Diabetes Mellitus and Pernicious Anemia

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SUMMARY

From 1959 to 1968, thirty-six cases of pernicious anemia (PA) were noted in 11,144 patients with diabetes mellitus (DM) at the Joslin Clinic (incidence 3.2/1,000). Of the thirty-six, only one was not insulin dependent. The female to male ratio was 7:5. Age ranged from thirty-four to eighty-one years. In twenty-eight patients with DM, a mean period of 12.6 years elapsed from time of diagnosis of diabetes mellitus to development of PA. In eight, PA preceded DM by a mean period of 6.6 years. Vitamin B12 deficiency neuropathy was present in nine patients and in only six of these was there clinically recognizable anemia. Hypothyroidism was present in two patients.

Histochemical and immune abnormalities common to both disorders are reviewed and possible causes for association are discussed. DIABETES *19*:719-23, October, 1970.

The association of diabetes mellitus and pernicious anemia is well known, having been first observed by Parkinson.[1] Root[2] in 1931 reported nine cases from the Joslin Clinic, in addition to forty-eight cases discovered from unpublished records and a survey of the literature. Patients with diabetes mellitus appear to have a greater tendency to develop pernicious anemia than individuals in the general population, in which the frequency of pernicious anemia is estimated to be approximately 1.3 per 1,000.[3-7] The reported frequency of manifest anemia is variable ranging from 2.0 per 1,000 to 30 per 1,000 (table 1). The prevalence of latent pernicious anemia, as diagnosed by antibody studies, is 4 per 100 in insulin-dependent compared to nil in noninsulin-dependent diabetics.[16] The cause for the association is not clear.

It is our purpose to report the frequency of the association of these two disorders in North American population as diagnosed by readily available present methods.

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MATERIAL AND METHODS

During the ten-year period from January 1959 to December 1968, thirty-six cases of pernicious anemia were noted in 11,144 diabetic patients hospitalized on the Joslin Clinic service of the New England Deaconess Hospital. In all, fifty cases diagnosed as having both diabetes mellitus and pernicious anemia were reviewed but fourteen were excluded for lack of complete studies and response to vitamin B12, leaving thirty-six which satisfied the criteria for diagnosis of pernicious anemia.[17] Eleven of the thirty-six had been diagnosed elsewhere; several of these were reinvestigated. The follow-up ranged from one month to 183 months (average forty-one months). Seven were lost to follow-up, but the anemia was in remission at the last visit.

RESULTS

Frequency: In the present observations the prevalence of pernicious anemia diagnosed in patients with diabetes was 3.2 per 1,000.

Age and sex: There were twenty-one females and fifteen males. The youngest patient was thirty-four and the oldest, eighty-one years of age.

Race: Of the thirty-six cases, twenty-two were of North European, six of Jewish, one of Negro, one of Italian, and six of Eastern European extraction.

Family predisposition: Only one (Patient 31) had a

TABLE 1

Frequency of pernicious anemia in diabetic patients

Author (Reference)	Diabetes	Pernicious anemia	Incidence per 1,000
Goudsmit[8]	1,650	5	3.3
Murphy and Moxon[9]	827	3	3.6
Watson[10]	949	10	10.5
Beckert[11]	900	9	10.0
Hagen[12]	1,000	2	2.0
Gassman and Shneeweiss[13]	4,104	15	3.7
Dotevall[14]	1,218	12	9.8
Panzram[15]	7,129	16	2.2
Arapakis et al.[6]	100	3	30.0
Total	17,877	75	4.2

brother with pernicious anemia. The family history was positive for diabetes mellitus in twenty-five, negative in eleven. In eight patients in whom the diagnosis of pernicious anemia preceded that of diabetes, five had a family history of diabetes mellitus and none of pernicious anemia.

