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Syndrome of the month

Wolfram (DIDMOAD) syndrome

T G Barrett, S E Bundey

Abstract

Wolfram syndrome (MIM 222300) is the association of juvenile onset diabetes mellitus and optic atrophy, also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness). Patients present with diabetes mellitus followed by optic atrophy in the first decade, cranial 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. Other abnormalities include primary gonadal atrophy. Death occurs prematurely, often from respiratory failure associated with brainstem atrophy. Most patients eventually develop all complications of this progressive, neurodegenerative disorder. The pathogenesis is unknown, but the prevalence is 1 in 770 000 in the UK and inheritance is autosomal recessive. A Wolfram gene has recently been mapped to chromosome 4p16.1, but there is evidence for locus heterogeneity, and it is still possible that a minority of patients may harbour a mitochondrial genome deletion. The best available diagnostic criteria are juvenile onset diabetes mellitus and optic atrophy, but there is a wide differential diagnosis which includes other causes of neurodegeneration.
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In 1938, Wolfram and Wagener[1] reported four sibs with diabetes mellitus and optic atrophy; the oldest had diabetes mellitus from 8 years, optic atrophy from 11 years, and when examined at 18 years visual acuity was reduced to counting fingers. Her brother developed poor vision at 6 years and diabetes mellitus at 10 years. When examined at 15 years he had bilateral optic atrophy, with visual acuity reduced to hand movements only in the better eye. A younger brother developed diabetes mellitus at 7 years; his vision had been documented as normal at 6 years, but on examination at 8 years he had optic atrophy and visual acuity was 6/30 in each eye. This boy was reported again[2]; he had developed neurological symptoms and had been diagnosed as atypical Friedreich's ataxia. The fourth affected child developed diabetes mellitus aged 5 years and optic atrophy aged 7 years. Eighteen years later, two of the four affected sibs were almost completely blind and had developed "cord" (neurogenic) bladders; three had hearing loss.[3]

Since the original description of Wolfram and Wagener,[1] there have been over 200 case reports, adding diabetes insipidus, renal outflow tract, neurological and other endocrine abnormalities to the clinical features. Inheritance has been established as autosomal recessive; however, clinical overlap with other disorders focused interest on the possibility that the syndrome may be caused by defects in both nuclear and mitochondrial genomes.

Clinical features

There have been several large reviews[4–6] and two cross sectional case finding studies.[7 8] Most of the data on clinical features and natural history come from a UK nationwide study of 45 patients.[8]

The UK study outlined the natural history schematically as shown in fig 1.[8] The complications are shown by age of presentation in table 1. The study took and validated its ascertainment criteria as juvenile onset (under 20 years) diabetes mellitus and optic atrophy, thus present in all the patients. Most patients present with diabetes mellitus, although optic atrophy or diabetes insipidus may unusually present first. Diabetes mellitus presents at a median age of 6 years (range 3 weeks-16 years) and is non-autoimmune, insulin deficient, and non-HLA linked. Microvascular complications are rare and seem to develop slower than in the more common type 1 diabetes.[7]

Progressive optic atrophy presents at a median age of 11 years (6 weeks-19 years), with

Table 1 UK Study of 45 Wolfram patients: complications occurring by different ages

Age attained (y)	10	20	30	40	45
Complications	(n=43)	(n=36)	(n=27)	(n=8)	(n=4)
Diabetes mellitus	32 (74%)	36 (100%)			
Optic atrophy	17 (40%)	36 (100%)			
Diabetes insipidus	7 (16%)	20 (56%)	23 (85%)	8 (100%)	4 (100%)
Deafness	7 (16%)	15 (42%)	18 (67%)	5 (62%)	2 (50%)
Renal	3 (7%)	13 (36%)	15 (56%)	5 (62%)	4 (100%)
Neurological	1 (2%)	2 (6%)	11 (41%)	5 (62%)	4 (100%)

