

RECURRENT MACULAR EDEMA AND STROKE SYNDROME IN TYPE 1 DIABETES MELLITUS WITH POTENT ENDOTHELIAL CELL INHIBITORY AUTOANTIBODIES

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ABSTRACT

Objective: To describe a case of type 1 diabetes mellitus with recurrent macular edema and stroke in association with potent endothelial cell inhibitory autoantibodies.

Methods: The clinical, radiologic, and biochemical data from the study patient are presented, as is the bioactivity in endothelial cells from the immunoglobulin G fraction of the patient's serum.

Results: A 52-year-old man with a 15-year history of poorly controlled type 1 diabetes mellitus had diabetic autonomic neuropathy, gastroparesis, depression, macular edema, proliferative retinopathy, diabetic nephropathy, refractory hypertension, and transient ischemic attacks that progressed to recurrent strokes despite aspirin therapy. Magnetic resonance imaging of the brain showed multifocal, bilateral ischemic infarcts consistent with recurrent stroke affecting small vessels. The patient's serum contained endothelial cell inhibitory autoantibodies; the titer doubled during a 2-year period when the patient required repeated focal laser to treat macular edema and experienced transient ischemic attacks. The IgG autoantibodies induced stress fiber formation and apoptosis in endothelial cells and inhibited neurite outgrowth in rat pheochromocytoma PC12 cells.

Conclusions: Low concentrations of purified autoantibodies (1–2 $\mu\text{g/mL}$) induce endothelial cell contraction in vitro, suggesting a role for autoantibodies in modulating endothelial cell permeability, which may affect multiple target organs. Potent IgG autoantibodies may be a useful marker (with a possible pathophysiologic role) in an unusual syndrome characterized by poorly controlled diabetes, hypertension, dementia, and recurrent small-vessel stroke. (**Endocr Pract.** 2010;16:842–850)

Abbreviation:

LDL = low-density lipoprotein

INTRODUCTION

Microvascular disease is a hallmark of long-standing type 1 and type 2 diabetes mellitus. Recent evidence suggests that retinal vascular changes are a marker for an increased risk of dementia or cognitive dysfunction in older persons with or without hypertension, respectively (1). Hypertension, but not diabetes per se, is also strongly associated with a subtype of small-vessel stroke (2), which itself is associated with the risk for dementia (1). Although the precise etiology of small- or medium-vessel stroke is unclear, autoimmune disease can cause small-, medium-, or large-vessel vasculitis (3), raising the possibility of several different (possibly interrelated) underlying mechanisms in individual patients with type 1 diabetes mellitus.

CASE PRESENTATION

A 52-year-old white man presented to the veterans affairs outpatient medical clinic in 2002 with a 15-year history of type 1 diabetes. His last episode of diabetic ketoacidosis had occurred in 1998. He was being treated with a split, mixed regimen of neutral protamine Hagedorn and regular insulin twice daily. Medications included an angiotensin-converting enzyme inhibitor and a statin. Medical history was notable for malignant hypertension,

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hyperlipidemia, diabetic retinopathy, gastroparesis, painful polyneuropathy, diabetic diarrhea, posttraumatic stress disorder, anxiety disorder, and depression. There was no history of coronary artery disease. Family history was notable for diabetes mellitus in his mother. He quit smoking cigarettes in 1993 and reported no alcohol or drug use. The patient was a retired toolmaker who was unemployed because of medical and psychological issues. Physical examination showed a thin, anxious man with rapid, pressured speech; blood pressure of 169/82 mm Hg; and decreased sensation to light touch in the bilateral lower extremities in a symmetric stocking-glove distribution.

Laboratory Studies

The initial laboratory studies were remarkable for the following values: hemoglobin A_{1c}, 9.9%; serum creatinine, 1.1 mg/dL (Table 1); dipstick-positive proteinuria with microscopic hematuria; total cholesterol, 260 mg/dL; low-density lipoprotein (LDL) cholesterol, 142 mg/dL; high-density lipoprotein cholesterol, 39 mg/dL; serum triglycerides, 393 mg/dL; normal serum potassium concentration; and normal anion gap.

Initial Treatment

The patient's insulin regimen was adjusted to decrease his risk for unrecognized, severe hypoglycemia. Several different antihypertensive medications were prescribed; however, the patient's hypertension was poorly responsive to treatment with a combination of antihypertensive medications. He was intolerant to dihydropyridine calcium channel blockers, which he associated with profound muscle weakness, and thiazide diuretics, which he associated with flank pain. He experienced gastrointestinal intolerance to moderate dosages of statin drugs and was nonadherent to the long-term use of statins.

