

Diabetes mellitus, diabetes insipidus, and optic atrophy

An autosomal recessive syndrome?¹

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SUMMARY Twenty-one families were selected from the published reports in which the proband had the triad of juvenile diabetes mellitus, diabetes insipidus, and optic atrophy. The data were consistent with the hypothesis of an autosomal gene which, in the homozygote, causes juvenile diabetes mellitus and one or more of diabetes insipidus, optic atrophy, and nerve deafness. Heterozygotes appear to have an increased probability of developing juvenile diabetes mellitus.

The triad of juvenile diabetes mellitus, pitressin-sensitive diabetes insipidus, and optic atrophy occurs in the same patient often enough to suggest that it represents a syndrome (Rose *et al.*, 1966; Jean *et al.*, 1970). The syndrome occurs in sibs, and in the offspring of consanguineous parents, often enough to suggest autosomal recessive inheritance (Herrera-Pombo *et al.*, 1971; Sunder *et al.*, 1972; Marquardt and Loriaux, 1974; Damaske *et al.*, 1975) though the fit to a 25% segregation ratio has not been tested. Nerve deafness appears to be an additional feature in some cases. Components of the triad also occur together in various combinations, and occasionally in association with other inherited diseases such as Friedreich's ataxia, Laurence-Moon-Biedl syndrome, Refsum syndrome, and Alstrom syndrome (Rose *et al.*, 1966). It is not clear whether patients with only 2 components of the triad represent variable expressivity of the same mutant gene that causes the triad, or allelic mutants, or non-allelic mutants.

Segregation analysis is complicated by the variable age of onset of the component features, and the syndrome is so rare that data must be pooled from the literature, which creates a number of problems including variable quality of reporting, failure to identify probands, and the greater likelihood of unusual cases being selected for publication.

To obtain more reliable figures for genetic counselling, families from the literature were selected in

which at least 1 member had the full triad and the frequency of the combinations of component features was examined in the sibs. The families are presented in the Table. There were 21 sibships, containing 77 children. Assuming (for the moment) that there was a proband in each family, there were 6 sibs with the full triad, 3 with diabetes mellitus and diabetes insipidus, 5 with diabetes mellitus and optic atrophy, 1 with diabetes insipidus only, 7 with diabetes mellitus only, and 28 unaffected. These are, of course, minimum estimates of frequency of the features, as some sibs are below the maximum age of onset. Diabetes mellitus occurred first, or concurrently with one of the other two in 28 cases, diabetes insipidus occurred first in 2 and optic atrophy in 2. The mean age of onset was 7.7 years for diabetes mellitus (range 2 to 15), 10.3 for diabetes insipidus (range 1 to 18), and 10.3 for optic atrophy (range 4 to 18). There was no significant deviation from the normal sex ratio.

The most likely hypothesis appeared to be that the triad was caused by an autosomal recessive gene, but that in some homozygotes either diabetes insipidus or optic atrophy is not expressed. To test this hypothesis all children with either the full triad, or with diabetes mellitus and diabetes insipidus or with diabetes mellitus and optic atrophy were assumed to be homozygotes. Assuming single ascertainment, i.e. removing 1 child with the full triad per family (Fraser and Nora, 1975), there are 14 homozygotes among 50 sibs or 28.0% close to the expected 25% for an autosomal recessive trait.

Assuming complete ascertainment (i.e. removing child with the triad per family, but counting the family once for each child with the triad) the segre-

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*Diabetes mellitus, diabetes insipidus, and optic atrophy*Table 1 *Sibships of patients with diabetes mellitus, diabetes insipidus and optic atrophy*

Family	No. of children with:					Total
	DM, DI, OA	DM, DI	DM, OA	DM	DI	
Bretz <i>et al.</i> (1970)	2					3
Casa (1955)	2			3		9
Damaske <i>et al.</i> (1975)	3					6
DeLawter (1949)	1					1
Demaillly <i>et al.</i> (1969)	1 (1)					4
De Sanctis <i>et al.</i> (1972)	1					2
Goddon <i>et al.</i> (1973) 1	1 (1)		1	1		5
Goddon <i>et al.</i> (1973) 2	1					3
Gunn <i>et al.</i> (1976) 1	1 (1)					3
Gunn <i>et al.</i> (1976) 2	1 (1)					2
Herrera-Pombo <i>et al.</i> (1971) 1	1				1	2
Herrera-Pombo <i>et al.</i> (1971) 2	1 (1)			1		5
Ikkos <i>et al.</i> (1970)	1		2 (1)	1		5
Jean <i>et al.</i> (1970)	1 (1)	1	1			3
Laffay and Lestradet (1974) 5	1	1				3
Laffay and Lestradet (1974) 7	1		1			4
Marquardt and Loriaux (1974)	2 (2)					2
Moore (1971)	1 (1)					1
Najjar and Mahmud (1968)	1			1		2
Raiti <i>et al.</i> (1963)	1	1				4
Sunder <i>et al.</i> (1972)	2					2
	27 (10)	3	5 (1)	7	1	71

Numbers in brackets represent those with nerve deafness.

