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Drug-induced iatrogenic intraparenchymal hemorrhage

Samir Lapsiwala, MD*, Roham Moftakhar, MD, Behnam Badie, MD

Department of Neurosurgery, University of Wisconsin Hospital and Clinics, 600 Highland Avenue, H4/3 CSC, Madison, WI 53792, USA

Intracerebral hemorrhage is bleeding into the brain parenchyma with possible extension into the ventricles and subarachnoid space. Each year, approximately 37,000 to 52,400 people suffer from intraparenchymal hemorrhage (IPH) in the United States [1]. This rate is expected to rise dramatically in the next few decades as a result of the increasing age of the population and a change in racial demographics. IPH accounts for 8% to 13% of all stroke cases and is associated with the highest mortality rate.

Primary IPH, which accounts for approximately 85% of cases, results from spontaneous rupture of small vessels caused by chronic hypertension or amyloid angiopathy. Secondary IPH occurs in a few cases and is associated with vascular malformations, tumors, impaired coagulation, or drug use. Spontaneous or nontraumatic IPH is found more commonly in men, elderly populations, and certain races, such as African Americans. Hypertension is the most important risk factor, especially when it is not controlled.

The purpose of this article is to discuss the nontraumatic causes of IPH, excluding hypertensive hemorrhage, amyloid angiopathy, and vascular anomalies. Many sources use the terminology *hemorrhagic stroke* and *intracerebral* or *intraparenchymal* hemorrhage interchangeably and do not report them as separate entities. IPH results from the rupture of an arteriole and formation of a blood clot in the parenchyma of the brain with displacement of the brain tissue. Conversely, hemorrhagic stroke, a thromboembolic phenomenon, is caused by lysis of the thrombus and reperfusion of infarcted brain with compromised capillaries.

Iatrogenic intraparenchymal hemorrhage

Iatrogenic IPH can be divided into two broad categories: those caused by self-administration of substances with toxic effects and those caused by administration of therapy by the medical community. One can further divide the second category into two subgroups: IPH caused by invasive procedures and IPH caused by medical treatment.

With any invasive procedures, the threat of intraoperative and postoperative hemorrhage is always a concern. Since the time of Harvey Cushing, we have made many technologic advances in the field of intraoperative hemostasis and diagnosis of postoperative hematoma. Now, with medical advancement in minimally invasive stereotactic and endovascular surgeries, the risk of causing intra- or postprocedural hematoma is slightly higher, because these procedures place the surgeon without immediate access to the site of hemorrhage.

Overall, the risk of clinically significant postoperative IPH is low. Kalfas et al [2] reported that of 4992 intracranial procedures performed over an 11-year period at the Cleveland Clinic, only 40 patients (0.8%) experienced postoperative signs or symptoms of intracranial hematoma. Of these 40 hematomas, 24 (0.5%) were IPH. Another study reported that of 1547 patients with normal platelet counts who underwent craniotomies, only 25 (1.6%) had postoperative intracranial hematoma [3]. The actual rate of IPH, however, may be higher than reported, because small asymptomatic IPH was not detected in these two studies.

* Corresponding author.
E-mail address: Lapsi@neurosurg.wisc.edu (S. Lapsiwala).

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Fukamachi et al [4] reported a survey of 1074 patients undergoing craniotomies who received pre- and postoperative CT scans and found that 116 (10.8%) of these patient had IPH. Sixty-four percent of IPHs were classified as small (<3 cm), and findings of IPHs greater than 3 cm occurred in 3.9% of craniotomies.

Certain perioperative risk factors, such as defects in hemostasis, thrombocytopenia, intra- and postoperative hypertension, and craniotomy for trauma, have been associated with an increased risk of postoperative IPH. In the study done by Chan et al [3], up to 40% of nontrauma patients undergoing craniotomies with a perioperative platelet count below 150,000 developed postoperative intracranial hematoma, and 20% died.

Intracranial pressure monitoring

Intracranial pressure (ICP) monitoring is routinely used in the management of patients with traumatic and nontraumatic neurologic disorders. This technique is valuable for the detection of increased ICP and as a therapeutic modality. Common methods of monitoring ICP include placement of a ventricular catheter or a subarachnoid/subdural monitor. Both techniques have advantages and disadvantages. Ventriculostomy catheters can measure pressures accurately at wide ranges and provide means of treatment via cerebrospinal fluid (CSF) drainage. Subarachnoid monitors are less invasive and carry a lower risk because they do not penetrate brain parenchyma. Although both techniques have clinical value, they have been reported to cause IPH formation.

Separate reports on 650 patients from the University of Virginia and 120 patients from Italy revealed no hemorrhagic complications after subdural ICP monitor placement [5,6]. Shapiro et al [7] retrospectively analyzed 244 patients who underwent intraparenchymal cerebral pressure monitoring for various causes and reported intracranial hemorrhage (ICH) in 2 patients (0.8%), both with hepatic dysfunction. Thus, overall risk of development of IPH with placement of subarachnoid monitors is less than 1%. Subdural bleeding is more common and strongly associated with coagulopathy.

As reported in several series, the risk of ICH is higher with placement of ventriculostomies than with subarachnoid monitors. Narayan et al [8] reported the results of ICP monitoring in 207 patients, of whom more than 90% were monitored by means of ventriculostomy. Three patients (1.4%) in this series acquired ICH. Other large series also have reported the risk of hemorrhage to be approximately 2% with ventriculostomy catheter placement [9]. Once again, coagulopathy is a major contributing risk factor to this complication. Most authors recommend an International Normalized Ratio (INR) less than or equal to 1.3 and platelet counts of more than 100,000 before placement of ICP monitors.