In twenty-eight cases, the diagnosis of diabetes mellitus preceded that of pernicious anemia by one to thirty-eight years, whereas in eight patients, pernicious anemia was noted one and one-half to eight years earlier than diabetes mellitus. In the former group all were insulin dependent except one, whereas in the latter all eight required insulin when they developed diabetes mellitus.

Hematological findings (table 2): In twenty-one patients the bone marrow was examined and found megaloblastic in all except Patients 3 and 20 who had received previous vitamin B12 therapy. In Patient 3, B12 treatment had originally been given for diabetic neuropathy. Schilling's test was diagnostic in all except in Patients 13, 14, 15 in which the results suggested a malabsorption component. All three, however, had histamine-fast achlorhydria and responded to B12 treatment. Patient 32 left the hospital before Part II of Schilling's test could be performed. Achlorhydria was noted in all patients. Lactic dehydrogenase was elevated only in four of eleven studied. Four had normal lactic dehydrogenase values even in the presence of megalo-

TABLE 2

Hematologic findings

Case no.	Hb. G.%	MCV	MCH	MCHC%*	WBC/ mm³	Platelet mm³ × 1,000	Retic. %	Peripheral smear	Megaloblastic bone marrow	Free acid‡	Lactic dehydrogenase (N=60-140μ)	Schilling test part I	Schilling test part %	Schilling test part II
1	6.3	92	40	36	4,100	150	1.0	†MH;HSN	+	AB	570		—	
2	9.3	120	37	31	N	N	0.5	MH	+	AB	120		—	
3	10.2	108	31	28	N	N	1.8	MH	Normoblastic	AB	105	5.0		10.5
4	9.6	125	43	34	N	N	0.8	MH	—	AB	116	0.8		12.2
5	8.3	119	39	33	N	N	0.5	MH	+	AB	—		—	
6	9.0	167	57	31	N	N	6.0	MH;HSN	+	AB	—	0.9		12.0
7	6.5	—	—	—	3,900	121	1.7	MH;HSN	+	AB	362	1.0		16.0
8	8.7	—	—	—	N	N	0.2	MH	+	AB	—		—	
9	4.4	—	—	—	4,100	132	0.6	MH;HSN	—	AB	—		—	
10	11.0	—	—	—	N	N	1.2	MH	+	AB	—		—	
11	11.2	114	34	30	N	N	—	MH;HSN	—	AB	—		—	
12	9.5	—	—	—	N	N	1.8	MH	—	AB	—	2.6		13.0
13	9.1	114	36	32	N	N	1.0	MH;HSN	+	AB	—	0.4		1.4
14	5.4	133	46	34	4,400	—	3.4	MH;HSN	+	AB	1,404	0.029		3.7
15	10.6	103	31	30	N	N	1.1	MH	+	AB	107	0.7		5.5
16	7.8	113	35	31	2,200	116	2.9	MH	+	AB	319		—	
17	11.2	112	35	32	3,100	140	1.2	MH;HSN	+	AB	101	2.1		21.9
18	11.9	141	43	30	N	N	2.7	MH	—	AB	—		—	
19	13.0	—	—	—	N	—	1.0	MH	—	AB	—		—	
20	13.7	—	—	—	N	N	1.2	Normal	Normal	AB	—	Positive by hx.		
21	12.2	100	32	32	N	N	0.5	MH	—	AB	78	1.35		12.0
22	12.3	—	—	—	N	N	0.8	Normal	—	AB	—		—	
23	16.9	95	34	32	N	N	—	Normal	—	AB	—		—	
24	12.4	189	46	25	N	N	0.7	MH	+	AB	—		—	
25	6.4	92	27	29	N	N	—	MH	+	AB	122	1.9		25.0
26	15.5	111	34	31	N	N	0.6	Normal	—	AB	—		—	
27	14.8	96	31	33	N	N	—	—	—	AB	—		—	
28	13.8	—	—	—	N	N	—	—	—	AB	—		—	
29	16.4	—	—	—	N	N	—	—	—	AB	—	2.0		19.5
30	9.9	—	—	—	N	N	2.0	MH	—	AB	—		—	
31	7.3	95	30	31	N	N	1.4	MH	+	AB	—		—	
32	9.8	133	42	31	2,850	146	2.2	MH;HSN	+	AB	—		—	
33	9.3	126	40	31	N	N	2.3	MH;HSN	+	AB	—	0.44		§
34	8.0	122	42	32	3,600	N	1.0	MH	+	AB	—		—	
35	12.4	—	—	—	N	N	—	MH	—	AB	—		—	
36	12.6	—	—	—	N	—	—	Normal	+	AB	—		—	