Follow-Up

Over a 7-year follow-up period, the patient's blood pressure ranged from 140/85 to 205/100 mm Hg, and his LDL-cholesterol concentration ranged from 100 to 205 mg/dL. He experienced an approximate doubling in his serum creatinine concentration (Table 1). He required multiple focal and panretinal laser photocoagulation treatments to both eyes for recurrent macular edema and proliferative retinopathy (Fig. 1A, 1B). He lost 7 lines of letters on the Snellen 20/20 visual acuity chart (right eye, Fig. 1B). During years 2 to 4 of follow-up, the patient experienced several transient ischemic attacks despite aspirin therapy (Table 1). A workup, which included magnetic resonance imaging, electroencephalography, and carotid artery ultrasonography, was negative for stroke, epileptogenic focus, or carotid artery stenosis. Echocardiography revealed left ventricular hypertrophy, 1+ tricuspid and mitral valve regurgitation, and aortic sclerosis. Serology studies were negative for the presence of IgG, IgM anticardiolipin, or antineutrophil cytoplasmic antibodies. Antithrombin III activity was within the reference range.

The titer of circulating endothelial cell inhibitory autoantibodies increased between follow-up years 2 and 4 (Fig. 1C) despite improvement in glycemic control during the same period (Table 1). In year 5, the patient relocated to another state. During a brief return visit to New Jersey, he presented with the new onset of permanent right-sided weakness and numbness affecting the face and arm and new gait disturbance. He was admitted to the New Jersey Veterans Affairs Hospital. Magnetic resonance imaging revealed new multiple lacunar infarcts in the right basal ganglia and frontal lobe, as well as a resolving ischemic infarct in the posterior limb of the left internal capsule (Fig. 2). Dipyridamole was added to aspirin therapy. Two years later, the patient presented with confusion, short-term

Table 1
Indices of Glycemia, Renal Function, and Neurologic Events During 7 Years of Follow-Up or Observation in a 52-Year-Old White Male Patient

Parameter	Follow-up year						
	1	2	3	4	5	6	7
Hemoglobin A _{1c} , % ^c	9.9	8.4	8.3	9.4	11.5	8.7	9.1
Serum creatinine, mg/dL	1.1	1.3	1.4	1.4 (2.7) ^a	1.6 (2.5) ^a	1.8 (2.6) ^a	1.9
Neurologic events, No. and type	0	TIA	TIA ^b	TIA	2 CVA	2 CVA	0

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack.

^a Number in parentheses indicates the albumin to creatinine ratio.

^b Workup including magnetic resonance imaging, electroencephalography, and carotid ultrasonography.

^c Hemoglobin A_{1c} and serum creatinine values represent the mean of at least 3 determinations in each follow-up year.