Stereotactic surgery

Stereotactic surgery has played an integral role in the diagnosis and management of brain lesions for many decades. Since the advent of CT scans, use of procedures like stereotactic brain biopsies and drainage of intracerebral abscesses and hematomas has become widespread. With the advancement in imaging, our precision has improved and the rate of complications, such as ICH, has declined. The overall risk of ICH from stereotactic surgery is low but varies slightly depending on the indication for surgery.

In 1974, Crevier [10] described an 0.8% incidence of ICH in 21,000 patients who received thalamotomy for pain control. One half of patients with ICH died, and one third became hemiplegic. A more recent series of 26 patients with Parkinson's disease who underwent microelectrode-guided stereotactic unilateral pallidotomy revealed four (15%) hemorrhagic complications. One deep cerebral hemorrhage was fatal, and three nonfatal frontal lobe hemorrhages resulted in language and behavioral deficits [11].

Hosobuchi [12] reported on 122 patients with implantation of electrodes for pain control. Five patients suffered hemorrhagic complications, of which two were intracerebral and three were intraventricular in location. One patient from each group died. Mendez et al [13] reported use of neural transplantation cannulas and microsystem catheters in 8 patients with Parkinson's disease. A total of 16 transplantation operations and 64 trajectories were performed. No complications of hemorrhage were reported.

Brain biopsy for diagnosis of a neoplasm is the most common application for stereotactic surgery. Kelly et al [14] reported no complications in 40 patients undergoing 195 passes for biopsies. Field et al [15] studied a series of 500 biopsy patients with postoperative CT scanning. Among 40 patients (8%) who developed ICH, 6 (1.2%) deteriorated clinically and 1 (0.2%) died. Symptomatic delayed neurologic deficits caused by IPH were

noted in 2 (0.4%) patients despite negative initial postbiopsy CT scans. A similar study from the Cleveland Clinic showed ICH on postoperative CT scans in 5 patients (1.8%) from a total of 269 stereotactic procedures between 1994 and 1998 [16]. An example of an IPH in an AIDS patient who showed immediate neurologic deterioration after a stereotactic brain biopsy is demonstrated in Figure 1.

Kulkarni et al [17] investigated the incidence of silent hemorrhage after stereotactic procedures by obtaining postoperative CT scans in 102 patients undergoing stereotactic biopsies. Sixty-one patients (60%) exhibited hemorrhage, 56 of which were intraparenchymal. Only 6 patients (5%) had neurologic deficits. Forty-three percent of these hemorrhages were less than 10 mm in diameter.

The risk of mortality from postoperative hemorrhage is low. In one series, only 1 of 184 cases of stereotactic biopsy resulted in a fatal hemorrhage [18]. Voges et al [19] reported that of 338 patients, 8 (2.4%) had hemorrhagic complications and 2 (0.6%) had a fatal outcome. In summary, although clinically silent hemorrhage after a stereotactic biopsy is common, it infrequently affects patient management and outcome. The overall clinically significant hemorrhage rate is less than 2%, with the mortality rate being even lower.

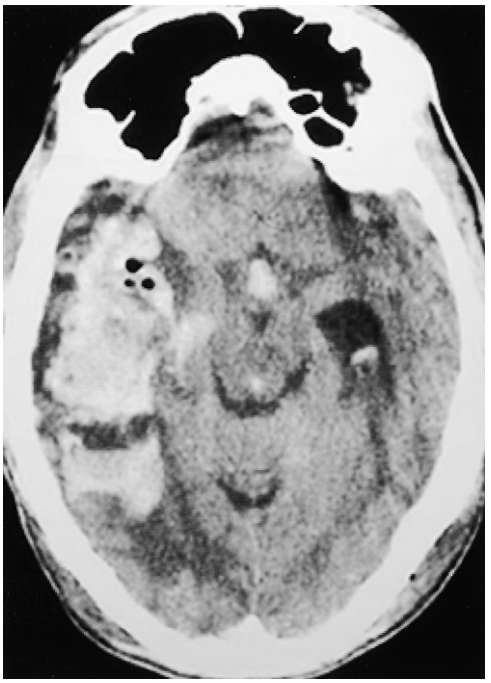

Fig. 1. A 54-year-old man with AIDS underwent a stereotactic biopsy of a brain lesion. After surgery, the patient had neurologic deterioration, and a CT scan demonstrated a large right temporal intraparenchymal hemorrhage.

Spinal procedures

ICH after lumbar puncture for spinal anesthesia or myelography is uncommon. Although most of the cases reported are subdural hematomas, IPH and subarachnoid hemorrhage (SAH) have been also reported. Whereas most IPHs that occur after spinal procedures are located in the supratentorial compartment, pontine hemorrhages have also been reported [20]. The most likely explanation for hemorrhage is patient emotional stress, causing transient hypertension during the procedure along with superimposed neurotoxicity from contrast medium.

A literature review by Yeh et al [20] found five cases of IPH associated with spinal procedures without preexisting brain lesions. One patient hemorrhaged after spinal anesthesia, and five hemorrhaged after myelography. Two patients received iohexol, two received metrizamide, and one received an unknown contrast medium. The interval between the procedure and the IPH ranged from 30 minutes to 7 days, and outcome was poor. Three patients died, and one became vegetative. Considering their frequent clinical applications, central nervous system hemorrhage seems to be an extremely rare complication of spinal procedures. To our knowledge, no cases of IPH have been reported after simple lumbar puncture for CSF acquisition.

