JoS JOURNAL OF STROKE

Journal of Stroke 2017;19(1):3-10
https://doi.org/10.5853/jos.2016.00864

Special Review

Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update

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Intracerebral hemorrhage (ICH) is the second most common subtype of stroke and a critical disease usually leading to severe disability or death. ICH is more common in Asians, advanced age, male sex, and low- and middle-income countries. The case fatality rate of ICH is high (40% at 1 month and 54% at 1 year), and only 12% to 39% of survivors can achieve long-term functional independence. Risk factors of ICH are hypertension, current smoking, excessive alcohol consumption, hypocholesterolemia, and drugs. Old age, male sex, Asian ethnicity, chronic kidney disease, cerebral amyloid angiopathy (CAA), and cerebral microbleeds (CMBs) increase the risk of ICH. Clinical presentation varies according to the size and location of hematoma, and intraventricular extension of hemorrhage. Patients with CAA-related ICH frequently have concomitant cognitive impairment. Anticoagulation related ICH is increasing recently as the elderly population who have atrial fibrillation is increasing. As non-vitamin K antagonist oral anticoagulants (NOACs) are currently replacing warfarin, management of NOAC-associated ICH has become an emerging issue.

Keywords Cerebral hemorrhage, Epidemiology, Incidence, Risk factors, Neurologic manifestations

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Received: July 16, 2016
Revised: December 18, 2016
Accepted: January 6, 2017

This work was supported by the Korea Health Technology R&D project (HI10 C2020) and by the Ministry of Health and Welfare, Republic of Korea (HI16C1078).

The authors have no financial conflicts of interest.

Introduction

Intracerebral hemorrhage (ICH) is usually caused by rupture of small penetrating arteries secondary to hypertensive changes or other vascular abnormalities.[1-3] In developed countries, the incidence of hypertensive ICH has decreased with the improvement of blood pressure control.[4] However, in developing countries, the burden of ICH has not decreased.[5] The outcome of ICH is variable, depending on hematoma volume, location, extension to ventricles, and other factors.[6] However, compared to ischemic stroke, ICH leads to higher mortality and more severe disability.[7] In this review, we will summarize the epidemiology, pathophysiology, risk factors, prognostic factors, and clinical manifestation of ICH.

Epidemiology

Incidence

ICH accounts for approximately 10-20% of all strokes[8,9] 8-15% in western countries like USA, UK and Australia,[10,11] and 18-24% in Japan[12] and Korea.[4] The incidence of ICH is substantially variable across countries and ethnicities. The incidence rates of primary ICH in low- and middle-income countries were twice the rates in high-income countries (22 vs. 10 per 100,000 person-years) in 2000-2008.[8] In a systematic review of 36 population-based epidemiological studies, the incidence rate of ICH per 100,000 person-years was 51.8 in Asians, 24.2 in Whites, 22.9 in Blacks, and 19.6 in Hispanics.[13] In a population-based US study identifying 1,038 patients who were hospitalized for ICH, American black people had a higher incidence of ICH compared to white people; per 100,000 person-years, 48.9 vs. 26.6.[14]

The incidence of ICH increases with advanced age.[15] A recent inpatient database study from the Netherlands based on retrospective cohort study reported that the incidence of ICH per 100,000 was 5.9 in 35-54 years, 37.2 in 55-74 years, and 176.3 in 75-94 years old in 2010. For all ages, the annual incidence rate per 100,000 persons was higher in men than in women; 5.9

vs. 5.1 in people aged 35-54 years, 37.2 vs. 26.4 in those aged 55-74 years, and 176.3 vs. 140.1 in those aged 75-94 years.[16] In a German study analyzing database of a regional prospective stroke registry between 2007 and 2009, 34% of 3,448 patients with ICH were aged 80 years or more.[17]