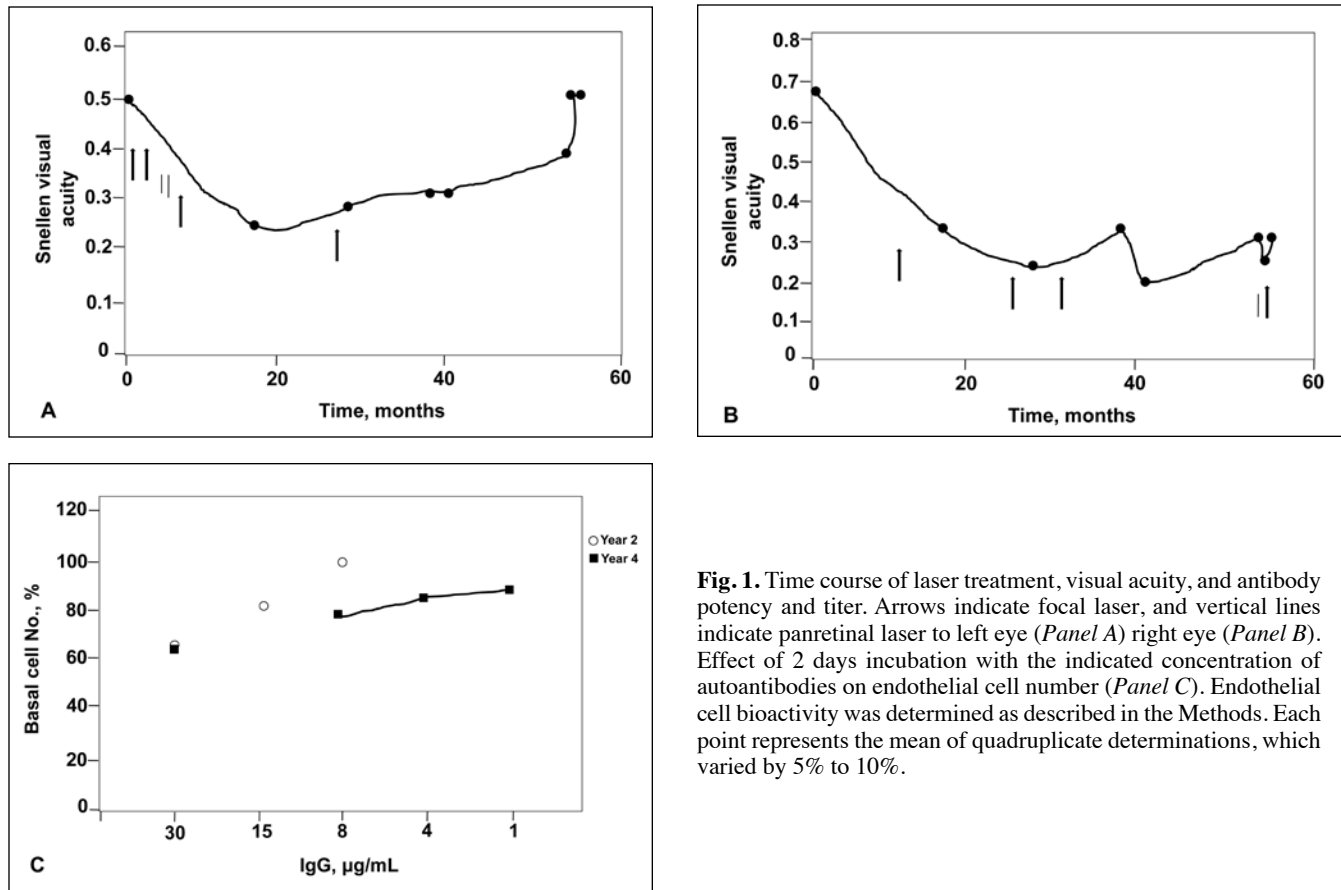


Fig. 1. Time course of laser treatment, visual acuity, and antibody potency and titer. Arrows indicate focal laser, and vertical lines indicate panretinal laser to left eye (*Panel A*) right eye (*Panel B*). Effect of 2 days incubation with the indicated concentration of autoantibodies on endothelial cell number (*Panel C*). Endothelial cell bioactivity was determined as described in the Methods. Each point represents the mean of quadruplicate determinations, which varied by 5% to 10%.

memory impairment, agnosia, and word finding difficulty. Repeated magnetic resonance imaging revealed new subacute or acute infarcts in the right cerebellum, left caudate nucleus, and right subcortical region and moderate-to-severe generalized cerebral atrophy. Computed tomography of the brain showed chronic small-vessel ischemic changes in the periventricular white matter.

METHODS

Plasma Samples

Informed consent for participation in the institutional review board–approved study was obtained before blood drawing to test for endothelial cell inhibitory autoantibodies. Blood drawing was performed in the morning, generally after an overnight fast. EDTA plasma was kept frozen (-70°C) for up to 4 years before assaying of protein-A-eluate fractions for bioactivity in endothelial cells. Bioactivity in protein-A eluate fractions from plasma or serum was previously shown to be stable for 5 years or longer at -20°C (4). Endothelial cell inhibitory activity in the protein-A eluate fractions from plasma is stable after storage at 0°C to 4°C for 6 months or longer.

Cell Culture and Growth Assays

Bovine pulmonary artery endothelial cells (Clonetics, Inc, San Diego, California) were maintained at 37°C in 5% $\text{CO}_2/95\%$ air in endothelial cell growth medium (EGM, Clonetics, Inc, San Diego, California) plus 10% fetal calf serum. Bovine pulmonary artery cells were passaged continuously and used between passages 4 and 10.

Colorimetric Estimation of Cell Number

Endothelial cell number assays were performed as previously reported (4). Confluent cells were trypsinized and plated at 1 to 10×10^3 cells/well in Medium 199 plus 10% fetal calf serum in 96-well plates. After 1 or 2 days of incubation for cells to reach 60% to 80% confluency, test fractions (1:50 or higher dilutions of protein A eluates of plasma) were added to wells in quadruplicate. After 2 days of incubation in the presence of test fractions, cells were washed with PBS and processed for the colorimetric estimation of cell number, ie, cell-associated acid phosphatase activity, as previously described (4). There was a linear relationship between endothelial cell number and optical density at 410 nm as previously described (4). Growth-promoting activity is expressed as a percentage of

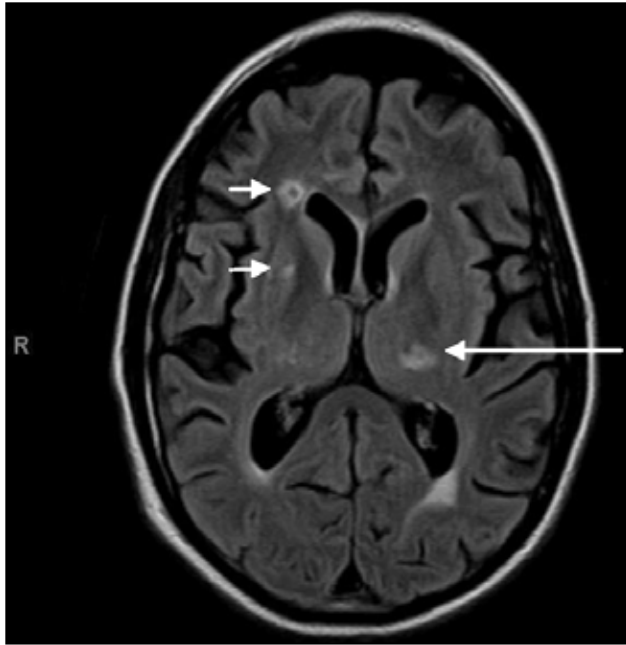


Fig. 2. Magnetic resonance imaging of the brain showing lacunar infarcts in the right basal ganglia and right frontal lobe (*small arrows*), as well as a resolving ischemic infarct in the posterior limb of the left internal capsule (*large arrow*).

