Association of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

The Wolfram or DIDMOAD syndrome

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SUMMARY Seven patients with a rare syndrome of diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), neurosensory deafness (D), atony of the urinary tract, and other abnormalities (Wolfram or DIDMOAD syndrome) are reported. Of the seven patients, three siblings were followed up for 10–17 years.

All seven patients had diabetes mellitus and optic atrophy; six had diabetes insipidus; and in the four patients investigated there was dilatation of the urinary tract. The severity of diabetes varied, and all required insulin for control of the hyperglycaemia. In one patient the course of the disease simulated maturity onset diabetes of the young; another presented with ketoacidosis; but none had haplotypes usually associated with insulin dependent diabetes mellitus. The diabetes insipidus responded to chlorpropamide, suggesting partial antidiuretic hormone deficiency. Onset of optic atrophy and loss of vision occurred relatively late and progressed slowly, although in one patient there was a rapid deterioration in visual acuity. Deafness was mild, of late onset, and of sensorineural origin.

A degenerative process affecting the central and peripheral nervous system can explain all the manifestations of the syndrome except diabetes mellitus. The pathogenesis of the diabetes mellitus remains obscure.

DIDMOAD syndrome, also known as Wolfram syndrome, is an acronym for diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness. Hydronephrosis, hydrourters, and dilatation of the urinary bladder are less commonly associated findings. Other rare manifestations include cerebellar dysfunction, oesophageal dysphagia, delayed puberty, aminoaciduria, anosmia, deposits of pigments in the retina, electrophotographic changes, colour blindness, episodic vertigo, and dysautonomia with labile regulation of body temperature. This syndrome is inherited as mendelian recessive with varying expressivity. Diabetes mellitus and primary optic atrophy are the most salient features. Several of the manifestations are progressive in nature. About 100 reported cases have been reviewed recently.1-3

We report on seven patients with DIDMOAD syndrome and describe the course of the disease in three siblings followed up for a period of 10–17 years.

Subjects and methods

Since 1966 DIDMOAD syndrome has been diagnosed in seven patients, two girls and five boys, at the American University of Beirut Medical Center. Three were siblings, a girl and two boys (cases 1, 2, and 3); the sister (case 2) had been reported previously in 1968.4 The age; sex; and age at onset of diabetes mellitus, diabetes insipidus, and visual and auditory changes are summarised in Table I.

HLA-A, HLA-B, HLA-C, and HLA-DR were determined by the microcytotoxicity test using antisera obtained from the Behring Institute.5 HLA-A, HLA-B, HLA-Cw2, HLA-Cw3, HLA-Cw4, and HLA-DR 2 were determined in the three siblings (cases 1, 2, and 3), their father, and unaffected brother. In one patient (case 6) only the HLA-DR profile was determined (Table 2).

Loss of hearing was classified according to the shape of the audiogram and speech discrimination
score. Histopathologic correlation was also analysed, by the method described by Schuknecht.6

Results

Diabetes mellitus. Six patients (cases 1, 2, 3, 4, 5, and 7) presented with polyuria and polydipsia, and the seventh patient (case 6) presented with diabetic ketoacidosis; all had diabetes. The average age at onset of diabetes was 5-7 years (range 4-8 years); all required treatment with insulin. Six patients were known diabetics at presentation. The average duration between the diagnosis of diabetes and presentation was three years. The average fasting blood glucose concentration at presentation was 24-1 mmol/l (range 4-8-47 mmol/l); average serum carbon dioxide concentration was 18 mmol/l (range 5-27 mmol/l). Two patients (cases 3 and 6) had ketonuria at presentation. One patient (case 5) stopped insulin treatment on three occasions. On the first, his blood glucose and carbon dioxide concentrations were 36-5 mmol/l and 15 mmol/l, respectively and he had no ketonuria eight months after stopping treatment. On the second, he had glycosuria but no ketonuria one month after discontinuing insulin treatment, and on the third occasion he had a serum glucose concentration of 50 mmol/l and carbon dioxide concentration of 18 mmol/l without ketonuria on the fifth day after stopping treatment. Three patients had severe limitation in mobility of the proximal interphalangeal joints. One patient had retinal proliferative changes. None was hypertensive or had gross proteinuria.

