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Spontaneous intracerebral hemorrhage: epidemiology, pathophysiology, and medical management

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Stroke is the third leading cause of death within the United States [1], and intracerebral hemorrhage (ICH) represents 10–15% of all strokes. It has been reported in the literature that intracerebral hemorrhage has a 30-day mortality rate of 30–40% [2,3]. Intracerebral hemorrhage is the leading cause of morbidity within the United States, with an estimated lifetime cost of $6 billion [4]. Taylor et al [5] estimated the incidence of stroke in the United States based on data published after 1980, and found that the incidence of a first stroke would increase from 401,100 to 1,017,900 between the years 1995 and 2050. The number of intracerebral hemorrhages would increase from 52,400 to 120,700 [6].

Intracerebral hemorrhage can be divided into primary and secondary ICH based on etiology. Primary ICH consists of spontaneous hemorrhages that result from hypertension or amyloid angiopathy. Common causes of secondary ICH include use of anticoagulation or thrombolytics, neoplasms, aneurysms, or vascular malformations [6]. The focus of this article is to discuss the epidemiology, pathophysiology, and medical management of intracerebral hemorrhage.

Epidemiology

The incidence of intracerebral hemorrhage ranges from 15–35 per 100,000 [3,7–10], however, there are differences between racial/ethnic groups. Qureshi et al [10] evaluated data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study and found that African-Americans had an estimated annual incidence of 50 per 100,000 compared to 28 per 100,000 in Whites. This difference was also found in a study completed by Broderick et al [8], which reported an incidence of 19 per 100,000 in African-Americans compared to 15 per 100,000 in Whites. It has been hypothesized that hypertension, limited access to health care, and educational differences result in the higher incidence within the African-American community. There is also a higher incidence of intracerebral hemorrhage in Japan [11,12], which was reported to be as high as 2.87 per 1000 males [12]. One proposed explanation for this difference is the high incidence of hypertension and low total cholesterol levels within the Japanese community, both of which are risk factors for ICH.

Risk factors

Modifiable risk factors

Hypertension

Hypertension is the most important risk factor for spontaneous intracerebral hemorrhage. In a population study completed by Brott et al [13] they reported the relative risk for prehemorrhage hypertension to be 3.9. If a more inclusive definition of prehemorrhage hypertension included patients with left ventricular hypertrophy based on electrocardiogram or chest radiograph, then the relative risk increased to 5.4. This compares to a relative risk of 2–4 in ischemic stroke [14]. Hypertension and isolated systolic hypertension have been found to increase fatal and nonfatal

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stroke, and several studies have reported reductions in both of these groups with antihypertensive treatment [15–18]. The Systolic Hypertension in the Elderly Program study revealed a 36% reduction in stroke with hypertensive treatment [17]. The role of hypertension in ICH has resulted in the American Heart Association to recommend hypertensive control as the primary preventive measure for ICH [19].

Alcohol

The ingestion of alcohol and cardiovascular/cerebrovascular illness has been studied extensively. Moderate consumption of alcohol has been shown to decrease an individual's risk for cardiovascular and ischemic stroke. Klatsky et al [20] performed a prospective cohort study that found alcohol consumption reduced the relative risk (range: 0.44–0.63) of ischemic stroke when compared to abstainers and former drinkers. However, consuming three or more alcohol equivalents per day resulted in a relative risk of 1.38 for ICH. The mechanism by which excessive alcohol use results in intracerebral hemorrhage is not precisely known. One hypothesis is that alcohol consumption results in hypertension, which is an independent risk factor for ICH. The elevation of blood pressure with alcohol consumption is supported by work completed by Klatsky et al [21], who reported significant differences in systolic and diastolic blood pressures in individuals who consumed three or more drinks per day. However, the Honolulu Heart Program [22] found that heavy alcohol consumption increased the risk of stroke independent of hypertension.

Cholesterol

Low serum cholesterol has been found both within the Japanese and American communities to be associated with an increased risk for ICH. The inverse relationship between ICH and serum cholesterol has been found in several Japanese studies [12]. This was also supported by data from the Multiple Risk Factor Intervention Trial [23], which found an increased risk of ICH in individuals with total cholesterol <160 mg per deciliter.

Smoking

There has been no study that specifically addressed the issue of smoking and ICH risk. However, Thrift and colleagues [24] performed a retrospective study, which showed that hypertension alone had an adjusted odds ratio of 2.45 and hypertension combined with smoking was 6.12. All patients should be instructed to undergo smoking cessation, in an attempt to minimize modifiable risk factors for ICH.

