Case report

DIDMOAD syndrome: a family with three affected siblings

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In 1938 Wolfram reported the occurrence of diabetes mellitus and optic atrophy in four of eight sibs.\(^1\) Over 100 similar cases have since been reported and several other clinical features have been described.\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) The genetic disorder is commonly known as DIDMOAD syndrome, the mnemonic for Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness. This report describes three siblings with this syndrome in a family of ten born to healthy non-consanguineous parents. The family has been briefly referenced in McKusick's catalogue of Mendelian inheritance in man.\(^5\)

CASE 1 (MG). A female born in 1959, presented with symptoms of diabetes mellitus at the age of eight. At that time she had diminished vision (N/34), deafness, and was considered to be educationally subnormal although attending a school for the deaf and blind. Ophthalmological examination revealed rotary nystagmus, a left convergent squint, early cortical cataracts and bilateral primary optic atrophy. She was treated with insulin, and during the next seven years she had frequent hospital admissions with hypo- or hyperglycaemic states. The co-existence of diabetes insipidus became apparent in 1974 at age 15, and polyuria was controlled with oral chlorpropamide. The same year she had to be admitted for long term care in a hospital for special care, due to behavioural problems. In 1975 she aspirated while eating, and required intensive resuscitation with artificial ventilation for ten days. While unconscious her serum osmolality remained normal without chlorpropamide, but on regaining consciousness polydipsia and polyuria recurred, the urine osmolality fell to 230 mosm/l and serum osmolality rose to 316 mosm/l. On recommencing chlorpropamide the serum osmolality improved to 304 mosm/l and urine osmolality to 762 mosm/l. Hypertonic saline infusion test was unsuccessful due to poor patient co-operation. Her other abnormalities included high tone deafness, bilateral hydronephrosis and hydroureters and incomplete emptying of the bladder. At the age of 19 she developed grand mal seizures. EEG showed non-specific abnormalities. In 1982 she aspirated again while eating and died.

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At autopsy the macroscopic abnormalities were pulmonary congestion and oedema, hypoplastic aorta, bilateral hydroureters, minimal hydrenephrosis, scarring of both kidneys suggestive of pyelonephritis and atrophic optic nerves. Microscopically, the lung changes were consistent with asphyxiation and early aspiration pneumonia. The pancreatic acinar pattern was well maintained, but islets were not readily seen, and those present were small. The kidneys showed chronic pyelonephritis with marked chronic inflammatory cells within the interstitial. Both optic nerves showed bilateral atrophy. Sections from the cerebral cortex and brain stem showed some oedema consistent with asphyxia.

CASE 2 (VG). A female born in 1962, developed diabetes mellitus when 5 years old. Diabetes insipidus was diagnosed in 1976 aged 14. Impairment of vision and hearing were noted early in life and like her sister, she attended a school for the deaf and blind. In 1975 she had been noted to have a large bladder, and intravenous urography demonstrated bilateral hydronephrosis, hydroureters and dilatation of the bladder. A micturating cystogram showed impaired bladder emptying but no ureteric reflux suggesting abnormal neurological control of bladder function. She attended the diabetic clinic at the Waveney Hospital, with occasional hospital admissions for urinary infections or poor diabetic control.

In 1988 aged 26 she was admitted after a fall at home, and subsequently vomited and aspirated, and was transferred to an intensive care unit for ventilation. She gradually recovered from aspiration pneumonia in the left lower lobe, but had impairment of swallowing on occasions necessitating tracheostomy to protect the airway. Her swallowing gradually improved and the tracheostomy healed. Four months later she was re-admitted with poor diabetic control, associated with aspiration pneumonia in the right lower lobe. She was again transferred to the intensive care unit for assisted ventilation, where she slowly recovered. To prevent further aspirations epiglottix–pexy was performed, feeding being maintained with a nasogastric tube as she was unable to swallow. She suffered recurrent cyanotic episodes, in one of which she died in January 1990. Permission for autopsy was refused.

CASE 3 (DG). A male was born in 1966, of average intelligence. He has had epilepsy since 1981; diabetes mellitus onset in 1980 aged 13, which is reasonably controlled on once-daily insulin; and diabetes insipidus onset in 1980 aged 14, controlled on desmopressin. Visual acuity is 6/24 in both eyes and he has perceptual deafness requiring a hearing aid.

