

24. Waller JL: Inotropes and vasopressors, *Cardiac Anesthesia Volume 2: Cardiovascular Pharmacology*. Edited by Kaplan JA. New York, Grunc and Stratton, 1983, pp 281-282
25. Makey AR, Bliss BP: Pulmonary embolectomy: A review of five cases with three survivals. *Lancet* 2:1155-1158, 1966
26. Allison PR, Dunnill MS, Marshall R: Pulmonary embolism. *Thorax* 15:273-279, 1960
27. Garvey JW, Wisoff G, Voletti C, Hartstein M: Haemorrhagic pulmonary oedema: Post-pulmonary embolectomy. *Thorax* 31:605-609, 1976
28. Modrey DL, Chiu RC: Pulmonary reperfusion syndrome. *Ann Thorac Surg* 27:206-215, 1979
29. Cabrol C, Cabrol A, Acar J: Surgical correction of chronic post-embolic obstructions of the pulmonary arteries. *J Thorac Cardiovasc Surg* 76:620-628, 1978
30. Tisi GM: Preoperative evaluation of pulmonary function validity, indications and benefits. *Am Rev Resp Dis* 119:293-310, 1979

Anesthesiology
61:200-202, 1984

Hypercoagulability in a Patient with a Brain Tumor

STUART WEINBERG, M.D.,* LYDIA PHILLIPS, M.D.,† REBECCA TWERSKY, B.A.,‡
JAMES E. COTTRELL, M.D.,§ KENNETH M. BRAUNSTEIN, M.D.¶

The association of coagulopathy with neoplastic disorders or craniocerebral trauma is well recognized.¹⁻⁴ However, few cases of coagulopathy or hypercoagulopathy have been reported in patients with primary brain tumors.^{5,6} Hypercoagulability can occur with chronic activation of the coagulation system during episodes of chronic disseminated intravascular coagulation (DIC). We present a patient with a primary brain tumor, hypercoagulability, and chronic DIC.

REPORT OF A CASE

A 47-year-old woman with a frontal meningioma was scheduled for craniotomy and tumor resection. She was taking no medication and had no previous surgery. There was no history of bleeding disorders, phlebitis, or use of oral contraceptives. On physical examination, she was an alert and oriented obese woman. Vital signs were within normal limits. Cardiac and chest examination were normal. A neurologic assessment revealed optic atrophy in the right eye and a left eye, which visualized only finger counting. Although she had mild paresis of both lower extremities, no sensory deficits could be elicited. A chest roentogram and electrocardiogram both were normal. Computerized tomography of the head revealed a circumferential well-marginated mass over the right sphenoid ridge; angiogram confirmed abnormal vasculature in the same region. There was no clinical evidence of increased intracranial pressure.

Significant laboratory values were as follows: hemoglobin 11.1 g/dl, hematocrit 31.8%, platelet count 240,000/mm³, and white blood cell count 11,700/mm³ with a normal differential. The admission prothrombin time (PT) was 12.8/11.3 s. Measurements of the activated partial thromboplastin time (aPTT) were made with the MLA Electra 750[®] automated coagulation analyzer and were 79.5/24, 93.8/24.8, and 100/24 (patient/control) s. Plasma fibrinogen levels were 115, 120, and 92 mg% (normal 200-400 mg%). Further hematologic investigation revealed an aPTT of 15/24 and 16/26 (patient/control) s when measured by the Mechrolab Clot-Timer[®], fibrin split products 1:64, plasma fibrinogen level 87 mg%, platelets 198,000/mm³, and Factor VIII level greater than 500% (normal 50-150%). Antithrombin III, a normal physiologic inhibitor of the coagulation cascade was measured as 116% (normal 80-120%).