Nonmodifiable risk factors

Nonmodifiable risk factors for primary intracerebral hemorrhage include age, sex, and race. The incidence or ICH within the elderly increases with age, and has been found to be an independent predictor of poor outcome at 6 months [2]. Male sex is also associated with a higher incidence of ICH, as is the African-American or Japanese race. The increased risk of ICH within the African-American population is most likely due to the increased incidence of hypertension and untreated hypertension, as described above. Within the Japanese population, the higher incidence of hypertension combined with lower cholesterol levels probably is responsible.

Pathophysiology

The brain's autoregulatory mechanisms allow the brain to maintain stable perfusion pressure over a wide range of blood pressures. It is the ability of the small- and medium-sized arterioles to change their vessel radius, which results in a stable perfusion pressure. The autoregulatory process is believed to account for the preferential changes seen in these vessels due to chronic hypertension. Chronic hypertension causes pathologic changes within the tunica media, termed lipohyalinosis. In one case series, Takebayashi and Kaneko [25] examined 20 lenticulostriate arteries obtained during surgery for evacuation of a hemorrhage, and 16 autopsy whole-brain specimens, which were status post-ICH. Forty-six out of 48 ruptured lenticulostriate arteries were examined using electron microscopy and found to have atrophy and fragmentation of the smooth muscles cells (lipohyalinosis). The most prominent changes were seen at bifurcation points within the vessel and in the middle and distal portions of the vessel. The most proximal segments of the middle cerebral arteries were less affected. Lipohyalinosis was found within both the hemorrhagic and nonhemorrhagic vessels examined. Takebayashi [26] then performed a comparison study between normotensive and hypertensive arteries. Again, the hypertensive vessels showed the classic "moth eaten" appearance within the media compared to normotensive vessels. Only two ruptured aneurysms were found within the specimens from Takebayashi and Kaneko's study [25], raising the question of the

importance of microaneurysms in ICH secondary to hypertension.

The role of microaneurysms is not as well understood, and there are currently two hypotheses to explain their formation. The first is that during the process of lipohyalinosis some vessels develop aneurysmal dilatations, and the second is that these aneurysms are the result of microhemorrhages or dissections within the wall of the vessel. As the blood is reabsorbed a thin fibrous sac or aneurysm is left. Challa, Moody, and Bell [27] analyzed brain sections from 35 hypertensive patients (four with ICH) and 20 normotensive patients using an alkaline phosphatase endothelial stain followed by light microscopy and high-resolution microradiography. Within their sample they found no evidence of microaneurysms, and postulated that microaneurysms have little to no relationship with intracerebral hemorrhage secondary to hypertension. It is unclear how significant microaneurysms are in ICH, and this remains an area for future research.

Cerebral amyloid angiopathy (CAA) is the result of amyloid being deposited within the media and adventitia of small- to medium-sized vessels. Amyloid angiopathy has a predilection for affecting the leptomeningeal and penetrating vessels of the cortex [28], and may undergo fibrinoid change, which has been traditionally described in hypertensive vessels. Masuda et al [29] analyzed 400 consecutive autopsies, in a Japanese community, for the presence of cerebral amyloid angiopathy and its correlation with 26 cases of ICH. Approximately 23% of the non-ICH autopsies had changes consistent with CAA, and the frontal lobes were most affected. Of the 26 cases of ICH only one (a cerebellar hemorrhage) was thought to be secondary to CAA. Vonsattel et al [30] compared CAA present within autopsies of patients with and without ICH, and found that the CAA was more severe in the patients with ICH. It appears based on the literature that the degree of CAA and not necessarily the presence of CAA increases the risk of ICH. Both Vonsattel [30], and Masuda [29] found fibrinoid necrosis associated with CAA. Because CAA is a disease that affects the elderly, it may account for a higher percentage of spontaneous ICH in the future, as our population ages.