Carotid endarterectomy

Eastcott and Rob [21] first published a report on carotid revascularization in the 1950s with successful removal of an atherosclerotic plaque and reanastomosis of the carotid bifurcation in a patient with transient ischemic attacks. Ten years later, Breutman et al [22] reported six cases of cerebral hemorrhage after carotid endarterectomy (CEA). With extracranial CEA being the most commonly performed vascular procedure, several major trials have shown a reduction in long-term stroke rates for patients undergoing surgery for symptomatic carotid stenosis [23,24]. Although ischemic cerebral infarction is the most widely reported perioperative complication, ICH may occur in association with the repair of a critically stenotic carotid lesion, previous stroke, hypertension, and anticoagulation.

In the hands of an experienced surgeon, CEA carries a 2% to 8% perioperative stroke rate [23,24]. The risk of ICH is just under 1% [25,26]. With an annual frequency of CEA in more than 100,000 Medicare beneficiaries, ICH likely occurs in almost 1000 patients in the US Medicare population alone [27].

Ouriel et al [26] reviewed records of patients experiencing symptomatic IPH after CEA during a 6-year period. Symptomatic IPH developed in 11 (0.75%) of 1471 patients undergoing CEA, accounting for 35% of 31 total perioperative neurologic events. Hemorrhage occurred a median of 3 days after surgery (range: 0–18 days). All 11 patients were hypertensive, and 7 conscious patients reported headaches. Massive hemorrhage and death occurred in 4 patients (36%).

The cause of IPH after CEA is believed to be a result of postoperative hyperperfusion. Sundt et al [28] documented an augmentation of cerebral blood flow after CEA. Furthermore, Piepgras et al [29] documented ipsilateral cerebral blood flow more than twice that of baseline in 14 patients with postoperative intracerebral hemorrhage. Mansoor et al [25] documented intracranial arterial changes in patients who died of an IPH after CEA and found changes similar to those seen in malignant hypertension, suggesting relative hyperperfusion. The hemorrhage occurs within the healthy brain tissue and not the infarcted tissue, adding more support to the hyperperfusion hypothesis.

Timing of CEA after a stroke in a patient with fixed neurologic deficit remains an important but unresolved question. Early surgery is associated with higher risk of IPH, whereas delayed endarterectomy exposes the patient to recurrent infarcts and carotid occlusion. Even though the issue on timing of CEA after cerebral infarction is not settled, most surgeons prefer to wait at least 3 weeks.

Carotid percutaneous transluminal angioplasty

Recently, percutaneous transluminal angioplasty (PTA) has been widely used for treatment of stenosis of extracranial arteries, especially in those patients not suitable to undergo surgery. Similar to the cerebral hyperperfusion syndrome seen after CEA, Schoser et al [30] described 2 patients with severe hyperperfusion syndrome from a series of 86 patients treated with PTA. One of these 2 patients suffered a putaminal hemorrhage.

Another series studied 82 patients who underwent 85 PTAs for symptomatic and more than 70% atherosclerotic stenosis of extracranial internal carotid artery (ICA) [31]. Although the overall complication rate for transient ischemic attack, stroke, and dissection was 4.9%, no cases of IPH, cerebral hyperperfusion syndrome, or death were reported in this study. In conclusion, PTA for stenosis of an extracranial carotid artery is an alternate treatment for patients who are not suitable for CEA. It carries comparable morbidity and mortality risks, but its long-term efficacy is unknown.

Diagnostic angiography

Diagnostic cerebral angiography is the procedure of choice in diagnosing vascular lesions such as arteriovenous malformations (AVMs), aneurysms, and certain cervical carotid diseases. Overall, these procedures are safe; the rate of all complications is approximately 1%, with a rate of permanent neurologic deficit below 0.2%. The rate of IPH has not been specified but is believed to be far less than the rate of thromboembolic infarcts [32,33].

Angioplasty for intracranial atherosclerosis

PTA is an endovascular technique that was first described in the 1960s by Dotter and Judkin for the treatment of peripheral vascular atherosclerotic disease. Since then, extensive experience has accumulated in the treatment of coronary, renal, and iliofemoral circulations. In 1980, Sundt et al [34] reported basilar artery angioplasty in two patients. At the present time, the two main indications for cerebral angioplasty are atherosclerotic disease and vasospasm.

Takis et al [35] reported on 10 patients with symptomatic atherosclerotic intracranial arteries who were treated with PTA. They were able to perform PTA in 8 of 10 patients with postprocedural residual stenosis of 50% or less in all of them. Complications included stroke (50%), vasospasm (63%), and arterial dissection. Five patients had good outcomes, whereas 3 patients had unfavorable outcomes. There were no cases of IPH reported.

A recent retrospective analysis of patients undergoing PTA for intracranial atherosclerotic lesions revealed a good outcome in 66 of 70 patients [36]. Complications included dissection (12 patients), transient ischemic attack (2 patients), and stroke (3 patients). Of 3 patients with strokes, 1 had IPH and 1 had hemorrhagic conversion.

As with CEA, cerebral hyperperfusion is a potential complication after PTA and stenting.

Meyers et al [37] reported that 7 of 140 patients (5%) had hyperperfusion syndrome after stenting of craniocervical arteries. Of these 7 patients, 1 suffered IPH. Thus, overall, PTA and stenting are the treatments of choice for patients who have failed all medical therapy or are too sick to undergo surgery. These procedures carry risk for complications such as strokes, dissections, and vasospasm, but the risk for IPH is 0.7% to 1.5%.

