Diabetes mellitus in Friedreich's ataxia

RICHARD L. HEWER, AND NORMAN ROBINSON

From the Department of Neurology, The United Oxford Hospitals, and the Department of Chemical Pathology, The National Hospital, Queen Square, London

The association of diabetes mellitus with Friedreich's ataxia has been reported from time to time. If such an association were firmly established, it could have important implications for the genetic background and possible aetiology of the two diseases.

Rossi (1893) appears to have been the first to describe the concurrence of diabetes mellitus with Friedreich's ataxia. In 1940, Schlezinger and Goldstein in a survey of the literature found 18 reported cases and added two of their own. Ashby and Tweedy (1953) discovered 11 more cases and reported a further pair of siblings. Thorén (1962) was able to discuss a total of 45 cases (five additional ones from the literature and seven of his own). Podolosky, Pothier, and Krall (1964) have recorded two further cases, while Niemann, Pernot, Manciaux, Tridon, Guinoiseau, and Charles (1964) have reported a pre-diabetic glucose tolerance curve in a child aged 8.

Most previous papers have simply reported single cases. However, Thorén (1962), in Sweden, made a systematic survey of 50 patients with Friedreich's ataxia, all of whom were aged 48 years or less. He found nine cases of known diabetes mellitus (an incidence of 18%). He performed an intravenous glucose tolerance test on 18 of his non-diabetic patients and found one minor abnormality.

In the present paper we report the frequency of diabetes mellitus in a series of 113 cases of Friedreich's ataxia. These observations are part of a wider study of the nosology of Friedreich's ataxia.

MATERIAL AND METHODS

One hundred and thirteen cases of Friedreich's ataxia from 87 sibships were investigated. Of these, 111 have been seen personally by one of us (R.L.H.). The following criteria were fulfilled in every case:

(1) onset of ataxia in early life (range 1·5 – 23 years, mean 10·45 years); (2) objective evidence of incoordination of the limbs; (3) progression of the neurological disorder without remission; (4) tendon areflexia or hyporeflexia. Most cases also had pes cavus, scoliosis, extensor plantar responses, and some loss of vibration and postural sensation in the legs. Approximately 90% of the cases had abnormalities of the electrocardiogram.

The patients were all asked if they had diabetes mellitus or if there were any family history of this. Seven patients were known diabetics (see Table I). Six patients had died by the time the study was finished. The remaining 100 patients were surveyed for evidence of latent diabetes. A preliminary Clinistix test was conducted on the patients who lived at a distance from London, and glucose tolerance tests were performed upon those showing glycosuria. Glucose tolerance tests were also performed on a further 29 cases who lived in or near London.

Throughout this study we have regarded a fasting blood sugar level of above 110 mg % as abnormal, and a fasting level above 120 mg % as diabetic. We have regarded a maximum blood sugar level of 180 mg % or above as being abnormal. A two-hour blood sugar level exceeding 120 mg % was also regarded as abnormal (College of General Practitioners, 1962).

Because of the known occurrence of glucose intolerance in immobile people, we have, throughout this paper, recorded the disability grading of each group of patients considered. No case was remarkably obese and none had any evidence of endocrine disorder.

KNOWN DIABETICS Seven patients were already under treatment for diabetes mellitus (Table I). Onset was at 16 years in one patient, 35 in another, and at 40 or more in the remaining five cases. All were chairbound at the time the diabetes was discovered. Six patients were being given insulin. A seventh (L.H.) probably required insulin but refused to have injections or to adhere to a diet. He had persistent 1 – 2% glycosuria.

THE CLINISTIX SURVEYS For geographical reasons it was not possible to perform glucose tolerance tests ourselves on all patients. A Clinistix survey was therefore undertaken initially on 70 patients in this series. Their physical disability was as follows: 18 could walk without assistance, 20 required some help with walking, 28 were chairbound, and four were totally bedridden.

Method The patients were instructed to test every urine specimen passed during a 24-hour period with a different Clinistix tape and to record on a postcard whether it went blue or remained white. Ten tapes (a sample of which had been tested for reliability) were enclosed. Cases showing persistent glycosuria had a glucose tolerance test arranged at the nearest hospital. The test was preceded by a 12-hour fast. A 50 g oral glucose load was given and blood sugar estimations were

made at half-hourly intervals for 2½ hours. Different hospitals do not necessarily employ exactly the same technique for estimating blood sugar levels and therefore it was not possible to ensure that an identical procedure was used in each case.