Neurologic dysfunction secondary to ICH is due to the initial hemorrhage with its associated mass effect and tissue destruction, hematoma enlargement (see Fig. 1), and further deterioration may be due to cerebral edema (see Fig. 2). Tissue hypoperfusion has been well documented within

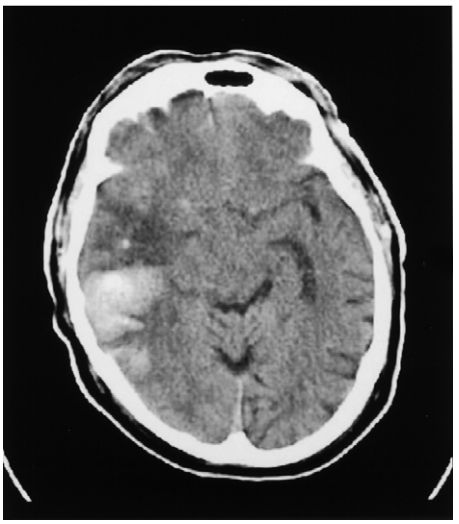

Fig. 1. Mechanisms of deterioration, hematoma enlargement.

rat models for ICH. Mendelow and Bullock performed a series of experiments within rats to evaluate the affects of contained versus uncontained ICH [31,32]. The uncontained ICH had a higher intracranial pressure and global reduction in cerebral blood flow (CBF) compared to the contained ICH. Contained ICH resulted in a focal reduction in CBF surrounding the hematoma, suggesting a local affect on microcirculation. Nehls et al [33] performed a series of experiments in rats to determine if the local reduction in CBF would continue over time. In this rat model they inflated a microballoon within the caudate to mimic the local mass effect from ICH, and then determined CBF at 5 minutes and 4 hours. The data showed that the local reduction in CBF continued to decrease over the 4 hours. Nehls then compared the changes in CBF within animals that had the balloon inflated for only 10 minutes compared to permanent inflation. The rats with transient inflation had a return to normal CBF levels within 24 hours, whereas the other group had continued reduction in CBF locally and globally within the ipsilateral hemisphere [34]. The reduction in cortical blood flow may be analogous to the penumbra, which represents neuronal areas at risk for progression to ischemia. This data supports the use of surgical evacuation to improve local tissue perfusion and mass effect in an attempt to minimize morbidity and mortality. However, despite experimental evidence of an ischemic penumbra, the depth,

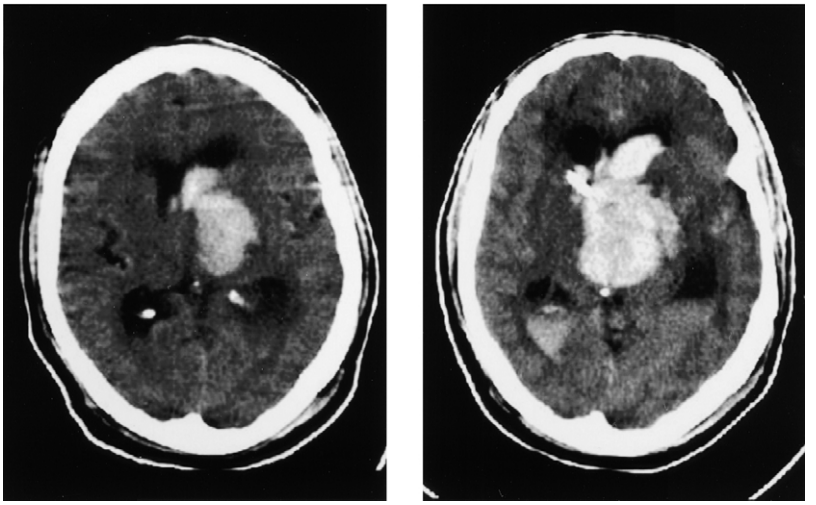

Fig. 2. Mechanisms of deterioration, cerebral edema.

duration, and volume of brain tissue involved is not considered adequate to contribute to the development of cerebral edema.

Hematoma enlargement

During the 1970s, and into the 1980s it was believed that the bleeding that occurred into an ICH stopped within the first hour, and that neurologic decline was secondary to mass effect and cerebral edema. However, during the 1990s, multiple case reports and retrospective case studies utilizing CT scans revealed this not to be true. Fujii et al [35] reviewed 419 cases of ICH and found, based on CT scans, that in 14.3% of the patients the ICH had increased in size on a follow-up CT scan. Based on their study, predictors of ICH expansion were an initial CT scan less then 1 hour from onset, liver and hemostasis dysfunction, and irregularly shaped hematomas. If the initial CT scan was performed within the first hour, the incidence of hematoma growth was 26.1% compared to 1.4% if the initial CT scan was greater then 6 hours after onset. Kazui et al [36] confirmed the higher incidence of hematoma enlargement early after initial onset. In their study 36% of patients who had their initial CT scan within 3 hours revealed enlargement on follow-up imaging. Brott et al [37] reported a 26% incidence of hematoma enlargement if the initial CT scan was within 1 hour. They attempted to identify predictors of hematoma enlargement based on CT findings, blood pressure, or hematoma location, but could not identify any predictors that were statistically significant. However, there was a suggestion that thalamic hemorrhages enlarged more frequently. Unfortunately, at this time the pathophysiology of hematoma expansion is not understood.