DM, diabetes mellitus; DI, diabetes insipidus; OA, optic atrophy

gation ratio is 20/67, or 29.9%, still reasonably close to the expected 25%. These values probably overestimate the true segregation ratio since familial cases are more likely to be reported than isolated ones. It seems unlikely, however, that correction of this bias will lower the estimated segregation ratio appreciably below 25%.

Thus the data fit the hypothesis of autosomal recessive inheritance assuming that the homozygote has diabetes mellitus and at least 1 other component of the triad, though we cannot, in our present state of knowledge, rule out the possibility of a small admixture of phenocopies. The hypothesis is further supported by the fact that 2 of the 21 pairs of parents are first cousins (Herrera Pombo *et al.*, 1971, 1 and 2), and 2 are second cousins (Ikkos *et al.*, 1970; Najjar and Mahmud, 1968).

Inspection of the pedigrees suggests that there is an unusual number of cases of juvenile diabetes mellitus in the near relatives of patients. This is difficult to measure in the extended families because of possible reporting biases, but there can be no doubt that 7 cases of juvenile diabetes mellitus among 36 sibs without the syndrome far exceeds the population frequency. To consider these as homozygotes with incomplete expression of the mutant phenotype would result in an unsatisfactory fit to the expected 1 in 4 segregation ratio. The most reasonable hypothesis is that they represent the expression of the heterozygous mutant gene. This has been suggested for other mutant genes causing severe diseases in the

homozygote, such as Fanconi anaemia and ataxia telangiectasia (Swift, 1973). The 36 non-homozygous sibs would be expected to contain 24 heterozygotes, so the minimum estimate of the probability of diabetes mellitus appearing in a heterozygote would be about 30%. The 1 sib with diabetes insipidus only may develop diabetes mellitus later, or represent another occasional expression of the mutant gene in the heterozygote.

The association with nerve deafness is more difficult to evaluate, as many case reports made no reference to deafness, and in 7 of the 11 deaf patients in this series the defect was detected only by audiogram. However 9 of 28 patients with the complete triad (32%) or 11 of the 35 homozygotes as defined (31%) had a detected auditory defect.

The basis for the pleiotropic action of the postulated homozygous mutant gene is unknown. It is unlikely that the optic atrophy is a secondary consequence of diabetes mellitus, since it may occur first, and differs clinically from diabetic retinopathy. Possibly the adhesive arachnoiditis in the area of the optic chiasma, reported in the 2 cases in which craniotomy was done is a clue to the common factor (DeLawter, 1949; Sunder *et al.*, 1972). Since Sunder's case occurred in the affected sib of an affected patient it is not likely to have been infectious, but more probably a reaction to a degenerative process which might affect various hypothalamic and other structures in the area.

The frequency of the syndrome is reported as about 1 in 150 juvenile diabetics (Gunn *et al.*, 1976). If the

population frequency of juvenile diabetes mellitus is about 0.15% the population frequency of the syndrome (i.e. homozygotes for the mutant gene) would be 1 in 100 000. However, if this figure is used to calculate the frequency of heterozygotes, and assuming that 30% of the heterozygotes have diabetes mellitus, the frequency of diabetes mellitus due to heterozygosity for this gene would be higher than the frequency of all diabetes mellitus, which is unreasonable. Presumably the true frequency of the syndrome is considerably lower than its frequency in diabetic clinics would suggest.

Whether the families in which diabetes mellitus appears with diabetes insipidus only, or optic atrophy only (Rose *et al.*, 1966; Rorsman and Soderstrom, 1967; Stevens and MacFadjen, 1972; Sauer *et al.*, 1974) are examples of the same syndrome with incomplete expression, is not clear. The fact that over half the affected sibs in the present study did not have the complete triad (8/14) suggests that this is the case. Furthermore, 1 patient with the triad had a sib with diabetes mellitus and diabetes insipidus and 1 with diabetes mellitus and optic atrophy (Jean *et al.*, 1970). Of the 8 patients with incomplete expression, 3 (Jean *et al.*, 1970; Laffay and Lestrade 1974; Raiti *et al.*, 1963) were older than sibs with full expression, 1 of them being 18, suggesting that the incomplete expression is not entirely a matter of variable age of onset. It may be possible to clarify the question of genetic heterogeneity by critical examination of more adequate data, identification of the underlying biochemical defect or the demonstration of linkage.

The results suggest that parents of a child with diabetes mellitus, diabetes insipidus, and optic atrophy may be advised of the likelihood that each sib has 1 chance in 4 of developing diabetes mellitus and either or both of diabetes insipidus and optic atrophy, and an additional chance of approximately 1 in 5, of developing diabetes mellitus alone. Those who develop the syndrome, partial or complete, have about 1 chance in 3 of having an auditory defect, which may range from asymptomatic to severe. The same figures probably apply to at least a majority of cases of the incomplete syndrome, where diabetes mellitus is combined with either diabetes insipidus or optic atrophy. These gloomy predictions are not likely to be welcomed by the families concerned, and unfortunately the syndrome will often appear after subsequent children have been born. At least, early diagnosis may be an aid to better management.

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