Diabetes insipidus. Diabetes insipidus was recognised in five patients and suspected in a sixth. The average age at diagnosis of diabetes insipidus was 8-8 years (range 5-11 years).

Diabetes insipidus was shown by water deprivation test or hypertonic saline infusion test in five patients. In one patient neither test was performed; he had polyuria and polydipsia unrelated to glycosuria, which both decreased after the administration of chlorpropamide. Five of the six patients with diabetes insipidus responded to treatment with chlorpropamide with an average reduction in volume of urine of 65% (range 50-80%). One patient (case 5) showed no response to treatment with chlorpropamide but did respond to intramuscular Pitressin Tannate in oil.

Ophthalmologic findings. Optic atrophy was present in all seven patients. The average age at diagnosis of optic atrophy was 12 years (range 6-24 years). Six patients had decreased visual acuity, which led to the diagnosis. One patient (case 2) was found to have optic atrophy on routine physical examination. The average age at onset of decreased visual acuity was 10-8 years (range 7-17 years). Only one patient had a diabetic retinopathy.

Table 1 Clinical presentation

<table>
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<th>2</th>
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<td>F</td>
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<td>F</td>
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<td>10</td>
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<td>3</td>
<td>&lt;3</td>
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<td>25</td>
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<td>**</td>
<td>Yes</td>
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* National Centre for Health Statistics growth charts.
** Not studied.

Table 2 HLA typing* of three siblings, parents, and unaffected brother†

<table>
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<tr>
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<td></td>
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<td>Mother</td>
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<td>bd</td>
</tr>
<tr>
<td>Case 3</td>
<td>ac</td>
</tr>
<tr>
<td>Unaffected brother</td>
<td>ac</td>
</tr>
</tbody>
</table>

* In addition, case 6 was DR5 positive, DR2 negative.
† All were negative for HLA-DR2, Cw2, Cw3, and Cw4.
‡ Haplotype assumed from offspring.
One patient (case 1) had 20/20 vision in both eyes and normal fundi between 8 and 14 years of age. At 24 years of age his vision was limited to near face hand motion, and he had bilateral optic atrophy and proliferative diabetic retinopathy. He was not seen between ages 14 and 24 years. Another patient (case 2) had a visual acuity of 20/20 in both eyes and normal visual fields at 6 years of age. Fundoscopy showed questionable bilateral temporal pallor of the optic discs with retinal pigmentary degeneration and absent foveal reflex in the macular area. Five years later her visual acuity decreased to 20/40 bilaterally. Her visual fields showed generalised constriction, and the temporal pallor of the optic discs became more pronounced. At 14 years of age her visual acuity became 20/100 bilaterally, the visual fields developed central defect, and she had optic atrophy. By 23 years of age she had visual acuity of near face hand motion, and the macula and vessels were normal.

A further patient (case 3) had normal visual acuity and a normal fundoscopic examination when first seen at 5 years of age. At 12 the visual acuity had reduced to six meters in both eyes, and he had bilateral optic atrophy. At 16 years his visual acuity decreased to 3-5 m counting fingers.

One patient (case 4) had vision of 20/20 in both eyes with normal visual fields and fundi when first seen at the age of 6. At 10 years she complained of decreased visual acuity; her vision was 20/50 bilaterally. Visual fields showed bilateral temporal field defects and generalised constriction; she had mild pallor of the optic discs. Three months later her vision decreased to 20/70 bilaterally and pallor of the optic discs was more pronounced, especially on the left hand side. There was no further progression 12 months later.