Angioplasty for vasospasm after subarachnoid hemorrhage

With improved catheter technology and increased experience with intracranial PTA for atherosclerosis, angioplasty treatments for vasospasm are possible. Several groups have reported outcome data from this procedure. Higashida et al [38] published clinical trial data on 28 patients treated for 99 vascular territories. Clinical improvement was observed in 17 patients (61%), whereas 2 patients (7.1%) had complications of vessel rupture causing IPH. Recently, Bejjani et al [39] reported on 31 patients with 43 aneurysms and total of 81 dilated vessels. They reported two deaths, which were not related to angioplasty, and 23 patients with dramatic or moderate improvement. Similarly, Eskridge et al [40] reported the results of 50 consecutive patients with vasospasm secondary to SAH who were treated with balloon angioplasty after failure of medical management. Twenty-eight patients (61%) showed sustained neurologic improvement within 72 hours of angioplasty. Three patients (6%) deteriorated after the procedure, and 2 (4%) died as a result of vessel rupture.

Angioplasty is widely used in the management of symptomatic cerebral vasospasm after SAH. It carries a risk of 0% to 7% for vessel rupture, SAH, or IPH. Not surprisingly, hemorrhagic complications of this therapy, although infrequent, are usually fatal. Polin et al [41] assessed the efficacy of angioplasty to treat vasospasm after SAH and concluded that angioplasty is effective in reversing angiographically confirmed vasospasm but its superiority to medical management for symptomatic vasospasm is questionable.

Treatment of arteriovenous malformations and aneurysms

The treatment of cerebral and spinal AVMs remains among the most challenging aspects of neurosurgery. Therapeutic options in the treatment of AVMs include the endovascular approach, microsurgical excision, and radiosurgery. In the immediate treatment period, there is a risk of IPH from feeding vessel rupture or injury directly from residual AVM as well as from adjacent normal parenchyma. A detailed discussion of AVMs, aneurysms, and their treatment is addressed elsewhere in this issue.

Thrombolytic therapy for myocardial infarction

The treatment goal in patients experiencing acute myocardial infarction (MI) is to preserve myocardium by means of acute recanalization of coronary arteries. Acute coronary thrombolysis no longer requires local thrombolytic administration but rather systemic intravenous administration. Thrombolytic therapy provides definite improvement in the morbidity and mortality associated with acute MI; however, this therapy inherently involves a risk of hemorrhage. Although the incidence of ICH is low, high fatality rates and substantial disability among survivors are characteristic of this complication.

Before coronary thrombolysis became the primary treatment for MI, approximately 1% of patients with MI suffered strokes. Approximately 0.4% of these strokes were attributable to hemorrhage [42]. Subsequently, in tens of thousands of patients treated with fibrinolytic agents as well as anticoagulants, the overall stroke incidence was virtually identical to that seen without anticoagulants alone, but the incidence of IPH was slightly higher.

The Thrombolysis in Myocardial Infarction (TIMI) trial examined the effect of intravenous recombinant tissue plasminogen activator (tPA) in the setting of acute MI at two doses: 150 mg and 100 mg. All patients received aspirin and intravenous heparin. The risks of IPH were 1.9% and 0.5% for 150 mg and 100 mg of tPA, respectively [43]. The Global Utilization of Streptokinase and tPA of Occluded Coronary Artery (GUSTO-1) trial randomized 41,021 patients in 1081 hospitals in 15 countries in one of four thrombolytic treatment strategies. ICH rates were 0.46%, 0.57%, 0.70%, and 0.88% among patients treated with streptokinase plus subcutaneous heparin, streptokinase plus intravenous heparin, accelerated tPA, and combination therapy, respectively. Sixty percent of patients with ICH died, and 25% were disabled [44]. In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico trial, IPH occurred in 0.3% and 0.4% of patients treated with streptokinase and tPA, respectively [45].

Sobel [42] pooled data from nine major trials (N = 6375) of patients treated with tPA and intravenous heparin (European Cooperative Study Group-5, Anglo-Scandinavian Study of Early Thrombolysis (ASSET), TIMI-B, National Heart Foundation (NHF) Australia, TIMI-II, Randomized angiographic trial of recombinant tissue-type plasminogen activator (alteplase) in myocardial infarction (RAAMI), Thrombolysis in Coronary Occlusion (TICO), and studies by Topol and his colleagues and Guerci and his colleagues [both in 1987]) and reported an ICH rate of 0.5%.

To better evaluate the pattern of hemorrhage, CT scans of 244 patients suffering from symptomatic IPH in the GUSTO-1 trial were analyzed. Most hemorrhages were reported to be large, solitary (66%), lobar (77%), confluent (80%), and intraparenchymal (82%), with a blood–fluid level (82%) and with little edema [46]. The factors associated with IPH in thrombolytic therapy include older age, female sex, African American ethnicity, systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 100 mm Hg or higher, history of stroke, tPA dose more than 1.5 mg/kg, and low body weight [47]. The 30-day mortality rate in patients with IPH in the GUSTO-1 trial was 59.7% [48].

Thrombolytic therapy for acute stroke

Stroke is the leading cause of disability in the United States and the third leading cause of death. Traditional care for patients with stroke has focused on treating complications and preventing recurrent strokes. With encouraging results in thrombolytic treatment of acute MI, many trials have evaluated the use of thrombolytics in the treatment of acute stroke.