the control cell number for cells grown in the absence of test protein-A eluate fractions. Significant inhibitory activity ($\leq 90\%$) is defined as that occurring outside the normal range for control unexposed cells. Each point represents the mean of quadruplicate determinations. The average intra-assay and interassay coefficients of variation were 6% and 11% at 1:50 dilution of protein-A-eluted fractions from plasma ($n = 4$ assays).

Protein-A Affinity Chromatography

Protein A chromatography was performed as previously described (4). Four-tenths mL aliquots of plasma were adjusted to pH 8.0 by adding 0.8 mL 100 mmol/L Tris (pH 8). After syringe filtration to clarify samples, 1 mL was applied to a 1-mL column of packed protein-A beads (Pierce Chemical Co, Rockford, Illinois) equilibrated in 100 mmol/L Tris, pH 8.0. The column was washed and eluted as previously described (4). The eluate fractions containing nearly all the recovered protein were pH neutralized and stored at 0°C to 4°C. Inhibitory activity in protein-A eluate fractions was unchanged, appearing in the retentate fraction after dialysis (10 mmol/L phosphate, pH 7.4) and ultrafiltration on a 10-kDa cutoff membrane (Centricon-10; Millipore Corp, Bedford, Massachusetts). All fractions were sterile filtered (Millipore Corp, Bedford, Massachusetts; 0.2 μm) before assay for growth-promoting activity.

Liposorber Chromatography

An aliquot of plasma or serum (0.1-0.15 mL) was adjusted to 1 mL with 10 mM Tris, 0.15M NaCl, and then applied to 1 mL of dextran sulfate cellulose (DSC, Liposorber) equilibrated in saline, 10 mM Tris, 0.15 M NaCl (pH 7.4). The column was washed with 10 mL saline, 10 mM Tris (pH 7.4), and then eluted stepwise with 5 \times 1-mL aliquots of 10-mM Tris-HCL, 1M NaCl (pH 7.4). The flow-through and the second 1 mL eluate fraction—the latter contained nearly all the recovered bound protein—were assayed for protein concentration and sterile filtered (Millipore Corp, Bedford, Massachusetts; 0.2 μm) before assay for growth-promoting activity. Following Liposorber chromatography, 0.5 mL of the liposorber eluate fraction was adjusted to 1 mL with 100 mmol/L Tris (pH 8.0) and applied to a 1-mL column of packed protein-A beads (Pierce Chemical Co, Rockford, Illinois) equilibrated in 100 mmol/L Tris (pH 8.0). The column was washed and eluted using methods similar to those described above.

PC12 Cells/Neurite Outgrowth

Undifferentiated rat PC12 cells obtained from ATCC (Manassa, Virginia) were grown in DMEM containing 10% horse serum and 5% fetal calf serum. Cells were plated at low density in 35-mm dishes. Medium was changed to DMEM with 1% horse serum and 0.5% fetal calf serum after allowing 24 hours for cell attachment. Next, recombinant human bFGF (10 ng/mL) in the presence or absence of human IgG test fractions or the Rho kinase inhibitor Y27632 were added to dishes in duplicate or triplicate. Groups of 50 to 100 cells per dish were counted at baseline and regular intervals for up to 8 days after the addition of test factors. Neurite outgrowth represents the percentage of PC12 cells expressing more than 1 neurite. A neurite is defined as a cell process that is at least 2 cell diameters in length. Results (mean \pm standard deviation) are expressed as percentage of PC12 cells expressing neurites compared with percentage of neurite expression in cells grown with 10 ng/mL human bFGF.

Protein Determinations

Protein concentrations were determined by a bicinchoninic acid protein assay kit (Pierce Chemical Co, Rockford, Illinois).

Statistics

All data are presented as mean \pm 1 standard deviation as indicated. Comparisons were made by paired and unpaired Student *t* tests.

EFFECTS OF AUTOANTIBODIES IN ENDOTHELIAL AND PC12 CELLS

Thirty $\mu\text{g/mL}$ concentrations of the protein A eluate fraction from plasma caused a dose-dependent decrease in

endothelial cell survival (up to 40%) after 48 hours (Fig. 1C). Within 10 to 30 minutes after exposure to plasma IgG, endothelial cells contracted (Fig. 3A, 3B) and stress fibers formed (Fig. 3C, 3D). These changes were associated with large, dose-dependent increases in intracellular calcium concentration (not shown). The ensuing cell death morphologically resembled “anoikis,” a process of

detachment-associated apoptosis (Fig. 3E). Cell death was not prevented by coincubating autoantibodies with 200 pg/mL concentrations of recombinant human bFGF, a potent endothelial cell survival factor (Fig. 3F).

