Quebec Cooperative Study
of Friedreich's Ataxia

Friedreich's Ataxia and Oral Glucose Tolerance:

II. The effect of ingested glucose on serum growth hormone in homozygotes, obligate heterozygotes and potential carriers of the Friedreich's Ataxia gene

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SUMMARY: *Homozygotes, obligatory heterozygotes and potential carriers of the Friedreich's Ataxia gene were tested with an oral glucose tolerance in order to assess a. the prevalence of abnormalities in glucose handling, b. the secretory pattern of two "diabetogenic" hormones, growth hormones and prolactin and c. to evaluate the possibility for detection of an abnormal trend in these hormones to be used as a genetic marker. Despite the high prevalence of glucose abnormalities horizontally and vertically in these families, the basal output and responses of these metabolic hormones to a glucose challenge were appropriate and thus not characteristic of any of the above groups.*

RÉSUMÉ: *Nous avons étudié chez des homozygotes, des hétérozygotes obligatoires et des porteurs possibles du gène d'Ataxie de Friedreich la tolérance au glucose oral afin d'évaluer a) la prévalence des anomalies du comportement du glucose b) le pattern secrétoire de deux hormones "diabétogéniques", l'hormone de croissance et la prolactine, et c) d'évaluer la possibilité d'utiliser ces résultats comme marqueur du gène. Malgré la prévalence élevée d'anomalies du glucose horizontalement et verticalement dans ces familles, la production basale et la réponse de ces hormones métaboliques à un stress glucosé furent normales et non caractéristiques d'un ou l'autre des groupes étudiés.*

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INTRODUCTION

Friedreich's ataxia is an autosomal recessive progressive disease initially affecting the dorsal columns of the spinal cord but also affecting cerebellar cortex and nuclei, and peripheral nerves. It usually manifests in puberty and has an inexorable course.

Many of the degenerative CNS diseases have been associated with endocrinological abnormalities and in particular with derangements of carbohydrate homeostasis. Chemical diabetes has been reported in as many as 18% of patients with Friedreich's ataxia. Similarly, in Friedreich's ataxia and Huntington's chorea abnormalities in growth hormone (GH) dynamics have been reported (Caraceni et al., 1977; Collu et al., 1977).

In order to assess whether the reported aberrant GH dynamics is a familial characteristic of Friedreich's ataxia and/or is primarily associated with carbohydrate intolerance (as it has been well documented in juvenile diabetes mellitus), we studied the effect of an oral glucose load (OGTT) upon growth hormone (GH) in 12 families with Friedreich's ataxia. In addition, in view of published data showing that CNS disease and metabolic disorders affect serum prolactin (PRL) we also evaluated its serum values in Friedreich's ataxia families.

MATERIALS AND METHODS

From a total of 12 families we studied 9 patients, 13 parents and 11 siblings. Parents from two patients were unavailable (patients 6 and 7). Friedreich's ataxia children from families XI and XIV were found to have normal fasting values but were not studied completely, thus are not reported. One patient with Friedreich's ataxia, who was an insulin dependent diabetic, was not tested nor were her parents. Her siblings were tested and reported here (Nos. 3 and 4); two sisters were affected by both Friedreich's ataxia and diabetes. A strong history for diabetes mellitus was elicited from the paternal side. Of all the family members tested patients 1, 5, 6, 7, and 9 were in wheel-chairs. All the subjects were instructed to eat an adequate carbohydrate diet for the 3 days prior to the OGTT. The test was done in a sitting position after 12 hours of fasting with 100 gms of glucose in lemon juice. A needle was placed in the antecubital vein and kept open with a mixture of sodium citrate and normal saline and clamped in between blood drawings. Samples were taken at times 0, 30 minutes, 60 minutes, 90 minutes, 120 minutes and 180 minutes.

Blood glucose was analyzed using the auto-analyzer. Blood taken for GH and PRL measurements was spun down, the serum separated and frozen until assayed using previously described techniques (Roth et al., 1963; Hwang et al., 1971).

The criteria for labelling a glucose tolerance as abnormal according to Danowski 1975 or NIH recommendations are found in the preceeding publication. The growth hormone data was analyzed using the guidelines laid out by Roth et al., (1963) in their initial experiments on GH dynamics using the oral GTT.

