Quebec Cooperative Study
of Friedreich's Ataxia

Friedreich's Ataxia and Oral Glucose Tolerance:

I. The effect of ingested glucose on serum glucose and insulin values in homozygotes, obligate heterozygotes and potential carriers of the Friedreich's ataxia gene.

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SUMMARY: *Glucose tolerance and insulin release were evaluated in 16 families with Friedrich's ataxia. Impaired glucose tolerance differed in incidence according to the method of evaluation, but was increased in number in parents and siblings of Friedreich's cases. Insulin output was not quantitatively different from normal, although the insulin peak was often delayed. This finding, in association with impaired glucose tolerance, suggest a defect in glucose entry into cells.*

RÉSUMÉ: *Nous avons évalué la tolérance au glucose et la libération de l'insuline dans 16 familles avec ataxie de Friedrich. La prévalance d'anomalies de la tolérance au glucose diffère selon la méthode d'évaluation employée, mais il ne fait aucun doute qu'il y a une augmentation de ces anomalies chez les parents et la fratrie des patients ataxiques. La libération d'insuline n'était pas quantitativement différente de la normale, mais le pic d'activité était souvent retardé. Cette donnée, associée à l'intolérance au glucose, suggère un défaut au niveau de la pénétration cellulaire du glucose.*

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INTRODUCTION

Neuroendocrine and metabolic disturbances have been recently reported in degenerative hereditary diseases of the central nervous system such as Huntington's chorea and Friedreich's ataxia (Caraceni et al, 1977; Collu et al, 1977; Shapcott et al, 1976; Draper et al, 1979). A high incidence of glucose intolerance has been found among patients with Friedreich's ataxia (Shapcott et al, 1976) and is thought to be due, among other factors to the absence of exercise and immobilization of these patients. Furthermore, preliminary data has indicated that there may be a familial component (Draper et al, 1979; Andermann et al, 1976).

In order to establish whether the above factors are involved, we assessed glycemia and insulin release to orally ingested glucose in families of patients with Friedreich's ataxia (parents and siblings) with or without the neuromuscular deficits.

PATIENTS

Our study group consisted of 16 families. Among them at least one member of each family had Friedreich's ataxia defined by well established criteria (Geoffroy et al, 1976). Practically all patients had varying degrees of ataxia ranging from impeded mobility to movement with difficulty and assistance. None of the siblings or parents had any neuromuscular disorder and none of the families was on any medications affecting pancreatic function or other endocrine glands. The parents differed from the offsprings in terms of body weight: 11 of 15 were overweight whereas the siblings were around ideal weight and the patients were largely underweight (9 out of 15).

METHODS

All subjects were instructed to eat an adequate carbohydrate diet (> 250 grams daily for three days) and report to the nursing station after overnight fasting. An indwelling catheter was placed in an antecubital vein and blood was collected at 30 minute intervals for three hours for the determination of blood glucose (G), insulin (I), growth hormone (GH) and prolactin (PRL). Blood glucose was determined by auto-analyser and insulin by standard radioimmunoassay technique (Keen et al, 1979).

A glucose curve was interpreted using guidelines established by Danowski et al (1975) and the National Institute of Health (Keen et al, 1979) (Table 1). The area under the curve (AUC) for glucose (AUC-G) or insulin (AUC-I) was calculated by using the formula:

$$\frac{1\,(0\text{ min. value})+2\,(30\text{ min})+3\,(60\text{ min})+2\,(120\text{ min})}{4}$$

The elevation of insulin release per glycemia achieved following glucose ingested was evaluated by regression analysis. The student's T test (two tailed) was applied to compare the AUC-G and AUC-I among groups.

Measurements of glycosylated hemoglobin (AIC) levels were made with the use of a kit.

RESULTS

A. Family Histories

In at least 50% of the various groups tested there was a positive family history for diabetes (Tables 2, 3, 4). Of interest was the fact that among homozygotes (F.A. patients) and obligatory heterozygotes (parents) a

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TABLE 1

Criteria For Interpretation Of The Oral Glucose Tolerance Test

DANOWSKI CRITERIA	NIH CRITERIA
Sum of values at: 0, 30, 60, 90, 120 min.	Fasting <120; 2 Hr. Values <120 - Normal
<500 - Normal (N)	Fasting <120; 2 Hr. Values >120 <180 - IGT
>501 - <650 - Mildly Intolerant (Mild)	Fasting <120; 2 Hr. Values >180:
>651 - <800 - Moderately Intolerant (Mod)	if sum of 1 + 2 hr. <500 - IGT
>801 - Diabetic (D)	if sum of 1 + 2 hr. >500 - D
	Fasting >120 - D

positive history for diabetes was elicited with a higher frequency among those members with an abnormal glucose tolerance or diabetes than those with a normal one i.e. patients 62.5% vs 33%; parents 60% vs 20%.

