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HYPERTRIGLYCERIDEMIA IN A FAMILY WITH A HIGH INCIDENCE OF TYPE II DIABETES

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SUMMARY

Fourteen individuals from two generations of a family with a high incidence of type II diabetes were studied. Six out of twelve siblings (50%) developed diabetes between 24 and 45 years of age. They were the product of a non diabetic father, whose family had a high incidence of diabetes, and a diabetic mother (age of onset = 52 years) whose family history was negative for diabetes. The duration of diabetes in the siblings at the time of the study ranged from 3 to 13 years. Only one required insulin for control of the hyperglycemia while the others were treated with oral hypoglycemic agents and/or diet. Hypertriglyceridemia was present ind 5 of the 6 diabetic sibligs (83%) and in several other non-diabetic members of the family and was highly correlated with age ($r = 0.86$; $p < 0.01$), but not with the body mass index or diet. It is proposed that a common genetic trait might account for both metabolic dysfunctions.

INTRODUCTION

Hypertriglyceridemia with elevated VLDL levels is frequently present in patients with non-insulin dependent diabetes(3, 5). The degree of hypertriglyceridemia is highly variable as is the severity of hyperglycemia. Several authors have postulated that the primary abnormality of plasma triglyceride metabolism in type II diabetes is the overproduction of VLDL particles(5). The excessive secretion of VLDL into plasma is probably due to the simultaneous presence of hyperinsulinemia, hyperglycemia, and incresed release of the free fatty accids from mesenteric fat into the portal blood(5).

In addition, several secondary types of hypertriglyceridemia are often associated with the adult diabetic syndrome. For example, obesity which occurs in a very high percentage of patients with adult onset diabetes, is associated with elevated plasma triglyceride levels and obesity, independent of diabetes, could thereby play a role in the hypertriglyceridemia of the diabetic state(1). In addition, diabetes could also occur in individuals who coincidentally had familial hypertriglyceridemia with the net effect being a "diabetic-hyperlipemic syndrome"(5).

In this paper we describe a very high incidence of diabetes mellitus in a family in which hypertriglyceridemia, in the absence of morbid obesity was present in almost all individuals. In these patients, a common genetic trait might be the cause of both dysfunctions.

PATIENTS AND METHODS

The propositi were patients of a Metabolic Disease Clinic at the Instituto de Investigaciones Clínicas, Facultad de Medicina, University of Zulia. In all the patients a complete history was obtained, including age and symptoms at diagnosis, details of treatment, and whether they had ever had any episodes of ketoacidosis. They were classified as having Type II diabetes following the criteria of the National Diabetes Data Group(4). At the time of the study, anthropometric measurements were performed to determine the nutritional state of the subjects, and the body mass index (BMI) was calculated as weight (Kg)/height (m^2).

Whenever possible, a 75 g oral-glucose-insulin-tolerance test was carried out on apparently non-diabetic individuals. Fasting venous blood was taken for biochemical analysis of serum glucose (using the glucose oxidase method, Gluco-Kit, Venezuela), glycosilated hemoglobin (Human, West Germany), cholesterol (by the enzymatic method of Sigma Chemi-

cal Company, St. Louis, USA), HDL-cholesterol (by the same enzymatic method of Sigma after precipitation with phosphotungstate), triglycerides (by the enzymatic method of Human, West Germany) and total lipids (Labtest Sistemas Diagnosticos, Ltda., Brasil). Immunoreactive insulin was determined by a solid phase radioimmunoassay (Diagnostic Products Inc., USA).

RESULTS

The pedigree of the Q family is shown in Fig. 1. As can be seen, propositus II-11, a man with a high incidence of type II diabetes mellitus in his family, married a woman (propositus II-12) who developed diabetes mellitus at 52 years of age. She had no family history of diabetes. There is no apparent consaguinity between the families. At the time of the study, six of their siblings (Propositus III-13, III-14, III-16, III-18, III-20 and III-21) had developed diabetes with an age of onset between 24 and 45 years.