In our previous report, autoantibodies from adults with advanced type 2 diabetes and macular edema induced stress fiber formation and contraction in endothelial cells

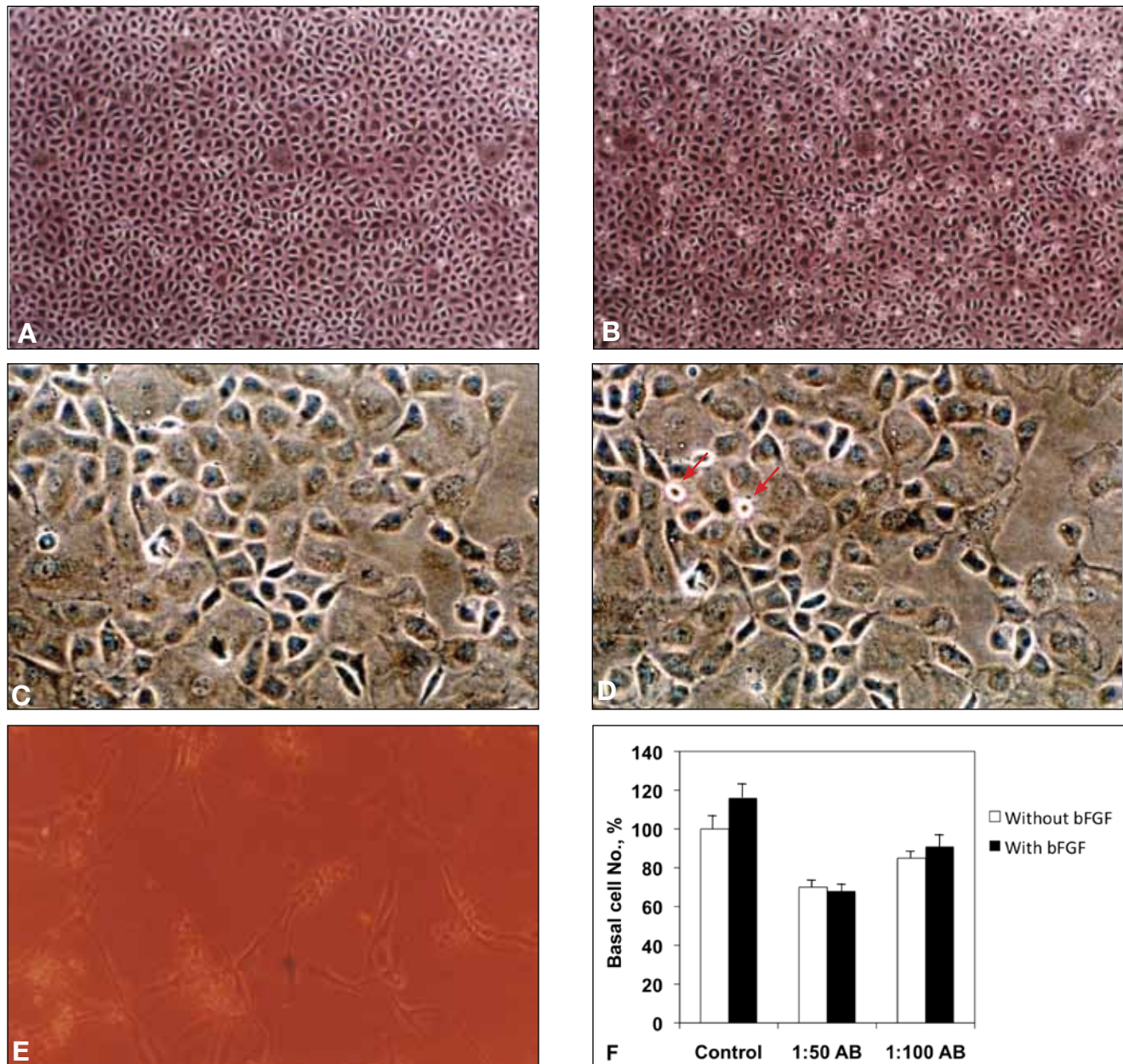


Fig. 3. Effect of patient antibodies on endothelial cells. *Panel A*, Control untreated cells shown at $\times 100$ magnification. *Panel B*, Cells contracted in response to a $2 \mu\text{g/mL}$ concentration of the autoantibodies. *Panel C*, Control endothelial cells at higher power, $\times 200$ magnification. *Panel D*, Cells contracted in response to $30 \mu\text{g/mL}$ concentrations of the antibodies and displayed stress fibers (arrows) associated with highly refractile, rounded cells. *Panel E*, After 48 hours incubation, cells incubated with $30 \mu\text{g/mL}$ antibodies detached or acquired a highly elongated appearance. Unstained cell images were obtained using a Nikon TMS, $\times 10$ lens (0.25), phase contrast microscope. *Panel F*, Coincubation with 200 pg/mL concentrations of recombinant human bFGF did not prevent endothelial cell apoptosis induced by 15 to $30 \mu\text{g/mL}$ concentrations ($1:100$ or $1:50$ dilution) of the antibodies. Error bars represent standard deviation of quadruplicate determinations.