B. O.G.T.T.

The percent of subjects (homozygotes : patients; obligatory heterozygotes : parents; and potential carriers : siblings) presenting with overt diabetes or IGT differed according to the criteria employed (Tables 2, 3, 4). Employing the Danowski criteria, abnormalities in glucose tolerance were identified with higher frequency (more than 50% in all groups). A significant ($p<0.001$) difference was found when comparing the area under the curve for glucose (AUC-G) between those with normal GTT and those identified as having IGT (mean ± S.D. values were 250.9±28 and 297.8±24.7 respectively).

No difference was found when comparing the insulin output (AUC-I) among groups. Furthermore, we were unable to establish a significant correlation between the AUC-G and the AUC-I analysed by linear regression when the insulin release was analysed qualitatively among those subjects

TABLE 2

Patients

NO.	FAMILY	INITIALS	B.W.	AGE	SEX	STATUS	DANOWSKI*	NIH*	AUC_G	AUC_I	HBAIC	FAM.HX.	Insulin ng/ml 0′	30′	60′	120
1	I	D.B.	-18%	24	M	W/C	D	D	561	42	10.8	+	8	17	23	28
2	II	S.G.	-16%	18	M	AMB	MOD	IGT	298	106	5.9	+	9	39	67	68
3	II	M.G.	-30%	16	M	AMB	MOD	IGT	277	118	6.0	+	10	56	77	59
4	VI	R.M.	-38%	29	M	W/C	MOD	IGT	285	69		+	5	35	40	40
5	VI	M.M.	-10%	23	F	AMB	MILD	N	242			+				
6	VII	L.N.	13%	37	M	AMB	MILD	N	251			-				
7	VII	Y.N.	IBW	40	M	W/C	MILD	IGT	278			-				
8	VIII	A.R.	-35%	44	M	W/C	MOD	IGT	326	208		+	7	90	108	160
9	IX	G.C.	- 8%	30	F	W/C	MOD	IGT	265	141		+	7	42	78	120
10	X	R.P.	-15%	15	M	AMB	MOD	IGT	321	283	8.2	-	16	180	163	135
11	XII	H.G.	5%	39	F	W/C	MOD	N	312			-				
12	XIII	J.V.	15%	17	F	AMB	N	N	139			-				
13	XIV	D.D.	7%	14	F	AMB	MILD	N	279			-				
14	XV	C.C.	16%	22	F	W/C	MILD	IGT	250	159		-	11	67	80	125
15	XVI	A.C.	-20%	14	M	W/C	MILD	N	228			+				

B.W.: Body weight
B.W.: Expressed as % age above I.B.W. calculated from Metropolitan Life Insurance figures.
M - Male F - Female
I.B.W.: Ideal body weight
W/C: wheelchair; AMB-ambulatory
D - Diabetic MOD - moderately intolerant MILD - mildly intolerant N - Normal IGT - Impaired Glucose Tolerance
*From Table 1

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TABLE 3

Parents

NO.	FAMILY	INITIALS	B.W.	AGE	SEX	DANOWSKI*	NIH*	AUC_G	AUC_I	HBAIC	FAM.HX.	Insulin ng/ml 0′	30′	60′	120′
1	I	J.B.	25%	54	F	D	D	358	133	9.8	+	13	70	63	94
2	II	M.G.	33%	42	M	D	IGT	329	212	6.3	+	22	65	120	168
3	II	M.G.	75%	42	F	MOD	IGT	293	160	6.3	-	12	51	70	158
4	III	S.G.	6%	36	M	MOD	IGT	311	105	8.7	-	12	83	61	36
5	III	R.G.	32%	37	F	MOD	IGT	349	257	5.4	+	16	98	170	153
6	V	A.L.	30%	79	F	D	D	543	221	9.1	+	28	73	168	110
7	VI	M.M.	16%	57	F	MILD	N	249	171	9.3	-	16	73	115	88
8	VIII	J.R.	25%	71	M	D	IGT	448			+				
9	VIII	D.R.	25%	68	F	MOD	IGT	270			+				
10	X	R.P.	33%	49	M	MOD	N	290	163	7.7	-	6	93	120	49
11	X	G.P.	20%	41	F	MOD	IGT	286	112	8.8	-	6	62	54	78
12	XI	J.D.	IBW	42	F	MOD	IGT	286	119		+	8	77	58	70
13	XI	P.D.	IBW	36	M	N	N	198	124		+	13	100	77	25
14	XIV	A.D.	15%	43	M	MILD	N	258	141	6.5	-	12	103	93	33
15	XIV	E.D.	IBW	38	F	MILD	N	281	141	6.7	-	9	71	89	74

