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Risk Factors for Delayed Diagnosis of Subarachnoid and Intracerebral Hemorrhage

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RISK FACTORS FOR DELAYED DIAGNOSIS OF SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE

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To identify risk factors for delayed diagnosis of subarachnoid (SAH) or intracerebral (ICH) hemorrhage in younger patients (ages 18 – 49), we performed a subsidiary case-control study among 702 subjects from the Hemorrhagic Stroke Project (HSP). Case subjects were the 54 HSP patients (7.7%) who did not receive an appropriate diagnostic evaluation (brain CT scan, and if CT negative, LP) within 24 hours of consulting a physician for symptoms consistent with hemorrhagic stroke. For each case subject with a delayed diagnosis, we identified two subjects from the HSP with a prompt diagnosis, all successfully matched on recruitment site. We calculated odds ratios (ORs) for the association between risk factors and delayed diagnosis.

Four features were associated with risk for delayed diagnosis (criteria: OR =2.0 or =0.5): initial evaluation in a physician's office (OR=23.1), absence of alarm symptoms (photophobia, loss of consciousness, focal weakness) (OR=4.6), no effortful activity preceding focal time (OR=5.5), and Hispanic ethnicity (OR=2.4). Risk factors associated with delayed diagnosis were different in patients who presented to the hospital compared to patients who presented to an office. In a separate analysis, risk factors associated with delayed diagnosis were different for patients with SAH compared with patients with ICH.

In conclusion, patients with SAH or ICH are at greater risk for a delay in their diagnosis if they do not have alarm symptoms, especially if they present to an office rather than a hospital emergency department. Efforts to reduce delayed diagnosis should be directed at primary care physicians who see low-risk patients with milder symptoms. Our findings also indicate that there are different risk factors associated with delayed diagnosis of hemorrhagic stroke based on location of presentation and on stroke type. Future research to understand and prevent delayed diagnosis must consider location of presentation and stroke type.

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After all the years, it's finally done!

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INTRODUCTION

I. Overview

Intracranial hemorrhage, including subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH), affects approximately 102,000 persons in the United States each year. SAH will be diagnosed in approximately 60,000 persons and ICH will be diagnosed in 42,000 persons. (1) SAH carries a mortality rate of approximately 55% in the first two months after initial bleed (2, 3), whereas ICH has a mortality rate between 35-52% in the first 30 days. (4-6) Of those who survive either SAH or ICH, the majority will be left with long-term disability.

A major advance in management of patients with intracranial hemorrhage has been the finding that early treatment improves outcome for patients with SAH. Studies by Kassell, *et al.* demonstrated that poor outcome was closely associated with vasospasm and re-bleeding and that the period of higher risk for re-bleeding was during the first three days after the initial event.(7, 8)

Early institution of therapy after SAH is associated with reduced risk of re-bleeding and improved functional outcome. (9, 10) Unfortunately, approximately 20% of patients experience a delay in diagnosis on their initial presentation and, thus, experience a delay in care. Although there have been many studies examining the effect of delayed diagnosis, the frequency and reasons for delay in diagnosis are currently not well known. While early institution of therapy of SAH has been studied, early institution of therapy for ICH is not well documented. Although early therapy is not documented for ICH, neurosurgeons believe in the importance of early diagnosis for ICH. (6)

The purpose of our study, therefore, is to examine the risk factors for delayed diagnosis of intracranial hemorrhage in both the hospital and the outpatient office settings.

II. Epidemiology

II.1 Subarachnoid Hemorrhage

Subarachnoid hemorrhage results when a blood vessel on the surface of the brain ruptures and bleeds into the space between the brain and the arachnoid. Usually, the vessel ruptures at a weakened area caused by an aneurysm, or dilatation, on a blood vessel (usually an artery). The most common type of aneurysm is a saccular protrusion attached to the artery by a small neck.

The incidence of SAH in North America is approximately 11-12 per 100,000. (1) Risk factors associated with risk of SAH include age, race, and gender. The incidence is greater in older people compared with younger people. The average age of onset of SAH is around 51 years, with most cases occurring in people over the age of 30. Although race is not associated with a difference in the incidence for aneurysm, it has been shown that certain populations in Japan and Finland have a higher rate of SAH from aneurysms. (2) The frequency of aneurysmal SAH in different countries most likely reflects the differences in population characteristics in those countries. In Cincinnati, a retrospective cohort study was conducted to determine whether there was a difference in the risk of ICH or SAH in African-Americans versus Caucasians. (11) Medical records, autopsy reports, and CT scans of all patients who were suspected of having an ICH or SAH

during the year were reviewed. When considering all age groups, there was a higher incidence of both SAH and ICH in blacks when compared to whites. Blacks had 2.1 times the risk of SAH of whites. (11) The problem with this study was that subjects were identified solely by the ICD-9-CM codes for ICH, SAH, cerebral aneurysm, arteriovenous malformation, and cerebrovascular accident. Patients were not actively identified on initial presentation to the hospital.

Aneurysms usually occur more frequently in men than women (4:1) up until the fifth decade of life. The prevalence of aneurysms is equal in men and women around the fifth decade. By the eighth decade, women have more aneurysms than men do (10:1). (2) Gender also appears to play a role in location of aneurysms. The proximal internal carotid is the site of more aneurysms in women, whereas the anterior communicating region is the more prevalent site in men. (2) Demographic characteristics are not the only factors that result in an increased risk of SAH. Clinical risk factors that lead to an increased risk of SAH include prevalence of hypertension or atherosclerosis and diet, tobacco, and alcohol habits.

Among all patients with a SAH, the mortality rate at one month is 45%, but most deaths occur in the first few days. (12) The leading causes of death are acute, effects from the initial hemorrhage, recurrent hemorrhage, and cerebral vasospasm (leading to rebleeding or ischemic brain damage, and infarction). The volume of blood after a SAH, calculated by CT scan, was significantly related to 30-day mortality. (12) The effects of the initial hemorrhage are related to mortality. Patients with a worse neurological outcome after their SAH tend to have a higher rate of mortality. The poorer the

neurological condition of the patient and the more blood present on the initial CT scan, the greater the likelihood of rebleeding.

Rebleeding is defined as recurrent hemorrhage due to inadequate hemostasis or arterial vasospasm, causing a clinical decline in a patient after a SAH. In the first few hours after SAH, up to 15% will re-bleed and up to 23 % will re-bleed within the first two weeks. (10, 13-15) These first few hours appear to be the most common time for rebleeding to occur, and early management is necessary to avoid risk of rebleeding. (12, 14) Mortality due to rebleeding has been reported to range from 50% to 80%. (10, 14) Medical treatments to control vasospasm and early surgical interventions effectively eliminate risk of rebleeding. (16)

Re-bleeding after a SAH event was studied by Hillman, *et al.* (17) Approximately 95% of patients hospitalized within 24 hours of symptom onset and 50% of patients hospitalized within 6 hours of SAH were studied. 60% of deaths were attributed to the initial bleeding episode, although 10% of patients admitted within 24 hours suffered from early rebleeding. Of the rebleeding patients, 82% died and 9% had a poor outcome. Most of the rebleeding occurred within the first 24 hours. (17) This finding is consistent with other investigations on re-bleeding after SAH. (12, 14, 18) In all studies, the peak incidence of rebleeding occurred within the first 24 hours after the initial hemorrhage, with a mortality rate between 74 – 85%.

The typical patient with SAH seeks care after the sudden onset of a severe headache often associated with loss of consciousness, focal neurological deficits, and nuchal rigidity. The headache is usually continuous. Initially the headache is focal, but then generalizes as time passes.

About 8% to 10% of patients present with atypical symptoms, such as back pain, nausea, lethargy, and eye or facial pain, and a more gradual evolution symptoms. (19, 20) Table A lists the symptoms of 41 patients who had a delay in diagnosis of SAH after presentation to a physician. (21) Adams *et al.* (21) concluded that the presence of atypical symptoms led physicians to consider an alternate diagnosis than SAH. Other symptoms that have been identified in patients with SAH include acute chest pain, proctalgia, paraplegia, and leg pain. Patients can often present as confused, irritable, uncooperative, and can sometimes exhibit combative behavior. These atypical symptoms, which were determined to be those symptoms with a prevalence < 25%, may distract attention from the bleed by impeding examination by the physician.

Diagnosis of SAH is made when blood is seen in the subarachnoid space either by CT scan, angiography, lumbar puncture (LP) or at autopsy. Strategies for diagnosis of SAH include a brain CT scan. However, in 3-4% of cases, the CT scan is normal. (22, 23) When a patient has a clinical syndrome consistent with SAH and a normal brain CT, current guidelines recommend that physicians perform an LP to test for red blood cells and xanthrochromasia in the CSF. (1) Xanthrochromia is a yellowish discoloration of the CSF supernatant when the CSF is centrifuged that is a result of degradation of red blood cells in the subarachnoid space. The disintegration of erythrocytes releases oxyhemoglobin into the CSF, which is then converted into bilirubin. Because there exists a risk of deterioration after LP due to herniation in patients with suspected SAH, a CT scan and a neurological examination should be performed before the LP is done.

Poor outcome of patients affected by SAH are most closely related to three baseline variables: 1) neurological condition of the patient on admission 2) volume and

location of initial bleed and 3) patient's age and compliance of the brain parenchyma. (21-22) Of these three prognosticators, the neurological condition, particularly the level of consciousness, is the most important determinant. (18) Prognosis of patients with SAH can be estimated based on a clinical grading system called the Hunt and Hess Scale, shown in Table B.

Prognosis can also be correlated to the Glasgow Coma Scale (GCS), shown in Table C. The Glasgow Coma Scale is the most widely used scoring system used in quantifying level of consciousness following traumatic brain injury. A lower GCS score usually leads to higher mortality. On initial presentation after the brain injury, the best eye opening response, the best verbal response, and the best motor response are determined. The score (E+V+M) represents the sum of the numeric scores of each of the categories.

The presence of other factors, such as hypertension and smoking or alcohol history also decreases chance for survival. Location of aneurysm also affects the prognosis, with posterior circulation aneurysms having a higher mortality rate.

II.2 Intracerebral Hemorrhage

Intracerebral Hemorrhage refers to bleeding into brain tissue, not from subarachnoid hemorrhage. The incidence of ICH in North America is approximately 4-6 per 100,000 persons per year. (1) The incidence of ICH is low among persons below the age of 45 years and increases dramatically from age of 65 years. After the age of 75 years of age, the incidence of ICH plateaus or decreases, due to reasons which are not

clear, but are speculated to be due to other diseases causing mortality before ICH can manifest itself. ICH also tends to occur more frequently in men, the difference most likely because of presence of established risk factors for ICH. (6)

Race and ethnicity are important determinant of the risk for ICH. Asians, in particular the Japanese, have a 2-3 times increased risk for ICH compared with other countries. (6) In the United States, the risk of ICH is increased 2-3 fold in African-Americans compared with Caucasians. (11) Under the age of 75 years, blacks had a 2.3 times greater risk of ICH than whites. This may be attributed to the increased incidence of hypertension among African-Americans. (11) Other clinical risk factors for ICH include diagnosis of hypertension, excessive alcohol consumption, anticoagulants, drug use, and hypocholesterolemia.

Patients with ICH typically present with sudden onset of severe headache, vomiting, depressed consciousness, and focal neurologic signs. Other symptoms include seizures and nausea. There can be a progressive worsening of symptoms after the initial abrupt headache. ICH frequently occurs during the day, with a peak in the morning just after awakening. Hemorrhage is usually associated with activity. Symptoms associated with ICH can vary with intensity and location of the bleed. Severe headache is reported in only 30-40% of cases. One-third of patients with ICH do not report any headache. (6) Although most cases of ICH have been attributed to hypertension, there is an increasing number cases in patients for whom there has not been a diagnosis of hypertension. ICH in these patients may be associated with non-hypertensive mechanisms that include aneurysms, tumor, vascular malformations, vasculopathies, and disorders of coagulation.

