Purpose: To report a case of Wolfram syndrome characterized by early onset diabetes mellitus and progressive optic atrophy.

Case Report: A 20-year-old male patient with diabetes mellitus type I presented with best corrected visual acuity of 1/10 in both eyes with correction of -0.25+1.50@55 and -0.25+1.50@131 in his right and left eyes, respectively. Bilateral optic atrophy was evident on fundus examination. The patient also had diabetes insipidus, neurosensory deafness, neurogenic bladder, polyuria and extra-residual voiding indicating atony of the urinary tract, combined with delayed sexual maturity.

Conclusion: One should consider Wolfram syndrome in patients with juvenile onset diabetes mellitus and hearing loss. Ophthalmological examination may disclose optic atrophy; urologic examinations are vital in such patients.

Keywords: Diabetes Mellitus; Diabetes Insipidus; Deafness; Optic Atrophy
CASE REPORT

A 20-year-old male patient, a known case of diabetes mellitus type I from 7 years before, presented to a private ophthalmology office. His blood sugar was inadequately controlled even with insulin injections. His parents were consanguineous but healthy, however his grandparents were diabetic. Best-corrected visual acuity was 1/10 in both eyes with -0.25+1.50@55 and -0.25+1.50@131 in his right and left eyes respectively. Intraocular pressure was 14 mmHg in both eyes and biomicroscopic examinations were completely normal. Fundus examination showed advanced bilateral optic atrophy but no sign of diabetic retinopathy (Figures 1, 2). Laboratory studies and dehydration test confirmed diabetes insipidus. An audiologic examination revealed neurosensory deafness. Magnetic resonance imaging (MRI) of the brain and lumbar spine was normal. Both kidneys were larger than normal and showed signs of moderate hydronephrosis on ultrasonographic evaluation. The bladder wall had a trabecular pattern and the urinary tract was dilated on both sides. The patient had 170 ml post-voiding bladder residue. Urologic examination and sonographic findings were consistent with a neurogenic bladder (Figure 3). The patient also had polyuria and extra-residual voiding which indicated atony of the urinary tract. Urogenital examination revealed some degree of delayed sexual maturation.

DISCUSSION

Wolfram syndrome is a progressive autosomal recessive neurodegenerative disorder. Hallmarks of the syndrome are diabetes mellitus, which is usually the first sign of the disease (median age at diagnosis, 6–15 years), and optic atrophy (median age at diagnosis 11 years). Optic atrophy in a diabetic patient necessitates audiometry and intravenous pyelography. In our patient the majority of symptoms became manifest by the second decade of life and a correct diagnosis had been made when he was 15 years old.

Hearing loss, mainly in high frequencies, may be present in 48% of patients and diabetes insipidus of hypothalamic origin may occur in the third decade of life in up to 75% of cases. Dilation of the urinary tract is observed in 45%
of cases which may be secondary to chronic high urine flow rates (diabetes insipidus) or neuronal degeneration at various levels of the urinary tract.\(^{11}\) Atony of the bladder and the whole urinary tract may also be observed. Additionally, retinal pigmentary changes, spinocerebellar degeneration, delayed sexual maturation, a small sella turcica and male hypogonadism due to primary gonadal failure have been reported with DIDMOAD syndrome.\(^{12-14}\)

Differential diagnoses include congenital rubella syndrome, Leber’s hereditary optic atrophy, and thiamine responsive anemia with diabetes mellitus and deafness. The association of diabetes mellitus with 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.\(^8\)

The pathogenesis of the disease remains unknown, but positional cloning studies in families with Wolfram syndrome have identified linkage peaks on the short arm of chromosome 4 (4p16.1). Mutations in the gene encoding wolframin (WFS1), which maps to that region, have also been shown to cause the syndrome.\(^{15,16}\) Nevertheless, the wide spectrum of clinical manifestations affecting several organs and tissues, suggests mitochondrial DNA (mtDNA) involvement.

