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VARIOUS CLINICAL ASPECTS OF DIDMOAD (WOLFRAM) SYNDROME*

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SUMMARY: Ökten A, Gedik Y, Demirci A, Mocan H, Erduran E, Aslan Y (Departments of Pediatrics and Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Various clinical aspects of DIDMOAD (Wolfram) syndrome. Turk J Pediatr 1995; 37: 235-240.

The association of juvenile diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy (OA) and sensorineural deafness (D) is known as DIDMOAD or Wolfram syndrome. Aside from these four cardinal features, a wide variety of abnormalities of the nervous system, urinary tract and endocrine glands have been described in this syndrome.

In this report, the clinical features of six patients with DIDMOAD syndrome are presented. All six patients had DM. Five of the six patients had DI, five OA and five displayed abnormal audiogram findings. In addition, two had goiter, two delayed puberty, one seizure and one mental retardation with depression attacks. Urinary tract dilatation was recorded in five patients.

Four patients developed typical complications of DM. One of them had overt nephropathy and arthropathy despite the short duration of DM. In addition, this patient had diabetic retinopathy, which is considered to be rare in this syndrome. *Key words: diabetes mellitus, diabetes insipidus, optic atrophy, deafness.*

The association of juvenile diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy (OA) and sensorineural deafness (D), known as DIDMOAD syndrome, was first described by Wolfram in 1938[1,2]. Aside from these four cardinal features, the clinical picture may be accompanied by a wide variety of other abnormalities affecting the nervous system, urinary tract and endocrine glands[2].

An autosomal recessive mode of inheritance has been well documented in DIDMOAD syndrome[2,3]. However, recently it has been shown that some cases may have mitochondrial-mediated inheritance[4].

In this report, various features of the disease are discussed in six cases with DIDMOAD syndrome.

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Material and Methods

To date, DIDMOAD syndrome has been diagnosed in six cases at Karadeniz Technical University Faculty of Medicine. Venous blood samples were drawn from these six patients to evaluate serum glucose, urea, creatinine, electrolytes and HbA_{1c} levels. In addition, urinary output was measured and creatinine clearance was claculated at three-month intervals.

The thyroid functions, antithyroid antibodies, daily albuminuria and β_2 microglobinuria were measured at six-month intervals.

The following tests were performed in all patients annually: chest radiogram, ultrasonography of the kidney and bladder, intravenous pyelography (IVP), audiography, electromyography (EMG), electrocardiography, echocardiography, electroencephalography (EEG) and cranial magnetic resonance imaging (MRI).

Results

Age, sex, age at onset of DM, DI, various clinical features of patients, and parents' consanguinity are summarized in Table I.

Table I: Clinical Presentation

Case	1	2	3	4	5	6
Sex	F	F	M	F	F	F
Age when last seen (years)	15	13	19	18	15	9
Age at onset of:						
Diabetes mellitus	14	4	6	7	7	9
Diabetes insipidus	14	8	—	10	12	9
Optic atrophy	—	+	—	+	+	+
Abnormal audiogram	+	+	+	+	+	—
Dilatation of urinary tract	—	+	—	+	+	+
Additional endocrine disorders	Goiter	Delayed puberty	—	—	Goiter Delayed puberty	—
Neurologic, pyschiatric status	UR	UR	Seizure	Depression Mental retardation	UR	UR
Parents' consanguinity	—	+	+	+	—	+

UR: Unremarkable.

All six patients had DM and required treatment with insulin. DI was diagnosed in five o six patients and treated with desmopressin. In the patients with DI, the normal hyperintensity of the posterior hypophysis, which shows antidiuretic hormone supply, was absent on MRI (Fig. 1a). Although OA was determined in four patients and abnormal audiogram findings in five, only one case had

decreased visual acuity and hearing loss. As shown in figures 1a and 1b, OA was demonstrated on MRI. Dilatation of the urinary tract was determined in four of six patients, as shown in Figures 2a and 2b.

