Familial syndrome of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (didmoad) in childhood

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Marquardt and Loriaux (1974) describe a kinship of two siblings with the combination of diabetes mellitus, diabetes insipidus, and optic atrophy in which there was additional evidence of renal tract dilatation, amino-aciduria, and neurosensory hearing deficit. These authors cite 41 cases of optic atrophy and diabetes mellitus reported since an association of these conditions was first described by Wolfram (1938). Damaske, Cohen, Gutman, and Schumacher (1975) reassess these and three more cases to review a full syndrome of diabetes mellitus, diabetes insipidus, and optic atrophy. A total of 22 cases of the full syndrome are presented in these two publications.

Combining the information in these two publications the full syndrome consists of diabetes mellitus, diabetes insipidus, optic atrophy, neurosensory deafness, urinary tract abnormalities (such as hydronephrosis and neurogenic bladder, probably secondary to diabetes insipidus), and amino-aciduria. Several cases have also had retinal pigmentary disturbance, ataxia, gynaecomastia, intermittent or complete amenorrhoea, hypoandrogenicity, and episodic seizures.

The onset of diabetes mellitus in all of these cases was in infancy or youth. Often two or more siblings were affected but no other members of the family were involved, save occasionally for a history of diabetes mellitus in the family. The sexes were equally affected (Damaske and others, 1975), and although diabetes mellitus usually preceded both diabetes insipidus and optic atrophy this was not always so. The diabetes insipidus often remained undiagnosed until the children continued to have polyuria despite effective therapy for their diabetes mellitus. The severity of each of the three major findings (diabetes mellitus, diabetes insipidus, and optic atrophy) varied, although diabetes mellitus seems to be a constant finding (Sunder, Danowski, Kenny, Khurana, Sun, Nolan, and Stephan, 1972). The other findings in these patients such as neurosensory deafness, urinary tract abnormalities, and

amino-aciduria were also highly variable, but may have been missed in earlier cases (Tunbridge and Paley, 1956).

No patients with this syndrome have come to necropsy, although two have undergone craniotomy. In these (Sunder and others, 1972; DeLawter, 1949) the only abnormal findings were arachnoiditis in the region of the optic chiasm. Single cases of the syndrome have occurred at the age of 14 after head trauma (Chute, Rebham, Bain, and Kruffy, 1962), with haemorrhagic softening of the hypothalamus (Chute and others, 1962), and after a prolonged febrile illness of unknown origin (Rose, Fraser, Friedmann, and Kohner, 1966). One case has been reported of a patient with Laurence-Moon-Biedl syndrome who also had diabetes mellitus, diabetes insipidus, and optic atrophy in addition to retinitis pigmentosa (Faccaro and Gastaldi, 1952).

The combination of diabetes mellitus, diabetes insipidus, and other less common pituitary abnormalities strongly suggests that the causative lesion is in the region of the hypothalamus, but the pathogenesis remains a mystery. The frequent involvement of siblings is strong evidence for a genetic origin, although there is only one report of the condition affecting more than one generation (Shaw and Duncan, 1958). The mode of the inheritance, if it is indeed a single genetic abnormality, would be most consistent with an autosomal recessive gene (Rose and others, 1966; Sunder and others, 1972; Bretz, Baghdassarian, Graber, Zacherle, Norum, and Blizzard, 1970).

For convenience we refer to this condition as the DIDMOAD syndrome, from the initial letters of the component disorders: Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness. We report two siblings with the syndrome. They are the 23rd and 24th reported cases of the primary triad.

Case reports

CASE I

A boy aged 13 was referred to the University Hospital, Iowa City, in March 1974 with a history of recurrent enuresis, which had begun about 1½ years before,

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FIG. 1 Visual fields in Case 1, 18 July 1974

some difficulty in initiating micturition, and some hesitancy. There were no other urinary symptoms of recent onset, although there was a long history of frequency of micturition (about every two hours) and a high daily fluid intake. Past medical history was uneventful save for gradually deteriorating visual acuity over about the preceding two years. The patient had had visual acuities of 20/20 in each eye when at kinder-

garten, but two years later, in 1969, they had deteriorated to 20/60 in each eye. There was also some 'minor disc pallor'. In 1972 the acuity was about 20/100 in each eye. An intravenous pyelogram before referral had shown severe hydronephrosis and a large bladder, and a micturating cystogram had shown much reduced bladder function.

On admission to the University Hospital the urinary

FIG. 2 Visual field in Case 1, 19 June 1975

findings were confirmed, and on cystourethroscopy a valve-like obstruction was seen in the region of the veru montana. Urine volumes appeared to be unusually large and urinary specific gravities unusually low. Daily urine output was about 11 litres. The child was referred for consideration of diabetes insipidus. A water deprivation test was strongly positive, with 9 hours of water deprivation resulting in an increase in urinary specific gravity from 1001 to only 1004 and a loss of body weight of 2 kg. A pitressin stimulation test showed a rise in urinary specific gravity to 1022 and a maximum urine osmolality of 454 mOsm. In view of the recent onset of diabetes insipidus in association with bilateral optic atrophy a full neurological investigation was done to exclude mass lesions in the region of the sella turcica. Clinical examination was normal save for bilateral optic atrophy. Skull and chest radiographs were interpreted as normal, as also were brain scan, spinal fluid examination, EEG, optic foraminae radiographs, and EMI scan. A right carotid angiogram was normal save for slight upward tilt of the anterior cerebral artery, which was of doubtful significance. Pneumoencephalography was interpreted as normal. A random blood sugar investigation was reported as abnormal, and a glucose tolerance test showed evidence of clinical diabetes mellitus. Treatment was begun with diet and insulin, although insulin was later discontinued.

