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DIABETES MELLITUS, DIABETES INSIPIDUS, OPTIC ATROPHY AND DEAFNESS (DIDMOAD SYNDROME)*

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Two patients with diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy (OA), deafness (D) and dilatation of the urinary tract-the so-called DIDMOAD syndrome are presented. In one of the patients, the presenting components were DI and OA. In the second case, DM was the first manifestation to be diagnosed, and in this patient the course of the syndrome was complicated by associated epileptical activity disorders, and later septicemia. The admission of these patients led us to review the literature describing this syndrome. *Key words: diabetes mellitus, diabetes insipidus, hydronephrosis, neuronal degeneration.*

In 1938, Wolfram[1] published a report from The Mayo Clinic describing the incidence of diabetes mellitus (DM) and optic atrophy (OA) in four siblings. Since then, the association of juvenile diabetes mellitus, diabetes insipidus (DI), optic atrophy and sensorineural deafness (D),known as DIDMOAD or Wolfram syndrome, has become more frequently recognized. DIDMOAD syndrome has a B autosomal recessive mode of inheritance[2,3], and, therefore, can be expected to occur more often in our country, where the rate of consanguinity is high. For this reason, more attention should be given to evaluating patients with DM or DI.

Hydronephrosis, hydroureter, and dilatation of the urinary bladder are often associated with DIDMOAD syndrome[3-5]. Since the onset is in childhood, and urinary tract dilatation is responsive to treatment, components of this syndrome should be searched for more often. This report describes two cases with DIDMOAD syndrome.

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Case Reports

Case 1

A 14-year-old boy, the seventh child in the family, was admitted to the Hacettepe University Children's Hospital with complaints of hyperglycemia and ketosis. The first-born child in the family, diagnosed as having DM type I, had died at the age of thirteen. The patient was the result of a normal delivery. He had had complaints of polyuria and polydypsia since he was nine years old. At the age of eleven, a diagnosis of diabetes mellitus was established, and he received desamino-D-arginyl vasopressin (DDAVP) in a dose of 5 μg b.i.d. by nasal insufflation. Examination of the fundi, at the time, revealed bilateral optic atrophy, however, no signs of retinopathy were noted. Ultrasonography demonstrated bilateral hydronephrosis and hydroureter. Renal function was normal and creatinine clearance 110 ml/min. On the patient's last admission, glycosuria associated with a fasting blood glucose of 400 mg/dl and ketosis were noted.

TABLE I: Clinical Presentation of the Patients

	Case No. 1	Case No. 2
Sex	M	F
Age (yrs)	14	11
Height (percentile)	5	5
Weight (percentile)	5	5
Age (yrs) at onset of		
Diabetes mellitus	14	7
Diabetes insipidus	11	11
Neurosensory hearing loss	14	11
Dilatation of urinary tract	Yes	Yes
Electroencephalogram	Normal	Subcortical instability and dysrrhythmia
Brain scan	Normal	Cortical atrophy and infarcts
Abnormal audiogram	Yes	Yes
Abnormal VER	Yes	Yes
Abnormal BAER	Yes	Yes
Family history of DM	Yes (Type I)	Yes (Type II)
Endogenous creatinine clearance	Normal	Impaired
Parental consanguinity	Distant	First cousins

The patient's condition was subsequently stabilized with the daily administration of a combination of 16 units NPH and 8 units crystalline insulin. Neurological examination was normal, except for the presence of optic atrophy.

An audiogram indicated bilateral sensorineural hearing loss. Skull x-rays, CT scan and electroencephalography were completely normal. Visual-Evoked Response (VER) and Brain Stem Auditory-Evoked Response (BAER) revealed bilateral optic atrophy and sensorineural deafness, respectively. Since polyuria and polydypsia were still present, the dose of DDAVP was increased to 10 μg/day.

Case 2

An 11-year-old girl, the first-born child of healthy parents who were first cousins, was admitted to the Hacettepe University Children's Hospital in a ketoacidotic state. The patient was the result of an uncomplicated delivery and had a normal early childhood. When evaluated at age seven, the diagnosis of DM was established, and insulin treatment was initiated. She complained of progressive visual and hearing deterioration in the last few months.