Diagnosis of ICH is typically made when blood is seen within the brain parenchyma on CT scan or MRI.

Prognosis after ICH is largely dependent on location of the lesion. The most common location of ICH is within the putamen (40%). (6) The clinical spectrum of putaminal hemorrhage ranges from small, asymptomatic lesions to large fatal lesions. Mortality from putaminal hemorrhage ranges between 20-40%. Thalamic hemorrhage accounts for 10-15% of ICH. Mortality rates have varied based on previous studies, but there appears to be a direct correlation between size of the hemorrhage and mortality. Caudate hemorrhage accounts for 5-7% of all ICH, and prognosis is generally good for patients, with most experiencing complete recovery. Pontine hemorrhage accounts for approximately 5% of all ICH, and when the hemorrhage involves the paramedian area bilaterally, the hemorrhage is usually fatal. Those who survive are neurologically devastated. Smaller pontine hemorrhages found in the basis pontis usually carry an excellent prognosis. Cerebellar hemorrhage of the hemispheres accounts for 10% of ICH, with a mortality rate of approximately 30%. Prognosis depends on level of clinical function, especially level of consciousness, after the acute event.

Long-term outcome after ICH was related to the acute hemorrhage. Case-fatality from ICH is approximately 35% to 52%. (4, 5) Mortality rates for ICH range from 20% to 40%, although the mortality in Asian countries appears to be 2 to 3 times greater than in Western countries. (6) Among those who survive 30 days, 50% to 70% have an excellent recovery and are able to function independently 6 months to a year after the acute hemorrhage. (6) Large hemorrhage size, ventricular hemorrhage, and older age are

associated with increased risk for poor functional recovery. Recurrent hemorrhage is rarely seen after ICH, except in hemorrhages that were not related to hypertension.

SAH and ICH are very different entities with regards to risk factors, pathophysiology, and initial clinical presentation. Therefore, to examine hemorrhagic stroke as one entity including both SAH and ICH may not necessarily be an effective analysis. In order to determine whether risk factors for delayed diagnosis of hemorrhagic stroke will be consistent for both SAH and ICH, risk factors need to be studied for each hemorrhagic stroke type separately.

III. Importance of Early Diagnosis

Early diagnosis of both SAH and ICH is necessary to improve outcome in survivors of the hemorrhage. By recognizing hemorrhage at its initial presentation, many treatment options are available for the patients, from medical to surgical treatments. However, after the first 2-3 days post-bleed, treatment options are limited, and brain damage from inflammation or from the hemorrhage cannot be reversed. (16)

The optimal time for aneurysm surgery was studied in the International Cooperative Study on the Timing of Aneurysm Surgery. (7, 8) A prospective, observational clinical trial was conducted to determine the best time in relation to the hemorrhage for surgical treatment of ruptured intracranial aneurysms. 3521 patients hospitalized within three days of SAH were enrolled from sixty-eight centers. Patients were grouped into prespecified "planned" surgery intervals. The day of the SAH event

was defined as day=0. The planned surgery intervals were determined by the neurosurgeon as soon as the diagnosis of SAH was made. Outcome rates consisted of those patients whose surgery was planned but who were not operated on in addition to those patients who actually had surgery. If a patient was admitted on Day 2 and had surgery planned for between Days 7 and 10 but rebled and die on Day 6, mortality was attributed to planned surgery of interval Days 7 to 10. If a patients was scheduled to have surgery between Days 7 and 10 but deteriorated on Day 6, then recovered to have surgery with a favorable outcome on Day 12, this good result would be credited to planned surgery interval Days 7 to 10. The postoperative risk following early surgery is equivalent to the risk of rebleeding and vasospasm in patients waiting for delayed surgery. Analysis of these prespecified intervals demonstrated that there was no difference in early (0 to 3 days after the bleed) or late surgery (11 to 14 days). Outcome was worse if surgery was performed in the 7 to 10-day post-bleed interval. Surgical results were better for patients operated on after 10 days. Overall, early surgery was neither more hazardous nor beneficial than delayed surgery. Although 24% of patients originally scheduled for surgery at 11-14 days and 38% of patients originally scheduled for surgery at 15+ days, results could still be made to determine the best length of time post-SAH that surgery should be performed. Outcomes of patients who had surgery within three days of SAH were optimal, with 60% of the patients having a good outcome and few neurological deficits. (7, 8)

Other studies have also shown that early diagnosis and early institution of therapy of SAH improves functional outcome and decreases morbidity among patients with SAH. (24-26) However, it also has been documented in multiple studies that recognition of the

SAH is very difficult. In a study on minor leak and outcome in patients whose diagnosis was either prompt or delayed, mortality for those patients who had a recognized minor leak that was treated before a major rupture (0%) was much better than for those patients whose minor leak was not identified (52%). (24)

There is a need for prompt recognition of SAH because some patients with a ruptured aneurysm will rebleed within the first two weeks after the SAH. Despite the evidence that early therapy improves outcome, the average interval between onset of symptoms of intracranial hemorrhage and diagnosis is approximately 5-11 days and 18% of patients do not seek care for > 24 hours. (27) Previous reports of SAH indicate that for 13-50% of patients, diagnosis is significantly delayed. (20-23, 27, 28) The studies on delayed diagnosis of SAH were able to identify presenting symptoms of those patients with a delayed diagnosis, however none were able to determine specific risk factors that led to the delay.

IV. Delayed Diagnosis of Hemorrhagic Stroke

There are 10 prior cross-sectional studies that were done to determine outcome of delayed diagnosis of SAH, shown in Table D. Only one (Kassell, *et al.*, 1985) (20) also investigated delayed diagnosis of ICH. There are five studies of delayed diagnosis that will be discussed, in addition to a recent review of some prior studies of delayed diagnosis of SAH.

Adams *et al.* (21) performed a cross-sectional study by reviewing charts of 182 patients admitted to the University of Iowa Hospital for SAH secondary to ruptured

aneurysms. All cases of SAH were confirmed by CSF examination, angiography, operation, or autopsy. Although delayed diagnosis was never defined, the assumption is that the patients with a delayed diagnosis were those patients who received a diagnosis different from SAH upon presentation to a physician with their symptoms. Of the 182 patients admitted, 41 (23%) had a delay ranging from one to twenty-seven days in the diagnosis of SAH. However, upon reviewing the patient's history and chart, Adams noted that not all of the misdiagnosed cases were of atypical presentation or mild symptoms. Headache was the chief complaint in 33 of the 41 patients (80%) in the patients with delayed diagnosis. In fact, the 41 patients had a delay in diagnosis of SAH even though headache, vomiting, and loss of consciousness were the common presenting symptoms. The delay was attributed to local physicians making an alternate diagnosis, although the delay by the hospital staff in the emergency department did not appear to be included in the study.

Adams *et al.* (21) nicely summarizes what symptoms each patient had at the time of initial presentation for the SAH. The alternate diagnoses were noted and reasons were discussed as to why the alternate diagnoses were given. Infectious illness was the diagnosis given to patients who presented with fever, malaise, nausea, vomiting, and headache without evidence of focal neurological signs. Migraine and sinusitis were other common diagnoses. Patients with severe neck pain and headache were diagnosed with cervical disk herniation or neck strain. Based on the results of the chart review, Adams *et al.* concluded that a more careful search for SAH should be done in patients who present with atypical symptoms. Also, he reiterated that prompt investigation with CT scan and/or lumbar puncture to look for xanthrochromasia is the most useful diagnostic

procedures to evaluate intracranial hemorrhage. This study is a concise look at the symptoms of SAH on initial diagnosis, even recording the atypical symptoms seen. However, the analysis of symptoms did not go beyond determining symptoms. No analysis was done to see whether a certain symptom was a risk factor for the delayed diagnosis of SAH.

In 1985, Kassell *et al.* (20) reviewed medical records for all hospitalized patients during July 1977 and July 1983 with a discharge diagnosis of SAH at the University of Iowa to determine the length and cause of delayed referral. Physicians referred only 36% of the patients to the Acute Stroke Care and Monitoring Unit within 48 hours of clear cut, recognizable signs or symptoms of SAH. The definition of the clear and recognizable signs and symptoms of SAH was not given. Most patients were referred to the neurosurgical stroke service several days after onset of SAH, which was detrimental to patient care and contributed to greater morbidity and mortality.

Delays were broken down into 6 categories: physicians' diagnostic problems, which was defined as failure of physicians to make or suspect a diagnosis of SAH (37%); delayed referral policy, defined as a decision by the referring physician to delay transfer of the patient until the neurological status had improved or until an arbitrary number of days had passed (23%); logistics, defined as delays due to scheduling or completion of diagnostic tests (CT or angiography), initiation of treatment, or arrangements for transportation (12%); failure of patients to seek medical attention (8%), unstable condition (7%), or other (13%). The more common causes for delayed diagnosis were due to physician failure to recognize the diagnosis and delays in referral policies. These both were thought to be avoidable causes for delay. Kassell *et al.* (20) therefore

concluded that public health and primary physician education was necessary to reduce the number of patients with delayed neurosurgical care. The problem with this study is that it only included patients who were transferred to the neurosurgical acute stroke unit from outside the hospital. It never mentioned patients who were seen at the emergency room. Also, only SAH was studied at this time.

Schievink *et al.* at the University of Amsterdam (27) conducted a cross-sectional retrospective chart review of 334 patients admitted to the neurosurgical unit between August 1979 and January 1987 with SAH due to aneurysmal rupture confirmed by LP, CT, operation, angiography, or autopsy. Causes of delayed diagnosis were divided into three categories used by Kassell *et al.* (20), which included patient delay, delay from misdiagnosis, and hospital delay. Patients who presented to the hospital in bad clinical condition were more promptly referred to the neurosurgery department compared to those patients in good clinical condition. There was a delay in referral to the neurosurgery unit in164 of 334 (49%) patients with SAH. Of those patients whose referral was delayed, failure of patients to seek medical attention caused delay in 29 (18%) patients. Physicians' diagnostic errors were responsible for delay in 95 (58%) patients. A delay at the referring hospital occurred in 97 (59%) patients. The delay caused by physician diagnostic errors averaged 10.5 days. In more than 40% of the cases, patient delay in seeking medical attention was followed by a physician's diagnostic error. This was attributed to the less severe symptoms found in these patients.

Schievink (27) concluded that physicians were unfamiliar with SAH and that this is the cause for the large number of incorrect diagnoses. He attributes this to the fact that an average general practitioner would only see aneurysmal SAH once every 3 – 4 years.

It was concluded that educating the public, medical students and physicians about the signs and symptoms of SAH and the importance of prompt therapy to improve overall outcome should help to decrease the number of incorrect diagnoses of SAH. Although this study was a good evaluation of causes for delayed diagnosis in a large population, because of the specialized neurosurgical center, the study included an overrepresentation of posterior circulation aneurysms. Also, it was not defined whether the patients were referred from physicians' offices or from the emergency room.

In his study of SAH in the emergency department, Fontanarosa (23) found that 16 of 109 patients (15%) had a delayed diagnosis. These patients presented to physicians with headache, but an otherwise normal neurologic exam. The patients did not present with neck stiffness and the headache typically had lasted a couple of days. Of note, none of the 16 patients who were incorrectly diagnosed had a lumbar puncture performed.

To study prevalence and outcome of patients with cerebral aneurysm who were misdiagnosed on initial medical presentation, Mayer *et al.* (22) conducted a retrospective chart review of 217 patients. Patients were studied in four tertiary-care neurosurgical centers. Misdiagnosis was said to have occurred if the initial medical evaluation did not consider the possibility of intracranial aneurysm or if the diagnosis of aneurysm was delayed by more than 24 hours from the time of presentation to medical attention with symptoms consistent with intracranial aneurysm. Of the 217 patients in the study, 54 patients (25%) with cerebral aneurysms were misdiagnosed on first presentation to a healthcare professional for symptoms or signs of cerebral aneurysm and were initially misdiagnosed. This misdiagnosis was associated with worse clinical outcome.

