Morbidity and Mortality in the Wolfram Syndrome

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OBJECTIVE — To determine the major causes of morbidity and mortality in the autosomal recessive Wolfram syndrome, which is defined by diabetes and bilateral progressive optic atrophy with onset in childhood or adolescence.

RESEARCH DESIGN AND METHODS — We abstracted and reviewed the medical records of 68 confirmed cases of Wolfram syndrome identified through a nationwide survey of endocrinologists, ophthalmologists, institutes, and homes for the blind. We also reviewed all available autopsy records.

RESULTS — The most common causes of morbidity and mortality were the neurological manifestations of this syndrome and the complications of urinary tract atony. There was a lower frequency of diabetic ketoacidosis, no histologically proven diabetic glomerulosclerosis, and less severe, more slowly progressive, diabetic retinopathy than in classic type I diabetic patients. Mortality in Wolfram syndrome is much higher than in type I diabetes; 60% of Wolfram syndrome patients die by age 35. Recognition of these clinical differences from classic type I diabetes is important for the proper management of Wolfram syndrome patients.

CONCLUSIONS — Identification of Wolfram syndrome patients among all diabetic patients presenting in childhood or adolescence is important because the management of patients with this syndrome is different from that of patients with classic type I diabetes.

The Wolfram syndrome is defined by the occurrence of juvenile onset diabetes mellitus and bilateral optic atrophy; diabetes insipidus, deafness, and urinary tract dilatation are also noted frequently (1,2). It is inherited as an autosomal recessive single gene syndrome, as shown by the frequent occurrence in male and female siblings and the elevated rate of parental consanguinity (3). The Wolfram syndrome gene is of particular interest because it causes diabetes mellitus in homozygotes and predisposes homozygotes and heterozygotes to psychiatric illness (4,5).

Medical records for 68 Wolfram syndrome patients, collected during a genetic-epidemiological study, provided substantial new information about the clinical history of this syndrome.

RESEARCH DESIGN AND METHODS

— From 1983–1986, we wrote to endocrinologists and ophthalmologists at major medical centers in the U.S. and to institutes and homes for the blind to ask for referral of any cases of Wolfram syndrome. All Wolfram syndrome patients seen at the Joslin Diabetes Center and the New England Deaconess Hospital were reviewed in 1984.

We identified 166 presumed cases of Wolfram syndrome. Of these, 98 cases were excluded from the study for one of the following reasons: the patient could not be located; the patient did not meet the diagnostic criteria for Wolfram syndrome; the referring physician or patient refused participation in the study; or the patient did not reside in the U.S. Each patient or his or her parents completed a health questionnaire that asked about hospitalizations and contained a checklist of illness-related questions. Informed consent was used to obtain hospital records of the diagnostic workup and of all major hospitalizations. Any previously published report describing the patient was obtained. For each deceased patient, the death certificate and autopsy report, when available, were obtained.

We reviewed and abstracted the records of all 68 cases to determine the sources of morbidity and mortality for patients with this syndrome.

RESULTS

— The 68 Wolfram syndrome patients came from 44 families in 23 states throughout the U.S. All had

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Received for publication 31 March 1995 and accepted in revised form 27 July 1995.

ADH, antidiuretic hormone; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

been born between 1940 and 1980. There were 35 men and 33 women patients in the study. Twenty-seven patients had been reported on previously (3,6–14).

Glucose tolerance

Diabetes was diagnosed at 1–26 years of age (mean 8.2 years; median 6.5 years). It was the first manifestation of Wolfram syndrome in 84% of the patients. Sixty-six patients were treated with insulin from the time their diabetes was diagnosed. Two patients were treated initially with diet for 1 1/2 and 8 years before they required insulin. Although they were asymptomatic at the time, glucose intolerance was detected in both of these patients when they were tested after diabetes was diagnosed in their symptomatic older siblings.

Diabetic ketoacidosis was the presenting feature in only two Wolfram syndrome patients, led to hospitalization in seven others, and was documented in the charts of an additional six. In 15 patients, clinically significant hypoglycemic episodes had been documented, and 3 had nonketotic diabetic coma.

There were 11 patients who had autopsies. In nine of these, loss of β-cells or atrophy of the islets of Langerhans was noted.

Visual loss

The age at diagnosis of optic atrophy was ascertained for 64 of the 68 patients. The mean age of diagnosis was 13.1 years (median 12.6; range 6–30 years). In seven patients optic atrophy was diagnosed before diabetes. In four patients, the age at which optic atrophy was diagnosed could not be determined.