via activation of the Rho A/Rho kinase signaling pathway (5). In the present study, coincubation of endothelial cells with (10 μ M) Y27632, a specific Rho kinase inhibitor, prevented stress fiber formation by the type 1 diabetes autoantibodies ($n = 2$, data not shown). Activation of the Rho kinase signaling pathway in neurons was reported to inhibit neurite extension (6). Because the study patient had a wide range of neurologic disease manifestations, we next tested the autoantibodies for effects in differentiated rat pheochromocytoma (PC12) cells that exhibit long branching neurites in the presence of 10 ng/mL bFGF.

The type 1 diabetic plasma autoantibodies caused a dose-dependent, substantial inhibition of neurite extension in differentiated PC12 cells (Fig. 4A, 4B). Inhibition of PC12 neurite outgrowth induced by the autoantibodies was completely prevented by coincubating with 1 μ M concentrations of the Rho kinase inhibitor Y27632 (Fig. 4B). In preliminary experiments, 30 μ g/mL concentrations of the autoantibodies decreased PC12 cell survival by 30% in the presence of 10 ng/mL bFGF (data not shown). Protein A eluate fractions from 5 age-matched, nondiabetic control subjects had no significant effect on bFGF-induced, PC-12 neurite extension or on endothelial cell number (data not shown).

LDL-cholesterol concentration is a known risk factor for nonhemorrhagic stroke (7). In patients with familial hypercholesterolemia or with moderate to severe hypercholesterolemia and intolerance to statin medications, LDL apheresis substantially lowers LDL-cholesterol concentrations. One such method uses dextran sulfate cellulose (DSC, Liposorber) to bind and remove apolipoprotein B from the circulation (8). Since other circulating positively charged substances (including immunoglobulins) may also be removed from plasma (9), we tested whether endothelial

cell inhibitory autoantibodies in lipemic samples of the patient's plasma bind to Liposorber (DSC) *in vitro*. The Liposorber eluate fraction displayed moderate endothelial cell inhibitory activity (78%), and there was no inhibitory activity in the Liposorber flow-through fraction (Fig. 5A). After the Liposorber eluate was applied to a protein A column, nearly all of the inhibitory activity was recovered in the protein A eluate fraction (Fig. 5A). Activity in the protein A eluate fraction was substantially more inhibitory (50%) than activity in the starting Liposorber eluate fraction (78%; $P = .002$, Fig. 5A). It caused dose-dependent inhibition of endothelial cell survival, approximately 1 μ g/mL decreased endothelial cell number by 33% (Fig. 5B), and had an apparent molecular weight greater than 30 kD, consistent with the possibility that it is IgG-like.

DISCUSSION

Antiendothelial cell antibodies occur in a substantial proportion of patients with systemic autoimmune diseases such as systemic lupus erythematosus or vasculitis (3). They have also been reported in type 1 diabetes in association with proliferative retinopathy (10). Although an *in vivo* pathogenic role for endothelial cell autoantibodies has not been firmly established, autoantibodies from patients with lupus or vasculitis can have profound effects on endothelial cell survival and/or migration *in vitro* (11,12). Evidence that antiendothelial cell antibodies in lupus may be pathogenic derives from their association with renal disease activity (11) and a report that infusion in rodents of monoclonal antibodies directed against HSPG purified from glomerular basement membranes causes acute proteinuria (13). We reported the baseline occurrence of endothelial cell inhibitory autoantibodies in 30% of 162