Most of the patients who were misdiagnosed were patients in good clinical condition whose course were more likely to deteriorate clinically. Patients were followed based on rebleed and deterioration. Patients were clinically graded on initial presentation using a modified Hunt and Hess grading scale. Grade was established based on best condition achieved within the first 24 hours after initial medical presentation: Grade 1: headache and seizure only; Grade 2: any meningeal symptoms and signs; isolated cranial nerve palsy, nausea, or vomiting; Grade 3: altered level of consciousness; Grade 4: coma; Grade 5: coma plus hemodynamic instability. Rates of misdiagnosis were determined for each clinical grade. For patients with symptoms of grades 1 or 2, 46 of 121 patients (38%) were misdiagnosed on initial presentation. For patients with altered levels of consciousness, 6 of 56 patients (11%) were misdiagnosed on initial presentation. For grades 4 and 5, 2 of 40 patients (5%) who were unconscious were misdiagnosed initially.

In evaluating the outcome of patients, twenty-six of 54 misdiagnosed patients (48%) rebled or deteriorated after initial presentation to medical attention before correct diagnosis and management was given. This was compared to only 4 out of the 163 (2%) correctly diagnosed patients. This difference was statistically significant. In addition, for patients with clinical grades 1 or 2, 68 of 75 (91%) of patients who were correctly diagnosed had an excellent/good outcome compared with 24 of 45 (53%) of patients who were initially misdiagnosed. Studying poor outcome or death in patients with clinical grades 1 or 2, 3 of 75 (4%) of patients with correct diagnosis had poor outcome compared with 16 of 45 (36%) of patients with misdiagnosis. Even though this study was not designed to identify risk factors for misdiagnosis, the authors reported that most missed cases occurred because physicians did not consider the diagnosis of SAH (and

order a CT scan or a lumbar puncture) in the differential diagnosis of patients' complaints.

Ferro *et al.* (28) looked at the causes of delayed diagnosis and referral of patients with SAH. A prospective study was conducted of 112 patients who presented to the departments of neurology and neurosurgery in Portugal from January 1985 to December 1987 with SAH confirmed by CT scan and/or LP or angiography. Demographic and clinical data was recorded on admission. The causes of delayed referral were split into categories originally used by Kassell *et al.*(20), including failure of the patient to seek medical treatment, physicians' diagnostic error, and delayed transfer policy.

This study found that the main cause of delayed referral to the neurology or neurosurgery departments was physician inability to diagnose SAH in the 39 (70%) patients with symptoms consistent with SAH. This study did recognize that delay due to physician failure to consider the diagnosis does not only occur in private physician offices. Many times, the diagnostic error can occur in the emergency room, and, in fact, 13% of the patients with delayed admission in this study were misdiagnosed in an emergency room setting. The primary physician correctly diagnosed twenty-three percent of the patients with a delay in admission, but there was a delay in transfer of the patient to the hospital in time for treatment. Patients' age or sex, presence or severity of headache, history of hypertension, blood pressure at onset, or initial symptoms (loss of consciousness, focal symptoms) were not factors that led to early diagnosis or referral. Instead, early diagnosis and referral were strongly influenced by the severity of the clinical picture. The main factor leading to physician delayed referral was mild clinical symptoms on presentation. The severity of the initial hemorrhage also correlated with the

length of delay in referral. The authors concluded that improving diagnostic referral is dependent on physicians' education rather than public education.

The remaining cross-sectional studies about delayed diagnosis of SAH were able to identify symptoms and outcome of delayed diagnosis of SAH, with results resembling those previously described.

Edlow *et al.* (29) reviewed various studies regarding misdiagnosis of subarachnoid hemorrhage and came to three conclusions: 1) physicians consistently misdiagnose SAH; 2) the patients with the greatest likelihood of benefiting from surgery are the ones who most often receive an incorrect diagnosis; 3) early complications develop in patients with an incorrect diagnosis, resulting in worse outcomes in these patients than in those initially given a correct diagnosis. Many patients with SAH present with findings that deviate from the classic presentation. Patients with atypical symptoms can present with SAH during nonstrenuous activity or sleep. The headache they suffer may present in any location. Alternatively, headache may not be present at all, with the patient's discomfort only evidenced by neck pain. Edlow's review of the literature concluded that most warning headaches are indications of unrecognized subarachnoid hemorrhages that can be diagnosed by appropriate methods. In addition, properly performed and interpreted CT and lumbar puncture in patients with acute, severe headache will best identify the majority of patients with SAH.

A common conclusion of the prior studies was that physician education would help physicians to keep hemorrhagic stroke in mind so that they will be able to promptly identify the diagnosis and refer patients to neurosurgical centers so that early intervention can be implemented. A study of whether an educational program for primary care

physicians would reduce misdiagnosis or delayed diagnosis of SAH was conducted in Sweden. (30) Both the local city population and the nine surrounding community hospitals use the same neurosurgical center. Fridriksson *et al.* (30) instituted a teaching program in the physicians' offices in the local city population that usually refer their neurosurgical patients to the center. Teaching focused on recognizing the most common clinical presentation of sudden onset of headache as a sign of SAH. In addition, maintaining individual follow-up of all referred cases opened communication between the community physician and the neurosurgeon. No extra contact was made with the remaining community hospitals. Outcome of patients was evaluated at 6 months after SAH. A good outcome was defined as patients without neurological deficits (except isolated cranial nerve palsy) returning to their premorbid activities. The educated population had 35 cases of ruptured aneurysms with only 1 patient (3%) having a delay in referral by the local city physician. However, in the remaining population that was not given the teaching program, 4 of 152 (3%) patients had a delayed referral and 14 of 152 patients (9%) had a misdiagnosis of warning episodes. Therefore, the total of 18 of 152 patients (12%) had some form of delayed referral of their ruptured aneurysm. Conclusions were that the focused attention to sudden onset headache through the teaching program alerted local physicians to diagnose SAH at the first hemorrhagic event in a higher percentage than average. Therefore, fewer individuals had a misdiagnosis of their hemorrhagic stroke on transfer to the neurosurgical center. Based on these results, one could argue that identifying the risk factors for delayed diagnosis of hemorrhagic stroke and incorporating them into a teaching program for physicians may be beneficial to reduce delay.

In summary, previous cross-sectional studies have studied the effects of delayed diagnosis of SAH. In Iowa, Adams *et al.* (21) reviewed the charts of 182 patients with SAH secondary to ruptured aneurysms and noticed that 41 patients had a delayed diagnosis. Adams identified the symptoms of the 41 patients with a delayed diagnosis, however he did not analyze whether the atypical symptoms were a risk for delayed diagnosis. Kassell *et al.* (20) reviewed medical records for all hospitalized patients with a SAH to determine the length and cause of delayed referral. It was determined that physician failure to recognize the diagnosis was the most common cause for delayed diagnosis. In Amsterdam, Schievink *et al.* (27) conducted a chart review of 334 patients admitted to a neurosurgical unit with SAH and noticed that there was a delay in referral of 164 patients. Physician's diagnostic error was the most common cause for delay in 58% of the patients, and it was concluded that the incorrect diagnoses were most likely the result of physicians being unfamiliar with SAH. Mayer *et al.* (22) conducted a chart review of 217 patients with cerebral aneurysm to determine the prevalence and outcome of patients with cerebral aneurysm who were misdiagnosed on initial medical presentation. 54 of the 217 patients were cerebral aneurysms were misdiagnosed on first presentation to a healthcare, and the delay in care of these patients was associated with a worse outcome. Ferro *et al.* (28) studied the causes of delayed diagnosis and referral of patients with SAH. Physician inability to recognize the diagnosis was the most common cause of delayed referral in 39 of the 112 patients. In all of these studies, delayed diagnosis was recognized to lead to worse outcome, but no analysis of symptoms associated with delayed diagnosis was performed.

The problem of delayed diagnosis is most commonly due to physicians failing to consider the diagnosis of hemorrhagic stroke. There has not yet been a study adequately designed to examine the full spectrum of risk factors for delayed diagnosis and thus determine the features that are associated with a delayed diagnosis. Additionally, there have been many studies with regards to delayed diagnosis of SAH, but few have examined delayed diagnosis of ICH. Finally, there has not yet been a study to compare delay of diagnosis in the emergency room setting versus a physicians' office or telephone consult.

STATEMENT OF PURPOSE AND HYPOTHESIS

The purpose of this study is to identify the risk factors associated with delayed diagnosis of non-traumatic intracranial hemorrhage. We hypothesize that symptom characteristics, site of care, headache history, and demographic variables may affect risk for delayed diagnosis. The study will also identify if there is a difference between delayed diagnosis of SAH and ICH based on the risk factors. Finally, risk factors for delayed diagnosis will be evaluated to determine if there is a difference based on location of initial contact. The results of this study will be useful to establish guidelines for recognizing subarachnoid and intracerebral hemorrhage to aid physicians in early recognition of hemorrhage, thus decreasing morbidity and mortality.

RESEARCH METHODS

Overview

This study is designed as a subsidiary case-control study within a larger case-control study of the causes of hemorrhagic stroke in young persons, the Hemorrhagic Stroke Project (HSP). (Figure 1)

Hemorrhagic Stroke Project (HSP)

HSP Selection of Cases

Between December 1994 and July 1999, case subjects with hemorrhagic stroke were recruited from hospitals located in Connecticut, Southern Massachusetts, Southern Ohio, Northern Kentucky, Rhode Island, and Texas. Active surveillance of all admissions at each of the participating hospitals identified patients with hemorrhagic stroke. Surveillance involved review of admission rosters and direct monitoring of admissions by one or more designated individuals, such as a discharge planner or stroke nurse. In order to check completeness of case identification, discharge rosters were reviewed from each participating hospital during the mentioned time period.

Eligibility criteria for case subjects included admission to a participating hospital, age between 18 and 49 years (inclusive), symptomatic primary subarachnoid hemorrhage (SAH) or primary intracerebral hemorrhage (ICH), and ability to participate in a direct interview within 30 days of the stroke event. Patients with other diagnoses, including

subdural hematomas and hemorrhages associated with ischemic infarcts, trauma, thrombolytic therapy, or cerebral vein thrombosis were not eligible for this study.

Diagnosis of SAH was based on the presence of a high intensity signal in the subarachnoid space by computed tomography (CT) or by lumbar puncture (LP) showing xanthochromasia not explained by other etiologies (e.g. liver disease, increased CSF protein, hypervitaminosis A). An ICH was diagnosed by a CT scan showing a hyperintense signal within brain parenchyma. If other studies were not diagnostic and after consultation with a neuroradiologist, magnetic resonance imaging (MRI) was accepted for the diagnosis of SAH or ICH. Exclusion criteria included prior stroke and brain lesion predisposing to hemorrhage risk (e.g. arteriovenous malformation, vascular aneurysm, or tumor) known to exist prior to the index event. Patients were also excluded if they first experienced stroke symptoms after being in the hospital for 72 hours for an unrelated matter.

The treating physician gave permission to contact each potential case subject. Once permission was received, a researcher met with the patient and reviewed pertinent data to confirm eligibility. Eligible patients were invited to participate and give verbal informed consent. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of potential risk factors. Case subjects who did not speak English were interviewed using a translator who, with rare exception, was not a relative or acquaintance. Most interviews were conducted in the hospital, but some were completed at home and three were complete by telephone.