In the early 1990s, reports on the first two randomized controlled trials of intravenous recombinant tPA were published. Patients in both trials underwent cerebral angiograms to identify the site of arterial blockage before initiation of therapy. A total of 129 patients, all within 6 hours of symptom onset, were randomized into either the treatment or the placebo group. Mori et al [49] reported a recanalization rate of 50% at 1.17 mg/kg of intravenous tPA and 44% at 0.73 mg/kg of intravenous tPA versus 17% in the control group. Similarly, Yamaguchi and Kikuchi [50] showed 57% recanalization rate in patients treated with 0.73 mg/kg of intravenous tPA versus 24% in patients treated with placebo. In the report by Mori et al [49], hemorrhagic complications occurred in 30% and 56% of high-dose and low-dose groups, respectively, versus 33% in the placebo group. In the trial by Yamaguchi and Kikuchi [50], however, the hemorrhagic complication rate was 47% in both the treatment and placebo groups.

The National Institute of Neurological Disorder and Stroke trial randomized 624 patients into the placebo and recombinant tPA (0.9 mg/kg administered intravenously) arms. Time from stroke symptom onset to treatment was less than 3 hours in every patient. In the treatment group, 43% of patients had minimal to no disability versus 26% in the placebo group. Symptomatic IPH occurred in 6% of patients in the treatment group versus 1% in the placebo group. Mortality as a result of ICH was 2.9% in the treatment group versus 0.3% in the placebo group. The overall 90-day mortality rate was 17% in the treatment group versus 21% in the placebo group [51]. In the European Cooperative Acute Stroke Study I and II, patients were treated within 6 hours of onset of symptoms with either placebo, 0.9 mg/kg of recombinant tPA, or 1.1 mg/kg of recombinant tPA. Patients showed similar rates of recovery as in the National Institute of Neurological Disorder and Stroke study; an IPH rate of 9% was reported in the treated group and an IPH rate of 3% was reported in the placebo group. Although the mortality caused by IPH was significantly higher in the treatment group (6.3% and 3.0%) versus the placebo group (2.4% and 1.0%), the 90-day mortality rate was similar in both groups [52,53].

Intra-arterial thrombolysis, an alternative to intravenous thrombolytic therapy involves a cerebral angiogram to identify the site of occlusion and direct delivery of thrombolytic therapy into the clot. There have been two randomized controlled trials of intra-arterial thrombolytic therapy using prourokinase. The Prolyse in Acute Cerebral Thromboembolism I study assessed the safety and recanalization rate compared with placebo in 46 randomized patients. Overall, the recanalization rate was 58% in the treatment group versus 14% in the placebo group. There was an increase in symptomatic IPH in treated patients at 24 hours (15% versus 7%); however, the difference narrowed to 15% versus 14% at 90 days. Overall mortality was less in the treatment group than in the placebo group, and mortality caused by IPH was 4% in the treatment group versus 7% in the placebo group [54]. Similarly, the Prolyse in Acute Cerebral Thromboembolism II trial randomized 180 patients to intra-arterial prourokinase versus placebo. Overall, patients treated with recombinant

prourokinase had a significantly better functional recovery at 90 days than patients treated with placebo, and they had a much better recanalization rate (66% versus 18%). Symptomatic IPH occurred in 10% of the treatment group versus 4% of the placebo group, but 90-day mortality rates were comparable (25% in treated group versus 27% in placebo group) [55]. Figure 2 demonstrates an IPH in a patient who received intra-arterial thrombolysis after an acute stroke.

In summary, thrombolytic therapy for acute stroke exemplifies the delicate balance between risk and benefit. These randomized trials have shown that the benefits clearly outweigh the risks. Whereas treated patients may have higher morbidity and mortality from IPH immediately, the 90-day mortality rate is either the same or better in the treatment groups.

Thrombolytic therapy for vasospasm

Vasospasm is an inevitable complication seen after SAH. Delayed neurologic deficits as a result of ischemia caused by vasospasm often result in great morbidity and mortality. Although many factors may be responsible for the vasospasm, irritation of blood vessels by blood and its byproducts has been implicated in this process. Many centers have attempted to prevent vasospasm by administering recombinant tPA and urokinase intrathecally along with cisternal drainage to remove the subarachnoid blood clot.

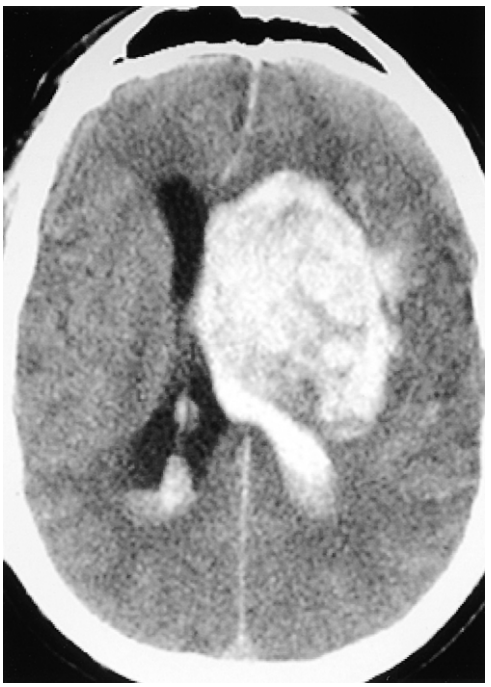

Fig. 2. A 57-year-old woman presented with acute stroke. Initial screening CT was normal, and intra-arterial thrombolysis was administered. Approximately 6 hours later, she acutely declined, and a follow-up CT scan revealed a large intraparenchymal hemorrhage with intraventricular extension.

