonuria and is insulin requiring. Children are negative for glutamic acid decarboxylase antibodies and have decreased fasting and stimulated C-peptide levels, which reflect the non-immune insulin-dependent nature of DM. Non-immune insulin-dependent DM in these patients could result from hypothalamic degeneration although pancreatic β -islet cell loss is part of a specific defect of neuro

vision and reduced visual acuity at a median age of 12 years and progresses to perception of only light and dark in a median of 8 years. There could be associated diabetic retinopathy. The cause for blindness is severe axonal loss and demyelination of optic nerves, chiasm and tracks. Visual impairment can be corrected with eyeglasses. For patients with diabetic retinopathy, normalization of glucose levels can help reverse or halt the progression of microvascular changes of the eye. No treatment exits for OA. However, blind school, computers with software for blind, listening to books on tape could accommodate the visually disabled and help build self esteem, confidence as well as maximizing school performance.

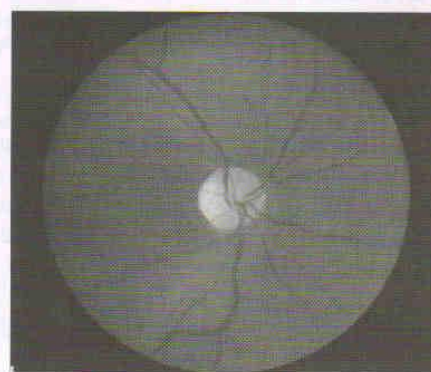
Diabetes insipidus: Polyuria, nocturia, enuresis, very dilute clear odorless urine with biochemically

Clinical course of Wolfram syndrome

Complication	Prevalence (approximately)	Median age of onset
Diabetes mellitus	100%	6 years
Optic atrophy	100%	12 years
Diabetes insipidus	70%	15 years
Urinary tract abnormalities	66%	15 years
Deafness	66%	15-16 years
Neurological symptoms	60%	15-16 years
Psychiatric problems	50%	Any age
Gastrointestinal symptoms	25%	Any age
Heart problems	10%	Any age
Death		30 years

ectodermal amine precursor uptake decarboxylation derived cells in the pancreas and in the supra optic and para ventricular nuclei.⁹ DM can be controlled with daily routine of insulin injections, diet, exercise and frequent testing for blood glucose levels.

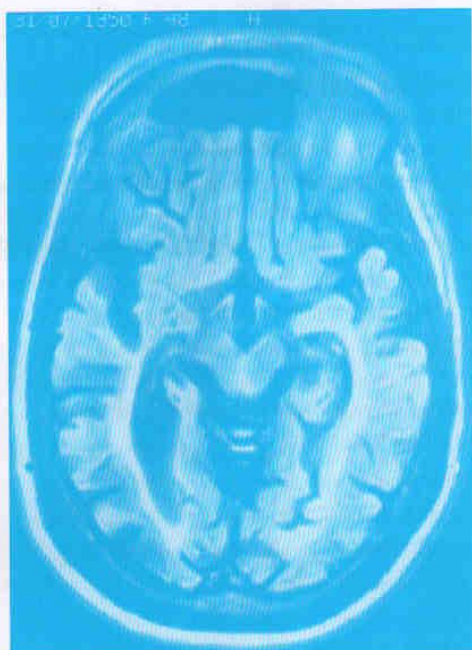
Optic atrophy: OA manifests with loss of color



Fundoscopy: Pale disc

raised serum osmolality and decreased urine osmolality and suggests the presence of DI. Water deprivation test followed by arginine vasopressin

administration should be performed to confirm the same. The median age onset is 15 years (range 2-41). Histopathological and clinical studies demonstrated that this complication is due to atrophy and gliosis of supraoptic and paraventricular neuro-hypophysial system, leading to the deficiency of vasopressin that is responsible for concentration of urine. A synthetic vasopressin as nasal spray or a long acting synthetic ADH substitute can be useful in reducing excessive urination due to DI and these drugs may reduce or eliminate the need for vasopressin in some patients.