HSP Selection of Controls

Two matched control subjects were identified for each case subject. Matching criteria included: gender, ethnic group (African-American versus non-African-American), and age (within 3 years for case subjects less than 30 years and within 5 years for cases 30 years of over). All control subject interviews had to be completed within 30 days of the case's stroke event to minimize seasonal differences in the likelihood of exposure to cough/cold remedies. A computer-generated list of random telephone numbers (matching the first three digits of the case subject telephone number) was used to identify potential control subjects. Eligibility criteria for control subjects were the same as for case subjects except for those criteria related to the stroke event. Once an appropriate control subject was identified, he or she was invited to participate. The interview was then conducted in person in the control subject's home, a doctor's office, or by telephone. Control subjects who traveled long distances for the interviews were offered twenty dollars to defray the cost of their expenses.

HSP Specification of Focal Time

Each case subject was assigned a focal time. The focal time was defined as the calendar day (i.e. index day) and time of day that marked the onset of symptoms plausibly related to hemorrhage and that caused the case subject to seek medical attention. To establish the focal time, a detailed account of the patient's symptoms from onset to diagnosis was obtained. When necessary, acquaintances or witnesses were

consulted to determine the course of the illness. As expected, there were patients who had symptoms compatible with a hemorrhagic stroke that predated the onset of symptoms that caused them to seek medical attention. For those patients, the onset of early symptoms was defined s the secondary (alternate) focal time. The focal time for control subjects was defined by the day of the week and time of day that marked the case subject's focal time. The index day was set within 7 days of the control interview.

Delayed Diagnosis Study

Selection of Case Subjects for the Study on Delayed Diagnosis

HSP case subjects for whom diagnosis of SAH or ICH was delayed were selected as the case subjects for the study on delayed diagnosis. These case subjects with delayed diagnosis will be referred to as "patient" for the study on delayed diagnosis. Delayed diagnosis was defined when HSP case subjects did not receive an appropriate diagnostic evaluation within twenty-four hours of consulting a physician for symptoms consistent with SAH or ICH. Consultation could have been in person or by telephone. An appropriate diagnostic evaluation was recognized when a CT scan was obtained. An additional requirement for SAH was that an LP must be performed if the CT scan was negative. Among the 702 case-subjects in the HSP, patients for the delayed diagnosis study were identified with two strategies. First, during the subject interview, all subjects were asked, "Did you see a physician in the 2-week period before the index date?" Second, case subjects were identified by a manual search of each subjects' research

record, which included discharge summaries, admit notes, and histories of the stroke event recorded by research associates.

Selection of Controls for the Study on Delayed Diagnosis

HSP subjects who received a prompt, correct diagnosis were eligible as control subjects in the delayed diagnosis study. Each patient was matched to a control subject according to research site because we believed that geographical location might be associated both with features we were studying and a delayed diagnosis. To operationalize matching, control subjects were chosen as the next two patients enrolled in the HSP after the case subject. To achieve greater statistical power, we selected two controls for each case subject.

Baseline Data

All data was obtained from the HSP database except when noted with an "*". Data marked by "*" was obtained from the research forms, which contain a description of the neurologic event as given by the patient. These narratives included an account of symptoms, precipitating activities, and actions taken by the patient during the symptoms of their stroke event. The specific data collected were grouped into demographic and historical features, symptom features, and diagnostic features. Features are shown in the following table:

Features Selected for Data Collection

Demographic and Historical Features	Symptom Features	Diagnostic Features
Age	Headache	Location of Presentation (Hospital vs. Office vs. Telephone) *
Gender	Photophobia	
History of Migraine Headaches	Nausea/Vomiting	
Ethnicity	Loss of Consciousness *	
Socio-economic Status	Focal Neurological Symptoms	
Presence of Risk Factors (Hypertension, Cigarettes, and Cocaine)	Facial Pain *	
Family History	Neck Pain	
Insurance Status	Upper Respiratory Tract Symptoms (URI, Allergies, Nasal Congestion)	
	Activity at Onset	

Selection of Features

We hypothesized that certain demographic and historical features, symptom features, and diagnostic features of patients may have an association with delayed diagnosis of hemorrhagic stroke. Our hypothesis was made based on the fact that physicians make their diagnoses based on recognition of historical occurrences and physical exam. Of the demographic features, we hypothesized that young age would be associated with delayed diagnosis because the typical patients with SAH or ICH are thought to be older persons with medical risk factors. We also hypothesized that ethnicity could play a role in delayed diagnosis, with Hispanic ethnicity holding the most association with delayed diagnosis and Black ethnicity holding the least association with delayed diagnosis. For gender, we hypothesized that females would be more likely to have a delayed diagnosis because of the protective effects of estrogens on the cardiovascular system.

Of the historical features, we hypothesized that having a history of migraine diagnosis, no history of hypertension, no history of smoking, and no primary family history would be associated with increased risk for delayed diagnosis because a migraine diagnosis could skew the physician's perception of a headache. Patients without a high risk of cardiovascular disease (hypertension, smoking, and family history) would be more likely to have a delayed diagnosis because they are seen as "low-risk" patients. We also hypothesized that having no college education and having no insurance would be associated with an increased risk for delayed diagnosis secondary to bias from financial burdens.

Of the symptom features, we hypothesized that no photophobia, no loss of consciousness, no focal neurological symptoms, the combination of which will be referred to as no alarm symptoms, will have increased association with delayed diagnosis of hemorrhagic stroke. This is because mild symptoms will most likely lead a physician to not consider a diagnosis of hemorrhage. Patients who present without facial or neck pain or without a headache would also be likely to have a delayed diagnosis because these symptoms are common to the presentation of hemorrhagic stroke. We also hypothesized that nausea and vomiting symptoms would be associated with an increased risk of delayed diagnosis because the symptoms could distract the physician into diagnosing a gastrointestinal disorder. The presence of upper respiratory tract infection symptoms, allergies, or nasal congestion, which will be combined into upper respiratory tract symptoms, within the last two weeks prior to the stroke event will be associated with an increased risk of delayed diagnosis because these symptoms can distract the physician into attributing these symptoms to an upper respiratory tract cause. Finally, if the patient did not have an effortful activity preceding their stroke event, we hypothesize that this will be associated with an increased risk of delayed diagnosis.

For diagnostic features, location of initial evaluation in a physician's office or by telephone, which will be combined and referred to as office, will be associated with increased risk of delayed diagnosis because of the lack of diagnostic equipment, such as a CT scanner, in the office setting. Patients who present to a physician's office will be compared with patients who present to a hospital emergency room.

Analytic Strategy

Odds ratios were calculated for the association between pre-specified suspected risk factors and risk for delayed diagnosis. Chi-square was used to calculate p-values. Features were considered to be associated with delayed diagnosis of hemorrhagic stroke if the odds ratios were greater than or equal to 2.0 or less than or equal to 0.5. To confirm their independent association with risk for hemorrhagic stroke, features with and odds ratio =2.0 or =0.5 were included in a multivariable logistic regression analysis. Features were considered confirmed if their adjusted odds ratios remained =2.0 or =0.5.

RESULTS

I. Study Participants

Between December 1994 and July 1999, 702 case subjects were recruited for the Hemorrhagic Stroke Project from hospitals located in Connecticut, Southern Massachusetts, Southern Ohio, Northern Kentucky, Rhode Island, and Texas. Among all case subjects, the diagnosis of intracranial hemorrhage was delayed for 54 patients (7.7%) and prompt for 648 patients (92.3%). For each patient with a delayed diagnosis, we identified two control subjects. Patients were matched (100%) to control subjects by geographic location.

II. Delayed Diagnosis Study Participants

To identify features associated with increased risk for delayed diagnosis we compared patients with delayed and prompt diagnosis, as shown in Table E. Features are described according to our hypotheses of how each feature may contribute to a delayed diagnosis. The median age for patients was 40 years compared with 43 years for control subjects. Of the patients, 34 of the 54 (63%) were ethnically Caucasian, 8 of the 54 (15%) were Black, and 8 of the 54 (15%) were Hispanic. Of the control subjects, 76 of 108 (70%) were Caucasian, 21 of the 108 (20%) were Black, and, 8 of the 108 (7%) were Hispanic. A similar number of patients (50%) and control subjects (53%) were female.

III. Risk Factors for Delayed Diagnosis in The Overall Cohort

Table E compares patients and control subjects with respect to demographic and historical features, symptom features, and diagnostic features. Eight features were associated with risk for delayed diagnosis (criteria = odds ratio=2.0 or =0.5). Compared to patients with a prompt diagnosis, patients with a delayed diagnosis tended to be of younger age (odds ratio=2.0, p=0.05), of Hispanic ethnicity (compared to non-Hispanic ethnicity) (odds ratio=2.2, p=0.14), non- hypertensive (odds ratio=2.0, p=0.04), and less educated (odds ratio=0.5, p=0.05). Compared to patients with a prompt diagnosis, patients with a delayed diagnosis more often presented without alarm symptoms (photophobia, loss of consciousness, and focal neurological symptoms) (odds ratio=5.3, p=<0.01) and reported no effortful activity preceding their stroke event (odds ratio=3.0,

p=0.08). However, compared to patients with a prompt diagnosis, patients with a delayed diagnosis were less likely to have no headache (odds ratio=0.2, p=0.02). Finally, compared to patients with a prompt diagnosis, patients with a delayed diagnosis more often initially presented to a physician's office rather than an emergency room (odds ratio=18.3, p=<0.01).

Table F shows the results of the multivariable analysis, which includes the eight features with a bivariate odds ratio that were statistically significant according to the criteria of an odds ratio =2.0 or =0.5. Among the eight variables in the multivariable analysis, there were four that remained independently associated with risk for delayed diagnosis (criteria odds ratio =2.0 or =0.5): 1) office evaluation (adjusted odds ratio 23.1), 2) no alarm symptoms (adjusted odds ratio 4.6, with a 13% change), 3) no effortful activity (adjusted odds ratio 5.5), and 4) Hispanic ethnicity (adjusted odds ratio 2.4). Four variables were not longer independently associated with delayed diagnosis. For no history of hypertension, the adjusted odds ratio was 1.5. For age <40, the adjusted odds ratio was 1.2. For no college education, the odds ratio was 0.9. For no headache present, the odds ratio was 0.6.

IV. Risk Factors for Delayed Diagnosis According to Type of Initial Contact

Because location of initial presentation was associated with such a large adjusted odds ratio (23.1), we hypothesized that persons who present to an office may be sufficiently different to warrant a stratified analysis. Accordingly, we examined the association between location of presentation and risk feature separately for patients with

prompt and delayed diagnoses. Our criteria for declaring that a feature was different with regards to risk of delayed diagnosis by location of presentation was if the odds ratio was =2.0 in one location and the odds ratio was <1.2 in the other location or if the odds ratio was =0.5 in one location and the odds ratio was >0.8 in the other location. Additionally, our criteria for declaring that a feature was a risk factor for delayed diagnosis in both locations of presentation was if the odds ratio was =2.0 in both locations. Our criteria for declaring that a feature was a protective factor for delayed diagnosis in both locations of presentation was if the odds ratio was =0.5 in both locations. Our criteria for declaring that a feature was associated with an increased risk for delayed diagnosis in one location and neutral in the other was if the odds ratio was =2.0 in one location and between 1.2-2.0 in the other. Our criteria for declaring that a feature was considered to be protective for delayed diagnosis in one location and neutral in the other was if the odds ratio was =0.5 in one location and between 0.5 and 0.8 in the other. The results of the stratified analysis are displayed in Table G.