In one (case 5) there was decreased visual acuity by the age of 8; his vision was then reduced to counting fingers at 2-5 m in the right eye and 5 m in the left eye. There was a generalised constriction in his visual fields, poor discrimination of colours (green, red, and blue), and he had bilateral optic atrophy.

Two patients (cases 6 and 7) had reduced visual acuity and bilateral optic atrophy when first seen at 14 and 10 years of age, respectively. In addition, in case 6 there were pigmented changes in the retina.

Audiological findings. Decreased hearing was present in the three siblings. Two patients (cases 4 and 6) had abnormal audiograms without subjective evidence of hearing loss. Cases 5 and 7 had normal audiograms. The average age at onset of decreased hearing was 16-6 years (range 13-20 years).

Three patients (cases 1, 4, and 6) had bilateral symmetrical hearing loss, and two others (cases 2 and 3) had a bilateral non-symmetrical pattern. High frequency sensorineural hearing loss with a sharp descending pattern starting at 2 kHz was noted in four patients (cases 2, 3, 4, and 5). Speech discrimination scores were 96% (normal=96% or above), and the average speech reception threshold was 22.5 db (range 0-40 db) (normal=0 db). This was consistent with a sensory type of hearing loss (affection of the organ of Corti). Cases 1 and 4 had a flat audiogram curve pattern with equal thresholds at all frequencies; the speech reception threshold was 37.5 db (range 30-40 db). This audiometric pattern was consistent with atrophy of the stria vascularis, the main source of ‘nutrient’ supply to the inner ear. Audiograms from two patients (cases 2 and 3) showed persistently descending threshold patterns with speech discrimination score of 80% and speech reception threshold of 45 and 60 db, respectively. These findings, consistent with Schuknecht’s ‘cochlear conductive hearing loss’, indicate a degenerative process in the spiral ligament (a fibrous structure within the cochlea) on which the structural integrity of sense organs depends.

Audiograms performed on the father and brother of the three affected siblings were normal. Evoked response audiometry of cases 1, 3, and 4 showed no retrocochlear condition.

HLA typing. Table 2 shows the results of HLA typing. No patient had the antigens commonly associated with insulin dependent diabetes mellitus—namely HLA-B8 and HLA-B15. None had the HLA-DR2 antigen, which has been suggested to be associated with DIDMOAD.

Radiological findings. Intravenous pyelography and voiding urethrocystogram were performed on four patients (cases 1, 4, 5, and 6) at the ages of 23, 10, 9, and 13 years, respectively. Case 1 did not have diabetes insipidus. Intravenous pyelography showed bilateral and severe hydronephrosis and hydro-ureters in cases 1, 5, and 6 and mild bilateral vesicourethral reflux but no hydronephrosis in case 4. Voiding urethrocystogram examination showed large flaccid atonic urinary bladders in cases 1, 4, and 6.

Three patients (cases 1, 5, and 6) had spina bifida occulta. One patient (case 6) had a normal myelogram; four (cases 1, 2, 3, and 7) had normal skull radiographs; and two (cases 1 and 4) had normal computed tomograms of the skull.

Other findings. One patient (case 7) had cerebellar deficits on neurological examination. Another patient (case 1) had dysphagia and intolerance to
cold. Three patients who had reached pubertal age did not have hypogonadism.

All seven patients were small and underweight for age. None had vertigo or hyperpyrexia. Our patients were not tested for aminoaciduria.

**Family history.** Three patients (cases 1, 2, and 3) were siblings whose parents were distant relatives; their other brother and sister were not affected. The paternal grandfather had adult onset diabetes mellitus. Oral glucose tolerance tests performed on the parents were normal. Audiograms, visual fields, and fundoscopy performed on the father and unaffected brother were normal. HLA typing was performed on the siblings, the father, and the unaffected brother; Table 2 shows the results. The parents of one patient (case 5) were first cousins. The parents of the rest of the patients were not consanguineous. One patient (case 6) was the third in a sibship of four. The father and paternal grandmother had adult onset diabetes mellitus.

