A CASE OF WOLFRAM SYNDROME IN TRIPLETS: SOME NEWLY RECOGNIZED FEATURES

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In 1938, Wolfram described four siblings with diabetes mellitus and optic atrophy.[1] The consistent features of Wolfram syndrome, sometimes referred to as DIDMOAD, are diabetes insipidus, diabetes mellitus, optic atrophy and sensorineural deafness.[2,3] The majority of families show autosomal recessive inheritance, although a mitochondrial form has been described.[4,5] While the idiopathic type I diabetes mellitus occurs at a median age of six years, the optic atrophy presents at a median age of 11 years.[2] Diabetes insipidus and the sensorineural deafness usually occur during the second decade.[2,6]

Several findings may be associated with Wolfram syndrome, such as urinary tract atony and dilatation, cerebellar ataxia, myoclonus, gastrointestinal dysmotility, primary gonadal atrophy and psychiatric disorders.[2,3,6-8] Whether the urinary tract findings are secondary to the associated diabetes insipidus or to a primary autonomic dysfunction is controversial.[2,7] The median age at death is between 30 and 35 years, usually caused by central respiratory failure secondary to brain stem atrophy, or due to the complications of the urinary tract involvement.[2,3] Although affected individuals are usually present in one sibship of a family, reports of concordantly affected twins are scarce.[1] We report here the occurrence of Wolfram syndrome in triplets, two of whom are identical females. We also describe a previously unreported gastrointestinal finding and the presence of urinary tract dilatation, despite the absence of diabetes insipidus.

Patients and Methods

The triplets, one male and two females, were conceived naturally to normal healthy parents who are first cousins. There was a family history of similar conditions among siblings, although this was not clearly stated by the family.

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Patient 1

The 14-year-old male patient was a product of an uncomplicated pregnancy, except for the multiple gestation. He was diagnosed with diabetes mellitus at the age of 10 years, for which he is receiving insulin with rather poor control of his blood sugar. His height was 153 cm (10th percentile) and his weight was 42 kg (10th percentile). His scholastic performance is average. He has bilateral optic nerve atrophy and moderate bilateral sensorineural deafness at high frequency, both discovered during his work-up. He is currently showing normal development of secondary sexual characteristics, denoting onset of puberty.

Patients 2 and 3

The two female patients, who are identical, acquired diabetes mellitus at the same age as their brother, and also have had a similar course of the disease. Their heights were 135 and 136 cm (below 3rd percentile), and their weights were 31 and 29 kg (below 3rd percentile), respectively. They both perform poorly in school and have bilateral optic nerve atrophy and sensorineural deafness at high frequency, which were discovered during their work-up. Both girls show early breast buds, denoting onset of puberty.

Work-up

As part of a larger clinical study of patients with Wolfram syndrome, the triplets underwent a detailed laboratory evaluation that included complete blood count, blood urea nitrogen, serum creatinine, alanine transferase (ALT), aspartate transferase (AST), serum cholesterol and triglycerides, serum electrolytes, serum osmolality and glutamic acid decarboxylase (GAD) antibodies. We measured the volume of a 24-hour collection of urine and performed a water deprivation test for about 6 hours. The radiological evaluation included a brain and pituitary MRI, intravenous urogram (IVU) and an echocardiogram. Electroencephalogram (EEG) and nerve conduction studies (NCS) were done. Dynamic pituitary profile included gonadotropic-releasing hormone, thyrotropin-releasing hormone and insulin stress tests. Upper gastrointestinal endoscopy was performed on all three patients.

To test for the genetic identity of the females, we performed genotyping for all three siblings, with almost 100 tri- and tetranucleotide repeat highly polymorphic markers (STRPs), as a part of a genome-wide search for a second locus for the disorder.[9] The assay was PCR-based, and the amplified products were analyzed on a 6% denaturing polyacrylamide gel, and silver stained. We also performed HLA typing for two loci, DPB and DQB for the three patients, utilizing a haplotype analysis kit (INNOGENETICS).