Cerebral edema

Cerebral edema (CE) typically develops over the first 24–96 hours [38]. The clinical effect of increasing edema depends on the resultant change in tissue shifts and tissue perfusion. In some patients there will be no clinical manifestation or long-term affect from the increase in cerebral edema, and the edema will slowly resolve over weeks. However, in many patients CE may result in more tissue shift and new clinical symptom progression. For this reason, cerebral edema has been studied extensively within animal models in an attempt to understand the pathophysiology and develop possible treatment strategies.

Initial perihematomal edema that occurs within hours of symptom onset was studied with a pig model created by Wagner et al [39]. In this study, autologous blood was injected into the right frontal hemisphere, and the pigs were sacrificed at 1, 3, 5, and 8 hours to determine the water content and affect of the ICH on the blood–brain barrier (BBB). The results revealed a 10% increase in perihematomal water content within 1 hour of blood infusion. The edematous regions were highly immunoreactive for serum proteins within the extracellular space, suggesting that the edema was extracellular and not intracellular. They also studied the permeability of the BBB, and found

that within 8 hours the BBB was still intact, suggesting that the serum proteins were present secondary to the hematoma. This study provided evidence to explain the initial edema found in the perihematomal region, but did not address the more important edema that develops 24–72 hours after symptom onset.

Lee et al [40] performed a series of experiments in rats to try to determine if factors within the hemorrhage could be responsible for this more serious edema. In one series of experiments they evaluated the affect of purified thrombin on edema formation by injecting 10 μL of a thrombin solution into the right basal ganglia of rats. There was two study groups: group I received 1 U/μL, and group II received 10 U/μL of a thrombin solution. The rats were sacrificed after 24 hours and the brain water content was calculated. It was found that the 1-U/μL group developed a significant increase in brain water compared to the contralateral hemisphere, and the 10-U/μL group had significant increase in brain water within the ipsilateral and contralateral cortex and basal ganglia. In fact, the 10-U/μL group had a 33% mortality compared to zero within the 1-U/μL group. Subsequently, they studied the affect of two thrombin inhibitor agents, hirudin and Nα-(2-Napthalenesulfonyl-glycl)-4-DL-phenylalaninepiperidide (α-NAPAP), which prevented the changes in brain water content and mortality associated with injection of thrombin. In another series of experiments [41] they evaluated the ability of various blood constituents (saline, plasma, concentrated blood cells, and whole blood) to cause edema. Each injection was 50 μL and the animals were sacrificed after 24 hours. Only whole blood was found to induce CE, so they then compared serum, plasma, and plasma with prothrombinase complex in another series of rats. This experiment revealed that serum or plasma alone did not result in edema formation, but once factors within the clotting cascade were added (prothrombinase complex) edema formation resulted. They concluded that thrombin was essential to CE formation [41], and then studied the relationship between thrombin and fibrinogen. Lee et al [42] utilized a synthetic clot with and without fibrinogen and with and without thrombin to try and elucidate the role of fibrinogen in edema formation, and concluded that thrombin-associated CE was independent of fibrinogen. How thrombin caused CE was then investigated [43], and it was found that thrombin resulted in BBB disruption and cell death, and had no effect on CBF or vasoreactivity. Lee and colleagues concluded that thrombin-associated edema was the result of BBB disruption and cytotoxic effects on individual cells within the brain.

