



Intracerebral Hemorrhage

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Case Presentation

A previously healthy 57-year-old retired police officer is sitting with his wife having lunch when he suddenly develops a severe headache, nausea, and left arm and leg weakness. While he minimizes his difficulties, the wife is very concerned and calls 911. With the wife's description of the symptoms, the nearest EMS ambulance is dispatched for a possible stroke. Upon arrival, they find the man sitting with his head down on the kitchen table and his left arm hanging down to his side but still with reasonable grip strength. He will answer questions but appears sleepy. They begin transport and obtain basic medical information from the wife. The patient has a history of hypertension and hyperlipidemia, and has smoked for most of his adult life. He takes an aspirin every morning in addition to his other medications. The EMS personnel establish the time of onset to be approximately 12 noon.

While enroute to the hospital, the EMS personnel perform a neurologic screening scale, which suggests the patient is having a stroke. They also obtain an initial set of vital signs, which reveal the patient to be very hypertensive (220 systolic and 120 diastolic). His serum glucose by finger stick is 110 and the cardiac monitor shows a normal sinus rhythm. The EMS personnel suspect a hemorrhagic stroke and they notify the destination hospital enroute.

Key Learning Points

- Spontaneous intracerebral hemorrhages are dynamic processes and early hemorrhage growth is common
- Many patients with ICH require early adjunct care, such as airway management, seizure control, and blood pressure management
- General medical management plays an important role in minimizing secondary injury
- Like ischemic stroke, the best chance for improving outcome is to intervene very early
- Correction of coagulopathies need to be performed as fast as possible
- New ultra-early haemostatic therapies may provide a significant tool for the emergency physician
- While not universal, some patients may benefit from surgery. Involve neurosurgeons early.

Introduction

Despite the 1990's being declared the Decade of the Brain, no targeted therapy was developed to address the significant mortality and morbidity associated with spontaneous intracerebral hemorrhage. The study of targeted therapy for ICH has lagged behind those for acute ischemic stroke (AIS). Significant advances did occur however which gave the medical community a better understanding of the physiology of ICH and began to demonstrate the dynamic nature of hemorrhage progression. A decade later we are finally on the cusp of developing directed therapies to address this devastating form of stroke.

Epidemiology and Pathophysiology

Morbidity and Mortality

ICH represents roughly 15-30% of all strokes. While occurring less frequently than ischemic stroke, it is associated with significantly greater mortality and morbidity. ICH has a mortality of almost 50% one year after the event, with most mortality occurring in the first month and over 20% within the first 7 days. Similarly, few patients with ICH regain independence. Less than 20% are independent at 6 months after their hemorrhage. And unlike ischemic stroke, most mortality is associated with the effects of the hemorrhage itself, not from secondary complications.

Location

Lobar hemorrhages (35%) typically develop in older patients due to chronic damage from beta-amyloid deposition in the cortical and leptomeningeal vessels. In younger patients lobar hemorrhages are associated with vascular abnormalities such as arteriovenous malformations or cavernous hemangiomas. Non-lobar hemorrhages typically occur in the putamen, pons, thalamus (collectively 50%), cerebellum (10%) and brainstem (5%). Non-lobar hemorrhages develop in small 50-200 μ m vessels secondary to hypertensive arteriolosclerosis.

Risk factors (spontaneous ICH)

| Common | Less common / Developing |
|------------------------------------|--|
| Hypertension (#1) | Cerebral venous thrombosis |
| Age | Infections (mycotic aneurysms, vasculitis) |
| Race (Asian > AA > Caucasian) | Neoplasm |
| Excessive alcohol use | Vascular malformations |
| Tobacco use | |
| Anticoagulant use / coagulopathies | Apolipoprotein E |
| Cocaine / PPA | |

Evaluation

History

Despite the widely accepted belief that patients with ICH have maximal symptom severity at onset, similar to AIS and subarachnoid hemorrhage (SAH), several studies have shown most patients actually have a progression of symptoms from onset. This is consistent with studies from the 1990s, which demonstrated hemorrhage growth in nearly 40% of patients presenting within 3 hours from symptom onset.¹ Initial symptoms of ICH include decreased level of consciousness (approximately 50%), headache (40%), vomiting (40-50%), and hypertension (80-90%). While these findings may suggest the patient has an ICH, only neuroimaging can adequately discriminate between ischemic and hemorrhagic stroke.

Physical examination

The general examination looks for signs of trauma, which may be responsible for the patient's ICH, and signs of associated injury. Specific neurologic deficits correlate with the location of the ICH similar to deficits in AIS associated with vascular distribution.

Laboratory

STAT laboratory orders should include complete blood count, coagulation parameters (fibrinogen, PT, PTT, INR), serum electrolytes, and liver function tests. Additionally a type and screen should be sent to the blood bank. Additional labs and diagnostics (chest x-ray and ECG) should be ordered as required by the patient's comorbidities.