Visual acuities were 20/200 in each eye for distance, improving to 20/100 in each eye for near, and to 20/70 when tested binocularly for near. Anterior segment examination was completely normal, as were ocular motility, intraocular pressure, and pupillary examination (although later pupillography showed minor reduction in the pupillary light reaction and increase in the latency of this reaction). There was bilateral optic atrophy and

minimal pigment mottling at both maculae. Visual fields showed bilateral dense central scotomata and arcuate type defects (Fig. 1). There was a dense achromatopsia consistent with the degree of visual acuity and visual field loss. Fluorescein angiography was normal. Serum cortisol levels were reduced at 13.1 (8 am) and 8.8 $\mu\text{g}/100\text{ ml}$ (10 am), the normal range for this laboratory being 10–22 $\mu\text{g}/100\text{ ml}$ for morning specimens. T_3 , T_4 , and T_8 radioimmunoassay were all normal. Serum biochemical values and haematology scan were unremarkable save for raised blood sugar. Audiography showed no hearing loss.

The patient was discharged with a diagnosis of (a) pitressin-sensitive diabetes insipidus; (b) chemical diabetes mellitus; (c) bilateral optic atrophy; and (d) bilateral hydronephrosis and bladder dysfunction, probably secondary to diabetes insipidus.

Treatment at that time consisted of pitressin injections, urocholine, and urinary antibiotic. This treatment remained essentially unchanged until May 1975, when the diabetes mellitus had become more apparent with blood sugars in the region of 335–411 mg/100 ml. Oral hypoglycaemic therapy was inadequate and insulin treatment was begun. Regular ophthalmological review showed no change in visual acuity, motility, or appearance of the anterior or posterior segment, but there was some evidence of further left visual field loss at the last review in June 1975 (Figs 1 and 2).

CASE 2

A 16-year-old girl, sister of the patient in Case 1, was first examined at University Hospital in July 1974. There was a long history of high daily fluid intake and polyuria, but otherwise the medical history was normal

FIG. 3 Visual fields in Case 2, 17 July 1974

up to the age of 12 years. At that time a diagnosis of diabetes mellitus had been made and treatment begun with insulin. Despite treatment high fluid intake and polyuria persisted and resulted in her referral to us after we had seen her brother for similar symptoms.

The patient's height and weight were normal for her age, and there was no abnormality on general clinical examination save for bilaterally pale optic discs and

glycosuria. Haematological and biochemical investigations were normal except for a raised random blood sugar of 218 mg/100 ml. Chest and skull radiographs were normal. T_4 was normal (7.7 μ g/100 ml) and there was no evidence of growth hormone or gonadotrophin deficiency. An intravenous pyelogram showed bilateral hydronephrosis with good renal function, and a cystometrogram showed a dilated bladder with

residual urine. Urine specific gravities throughout her stay in hospital remained in the region of 1.013 or less. The results of a water deprivation test were equivocal and though the patient probably had diabetes insipidus the condition was mild and certainly did not require pitressin therapy.

The visual acuities were 20/70 right eye and 20/50 left eye with maximum correction. Anterior segment examination was normal, as were ocular motility, intraocular pressure, and pupillary examination. Fundoscopy showed bilateral, though minor, optic atrophy, especially at the temporal margin of the discs. The visual fields showed bilateral arcuate defects of fairly minor degree (Fig. 3). Colour vision and fluorescein angiography were normal. The patient was discharged with a diagnosis of (a) clinical diabetes mellitus, (b) bilateral optic atrophy, (c) bilateral hydronephrosis and dilated bladder with residual urine, and (d) possible borderline diabetes insipidus.

Treatment at this time was insulin and urocholine. On follow-up there was no real alteration in symptoms or signs and, in particular, there was no change in ophthalmic findings and no apparent progression of visual field or acuity deficits. An audiogram was normal save for some loss in the higher frequency range (Fig. 4).

FAMILY HISTORY

Both these children were the result of normal pregnancies and, apart from the usual childhood diseases, they had suffered no serious illnesses. Diet for the affected cases, as for the entire family, was normal and complete, and there was no history in either case of any significant previous trauma. The affected children were two of four siblings. After full ocular examination of both the unaffected siblings, both parents, and all of the parents' siblings, including visual acuity, Goldmann visual field, and fundus examination, there was no evidence that any other member of the family was visually affected (Fig. 5).

Conclusion

A hereditary syndrome probably exists consisting of (a) diabetes insipidus, (b) diabetes mellitus, (c) optic atrophy, and (d) deafness. The severity of each of the parts of this syndrome is variable,

FIG. 4 Audiogram in Case 2, 16 June 1975

FIG. 5 Family tree

and different patients, even within the same kinship, show differing clinical patterns. The primary triad, however, is present often enough for it to be advisable to make a careful search for the full spectrum of abnormalities in children (and their siblings) presenting with diabetes mellitus and optic atrophy. The pathogenesis of the syndrome is unknown, but it may be that it is familial, and if genetic, the inheritance is most probably autosomal recessive.

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