RESULTS (TABLE I)

Fasting serum GH and PRL values were normal in all members of the

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families (patients, siblings, parents) with one exception (Patient no. 2) in whom the abnormal GH values was most likely due to a stress response. The changes in serum GH during the OGTT were within the norms established previously and showed no relationship to the status of glucose tolerance. Similarly, no abnormalities were detected in serum PRL.

DISCUSSION

Our evaluation of GH dynamics as assessed by an OGTT in patients with Friedreich's ataxia showed only one patient with a level of basal GH in the pathologically elevated range (>10). His response to the oral glucose was normal in spite of the fact that he was moderately intolerant by the Danowski criteria in his disposal of the glucose load. In the rest of the patients as well as in the parents and siblings, serum GH values showed a normal response pattern to the ingested glucose. No paradoxical increase was seen in those subjects in whom baseline GH values were at the lowest levels. Three of 9 patients, 7 of 13 parents and 5 of 11 siblings had low fasting GH values. This is a phenomenon seen in normal populations and more often in obesity. Whether the latter applies to the overweight parents needs further exploration. Provocative testing with dopaminergic agonists or insulin hypoglycemia might further identify responders and poor or non responders.

Earlier reports implied a hypothalamic derangement in Friedreich's ataxia (Collu et al., 1977). Our data, showing normal basal PRL values, suggest that if there is one, it does not affect diffusely the hypothalamic nuclei or the dopamine-rich hypothalamic components involved with the

TABLE I

Fasting Serum Prolactin and Growth Hormone Responses to an Oral Glucose Load (GTT) in Patients with Friedreich's Ataxia and Their Relatives

	Subject No.	Family No.	Sex	Age	%Deviation From IBW	Rating for OGTT Danowsky	Rating for OGTT NIH	Basal Serum Prolactin (ng/ml)	Serum Growth Hormone (ng/ml) Time in Minutes 0	30	60	90	120	190
Patients	1	I	M	24	-18%	D	D		1.1	1.8	1.5	1.5	1.1	1.4
	2	II	M	18	-16%	MOD	IGT	13.3	2.6	11.8	4.4	1.8	1.2	<1.0
	3	II	M	16	-30%	MOD	IGT	15.1	4.9	1.2	1.1	<1.0	<1.0	19.4
	4	V	M	34	25%	MOD	IGT		2.3	2.2	1.1	1.6	1.6	1.1
	5	VI	M	29	-38%	MOD	IGT		8.3	3.0	1.5	<1.0	1.8	1.2
	6	VIII	M	43	-35%	MOD	IGT		<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	7	IX	F	30	- 8%	MOD	IGT	11.1	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	8	X	M	15	-15%	MOD	IGT		8.9	11.4	2.7	1.7	1.4	
	9	XV	F	22	-16%	MILD	IGT	12.7	4.4	2.7	1.0	1.0	1.0	1.0
Parents	1	I	F	54	25%	D	D		1.5	1.1	1.3	1.7	1.2	1.0
	2	II	M	42	33%	D	IGT	14.6	1.0	1.0	1.5	1.0	1.2	1.1
	3	II	F	42	75%	MOD	IGT	20.0	<1.0	1.0	1.0	<1.0	<1.0	3.0
	4	III	M	36	6%	MOD	IGT		2.2	1.5	1.8	1.0	1.3	1.4
	5	III	F	37	32%	MOD	IGT		5.0	3.0	2.4	1.8	1.6	7.4
	6	V	F	78	30%	D	D		1.8	1.4	1.4	2.2	5.0	1.4
	7	VI	F	57	16%	MILD	N		3.9	2.2	1.6	1.9	2.4	3.7
	8	X	M	49	33%	MOD	N		1.8	1.2	1.1	1.5	<1.0	1.9
	9	X	F	41	20%	MOD	IGT		3.3	1.4	1.3	1.3	<1.0	1
	10	XI	F	42	IBW	MOD	IGT		9.4	2.6	1.6	1.5	1.5	5.2
	11	XI	M	35	IBW	N	N		2.2	1.6	1.1	1.5	1.8	
	12	XIV	M	43	15%	MILD	N	7.4	1	1	1	1	1	2.6
	13	XIV	F	38	IBW	MILD	N	9.1	1.1	<1	<1	<1	<1	<1
Siblings	1	I	M	19	-13%	MOD	IGT		1.3	<1.0	1.3	1.7	1.0	<1.0
	2	III	M	16	- 7%	MILD	N		7.6	6.4	2.7	1.8	1.4	3.0
	3	IV	F	29	4%	MOD	N	12.2	6	<1	<1	<1	<1	<1
	4	IV	F	41	13%	MOD	IGT	11.0	<1	1.0	<1	<1	<1	<1
	5	V	F	44	7%	MILD	N		3.2	1.7	1.4	<1.0	2.9	2.9
	6	V	M	53	25%	MOD	IGT		1.0	1.0	<1	1.1	1.7	<1.0
	7	V	M	40	6%	MOD	IGT		1.0	1.2	1.1	1.0	1.1	1.4
	8	X	F	12	IBW	MILD	N		1.3	1.3	1.0	2.0	8.7	1.7
	9	X	M	13	-25%	MILD	N		2.2	1.0	<1.0	1.0	1.4	15.2
	10	XI	F	11		MOD	IGT		1.8	1.4	1.2	1.2	1.5	1.1
	11	XI	F	13		N	N		5.8	1.3	1.8	1.0	1.1	