Physical examination on admission revealed a severely ill child in a ketoacidotic coma. The blood pressure was 110/60 mm Hg. She was severely dehydrated, had Kussmaul respiration, and was spastic with diminished deep tendon reflexes. Funduscopic examination showed bilateral optic atrophy but there was no evidence of diabetic retinopathy. In addition to hyperglycemia, ketonemia and metabolic acidosis, her renal function was impaired. Laboratory studies revealed a BUN of 108 mg/dl, serum creatinine 6.5 mg/dl, uric acid 10.6 mg/dl, calcium 7 mg/dl, and phosphate 7.4 mg/dl. Creatinine clearance was 20 ml/min/1.73 m^2. Ketonuria and 8-10 white blood cells per high magnification field were noted in the urine sediment with a specific gravity of 1001. The hemoglobin was 6.75 g/dl and the blood film revealed hypochromia. The white blood cell count was 31,000/mm^3, with 86% neutrophils. Urine osmolality was found to be 170 mOsm/kg H_2O and serum osmolality 300 mOsm/kg H_2O. Skull x-rays were normal. CT scan of the brain showed cortical atrophy and infarcts which were interpreted as diabetic angiitis. The electroencephalogram showed diffuse epileptiform activity and dysrrhythmia. VER and BAER revealed bilateral abnormal P response consistent with optic atrophy and sensorineural deafness, respectively

The patient was treated with intravenous insulin therapy, appropriate fluid and electrolyte solutions and antibiotic therapy for the urinary infection. Despite the antibiotic treatment, we were unable to control an overwhelming infection. Her clinical condition deteriorated and gross intestinal bleeding began. She died on the nineteenth day of admission, due to hypovolemic septic shock.

Discussion

DIDMOAD syndrome has become an entity which is frequently observed in diabetic patients. Besides the four main features associated with this syndrome, namely, diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and sensorineural deafness (D), various other disorders including ataxia, neurogenic bladder, epilepsy, infantilism, retinal pigmentation, congenital heart disease, myocarditis, cataract and obesity have also been noted[6].

Many patients have been reported to have OA prior to the onset of DM which supports the primary nature of optic involvement. In fact, primary optic atrophy without retinitis pigmentosa may be regarded as a specific sign of the syndrome, and deserves special attention. In our patients, progressive OA without retinitis pigmentosa was one of the main features but diabetic retinopathy was not present.

The occurrence of hydronephrosis, hydroureter, and an enlarged bladder has been previously described in this syndrome[3,7-9]. Minimal signs of peripheral neuropathy and an absence of obstruction are factors usually attributed to DI [9]. Hydronephrosis and hydroureter are well known complications of DI. In the series reported by Balci et al[7,8], one patient had both hydronephrosis and hydroureter, which were detected years after the onset of DI. Although renal function in DI is well maintained, it has been shown that it may eventually become impaired. As described in the literature, endogenous creatinine clearance has been found to be decreased in some cases, as in our second patient[5].

HLA-typing studies have been carried out on patients with DIDMOAD syndrome to see if any similarities exist between this syndrome and insulin-dependent diabetes mellitus. The results and the absence of islet cell antibodies suggest that the pathogenesis of DM in DIDMOAD syndrome is different[10].

Cremers et al[5] reported deafness in 39 of the 88 patients reviewed in the literature up to 1977. The audiograms of our patients revealed bilateral sensorineural deafness, and BAER confirmed the results. So far, the reports do not clearly indicate the involvement of afferent fibers from the middle and upper cochlear coils[3].

In 1976, Gunn et al[11] described another four patients with DM, OA, DI and sensory nerve deafness. They suggested that this clinical syndrome might be systemic degeneration involving the optic nerve, supraoptic and paraventricular nuclei and the eighth cranial nerve, and that the association of DM could be through the APUD cell series.

On the other hand, clinical and necropsy studies give good evidence of a specific neuronal degeneration as the pathogenesis of DI, OA and deafness. There are also some reports which suggest a direct neuronal degenerative process in the

pathogenesis of the dilatation of the urinary tract. The correlation of DM with these proposals and the explanation of the etiology of this entity remain obscure. New cases, however, might serve to shed light on the pathogenesis of this syndrome.

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