*MCV-Mean corpuscular volume; MCH-Mean corpuscular hemoglobin; MCHC-Mean corpuscular hemoglobin concentration.

†MH-Macrocytic hyperchromia; HSN-Hypersegmented neutrophils.

‡Free acid in stomach by Diagnex Blue and/or histamine stimulation; AB-Absent; N-Normal.

§Not done.

blastic bone marrow.

Neurological manifestations: Characteristic vitamin B12 deficiency neuropathy[18] as differentiated from diabetic neuropathy[19] was present in nine patients (table 2). In only six of these patients was there clinically recognizable anemia.

Associated hematological and endocrine diseases (table 3): Iron deficiency anemia was present only in two patients as shown by serum iron values of 49 and 57 mcg. per cent respectively. Hypothyroidism was present in two and hyperthyroidism in one.

DISCUSSION

Whether autoantibodies cause or are the result of disease processes is controversial. The presence of antibodies to gastric intrinsic factor and parietal cell in diabetes as well as in pernicious anemia is suggestive of similarity in their etiology.[20,21] The high prevalence of organ specific antibodies in pernicious anemia, idiopathic Addison's disease, thyroid disease and the frequent association of these disorders with diabetes mellitus suggests that autoimmunity may have a relevant part in a common pathogenesis of these conditions.[22-29]

TABLE 3

Diabetes and associated diseases

Case no.	Age	Sex	Duration* in years DM	PA	Insulin Rx	Assoc.† disease	SCAD‡
1	34	F	8	—	+	—	—
2	61	M	15	—	+	—	—
3	72	F	17	—	+	—	—
4	68	F	10	—	+	—	—
5	56	M	7	—	+	—	—
6	65	F	4	—	+	—	+
7	58	M	11	—	+	—	—
8	63	M	25	—	+	—	—
9	61	F	3	—	+	—	+
10	76	F	3	—	+	—	—
11	69	F	11	—	+	—	—
12	60	M	31	—	+	—	—
13	75	F	23	—	+	sickle cell trait	+
14	67	F	9	—	+	—	—
15	57	M	13	—	+	—	—
16	58	F	38	—	+	—	—
17	64	F	15	—	+	iron def. anemia	+
18	76	M	14	—	+	iron def. anemia	+
19	46	F	2	—	+	—	—
20	57	F	14	—	+	—	—
21	66	M	4	—	+	—	—
22	56	F	—	1	+	—	—
23	56	M	—	9	+	—	—
24	58	M	—	8	+	—	—
25	81	M	—	½	+	—	—
26	74	F	—	8	+	—	—
27	60	F	—	1½	+	—	+
28	44	M	—	7	+	hypo-thyroidism	+
29	71	M	—	2	+	hyper-thyroidism	+
30	70	F	10	—	+	—	+
31	67	M	18	—	+	—	—
32	73	F	11	—	+	—	—
33	68	M	12	—	+	—	—
34	73	F	11	—	+	—	—
35	79	F	1	—	OHA§	—	—
36	48	F	5	—	+	hypo-thyroidism	—

*Duration in years of diabetes mellitus (DM) before pernicious anemia (PA) and PA before DM.
†Associated disease—Endocrine and hematological disorders.
‡SCAD—Subacute combined degeneration of cord.
§OHA—Oral hypoglycemic agent.