In 56 patients with serial measurements, the mean age at which visual acuity was 20/200 bilaterally was 19.3 years (median 18 years; range 11–35 years). The mean time from the clinical diagnosis of optic atrophy to legal blindness was 6.7 years.

Proliferative retinopathy was reported for four Wolfram syndrome patients, all of whom had diabetes for at least 15 years. Background retinopathy was observed in 18 other patients. There was no diabetic retinopathy in 17 of the 26 Wolfram syndrome patients who had had diabetes for at least 15 years.

Table 1— *Neurological manifestations in 68 patients with Wolfram syndrome*

Manifestation	No. patients
Pupillary abnormalities	28
Peripheral neuropathy	25
Ataxia	21
Bulbar dysfunction	14
Developmental disabilities	7
Anosmia	6
Primary seizure disorder	6
Intention tremors	4
Chorea	1

Neurological disease

Forty-seven of the Wolfram syndrome patients had evidence for neurological dysfunction in addition to the characteristic optic atrophy of Wolfram syndrome (Table 1).

High-tone neurosensory hearing loss was found in 35 patients; the average age of diagnosis of hearing loss was 14.6 years (median 15 years; range 1–29 years). Nine patients had seizures associated with hypoglycemia, in addition to the six patients with a primary seizure disorder. The mean age of onset of seizures was 27.7 years (median 19 years; range 9–43 years). Twenty-one patients had some degree of ataxia.

Diabetes insipidus

Partial or complete diabetes insipidus was present in 35 patients with a mean age at diagnosis of 15.5 years (median 14.8 years; range 4–41 years). Of these 35 patients, 25 were treated with antidiuretic hormone (ADH) (as Pitressin tannate or deamino-8-D-arginine vasopressin), two with both chlorpropamide and ADH, and one with chlorpropamide alone. Seven patients needed no treatment for their diabetes insipidus.

Table 2—*Urinary tract manifestations in 37 Wolfram syndrome patients with dilated neurogenic bladders*

Manifestation	No. patients
Hydronephrosis, hydroureter, or both	27
Urinary tract infections	31
Impaired renal function as evidenced by uremia, elevated BUN, or elevated creatinine	21

Urinary tract disease

Dilated neurogenic bladders were reported for 37 Wolfram syndrome patients (Table 2) with a mean age of onset of 17.4 years (median 15.2 years; range 7–41 years). Twenty-one patients had impaired renal function as evidenced by either uremia, elevated blood urea nitrogen (BUN), or elevated creatinine. All patients with impaired renal function had neurogenic bladders, and 18 of them had definite evidence of either episodic or chronic cystitis or pyelonephritis. Three patients had malignant hypertension and chronic bilateral upper urinary tract obstruction, chronic obstructive uropathy bilaterally, and autopsy evidence of mild chronic renal pyelitis.

The characteristic lesions of diabetic glomerulosclerosis were not found in any of the 11 patients on whom autopsies were done, although the mean length of duration of diabetes at the time of death was 23 years (range 13–35 years). The mean age at death was 28 years in these 11 patients (range 19–38 years). Five patients had autopsy evidence of either chronic cystitis or chronic pyelonephritis.

In eight patients surgical procedures were performed to improve urinary incontinence: bladder neck resection in six patients, hemicystectomy in one patient, and cutaneous vesicostomy in one patient. No improvement of incontinence was reported after bladder neck resection. In three patients, bilateral ureterostomies

