DIDMOAD Syndrome (Wolfram Syndrome) with Megacystis, Megareuter and Hydronephrosis

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A case of DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and nerve deafness) occurring as an autosomal recessive disorder is described. The patient presented with diabetes mellitus, diabetes insipidus, severe urinary tract dilatation, and asymptomatic involvement of optic and auditory nerves. The diabetes insipidus had both neurogenic and nephrogenic components. A marked reduction in urinary output was demonstrated following the administration of desmopressin. The possible factors that lead to functional obstruction with consequent urinary tract dilatation are discussed. Bladder neck resection was performed and an ileal conduit was constructed. Following the surgery there was an improvement in glomerular function.

The DIDMOAD syndrome is a rare familial disease characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and nerve deafness. Wolfram was the first to describe the presence of diabetes mellitus and progressive optic atrophy in siblings, hence the eponym Wolfram syndrome.\textsuperscript{1} Urinary tract dilatation is a common component of the syndrome which varies from mild hydronephrosis to megaureter and megacystis.\textsuperscript{2-4} The autosomal recessive character of this hereditary syndrome has been well demonstrated.\textsuperscript{5,9,10} We present here a review of this rare syndrome and report its occurrence in a young male.

Case Report

A 17-year-old Libyan male presented with distension of abdomen, polyuria, and extreme thirst. He developed IDDM at the age of 12 years and was being treated by two doses of lente insulin daily. At age 15 years he noticed increasing polyuria and polydipsia with lack of urinary control and gradual distension of abdomen despite fairly well controlled diabetes mellitus. The older brother and sister of the patient died at the age of 16 and 18 years respectively. Their case records were reviewed. At the time of death both were blind and had known insulin dependent diabetes mellitus (IDDM) and diabetes insipidus. The brother also had severe urinary tract abnormalities. Although both cases remained undiagnosed, the history and case records suggest that they may also have suffered from DIDMOAD syndrome. On physical examination the patient looked much younger than his chronological age (height 148 cm and weight 42 kg vs normal height and weight at the age of 17 years of 172.7 cm and 63.05 kg respectively). Abdominal distension was striking and the urinary bladder was palpable above the umbilicus.
However, there was no pain or difficulty in micturition. The daily urine output varied from 16 to 18 litres. Although the patient denied any diminution of vision, ophthalmological examination revealed bilateral optic atrophy and background diabetic retinopathy. The visual acuity was 6/36 in both eyes and slit lamp examination revealed a delayed pupillary reaction to direct and indirect light. There were no signs of peripheral or autonomic neuropathy or other abnormality of the central nervous system.

The investigations included an intravenous pyelogram which showed gross dilatation of the right ureter and calyces and a non-functioning left kidney (Fig. 1). No reflux was demonstrated on a micturating cystogram. The urethrogram was normal and cystoscopy showed a voluminous bladder with trabeculation and normal ureteric orifices. The urine was sterile and the blood urea and creatinine were 100 mg/dl and 2.2 mg/dl respectively. The 24-hour urine specific gravity was 1004. The water deprivation test (Dash test) suggested cranial diabetes insipidus (Table 1). The patient was treated initially by daily injections of vasopressin tannate-in-oil and later with 1-desamino-8-D-arginine vasopressin (desmopressin) 10 μg twice daily by nasal insufflation with good clinical response. The daily urine output reduced from 14–16 litres to 5–6 litres and 24-hour urine specific gravity rose to 1011.

Significant bladder distension and urinary incontinence however, persisted despite regular emptying of the bladder. The patient was referred to a urology unit abroad where a bladder neck resection and ileal conduit diversion was performed. His blood urea and creatinine fell from the immediate preoperative level of 120 mg/dl and 3 mg/dl respectively to 60 mg and 1.2 mg/dl respectively. A postoperative intravenous urogram showed satisfactory resolution of the upper urinary tract distension. The mean plasma glucose on a split dose of lente insulin (40 U morning, and 20 U evening) was 141 mg/dl. The plasma glucose profile was as follows: FPG 120 mg/dl; 2 h after breakfast 184 mg/dl; before lunch 132 mg/dl; 2 h after lunch 163 mg/dl; before dinner 112 mg/dl; 2 h after dinner 176 mg/dl; 3.30 a.m. 102 mg/dl. There was no significant glucosuria. Although the patient did not notice any defect of hearing the audiogram showed bilateral nerve deafness, more marked in the high frequencies. Radiographs of skull, pituitary fossa and chest, and CT brain scan were normal. Other investigations performed included haemoglobin, white blood cell count, erythrocyte sedimentation rate, serum

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<th>Plasma osmolarity (mOsm/kg)</th>
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<td>5 h after vasopressin</td>
<td>8 h vasopressin</td>
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<td>0-1 h</td>
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electrolytes, serum calcium, phosphate, uric acid, bilirubin, alkaline phosphatase, lactic dehydrogenase, oxalacetic transaminase, serum follicular stimulating and leukotizing hormones, serum cortisol, serum T₃, T₄, and thyroid stimulating hormone, cholesterol, and protein electrophoresis—all were normal.