Antibodies to gastric mucosa were detected in 22 per cent of diabetic patients by Moore and Neilson.[20] Wawrzyniak[21] noted antibodies to gastric mucosa in 44 per cent of diabetics and 71 per cent of patients with pernicious anemia. The prevalence of antibodies to gastric intrinsic factor and parietal cell in insulin-dependent diabetics has been observed to be 4 per cent and 28 per cent respectively, whereas in noninsulin-dependent diabetics 0 per cent and 14 per cent and in controls 1 per cent and 11 per cent have been noted.[16]

Faber[30] offered a hypothesis—neither proved nor disproved—that gastritis is a progressive disease eventually developing into a final state accompanied by pernicious anemia. Fixa et al.[31] found chronic gastritis in 65 per cent of diabetics compared to 46.3 per cent in controls. Gastritis occurred most frequently in older diabetics. Low serum pepsinogen values characteristic of atrophic gastritis and gastric atrophy were nearly three times as common in diabetics as in healthy controls.[6] The insulin-dependent patients are at greater risk of developing gastric atrophy than patients who do not need insulin.[6] Indeed this was true in our series with thirty-five of thirty-six patients being insulin dependent.

Opinions stated in the literature differ concerning gastric acid secretion in diabetes mellitus. Dotevall[32] found achlorhydria under basal conditions and after maximal histamine stimulation in 17 per cent of diabetic patients. The incidence of achlorhydria and hyposecretion was high in cases with late complications. Prolonged intravenous infusion of 10 per cent glucose solution has been shown to produce decreased gastric acid concentration.[33] In contrast, normal acid secretory responses were found in diabetes by Marks et al.[34] Aylett[35] found no statistically significant difference in output of acid between diabetic and normal subjects. From these observations achlorhydria itself can hardly explain the association of pernicious anemia and diabetes mellitus. Gastric analysis was, however, helpful diagnostically in our series; achlorhydria was noted in all patients.

Immunological data to date suggest the existence of an association between pernicious anemia and thyroid disease.[22-25] Moore and Neilson[20] and Simkins[26] demonstrated antithyroid anitbodies to be more common in diabetics than in controls. Current opinion would ascribe this to focal thyroiditis. The presence of thyroid microsomal antibodies has been shown to be associated in elderly patients with focal thyroiditis.[33] Probably this lesion does not progress to clinical hypothyroidism in elderly patients. In younger persons, however, the presence of antibodies may perpetuate the inflammatory lesion to cause clinical hypothyroidism. This may explain the association of hypothyroidism in two of our patients. Association of hypothyroidism with diabetes mellitus has also been noted by Moore and Neilson.[20] The coexistence of hypothyroidism and nontuberculous adrenal insufficiency (Schmidt's syndrome) with diabetes mellitus has been noted in extensive reviews.[28-29] One might speculate that diabetes with Schmidt's syndrome represents a part of the spectrum of multiple endocrinopathies or fits into the currently popular autoimmune galaxy of diseases.

The occurrence of subacute combined degeneration without anemia needs emphasis. Relationship between anemia and neuropathy is not clear. Degeneration of the spinal cord is believed to be due to anemia, but only 10 per cent of patients suffer from both.[18] The frequency of neuropathy in the absence of anemia is not known. In the present series three of the nine patients had neurological manifestation with normal hematological findings. Differentiation from diabetic neuropathy at times may be difficult. Determination of serum vitamin B12 levels when available, Schilling's test and/or methyl malonic acid (M.M.A.) of greater than 40 mg./24 hr. urine, after 10 gm. valine load establishes the definite diagnosis of vitamin B12 deficiency neuropathy. An interesting observation is that the highest excretion of M.M.A. is found in some patients with subacute combined degeneration with slight anemia[36] and in a patient with cerebral involvement.[37]

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