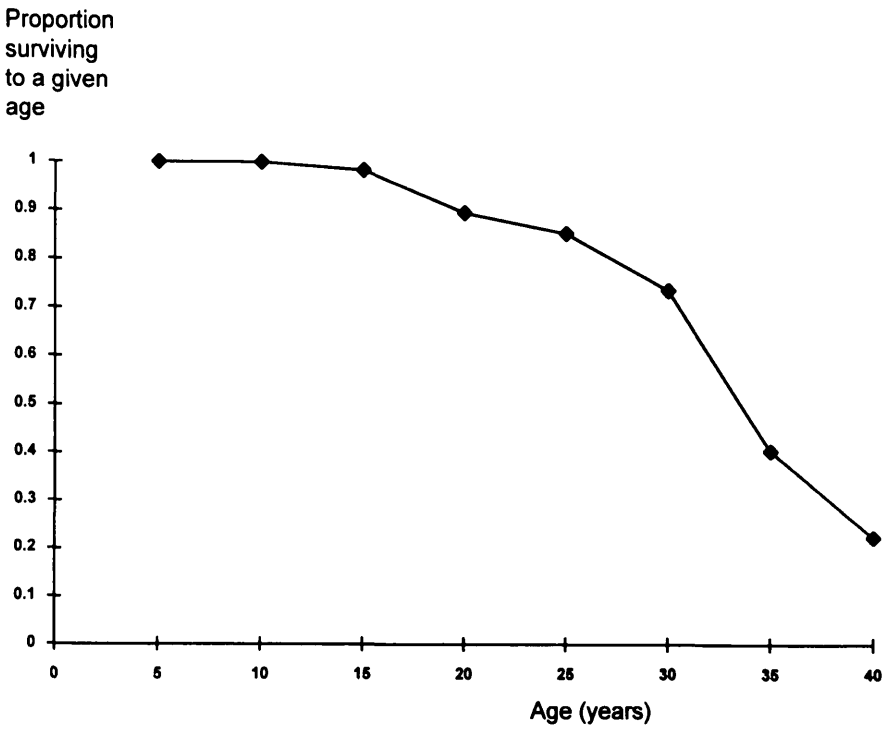

Figure 1—*Lifetable analysis of survival of patients with the Wolfram syndrome.*

were performed to treat bilateral hydronephrosis. Twelve patients (eight women and four men) performed intermittent self-catheterization for urinary incontinence.

Pituitary-gonadal function

Of the men with Wolfram syndrome, 12 were noted to have small, soft, atrophic testes, and 3 were also noted to have detectable gynecomastia. Testicular biopsy was performed in two patients; fibrosis and atrophy of the seminiferous tubules were noted with decreased spermatogenesis. Leydig cells appeared normal in the one patient for whom a comment was made.

Gonadotropins were elevated in three of the four male cases for whom they were assayed (luteinizing hormone [LH] values 22, 42, and 63 and follicle-stimulating hormone [FSH] values 23, 42.7, and 40). Levels were low in the fourth patient (FSH 1–5 and LH 1). The partners of three male homozygote subjects had six pregnancies, resulting in four spontaneous abortions and two normal deliveries. There were three normal pregnancies and deliveries in two of the 30 women (age >20 years) in our series.

Cardiac abnormalities

The three patients with cardiac anomalies included two with tetralogy of Fallot and one with pulmonic valve stenosis. Many Wolfram syndrome patients had sinus tachycardia, and atrial and ventricular arrhythmias were also observed.

Congenital malformations

In addition to the major cardiac malformations described above, each of the following were noted in the records of one or two patients: abnormal pinnae of the ears, spina bifida occulta, persistent fetal lobulation of the kidney, congenital hypoplasia of the vitreous humor, short fourth metacarpals, first-degree hypospadias, and strabismus. It is likely that other minor malformations were not documented.

Mortality

Twenty-three of the patients in this series had died by June 1989. The mean age at death was 28 years (median 28.0 years; range 14.75–43.5 years). According to a standard lifetable analysis, 60% of Wolfram syndrome patients die by age 35 (Fig. 1).

For 13 of the deaths, the cause of death was determined easily from the clinical course or the postmortem findings. Four of these were attributed to the progressive renal disease in subjects with urinary tract atony and recurrent urinary tract sepsis. Two deaths followed severe hypoglycemic reactions.

For 10 of the deaths, however, the immediate cause of death was not evident from all available records. Three patients, including one hospitalized for dementia, experienced unexpected cardiopulmonary arrest with no cause found at autopsy. Nine of the 23 deaths occurred in patients who had evidence of extensive central nervous system dysfunction, manifest by autonomic dysfunction, chronic organic brain syndrome, absence of the gag reflex, and recurrent aspiration.

CONCLUSIONS— Physicians caring for patients with diabetes should be aware of the Wolfram syndrome, since the major sources of morbidity and causes of mortality in this syndrome are distinctly different from those in type I diabetes. The presence of Wolfram syndrome should be suspected in young diabetic patients whenever there are visual deficiencies unexplained by retinopathy, excess urine volume unexplained by hyperglycemia, auditory difficulties, or prominent neurological or psychiatric symptoms. When Wolfram syndrome is suspected, vigorous efforts should be made to detect early optic atrophy. Bilateral optic atrophy and diabetes are, as stated earlier, the defining characteristics of Wolfram syndrome.

The present case series demonstrates that mortality is much higher in Wolfram syndrome than in type I diabetes. From our data, we estimated that

60% of Wolfram syndrome patients will die by age 35 years. In a cohort of conventionally treated patients with classic type I diabetes, 50% are expected to die by age 50 (15,16). While 25% of deaths in type I diabetes are due to myocardial events (17), no patient in this series, or in previous reports, had clinical or autopsy evidence of significant coronary heart disease. Similarly, although 30–40% of type I diabetic patients develop end-stage renal disease primarily from diabetic glomerulosclerosis (15,16), the distinctive histopathological features of this complication were not observed in this series or in Wolfram syndrome patients previously reported. Wolfram syndrome patients die primarily from their progressive neurological disorder and from the complications of urinary tract dilatation and infection.