Results of first Clinistix survey Of the 70 patients who were sent Clinistix tapes, only four failed to return the postcard giving the results of the test.

Ten patients showed glycosuria. Four showed glycosuria only once during 24 hours; these patients were instructed to repeat the test. Three gave completely negative results on the second occasion and one failed to return the result. These four were regarded as showing no glycosuria, and glucose tolerance tests were not performed.

The other six patients all showed glycosuria on two or

more occasions during the 24-hour test period. One patient, on large doses of steroids for rheumatoid arthritis, was excluded from the series. One patient was pregnant: a glucose tolerance test on her was normal.

Glucose tolerance tests were available on the other four patients (Table II). Two—I.G. (bedridden) and J.P. (chairbound)—showed diabetic curves with fasting blood sugar levels of 120 mg % or above, together with very high two-hourly levels. In another—E.W. (chairbound)—the test was mildly abnormal with a high maximum level, a high two-hour level, and a normal three-hour level. One patient—S.B. (chairbound)—showed high maximum blood level and an elevated two-hour level. A final case (J.M.), still able to walk with help, showing glycosuria, gave a normal glucose tolerance curve.

Results of the second Clinistix survey Forty-seven

TABLE I
CASES OF KNOWN DIABETES MELLITUS

Case	Sex	Age (yr)	Age at onset of ataxia (yr)	Age D.M. discovered (yr)	How D.M. was found	Insulin	Family history of D.M.	Neurological family history
H.S.	F	41	10	35	Routine urine test	20 u. daily, poor control	None	3 sibs also have F.A. but no evidence of D.M.
J.J.	F	20	10	16	Polyuria, thirst	40 u. a day	Maternal grandmother	3 sibs also have F.A. but no evidence of D.M.
L.H.	M	43	21	40	Thirst	Constant glyco-suria, refuses insulin	None	Nil
D.G.	F	63	19	57	Routine urine test	20 u. a day	Father and brother	2 sibs have Friedreich's ataxia, but are not diabetic
M.H.	F	67	12	62	Thirst	20 u., good control	Sister (G.H.)	Sib of G.H.
G.H.	F	67	18	58	Routine urine test	52 u., poor control	Sister (M.H.)	Sib of M.H.
W.C.	M	64	16	48	Routine urine test	20 u., poor control	Brother	Nil

F.A. = Friedreich's ataxia
D.M. = Diabetes mellitus

TABLE II
ABNORMAL GLUCOSE TOLERANCE TESTS ON PATIENTS SHOWING GLYCOSURIA IN THE CLINISTIX SURVEYS

Case	Sex	Age now (yr)	Disability	Glucose tolerance tests						Family history of D.M.	Comments
				0	½	1	1½	2	2½ or 3		
I.G.	F	38	Chair	120	265	255	205	185	—	None	Diabetic. Brother with Friedreich's ataxia had an abnormal glucose tolerance test (A.G. in Table III)
J.P.	F	37	Bedridden	152	234	294	282	268	221	Maternal aunt	Diabetic. Totally dependent on others
E.W.	F	24	Chair	100	230	198	130	186	85	None	Raised ½ hr, maximum and 2-hr levels
S.B.	F	33	Chair	90	140	185	150	130	100	None	Raised 1- and 2-hr levels
J.M.	M	13	Mildly ataxic	75	160	155	145	120	90	None	Raised 2-hr level

cases who had shown no glycosuria in the first place were tested again with Clinistix in an identical fashion. Nine of these failed to return their cards, 35 had no glycosuria, and three showed some glycosuria. Glucose tolerance tests on two of these patients were normal. The glucose tolerance test on the third—J.M. (mildly ataxic)—showed an elevated two-hour level and a normal three-hour level (Table II).