Usui et al [56] treated 111 patients with either intrathecal urokinase or tPA and found intrathecal treatment to be effective in lysing the subarachnoid clot and preventing vasospasm. There was one complication with asymptomatic intraventricular hemorrhage and no incidence of IPH. With other studies, intrathecal thrombolytics caused repeated SAH (1%–5.6%), most frequently followed by epidural hematoma (1%–1.8%) [57,58]. Risk of IPH from this therapy is not well reported and is generally believed to be small. There is no question that intrathecal thrombolytics facilitate drainage of subarachnoid clots; however, many authors have debated its role in the prevention of vasospasm [59].

Iatrogenic medical factors

Anticoagulation

The prevalence of many thromboembolic disorders, such as stroke, MI, and venous thrombosis, is known to increase with age. Thus, elderly patients represent those most likely to be treated with anticoagulant therapy. Unfortunately, anticoagulation therapy is a double-edged sword and may be associated with a risk of major bleeding. ICH is the most feared and lethal complication of anticoagulation therapy. Despite its therapeutic potential, the risks as well as potential benefits of anticoagulation must be carefully considered before initiation of therapy.

Heparin acts at multiple sites in the normal coagulation pathway to inhibit reactions that lead to the clotting of blood and the formation of fibrin clots. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated *Factor* X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has occurred, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin-stabilizing factor. Warfarin inhibits the synthesis of vitamin K–dependent clotting factors, which include

factors II, VII, IX, and X, the anticoagulant proteins C and S. Vitamin K, an essential cofactor for the postribosomal synthesis of these *Factors*, promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins, which are essential for biologic activity. Both heparin and warfarin increase the risk of systemic and intracranial bleeding.

Many recent studies have shown that IPH makes up approximately 70% of anticoagulant-related ICH. A study from central Finland identified 158 patients with primary IPH from a population of 116,000 over a 4-year period. The study found that of 158 patients, 14.8% were receiving anticoagulants versus only 1.6% of controls, suggesting that these agents increase the risk of IPH 7-fold [60]. A review by Hart et al [61] reports that oral anticoagulants increase risk of IPH by 7- to 10-fold and an absolute rate of 1% per year. The aggregate mortality rate is approximately 60% for patients who develop IPH as a result of anticoagulation. Patient factors and level of anticoagulation influence the incidence of IPH. Factors firmly linked to anticoagulant-related IPH include advanced age, level of anticoagulation, prior stroke, and hypertension. Atrial fibrillation, diabetes, concomitant use of antiplatelet agents, amyloid angiopathy, and lipohyalinotic and fibrinoid degeneration of arterioles have also been implicated [61,62]. Some precipitating factors include head trauma, acute alcohol intoxication, acutely elevated blood pressure, and severe migraine attack [61]. On CT scan, anticoagulation-related IPH is most often lobar with blood–fluid level and tend to expand with repeat imaging [63].

The treatment for symptomatic IPH is cessation of the anticoagulant. For heparin-associated hemorrhage, the agent should be stopped, and reversal with protamine should be considered strongly. For hemorrhage associated with warfarin, cessation of the agent, intravenous administration of fresh frozen plasma (FFP), and intramuscular administration of vitamin K are indicated. It may take several hours for this therapy to be effective.

Antiplatelet therapy

The possibility that aspirin use increases the incidence of IPH was first raised by the results of the US Physicians' Health Study. In this double-blind study, 11,037 physicians took 325 mg of aspirin every second day for an average of 60.2 months. A similar number of patients received placebo. Twenty-three of those in treatment group and 12 of those receiving placebo were diagnosed with hemorrhagic stroke based on review of their medical records. The difference in incidence was of borderline significance ($P = 0.06$) [64].

In the Swedish Aspirin Low-Dose Trial, 1360 patients were randomized to receive either 75 mg of aspirin daily or placebo [65]. After an average of 32 months of follow-up, seven IPHs had occurred in the treatment group versus three in the placebo group. A recent Australian study reviewed discharge and coroner records from 13 major city hospitals [66]. After excluding patients with IPH secondary to an AVM, tumor, clotting abnormalities, anticoagulant or thrombolytics therapy, and the ingestion of sympathomimetic drugs, 331 patients were identified with IPH. No increase in the risk of IPH was found among aspirin users or among those who took nonsteroidal anti-inflammatory drugs compared with controls.

In summary, from the evidence presently available, it is unclear whether aspirin use increases the risk of IPH. At worst, it seems that this risk is small.

Self-administered drugs

Sympathomimetics

Sympathomimetic drugs, such as cocaine, amphetamine, and ecstasy, are an increasingly common cause of IPH, particularly in younger and middle-aged individuals. One estimate of their contribution is provided by a study of 214 consecutive patients aged 15 to 44 years admitted to a hospital in San Francisco with a diagnosis of stroke [67]. One third of these strokes were IPH. Among the IPH patients, 34% reported drug abuse compared with 8% in the control group. In another study that reviewed the records of 3712 drug abusers, 13 (0.35%) patients were identified with neurologic deficits attributable to the use of cocaine [68]. Although ischemic manifestations were the most frequent neurologic deficits and occurred in 7 (54%) patients, 3 (23%) patients had SAH and 3 (23%) had IPH.

Transient hypertension, vasospasm, migraine, and vasculitis have been suggested as mechanisms of cocaine-induced hemorrhage. Citron et al [69] reported vascular changes of necrotizing angiitis, including arterial aneurysm and sacculation in the kidneys, liver, pancreas, and small bowel, by selective angiography. The finding of cerebral vasculitis was verified by pathologic studies in patients with cocaine use and multifocal ischemia.

