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Thrombosis Following Desmopressin for Uremic Bleeding

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An elderly patient with evidence of atherosclerosis and uremic bleeding diathesis developed two foci of cerebral thrombosis immediately after an infusion of desmopressin (DDAVP). Because large molecular weight multimers of von Willebrand factor (vWF) have been demonstrated to cause platelet aggregation under conditions of elevated fluid shear stress as occurs in atherosclerotic vessels, we investigated his plasma vWF at the time of the event and compared it to baseline values obtained 2 weeks later. Unusually large vWF multimers induced by the DDAVP infusion were present and likely contributed to the thrombotic process. Consequently, we believe DDAVP should be given with greater caution to patients with atherosclerosis.

Key words: von Willebrand factor, atherosclerosis

INTRODUCTION

The etiology of the hemostatic defect in uremic patients is unknown, but is probably multifactorial. Various modalities of treatment are used including desmopressin acetate (DDAVP), cryoprecipitate, and estrogens. Although studies have shown increased levels of von Willebrand factor (vWF) in uremic patients [1], some of the agents used to treat uremic bleeding may exert their effect by stimulating the secretion of unusually large vWF multimers by endothelial cells [2].

In this report we describe a patient who received DDAVP as therapy for the prolonged bleeding time associated with his uremic state and who shortly thereafter developed two cerebral thrombotic infarctions. Because of a postulated thrombogenic role, vWF quantitation and multimer analysis was obtained at the time of the cerebral thrombosis and compared to baseline values obtained subsequently.

CASE REPORT

A 93-year-old white male was hospitalized because of weakness and vomiting. His past medical history was significant for colon cancer with documented local pelvis spread. One year previously, the patient was mildly thrombocytopenic, with a platelet count of 100,000/μL; however no evaluation had been carried out. He had bilateral carotid bruits and a soft systolic murmur. The remainder of the physical examination including neurologic exam was unremarkable. His hemoglobin was 11.2 g/dL, WBC and differential counts were normal, and platelets were 80,000/μL. Prothrombin and partial thromboplastin times were normal. He had new onset uremia (serum creatinine of 7.0 mg/dL) with bilateral hydronephrosis by ultrasound. Computerized axial tomography showed thickening of the soft tissues around the bladder, and cystoscopy was planned. DDAVP (desmopressin acetate) was administered (0.3 mcg/kg, or 20 mcg total, IV over 30 min) in an effort to correct his prolonged bleeding time, greater than 15 min. Vital signs before, during, and immediately after infusion were normal, but 30 min later the patient was found to be confused, dysarthric, and with a left hemiparesis. A bleeding time performed at this time remained greater than 15 min. Other laboratory tests included a repeat platelet count of 81,000/μL and fibrin split products of $>$ 10, but $<$ 40 μg/mL. Prothrombin, partial thromboplastin, and thrombin times were normal, and fibrinogen was 290 mg/dL. Computerized axial tomography of his head done immediately showed only cortical atrophy, but repeated at 48 hours, showed two distinct focal areas of thrombotic infarction in the right parietal and right frontal

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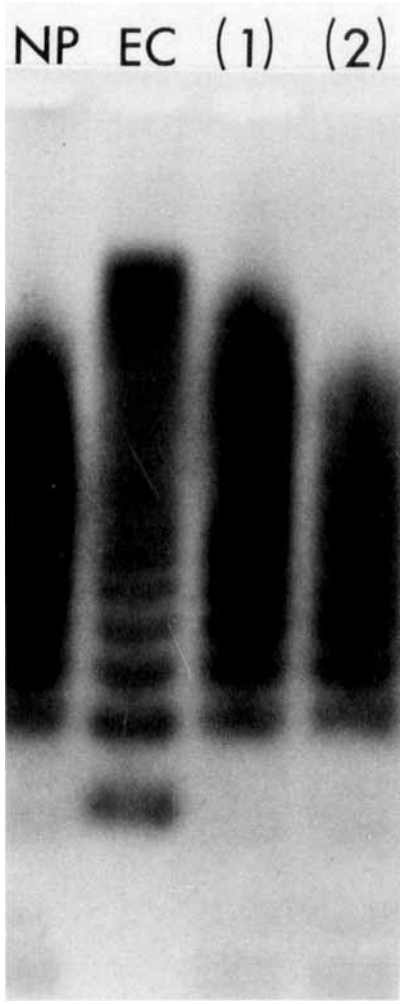

Fig. 1. vWF multimers were separated by sodium dodecyl-sulfate agarose gel electrophoresis, overlaid with [^{125}I]-antihuman vWF IgG, and analyzed by autoradiography using 1% agarose and a continuous buffer system. Lane 1: Patient plasma sample collected after DDAVP infusion. Lane 2: Patient sample collected 15 days later. EC: Sample of endothelial cell supernatant containing unusually large vWF multimers not found in normal plasma (NP).

lobes. The patient's neurological condition improved slightly over the ensuing weeks, but he was left with a residual left hemiparesis.

VON WILLEBRAND FACTOR STUDIES

Immediately after the change in neurologic states was noticed, approximately 30 min after the infusion of DDAVP, a blood sample was obtained and processed as described [3]. vWF antigen quantitated by enzyme-linked immune assay (Spectra VWT, Ramco Laboratories, Inc., Houston, TX) was 232% of normal pooled plasma. Multimer analysis revealed larger than normal vWF forms (Fig. 1). A similar blood sample obtained 2 weeks later, presumably representing baseline conditions, had a vWF antigen level of 161%, and the larger than normal multimers of vWF were not present.

DISCUSSION

DDAVP causes the release of preformed vWF from Weibel-Palade bodies in endothelial cells. This released vWF includes, in addition to all of the multimeric forms found in normal human plasma, unusually large vWF multimeric forms that are not present in normal circulation [2]. These unusually large vWF forms are capable, under conditions of elevated fluid shear stress similar to those that exist in partially obstructed atherosclerotic arterial vessels, of aggregating platelets [5].

The patient present in this report developed two cerebral arterial thrombi temporarily related to DDAVP administration. Unusually large multimeric forms of vWF were identified in his plasma after DDAVP and may have caused in vivo platelet aggregation contributing to the thrombotic event. The patient had bilateral carotid bruits; thus it is likely that cerebral atherosclerosis also was a factor.

Similar thrombotic complications following DDAVP have not been previously reported. However DDAVP is reported to aggravate a thrombotic thrombocytopenic purpura-like syndrome [6] and is contraindicated in patients with type IIB von Willebrand disease [7], in both causing enhanced vWF-mediated platelet aggregation. The release of unusually large multimers of vWF induced by aspariginase- [8] and cisplatin-based [9] chemotherapy has been implicated in similar thrombotic complications. Consequently we believe it is prudent to administer DDAVP with greater caution, especially to patients with atherosclerosis.

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NOTE ADDED IN PROOF

Since the submission of this report, a somewhat similar occurrence has been described that also suggests the need for caution in the administration of DDAVP. Bond L, Bevans D: Myocardial infarction in a patient with hemophilia treated with DDAVP. N Engl J Med 318:121, 1988.