Nine features had a different effect on risk for delayed diagnosis in the office and hospital: young age, female gender, history of migraine diagnosis, not currently a smoker, no college education, no alarm symptoms, nausea, upper respiratory tract symptoms, and stroke type of ICH. For three of these nine features (young age, history of migraine diagnosis, and no alarm symptoms) a delayed diagnosis was significantly increased when patients presented to the hospital, but were protective or neutral when patients presented to an office. For young age, the odds for delayed diagnosis was 2.0 among patients who presented to the hospital compared with 0.4 among patients who presented to the office. For history of migraine diagnosis, the odds for delayed diagnosis was 2.1 among patients

who presented to the hospital compared with 0.4 among patients who presented to the office. For no alarm symptoms, the odds for delayed diagnosis was 4.9 among patients who presented to the hospital compared with 1.1 among patients who presented to the office. For four of the nine features (female gender, not currently a smoker, upper respiratory tract symptoms, and stroke type of ICH), a delayed diagnosis was protective or neutral when patients presented to the hospital, but were significantly increased when patients presented to an office. For female gender, the odds for delayed diagnosis was 0.9 among patients who presented to the hospital compared with 2.0 among patients who presented to the office. For not currently a smoker, the odds for delayed diagnosis was 1.1 among patients who presented to the hospital compared with 3.2 among patients who presented to the office. For upper respiratory tract symptoms, the odds for delayed diagnosis was 0.9 among patients who presented to the hospital compared with 2.0 among patients who presented to the office. For stroke type of ICH, the odds for delayed diagnosis was 1.1 among patients who presented to the hospital compared with 4.3 among patients who presented to the office.

For the remaining two features (no college education and nausea), a delayed diagnosis was significantly decreased when patients presented to the office, but was neutral when patients presented to a hospital. For no college education, the odds for delayed diagnosis was 0.1 among patients who presented to the office compared with 1.0 among patients who presented to the hospital. For nausea, the odds for delayed diagnosis was 0.3 among patients who presented to the office, compared to1.5 among patients who presented to the hospital.

Only one feature was associated with an increased risk of delayed diagnosis in both the hospital and the office. For no effortful activity, the odds for delayed diagnosis was 4.2 among patients who presented to the hospital compared with 2.6 among patients who presented to the office.

One feature was associated with an increased risk for delayed diagnosis in one location and a neutral association in the other: no hypertension history. For no hypertension history, the odds for delayed diagnosis was 1.6 among patients who presented to the hospital compared with 3.0 among patients who presented to the office.

V. Risk Factors for Delayed Diagnosis According to Stroke Type

Because type of stroke of ICH was associated with such a large odds ratio (4.3) in the office location and because the pathophysiology of the diseases are substantially different from each other, we hypothesized that persons who present with a SAH may be different from those who present with an ICH. Accordingly, we examined the association between type of stroke type risk feature separately for patients with prompt and delayed diagnoses. Our criteria for declaring that a feature was different with regards to risk of delayed diagnosis by location of presentation was if the odds ratio was =2.0 in one location and the odds ratio was <1.2 in the other location. Additionally, our criteria for declaring that a feature was a risk factor for delayed diagnosis in both locations of presentation was if the odds ratio was =2.0 in both locations. Our criteria for declaring that a feature was a protective factor for delayed diagnosis in both locations of presentation was if the odds ratio was =0.5 in both locations. Our criteria for declaring

that a feature was associated with an increased risk for delayed diagnosis in one location and neutral in the other was if the odds ratio was =2.0 in one location and between 0.5-2.0 in the other. Our criteria for declaring that a feature was considered to be protective for delayed diagnosis in one location and neutral in the other was if the odds ratio was =0.5 in one location and 0.5 to 0.8 in the other. The results of the stratified analysis are displayed in Tables H and I.

Ten features had a different effect on risk for delayed diagnosis of SAH compared to ICH: Caucasian ethnicity, Black ethnicity, female gender, history of migraine diagnosis, no hypertension history, no neck pain, nausea, vomit, upper respiratory tract symptoms, and no effortful activity. For two of these ten features (no neck pain, and no effortful activity) a delayed diagnosis was significantly increased for patients with SAH, but was protective or neutral for patients with ICH. Black ethnicity was a significantly protective feature for delayed diagnosis of ICH, but was a risk for delayed diagnosis for patients with SAH. For no neck pain, the odds for delayed diagnosis was 2.9 among patients with SAH compared with 0.4 among patients with ICH. For no effortful activity, the odds for delayed diagnosis was 6.9 among patients with SAH compared with 0.9 among patients with ICH. For Black ethnicity, the odds for delayed diagnosis was 1.3 among patients with SAH compared with 0.4 among patients with ICH. For five of the ten features (Caucasian ethnicity, female gender, history of migraine diagnosis, no hypertension history, and nausea) a delayed diagnosis was significantly increased for patients with ICH, but was protective or neutral for patients with SAH. The remaining two features, vomiting, and upper respiratory tract symptoms, were significantly protective for delayed diagnosis of SAH, but were associated with risk for delayed

diagnosis of ICH. For Caucasian ethnicity, the odds for delayed diagnosis was 2.0 among patients with ICH compared with 0.6 among patients with SAH. For female gender, the odds for delayed diagnosis was 3.8 among patients with ICH compared with 0.3 among patients with SAH. For history of migraine diagnosis, the odds for delayed diagnosis was 2.4 among patients with ICH compared with 0.9 among patients with SAH. For no hypertension history, the odds for delayed diagnosis was 5.9 among patients with ICH compared with 1.0 among patients with SAH. For nausea, the odds for delayed diagnosis was 2.7 among patients with ICH compared with 0.6 among patients with SAH. For vomiting, the odds for delayed diagnosis was 1.5 among patients with ICH compared with 0.5 among patients with SAH. For upper respiratory tract symptoms, the odds for delayed diagnosis was 1.5 among patients with ICH compared with 0.5 among patients with SAH.

Two features were associated with an increased risk of delayed diagnosis in both SAH and ICH: no alarm symptoms and office evaluation. For no alarm symptoms, the odds for delayed diagnosis was 3.0 among patients who had a SAH compared with 18.5 among patients who had an ICH. For office evaluation, the odds for delayed diagnosis was 12.4 among patients who had a SAH compared with 47.3 among patients who had an ICH.

Three features were associated with an increased risk for delayed diagnosis in one location and a neutral association in the other: Hispanic ethnicity, no college education, and no headache present. For Hispanic ethnicity, the odds for delayed diagnosis was 1.9 among patients who had a SAH compared with 2.5 among patients who had an ICH. For no college education, the odds for delayed diagnosis was 0.6 among patients who had a

SAH compared with 0.4 among patients who had an ICH. For no headache present, the odds for delayed diagnosis was 0.7 among patients who had a SAH compared with 0.1 among patients who had an ICH.

DISCUSSION

Among 702 young men and women with hemorrhagic stroke, the diagnosis was delayed diagnosis for 54 (7.7%). Features associated with increased risk of delayed diagnosis were Hispanic ethnicity (adjusted odds ratio=2.4), no effortful activity preceding stroke event (adjusted odds ratio=5.5), no alarm symptoms (adjusted odds ratio=4.6), office evaluation (adjusted odds ratio=23.1).

This is the first study to demonstrate the importance of location of presentation in understanding the phenomenon of delayed diagnosis. Because of the magnitude of the adjusted odds ratio for the office evaluation features, we hypothesized that persons who present to an office may be sufficiently different from those who present to a hospital emergency room to warrant a stratified analysis. Our results did, in fact, show that features associated with delayed diagnosis were different based on location of initial presentation. There were nine features that had a different effect on risk for delayed diagnosis in the office and hospital: young age, female gender, history of migraine diagnosis, not currently a smoker, no college education, no alarm symptoms, nausea, upper respiratory tract symptoms, and stroke type of ICH.

Additionally, this is the first study to examine the association of risk features for delayed diagnosis in both SAH and ICH. Comparison of risk features for delayed diagnosis of SAH and ICH showed that features associated with delayed diagnosis of SAH were different from those associated with delayed diagnosis of ICH. Ten features had a different effect on risk for delayed diagnosis of SAH compared to ICH: Caucasian ethnicity, Black ethnicity, female gender, history of migraine diagnosis, no hypertension

history, no neck pain, nausea, vomit, upper respiratory tract symptoms, and no effortful activity.

The results of the overall cohort analysis conclude that patients who present to their physician's office with milder clinical symptoms (no alarm symptoms) are more likely to have a delay in diagnosis of hemorrhagic stroke. No alarm symptoms was associated with increased risk of delayed diagnosis because when patients present with mild symptoms, physicians usually think of less catastrophic causes. The usual presentation for ruptured aneurysm or intracranial bleed occurs when patients are performing activities that require some effort. Therefore, patients who present without having done any effortful activity preceding the onset of the hemorrhagic stroke are more likely to have a delay in diagnosis. Hispanic ethnicity may be associated with increased risk of delayed diagnosis because of a language barrier between patient and physician. Without an adequate interpreter, physicians may not obtain the full history of symptoms, and therefore, may not consider the diagnosis of hemorrhagic stroke.

In evaluating the features associated with delayed and prompt diagnosis, an important finding from our study was that most cases of delayed diagnosis of intracranial hemorrhage occurred in patients who presented to a physician's office. This has not been reported in previous studies. Prior studies never made a comparison between patients based on the location of initial presentation, and therefore, they have never demonstrated that location of initial examination is important. The one common conclusion of prior studies has been that physician diagnosis is the reason for delayed diagnosis. This conclusion merely recognizes that delayed diagnosis is common, however, it does not help to identify the features that are associated with delayed diagnosis. Our study, by

examining the features that become risk factors for delayed diagnosis, helps physicians to know what to look for so that SAH and ICH can be promptly diagnosed. We speculate that this increased risk of delayed diagnosis in the office location may be due to the fact that patients who present to an office or by telephone have milder symptoms. Our data supports this, as is seen in Table J, where there was a higher percentage of patients who presented to the office without alarm symptoms or facial pain. Also, more patients who present to the office or by telephone have symptoms that were not related to any effortful activity.

Our results also show that risk factors associated with delayed diagnosis are different among patients who initially present to a physician in a hospital versus in an office. No effortful activity is a feature that was associated with delayed diagnosis in both locations of presentation. Physicians look at the symptoms and the presenting history to determine a differential diagnosis of disease. Their differential diagnosis is based on previous cases of the disease they have encountered. Since most patients with SAH or ICH present with symptoms after exerting themselves, it is less likely for physicians to think of ruptured aneurysms or vessels in patients who had no history of exerting themselves when their symptoms began.

Features associated with delayed diagnosis in patients who present to the hospital, but not those who present to an office setting are: young age, history of migraine diagnosis, and no alarm symptoms. There is a tendency for delayed diagnosis of hemorrhagic stroke in younger patients who present to the hospital because physicians do not commonly think of hemorrhagic stroke in a younger person. Additionally, physicians in an office may be more concerned about younger patients who present to them because

younger patients are usually healthy and any symptoms that are persistent are not ordinary. Therefore, physicians in an office may have a lower threshold to send younger patients for further evaluation. A history of migraine diagnosis may result in delayed diagnosis in the hospital, especially if the presenting symptoms are mild, because migraine or tension headaches are the more common diagnoses seen in the emergency room compared to hemorrhagic stroke. In the office, if a patient has a history of migraine diagnosis, multiple headaches will lead the physician to send the patient for a work-up. When the patient does not have any alarm symptoms, the mild symptoms in patients who present to the hospital leads the physicians toward a milder differential diagnosis. Physicians in the office setting may send the patient for a work-up, even though the presenting symptoms may be mild, because they reason that if the symptoms were bad enough for the patient to make an appointment, there must be some validity to the symptoms.

There are three features that are associated with a delayed diagnosis in the office or telephone setting, but are neutral in the hospital: female gender, no history of smoking, and upper respiratory tract infection symptoms. The presence of these features made no difference when the patient presented to a hospital. However, when patients who presented to an office or by telephone with these features, they were more likely to have a delayed diagnosis. This may be due to the fact that physicians in the office or by telephone tend to downplay the complaints of women, especially if the woman has complained before of symptoms such as headache. Physicians in an office also see multiple cases of allergies and nasal congestion, that a person who presents with upper respiratory tract infection symptoms is most likely to have a cold or allergies.