Discussion

Genetics
The patient described above had diabetes insipidus, diabetes mellitus, optic atrophy, and nerve deafness and thus fulfills the criteria for the DIDMOAD syndrome. The probable occurrence of the DIDMOAD syndrome in three siblings of unaffected but closely related parents suggests recessive inheritance. The autosomal recessive character of the syndrome has been well demonstrated in various case studies. In an analysis of available data on HLA-DR antigens in 36 patients, a conclusive positive association between the DIDMOAD syndrome and the HLA-DR2 haplotypes was found. This is in stark contrast with typical IDDM which is negatively associated with HLA-DR2. This favors the view that diabetes mellitus in the DIDMOAD syndrome is not of autoimmune origin.

Diabetes insipidus
The precise cause of diabetes insipidus in the DIDMOAD syndrome is somewhat uncertain although it is thought to arise because of vasopressin deficiency aggravated by a nephrogenic component which is secondary to urinary tract dilatation. In our case an initial response to desmopressin and a further improvement in glomerular function following the drainage procedure points to both neurogenic and nephrogenic diabetes insipidus.

Urinary tract abnormalities
The occurrence of hydrenephrosis, hydrourerter and megalocystis has been described in various studies. The urinary tract has however, been normal in some cases of this syndrome—a fact which remains unexplained. There is no evidence that urinary tract dilatation is due to organic obstruction. The following mechanisms of urinary tract dilatation have been proposed:

1. Progressive passive dilatation of the urinary tract due to high urine flow rate caused by diabetes insipidus. This explanation is congruous with the observation that megaloureter and megalocystis occur both in hereditary nephrogenic diabetes insipidus and hereditary antidiuretic hormone sensitive diabetes insipidus. Urinary tract dilatation however, does not develop in adult onset diabetes insipidus. This could possibly be due to high flow rate operating over a shorter period or because the childhood tract is more susceptible to dilatation.

2. Functional obstruction. The increased urine volume with repeated neglect or regular emptying may lead to an increased bladder size with muscular hypertrophy and progressive obstruction of the intramural portions of the ureters. In our case functional obstruction was possibly accountable for significant bladder distension and urinary incontinence that persisted following desmopressin.

3. Secondary diabetic focal neuropathy of the urinary tract. This is not likely as in this case and many other previous reports there was no evidence of diabetic autonomic or somatic neuropathy.

4. Primary focal degenerative neuropathy of the urinary tract.

Pathogenesis
The pathogenesis of this syndrome remains obscure. No single anatomical lesion can explain the occurrence of diabetes insipidus, diabetes mellitus, optic atrophy, and nerve deafness. Investigations for intracranial pathology in our case and in previous cases have not been helpful. Detailed endocrine studies have been made of hypothalamic, pituitary, and thyroid function but there was nothing to suggest generalized pituitary or hypothalamic disease. A focal progressive neuropathy affecting the optic and vestibular nerves, hypothalamus and urinary tract may explain various expressions of the syndrome. Immunohistological studies of the bladder wall and ureter have demonstrated a marked diminution of nerve fibres but it remains uncertain whether it is the cause of urinary tract dilatation or a consequence of it.

Diagnosis and Treatment
Since all four components of the syndrome may not be present at the time of presentation asymptomatic patients with diabetes mellitus and optic atrophy should be regularly screened for deafness by audiogram and for diabetes insipidus by water deprivation test. They should also be investigated radiologically to detect urinary tract dilatation at a stage before renal function is damaged. If diabetes insipidus is discovered and the patient is asymptomatic or if there is dilatation of the urinary tract, treatment with desmopressin should be started. The patient should be instructed to empty his bladder completely and regularly to prevent distension which may be asymptomatic. If the urinary tract dilatation progresses on treatment, or investigation shows localized obstruction, operative intervention may be necessary to preserve the renal function.
Prognosis
The prognosis of DIDMOAD syndrome remains uncertain. In long-standing cases chronic complications of diabetes may develop such as the diabetic retinopathy which occurred in this present case, but by and large chronic complications of diabetes are infrequent and mild.\(^6\) The long-term consequences of renal tract dilatation are also unclear; in the short term either drug therapy or surgical treatment leads to improvement.\(^6\) The optic atrophy may result in blindness by early adult life, but the deafness generally remains mild. The life expectancy compared with that of other diabetics remains uncertain. Avoidance of consanguinity decreases frequency of occurrence of the disease but does not eliminate it.

References