She was premedicated with droperidol 2.5 mg and glycopyrrolate 0.2 mg iv. A difficult endotracheal intubation was anticipated because of obesity. An awake orotracheal intubation was accomplished using topical and transtracheal applications of lidocaine as well as diazepam 2.5 mg and fentanyl 0.2 mg iv. Subsequently, thiopental 500 mg in divided doses and pancuronium 10 mg were administered iv. Following intubation of the trachea, blood pressure remained stable at approximately 140/80 mmHg throughout the 12-h operation. Anesthesia was maintained by inhalation of nitrous oxide and isoflurane in addition to fentanyl and pancuronium iv. Fibrinogen levels and platelet counts were obtained every 2 h throughout the case and ranged from 129 to 170 mg% and 135,000-186,000/mm³, respectively. Thirteen units of cryoprecipitate were given immediately prior to surgery, and an additional eight units were given intraoperatively because of the decrease in fibrinogen levels. Total fluids administered were crystalloids 5,350 ml, whole blood 500 ml, packed erythrocytes seven units, and fresh frozen plasma six units. Estimated blood loss was 1,000 ml. A complete resection of the tumor could not be accomplished because of marked perivascular extension and infiltration.

Continuous mild bleeding from the oropharynx was noted 5 h postoperatively, and laryngoscopy failed to reveal the site of bleeding. The platelet count was 69,000/mm³, and five units of platelets and two units of fresh frozen plasma were administered. Platelet count and fibrinogen level increased so that by the third postoperative day platelet count was 140,000/mm³ and fibrinogen 340 mg%. On the 6th postoperative day the platelet count again decreased to 92,000/mm³. Fibrinogen decreased to 120 mg% and fibrin degradation products increased. There were no abnormalities in the PT or aPTT. Administration of additional cryoprecipitate, whole fresh blood, fresh-

* Assistant Instructor, Department of Anesthesiology.

† Assistant Instructor, Department of Anesthesiology.

‡ Medical Student.

§ Professor and Chairman, Department of Anesthesiology.

¶ Assistant Professor.

Received from the Department of Anesthesiology, State University of New York at Downstate Medical Center, Brooklyn, New York. Accepted for publication January 4, 1984.

Address reprint requests to Dr. Weinberg: Department of Anesthesiology, State University Hospital, Downstate Medical Center, 450 Clarkson Avenue, Box 6, Brooklyn, New York 11203.

Key words: Blood: hypercoagulable state, partial thromboplastin time. Anesthesia: neurosurgery.

frozen plasma, and platelets prevented further bleeding. The coagulopathy subsided over the next 2 days and the patient made an otherwise uneventful recovery.

DISCUSSION

Three general mechanisms have been postulated to account for tumor induced activation of the coagulation system. They include secretion or exposure on the tumor cell surface of molecules capable of activating the coagulation system; nonspecific activation resulting from release of intracellular tissue thromboplastin; and activation of the host immune system resulting in the induction of procoagulant activity in lymphoid cells and leukocytes.⁷

Primary brain tumors rarely are associated with DIC; an intact blood brain barrier may prevent interaction between the tumor and coagulation mechanisms and thereby prevent activation of procoagulant activity. This is consistent with recent investigations with assays of fibrinopeptide A (FpA), a sensitive marker for increased thrombin activity, which have indicated that tumor induced thrombin activation often occurs in extravascular sites not accessible to heparin.⁸ Previously reported cases of DIC associated with brain tumors have occurred in young women with oligodendroglioma located totally or partially within the ventricular system.^{5,6} Brain tissue is a rich source of tissue thromboplastin⁹ and damage to the choroid plexus and ventricular wall may allow thromboplastic material into the general circulation. Our patient had a highly vascular frontal meningioma with no extension to the ventricular system. Tumor induction of procoagulant activity or introduction of tissue thromboplastin into the general circulation could have occurred via endothelial disruption of the tumor vessels. Further studies using the FpA assay may suggest a greater incidence of coagulopathy in patients with primary brain tumors.

The clinical presentation of tumor-induced coagulopathy is variable, and the disorder may be associated with thrombophlebitis, hemorrhagic phenomena, or arterial embolization.¹ Laboratory investigation may reveal hypofibrinogenemia; thrombocytopenia; increased fibrinogen-fibrin degradation products (FDP); increased fibrinolytic activity; decreased Factor V, VIII, and X; microangiopathic hemolytic anemia; and the presence of abnormalities in prothrombin, partial thromboplastin, and thrombin times. These findings share a common pathophysiologic basis, the sustained activation of thrombin with increased coagulation of fibrinogen and enhanced fibrinolysis. The balance between fibrin production and increased fibrinolysis determines the extent of intravascular thrombosis. When these disturbances are mild and persistent, the process is described as chronic DIC.