Table I details the clinical characteristics of the Q family. Ten of the 12 siblings were men and two were women; all the diabetics were men. Their ages, at the time of the study, ranged from 23 to 49 years. Their BMI'S were between 19.8 and 29.7. In four of the propositi (III-13, III-17, III-20 and III-22) some degree of hypertension was recorded but none had any overt cardiovascular disease. None of the diabetic offspring reported any episodes of ketoacidosis. The mother and one of the diabetics siblings received insulin to control the hyperglycemia, while the rest were treated with oral hypoglycemic agents and/or diet. None had routine medical followup.

The biochemical profiles of the family is recorded in Table II. The fasting glycemic values were all under 180 mg/dl, even among the diabetics, although the glycosilated hemoglobin levels revealed that in four of them were over 8% (normal values = 6-8%). The fasting insulin values were somewhat high (normal values = 14.5 ± 2.4 uU/ml) in most of the diabetics. The insulin values measured 2 h after the glucose load were increased only in the father (Propositud II-11) (Normal values for postprandial insulin in our laboratory = 80 ± 9 uU/ml).

The lipid profiles revealed a very high incidence of hypertriglyceridemia. Eight of the subjects (the father and 7 siblings, five diabetics and even three of the non-diabetics) had triglyceride levels greater than 150 mg/dl. A highly significant correlation was found between the triglyceride values and age (Fig. 2). The cholesterol values were found to be at the up-