Key — see Table II

with IGT, over 75% of whom had a delayed insulin peak or a second spike.

C. Hemoglobin A_1C

Abnormally elevated values were found in 3 out of 4 diabetic family members. Among the rest, mildly elevated values were seen in some members with IGT although this was not consistent. One "normal" (by NIH criteria) parent had as high a value as that seen in a diabetic patient (see Table 3).

DISCUSSION

Previous investigators had found a high incidence of diabetes or abnormal glucose tolerance among patients with Friedreich's ataxia (Shapcott et al, 1976; Draper et al, 1979; Andermann et al, 1976). Our data is in agreement with these reports. In addition we now report that an impaired glucose tolerance is also present among obligatory heterozygotes and potential carriers. This finding could be taken to suggest a genetic defect in carbohydrate homeostasis in Friedreich's ataxia. The strong association, however, between family history and IGT may

TABLE 4

Siblings

NO.	FAMILY	INITIALS	B.W.	AGE	SEX	DANOWSKI*	NIH*	AUC_C	AUC_I	HBAIC	FAM.HX.	Insulin ng/ml 0′	30′	60′	120
1	I	K.B.	-13%	19	M	MOD	IGT	289	100	9.0	+	11	68	42	64
2	III	D.G.	- 7%	17	M	MILD	N	221	77	8.0	+	13	55	42	29
3	IV	N.B.	4%	29	F	MOD	N	275	110		+	15	42	69	66
4	IV	D.L.	13%	41	F	MOD	IGT	308	219		+	15	50	120	200
5	V	M.L.	7%	44	F	MILD	N	246	107	6.0	+	11	45	76	49
6	V	A.L.	6%	40	M	MOD	IGT	306	116	6.4	+	11	45	69	78
7	VIII	G.R.	IBW	45	M	MOD	IGT	304			+				
8	X	M.P.	0%	12	F	MILD	N	235	302	8.1	-	4	195	195	110
9	X	C.P.	25%	13	M	MILD	N	256	117	5.4	-	9	78	78	44
10	XI	N.D.	IBW	11	F	MOD	IGT	296	274		+	15	158	158	145
11	XI	D.D.	IBW	13	F	N	N	206	474		+	39	333	300	145

Key — see Table II

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be taken to suggest that the IGT is due to a hereditary factor unrelated to the Friedreich's ataxia genetic background. Of course, if there were a method i.e. HLA typing, chromosome banding or other marker, whereby one could show a positive correlation with the IGT then one could infer that there is a common link between Friedreich's ataxia genes and expression of IGT. Although our data cannot evaluate this possibility they offer other pathophysiologic insights. The findings of IGT in parents and siblings (in addition to patients) who suffer no neuromuscular disease suggests that the role of muscular immobility in glucose disposal, if anything, is restricted. Furthermore, the absence of insulinopenia in all groups with IGT indicates that at the early stages of glucose intolerance there is no quantitative defect in insulin release. Our finding that over 75% have a delayed insulin peak or a second late insulin rise following orally provoked hyperglycemia suggest a qualitative disturbance in insulin release mechanism as described in early diabetes. On the other hand, the presence of hyperglycemia despite a normal (quantitatively) insulin output suggests that there is a defect in the cellular components associated with glucose entry. Since this was observed both in the overweight parents and normal underweight siblings and patients, body weight does not seem to be of great importance; one has rather to propose a disorder situated after the binding of insulin to its receptor (which seems to be intact at least for erythrocytes) (Shapcott et al, 1976).

Thus, it appears that the IGT can be explained on a dual basis: abnormal insulin release and insulin action. Whatever the cause we suggest that all subjects with IGT be properly treated in order to avoid possible long term complications.

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