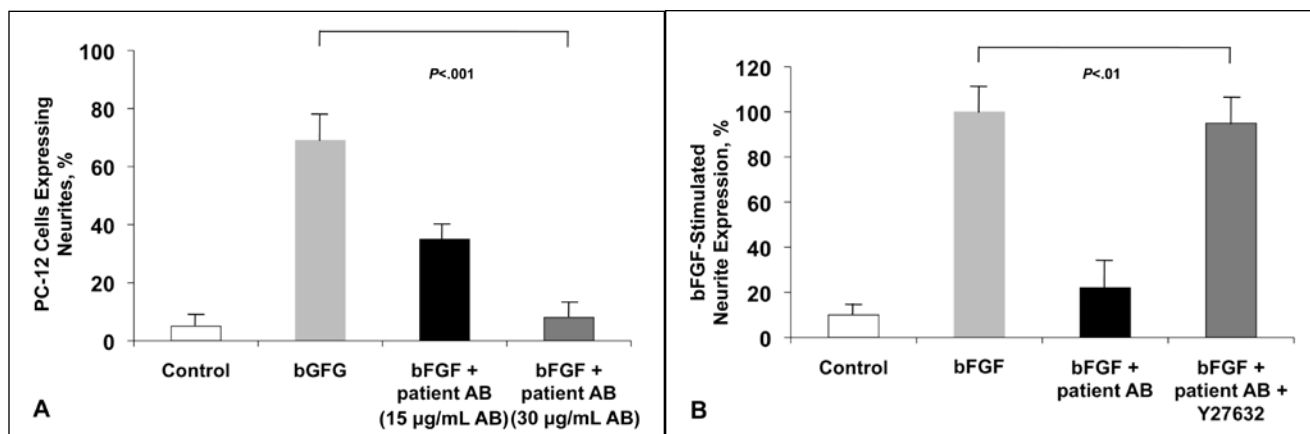


Fig. 4. Panel A, Rat pheochromocytoma PC12 cells were cultured with or without (control) 10 ng/mL bFGF in the presence or absence of the indicated concentration or, Panel B, 30 μ g/mL patient antibodies (AB) for 6 days. Addition of 1 μ M Y27632 completely reversed antibody-mediated inhibition of bFGF-stimulated neurite outgrowth. Results represent mean (standard deviation) of duplicate determinations. Neurite expression ranged from (7% to 9%, mean 8%) in response to 30 μ g/mL of the patient AB ($n = 3$ experiments). Similar, but less potent, inhibition of neurite expression was obtained in 30 μ g/mL antibody concentrations from 3 type 2 diabetic patients with maculopathy and/or nephropathy.

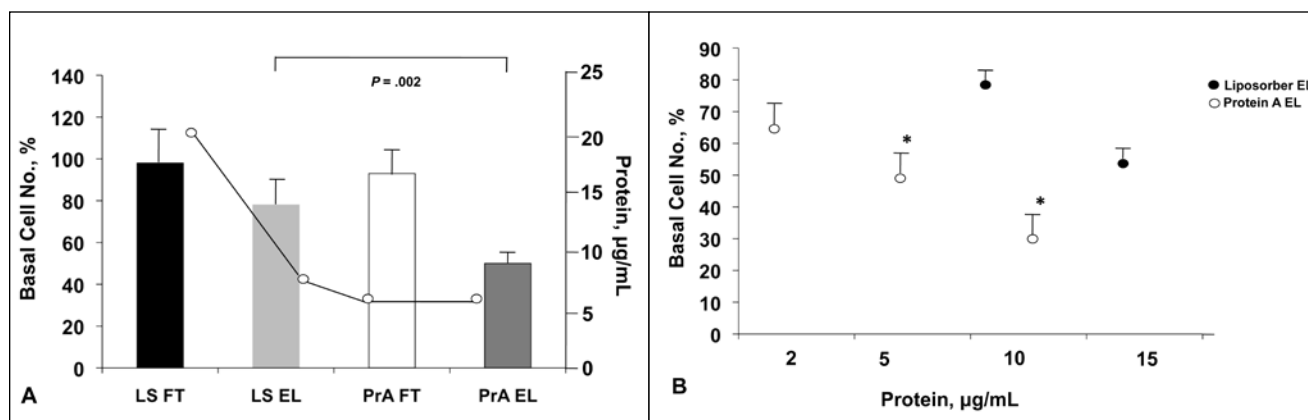


Fig. 5. Purification of patient autoantibodies using low-density lipoprotein apheresis, Liposorber (LS). *Panel A*, Moderate inhibitory activity was recovered in the 1 M NaCl eluate fraction after applying lipemic patient serum to a Liposorber column. The protein A eluate fraction (PrA EL) obtained after applying the Liposorber eluate (LS EL) fraction to a protein A column had significantly more inhibitory activity than the protein A flow through (FT) or starting LS EL fraction, $P = .002$. *Panel B*, Inhibition of endothelial cell survival (after 2 days) by the PrA EL fraction was dose-dependent and significantly exceeded inhibition from nearest, higher concentration of the LS EL fraction. Asterisks indicate $P < .01$. Error bars represent standard deviation of quadruplicate determinations. Similar results were obtained in plasma or serum from 4 type 2 diabetic patients and 1 additional type 1 diabetic patient, of whom, all had macular edema or proliferative retinopathy, 3 had nephropathy, and 1 had multiple small-vessel strokes. Mean endothelial cell activity was $(76 \pm 8\%; n = 5)$ in the IgG fractions that contained 5 to 10 $\mu\text{g/mL}$ protein after sequential Liposorber and protein A chromatography. Liposorber and protein-A chromatography were performed as described in the Methods.

patients with advanced type 2 diabetes in association with a significantly increased 5-year risk for requiring laser photocoagulation treatment in the VA Diabetes Trial (14). In previous studies (4,5), the baseline occurrence of significant inhibitory autoantibody activity in normal control populations was significantly lower than that found in various pathologic states including diabetes (10), mixed connective tissue disorders (15), or cancer (4), and it had an estimated prevalence of approximately 12% (10).