Comment on the Clinistix surveys　Of the original 70 cases, four failed to return their cards and one was on a large dose of steroids. Of the 65 patients remaining, eight showed glycosuria in two or more urine specimens passed during a 24-hour period. Two of these had fasting blood sugar levels of 120 mg % or above and have been classified as diabetic. One was bedridden and the other was chairbound. Two chairbound cases showed normal fasting levels, a high maximum level, a raised two-hour level and a normal three-hour level. One mildly ataxic boy showed an elevated two-hour level. For reasons mentioned below, we have simply recorded our findings on these latter patients and have not labelled them as being pre-diabetic.

GLUCOSE TOLERANCE TESTS　Thirty additional patients had glucose tolerance tests performed. In 27 cases the test was performed by ourselves and in a further three the tests were performed elsewhere. Nine were mildly ataxic, four required help with walking, 13 were chairbound, and four were bedridden.

Method　The patients were all taking an unrestricted diet. All patients were fasted for 12 hours before the test. Capillary blood was used. After withdrawing a blood sample, 50 g glucose in 200 ml. flavoured water was drunk within five minutes. Zero time was taken at the beginning of the drink. Samples of capillary blood were taken at 30-minute intervals until two hours, with a final sample at three hours.

Blood glucose was analysed in duplicate both by the glucose oxidase method (Marks, 1959) and a colorimetric method (Asatoor and King, 1954). Only the glucose oxidase data have been recorded, but results from the two methods were in agreement. Blood from 11 normal controls, used for spot checks during the investigation, gave a mean fasting blood sugar level of 69 mg ± 8·6%. The maximum blood sugar level did not exceed 152 mg % in any case, and the mean two-hour level was 85·5 ± 27%.

Results　Glucose tolerance tests were normal in 21 and abnormal in nine (Table III). Fasting levels were normal in every case. One mildly ataxic boy (R.H.) showed an elevated two-hour level only. Eight cases showed an elevated two- and three-hour blood sugar level. In three of the eight the blood sugar rose above 180 mg % at some time during the test. All eight cases were chairbound or bedridden and it is noteworthy that the greatest abnormality occurred in two siblings (M.T. and F.T., Table III), who showed maximum blood sugar levels of 415 mg % and 284 mg % respectively.

TABLE III

ABNORMAL GLUCOSE TOLERANCE TESTS OCCURRING IN THE G.T.T. SURVEY

Case	Sex	Age now (yr)	Disability	Glucose tolerance tests						Family history of D.M.	Comments
				0	½	1	1½	2	2½ or 3		
M.Ta.	F	46	Chair	71	115	142	140	176	163	1 sister died at 19 with F.A. and D.M.	Raised 2- and 3-hr levels
J.M.	F	33	Bedridden	73	101	139	150	129	137	Not known	Raised 2- and 3-hr levels
R.C.	F	60	Bedridden	75	86	168	172	142	149	Not known	Raised 2- and 3-hr levels
B.G.	F	56	Chair	80	150	166	230	214	189	Father and brother had D.M. Sib of R.G.	Maximum level, 2-hr and 3-hr levels all raised
R.G.	F	62	Chair	69	115	123	107	123	128	Father and brother have D.M. Sib of B.G.	Mild elevation of 2- and 3-hr levels
M.T.+	F	37	Bedridden	104	201	415	237	197	188	Sib of F.T. Family history otherwise negative.	A particularly severely disabled patient. Normal fasting level but G.T.T. otherwise very abnormal
F.T.+	M	35	Bedridden	95	247	284	127	126	167	Sib of M.T.	Rapid and high rise in blood sugar level; 2- and 3-hr levels raised
A.G.+	M	46	Chair	75	125	125	120	120	—	Sister (I.G. in Table II) has a diabetic G.T.T.	Elevated 2-hr level
R.H.	M	14	Mildly ataxic	70	116	136	108	125	101	Maternal grandfather	Mild elevation of 2-hr level, otherwise normal

+G.T.T.s done at local hospital.
For convenience only the glucose oxidase results are shown.

D.M. = Diabetes mellitus
F.A. = Friedreich's ataxia
G.T.T. = Glucose tolerance test.

SUMMARY OF RESULTS Of 113 cases of Friedreich's ataxia, seven were known diabetics before the survey began (Table I). We have discovered a further two undoubted cases (Table II), giving a total incidence of 8% in our series.

