Hemostasis activation in patients undergoing brain tumor surgery

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Patients undergoing brain tumor surgery are at high risk for the occurrence of a thromboembolic event. To identify a laboratory marker suitable for risk estimation the authors studied the perioperative time pattern of routine coagulation parameters and the specific hemostasis activation marker D-dimer in 28 consecutive patients at high risk (11 patients with glioma and eight patients with meningioma) and low risk (9 patients with metastases) for thromboembolism, as previously reported. As is typical during major surgery, most of the routine parameters declined, probably because of hemodilution, and recovered postoperatively to values higher than baseline, probably because of an acute-phase reaction. On Days 2 and 7 after surgery no difference in the routine parameters was recorded between patients at high (meningioma and glioma) and low risk (metastases). The level of D-dimer was elevated at baseline in patients with metastases, indicating a hemostatic hyperactivity that is usual in cancer patients. During surgery a marked increase in D-dimer levels occurred in patients with meningioma and glioma (pre- and postoperative median 90/2000 and 100/1020 ng/ml, respectively), but the increase was less pronounced in patients with metastases (320/660 ng/ml). Postoperatively, D-dimer declined in patients with metastases to lower levels than preoperatively (Day 7, 270 ng/ml); in patients with meningioma or glioma, however, D-dimer levels remained elevated until Day 7 (450 and 200 ng/ml). These results indicate that levels of D-dimer correlate with the reported high risk for thromboembolism in patients with meningioma and glioma, and D-dimer should be evaluated for its use in estimating individual risk and the efficiency of its use in the control of prophylactic treatment.

Key Words * brain surgery * hemostasis activation * D-dimer * meningioma

A high incidence of postoperative thromboembolic events has been reported in patients undergoing brain tumor surgery and is a leading cause of mortality when pulmonary embolism develops.[4,6,7,10] The risk for thrombosis has been reported to be different among the various types of brain tumors; it is highest for patients with meningioma (72%), followed by patients with glioma (60%), and markedly lower for patients with brain metastases (20%).[6] Despite the severity of clinical consequences the literature holds rather little information about the hemostatic mechanisms leading to the high risk of postoperative thrombosis among these patients. Possible mechanisms might be: 1) a preexisting hypercoagulated state in brain tumor patients; 2) an intraoperative influx of thromboplastic substances from the brain tissue into the circulation; and/or 3) the enormous intraoperative stress combined with the long postoperative bed rest after brain surgery.

In a recent investigation[5] abnormalities of the fibrinolytic system were found in many patients preoperatively. The clinical relevance of these findings was deduced from a statistically significant correlation between the amount of fibrinolytic products found in the resected brain tumor and the occurrence of postoperative thrombosis.[6] In a later study[2] in which the patterns of hemostatic parameters in patients undergoing brain or abdominal surgery were compared, a more pronounced postoperative hypercoagulability in brain surgery patients was deduced from shorter activated partial thromboplastin time (aPTT) and bleeding time, probably caused by higher plasma levels of coagulation factor IX and von Willebrand factor, respectively.

Chandler[1] stated in a commentary on a study by Iberti, et al.,[2] "It would be very important to look for this phenomenon in neurosurgical patients with different diagnoses and also to follow these values several days postoperatively." Following Chandler's suggestions, we investigated the perioperative time pattern of hemostasis activation in patients undergoing brain surgery for removal of glioma, meningioma, or metastases using routine coagulation parameters and a specific marker for hemostasis activation.