The Global Burden of Disease 2010 Study showed a 47% increase in the absolute number of hemorrhagic stroke (including ICH and subarachnoid hemorrhage) worldwide between 1990 and 2010. The largest proportion of ICH incident cases (80%) and deaths (63%) occurred in low- and middle-income countries such as Sub-Saharan Africa, Central Asia and Southeast Asia. During the two decades, the age-adjusted incidence rate of hemorrhagic stroke reduced by 8% (95% confidence interval [CI]: 1–15) in high-income countries, whereas it increased by 22% (95% CI: 5–30) in the low- and middle-income countries.[5] A population-based study in the United Kingdom showed that the incidence of ICH associated with hypertension in patients less than 75 years of age has declined since the early 1980s with the improved control of hypertension. However, for all ages, the number of ICH cases remained stationary, which was likely to be attributed to an increase of non-hypertensive lobar ICH presumably caused by amyloid angiopathy in elderly people aged over 75 years and a recent increase in ICH associated with antithrombotic therapy. As the population ages, the incidence of ICH due to amyloid angiopathy may further rise in the future.[18] The incidence of ICH in Japan has declined significantly due probably to the better control of hypertension.[12] In Korea, there has been no population-based study on the trend of the ICH incidence. Estimation based on nationwide health insurance database indicates that the incidence of hemorrhagic stroke in Korean people aged between 35-74 years decreased annually by 1.82%.[4] On the other hand, a systematic review of 56 population-based studies showed that the overall age-adjusted incidence rate of primary ICH by pooling data from high-income countries showed no significant change between 1980 and 2008.[8]

Fatality

A case fatality rate of ICH is approximately 40% at 1 month and 54% at 1 year. Only 12% to 39% of patients achieve long-term functional independence. A meta-analysis of ICH outcomes between 1980 and 2008 showed no appreciable change in case fatality rate over that time period,[13] but retrospective studies of large cohorts in the United Kingdom and United States showed a significant decrease in case fatality since 2000.[19,20] A worldwide stroke epidemiology study revealed that early stroke case fatality (21-day to 1-month) varied substantially among countries and study periods; the case fatality rate was 25-30% in high-income countries while it was 30-48% in low- to middle-income countries.[8] Decrease in the ICH fatality rate might be attributed to the improvement of critical care.[21] In Korea, the case-fatality rate of ICH estimated from the nationwide insurance database was high as 35% in 2004. However, the in-hospital 30-day case-fatality rate in 2009 was much lower as 10.2%.[4]

Pathophysiology

Hypertensive vascular change

ICH is usually caused by ruptured vessels that are degenerated due to long-standing hypertension. Responsible arteries show prominent degeneration of the media and smooth muscles.[2] Fibrinoid necrosis of the sub-endothelium with micro-aneurysms and focal dilatations may be seen in some patients. Lipohyalinoses, prominently related to long-standing hypertension, is most often found in non-lobar ICH[22] whereas cerebral amyloid angiopathy (CAA) is relatively more common in lobar ICH.[23]

Cerebral amyloid angiopathy

CAA is characterized by the deposition of amyloid-β peptide at capillaries, arterioles, and small- and medium-sized arteries in the cerebral cortex, leptomeninges, and cerebellum.[24] CAA in the cerebral small vessel leads to sporadic ICH in elderly people, commonly associated with variations in the gene encoding apolipoprotein E epsilon 2 and 4 in chromosome 19.[25,26] Duplication of the APP locus on chromosome 21 is also found in families with familial early-onset Alzheimer disease and CAA. CAA-related ICHs occur mainly in the elderly subjects while a rare familial syndrome may manifest in relatively young patients.[25]

Molecular pathophysiology

The initial injury mechanism in ICH is compressing brain parenchyma by hematoma's mass effect, resulting in physical disruption of parenchymal architecture.[27] Increased intracranial pressure due to expansion of hematoma can affect blood flow, mechanical deformation, neurotransmitter release, mitochondrial dysfunction and membrane depolarization. As a result, neuronal injury in perihematomal area contains the edema and inflammatory environment by blood-derived factors.[28–30] A secondary mechanism of brain injury is related to clotting cascade, in particular thrombin, after endothelial damage and hemoglobin breakdown.[31–33] Thrombin causes inflammatory cells to infiltrate the brain, proliferation of mesenchymal cells, formation of brain edema and scar tissue.[34] Thrombin binds to protease-activated receptors 1 and activates the central nervous system microglia and complement cascade. As a result, multiple immune pathways are activated, which contributes to apoptosis and necrosis. Heme influx in neuron after endothelial damage leads to iron re-

https://doi.org/10.5853/jos.2016.00864

lease and neuronal insult.[1,2,7]