Twelve further cases showed abnormalities of the glucose tolerance curve. All had normal fasting levels and raised two-hour levels. Seven also had an elevated three-hour level. Five had a maximum blood sugar level in excess of 180 mg %. Ten of the twelve were chair- or bed-ridden. Two mildly ataxic boys showed only a raised two-hour level. One patient with heavy glycosuria was excluded because she was having large doses of steroids.

DISCUSSION

It is well known that immobility is a potent cause of apparent glucose intolerance. Thus Blotner (1945), when surveying 86 chronically bedridden, non-diabetic patients, found that the fasting blood sugar levels were above 130 mg % in six cases, between 106 and 124 mg% in 20 cases and between 70 and 105 mg % in 37 cases. In 47 cases the three-hour levels ranged between 140 mg % and 278 mg %. Hecht, Weisenfeld, and Goldner (1961) found that in 27 hospitalized patients, nine of whom were bedridden, the fasting blood sugar levels were normal, but that the three-hour levels were raised. On the basis of this work, we have been reluctant to diagnose diabetes mellitus in severely crippled patients unless there is marked elevation in the fasting blood sugar level. All our cases of diabetes mellitus have persistent glycosuria with fasting blood sugar levels of 120 mg % or above (eight had fasting levels above 140 mg %).

Our results are in some contrast to those of Thorén (1962). Thorén surveyed 50 patients with Friedreich's ataxia having a mean age of 21·9 years (9-48). He found nine diabetics, giving an 18% incidence. All cases of diabetes were recognized some years after the ability to walk had been lost. Six of our 112 patients (5·4%) had developed diabetes before the age of 49. The mean age of onset of diabetes in these six cases was 39·8 years (range 16–48 years). Our total incidence of 8%, irrespective of age, is also well below that found by Thorén (1962).

The incidence of diabetes mellitus among the general population has been determined by a number of surveys. All surveys give figures well below 2%. Thus Wilkerson and Krall (1947) found an incidence of 1·7%, Andrews (1957) found an incidence of 0·56%, and Walker and Kerridge (1961) one of 1·4%. Our figures and those of Thorén, for the co-existence of diabetes mellitus and Friedreich's ataxia, are in excess of the figures obtained from population surveys.

It is well known that the incidence of diabetes mellitus increases considerably with the advancing age of the population considered. Moreover, there are no generally accepted standards of glucose tolerance in the older age group (*Lancet*, 1963). Our series contained 21 cases aged 40 and over.

An attempt has been made to compare the frequency of diabetes mellitus in patients with Friedreich's ataxia with neurologically normal members of affected sibships. The 112 probands with Friedreich's ataxia came from 87 sibships containing 286 siblings. One hundred and thirty of these 286 had Friedreich's ataxia and 10 also had diabetes mellitus (7·7%). Two of the 156 siblings not affected with Friedreich's ataxia were diabetics.

Diabetes occurred in only nine of the 87 sibships. These nine sibships all contained patients with both Friedreich's ataxia and diabetes. There were 55 siblings in the nine sibships (Table IV). Twenty-four (mean age 40·1 years, range 16–67 years*) had Friedreich's ataxia and 10 of these also had diabetes (mean age of onset 40·5 years, range 16–62 years*). Thirty siblings (mean age 42·4 years, range 13–66*) did not have Friedreich's ataxia and two of these had diabetes.

The above figures appear to suggest that diabetes occurs more commonly in those siblings with Friedreich's ataxia than those who were neurologically normal. At present this suggestion cannot be regarded as proved in view of the small numbers of cases involved.

It is relevant to consider briefly what other neurological disorders are associated with diabetes. Kendall (1953) reported that five out of 17 males with disseminated sclerosis had diabetes mellitus. However, of 36 women none had diabetes mellitus. She did not give the immobility grading of her patients, but all were inmates of a chronic hospital for the incurable. Droller and Powell (1956) found that an initially diabetic curve could be corrected to normal in cases of disseminated sclerosis by prior feeding with 100 g glucose daily for three weeks. No definite association between disseminated sclerosis and diabetes mellitus has been shown to exist. Steinke and Tyler (1964) investigated 11 patients with amyotrophic lateral sclerosis and found that nine of them exhibited an abnormality in glucose utilization which was detectable by oral or intra-venous tolerance tests or by the blood glucose response to tolbutamide. Rose, Fraser, Friedmann, and Kohner (1966) reported seven cases of juvenile diabetes mellitus coexisting with optic atrophy and defects including deafness. In general, it apears that no other neurological disease is constantly associated with an increased incidence of diabetes.

