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Familial Optic Atrophy with Diabetes Mellitus

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Abstract: Familial optic atrophy with diabetes mellitus. J. D. Wilson, R. W. Simpson, M. L. Wahlqvist, I. Favilla and B. D. Tait, *Aust. N.Z. J. Med.*, 1982, **12**, pp. 48–51.

A family of eleven members is described in which three siblings have optic atrophy, two of whom are insulin dependent diabetics, while the other has glucose intolerance. No evidence was found to suggest an autoimmune basis for this syndrome. There was no direct evidence that genetic susceptibility to this syndrome is HLA linked. The presence of DR2 and the absence of DR3 and DR4 in the affected individuals suggests that the diabetes mellitus in this syndrome is distinct from the common form of insulin-dependent diabetes mellitus.

Key Words: Familial optic atrophy—Diabetes mellitus.

Introduction

The combination of diabetes mellitus and optic atrophy without diabetic retinopathy is rare. It may occur in association with craniopharyngiomas[1] and a variety of inherited degenerative neurological syndromes including Charcot-Marie-Tooth neuropathy, Friedreich's ataxia[2], Refsum's syndrome[3], Laurence-Moon-Biedl syndrome[4] and Alstrom's syndrome.[5] The combination has been described within sibships in the absence of the above conditions[6] and these patients often develop diabetes insipidus and high frequency hearing loss. Recently, 88 such cases from the literature were reviewed by Cremers *et al.* with personal observations on three new patients.[7] The pattern of inheritance of this syndrome is considered to be autosomal recessive, but its pathogenesis remains obscure. The aim of the present study is to report a family of which three siblings have optic atrophy, two of whom have insulin dependent mellitus and the other impaired glucose tolerance. Special reference to genetic markers and possible aetiological mechanisms will be made.

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Patients and Methods

The entire family was available for study. The families of both parents migrated to Australia from Europe two generations ago. A family tree is shown in Figure 1. For the purposes of identification the subjects were numbered 1–11 in descending order of age. While there is a family history of non-insulin dependent diabetes mellitus affecting the maternal grandmother, great uncle and great-grandmother, there is no history of associated optic atrophy. There is no history of large birth weight babies in the family. Subject 7 developed visual impairment at the age of seven and three years later developed mild polyuria and polydypsia. She was diagnosed as diabetic one year later and is currently controlled on 36 units of insulin per day. Subject 9 developed visual impairment at the age of eight and polyuria and polydypsia two years later. At that time he was diagnosed as diabetic and is now on 128 units of insulin per day. Neither of these siblings had a "honeymoon" phase of their diabetes and neither has had episodes of ketoacidosis.

Oral glucose tolerance tests (40 g glucose per square metre surface area) were carried out on all members of the family. Blood samples were obtained in the fasting state and 30, 60, 90 and 120 min after ingestion of the glucose for measurement of plasma glucose levels. Serum insulin levels were measured in the nine non-diabetic members of the family and C-peptide levels in the two diabetic members. Plasma glucose was measured with a Yellow Springs glucose analyser which uses a modified hydrogen peroxide electrode and serum insulin and C-peptide were measured by radioimmunoassay.[8–10] Blood samples were also obtained in the fasting state for radioimmunoassay of serum vitamin B12 using a ^{57}Co vitamin B12 assay kit (Diagnostic Products

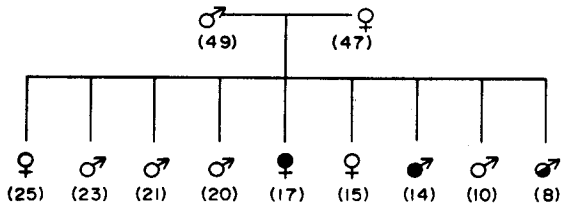

FIGURE 1. Family tree showing the ages of individual members at the time of study. ●—diabetes mellitus and optic atrophy. ◑—glucose intolerance and optic atrophy.