There are two features that are protective for delayed diagnosis in patients who initially present to an office or by telephone: nausea and no college education. Nausea may lead to a more prompt diagnosis because nausea is a symptom that is commonly associated with a neurological etiology. Therefore, patients will get worked up quicker. Patients with a college education who presented to an office or via telephone had a significant risk of delayed diagnosis of hemorrhagic stroke. Perhaps this is due to physicians being reluctant to send college educated patients to the emergency room for mild symptoms. Alternatively, educated patients may downplay their symptoms because they reason that their symptoms are probably something insignificant. Also, physicians may feel more comfortable to follow educated patients instead of immediately treat because they believe that educated patients will be able to recognize worsening symptoms and seek additional medical care if their symptoms get worse. On that line of reasoning, less educated patients who present to their physician's office or by telephone would be more readily sent to the emergency room for fear that the less educated patient will not return for medical care if they are sent away.

A feature associated with risk of delayed diagnosis in the office only is no history of hypertension. This risk factor is also slightly increased in patients who present to the hospital. Once again, physicians are trained to recognize constellation of symptoms and histories. Since studies have proven that hypertension leads to vessel disease and coronary artery disease, it is less likely for physicians to think that patients without hypertension could have pre-disposing features that would lead to hemorrhagic stroke.

A feature associated with risk of delayed diagnosis in the hospital only is Hispanic ethnicity. This is most likely due to a language barrier in the hospital. Hispanic

patients who have a primary care physician usually go to a clinic with a physician who speaks Spanish, leading to a direct interpretation of the history by the medical provider.

Our study of risk factors demonstrates the importance of distinguishing patients who present to a hospital versus patients who present to an office or by telephone. Two conclusions can be drawn from this portion of our study (Table G). It appears that there are different risk factors pertaining to delayed diagnosis in the different settings of medical care and that it may be inappropriate to combine patients who present to a hospital for their care and patients who present to an office or call a physician via telephone. One limitation of this portion of the study is that there were so few patients with prompt diagnosis who presented to an office or via telephone. With such a small n, it was hard to draw more conclusions based on office or telephone presentation. A clear conclusion is that absence of alarm symptoms is an important factor of delayed diagnosis in the hospital emergency room. Also, patients with a college education who present to an office or via telephone need to have more prompt action taken for their mild symptoms that are consistent with SAH or ICH.

Analyzing the risk factors by stroke type reveals that features of presentation of SAH and ICH are distinct from the other. There are two features associated with a risk for delayed diagnosis of both SAH and ICH: no alarm symptoms and office presentation. Presentation with mild symptoms consistent with SAH or ICH will lead most physicians to think of other diagnoses than hemorrhagic stroke. Presentation to an office with symptoms consistent with SAH or ICH is associated with an increased risk of delayed diagnosis. As discussed previously, the increased risk of delayed diagnosis in the office could be because patients who go to a physician's office present with milder symptoms

than patients who go immediately to an emergency room for symptoms that frighten them.

It is known that the pathophysiology of SAH and ICH are very different. The typical presentation of each disease is distinct from the other. This became apparent in the evaluation of risk features for delayed diagnosis based on location of presentation, where ICH was associated with such an odds ratio of 4.3. We hypothesized that features associated with delayed diagnosis in persons who present with a SAH may be different from those in persons who present with an ICH. There were ten features examined that had a different effect on risk for delayed diagnosis of SAH compared to ICH: Caucasian ethnicity, Black ethnicity, female gender, history of migraine diagnosis, no hypertension history, no neck pain, nausea, vomit, upper respiratory tract symptoms, and no effortful activity.

For three of these ten features (Black ethnicity, no neck pain, and no effortful activity) a delayed diagnosis was increased for patients with SAH, but was protective or neutral for patients with ICH. The usual presentation of SAH is acute onset of headache with decreased consciousness and nuchal rigidity due to a ruptured aneurysm, commonly associated with increased intracranial pressure due to some strenuous activity. Therefore, if a patient does not have neck pain, physicians are led to think that a headache is a migraine or tension headache. Also, if there is no effortful activity at the onset of symptoms, physicians may think that the symptoms are from something else besides SAH. Black ethnicity is a protective feature for delayed diagnosis of ICH. This may be attributed to the fact that physicians are aware that people of Black ethnicity have a

higher risk of hypertension and coronary artery disease. Therefore, when people of Black ethnicity present to a physician for any symptoms, they are more likely to be worked up.

For five of the ten features (Caucasian ethnicity, female gender, history of migraine diagnosis, no hypertension history, and nausea) a delayed diagnosis was significantly increased for patients with ICH, but was protective or neutral for patients with SAH. It is unclear why Caucasian ethnicity may be associated with delayed diagnosis of ICH. Female gender may lead to an increased risk of delayed diagnosis because women may have migraine headaches associated with their menstrual cycle, so headache symptoms may be attributed to other illnesses. History of migraine headaches may be associated with increased delay in diagnosis of ICH because headaches may be attributed to the migraine diagnosis than hemorrhage. Since the usual patients with ICH are hypertensive, if a patient does not have a history of hypertension, the diagnosis of ICH will fall lower on the differential. Nausea is associated with a delayed diagnosis of ICH because nausea can be attributed to GI distress, and therefore be overlooked as a symptom of ICH.

The remaining two features, vomiting and upper respiratory tract symptoms, were significantly protective for delayed diagnosis of SAH, but were associated with risk for delayed diagnosis of ICH. Vomiting is one of the signs seen with increased intracranial pressure, which leads physicians to get a CT scan in order to rule out increased intracranial pressure. Blood from SAH can be seen easily on CT scan. CT scan may not pick up some ICH. Upper respiratory tract symptoms may also lead to diagnostic evaluation by CT scan or MRI, which allows blood to be picked up. Again, diagnostic studies may not pick up small ICH.

Three features were associated with an increased or decreased risk for delayed diagnosis of ICH and a neutral effect on SAH: Hispanic ethnicity, no college education, and no headache present. Hispanic ethnicity tends to be a risk for delayed diagnosis of ICH, but has a neutral (albeit barely neutral) effect on SAH. This may be due to severity of symptoms from ICH versus SAH. If the patient presents with small hemorrhages in the basal ganglia due to ICH, it may be difficult for the physician to locate a focal neurological deficit, whereas if an aneurysm ruptures, as in SAH, focal deficits are usually more obvious. Therefore, less interpretation is required when evaluating a patient with ruptured SAH, possibly accounting for the difference in Hispanic ethnicity. Features that are protective for delayed diagnosis of ICH are no college education and no headache. Reasons for delay if a patient is more educated have been discussed previously. However, no headache as a protective feature may be because of location of the ICH. Some patients with ICH present without any headache, but with other neurological deficits. These patients are more likely to be worked up, thereby leading the results to consider no headache as a protective feature.

The results of our study are strikingly different from previous studies on delayed diagnosis of SAH. Only 54 of 702 (7.7%) patients had a delayed diagnosis of hemorrhagic stroke. This estimate compares to 15% to 64% in other published research. (20)(18) The reason that our estimate may be lower than other studies include: 1) we only enrolled patients who survived their hemorrhagic stroke 2) younger patients are more likely to seek medical care, and 3) the rigorous case definition that was strictly adhered to minimized misclassification. In terms of patient selection, our cohort excluded people who had died from their neurological event. However, based on our data thus far, most

of the patients who have a delayed diagnosis are more likely to have worse outcome. Therefore, excluding those who had died would only support our results that delayed diagnosis leads to increase morbidity and mortality. In terms of methodology, bias was minimized during data collection by including participants not only presenting at the hospital, but also presenting initially to a physician in an office or by telephone. Additionally, trained individuals who used active surveillance to identify patients collected data from hospitals in four geographical regions. There was no doubt of diagnosis in our study because of the strict definition of delayed diagnosis that was adhered to throughout the study requiring that a diagnosis of SAH or ICH be proven with a CT scan or by LP. To minimize recall bias, patients were asked the same questions regarding their event from an interview booklet. Additionally, medical records were read, and patients and family members were interviewed in detail to classify the patient according to pre-specified criteria for delay. We are confident that this study is a true estimate of risk factors for delayed diagnosis of SAH and ICH.

Conclusion

In summary, our study has shown that features associated with increased risk of delayed diagnosis were Hispanic ethnicity, no effortful activity preceding stroke event, no alarm symptoms, and office evaluation. When we further stratified the analysis based on location of presentation, our study showed that the features associated with delayed diagnosis of hemorrhagic stroke were different in patients who presented to an office compared with an emergency room. Finally, stratification by stroke type determined that

SAH and ICH must be studied separately, as risk factors for delayed diagnosis of SAH differed from those of ICH.

The results of our study will be helpful to recognize those patients with hemorrhagic stroke who do not present with the classic symptoms for SAH or ICH. By recognizing the features that are associated with delayed diagnosis of hemorrhagic stroke, prompt diagnosis can be made and early patient referral for treatment can be implemented. Early patient referral will help to decrease risk of vasospasm and re-bleed in the 3-4 days following the initial event, and thus decrease the morbidity and mortality rates of patients with intracranial hemorrhage. (16, 20, 22)

Stratifying the risk features showed that there are different risk factors for delayed diagnosis based on location that patients present to with their initial symptoms of hemorrhagic stroke. An important conclusion is that patients were more likely to have a delayed diagnosis if they went to see a physician in an office. Results for associated risk factors based on location of presentation were consistent with the initial analysis of features leading to increased risk of delayed diagnosis. Young patients who presented to the office without any alarm symptoms were more likely to have a delayed diagnosis. The results of this case-control study have also shed some light on the risk factors that can lead to delayed diagnosis of ICH. Risk factors for delayed diagnosis of SAH and ICH are very different, which supports the fact that clinical features of SAH and ICH should be studied as separate diseases rather than be combined as hemorrhagic stroke. Our study has shown that there are many features of patients who present with ICH which need to be considered in patients who come with symptoms suggestive of ICH. In particular, physicians who see young women with no history of hypertension in their

office or who speak with them via telephone need to consider the diagnosis of ICH more strongly. In addition, further history and evaluation need to be obtained in patients who present with headache in order to be sure that a diagnosis of ICH is not missed.

There have been many studies investigating delayed diagnosis in subarachnoid hemorrhage, but only one study that included delayed diagnosis in intracerebral hemorrhage. (22) These studies have been able to determine the outcome of the patients after the delay, but none have been able to determine factors that can lead to delayed diagnosis. In addition, the studies performed were cross-sectional studies, which could not statistically conclude that certain risk factors were present for the delay in diagnosis.

The results of our case-control study will aid physicians to be able to recognize presentations of SAH and ICH in order to promptly diagnose the hemorrhagic stroke and refer the patient for treatment as quickly as possible to reduce morbidity and mortality. The need to study ICH and SAH as separate entities is not a new idea, however, never before was the data regarding risk factors of presenting symptoms statistically analyzed. Our results show clearly that SAH and ICH must be looked at separately when studying risk factors that may lead to delayed diagnosis of each stroke type. Our results also show that there is a difference in the risk factors associated with delayed diagnosis in the office setting compared with the hospital. To further understand the phenomenon of delayed diagnosis and identify strategies to prevent it, it will be important to account for the important delay occurring in the office and to recognize that the risk factors for delayed diagnosis may be different according to where a patient initially presents.

Implications

Implications of our study show that efforts are needed to reduce delay in diagnosis among primary care physicians and hospital physicians who see low-risk patients who may present with mild initial symptoms. Features associated with delayed diagnosis of SAH were vastly different from those associated with delayed diagnosis of ICH, proving that it is not sufficient to study hemorrhagic stroke as one entity. Each specific stroke type needs to be studied on its own to determine more specific features associated with delayed diagnosis of each individual stroke type.

