DSM-III R, DIAGNOSTIC AND STATISTICAL MANUAL, THIRD EDITION, REVISED.

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Autonomic Neuropathy in Newly Diagnosed Diabetes Mellitus

Two papers in the July 1992 issue of *Diabetes Care* (1,2) discuss neuropathy in patients with newly diagnosed diabetes. Recently, severe early-onset polyneuropathy has been reported in IDDM (3). We examined autonomic function in 50 newly diagnosed diabetic patients in four groups: 21 had IDDM (group 1), 14 had NIDDM (group 2), 10 had GDM (group 3; 9 of the patients had NIDDM on retyping after delivery), 5 newly diagnosed diabetic patients (group 4) had chronic alcoholic liver disease, another risk factor for autonomic failure (4). We evaluated heart rate responses to deep breathing, Valsalva maneuver, and standing up, and blood pressure responses to standing up and sustained handgrip (5,6). Cardiovascular reflex testing was performed within 10 days after diabetes diagnosis in groups 1, 2, and 4 and in the period starting insulin therapy in group 3.

In our study, 3 patients (14%) with IDDM, 6 (43%) with NIDDM, 4 (40%) with GDM, and all 5 diabetic patients with alcoholic liver disease (100%) had at least one abnormal parameter. Table 1 shows the results in the five tests. In the 3 IDDM patients with autonomic dysfunction, the interval between the onset of symptoms (polyuria, polydipsia, weight loss) and the diagnosis of diabetes was >4 mo, rising to 1.5 yr. Symptoms were not present in the other groups; in these subjects, diabetes was diagnosed by laboratory screening. Among GDM patients with autonomic damage, 1 had IDDM and 3 had NIDDM on retyping. In these 3 patients the duration of untreated hyperglycaemia—identified by past medical records—was 3 mo in 2 subjects and 5 mo in the third patient (mean value, 3.66 mo), whereas the mean value of this period was 1.4 mo in GDM patients with normal autonomic function. The mean duration of pregnancy was 26 wk in the 3 patients with autonomic dysfunction and 16 wk in patients without autonomic neuropathy when cardiovascular testing were performed. Among GDM patients with NIDDM on retyping, a big baby (>4500 g) was present in the history in 2 of 3 patients with autonomic failure and in 1 of 6 patients with normal reflex tests. Positive familial history—diabetes in parents—occurred in these two subgroups in 2 of 3 and in 2 of 6 patients, respectively. Even though as a result of the small number of GDM patients a statistical significance could not be proved, our data suggest that some inequality may exist between GDM patients with and without autonomic neuropathy.

Metabolic factors seem to have a dominant role in the progression of neuropathy (1,3). Similarly, long-lasting unrecognized or untreated metabolic disturbances are the most probable causes of autonomic neuropathy in newly diagnosed diabetic patients. Autonomic neuropathy may be present even in GDM—although this has not been studied, to our knowledge. To prevent it, early adequate treatment of GDM seems to be very important. Therefore, general screening of diabetes in pregnancy would be desirable—as early as possible in patients at higher risk.

Alcoholism, liver disease, and other etiological factors of autonomic neuropathy also should be taken into

Table 1—*Cardiovascular reflex test results*

		Abnormal test results (*n*)				
	N	Deep breathing test	30/15 Ratio	Valsalva ratio	Sustained handgrip test	Blood pressure response to standing
IDDM	21	2	2	0	0	0
NIDDM	14	4	2	0	2	1
Diabetes plus ALD	5	4	5	3	4	1
GDM	10	1	3	0	0	0

consideration when autonomic function is assessed in diabetes, particularly in newly diagnosed diabetic patients.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; GDM, GESTATIONAL DIABETES MELLITUS; ALD, ALCOHOLIC LIVER DISEASE.

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Marked Decrease in Serum HDL Cholesterol Levels by Combined Probucol-Pravastatin Treatment in Hypercholesterolemic NIDDM Patients

We report two cases of NIDDM patients who showed marked decrease in serum HDL-cholesterol levels by combined probucol-pravastatin treatment.

Case 1 was a 70-yr-old woman who had been diagnosed with NIDDM 15 yr previously. She had been treated with diet alone (prescribed diet was 1440 kcal/day), and she had no diabetic retinopathy or nephropathy. As shown in Table 1, probucol treatment did not change serum levels of TC, TG, or HDL cholesterol. Then, pravastatin was added. Five months after combined probucol-pravastatin treatment, TC, and TG did not change, whereas HDL cholesterol decreased markedly. This decrease in HDL cholesterol continued during combined probucol-pravastatin treatment for 9 mo. After the cessation of pravastatin administration, the HDL-cholesterol level increased.

Case 2 was a 47-yr-old woman who had been diagnosed with NIDDM 7 yr earlier; she had been treated with diet (prescribed diet was 1440 kcal/day) and tolbutamide 250 mg/day. She had diabetic retinopathy and nephropathy. As shown in Table 1, probucol or pravastatin treatment did not change serum levels of TC, TG, or HDL cholesterol. Then she was treated with combined probucol-pravastatin. Combined probucol-pravastatin treatment did not change serum TC or TG levels, whereas the HDL-cholesterol level decreased markedly.

In these two NIDDM subjects, a marked decrease in HDL cholesterol was observed 4–5 mo after the combined probucol-pravastatin treatment, but without a change in serum TC and TG levels. Physical and laboratory examinations revealed no intercurrent illness that caused the low HDL-cholesterol concentrations during follow-up. Although it is not clear why pravastatin alone did not decrease the plasma LDL-cholesterol level, ~10% of hypercholesterolemic NIDDM patients did not respond to pravastatin in our clinic. Because the analysis of serum lipid revealed no change in TC, TG, or HDL cholesterol 2 mo after combined probucol-pravastatin treatment, long-term administration of combined probucol-pravastatin may be necessary to decrease the HDL-cholesterol level. Although it has been reported that either probucol (1,2) or pravastatin (2,3) is a useful drug for treating hypercholesterolemia associated with NIDDM, careful observation is needed during combination therapy of probucol and pravastatin in hypercholesterolemic NIDDM patients.

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HDL, HIGH-DENSITY LIPOPROTEIN; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; TC, TOTAL CHOLESTEROL; TG, TRIGLYCERIDE; LDL, LOW-DENSITY LIPOPROTEIN; VLDL, VERY-LOW-DENSITY LIPOPROTEIN; CV, COEFFICIENT OF VARIATION.

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