CLINICAL MATERIAL AND METHODS

Patient Selection and Characteristics

After obtaining Institutional Review Board approval and informed consent from each individual, we studied 28 consecutive patients (11 women and 17 men) undergoing elective surgery for brain tumor removal. No patient had a history of bleeding or thromboembolic disorders. No patient was taking anticoagulant, antiplatelet-aggregating, or antiinflammatory drugs within 2 weeks of surgery. Computerized tomography scans and/or nuclear magnetic resonance images were routinely obtained preoperatively to detect tumor size, location, and intracranial bleeding. Based on the results of histological findings in the tumor, patients were assigned to one of three subgroups. One subgroup was composed of 11 patients with glioma, the second subgroup contained eight patients with meningiomas, and the third subgroup comprised nine patients with metastatic brain tumor; all tumors were located in the supratentorial area. The mean age of patients with glioma was 45 years, those with meningioma 60 years, and those with metastases 64 years. The mean duration of surgery, from skin incision to closing of the wound, was 5.2 hours in patients with glioma, 6.5 hours in patients with meningioma, and 3.9 hours in those with metastases (difference $p < 0.05$ glioma vs. metastases). All patients underwent operation using routine trepanation and standard microsurgical procedures. In most of the cases of glioma the tumor was subtotally removed and in cases of metastases it was completely resected. In all cases of meningioma they were located at the convexity of the brain or the falx and could be completely removed. None of the tumor was embolized preoperatively. The demographic tumor and surgery data for the 28 individual patients are summarized in Table 1.

Sex, Age (yrs)	Histology/Grade	Max Tumor Diameter* (cm)	Duration of Surgery (hrs)
patients with glioma			
M, 44	astrocytoma / I	3	5
M, 24	astrocytoma / II	6	7
M, 32	astrocytoma / II	4	8
M, 30	oligoastrocytoma / I	6	8
M, 17	oligoastrocytoma / II-III	4	4.5
F, 63	oligoastrocytoma / III	3.5	4
F, 61	oligoastrocytoma / III	6	6
F, 62	glioblastoma / IV	3	4
M, 37	glioblastoma / IV	7	5
M, 62	glioblastoma / IV	5	6
F, 64	glioblastoma / IV	5.5	4
patients with meningioma			
F, 62	endotheliomatous	5	6
F, 46	endotheliomatous	5	6
F, 74	endotheliomatous atypical	4	7.5
M, 65	endotheliomatous atypical	6	4
F, 73	endotheliomatous atypical	4	5.5
M, 56	fibroblastic-endotheliomatous	5.5	9
F, 54	fibroblastic-endotheliomatous	2	11
F, 48	malignant anaplastic	3	3.5
patients with metastatic brain tumor			
M, 65	adenocarcinoma colon	3	3
M, 52	adenocarcinoma lung	6	5
M, 61	adenocarcinoma lung	3	2.5
M, 61	adenocarcinoma prostate	5	6
M, 70	epidermoid lung carcinoma	4	3.5
F, 70	solid breast carcinoma	5	3.5
M, 69	solid lung carcinoma	6	2.5
M, 50	solid lung carcinoma	4	5.5
M, 79	transitional cell bladder	7	4
* Max = maximum .			

Blood samples were drawn by venipuncture before anesthesia was induced in the patient, and again after the scalp incision was closed, as well as at 1, 2, and 7 days after surgery, in a 1/10-volume of 3.8% Na₃ citrate, centrifuged at 2.200 G and 4°C, and the supernatant plasma was apportioned. Prothrombin time (PT) (Normotest; Nycomed, Oslo, Norway), aPTT (Actin FS; Baxter, Miami, FL), and fibrinogen (Testthrombin; Behring, Marburg, Germany) were measured on a coagulometer (CA 5.000; Toa Sysmex, Kobe, Japan) and antithrombin III (ATIII) on an analyzer (ACA IV; Dupont, Wilmington, DE) from fresh samples. Levels of cross-linked fibrin degradation products (D-dimer) were measured by enzyme-linked immunosorbent assay (DIMER-TEST; Agen, Brisbane, Australia) from thawed samples stored at -70°C.

Statistical Analysis

Because normal distribution of the parameters was improbable, data are described in medians and quartiles. Differences in results were calculated to determine significance using the Kruskal-Wallis test and correlations between parameters were assessed by the Spearman rank-order method.

RESULTS

There were no intraoperative complications that might cause additional bleeding, such as perforation of greater vessels or a venous sinus.