**Discussion**

The presence in addition to the severity, age at onset, and rate of progress of the manifestations of the various components of the DIDMOAD syndrome were not uniform in our patients.

Diabetes mellitus, present in all our patients, was a universal finding in previously reported cases. Diabetess mellitus was the first manifestation in our seven patients compared with 76% of the cases reviewed by Cremers et al. All our patients required treatment with insulin to control the diabetes. The severity of diabetes mellitus, however, was variable; one patient was admitted with ketoacidosis, suggesting insulin dependent diabetes mellitus, and another patient had a course suggestive of maturity onset diabetes of the young. On three occasions after discontinuing treatment with insulin this patient failed to develop ketosis or acidosis. Recurrent ketonuria and ketoacidosis were not a problem in any of our patients. Variations in the severity of diabetes mellitus in DIDMOAD syndrome have been reported by others. The patients reported by Bretz et al. were described as requiring low dose insulin. One patient described by Richardson and Hamilton discontinued treatment with insulin for several months but did not develop ketosis. The patients reported by Page et al. however, rapidly developed ketonuria and two had ketoacidosis.

The HLA antigens in our four patients were not consistent with those most commonly associated with insulin dependent diabetes mellitus—namely, HLA-B8 Dw3 and HLA-B15 Dw4. Other reports also failed to find an association of these antigens in patients with DIDMOAD syndrome. Monson and Deschamps et al. found HLA-DR2 antigens in their patients with DIDMOAD syndrome. Such an HLA association was not found in our patients or those reported by Stanley et al. Our findings (Table 2) present evidence against the linkage of DIDMOAD gene to chromosome 6 (major histocompatibility region) as the three affected siblings each received a different combination of haplotypes from the parents. Dreyer et al. found a normal number of insulin receptors on red blood cells and normal affinity of these receptors to insulin in two patients with DIDMOAD syndrome. No other studies of insulin receptors in such patients have been reported.

Limited mobility of joints was found in three of our patients—namely, in the three siblings with the longest duration of diabetes mellitus. Only one patient, the eldest of the three siblings, had diabetic retinopathy. Whether the variations in the course of diabetes mellitus in our patients represent a heterogeneity in the aetiology or a spectrum of severity of the disease is difficult to ascertain, particularly as plasma concentrations of proinsulin or the C peptide were not determined.

Diabetes insipidus was present in six of our patients. In other reported series the incidence of diabetes insipidus has varied from 40–60%. The response of six of our patients to chlorpropamide is consistent with partial antidiuretic hormone deficiency as chlorpropamide is thought to improve the symptomatology of diabetes insipidus, either by enhancing the action of antidiuretic hormone on the distal tubules and collecting ducts3 or by increasing the secretion of antidiuretic hormone. The amelioration of the symptoms of diabetes insipidus in patients with DIDMOAD syndrome after administration of chlorpropamide has been reported by others. Richardson and Hamilton, however, found low concentrations of serum antidiuretic hormone in three patients with DIDMOAD syndrome that did not increase after water deprivation.

The diagnosis of diabetes mellitus preceded that of diabetes insipidus in all our patients. This is not a universal finding, however; diabetes insipidus has been described to precede diabetes mellitus in patients with DIDMOAD syndrome.

The diagnosis of diabetes insipidus was probably delayed in many patients because of the common symptomatology of polyuria and polydipsia in both diseases. After diabetes mellitus has been diagnosed the persistence of symptoms is often related to poor control of the diabetes mellitus rather than the presence of diabetes insipidus.
Association of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

Optic atrophy was present in all our patients. This finding was universal in patients reviewed in other series. The average age at onset of decreased visual acuity was 10 years. The rate of progress was variable, spanning over several years in some and precipitous in others. Deterioration of vision, from normal to near blindness, was found in the three siblings with the longest follow up. This is in accord with the findings of Lessell and Rosman.