Risk factors

Modifiable risk factors include hypertension, cigarette smoking, excessive alcohol consumption, decreased low-density lipoprotein cholesterol, low triglycerides and drugs including anticoagulant, antithrombotic agent, and sympathomimetics. Non-modifiable risk factors include old age, male sex, CAA, and Asian ethnicity (Table 1).[35,36] The INTERSTROKE study, an international case-control study of 6,000 individuals in 22 countries worldwide, showed that hypertension, smoking, waist-to-hip ratio, diet, and high alcohol intake were major risk factors for ICH, and these modifiable risk factors accounted for 88.1% of the population-attributable risk.[37]

Hypertension is the most important risk factor for spontaneous ICH, and the contribution of hypertension is greater for deep ICH than for lobar ICH;[38,39] hypertension is twice as common in patients with deep ICH as in those with lobar ICH.[40] Current smoking[35] and heavy alcohol consumption[41] are associated with increased risk of ICH. An Australian case-control study showed an inverse relationship between cholesterol level and the risk of ICH.[42] Another study found that low total cholesterol and Low-density lipoprotein cholesterol levels were associated with more severe ICH.[43] The use of warfarin increases the risk of ICH by two- to five-fold, depending upon the intensity of anticoagulation.[44] Anticoagulation-related ICH is nowadays increasing because of the increased use of oral anticoagulation in elderly population.[45] Antiplatelet therapy can increase the risk of ICH.

Table 1. Risk factors of intracerebral hemorrhage

Modifiable risk factors
Hypertension
Current smoking
Excessive alcohol consumption
Decreased Low-density lipoprotein cholesterol, low triglycerides
Anticoagulation
Use the antiplatelet agent
Sympathomimetic drugs (Cocaine, heroin, amphetamine, PPA and ephedrine)
Non-modifiable risk factor
Old age
Male sex
Asian ethnicity
Cerebral amyloid angiopathy
Cerebral microbleeds
Chronic kidney disease
Other factors suggested to be related the risk
Multi-parity
Poor working conditions (blue-collar occupation, longer working time)
Long sleep duration

PPA, Phenylpropanolamine.

Several case-control studies did not show an increased ICH risk with antiplatelet use,[42,46] but meta-analyses showed that antiplatelet therapy was associated with a small but significant increase in the ICH risk.[47,48] In addition, a meta-analysis showed that prior antiplatelet use was associated with an increased risk of death after the ICH,[49] and another studies demonstrated an increased risk of early hematoma growth with prior antiplatelet use.[50,51] In particular, dual antiplatelet therapy compared to antiplatelet monotherapy is likely to further increase the ICH risk. In patients with atrial fibrillation, the risk of ICH is almost twice as high with aspirin plus clopidogrel compared to aspirin alone (0.4 vs. 0.2 percent).[52]

Associations have been reported between ICH and sympathomimetic drugs such as cocaine, heroin, amphetamine, and ephedrine, particularly in young patients. Phenylpropaolamine in a relatively high dose was an independent risk factor for hemorrhagic stroke, particularly in women.[53] In a Korean case-control study, low dose of Phenylpropaolamine in cold remedies was also associated with an increased risk of hemorrhagic stroke in women.[54] Chronic kidney disease was found to increase the risk for ICH in a population-based study, and the association remained significant even after adjusting for covariates.[55] Chronic kidney disease may be a marker of cerebrovascular small vessel disease, which is the major mechanism of hypertensive ICH.[56] Platelet dysfunction in patients with chronic kidney disease might also account for the increased risk of ICH.