HLA typing of VG showed HLA – A38, A28, B44, B63. Typing of DG showed HLA – A1, A28, B8, B44, DR3, DR5. Typing was not possible for MG.

DISCUSSION

The family described is unusual in that each of the three affected members had all the major features of the syndrome (Table). Epilepsy, found in two of our patients, is not a recognised feature although EEG abnormalities have been previously reported. Only three previous autopsies have been reported, the gross findings being similar to our Case 1 except for the presence of a hypoplastic aorta. The main cause of death in Cases 1 and 2 was failure of brain stem function leading to aspiration pneumonia, and in Case 2 to loss of respiratory control. Axonal...
TABLE
Age of onset of the features of the DIDMOAD syndrome

| Feature               | Age of onset |
|-----------------------|--------------|
|                       | Case 1 (MG)  |
|                       | Case 2 (VQ)  |
|                       | Case 3 (DG)  |
| Diabetes mellitus     | 8            | 13           | 14           |
| Diabetes insipidus    | 15           | 17           | 14           |
| Deafness              | 14           | 14           | 17           |
| Optic atrophy         | 8            | 14           | 14           |
| Enlarged blindspot    | NC           | NC           | 14           |
| Hydroureter           | 16           | 17           | 17           |
| Atonic bladder        | 16           | A            | A            |
| Low intelligence      | 8            | 17           | N            |
| Behavioural problems  | 18           | 17           | A            |
| Epilepsy              | 19           | A            | 16           |
| Colour blindness      | NC           | NC           | 14           |
| Hyperalaninuria       | A            | A            | 14           |
| Treatment of diabetes insipidus | | | |
| Chlorpropamide only   | 15           | 17           | NT           |
| Vasopressin only       | NT           | NT           | 14           |
| Vasopressin + Chlorpropamide | NT   | 22           | NT           |

NC = Not co-operative, NT = Not tried, A = Absent, N = Normal.

degeneration and demyelination without gliosis has been found in the pons in previous post-mortem examination.\(^7\)

One third of patients with the DIDMOAD syndrome have had diabetes insipidus either at the time of presentation or subsequently. In all cases the polyuria could be partially or wholly controlled by exogenous vasopressin. This response to exogenous vasopressin suggests that the primary pathology is in the neurohypo-physial system. Nevertheless, in our patients chlorpropamide had been effective in controlling the diabetes insipidus particularly in its early phase, the beneficial effect of this drug probably being due to potentiation of the action of reduced levels of endogenous vasopressin on the renal tubules.

Cremers et al observed that diabetes mellitus was the presenting symptom in 78% of cases, the age of onset ranging from two to 34 years.\(^3\) The course of the diabetes mellitus is not thought to be different from insulin dependent diabetes. The presence of optic atrophy in a patient with insulin dependent diabetes of short duration should alert the clinician to the possibility of the DIDMOAD syndrome:\(^8\) the optic atrophy is progressive and eventually leads to blindness irrespective of diabetic control. Audiometric abnormalities have been reported in 60% of patients with high tone nerve deafness as the characteristic feature. Dilatation of the efferent urinary tract and bladder atony have frequently been found, these changes being predominantly due to the increased flow of urine, although autonomic dysfunction of the bladder may have been a factor in Case 2.
The syndrome is autosomal recessive. The male/female ratio in 89 cases is 46:43 and in a fifth of all reported cases there is parental consanguinity. HLA DR2 which is rare in insulin dependent diabetes has been frequently reported in the DIDMOAD syndrome, but as yet there is no consistent haplotype.\textsuperscript{9, 10} It is over fifty years since the syndrome was first described, but the pathological processes involving the pancreas, neurohypophyseal system, the optic and auditory nerves remain obscure. Perhaps with the developments of DNA technology, it may be possible to obtain a clearer understanding of the pathogenesis at a molecular level of this disabling genetic disorder.

We wish to pay tribute to the late Dr R J Skelly who first diagnosed the syndrome in this family. We are grateful to Dr D Hadden, Professor N C Nevin and Professor D Archer and their staff for their contribution to the diagnosis and management of the children in the family. Also to Professor Ingrid Allen for her helpful comments regarding the postmortem findings. More detailed reports on the neurohypophyseal histology will be available for Case 1.

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