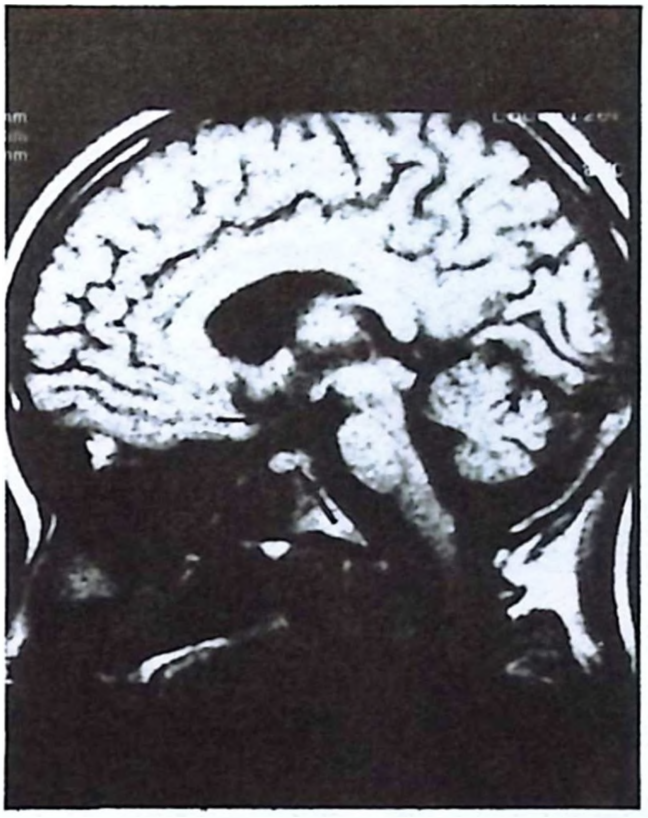

Fig. 1a: Sagittal T_1-weighted (TR/TE 400/20) image shows absence of hyperintense signal in the posterior hypophysial gland (large arrow) and atrophic prechiasmatic optic nerve (small arrow).

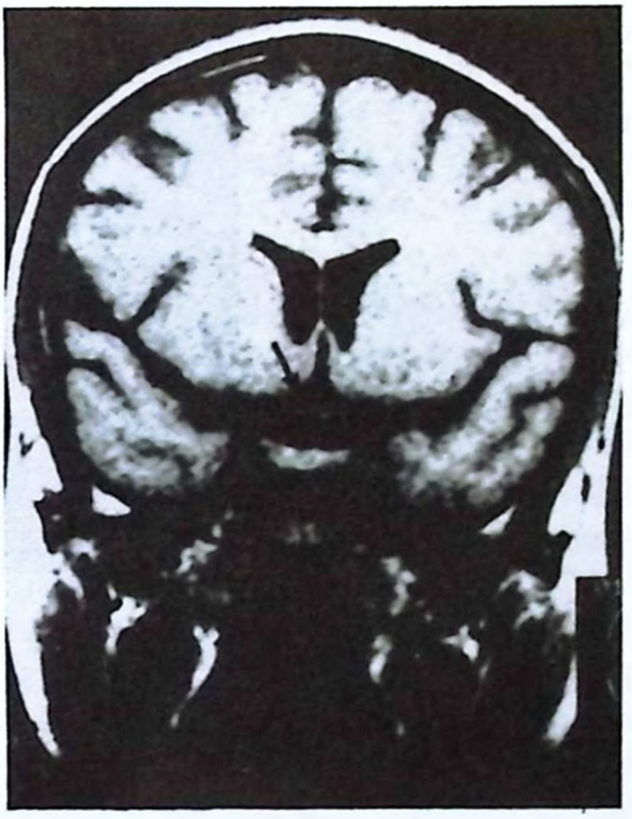

Fig. 1b: Coronal T_1-weighted (TR/TE 400/20) image shows atrophy in the optic chiasm (arrow).

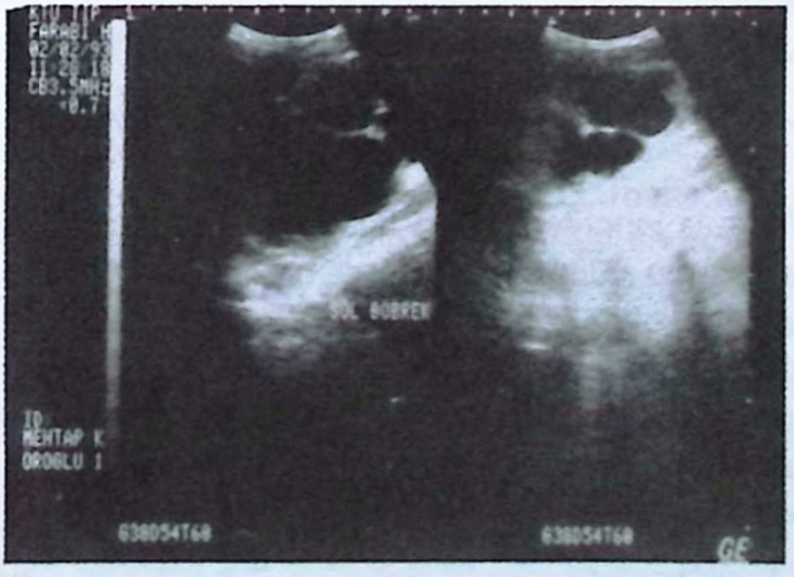

Fig. 2a: Ultrasonography shows hydronephrosis.