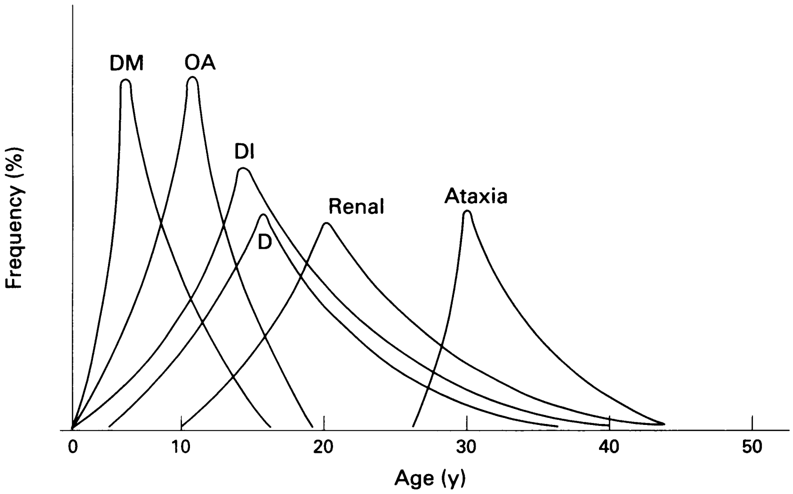

Figure 1 Natural history of Wolfram syndrome. DM=diabetes mellitus, OA=optic atrophy, DI=diabetes insipidus, D=deafness, Renal=renal tract abnormalities, Ataxia=neurological abnormalities (one patient presented at 5 years).

Figure 2 Scan from T1 weighted magnetic resonance imaging of brain of a 49 year old man with Wolfram syndrome. Arrow points to pituitary gland.

reduced visual acuity and loss of colour vision; most patients are registered blind with acuity reduced to counting fingers with a median of 8 years. Electrophysiological studies suggest that the site of pathology is the optic nerve.[9] Partial cranial diabetes insipidus occurs in about three quarters of patients at a median age of 14 years (3 months-40 years) and responds to vasopressin treatment. The cranial nature of the insipidus was clearly shown in seven patients,[10] and magnetic resonance imaging (MRI) showed loss of signal from the hypothalamus and posterior pituitary[11] (fig 2). Symptomatic sensorineural deafness develops in two thirds of patients at a median age of 16 years (5-39 years) and about a quarter of these require a hearing aid for high frequency loss. Dilated renal outflow tracts present in two thirds of patients at a median age of 20 years (10-44 years), with urinary frequency, incontinence, and recurrent infections. This appears to be a functional obstruction with bladder atony. Although some patients improve after treatment of diabetes insipidus with vasopressin,[12] a marked reduction in nerve fibre staining in a bladder wall biopsy suggests a primary neurodegenerative cause for this complication.[13]

Neurological features present at a median age of 30 years (5-44 years), commonly with truncal ataxia causing unsteady gait and falls. Other features include startle myoclonus, reduced limb reflexes, horizontal nystagmus, dysarthria, central apnoeas, loss of taste and smell, and hemiparesis. In a separate study, severe psychiatric symptoms of depression, psychosis, and organic brain syndrome were reported in up to 25% of patients.[14] All the above complications except the diabetes mellitus can be related to an underlying neurodegeneration. MRI of patients' brains typically show generalised brain atrophy, especially in the cerebellum, medulla, and pons (fig 2).

Other complications include primary gonadal atrophy and reduced fertility in most patients studied.[8] Despite this, successful pregnancies of healthy, unaffected children have been reported.[15] Gastrointestinal dysmotility is common, causing both constipation and diarrhoea. Respiratory symptoms of central apnoeas are probably under-reported.

The median age at death is 30 years (25-49 years); causes include central respiratory failure and renal failure secondary to infection. Few postmortem studies have been published[16-19]; the six patients reported confirmed central nervous system degeneration. Atrophy was seen in the hypothalamic nuclei, posterior pituitary, optic nerves and chiasm, vestibular nuclei, pons, medullary reticular activating system, substantia nigra, superior and inferior olives, and cerebellum. Microscopically, neuronal loss and axonal destruction was often accompanied by gliosis and scattered areas of demyelination in the cerebrum and cerebellum without inflammatory changes. Some of the features appeared similar to those seen in olivopontocerebellar atrophy.

Diagnosis

There is no diagnostic marker available at present for this syndrome; juvenile diabetes mellitus and optic atrophy remain the best available diagnostic criteria. Sibs of patients without these two features by 15 years of age will probably not develop the syndrome. Although there may be a milder subgroup, the diagnosis has devastating implications for patients and families.

The differential diagnosis includes congenital rubella syndrome, Leber's hereditary optic atrophy, and thiamine responsive anaemia with diabetes mellitus and deafness. The last is distinguished by the invariable presence of anaemia and profound early onset deafness but variable optic atrophy; it is better regarded as a separate syndrome (thiamine responsive anaemia syndrome) until these disorders are elucidated at the molecular level. The association of diabetes mellitus and optic atrophy also occurs in Friedreich's ataxia, Refsum disease, Alstrom syndrome, Lawrence-Moon syndrome, Kearn-Sayre syndrome, and deafness and diabetes in the "3243" mitochondrial DNA mutation.