The time patterns from baseline until Day 7 postsurgery of the routine coagulation profile consisting of PT, aPTT, fibrinogen, AT III and platelet count are presented in Table 2. Compared with patients harboring meningiomas or metastases those with glioma had lower PT values at all times, and these values were most pronounced during the early postoperative period ($p < 0.05$ vs. metastases); they had higher aPTT values at baseline and on completion of surgery ($p < 0.05$ vs. meningioma). Levels of fibrinogen and AT III declined during surgery in patients with glioma or meningioma. Patients with meningioma had the lowest platelet count at all times ($p < 0.05$ postoperative Day 1 vs. patients with either glioma or metastases). Patients with metastases maintained uniform levels of PT, fibrinogen, AT III, and platelets at all times, except at the end of the 1st postoperative week when the levels increased; this was the case in patients with glioma or meningioma. At Days 2 and 7 no routine parameter was significantly different between the three subgroups.

TABLE 2 ROUTINE HEMOSTATIC PARAMETERS IN PATIENTS UNDERGOING BRAIN SURGERY*					
Parameter	Preop	Postop	Day 1	Day 2	Day 7
PT (%)					
glioma	74 (64–89)	67† met (59–88)	69 (56–92)	72 (68–82)	88 (76–99)
meningioma	90 (82–100)	87 (75–98)	76 (65–91)	92 (70–102)	107 (88–120)
metastases	84 (78–97)	89† gli (78–94)	87 (70–98)	84 (62–96)	99 (77–101)
aPTT (in seconds)					
glioma	34 (27–37)	35† men (29–39)	32 (29–35)	32 (31–35)	32 (26–36)
meningioma	28 (24–32)	28† gli (27–30)	32 (29–33)	32 (27–34)	28 (23–30)
metastases	28 (27–33)	31 (27–32)	34 (29–37)	36 (29–37)	32 (28–35)
fibrinogen (mg/dl)					
glioma	211 (172–344)	194† met (151–278)	318 (220–331)	383 (337–421)	343 (294–373)
meningioma	187† met (136–241)	164† met (109–215)	217 (202–336)	305 (198–518)	348 (169–371)
metastases	266† men (240–395)	302† both (247–384)	335 (265–419)	399 (307–491)	300 (371–430)
AT III (%)					
glioma	106 (96–121)	89† met (82–96)	104 (98–120)	111 (101–119)	120 (110–126)
meningioma	109 (94–118)	97 (90–104)	113 (80–121)	109 (101–121)	121 (116–127)
metastases	105 (95–121)	102† gli (95–111)	109 (103–112)	110 (98–120)	115 (109–121)
platelets (g/L)					
glioma	236 (171–277)	233 (189–271)	222† men (193–260)	198 (161–228)	299 (236–350)
meningioma	200 (167–285)	158 (131–244)	147† both (115–205)	136 (109–204)	265 (224–314)
metastases	249 (218–264)	228 (188–310)	226† men (200–249)	222 (198–268)	300 (200–445)
* Data are expressed as median numbers; quartiles are given in parentheses.					
† Significance is attained at $p < 0.05$ in glioma (gli), meningioma (men), and metastases (met).					

The time pattern of the hemostasis activation marker D-dimer is presented in Table 3. Preoperatively, patients with metastases had higher levels of D-dimer than patients harboring glioma or meningioma. From baseline levels until the end of their operation all patients experienced a significant increase in D-dimer levels. The steepest increase was 20-fold in patients with meningiomas; in patients with glioma it was 10-fold; and in patients with metastases it was twofold. Levels of D-dimer in patients with meningioma and those with glioma remained commensurately higher for 1 week postsurgery than those in patients with metastases. In comparison to baseline, on Day 7, D-dimer levels in patients with meningioma were five times higher and, in patients with glioma they were twice as high, whereas in patients with metastases they were lower. Statistical analysis found weak but significant correlations in the whole group of patients between postoperative D-dimer levels at all sampling times and the duration of surgery ($r = 0.42, 0.28, 0.44$, and 0.33). In the subgroups, this correlation was significant only in patients with glioma on Day 7 ($r = 0.7$).