Results

The biochemical and the hematological results were within normal limits for all three patients, and the GAD antibodies were negative. The MRI was abnormal, showing absence of signal from the posterior pituitary in all three. The urinary system showed significant dilatation in the form of hydronephrosis and urinary bladder atony in patients 1 and 2. The gastrointestinal system showed peptic ulcers in patients 2 and 3. The ulcers were acute in appearance and *Helicobacter pylori* was found in the three patients. The dynamic testing for the pituitary was normal. The neurologic evaluation revealed normal EEG and NCS, while the echocardiogram was normal. The psychiatric evaluation showed poor spatial relationships as well as poor simple arithmetic skills in the females, while the male had a normal evaluation.

Although they all had low first void urine osmolality, their 24-hour collection of urine volume did not exceed 2 liters. The water deprivation test demonstrated ability to concentrate urine in all three. For example, the urine osmolality in patient 1 went from 267 osmol/L to 604 in four hours. The hourly urine volume was reduced in all three by 40%-90% over the four to five hours of the test.

The two girls had identical genotypes for the 100 tested markers, while the boy had a different pattern in about half of them. The two girls also showed identical haplotype patterns for the two HLA loci, while the boy had a different pattern. Considering that they had identical patterns for all these markers, the chances that the females are not identical twins are extremely small.

Discussion

The triplets reported here have, at the age of 14 years, three out of the four cardinal features of Wolfram syndrome. It is of note that they all developed the diabetes mellitus at the same time and as expected in this syndrome, the three had negative GAD antibodies.[10] To our knowledge, Wolfram syndrome has not been reported in triplets before or even in identical twins. The genotyping data provides sufficient evidence that the two girls are identical.

Two of the triplets have asymptomatic peptic ulcer disease, which has not been reported previously. Although this might be coincidental, its significance remains to be determined by screening more patients. Currently, we are studying this new finding in more detail in Wolfram syndrome patients from other families and their normal siblings. The absence of the posterior pituitary signal was uniform for the three cases and this has been reported in previous studies.[2,6]

Two out of the three patients presented at an early age with asymptomatic dilated urinary tract which was not associated with high urine output. This finding was unexpected, since urinary tract complications usually occur later in life or presumably in association with the diabetes insipidus.[1,2] Whether this was found early due to the extensive evaluation done in this instance or is of true early onset will be determined by screening more patients with the disorder. At this point, we recommend that patients with Wolfram syndrome be screened periodically for urinary tract dilatation as early as the beginning of the second decade. Also, the function of the kidneys should be evaluated periodically despite the absence of high urine output.

Wolfram syndrome is a multisystem, progressive disorder with many manifestations which are being discovered because of developments in new investigative technology, as well as improvement in life expectancy. The disorder should be kept in mind particularly in our part of the world, where consanguinity is prevalent.

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References

1. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc 1938;13:715-8.
2. Barrett TG, Pouton K, Bundey S. DIDMOAD syndrome: further studies and muscle biochemistry. J Inherit Metab Dis 1995;18:218-20.
3. Kinsley BT, Dumont RH, Swift M, Swift RG. Morbidity and mortality in the Wolfram syndrome. Diabetes Care 1995;18:1566-70.
4. Polymeropoulos MH, Swift RG, Swift M. Linkage of the gene for Wolfram syndrome to markers on the short arm of chromosome 4. Nature Genet 1994;8:95-7.
5. Rotig A, Cormier V, Chatelain P, Francois R, Saudubray J-M, Rustin P, Munnich A. Deletion of mitochondrial DNA in a case of early-onset diabetes mellitus, optic atrophy and deafness (Wolfram syndrome, MIM 222300). J Clin Invest 1992;91:1095-8.
6. Rando TA, Horton JC, Layzer RB. Wolfram syndrome: evidence of diffuse neurodegenerative disease by magnetic resonance imaging. Neurology 1992;42:1220-4.

7. Aboseif S, Gasparini M, Schmidt R, Tanagho E. Wolfram (DIDMOAD) syndrome and its urological manifestations. Br J Urol 1993;72:106-11.
8. Cillino S, Anastasi M, Lodato G. Incomplete Wolfram syndrome: clinical and electrophysiologic study of two familial cases. Graefes Arch Clin Exp Ophthalmol 1989;227:131-5.
9. Yuan B, Valske D, Weber JL, Beck J, Sheffield VC. Improved set for short-tandem repeat polymorphisms for screening the human genome. Am J Hum Genet 1997;60:459-60.
10. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 1995;346:1458-63.