Additionally, it appears that features associated with delayed diagnosis are different based on location of initial presentation of symptoms. We recognize that evaluation of SAH and ICH based on location of initial medical contact was limited in this study because of small numbers. However, the results that were obtained show that it would be worthwhile for future studies examining delayed diagnosis to separately evaluate the risk factors of those patients who initially present to a physician's office from the patients who initially are seen in the emergency room.

Additional studies are necessary to further understand delayed diagnosis of hemorrhagic stroke and to evaluate risk factors for delayed diagnosis in the hospital separate from the risk factors for delayed diagnosis in the physician's office. By recognizing that most delayed diagnoses occur in an office, future studies will be able to determine the specific symptoms that physicians need to be aware of in each location of evaluation in order to reduce the incidence of delayed diagnosis of hemorrhagic stroke.

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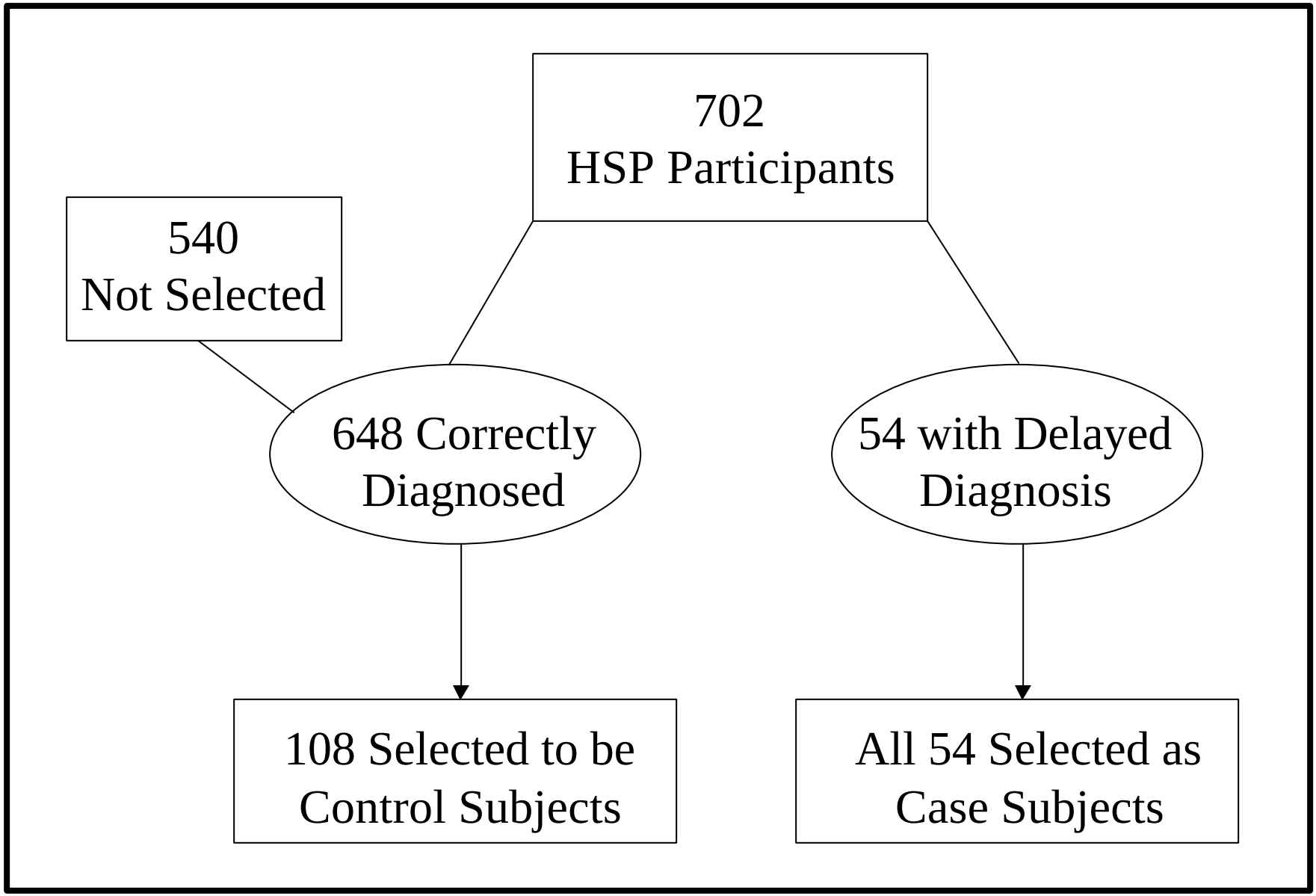

Figure 1. Diagram of Cohort Assembly

Table A:

Presenting Symptoms of Subarachnoid Hemorrhage in 41 Patients with Delayed Diagnosis
(Adams, et al., *JAMA* 244:794-796, 1980)

Symptom	**No. of Patients (%)**
Headache	35 (85)
Nausea	18 (44)
Vomiting	14 (34)
Brief Loss of Consciousness	13 (32)
Neck Stiffness or Pain	6 (15)
Hemiparesis	6 (15)
Vertigo	6 (15)
Faintness	5 (12)
Confusion	3 (7)
Convulsions	3 (7)
Coma	3 (7)
Hearing Loss	3 (7)
Visual Loss	2 (5)
Diploplia	2 (5)
Malaise and Diffuse Aches	2 (5)
Photophobia	1 (2)
Back Pain	1 (2)

Table A (continued):

Presenting Symptoms of Subarachnoid Hemorrhage in 41 Patients with Delayed Diagnosis
(Adams, et al., *JAMA* 244:794-796, 1980)

Leg Pain	1 (2)
Ataxia	1 (2)
Speech Disturbance	1 (2)
Chest Pain	1 (2)
Paraparesis	1 (2)

Table B: The Hunt and Hess Scale for Grading of Subarachnoid Hemorrhage

Grade	Motor Deficit
0	Intact aneurysm.
1	Asymptomatic. Mild headache and slight nuchal rigidity.
1a	No acute meningeal/brain reaction but with fixed neurological deficit.
2	Cranial nerve palsy. Moderate to severe headache. Nuchal rigidity.
3	Mild focal deficit. Lethargy or confusion.
4	Stupor. Moderate to severe hemiparesis. Early decerebrate rigidity.
5	Deep coma. Decerebrate rigidity. Moribund appearance.

Table C: The Glasgow Coma Scale*

Glasgow Coma Scale		
Eye Opening (E)	**Verbal Response (V)**	**Motor Response (M)**
4=Spontaneous 3=To voice 2=To pain 1=No Eye Opening	5=Normal conversation 4=Disoriented conversation 3=Words, but not coherent 2=Incomprehensible sounds 1=No Sounds	6= Obeys commands fully 5=Localizes to noxious stimuli 4=Withdraws from noxious stimuli 3= Abnormal flexion, i.e. decorticate posturing 2= Extensor response, i.e. decerebrate posturing 1= No response

* Glasgow Coma Score is calculated as E+V+M

Table D: Summary of Previous Studies on Delayed Diagnosis of Intracranial Hemorrhage

Study (Year)	Study Type	Method of Patient Selection	Source of Data	Stroke Type Studied	Number of Patients	Delayed Diagnosis n (%)
Adams et al. (1980)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	182	41 (23)
Jain et al. (1983)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	90	31 (34)
Kassell et al. (1985)	Cross-Sectional	Discharge Diagnosis	Medical Records, patients, family members, physicians	SAH	150	56 (37)* 96 (64)
Schievink et al. (1988)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	334	52 (16)* 164 (49)
Fontanarosa (1989)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	109	16 (15)

* This percentage reflects delayed diagnosis due only to physician diagnostic error.

Table D: Summary of Previous Studies on Delayed Diagnosis of Intracranial Hemorrhage

Study (Year)	Study Type	Method of Patient Selection	Source of Data	Stroke Type Studied	Number of Patients	Delayed Diagnosis n (%)
Ferro et al. (1991)	Cross-Sectional	Triage Surveillance	Data Collected at Time of Admission; followed until referral to neurosurgical unit	SAH	112	56 (50)
Chan et al. (1991)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	94	15 (16)
Sved et al. (1995)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH	511	
Mayer et al. (1996)	Cross-Sectional	Discharge Diagnosis	Medical Records	SAH and ICH	217	54 (25)
Neil-Dwyer et al. (1997)	Cross-Sectional	Discharge Diagnosis	History and Data Collected at Time of Admission	SAH	136	69 (51)

* This percentage reflects delayed diagnosis due only to physician diagnostic error.

Table E: Baseline Features among patients with delayed and prompt diagnosis of hemorrhagic stroke*

Demographic and Historical Features	Delayed Diagnosis	Prompt Diagnosis	Odds Ratio	P-value
	N=54 n (%)	**N=108 n (%)**		
Age, years (median)	40	43		
Age < 40	24 (44)	31 (29)	2.0	0.05
Race/Ethnicity				
Caucasian	43 (80)	85 (79)	1.1	0.89
Black	8 (15)	21 (19)	0.7	047
Hispanic	8 (15)	8 (7)	2.2	0.14
Gender: Female	27 (50)	57 (53)	0.9	0.74
History of Migraine Headaches	10 (19)†	15 (14)†	1.5	0.40
No History of Hypertension	38 (70)	58 (54)	2.0	0.04
Not Currently a Smoker	25 (46)	54 (50)	0.9	066
No Family History	51 (94)	101 (94)	1.5	0.62
No College Education	27 (50)	71 (66)	0.5	0.05
No Insurance	9 (17)†	15 (14)†	1.3	0.62

* features are described in table according to hypothesis of how each feature would contribute to delayed diagnosis
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table E: Baseline Features among patients with delayed and prompt diagnosis of hemorrhagic stroke*

Symptom Features	Delayed Diagnosis	Prompt Diagnosis	Odds Ratio	P-value
	N=54 n (%)	N=108 n (%)		
No Alarm Symptoms	34 (63)	26 (24)†	5.3	<0.01
No Photophobia	45 (83)	79 (74)†	1.8	0.18
No Loss of Consciousness	50 (93)	85 (81)†	2.9	0.05
No Focal Neurological Sx	45 (83)	63 (58)	3.6	<0.01
No Facial Pain	53 (98)	105 (97)	1.5	0.72
No Neck Pain	35 (65)	57 (53)	1.6	0.14
No Headache Present	2 (4)†	18 (17)†	0.2	0.02
Nausea	27 (52)†	52 (50)‡	0.9	0.87
Vomiting	25 (48)†	57 (56)‡	1.4	0.36
Upper Respiratory Tract Sx	19 (39)‡	47 (46)‡	0.7	0.40
URI Symptoms	8 (16)‡	19 (18)‡	0.9	0.77
Allergies	9 (18)‡	25 (24)‡	0.7	0.43
Nasal Congestion	15 (29)	30 (29)‡	1.0	1.00
No Effortful Activity	50 (94)†	90 (85)†	3.0	0.08

* features are described in table according to hypothesis of how each feature would contribute to delayed diagnosis
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table E: Baseline Features among patients with delayed and prompt diagnosis of hemorrhagic stroke*

Diagnostic Features	Delayed Diagnosis	Prompt Diagnosis	Odds Ratio	P-value
	N=54 n (%)	**N=108 n (%)**		
Location of Evaluation: Office or Telephone	28 (52)	6 (6)	18.3	<0.01
Stroke Type: ICH	24 (44)	41 (38)	1.3	0.43

* features are described in table according to hypothesis of how each feature would contribute to delayed diagnosis
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table F: Results of a Multivariable Analysis for clinical features associated with increased risk for delayed diagnosis

Feature*	Adjusted OR	P-value
Office or Telephone Evaluation	23.1	<0.0001
No Alarm Symptoms	4.6	0.0013
No Effortful Activity	5.5	0.08
Hispanic Ethnicity	2.4	0.19
No History of Hypertension	1.5	0.41
Age < 40	1.2	0.68
No College Education	0.9	0.92
No Headache Present	0.6	0.51