Corporation). Parietal cell, intrinsic factor, thyroid, pancreatic β-cell, anti-smooth muscle, anti-mitochondrial and anti-nuclear antibodies were measured by indirect immunofluorescence.[11] HLA—A, B and DR typing was carried out on all members of the family.[12-14]

Ophthalmological assessment consisted of determining the corrected visual acuity, colour vision, visual fields, electroretinogram (ERG) and visual evoked responses (VER) of each subject. Colour vision was measured using the Farnsworth-Munsell 28 Hue test. Visual fields were charted on a Topcon Perimeter, filter density 0·315, with white targets of 1 mm^2 and 64 mm^2 and red target of 4 mm^2. Electroretinograms and visual evoked responses were carried out by the method of Favilla and Barry.[15]

Hearing was assessed by a qualified audiologist in a soundproofed room. All subjects had pure tone audiograms and if the results of these were felt to be outside the normal limits, cochlear function was assessed using a bone conductor oscillator. Speech discrimination was assessed using a prerecorded tape of a phonetically balanced word list. Tympanograms were performed using an impedence audiometer which was also used to test acoustic reflexes.

Results

Glucose Tolerance

The glucose and insulin responses to the oral glucose load are shown in Table 1. The criteria used for normality were those recommended by the World Health Organization for a 75 g oral glucose load, which approximates the glucose load given to the adults in this study. Diabetes mellitus is defined as a two hour plasma glucose exceeding 11·1 mmol/*l* and impaired glucose tolerance as a two hour level between 7·8 and 11·1 mmol/*l*. Subject 4 showed impaired glucose tolerance with high and progressively increasing serum insulin levels but as yet has not developed optic atrophy. Subject 11 had impaired glucose tolerance associated with optic atrophy. Fasting C-peptide levels in subjects 7 and 9 were 0·13 and 0·17 pmol/*l* respectively. Levels in four normal subjects ranged from 0·32 to 0·43 pmol/*l*. One hour after the glucose load C-peptide levels in both diabetic siblings had only risen by 0·13 pmol/*l* compared to rises of between 0·87 and 2·20 pmol/*l* in the normal subjects.

TABLE 1
Plasma glucose and serum insulin responses to an oral glucose load (40 g per square metre surface area)

	Plasma glucose (mmol/*l*)					Serum insulin (mU/*l*)				
	0	30	60	90	120	0	30	60	90	120
Subject	time (mins)					time (mins)				
1	4·0	6·4	6·9	4·2	4·2	7	23	50	26	19
2	3·7	5·1	6·9	5·9	4·2	6	32	56	54	28
3	4·2	6·5	5·7	5·5	5·6	11	60	52	46	72
4	4·9	9·1	11·6	11·3	9·7	6	46	58	96	118
5	4·2	7·8	5·7	4·1	4·4	6	41	39	19	26
6	4·0	5·7	6·8	5·5	5·7	8	50	62	50	56
7	13·4	17·7	22·2	24·3	24·1			Diabetic		
8	4·0	4·2	5·0	5·2	5·1	8	17	42	88	64
9	12·5	16·0	19·5	21·5	22·9			Diabetic		
10	4·2	6·2	5·4	4·2	4·8	11	51	65	30	56
11	3·2	5·6	7·1	10·1	8·3	7	17	26	42	42

TABLE 2
HLA haplotypes of the 11 family members

	Parents			Children							
Subject	1	2	3	4	5	6	7	8	9	10	11
Haplotype	a/b	c/d	a c	b d	a c	b/d	b/d	a/c	b d	a/d	a/d

a = A3, B7, DR2.
b = Aw24, Bw44, DR5.
c = A2, Bw16, DR2.
d = A28, x, DR2.

Autoantibodies

Parietal cell, intrinsic factor, thyroid, pancreatic β-cell, anti-smooth muscle, anti-mitochondrial and anti-nuclear antibodies were negative in all subjects. Serum vitamin B12 levels were in the normal range in all subjects in keeping with the absence of intrinsic factor antibodies.

HLA Haplotypes

The results of HLA typing are shown in Table 2. Four of the siblings are HLA identical (Numbers 4, 6, 7, 9) and these include the two with optic atrophy and diabetes and one with only impaired glucose tolerance. Subject 11, who has optic atrophy and impairment of glucose tolerance shares A28, X, and DR2 with his affected siblings and mother. None of the family has DR3 or DR4 but all have DR2.