The otologic findings in this group of patients indicate that deafness was not universal and when present was moderate, slowly progressive, bilateral, and of the sensorineural pattern. From the study of the audiogram patterns a degenerative process appeared to occur, involving multiple sensory or supportive structures in the cochlea. Such findings have been noted in histopathologic studies of temporal bones in patients with similar findings.

Abnormalities of the urinary tract, particularly dilatation of the bladder, were present in four of the patients who underwent urologic investigations. The incidence of these findings in the patients reviewed by Cremers et al was only 13%, which was probably an underestimation of the true incidence of dilatation of the urinary passages in DIDMOAD syndrome as this manifestation is usually asymptomatic and several of the patients had not been investigated systematically for its presence.

The less common manifestation of DIDMOAD syndrome found in our patients were short stature, colour blindness, deposits of pigments in the retina, cerebellar dysfunction, intolerance to cold, and dysphagia.

The aetiology of DIDMOAD syndrome remains undetermined. The syndrome is inherited as an autosomal recessive disease, as suggested by the genetic studies of pedigrees reported previously. The progressive course of diabetes insipidus, optic atrophy, deafness, and possibly the dilatation of the urinary passages may be explained by a gradual neuronal degenerative process. Niemeyer and Marquardt and Carson et al reported degeneration of the optic nerve and tract in addition to degeneration of the geniculate bodies, the pons, and the cerebellum at necropsy of patients who had had DIDMOAD syndrome.

Gunn et al and Carson et al described degeneration of the supraoptic and paraventricular nuclei in patients with DIDMOAD syndrome suffering from diabetes insipidus. Loss of hearing could also be explained on the basis of a degenerative process involving the stria vascularis, the sensory and neural end organs, but sparing the retrocochlear portion of the auditory system, as suggested by the audiologic findings in our patients. The dilatation of the urinary passages has been ascribed to diabetes insipidus by the regression of these findings after treatment with Desamino-d-Arginine-Vasopressin or Pitressin. The presence of these changes in the absence of diabetes insipidus in one of our patients (case 1) and in the patient reported by Dreyer et al suggests that a neuronal degenerative process may also be implicated in the pathogenesis of the dilatation of the urinary tract.

The only finding that cannot be explained by a degenerative process of the central or peripheral nervous system in patients with DIDMOAD syndrome is the severe intolerance to carbohydrates. The aetiology of diabetes mellitus in this syndrome remains obscure. The type of diabetes mellitus seen in our patients does not fit into any of the commonly accepted classifications of the disease because of the clinical and biochemical heterogeneity, the lack of an HLA association, and, in the few studied, the finding of normal numbers and affinities of insulin receptors.

References

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Fifty years ago

90th birthday tribute to Sir Thomas Barlow: infantile scurvy

Arch Dis Child 1935;10:211–336

The bound Archives volume of 1935 looks notably fatter on the bookshelf than those of 1934 and 1936. It carried essays occupying some 125 pages on various aspects of infantile scurvy. Four of these were written as a 90th birthday tribute to the then 'doyen of British medicine', Sir Thomas Barlow. His original article 'On cases described as “acute rickets” which are probably a combination of scurvy and rickets, the scurvy being an essential and the rickets a variable element' was also included, being reprinted from the 1883 Medico-Chirurgical Transactions, London. Sir Thomas, who was one of Jenner’s assistants early in his medical career, made many contributions to the clinical medicine of adults as well as children; but the more important was considered to be this recognition that the so called acute rickets was not rickets at all but infantile scurvy, and that this in turn was akin to adult scurvy save for greater bone involvement.

One of his 'juniors', Lord Horder, wrote a brief introduction to the essays and described the great affection and hero worship Sir Thomas aroused. During the course of his remarkable career, Sir Thomas was elected a Fellow of the Royal Society, was President of the Royal College of Physicians, a Physician to the Royal Household, and Physician Extraordinary to Queen Victoria, attending her in her last illness. He himself just failed to become a centenarian by a few months.

PAMELA A DAVIES
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