Since the initial identification of the WFS1 gene by Inoue et al.,\(^{17,18}\) different research groups have reported more than 50 distinct mutations in this gene. WFS1 protein presumably functions to maintain certain populations of neuronal and endocrine origin. Diabetes mellitus may result from hypothalamic degeneration, although loss of pancreatic \(\beta\)-islet cells as part of a specific defect in neuroectodermal amine precursor uptake and decarboxylation-derived cells in the pancreas and in the supraoptic and paraventricular nuclei has also been postulated. DI is thought to be related to atrophy and degeneration of the hypothalamus with loss of vasopressin-secreting neurons in the supraoptic and paraventricular nuclei, and degeneration of the posterior pituitary gland. The deafness is sensorineural and degenerative; atrophy of the vestibulocochlear nuclei and inferior colliculi may be responsible.\(^{19}\)

Due to variability of symptoms, Wolfram syndrome may be overlooked. The condition should be evaluated in a multidisciplinary manner and specific tests are necessary to make a precise diagnosis and disclose all components of the syndrome. Management requires cooperation between several specialists including an endocrinologist, neurologist, ophthalmologist and urologist.

REFERENCES

1. Fraser FC, Gunn T. Diabetes mellitus, diabetes insipidus and optic atrophy. An autosomal recessive syndrome? \textit{J Med Genet} 1977;14:190-193.

2. Gunn T, Bortolussi R, Little JM, Andermann F, Fraser FC, Belmonte MM. Juvenile diabetes mellitus, optic atrophy, sensory nerve deafness and diabetes insipidus - a syndrome. \textit{J Pediat} 1976; 89:565-570.

3. Cooper IS, Rynearson EH, Bailey AA, MacCarty CS. The relation of spinal cord disease to gynecomastia and testicular atrophy. \textit{Proc Staff Meet Mayo Clin} 1950;25:320-326.

4. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. \textit{Mayo Clinic Proc} 1938;13:715-718.

5. Strom TM, Hortnagel K, Hofmann S, Gekeler F, Scharfe C, Rabl W, et al. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. \textit{Hum Mol Genet} 1998;7:2021-2028.

6. Bundey S, Poulton K, Whitwell H, Curtis E, Brown IA, Fielder AR. Mitochondrial abnormalities in the DIDMOAD syndrome. \textit{J Inherit Metab Dis} 1992;15:315-319.

7. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. \textit{Lancet} 1995;346:1458-1463.

8. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. \textit{J Med Genet} 1997;34:838-841.

9. Dreyer M, Rudiger HW, Bujara K, Herberhold C, Kuhnau J, Maack P, et al. The syndrome of diabetes insipidus, diabetes mellitus, optic atrophy, deafness, and other abnormalities (DIDMOAD syndrome) Two affected sibs and a short review of the literature (98 cases). \textit{Klin Wochenschr} 1982;60:471-475.

10. Piccoli GB, Mezza E, Jeantet A, Segoloni GP. An uncommon genetic syndrome with acute renal
failure in a 30-year-old diabetic patient. Nephrol Dial Transplant 2003;18:206-208.

11. Tekgul S, Oge O, Simsek E, Yordam N, Kendi S. Urological manifestations of the Wolfram syndrome: observations in 14 patients. J Urol 1999;161:616-617.

12. Page MM, Asmal AC, Edwards CR. Recessive inheritance of diabetes: the syndrome of diabetes insipidus, diabetes mellitus, optic atrophy and deafness. Q J Med 1976;179:505-520.

13. Cremers CW, Wijdeveld PG, Pinckers AJ. Juvenile diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus, atonia of the urinary tract and bladder and other abnormalities (Wolfram syndrome). A review of 88 cases from the literature with personal observations on 3 new patients. Acta Paediatr Scand Suppl 1977;264:1-16.

14. Hyams SW, Adar H, Friedman E. Optic atrophy, diabetes mellitus, hypothalamic dysfunction and a small sella turcica. J Pediatr Ophthalmol 1977; 14: 106-108.

15. Ari S, Keklikci U, Caca I, Unlu K, Kayabasi H. Wolfram syndrome case report and review of the literature. Ann Ophthalmol (Skokie) 2007;39:53-55.

16. Cryns K, Thys S, Van Laer L, Oka Y, Pfister M, Van Nassauw L, et al. The WFS1 gene, responsible for low frequency sensorineural hearing loss and Wolfram syndrome, is expressed in a variety of inner ear cells. Histochem Cell Biol 2003;119:247-256.

17. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet 1998;20:143-148.

18. Kinsley BT, Swift M, Dumont RH, Swift RG. Morbidity and mortality in the Wolfram syndrome. Diabetes Care 1995;18:1566-1570.

19. Franks PW, Rolandsson O, Debenham SL, Fawcett KA, Payne F, Dina C, et al. Replication of the association between variants in WFS1 and risk of type 2 diabetes in European populations. Diabetologia 2008;51:458-463.