The type 1 diabetic patient discussed in this report had among the most highly potent endothelial cell inhibitory antibodies of all the subjects previously tested and an unusually wide spectrum of progressive disease manifestations. Despite refractory hypertension and type IV hyperlipidemia typical of poorly controlled diabetes, radiographic tests were negative for large-vessel disease affecting the carotid or vertebral arteries. Magnetic resonance imaging and computed tomography findings were consistent with a disease process that preferentially affected small- or medium-sized vessels. The clinical presentation, negative anti-cardiolipin and antineutrophil cytoplasmic antibody tests, and normal erythrocyte sedimentation rate make it unlikely the patient had a recognized form of systemic vasculitis.

Autoantibody-mediated effects in endothelial cells and neurons might account for several of the patient's disease complications. The Rho family of small GTPases regulates intracellular actin microfilaments involved in cell migration and neurite extension (6). In addition, Rho A/Rho kinase sensitizes vascular smooth muscle to calcium by interfering with myosin light chain dephosphorylation (16). Endothelial cell stress fiber formation, and endothelial cell

contraction induced by the autoantibodies may have contributed to increased permeability, which underlies macular edema, progression to nephropathy, and peripheral neuropathy or central nervous system pathology. Whether the autoantibodies also activate the Rho kinase signaling pathway in vascular smooth muscle cells, perhaps contributing to refractory hypertension, is not clear.

Sneddon syndrome is a small-vessel vasculitis characterized by livedo reticularis and recurrent stroke (17) in which roughly one-third of affected patients demonstrate antiendothelial cell antibodies (18). Our patient shared many of the same clinical signs, symptoms, and progressive clinical course as those reported in Sneddon syndrome including headache; hypercholesterolemia; treatment-refractory hypertension; involvement of fundi, kidneys, heart; and prolonged transient ischemic attacks progressing to multifocal recurrent strokes and dementia (19). There is no proven effective therapy to slow the disease progression in Sneddon syndrome (17). The data presented here suggest that a subset of the most potent inhibitory endothelial cell autoantibodies can be removed from lipemic plasma *in vitro* with an LDL-apheresis column comprised of dextran sulfate cellulose (Liposorber). Whether LDL-apheresis effectively prevents disease progression in recurrent, small-vessel stroke syndromes, such as antiphospholipid antibody-negative Sneddon syndrome or in this type 1 diabetic patient with potent endothelial cell inhibitory antibodies, is unknown.

LDL-apheresis (Liposorber) is approved in Japan for the treatment of focal segmental glomerulosclerosis—an idiopathic disorder characterized by nephrotic syndrome

that can progress to end-stage renal disease (20). In patients with focal segmental glomerulosclerosis in whom heavy proteinuria recurs following renal transplant, a circulating permeability factor with a molecular weight of approximately 50 kD, which bound to protein A columns has been implicated in disease causation (21). Although the immunoglobulin nature of the focal segmental glomerulosclerosis permeability factor remains unproven (22), dextran sulfate cellulose is also capable of removing specific kinds of autoantibodies such as anti-DNA antibodies from plasma in patients with systemic lupus erythematosus (9).

It is not clear whether endothelial cell inhibitory antibodies that co-eluted with lipoproteins in the Lipsorber eluate fraction from Lipsorber columns may have been physically associated with specific lipoproteins, eg, very low-density lipoprotein in the patient's plasma. Heparin sulfate proteoglycan is a receptor for apolipoprotein E that modulates neurite outgrowth in neurons (23), prevents vascular smooth muscle cell proliferation, and binds to lipoproteins (24). Because heparin sulfate proteoglycan is also a known target for autoimmunity (25), it was suggested that heparin sulfate proteoglycan released as a result of incipient renal injury may lead to the development of anti-heparin sulfate proteoglycan, endothelial cell inhibitory autoantibodies in subsets of advanced diabetes (26). The very low-density lipoprotein receptor is distributed on endothelium of capillaries and small arterioles of the brain where it has been suggested to provide a mechanism by which components of the circulating very low-density lipoprotein particle enter the brain (27). Taken together with the present data, these observations suggest a possible novel pathway linking antiendothelial cell antibodies with an unusual syndrome of poorly controlled diabetes, hypertension, dementia (28), and recurrent small-vessel stroke. Whether endothelial cell inhibitory autoantibodies that may have resulted from vascular injury or systemic autoimmunity contributed to one or more of the protean clinical manifestations seen in our patient, or are a marker for severe complications, requires much more study.

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DISCLOSURE

The author has no multiplicity of interest to disclose.

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