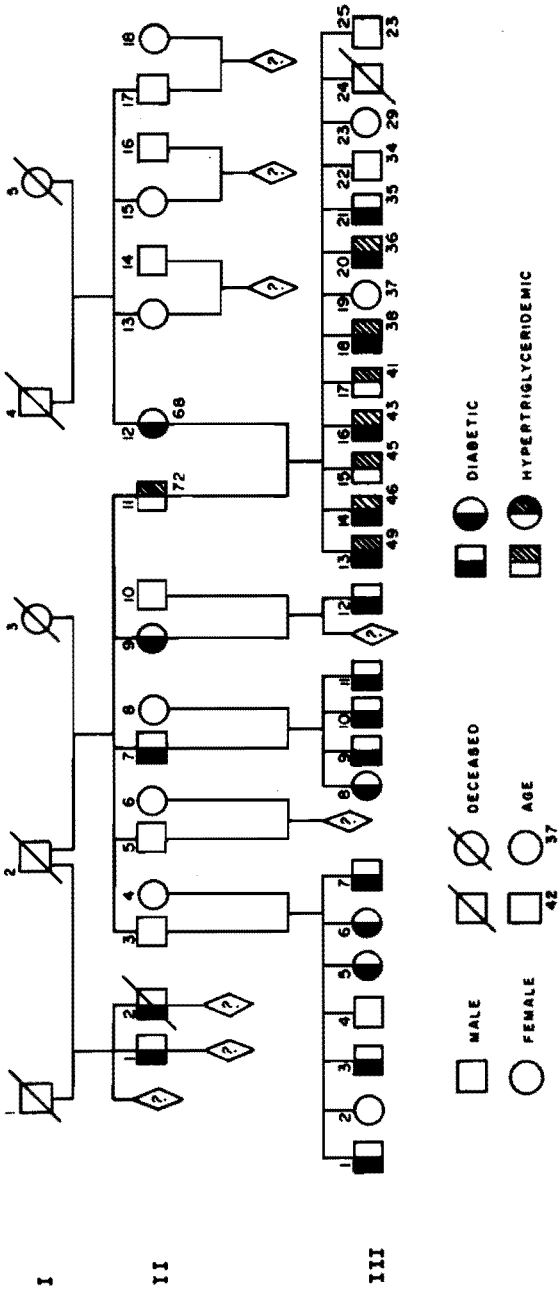

Fig. 1.– Pedigree of the O family

TABLE I
PHYSICAL PARAMETERS OF THE Q FAMILY

	Sex	Age (years)	Weight (Kg)	Height (m)	B.M.I. (Kg/m^2)	Duration of Disease (years)	Blood Pressure* (mm/Hg)	Treatment
II-11	M	72	70	1.61	27	--	155/85	--
II-12	F	68	58	1.57	23.6	15	150/80	Insulin
III-13	M	49	64	1.63	23.9	4	140/100	Diet
III-14	M	46	73	1.66	25.2	4	140/85	O.H. +, Ins. (Ocass.)
III-15	M	45	69	1.65	26.5	-	140/85	--
III-16	M	43	64	1.64	23.9	13	125/75	Insulin
III-17	M	41	66	1.63	24.9	-	160/105	--
III-18	M	38	82	1.70	28.4	11	140/78	O.H. (Ocass.) Diet
III-19	F	37	55	1.53	23.4	-	105/70	Diet
III-20	M	36	72	1.64	26.7	3	130/100	O.H. (Ocass.) Diet
III-21	M	35	82	1.70	28.3	6	120/80	--
III-22	M	34	90	1.74	29.7	-	150/100	--
III-23	F	29	47	1.54	19.8	-	-	--
III-25	M	23	89	1.76	28.8	-	140/80	--

* Sistolic/Diastolic

+ O.H. - Oral hypoglycemic agent.

TABLE II
BIOCHEMICAL PARAMETERS OF THE Q. FAMILY

	Serum glucose (mg/dl)		Serum Insulin (uU/ml)		HbAlc %	Triglycerides (mg %)	Cholesterol (mg %)	HDL-CHOL (mg %)	Total lipids (mg %)
	Oh	2h	Oh	2h					
II-11	100	125	27	360	6.6	237	211	32	768
II-12	179°	-	-	-	8.4	150	202	52	801
III-13	85°	-	37	-	6'9	334	213	35	798
III-14	144°	-	19	-	9.2	326	239	45	1012
III-15	82	117	7	34	5.6	316	177	38	658
III-16	175°	-	-	-	8.2	264	194	39	942
III-17	93	-	9	-	6.5	246	210	56	897
III-18	153°	-	66	-	6.6	188	150	34	700
III-19	64	-	11	-	6.5	90	812	57	638
III-20	111°	-	28	-	7.4	261	173	43	862
III-21	112°	-	13	-	9.3	114	204	42	588
III-22	94	105	23	121	7.9	132	168	49	688
III-23	81	77	8	30	-	-	-	-	-
III-25	72	-	21	-	6.5	76	151	38	441

° Diabetics

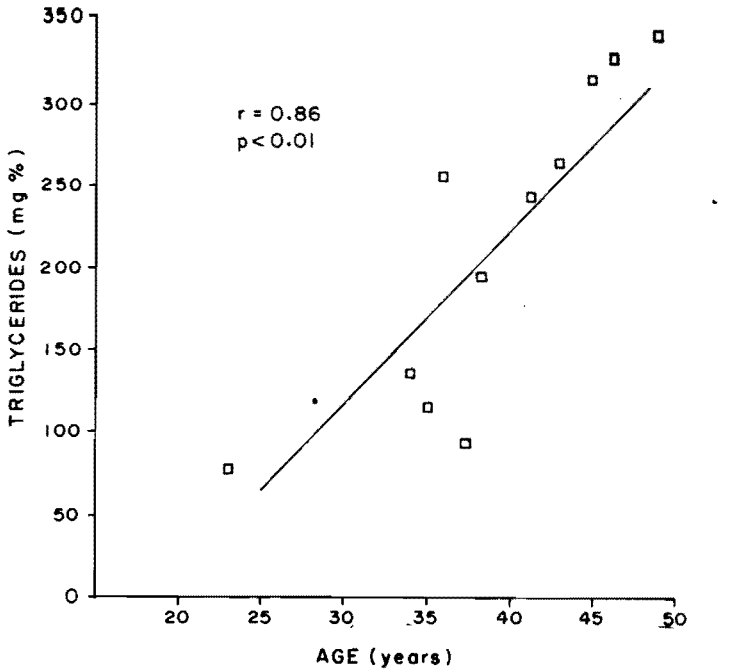

Fig. 2. - Relationship between triglyceride levels and age, in the members of the Q. family.

per limits of normal; HDL-cholesterol levels were slightly low. No correlation was found between the BMI'S and lipid levels.