D: Diabetic MOD: Moderate Intolerance IGT: Impaired Glucose Tolerance IBW: Ideal Body Weight Mild: Mild Intolerance

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control of PRL. In addition, our finding of normal serum GH dynamics, as assessed by an oral glucose tolerance test, may exclude an extended involvement of the ventromedial complex thought to be involved with glucoreceptor-related GH output (Martin, 1979).

In other hypothalamic derangements, like anorexia nervosa, and psychosocial dwarfism or the maternal deprivation syndrome, the basal GH may be elevated or normal, and the response to oral glucose variable — from a paradoxical elevation to normal suppression. In chronic debilitating diseases — which Friedreich's ataxia is — malnutrition, cirrhosis or cancer, a paradoxical GH response to oral glucose has been reported. While all our patients had Friedreich's ataxia, practically all were active and/or could ambulate, albeit with difficulty because of ataxia. It is possible that because of this we did not see the abnormalities of GH dynamics reported by others in patients with Friedreich's ataxia (Collu et al., 1977).

In summary, the above results suggest the presence of an abnormality in glucose handling in Friedreich's ataxia but do not indicate a relationship between this and the GH serum changes to glucose load. In addition, the failure to identify a trend in either PRL or GH dynamics when assessed horizontally (different families) or vertically (same families) indicates that if there is a hypothalamic effect, it is not involving basal secretion of the above two lactogenic-growth-promoting-diabetogenic hormones and/or the glucose dependant suppressibility of GH output. Further studies are needed with different neuro-endocrine strategies (Martin, 1979; Tolis and Franks, 1979) to assess whether an aberrant GH or PRL secretory pattern can be a hallmark of this debilitating disease.

REFERENCES

CARACENI, T., PANERAI, A.E., PARATI, E.A., COCCHI, D., and MULLER E.E. (1977). Altered GH and PRL responses to dopaminergic stimulation in Huntington's chorea. J. Clin. Endocrinol. Metab. 44: 870-875.

COLLU, R., GEOFFROY, G., MELANCON, S.B., and BARBEAU, A. (1977). Growth hormone levels in Friedreich's ataxia. Horm. Metab. Res. 9: 523-524.

DANOWSKI, T.S. (1975). Classifications of diabetes mellitus in Endocrinology and Diabetes. The Thirtieth Hannenmann Symposium, L.J. Kryston and R.A. Shah (eds.), Grune and Stratton Inc. pp. 321-328.

HWANG, P., GUYDA, H. and FRIESEN, H.G. (1971). A radioimmunoassay for human prolactin. Proc. Natl. Acad. Sci. (USA) 68: 1902-1906.

MARTIN, J.B. (1979). Pathophysiology of growth hormone. In Clinical Neuroendocrinology, G. Tolis, F. Labrie, J.B. Martin and F. Naftolin (eds.) Raven Press, pp. 269-278.

ROTH, J., GLICK, S.M., YALOW, R.S., and BERSON, S.A. (1963). Secretion of human growth hormone: Physiologic and experimental modification. Metabolism 12 (7): 577-579.

TOLIS, G. and FRANKS, S. (1979). Physiology and pathology of prolactin secretion. In Clinical Neuroendocrinology: A pathophysiological approach. G. Tolis, F. Labrie, J.B. Martin, F. Naftolin (eds.), Raven Press, pp. 291-318.