Neuroimaging

CT scanning remains the gold standard for initial neuroimaging in suspected ICH and will likely remain so in the coming decade. CT imaging not only defines the size and location of the hemorrhage but it can suggest the underlying cause of the hemorrhage and any secondary complications (intraventricular extension, hydrocephalus, and signs of herniation). Additional imaging, such as MRI or cerebral angiography may be required to further define the cause of the hemorrhage in atypical cases.

A simple method for calculating hematoma volumes was first published by Kothari et.al. where they simplified the equation for an ellipsoid volume into $ABC / 2$, where A, B, and C are the largest diameters in each orthogonal axis, with C typically being based on the number of CT slices the hematoma is seen on multiplied by slice thickness.² Volumetric measurement is especially helpful in following hemorrhage progression and determining early prognosis.

Management

The treatment of patients with ICH consists of emergency stabilization of the ABC's (airway, breathing, circulation), concurrent management of comorbidities, general supportive medical care with emphasis on neurologic protection and complication prevention, and lastly, targeted therapies to address the hemorrhage itself.

ABC's

Unlike ischemic stroke patients, patients with ICH frequently require acute interventions to maintain their airway and provide mechanical ventilation. A knowledgeable understanding of airway management is critical to minimize delays to intubation and to prevent unnecessary elevation in intracranial pressure associated with intubation. Thus rapid sequence intubation is the preferred method for intubation. Similarly, hypertension is a common associated finding and many patients require blood pressure management.

General medical care

Optimal blood pressure management remains unsettled.³ The goal is to balance the belief that hypertension may promote hemorrhage growth with concerns that reducing blood pressure may reduce perihematoma perfusion, especially in the setting of increased intracranial pressure (ICP).⁴ Current American Heart Association (AHA) guidelines provide criteria for blood pressure management using agents such as labetalol, enalapril, nitroprusside and nicardipine.⁵ These

guidelines will be updated in the coming year, and several randomized trials of blood pressure management in ICH are underway. Currently blood pressure management is initiated when the systolic blood pressure is greater than 180 mmHg or the diastolic blood pressure is greater than 105 mmHg. In those patients with ICP monitoring, blood pressure should be maintained to ensure cerebral perfusion pressure (CPP=mean arterial pressure- ICP) is maintained above 70 mmHg. While uncommon, hypotension should be managed by correction of any volume deficit first, then complemented with vasopressors, such as phenylephrine or dopamine to maintain systolic blood pressures > 90 mmHg.

Unlike AIS, seizures are relatively common in ICH; close to 25% of patients develop seizures typically within the first 24 hours from hemorrhage onset.⁶ A high index of suspicion must be maintained, especially in comatose patients, as many seizures may be nonconvulsive. Prophylactic anticonvulsants are not recommended. Typical agents to treat ICH related seizures include phenytoin and phenobarbital. Fortunately, most seizures associated with ICH do not require anticonvulsant therapy beyond the first month.

Neurologic protection

While not classically defined as neuroprotection, there is a growing body of literature which suggests tight glycemic control and maintenance of normothermia (<38.5°C) are important adjuncts to general care that minimize secondary neurologic injury. Recent guidelines for AIS call for initiation of insulin administration when serum glucose is above 200 mg/dL.^{5,7} Ongoing trials in AIS, and hopefully ICH, will finally provide unequivocal data supporting this practice. Similarly, it is well known that hyperthermia is detrimental to the acutely injured brain. Induced hypothermia is under investigation as a general neuroprotective strategy. For now, tight glucose control and maintenance of normothermia is recommended. No other pharmacologic neuroprotective strategy has been shown to be beneficial in ICH although several trials are ongoing.

Targeted therapies - medical

Until recently, targeted hematoma therapies generally involved correction of coagulopathies and coagulation parameters with the administration of blood products (fresh frozen plasma (FFP), platelets, etc). Specific corrections for warfarin associated hemorrhages include administration of vitamin K and FFP. ICH associated with unfractionated heparin should be treated with protamine. Most low-molecular weight heparins can also be treated with protamine. The new direct thrombin inhibitors pose a challenge as there is no specific antidote for this

class of drugs. Correction of coagulopathies should be started as quickly as possible.

The recent study of recombinant factor VIIa (rFVIIa) is the first study to provide clear evidence that by limiting hemorrhage growth, patients with ICH have less mortality and morbidity.⁸ In this phase II placebo controlled study, rFVIIa was administered to patients within 4 hours from symptom onset. As a group, patients who received rFVIIa had less hematoma growth and less perihematomal edema development at 24 hours. While the absolute volume difference between treatment and placebo groups was modest (4.5 ml), it was associated with an 11% decrease in mortality and a 16% reduction in patients with unfavorable outcomes. Serious thromboembolic events occurred in 7% and 2% of the treatment and placebo group respectively; thus proper patient selection will be essential if rFVIIa becomes standard of care. Like tPA for AIS, it is likely the emergency physician will be intimately involved in the administration of rFVIIa due to the narrow treatment window.