Magnetic resonance imaging showing marked generalized brain atrophy

Hearing loss: Symptomatic sensory neural hearing loss to both high frequency followed by low frequency sounds develops at the age 15-16 years and should be confirmed with audiogram. Deafness in these patients is due to dysfunction of the cochlear neurons, 8th nerve fibers and central nervous pathways at the level of brain stem and inferior colliculus, leading to decreased perception rather than defective transmission of sound to the nerve. Approximately 25% of patients with hearing impairment benefit from hearing aids.

Urinary tract abnormalities: Urinary tract dilatation and bladder dysfunction, usually in the form of a large, atonic bladder, are expected in about

66% of persons with WFS and present as symptoms of frequent urination, incontinence and recurrent infection of the bladder. The median age of onset is 15 years. Complete urological evaluation consisting of routine urine analysis, renal function tests, upper tract imaging with ultrasonography and video urodynamics is essential to detect the above abnormalities. These abnormalities may be the primary components of WFS which may partially be affected by other components such as DI, DM, myelopathy of the nerve supply of the bladder and the ureters. The nervous centers in the brain that control urination may also play a role. Apart from treating DI, other treatment modalities such as anticholinergics and clean intermittent catheterization should be added accordingly.

Other disorders: As age advances, impaired sexual development, central nervous system complications (loss of taste and smell, dysarthria, nystagmus, ataxia, startle myoclonus, seizure disorders), mental health disorders (depression, short-term memory loss and disinhibition) as well as features of cardiovascular and gastrointestinal autonomic neuropathy are likely to appear and hence to be screened periodically.

Differential diagnosis of WFS includes thiamine-responsive anemia syndrome, congenital rubella syndrome, Leber's hereditary optic atrophy, Refsum disease, Friedrich's ataxia, Alstrom syndrome and Lawrence-Moon-Biedl syndrome.

Long-term prognosis

The median age of death in these patients is 30 years and 60% of the people with WFS die at the age 35 years. Death can be caused by central respiratory center failure following brain stem atrophy, complications related to urinary tract atony, bulbar dysfunction (aspirations) and in some cases suicide secondary to depression.

There has been no treatment to reverse the underlying mechanism of neurodegeneration in persons with WFS and all cases reported till now have progressed to one or more of the above discussed life-threatening complications and premature death.

Although rare disorder yet WFS should be suspected in any individual presenting with insulin-dependent DM and OA within first three decades of life. Mutation testing offer the best opportunity to confirm diagnosis but may not alter the management. The absence of mutation does not rule out the

CLINICAL STUDY

diagnosis. Early adequate treatment avoids serious complications such as hyperglycemic, hyperosmolar, hypernatremic coma, and can improve the quality-of-life and survival. This disorder should be kept in mind particularly in our part of the world, where consanguinity is prevalent.

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Useful Kidney Sites

American Diabetes Association

1701 North Beauregard Street
Alexandria, VA 22311
Phone: 1-800-232-3472
Phone: 1-800-DIABETES (342-2383)
(national number that provides the most information)
Phone: 1-888-DIABETES (342-2383)
(local number that provides referrals and other information)
Internet: www.diabetes.org

Juvenile Diabetes Research Foundation International

120 Wall Street
New York, NY 10005-4001
Phone: 1-800-JDF-CURE (533-2873)
Phone: (212) 785-9500
Fax: (212) 785-9595
Email: info@jdfcure.org
Internet: www.jdf.org

Centers for Disease Control and Prevention

1600 Clifton Road, NE
Mail Stop G37
Atlanta, GA 30333
Phone: (404) 639-3311 (public inquiries)
Internet: www.cdc.gov

Joslin Diabetes Center

1 Joslin Place
Boston, MA 02215
Phone: (617) 732-2400
Internet: www.joslin.org

International Diabetes Federation

1 Rue Defacqz
B-1000
Brussels, Belgium
Phone: 32-2/538-5511
Fax: 32-2/538-5114
Email: idf@idf.org
Internet: www.idf.org