TABLE 3 D-DIMER LEVELS IN PATIENTS UNDERGOING BRAIN SURGERY*					
Parameter	Preop	Postop	Day 1	Day 2	Day 7
D-dimer levels (ng/ml)					
glioma	100 (60–370)	1020 (220–1400)	820 (220–1380)	410 (170–600)	200 (120–550)
meningioma	90† met (70–110)	2000† met (540–3440)	2150† met (680–3610)	980† met (320–1890)	450 (200–1420)
metastases	320† men (90–700)	660† men (200–800)	410† men (180–1060)	330† men (240–510)	270 (220–490)
* Data are expressed as median numbers; quartiles are given in parentheses.					
† Significance is attained at $p < 0.05$ meningioma (men) and metastases (met).					

DISCUSSION

Responding to the recent call[1] for an investigation into the perioperative activation of the hemostatic system in neurosurgical patients with different diagnoses we compared the perioperative pattern of routine hemostatic parameters using a specific marker for hemostasis activation in patients with glioma, meningioma, and brain metastases. Preoperatively routine profiles in all patients were unremarkable, although there were slightly lower PT ratios in patients with glioma and significantly higher D-dimer levels in patients with metastases. This finding is consistent with the observation made by Trousseau in 1868 in which he related thrombotic events to cancer[9] and the modern finding of elevated fibrin-fibrinogen degradation products (D-dimer is a subspecies) in carcinoma patients, which is most pronounced in those with metastatic disease.[3] In our study, the elevated baseline levels of D-dimer in patients with metastases were not surprising, but the normal levels in patients with glioma or meningioma were unexpected. This finding may have been due to smaller tumor masses in our patients compared with carcinoma patients with metastatic disease or a lower release of procoagulant active substances from glioma or meningioma cells than cancer or leukemic cells.

Postoperatively, the routine hemostatic profiles of patients with glioma and meningioma showed a decrease in most components, such as factors of the extrinsic coagulation system (PT test), fibrinogen, AT III, and platelet counts. This is a common finding in patients undergoing major surgery in whom blood lost intraoperatively is replenished, at least partly, with solutions free of hemostatic components (saline, albumin) and might therefore be interpreted as dilution effect. An additional mechanism contributing to the reduction of hemostatic components may be consumption by hypercoagulation, which

is likely because of the high D-dimer levels at the completion of the operation; however, to what extent consumption contributes to the reduction remains unclear from our data. In patients with metastases, in whom the duration of surgery and the need for blood substitution was less, the decrease in hemostatic components was also less and sometimes unnecessary. Shortening of the aPTT after surgery, which has been previously reported as a sign of hypercoagulation,[2] was not evident in our patients. However, the assumption by Iberti, et al.,[2] of a postoperative hypercoagulation is confirmed by our study because marked intraoperative activation of coagulation and fibrinolysis was evident from the dramatic increase in D-dimer levels in patients with glioma or meningiomas. Compared with patients undergoing coronary bypass surgery involving the extracorporeal circulation, in which hemostasis activation is commonly considered to be a serious complication,[8] the levels of D-dimer commonly found in our patients far surpass those of bypass patients (preoperative to postoperative levels in coronary bypass patients = X 3.4, patients with glioma X 10, and patients harboring meningioma X 20). Furthermore, our patients with glioma or meningioma showed a biphasic decline in D-dimers postoperatively; the first halving of levels occurred within 24 hours (from Day 1 to 2 postoperatively) the next halving lasted for more than 5 days. The delayed decrease between Days 2 and 7 might indicate a renewed generation of D-dimers by renewed hemostasis activation, either at the site of the operation or at another site such as in the deep leg veins. In contrast, patients with brain metastases experienced only a twofold increase of D-dimer levels and 1 week later levels were lower than those found preoperatively. Therefore, the surgically caused stress on the hemostatic system is markedly less, and, after overcoming the initial stress, surgery seems to improve the hemostatic situation. This improvement might be due to the removal of cancer masses with procoagulant activity.

We are aware that D-dimer levels do not constitute a parameter that is absolutely specific for thromboembolism, but the differences in its levels in the three subgroups strongly coincidences with the reported risk for postoperative thrombosis being highest in patients with meningioma (72%) and glioma (60%) and lowest in patients with brain metastases (20%).[6] However, further studies are needed to evaluate the clinical importance of D-dimer monitoring for the estimation of individual thromboembolic risk and the efficiency of prophylactic treatments.

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