More than 50% of the Wolfram syndrome patients in this series who died had severe neurological disabilities including apneic spells, organic brain syndrome or dementia, or bulbar dysfunction. Several patients had severe bulbar dysfunction that led to repeated episodes of aspiration of food or gastric contents, although it was not always clear that aspiration had led directly to the terminal event. The presence of bulbar dysfunction so severe that it led to aspiration was noted in the charts of many of the patients who died. Five other deaths resulted from end-stage renal disease or other consequences of urinary tract atony. Hypoglycemia was the direct precipitating event in two other deaths in this series.

Cardiac malformations and atrial and ventricular arrhthymias also occur in the syndrome. The Wolfram syndrome gene may predispose homozygotes to congenital conotruncal heart defects, since two tetralogies of Fallot and one pulmonic stenosis were observed in these 68 Wolfram syndrome patients. Pulmonic stenosis was reported previously in two Wolfram syndrome patients (18,19). In the general population congenital heart disease is found in 8.14 of 1,000 live births; 16 cases of tetralogy of Fallot were reported in 56,109 births (20). Conotruncal defects aggregate in families (21), suggesting a genetic basis for these congenital cardiac malformations. As three subjects in our series died from cardiopulmonary arrest for which no cause was found at autopsy, routine cardiological assessment and appropriate treatment of any dysrhythmia may decrease the cardiac mortality in this syndrome.

Almost all Wolfram syndrome patients are treated with insulin; there are no reports of successful long-term treatment with oral hypoglycemic drugs. In contrast with the findings in type I diabetes, ketoacidosis was infrequently seen as the initial presenting feature or during the illness in the present series and previous reports (22). Only 3% of our patients had diabetic ketoacidosis at presentation, while 30% of a population of patients with type I diabetes had diabetic ketoacidosis at the time of diagnosis (23).

Guidelines for the care of Wolfram syndrome patients can be derived from the observations in this case series. Each manifestation of the syndrome can appear in childhood, adolescence, or adult life, although diabetes and then optic atrophy are typically the first manifestations. The mean or median ages for detecting hearing loss, neurogenic bladder, and diabetes insipidus are the teenage years, while the severe neurological problems such as bulbar dysfunction and organic brain syndrome are usually observed after age 20. For an individual patient, of course, it is not possible to predict which manifestations he or she will have or the age at which they will appear.

The urinary tract atony associated with Wolfram syndrome is likely due to degeneration of the nerves serving the ureters and urinary bladder (24). It is unclear whether it is made worse by the large urine volumes associated with diabetes mellitus and diabetes insipidus. The presence of urinary tract symptoms should prompt early investigation to detect neurogenic bladder and diabetes insipidus because early detection and vigorous management of these manifestations may improve the quality of life and length of survival. If intermittent self-catheterization of the urinary bladder is called for, it may be desirable to teach this before visual impairment makes it too difficult to learn. Urinary tract infections may be prevented through the prophylactic use of antibiotics. Bladder neck resection appears to be ineffective in preventing renal impairment in Wolfram syndrome patients.

Treatment of psychiatric disorders with appropriate neuroleptic drugs may improve compliance with the diabetic regimen, prevent suicide attempts, and improve the quality of life. Careful, repeated examinations of bulbar function may lead to measures to prevent aspiration of food or gastric contents. Early detection and aggressive management of cardiac arrhythmias may also improve survival.

Although tight glycemic control reduces the frequency and severity of diabetic nephropathy and proliferative retinopathy in type I diabetes (25,26), there is no evidence that such control slows the progression of the neurodegenerative manifestations of Wolfram syndrome. Indeed, diabetic glomerulosclerosis is absent and proliferative retinopathy relatively unimportant in Wolfram syndrome patients. After 15 years of diabetes, 35% of Wolfram syndrome patients develop retinopathy, compared with 90% of a population of conventionally treated type I diabetes patients (15). Visual loss in Wolfram syndrome is almost always due to optic atrophy.

The Wolfram syndrome gene has been mapped to chromosome 4p (27). Identifying the Wolfram syndrome gene and understanding how it acts will tell us how mutations in this gene lead to the metabolic and nervous system abnormalities observed in this disorder. Genetic investigation offers the best opportunity for effective treatment or prevention of this syndrome.

Acknowledgments— This study was supported by National Institute of Mental Health Grant MH-45128.

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