DISCUSSION

We studied 12 siblings, the products of a type II diabetic mother and a non-diabetic father, whose family otherwise had a very high incidence of type II diabetes. The percentage of the siblings that developed diabetes was 50% (6/12) which led us to consider that the diabetic state in the siblings was inherited as a Mendelian dominant trait. The father, although he never had fasting hyperglycemia, and although his glycosilated hemoglobin levels were normal, consistently nonetheless had a hyperresponsive insulin pattern 2 h after an oral glucose load with slighly elevated glycemic values. He was also hypertriglyceridemic as were 7 of his 12 children (58%); hypertriglyceridemia was absent in the diabetic mother. The hypertriglyceridemia was highly correlated with age; levels reached 150 mg/dl by age 30-35.

It is possible that genetic forms of hypertriglyceridemia coexist with diabetes more frequently than would be expected by chance alone (1, 3).

However, Brunzell and colleagues (1) claim that diabetes mellitus and genetic forms of hypertriglyceridemia are independent entities. They based their conclusion on a similar prevalence of diabetes in the normolipemic (14.7%) and hyperlipemic (13%) relatives of subjects who had either diabetes in conjunction with hypertriglyceridemia or hypertriglyceridemia alone.

In our family the prevalence of diabetes among the hypertriglyceridemic subjects (5/7 = 71%) as well as the prevalence of hypertriglyceridemia in the diabetics (5/6 = 83%) was quite elevated and led us to postulate that in this particular family both hypertriglyceridemia and diabetes might be inherited as a common trait.

In our general population of diabetics we find a 55% incidence of hypertriglyceridemia; obesity is present in 58% of our diabetic subjects and likely accounts for some of the hypertriglyceridemia in such population (7). Therefore, in the absence of obesity, the prevalence of hypertriglyceridemia in the general population would likely be less than 55%.

The members of the family presented in this paper can not be considered obese, even though the BMI values of some were slightly elevated as define by the NDDG(4), a diet history did not reveal an altered diet that could explain the high lipid values. Thus, the diabetic non-obese subjects of this particular family had a substantially greater prevalence of hypertriglyceridemia compared to the prevalence of hypertriglyceridemia in our general diabetic population.

Other factors may be associated with hypertriglyceridemia such as hyperinsulinemia and abnormal apoprotein structure (2, 3, 6, 8). However in our subjects hyperinsulinemia was not a common feature among the hypertriglyceridemic and the apolipoprotein composition of a limited number of the siblings, studied by Dr. H.B. Brewer, NIDDK, NIH, USA (personal report), did not reveal any abnormality. In the absence of these factors, the persistant elevation of triglyceride may be explained by a coexisting primary hyperlipoproteinemia. Familia hypertriglyceridemia is a genetic disorder characterized by the presence of an increase concentration of VLDL in the serum of patients on normal diets(2) and the disorder is probably transmitted in an autosomal dominant fashion; the increase in serum triglycerides usually occurs in individuals older than 25 years(2). This type of familial hypertriglyceridemia seems to be present in our family.

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RESUMEN

Hipertrigliceridemia en una Familia con alta incidencia de Diabetes Tipo II. *Semprún de Fereira M., (Instituto de Investigaciones Clínicas, Facultad de Medicina, Universidad del Zulia, Apartado 1151. Maracaibo, Venezuela), Ryder E., García de Zambrano N., Campos G.* **Invest Clín** *28(4): 171-180, 1987.*– Se estudian 14 miembros de dos generaciones de una familia que presenta una alta incidencia de diabetes tipo II. Seis de doce hijos (50%), producto de un padre asintomático pero proveniente de una familia con alta incidencia de diabetes y una madre diabética (edad de comienzo =52 años) pero con historia familiar negativa para diabetes, desarrollaron diabetes entre los 24 y 45 años. La evolución de la enfermedad en los hijos, para el momento del estudio, es de 3 a 13 años. Solo uno requiere insulina para controlar la hiperglicemia; los otros se controlan con dieta y/o hipoglicemiantes orales. La hipertrigliceridemia estuvo presente en 5 de los 6 diabéticos (83%) y en varios otros miembros no diabéticos de la familia, estando altamente correlacionada con la edad ($r = 0.86$; $p < 0.01$) pero no teniendo correlación con el estado nutricional o la dieta. Se propone que en esta familia ambas alteraciones metabólicas puedan ser consecuencia de un rasgo genético común.

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