* Features were included in the model if the odds ratio in a bivariate analysis was > 2.0 or <0.5 (see Table E)

Table G: Features Associated with Delayed Diagnosis According to Type of Initial Contact

	Presented to Hospital				**Presented to Office/by Telephone**			
Demographic and Historical Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 26 n (%)	**N = 102 n (%)**			**N = 28 n (%)**	**N = 6 n (%)**		
Age < 40 Years	11 (42)	27 (26)	2.0	0.11	13 (46)	4 (67)	0.4	0.37
Race								
Caucasian	20 (77)	79 (77)	1.0	0.95	23 (82)	6 (100)	–	0.26
Black	6 (23)	21 (21)	1.2	0.78	2 (7)	0 (0)	–	0.50
Hispanic	6 (23)	8 (8)	3.5	0.03	2 (7)	0 (0)	–	0.50
Female	13 (50)	55 (54)	0.9	0.72	14 (50)	2 (33)	2.0	0.46
History of Migraine Dx	6 (24)†	13 (13)†	2.1	0.16	4 (15)†	2 (33)	0.4	0.29
No Hypertension History	17 (65)	55 (54)	1.6	0.29	21 (75)	3 (50)	3.0	0.22
Not Currently a Smoker	14 (54)	53 (52)	1.1	0.86	11 (39)	1 (17)	3.2	0.29
No Primary Family History	25 (100)†	95 (94)†	–	0.21	26 (93)	6 (100)	–	0.50
No College Education	17 (65)	66 (65)	1.0	0.95	10(36)	5 (83)	0.1	0.03
Not Insured	5 (20)†	15 (15)†	1.4	0.53	4 (14)	0 (0)	–	0.32

* indicates that these symptoms were present the 2 weeks before initial presentation to physician for symptoms consistent with hemorrhagic stroke
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table G: Features Associated with Delayed Diagnosis According to Type of Initial Contact

	Presented to Hospital				**Presented to Office/by Telephone**			
Symptom Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 26 n (%)	**N = 102 n (%)**			**N = 28 n (%)**	**N = 6 n (%)**		
No Alarm Symptoms	15 (58)	22 (22)†	4.9	0.0003	19 (68)	4 (67)	1.1	0.95
No Photophobia	21 (81)	75 (74)†	1.5	0.49	24 (86)	4 (67)	3.0	0.27
No Loss of Consciousness	23 (88)	79 (80)†	1.9	0.31	27 (96)	6 (100)	–	0.64
No Focal Weakness	22 (85)	57 (56)	4.3	0.007	23 (82)	6 (100)	–	0.26
No Facial Pain	25 (96)	99 (97)	0.8	0.81	28 (100)	6 (100)	–	
No Neck Pain	17 (65)	57 (56)	1.5	0.38	18 (64)	0 (0)	–	0.004
No Headache Present	1 (4)†	18 (18)	0.2	0.09	1 (4)†	0 (0)†	–	0.70
Nausea	15 (60)†	49 (49)†	1.5	0.35	12 (44)†	3 (75)†	0.3	0.25
Vomiting	15 (60)†	53 (54)‡	1.3	0.60	10 (37)†	4 (100)†	–	0.02
Upper Respiratory Tract Sx	11 (44)	46 (47)	0.9	0.76	8 (33)‡	1 (20)†	2.0	0.56
URI Symptoms*	4 (17)†	19 (19)†	0.9	0.84	4 (15)†	0 (0)†	–	0.35
Allergies*	5 (22)†	24 (24)†	0.9	0.80	4 (15)†	1 (20)†	0.7	0.80
Nasal Congestion*	9 (35)	29 (30)‡	1.2	0.67	6 (24)†	1 (17)	1.6	0.70
No Effortful Activity	24 (96)†	85 (85)†	4.2	0.14	26 (93)	5 (83)	2.6	0.46

* indicates that these symptoms were present the 2 weeks before initial presentation to physician for symptoms consistent with hemorrhagic stroke
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table G: Features Associated with Delayed Diagnosis According to Type of Initial Contact

	Presented to Hospital				**Presented to Office/by Telephone**			
Diagnostic Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 26 n (%)	**N = 102 n (%)**			**N = 28 n (%)**	**N = 6 n (%)**		
Stroke Type: ICH	11 (42)	40 (39)	1.1	0.77	13 (46)	1 (17)	4.3	0.18

* indicates that these symptoms were present the 2 weeks before initial presentation to physician for symptoms consistent with hemorrhagic stroke
† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table H: Features Associated with Delayed Diagnosis of Subarachnoid Hemorrhage

	SAH			
Demographic and Historical Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 30 n (%)	**N = 67 n (%)**		
Age < 40 Years	12 (40)	23 (34)	1.3	0.59
Race				
Caucasian	24 (80)	58 (87)	0.6	0.41
Black	5 (17)	9 (13)	1.3	0.68
Hispanic	4 (13)	5 (7)	1.9	0.36
Female	10 (33)	41 (61)	0.3	0.01
History of Migraine Diagnosis	4 (14)[†]	10 (15)[†]	0.9	0.91
No Hypertension History	19 (63)	42 (63)	1.0	0.95
Not Currently a Smoker	13 (43)	28 (42)	1.1	0.89
No Primary Family History	30 (100)	63 (94)	–	0.17
No College Education	16 (53)	43 (64)	0.6	0.31
Not Insured	5 (17)	11 (16)	1.0	0.98

[†] indicates that there are 1-3 subjects missing from the stated n
[‡] indicates that there are 4-6 subjects missing from the stated n

Table H: Features Associated with Delayed Diagnosis of Subarachnoid Hemorrhage

	SAH			
Symptom Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 30 n (%)	**N = 67 n (%)**		
No Alarm Symptoms	18 (60)	22 (33)†	3.0	0.01
No Photophobia	25 (83)	43 (64)	2.8	0.06
No Loss of Consciousness	26 (87)	53 (82)†	1.5	0.53
No Focal Neurological Sx	25 (83)	55 (82)	1.1	0.88
No Facial Pain	29 (97)	65 (97)	0.9	0.93
No Neck Pain	17 (57)	21 (31)	2.9	0.02
No Headache Present	1 (3)†	3 (5)†	0.7	0.80
Nausea	16 (55)†	42 (66)†	0.6	0.34
Vomiting	15 (52)†	44 (70)‡	0.5	0.09
Upper Respiratory Tract Sx	9 (33)†	34 (52)†	0.5	0.11
URI Symptoms (in 2 weeks)	2 (7)†	15 (23)†	0.3	0.07
Allergies (in 2 weeks)	6 (21)†	16 (25)†	0.8	0.74
Nasal Congestion (in 2 weeks)	8 (30)†	21 (32)†	0.9	0.80
No Effortful Activity	28 (97)†	53 (80)†	6.9	0.04

† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table H: Features Associated with Delayed Diagnosis of Subarachnoid Hemorrhage

	SAH			
Diagnostic Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 30 n (%)	**N = 67 n (%)**		
Location of Evaluation: Office or Telephone	15 (50)	5 (7)	12.4	<.0001

† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table I: Features Associated with Delayed Diagnosis of Intracerebral Hemorrhage

	ICH			
Demographic and Historical Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 24 n (%)	**N = 41 n (%)**		
Age < 40 Years	12 (50)	8 (20)	4.1	0.01
Race				
Caucasian	19 (79)	27 (66)	2.0	0.25
Black	3 (13)	12 (29)	0.3	0.12
Hispanic	4 (17)	3 (7)	2.5	0.24
Female	17 (71)	16 (39)	3.8	0.01
History of Migraine Diagnosis	6 (25)	5 (12)	2.4	0.18
No Hypertension History	19 (79)	16 (39)	5.9	0.002
Not Currently a Smoker	12 (50)	26 (63)	0.6	0.29
No Primary Family History	21 (88)	38 (93)	0.6	0.56
No College Education	11 (46)	28 (68)	0.4	0.07
Not Insured	4 (17)[†]	4 (10)[†]	1.9	0.40

[†] indicates that there are 1-3 subjects missing from the stated n
[‡] indicates that there are 4-6 subjects missing from the stated n

Table I: Features Associated with Delayed Diagnosis of Intracerebral Hemorrhage

	ICH			
Symptom Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 24 n (%)	**N = 41 n (%)**		
No Alarm Symptoms	16 (67)	4 (10)	18.5	<.0001
No Photophobia	20 (83)	36 (90)†	0.6	0.44
No Loss of Consciousness	24 (100)	32 (80)†		0.02
No Focal Weakness	20 (83)	8 (20)	20.6	<.0001
No Facial Pain	24 (100)	40 (98)	−	0.44
No Neck Pain	18 (75)	36 (88)	0.4	0.18
No Headache Present	1 (4)†	15 (37)	0.1	0.004
Nausea	11 (48)†	10 (26)†	2.7	0.07
Vomiting	10 (43)†	13 (33)†	1.5	0.42
Upper Respiratory Tract Sxs	10 (45)†	13 (36)‡	1.5	0.48
URI Symptoms (in 2 weeks)	6 (29)†	4 (10)†	3.5	0.07
Allergies (in 2 weeks)	3 (14)†	9 (23)†	0.6	0.42
Nasal Congestion (in 2 wks)	7 (29)	9 (24)‡	1.3	0.67
No Effortful Activity	22 (92)	37 (93)†	0.9	0.90

† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table I: Features Associated with Delayed Diagnosis of Intracerebral Hemorrhage

	ICH			
Diagnostic Features	**Delayed**	**Prompt**	**Odds Ratio**	**P-value**
	N = 24 **n (%)**	**N = 41** **n (%)**		
Location of Evaluation: Office or Telephone	13 (54)	1 (2)	47.3	<.0001

† indicates that there are 1-3 subjects missing from the stated n
‡ indicates that there are 4-6 subjects missing from the stated n

Table J: Comparison of Percentage of Patients and Control Subjects According to Type of Initial Contact

Demographic and Historical Features	**Presented to Hospital**	**Presented to Office or by Telephone**
	N = 128 n (%)	**N = 34 n (%)**
Age < 40 Years	38 (30)	17 (50)
Race		
Caucasian	99 (77)	29 (85)
Black	27 (21)	2 (6)
Hispanic	14 (11)	2 (6)
Female	68 (53)	16 (47)
History of Migraine Dx	19 (15)	6 (18)
No Hypertension History	72 (56)	24 (71)
Not Currently a Smoker	67 (52)	12 (35)
No Primary Family History	120 (95)	32 (94)
No College Education	83 (65)	15 (44)
Not Insured	20 (16)	4 (12)

Table J: Comparison of Percentage of Patients and Control Subjects According to Type of Initial Contact

Symptom Features	Presented to Hospital	Presented to Office or by Telephone
	N = 128 **n (%)**	**N = 34** **n (%)**
No Alarm Symptoms	37 (29)	23 (68)
No Photophobia	96 (76)	28 (82)
No Loss of Consciousness	102 (82)	33 (97)
No Focal Weakness	79 (62)	29 (85)
No Facial Pain	124 (97)	34 (100)
No Neck Pain	74 (58)	18 (53)
No Headache Present	19 (15)	1 (3)
Nausea	64 (52)	15 (48)
Vomiting	68 (55)	14 (46)
Upper Respiratory Tract Sx	57 (47)	9 (31)
URI Symptoms*	23 (19)	4 (13)
Allergies*	29 (24)	5 (16)
Nasal Congestion*	38 (31)	7 (23)
No Effortful Activity	109 (87)	31 (91)

Table J: Comparison of Percentage of Patients and Control Subjects According to Type of Initial Contact

Diagnostic Features	**Presented to Hospital**	**Presented to Office or by Telephone**
	N = 128 n(%)	**N = 34 n (%)**
Stroke Type: ICH	51 (40)	14 (41)