Visual Function

Three members with optic atrophy had corrected visual acuities of less than 6/24, severe red-green dyschromatopsia and constricted visual fields. None had evidence of diabetic retinopathy. The other members of the family showed normal optic discs and no retinal abnormality.

Electroretinogram

Control data, establishing a mean and standard deviation for a wave and b wave latency and amplitude, were determined by measuring the

E.R.G.'s of 40 eyes of 20 normal subjects.[15] The E.R.G.'s of all members of the family were within the established normal range.

Visual Evoked Response

Control data was established by measuring the V.E.R. in 33 normal subjects. The criteria for a normal V.E.R. were found to be a mean latency of 115·9 ms (S.D. ±9·0 ms) and a mean amplitude of 11·7 uV (S.D. ±7·0 uV) of the major positive wave. The V.E.R.'s of eight members of the family including one with diabetes mellitus and optic atrophy were within normal limits. The other two affected members had subnormal amplitudes but normal latencies of the major positive peak. One subject was not available for testing.

Hearing

Audiograms were normal in all subjects apart from a 40 decibel conductive loss in subject 4 associated with previous mastoid surgery. Speech discrimination was good in all subjects and acoustic reflexes were present with no reflex decay. Tympanograms were bilaterally compliant apart from the side of pervious surgery in subject 4.

Discussion

Wolfram was the first to describe juvenile diabetes mellitus and progressive optic atrophy in siblings.[6] The inheritance of this syndrome is thought to be autosomal recessive[16] and the incidence in this family would fit with that suggestion. It was later recognised that this syndrome may be associated with diabetes insipidus and perceptive hearing loss.[17] None of the patients described here has diabetes insipidus but only subject 9 was formally tested by water deprivation. None has perceptive hearing loss. However, in a review of 88 cases, Cremers *et al.* indicated that some of these symptoms may develop up to the age of 30 years.[7] Therefore it is possible that the patients described here may develop them in the next few years.

Diabetes mellitus in patients with this syndrome is of the insulin-dependent type. HLA phenotyping in populations of insulin-dependent diabetics shows an increased frequency of DR3 and DR4 with a concomitant decrease in DR2.[18] However, none of the patients described here has DR3 or DR4 and all have DR2. That suggests that the two diabetic siblings may have a type of diabetes mellitus distinct from the common form of insulin-dependent diabetes mellitus. The fact that one member of the family had impaired glucose tolerance associated with high insulin levels and that there was a family history of maturity onset non-insulin-dependent diabetes raised the question of whether any markers of that type of diabetes were present in this syndrome. One such marker, alcohol flushing following chlorpropamide[19] was tested for in only one affected sibling (Number 9) and found to be negative.

There is no direct evidence from this family that the genetic susceptibility to this syndrome is HLA linked. This is compatible with the findings in a family described by Stanley *et al.*[20] There is also no evidence to support an autoimmune basis for the syndrome. All antibody tests were negative in affected and non-affected members of the family.

The abnormalities in vision noted in the three patients described here are similar to those described by others.[7] The reduced visual acuity, severe dyschromatopsia and constricted visual fields are secondary to optic atrophy. The normal electroretinograms reflect normal pigment epithelium, normal retinal function and normal retinal and choroidal circulation. The V.E.R. results which were normal in one affected subject and abnormal in the other two more severely affected members are consistent with progressive axonal degeneration of primary optic atrophy. It would appear that the technique is not sensitive enough to detect minimal defects before the condition becomes obvious.

Diabetes in this family is more akin to non-insulin dependent diabetes mellitus (NIDDM) despite the fact that the two affected siblings require insulin treatment. The family requires further study when new markers for NIDDM are discovered. It will be interesting to see how many other siblings become affected with time. The link between the different facets of this syndrome remains obscure. There may be a link between the nutrition and function of the highly active optic nerve and the pancreatic β-cell due to a

lesion in the hypothalamus involving the optic tract and nearby glucose regulating centre. The association of diabetes insipidus with the optic atrophy in other reports suggests this type of lesion. Alternatively the genes concerned with optic nerve and pancreatic β-cell function may be adjacent on a chromosome.

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