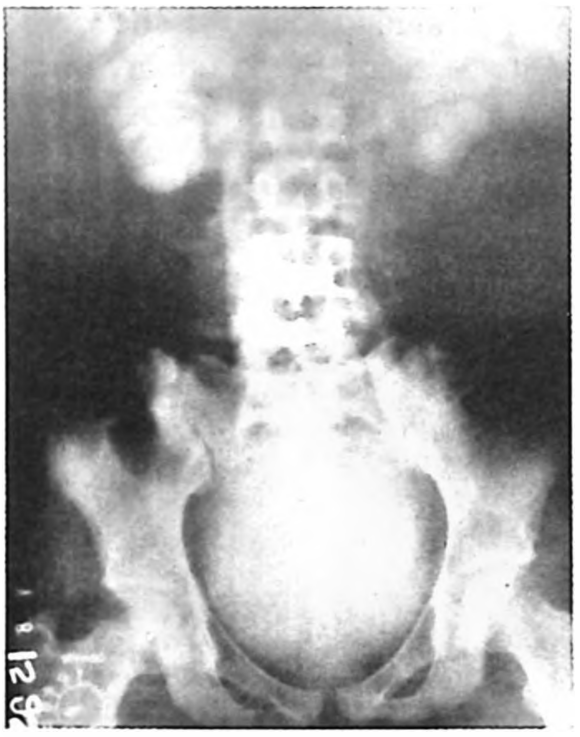

Fig. 2b: IVP shows bilateral, dilated urinary tract.

Long-term complications of DM in our patients are listed in Table II.

Table II: Diabetes Mellitus Complications in Six Patients with DIDMOAD Syndrome

Case	1	2	3	4	5	6
Retinopathy	+	–	–	–	–	–
Neuropathic changes on ENMG	+	+	–	+	+	–
Microalbuminuria	+	+	—	+	—	—
Overt nephropathy	+	—	—	—	—	—
Arthropathy	+	—	—	+	—	—
Cardiomyopathy	—	—	—	—	—	—

Discussion

DIDMOAD syndrome is inherited as an autosomal recessive pattern, and many but not all cases are the offspring of consanguineous parents[3]. In our series, four patients were the offspring of consanguineous parents, and two cases siblings. Although the frequency of DIDMOAD syndrome has been reported as one in 150, we diagnosed six patients out of 148 juvenile diabetics in our clinic. The high prevalence of this syndrome can be expected in our country, with its high rate of consanguineous marriages[5, 6].

Hydronephrosis, hydroureters and dilatation of the bladder have been reported as associated findings in this syndrome. The dilatation of the urinary tract is

considered to be a consequence of high diuresis associated with DI. Indeed, an improvement of the urinary tract is often noted with decreased urinary output by desmopressin treatment. However, it has been suggested that since dilatation may occur in the absence of DI, degeneration of the nerve supply to the ureters and bladder may be the primary cause[7, 8]. In our series, four patients had urinary tract dilatation, and all had DI. Although all patients responded to treatment with desmopressin and urinary output decreased from 4-6 L to 1.2-2 L daily, urinary tract dilatation improved in only one patient, the one case with no neuropathy (Case 6). This observation emphasizes the role of a degenerative process affecting the central and peripheral nervous system.

In addition to neurogenic bladder, a wide variety of neurologic features including ataxia, nystagmus, mental retardation and seizures have been reported in DIDMOAD syndrome[9, 10]. Atrophic changes with neuronal loss, gliosis and demyelination in the cerebellum and brainstem, and myelin pallor in the spinal cord tract have been described in autopsies[10, 11]. MRI studies have showed specific abnormalities that correlated with the cardinal neurologic features[10, 12]. According to its progressive clinical course and pathologic and radiologic findings, DIDMOAD syndrome may be considered a diffuse neurodegenerative disease[9-11]. One of our patients had seizures with pathologic changes on EEG, and another was mentally retarded and had episodes of severe depression. A prevalence of severe psychiatric illness is remarkable in DIDMOAD syndrome. The behavioral abnormalities could be related to widespread neuropathological changes, or the Wolfram syndrome gene itself may predispose to psychiatric episodes[13].

Endocrine abnormalities include delayed sexual maturation, growth retardation and hypothyroidism[2, 14]. We diagnosed an euthyroid goiter in two patients, but it is difficult to claim as a symptom associated ith DIDMOAD syndrome because the northern Black-Sea region of Turkey, where the patient is living is a well-known area of endemic goiter. Delayed puberty, recognized in two patients, might be a feature of the syndrome or may be explained by poor metabolic control and long duration of DM (8-9 years).

Four of our patients developed typical diabetic complications of longstanding DM, as in the common Type I variant. These findings correlate with previous reports[15], except in Case 1, who displayed a different clinical course of disease. She had overt nephropathy and arthropathy despite the short duration of DM (one year) and good metabolic control. Diabetic retinopathy, which is considered rare in this syndrome even in DM of long duration, was also found on fundoscopic examination[16].

An unexplained association of symptoms with an early onset and rapidly progressive course of this syndrome is consistent with an ATP-supply defect, which is so often seen in mitochondrial-mediated disorders[4]. In addition, different mitochondrial DNA mutations have been identified recently[17, 18]. These findings suggest that this syndrome also has a mitochondrial origin, at least in some

cases. Since mitochondrial dysfunction may explain the rapidly progressive course of disease, further genetic investigation should be done to evaluate these patients.

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