Chronic activation of the coagulation system can produce elevations of the levels of one or more clotting factors.¹⁰ Cooper *et al.* have identified three clinical patterns

of DIC; 1) a decompensated or coagulation factor depleted state with decreased fibrinogen, Factors V and VIII, decreased platelet count, and elevated FDP; 2) a compensated state in which the potentially depressed factors are normal; and 3) an overcompensated or hypercoagulable state in which fibrinogen and other factors are present in excess of normal.¹¹ Measured levels of coagulation factors and their inhibitors represent a balance between ongoing consumption and enhanced production. Antithrombin III, for example, is an acute phase reactant and ongoing consumption may depress levels into the normal range as has been reported in several patients with DIC and malignancy.¹²

At least two mechanisms for hypercoagulability therefore can be identified. Hypercoagulability may be evident clinically with thrombosis or embolization and reflect the balance between fibrin-clot formation and enhanced fibrinolysis or it can be subclinical and detected by *in vitro* acceleration of coagulation times. Although our patient initially had a markedly prolonged aPTT, further investigation indicated that true measurements actually were shorter than normal suggesting hypercoagulability. These artifactual readings can be attributed to the use of the MLA Electra 600® and 750® automated coagulation analyzers, which are designed to detect clot formation by a photocell sensing circuit that detects changes in optical density occurring with clot formation. During aPTT measurements these devices are standardized to detect the changes beginning at 15 s after the mixture of reagents and patient's plasma; if, however, clot formation occurs prior to 15 s, as occurred repeatedly in our patient, no change in optical density will be detected and the resulting digital readout will be abnormally prolonged. This explanation was confirmed by repeating the aPTT determination on the Mechrolab Clot-Timer® and fibrometer, which are semiautomated instruments not using optical density determinations. In addition, a manual tilt tube aPTT was performed.

The shortened aPTT values coincided with Factor VIII levels significantly increased above normal despite enhanced consumption and coagulation of factors. The clinical significance of the association between increased levels of clotting factors and hypercoagulability is unclear. Penick and Roberts¹³ have noted that increased levels of coagulation factors were not necessarily associated with hypercoagulability. Although our patient had no symptomatic evidence of hypercoagulability such as arterial embolization or thrombophlebitis, the presence of a markedly shortened aPTT in association with significant elevations in Factor VIII levels did suggest a subclinical or at least an *in vitro* hypercoagulable state. This association is supported by the finding that increased Factor VIII levels correlated with a shortened aPTT in a study of coagulation and fibrinolysis in 788 healthy 54-year-

old men.¹⁴ The correlation of a shortened aPTT with acceleration of *in vivo* coagulation mechanisms and increased clot formation is less certain. Even with enhanced clotting, our patient could have remained asymptomatic because of the increased rates of fibrinolysis suggested by elevated FDP levels. The simultaneous presence of an increased Factor VIII, a normal antithrombin III, and a depressed fibrinogen level suggest that chronic DIC can produce overcompensation in components of the coagulation system while leaving other components compensated or depleted.

Treatment of the underlying derangement is essential for control of a low-grade, chronic DIC. Since findings such as hemorrhage, thrombosis, and arterial embolization were not present preoperatively, we decided to avoid heparinization. This risk of worsening DIC with surgery, however, necessitated the preoperative transfusion of plasma factors and required frequent perioperative coagulation monitoring.¹⁵ As suspected a more fulminant coagulopathy manifested by hypocoagulability and bleeding did develop in the postoperative period but responded to further infusions of plasma factors and platelets.