Investigations

The most helpful investigations include islet cell antibodies, which are negative unlike many patients with type 1 diabetes mellitus, electrophysiology including visual evoked potentials and electroretinograms to confirm optic nerve pathology, and regular assessments of visual acuity. Audiograms should be performed as the deafness is often under-recognised. About 25% of patients may require hearing aids. Paired early morning plasma and urine osmolarity is useful to diagnose diabetes insipidus; this diagnosis is sometimes delayed if symptoms of thirst and polyuria are wrongly attributed to poorly controlled diabetes mellitus. Ultrasound of the renal tract and urodynamic studies are helpful to diagnose the renal tract dilatation and neuropathic bladders. Cranial imaging by magnetic resonance scans may show the characteristic abnormalities of atrophy, particularly of the brainstem. Finally, overnight sleep studies with oxygen saturation monitoring is helpful to detect central sleep apnoea.

Pathogenesis

Despite extensive investigations, the underlying causes of the neurodegeneration and diabetes mellitus remain unknown. The occurrence of symptoms often seen in mitochondrial DNA disorders (deafness, optic atrophy, diabetes mellitus, and ataxia) led to suggestions that some cases of Wolfram syndrome may be the result of mitochondrial abnormalities.[20] However, no consistent abnormality of either oxidative phosphorylation or mitochondrial genome rearrangement has been reported.[21] Several studies have been criticised on grounds of case definition or methodology; the most reliable report described a girl with typical clinical features and a complex III deficiency.[22] Both parents and an unaffected sib had a heteroplasmic 8.5 kb mitochondrial DNA (mtDNA) deletion. The amount of deleted mtDNA found in the patient was 23%, whereas in the parents and unaffected sister it ranged between 2% and 8% in different tissues.

Prevalence and family studies

Prevalence estimates vary from 1 in 100 000 in North America[23] to 1 in 770 000 in the UK[8] because of differences in methodology; the UK figure is probably more reliable. The prevalence in childhood is 1 in 500 000. Family studies indicate autosomal recessive inheritance, and there is no convincing evidence of an increased risk of type 1 diabetes or psychiatric illness in first degree relatives who may be carriers.[8] Assuming that the birth frequency is 1 in 500 000, then the carrier frequency can be estimated to be 1 in 350.[8] Parents and children have usually been healthy; there is a 25% risk for sibs to be affected and there is an increased prevalence of consanguinity in the parents.

Molecular studies

A Wolfram syndrome locus was mapped to the short arm of chromosome 4 using 11 families with two or more affected subjects.[24] A maximum lod score of 7.1 was found in the interval between the microsatellite markers D4S431 and D4S394. One family with an obligate recombinant between the disease and D4S431 was found, indicating that the disease locus is more likely to lie in the 7 cM region

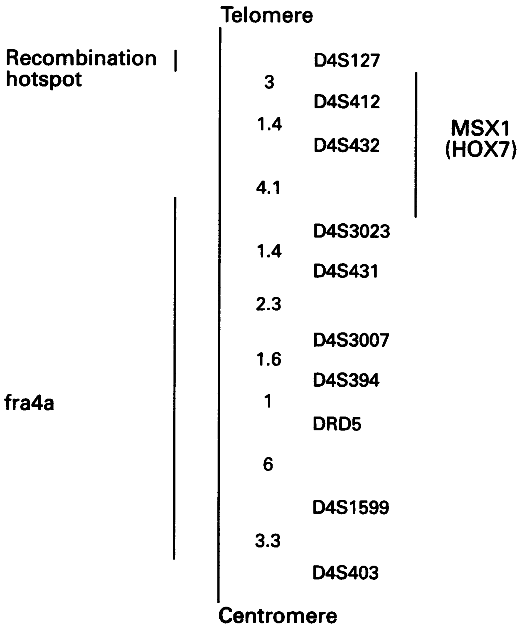

Figure 3 Genetic map of 4p16. Map distances are given in centimorgans.

between D4S412 and D4S431. No evidence for locus heterogeneity has been reported. Twelve families from the UK study were then investigated and confirmed linkage to chromosome 4p, with a maximum two point lod score of 4.6 with DRD5[25] (fig 3). One family with an atypical phenotype (congenital, non-progressive optic atrophy) was definitely unlinked to the region. Haplotype inspection of the remaining families (with typical phenotypes) showed crossover events during meiosis which placed the gene in the 5 cM interval between D4S432 and D4S431. Overlapping multipoint analysis also produced definite evidence for locus heterogeneity, with a maximum admixture lod score under heterogeneity of 6.2 in the same 5 cM interval.

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