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# Wolfram syndrome: DIDMOAD

DEBORAH J WAKE, VITTAL JADHAV, LAURIE R WHITTOME, IAN W CAMPBELL

## Introduction

**W**olfram syndrome is a rare autosomal recessive condition that predisposes to the development of type 1 diabetes mellitus (DM) and optic atrophy (OA). Other clinical features can include diabetes insipidus (DI) and deafness (D). When these are present the condition is often referred to as DIDMOAD. Renal tract abnormalities, psychiatric disorders, short stature and hypogonadism may also occur. We describe a case of DIDMOAD to highlight the difficult clinical management of this rare condition and discuss the genetic basis of the disease.

## Case History

A six-year-old school boy presented to the ENT department with a history that he had been dull of hearing for about one year. The audiogram showed bilateral sensori-neural hearing loss. At this stage, he also complained of thirst and polyuria and DM was confirmed with a random plasma glucose of 32.2 mmol/L. Glycaemic control was satisfactory with a before breakfast dose of Velosulin and Insulatard insulins.

Some two years later, the boy noticed deteriorating vision in both eyes which his optician could not improve with glasses. Ophthalmic examination showed bilateral optic atrophy, more so on the right than the left (see figure 1). The CAT scan showed no evidence of a chiasmal mass lesion or intra-cranial cause for the deteriorating vision. Hearing aid and extra + lenses for near vision gave improvement in his auditory and visual abilities. The vision in each eye was 6/24 and he was able to read N10. Two years later the vision was 6/36 and some 12 months later it had further deteriorated to 6/60. He was placed on the partially sighted register and low visual aids were prescribed.

A further two years later, despite good glycaemic control, he developed severe polyuria with nocturnal enuresis, and polydipsia. A formal water deprivation test confirmed diabetes insipidus which responded to intramuscular desmopressin (DDAVP). A diagnosis of cranial diabetes insipidus was made.

Testing for anterior pituitary hormones was normal. With the earlier normal CAT scan noted, a diagnosis of DIDMOAD syndrome was made. The DM remained well controlled with twice-

**Figure 1.** Optic disc pallor (atrophy) in eight-year-old DIDMOAD patient



daily Humalog Mix 25 insulin and the diabetes insipidus responded satisfactorily to desmopressin spray, 10 µg twice-daily. A renal tract ultrasound was performed which showed no bladder distension with a normal collecting system. The patient never developed any symptoms suggestive of urinary tract infection.

This young male did well at school and was working in one of the local banks when he died tragically at the age of 22 years along with both parents in a house fire.

## Discussion

### Clinical

Wolfram first described the features of DIDMOAD in 1936.<sup>1</sup> As originally reported by Wolfram, the syndrome described the association of DM and OA, but not the DI and D components. The earliest manifestation of DIDMOAD is usually DM (average age of diagnosis approximately seven years), followed by OA, then DI, then D. Audiometry and visual evoked potential often reveal degrees of hearing and visual loss which are not always clinically apparent. Renal abnormalities i.e. hydronephrosis and bladder abnormalities (ranging from large atonic bladders to low capacity, high pressure bladders with sphincter dyssynergia)<sup>2</sup> are found in most individuals often requiring specialist intervention. Short stature is common, puberty and menarche may be delayed and hypergonadotrophic hypogonadism and reduced fertility has been described. Peden *et al.* however described a successful pregnancy in one of their patients.<sup>3</sup>

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**Abbreviations**

CAT	computerised axial tomography
D	deafness
DI	diabetes insipidus
DM	diabetes mellitus
ENT	ear, nose and throat
OA	optic atrophy

**Genetics**

Wolfram syndrome is caused by a mutation in the WFS1 gene. The genetic basis for the disease was first discovered in 1998 by positional cloning; and mapped to chromosome 4p16.1.<sup>4,5</sup> WFS1 is an 8 exon gene encoding for a 890 amino-acid protein called wolframin which is thought to code for a novel endoplasmic reticulum calcium channel.

It's predominance in pancreatic beta cells and neurons may account for the clinical features. Screening individuals with Wolfram syndrome has revealed many different mutations in the WFS1 gene (mostly in exon 8) and the severity of the syndrome seems to be dictated by the severity and type of underlying mutation.<sup>6</sup>

Wolfram syndrome requires inheritance of two mutant alleles (autosomal recessive). The WFS1 carrier status was previously considered to be of little clinical significance, but several series have now reported an increased association with mood disorders

(major depression and bipolar disorder) in mutant gene carriers.<sup>7</sup> Understanding the underlying genetics has also allowed the prenatal diagnosis of the condition in families with a previously affected sibling,<sup>8</sup> and will hopefully provide the basis for future targeted treatments.

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