Increased intracranial pressure is a common sequela of ICH and is responsible for much of mortality and morbidity in ICH. Early intervention when ICP is above ≥ 20 mmHg is required to prevent often precipitous herniation and death. Osmotherapy remains the first approach to lowering ICP. Osmotic therapy typically consists of mannitol 20% (0.25-0.5g/kg every 4 hours) to maintain a serum osmolality of ≤ 310 mOsm/L. Moderate hyperventilation, with a target pCO₂ from 30-35 mmHg produces a drop in ICP from 25-30% within 30 minutes. Additional measure to minimize ICP also includes muscle relaxants and adequate sedation for patients receiving mechanical ventilation. Sedation is also important prior to procedures, such as endotracheal suctioning, nasogastric tube placement, etc, which cause transient elevations in ICP. Obstructive hydrocephalus also increases ICP and requires ventriculostomy for drainage of cerebral spinal fluid (CSF). Other therapies have been used in attempts to blunt ICP, but corticosteroids and glycerol have not been shown to be beneficial while barbiturates and hypertonic saline require additional study before their potential benefits become clear.

Targeted therapies - surgical

Intraventricular hemorrhage has been associated with worse outcomes, largely through obstruction of normal CSF flow. A ventriculostomy can remove excess CSF and monitor ICP, but have associated risks of infections and catheter tract hemorrhages. Recent pilot trials have also demonstrated faster resolution of

ventricular hematoma with the infusion of fibrinolytics via the ventriculostomy; ongoing trials will help determine the clinical impact of early ventricular blood removal.

Surgical removal of hematomas is fairly common despite the lack of compelling evidence that it impacts outcome. Hypothetical benefits of hematoma removal include reducing local mass effect and decreasing regional cytotoxicity produced by serum proteins in the hematoma. The International Surgical Trial in Intracerebral Hemorrhage (STICH trial), the largest study of surgical hematoma removal to date, was recently published.⁹ Despite enrolling 1033 patients, the investigators found no benefit in routine relatively early (within 24 hours from onset) supratentorial hematoma removal compared to standard medical management. Despite this negative trial, questions remain about aspects of surgical evacuation, such as timing of surgery, optimal hematoma location, surgical approach, endoscopic hematoma removal, and potential coadministration of hemostatic agents. Potential surgical candidates, identified in the AHA guidelines, include cerebellar hemorrhages greater than 3 cc associated with clinical deterioration or brain stem compression, ICH associated with structural lesions in patients with a chance for good outcome, and young patients with a moderate or large lobar hemorrhage who are clinically deteriorating.¹⁰

Miscellaneous

Prognosis

While it is difficult to specifically predict outcome in individual patients, GCS at presentation and volume of ICH have been shown to help predict general outcome.¹¹ In a study by Broderick and colleagues, patients with an initial ICH volume >60 cc (just 4 tablespoons!) and a presenting GCS < 9 had a 30 day mortality of 91%. Patients with an initial ICH volume of < 30 cc and a presenting GCS \geq 9 had a predicted 30 day mortality of 19%. Additional variables associated with worse clinical prognosis include intraventricular extension, ICH associated with anticoagulation, advanced age, and associated seizures.

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Patient Case Outcome

Emergency Department Course

Upon arrival in the Emergency Department (ED) he is triaged immediately to the trauma bay and met by the emergency physician and nurses. While the patient quickly receives a screening neurologic assessment, it is apparent that the patient's symptoms have progressed to where the left arm has minimal movement, and the patient's level of consciousness is mildly depressed (GCS 13). An IV is established while blood for laboratory tests is drawn. Facilitated by the advanced EMS notification, radiology is ready to perform the CT scan. It becomes immediately apparent that the patient has an intracerebral hemorrhage (ICH) in the left hemisphere. The official reading of a 40 cc ICH is called to the emergency physician while the patient is being returned to the ED.

Case Outcome

Over the subsequent 24 hours from ICH onset, the patient had a mild decrease in level of consciousness (GCS 11). Follow-up CT scans demonstrated mild hematoma enlargement, development of perihematomal edema, and mild midline shift, but no signs of intraventricular extension or herniation. Medical management over the first several days per the ICH pathway included blood pressure management with labetalol, aspiration precautions until cleared for soft diet by speech therapy, and DVT prophylaxis. The patient made a fair recovery after 2 weeks of inpatient recovery and now lives at home with assistance due to persistent left sided hemiparesis.