Hua et al [44] performed a three-stage experiment in rats to identify if complement is activated in the perihematomal region at 24 and 72 hours. In the first stage, they were able to identify complement factors C9 (component that binds to the plasma membrane allowing the formation of the membrane attack complex), C3d (a segment of C3), and clusterin (a complement inhibitor) in the perihematomal area with immunohistochemical analysis. In the second stage of the experiment they quantified the amount of C9 and clusterin utilizing Western blot analysis, and in the third stage they evaluated the ability of N-acetylheparin (a complement inhibitor) to prevent the development of edema. They were able to successfully identify complement factors and measured a sixfold increase in C9 levels in the perihematomal region. N-acetylheparin was found to reduce the ipsilateral brain edema at 24 and 72 hours, indicating that complement may be associated with both early and late edema. They concluded that complements role in perihematomal edema may be related to either red blood cell lysis or lysis of brain tissue. Lysis of red blood cells and the toxic effects of hemoglobin have been hypothesized to contribute to late edema formation. Xi et al [45] studied the ability of packed red blood cells, lysed red blood cells (RBCs), and hemoglobin to induce edema within 24 hours after infusion into the rat basal ganglia. Their results revealed that both lysed RBCs and hemoglobin induced edema, but the packed RBCs did not. Hemoglobin has been shown to induce lipid peroxidation [46], and its breakdown releases iron, which can form free radicals. RBC lysis within the hemorrhage can occur from two mechanisms: energy production failure, and membrane attack complex formation. This provides further evidence for the role of complement activation in late edema formation.

Based on the animal data discussed above, initial edema develops secondary to plasma proteins, which accumulate in the extra-vascular space. Initially the BBB is intact, and, therefore, these proteins most likely arise from the hematoma. After the initial hemorrhage the clotting cascade activates thrombin, which then causes disruption of the BBB and direct cytotoxicity. The disruption of the BBB leads to the activation of the complement system, which ultimately leads to membrane attack complex formation and cell (both neural and RBC) lysis. The clotting/complement cascade most likely

accounts for the edema seen at 24–72 hours. RBC lysis with hemoglobin toxicity and formation of free radicals probably accounts for the late onset edema, which remains for weeks after the initial hemorrhage. Based on this data several possible treatment strategies utilizing either thrombin or complement inhibitors are possible. Also, this data supports the removal of the RBC clot as a method to reduce late edema and further tissue destruction.

Management

Initial management of a patient with a known ICH is determined by the patient's level of consciousness and ventilatory status. The first priorities should be to assess the patient's airway, breathing, and circulatory function. Patients should be intubated to maintain proper oxygenation and airway patentcy. Both excessively high and low blood pressures should be immediately addressed to maintain adequate, but not excessive, cerebral perfusion pressure. In addition to early control of an individual's blood pressure, a detailed evaluation of the patient's coagulation status and history of anticoagulant use needs to be performed. The activated partial thromboplastin time, prothrombin time, and platelet count should be ascertained, and any abnormalities should be corrected with fresh frozen plasma or platelets accordingly. The decision to consider surgical treatment is based upon the patient's initial presentation, rapidity of decline, and the size and location of the hemorrhage. Neurosurgical decisions regarding surgical therapy are individualized for each patient based upon the above-mentioned factors as well as the patient's age and prognosis. If an intraventricular extension of a hemorrhage is present, the patient may require urgent placement of a ventriculostomy catheter to treat acute hydrocephalus.

Once the above decisions have been determined, close neurologic observation within an intensive care unit is required to monitor for neurologic decline secondary to hematoma expansion or complications of the hematoma. Neurological assessment should be completed every 2 hours for the first 24 hours, then every 4 hours for the next 48 hours, and then every shift there after. Standard medical therapy in the first several days following an ICH includes monitoring blood pressure, coagulation status, and hydration status. Blood pressure monitoring can be performed either invasively or noninvasively, depending upon the patient's overall status. Intravenous medications such as labetalol and sodium nitroprusside are typically utilized to control elevated blood pressures secondary to their rapidity of onset. Placement of a central venous catheter is favored to maintain appropriate intravenous access for treatment. A history of the patient's baseline systolic blood pressure should be obtained, and rapid correction of systolic hypertension should be avoided secondary to disordered cerebral autoregulatory mechanisms. In general, if a patient's baseline blood pressure is not known, a general guideline is to maintain pressures below 160/110 mmHg. Parenchymal intracranial pressure monitoring in patients with ICH is controversial, and decisions regarding placement of an intracranial pressure monitor should be made on an individual basis. Other general intensive care unit principals that should be followed include: monitoring of ventilatory status and extubation when appropriate, assessment of nutrition status and implementation of alimentary feeding via feeding tubes within the first 24 hours, and prevention of deep venous thrombosis with subcutaneous heparin, which is not contraindicated in patients with ICH.

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