*Taking ages at death as attained ages.

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TABLE IV

ANALYSIS OF THE NINE SIBSHIPS IN WHICH DIABETES
MELLITUS OCCURRED

Family	Consan-guinity	Sibling order	Sex	Age (yr)	F.A.	Diabetes (with age of onset in yr)
I	0	*1(W.C.)M	M	64	+	+(45)
		2	M	58	0	+(35)
II	0	1	M	50	0	0
		*2 (L.H.)M	M	44	+	+(40)
		3	F	46	0	0
III	0	1	M	17 (died)	0	0
		2	F	58 (died)	+	0
		*3(G.H.)F	F	67 (died)	+	+(58)
		*4(M.H.)F	F	67	+	+(62)
		5	F	66	0	0
IV	?	*1 (J.P.) F	F	37	+	+(35)
		2	F	?	0	0
		3	F	20 (died)	+	0
		4	M	30	+	0
V	0	*1 (H.S.) F	F	42	+	+(35)
		2	M	41	+	0
		3	M	31	0	0
		4	M	31	0	0
		5	M	28	+	0
		6	M	22	+	0
VI	Yes (parents were first cousins)	*1(D.G.) F	F	63	+	+(57)
		*2(R.G.) F	F	62	+	0
		3	M	60	0	+(unknown)
		4	M	57	0	0
		*5(B.G.) F	F	57	+	0
		6	M	48	0	0
		7	F	45	0	0
VII	0	1	M	24	0	0
		2	F	22	+	0
		*3(J.J.) F	F	20	+	+(16)
		4	F	19	+	0
		5	F	18	0	0
		6	M	14	+	0
		7	M	13	0	0
VIII	0	1	F	19 (died)	+	+(19)
		2	M	58	0	0
		3	F	56	0	0
		4	F	52	0	0
		5	F	14 (died)	0	0
		6	M	47	0	0
		*7 (M.Ta)	F	46	+	0
		8	F	43	0	0
IX	0	1	F	56	0	0
		2	F	55	0	0
		3	M	53	0	0
		4	M	48 (died)	+	0
		5	F	50	0	0
		6	F	49	0	0
		*7(A.G.) M	M	44	+	0
		8	F	43	0	0
		9	M	42	0	0
		*10 (I.G.)	F	38	+	+(38)
		11	F	36	0	0
		12	F	30	0	0

F.A. = Friedreich's ataxia.
*These patients were either diabetic or showed some abnormality of glucose tolerance. Further details are given in Tables I, II, and III.
N.B. The neurologically normal siblings have not been tested for evidence of latent diabetes.

The clinical features of the diabetes mellitus that occurs in Friedreich's ataxia cannot be distinguished from those occurring in neurologically normal patients. The diabetes is apparently always discovered after the onset of neurological disability. Histological examination of the pancreas has been carried out on two cases (Köhne, 1941). They were found to be small with a vastly reduced number of islets.

The cause of the increased incidence of diabetes mellitus in Friedreich's ataxia remains a matter for speculation. It may be that we are dealing with a highly pleiotropic gene. Such an explanation has been invoked to explain both the cardiac and the diabetic abnormalities in these patients. Possibly the diabetes has a direct neurogenic origin and could conceivably be due to lesions in the region of the hypothalamus although there is no histological evidence of this.

In conclusion, the evidence indicates that there is a slightly increased incidence of diabetes mellitus in Friedreich's ataxia. In all cases the diabetes has developed some years after the onset of neurological dysfunction. Most patients were severely disabled by the time that the diabetes was discovered. It seems possible that diabetes mellitus is more likely to occur in the neurologically abnormal members of affected families than in the normal ones, but this point cannot yet be regarded as proved.

SUMMARY

An investigation of the incidence of diabetes in 113 cases of Friedreich's ataxia has been made. Nine of these were found to be diabetic, giving a total incidence of 8%. Twelve further cases showed abnormalities of glucose tolerance amounting to diabetes mellitus. The association of diabetes with Friedreich's ataxia is discussed.

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