Alcohol

Several epidemiologic studies have demonstrated an increased risk of IPH in heavy alcohol drinkers, but the effect of small to moderate alcohol intake is unclear. Although several studies provide evidence for a protective effect, this conclusion may be premature.

An Australian study demonstrated an increased risk of IPH from heavy drinking (odds ratio = 3.4; 95% confidence interval: 1.4–8.4) among 331 case–control pairs. The odds ratio for moderate drinkers was 0.7 compared with nondrinkers [70]. Another study reported that male subjects drinking more than 100 g of alcohol per day and female subjects drinking more than 80 g/d experienced a 13-fold increase in the risk of IPH [71].

There are several possible mechanisms by which excess alcohol could lead to IPH. For example, intake of alcohol may raise blood pressure acutely and interfere with platelet function. In the case of chronic use of alcohol, a coagulation abnormality may develop secondary to liver failure. In summary, heavy use of alcohol is a risk factor for IPH, although the role of mild to moderate alcohol use is controversial.

Bleeding disorders

Thrombocytopenia

Thrombocytopenia is defined as a platelet count of less than 150,000. Usually, increased bleeding is not attributable to thrombocytopenia until the platelet count drops below 50,000. The risk of spontaneous life-threatening (eg, central nervous system, gastrointestinal) bleeding increases significantly at counts below 20,000 and substantially at counts below 10,000. A helpful diagnostic strategy is to differentiate disorders of marrow production from conditions that result in increased platelet use or sequestration. Generally, a bone marrow examination is used to help in this distinction. Use of agents that further impair hemostasis, such as aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants, is generally contraindicated in these patients.

Some of the causes of thrombocytopenia include marrow infiltration by tumors, storage diseases, or infectious agents that interfere with normal platelet production. Drug-induced thrombocytopenia is commonly iatrogenic (eg, after chemotherapy, radiotherapy, or heparin use) or secondary to ethanol use. Vitamin B_{12} and folate deficiency may also cause thrombocytopenia. Increased destruction of platelets may be caused by consumption or immunologic clearance such as that seen in immune thrombocytopenic purpura. Posttransfusion purpura is a rare syndrome characterized by the formation of alloantibodies, most commonly against the platelet surface antigen PLA1 in PLA1-negative patients who receive blood or platelet transfusions from PLA-positive donors. Thrombotic thrombocytopenic purpura is a systemic disorder characterized by platelet aggregation in the microcirculation. The complete clinical pentad, which is present in fewer than 30% of cases, includes consumptive thrombocytopenia, microangiopathic hemolytic anemia, fever, renal dysfunction, and fluctuating neurologic deficits.

The risk of IPH from thrombocytopenia increases with a drop in platelet count below 20,000. IPH is more commonly seen in newborns with thrombocytopenia because they have stress associated with vaginal delivery and undiagnosed low platelet counts. A survey was carried out in England to discover the frequency, circumstances, and outcome of IPH complicating immune thrombocytopenic purpura of childhood [72]. Over 20 years, 14 cases were discovered. Six patients survived the event with minimal or no sequel. An immediate precipitating cause was noted in four patients (two with AVMs, two with head trauma). The risk of hemorrhage was highest with a platelet count less than 10,000 to 15,000. In summary, thrombocytopenia poses a small risk for IPH, especially with a platelet count lower than 20,000.

Coagulopathy

Coagulopathy can be divided in two categories: inherited and acquired. Von Willebrand's disease is the most common inherited bleeding disorder and affects 1% of the population. The spectrum of disease is heterogeneous. Most forms are autosomal dominant. The Von Willebrand factor has two important functions: to facilitate adherence of platelets to injured vessel walls and to stabilize factor VIII in plasma. The X-linked forms, hemophilia A and B, account for 99% of inherited cases and are caused by deficiencies in factors VIII and IX, respectively. Acquired coagulation disorders include vitamin K deficiency, liver disease, and disseminated intravascular coagulation.

Intracranial bleeds are the second most common cause of death in hemophiliacs after AIDS. They occur in 10% of patients; approximately 50% of cases are associated with head injury, and 30% of such injuries are fatal. The etiology is

not apparent in 38% of cases (spontaneous cases), and the risk of development of an ICH is approximately 2% per year [73]. Bleeding may be subdural, epidural, or intracerebral. Subarachnoid bleeding occurs least commonly, but it carries the best prognosis.

Significant head injury must be treated early and intensively in patients with inherited coagulation disorders. Those with hemophilia A and B should immediately receive a sufficient concentrate of deficient factor to raise the plasma level to 100 U/dL. Samples for essential coagulation studies should be drawn before administration of replacement therapy, but treatment should not be delayed while waiting for results of these studies. Radiologic procedures, such as CT scanning, can be done while the therapeutic material is administered. Before the widespread use of factor VIII concentrates, the mortality rate after intracranial bleeding averaged 70%. In one series, replacement therapy given within 6 hours of head injury prevented any intracranial bleeding, and the mortality rate was 34% [74]. Because of these risks, patients with hemophilia should always have access to factor concentrates.

Tumors

Spontaneous IPH from primary as well as metastatic tumors has been well documented. Spontaneous ICH secondary to brain tumors represents 0.9% to 11% of nontraumatic ICHs, and the overall incidence of hemorrhage from intracranial tumors is approximately 1.3% to 9.6% [75–77]. It is important to note that the incidence of hemorrhage from metastatic tumors is higher than that from primary tumors. Mandybur [78] found that only 1 of 121 (0.8%) cases of glioma was associated with hemorrhage versus 13 of 92 (14.1%) cases of metastatic tumors. The most common metastatic brain tumors associated with hemorrhage are bronchogenic carcinoma, melanoma, choriocarcinoma, and renal cell carcinoma. Metastatic choriocarcinoma has the highest tendency of hemorrhage (50%), followed by melanoma (40%) [79,80]. Other metastatic tumors that can hemorrhage are fibrosarcomas, plasmacytomas, embryonal carcinoma, Wilms' tumor, hepatocellular carcinoma, ovarian carcinoma, and prostatic carcinoma [78,81–85].