An alternative explanation that does not invoke DIC as an underlying stimulus for increased Factor VIII levels is suggested by Gunn and Hampton,¹⁶ who demonstrated that stimulation of certain areas of the brain, including the reticular formation, mesencephalic central gray, lateral hypothalamic area, and the habencular interpeduncular tract result in increased levels of Factor VIII. This mechanism, however, would not account for the multiple coagulation disturbances in our patient and would not explain the progression from subclinical hypercoagulability to frank DIC with hypocoagulability and bleeding.

In conclusion, the following points should be emphasized: 1) automated coagulation analyzers may give artifactual elevations in aPTT determinations in hypercoagulable syndromes; 2) a hypercoagulable state with elevated levels of coagulation factor production and activation may be a manifestation of an evolving or chronic DIC; 3) patients with brain tumors not contiguous with periventricular and choroid plexus tissue also may be associated with coagulopathy, possibly through tissue thromboplastin release; and 4) the risk of coagulopathy in patients with brain tumors extends beyond the period of actual resection to several days postoperatively.

The authors thank Ms. Ellen L. Jackson for manuscript preparation and S. P. Rao, M.D., (Division of Pediatric Hematology) for editorial assistance.

REFERENCES

1. Sack GH, Levin J, Bell WR: Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: Clinical, pathophysiologic, and therapeutic features. *Medicine* 56:1-37, 1977
2. Vecht CJ, Smit Sibinga CT, Minderhoud JM: Disseminated intravascular coagulation and head injury. *J Neurol Neurosurg Psychiatry* 38:567-571, 1975
3. Goodnight SM, Kenoyer G, Rapaport S, Patch MJ, Lee JA, Kurze T: Defibrination after brain-tissue destruction. *N Engl J Med* 290:1043-1047, 1974
4. Auer L: Disturbances of the coagulatory system in patients with severe cerebral trauma. *Acta Neurochirurgica* 43:51-59, 1978
5. Vardi Y, Streifler M, Schujman E, Loewenthal M: Diffuse intravascular clotting associated with a primary brain tumour. *J Neurol Neurosurg Psychiatry* 37:987-990, 1974
6. Matjasko MJ, Ducker TB: Disseminated intravascular coagulation associated with removal of a primary brain tumor. *J Neurosurg* 47:476-480, 1977
7. Edgington TS: Activation of the coagulation system in association with neoplasia. *J Lab Clin Med* 96:1-4, 1980
8. Peuscher FW, Cleton FJ, Armstrong L, Stoepman van Dalen EA, van Mourik JA, van Aken WG: Significance of plasma fibrinopeptide A (FpA) in patients with malignancy. *J Lab Clin Med* 96:5-14, 1980
9. Astrup T: Assay and content of tissue thromboplastin in different organs. *Thromb Diath Haemorrh* 14:401-416, 1965
10. Cooper HA, Bowie EJW, Owen CA Jr: Chronic induced intravascular coagulation in dogs. *Am J Physiol* 225:1355-1358, 1973
11. Cooper HA, Bowie EJW, Owen CA Jr: Evaluation of patients with increased fibrinolytic split products (FSP) in their serum. *Mayo Clin Proc* 49:654-657, 1974
12. Bick RL, Dukes ML, Wilson WL, Fekete LF: Antithrombin III (AT-III) as a diagnostic aid in disseminated intravascular coagulation. *Thrombosis Res* 10:721-729, 1977
13. Penick GD, Roberts HR: Intravascular clotting: Focal and systemic. *Int Rev Exp Pathol* 3:269-328, 1964
14. Korsan-Bengtzen K, Wilhelmsen L, Tibblin G: Blood coagulation and fibrinolysis in a random sample of 788 men 54 years old. *Thromb Diath Haemorrh (Stuttg)* 28:89-98, 1972
15. Egan EL, Bowie EJW, Kazmier FJ, Gilchrist GS, Woods JW, Owen CA Jr: Effect of surgical operations on certain tests used to diagnose intravascular coagulation and fibrinolysis. *Mayo Clin Proc* 49:658-664, 1974
16. Gunn CG, Hampton JW: CNS influence on plasma levels of factor VIII activity. *Am J Physiol* 212:124-130, 1967