Massive IPH is uncommon as the initial sign of a brain tumor. The rate of brain tumors presenting as ICH has been reported to range from 0.8% to 24% [76,77,86]. Tumor as the cause of IPH is suspected when the hemorrhage is in a unusual location for more common etiologies, such as an aneurysm, AVM, trauma, or hypertension. In addition, contrast enhancement, multiplicity of the ICH surrounded by perifocal edema on imaging, can be used to differentiate tumors from other causes of IPH (Fig. 3). MRI is the most useful tool for diagnosis of hemorrhage caused by intracerebral tumors.

Hemorrhages associated with brain tumors include subarachnoid, subdural, epidural, or intraparenchymal tumors, with IPH being the most common [80,87]. IPH is more commonly caused by hemorrhage into the tumor than by hemorrhage into the brain parenchyma adjacent to the tumor [80]. In the series by Wakai et al [77], 30 of 45 hemorrhagic tumors (66.7%) showed intratumoral rather than peritumoral hemorrhage. The mechanism of hemorrhage is not well understood; however, several theories exist. Rupture of fragile and malformed blood vessels, emboli resulting in hemorrhagic infarction, invasion of the arterial wall by the tumor, vascular necrosis after radiation, sudden changes in the ICP gradient after CSF decompression, and metabolic factors in a rapidly expanding tumor may deprive portion of

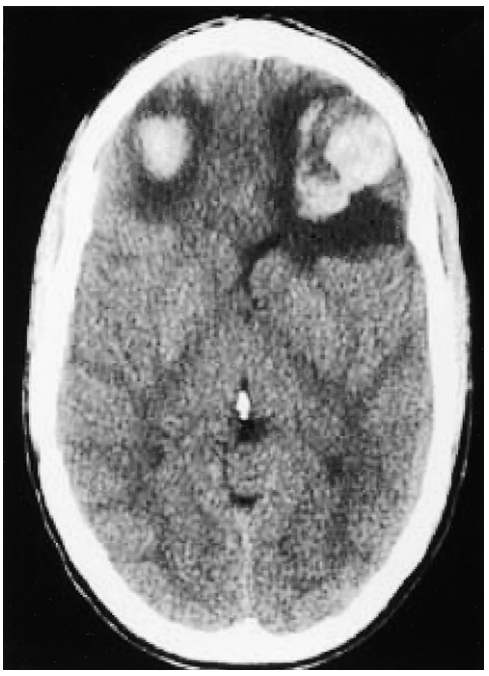

Fig. 3. A 17-year-old boy presented with acute mental status change. Head CT revealed bifrontal intraparenchymal hemorrhage with associated edema and mass effect. The patient was later diagnosed with metastatic testicular carcinoma.

the tumor of adequate nutrition and can lead to vessel rupture and hemorrhage [88–90].

Primary brain tumors, including benign tumors, may also present with spontaneous IPH. As mentioned, the incidence of hemorrhage from a primary tumor is lower than from a metastatic tumor. Among all the primary brain tumors, grade IV astrocytoma is associated with the highest incidence of hemorrhage. Wakai et al [77] and Lieu et al [84] reported the incidence of hemorrhage to be as high as 7.8%. Both oligodendroglioma and well-differentiated astrocytomas may also present with hemorrhage. Oligodendrogliomas have a higher rate of hemorrhage than well-differentiated astrocytomas [80]. The most common benign primary tumor associated with hemorrhage is pituitary adenoma. Other primary brain tumors associated with hemorrhage are medulloblastoma, neuroblastoma, hypothalamic pilocytic astrocytoma, hemangiopericytoma, neurocytoma, mixed glioma, and choroid plexus papilloma [77,91–95]. Figure 3 shows a head CT scan of metastatic testicular carcinoma in a 17-year-old boy.

The management of IPH caused by tumor depends on the size and location of the hemorrhage. Larger hemorrhage with mass effect may require surgical intervention, whereas smaller hemorrhage may not need immediate surgical treatment.

Other causes

Infectious causes of IPH are rare but have been reported with viral, bacterial, or fungal infections. Herpes encephalitis is the most common identified cause of severe sporadic viral encephalitis in the United States. Its estimated annual incidence is 1 in 250,000 to 500,000 persons. Herpes simplex virus encephalitis accounts for approximately 20% of the reported cases of encephalitis in the United States. With herpes encephalitis, patients occasionally develop hemorrhagic lesions in bilateral temporal lobes. IPH is uncommon. There are also reported cases of IPH from nosocomial aspergillosis infection and from mycotic aneurysm rupture [96].

Some indirect evidence suggests that pregnancy does increase the risk of IPH. Hemorrhage is associated with conditions unique to pregnancy, such as eclampsia, metastatic choriocarcinoma, and disseminated intravascular coagulation. In addition, there is a relative preponderance of IPH from AVMs and aneurysms in pregnant women. Various series estimate the incidence of IPH to be from 1 to 5 per 10,000 pregnancies. With a 30% to 40% mortality rate, IPH is responsible for 1 in 10 maternal deaths [97].

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