Cerebral microbleeds (CMBs)

CMBs are detected in 5 to 23 percent of elderly individuals.[57] The Framingham study showed that CMBs were more prevalent in individuals with advanced age and males.[58] In another studies, CMBs were associated with hypertension, diabetes mellitus, and cigarette smoking.[57,59] CMBs are associated with an increased risk of spontaneous ICH,[60] and may increase the risk of warfarin- or antiplatelet-associated ICH.[61] Therefore, both the benefit and risk should be considered for antithrombotic use in patients with CMBs.[62]

Other potential risk factors

Increased number of childbirths may be associated with an increased risk of ICH. Compared to women with nulliparity or uniparity, women with multiparity have a significantly higher risk for ICH with a trend of increasing risk with increasing parity.[63] Blue-collar occupation, longer working hours, and extended duration of strenuous work activity may be related to an increased risk of ICH.[64] It was also reported that long sleep duration greater than 8 hours was associated with an increased ICH risk.[65]

Table 2. Poor prognostic factors of intracerebral hemorrhage

Low score of Glasgow coma scale
Intracerebral hemorrhage volume (≥ 30 cm^3)
Intraventricular extension of hemorrhage
Infra-tentorial origin of Intracerebral hemorrhage
Old age (≥ 80)
Advanced white matter lesions
Underweight at admission
Hyperglycemia at admission
Chronic kidney disease (estimated glomerular filtration rate < 60 mL/minute/m^2)

Prognostic factors

Known poor prognostic factors of ICH include large hematoma volume, hematoma expansion, intraventricular hemorrhage, infra-tentorial location, old age, contrast extravasation on CT scan (spot sign) and the use of anticoagulation (Table 2). ICH Score, a simple clinical grading scale, may help stratify the risk; patients with high ICH score have a high mortality rate.[6] In Asian studies, fever, low initial Glasgow Coma Scale, large hematoma, intraventricular hemorrhage, and diabetes were independent predictors for poor outcome.[66,67] Acute brain bleeding analysis, a large case-control study, showed that extensive white matter lesion was associated with lower Glasgow Coma Scale score and higher mortality.[68] High glucose level at admission or at 24 hours was also associated with an increased risk of bed-ridden status or 30-day mortality,[69] Chronic kidney disease (glomerular filtration rate < 60 mL/minute/m^2) was also reported to be associated with poor outcome.[70] In addition to well known biological factors, early withdrawal of care might impact on the ICH outcome. In a US study, even after adjusting for predictors of ICH mortality, early do-not-resuscitate decision was independently associated with higher short- and long-term mortalities, suggesting that the decision of early withdrawal of care for ICH patients should be cautiously made.[71] The current US guidelines recommend the postponement of do-not-resuscitate orders until at least the second full day of hospitalization.[72]

Clinical manifestation

Although some individuals develop ICH during exertion or sudden emotional stress, most ICHs occur during routine activity. The neurologic symptoms usually aggravate over minutes or a few hours. The most common site of ICH is the putamen, and clinical presentations vary by the size and location of ICH.[73] Common ICH symptoms are headache, nausea, and vomiting. Headache is more common in patients with large hematomas, and is attributed to traction on meningeal pain fibers, increased intracranial pressure, or blood in the cerebrospinal fluid. Small, deep hematomas are rarely associated with headache. Vomiting is reported in about 50% of patients with hemispheric ICH, and more common in patients with cerebellar hemorrhages. It is usually associated with increased intracranial pressure. Patients with large ICH often have a decreased level of consciousness due to increased intracranial pressure and compression of the thalamus and brainstem. Stupor or coma indicates large ICHs that involve the brainstem reticular activating system.[74] Seizures reported in about 10% of patients with ICH and about 50% of patients with lobar hemorrhage. Seizures typically occur at the onset of bleeding or within the first 24 hours.[75] Neurological deterioration is common before and during hospital admission and may indicate early hematoma enlargement or worsening of edema.[1] Patients with a supratentorial ICH involving the basal ganglia or thalamus have contralateral sensorimotor deficits. Lobar hemorrhages may present with symptoms of a higher cortical dysfunction such as aphasia, neglect, gaze deviation, and hemianopia. In patients with an infratentorial ICH, signs of brainstem dysfunction occur such as ocular motor or other cranial nerve abnormalities, and contralateral motor deficits.[2] More than 40% of patients with CAA-associated ICH have some degree of cognitive dysfunction, and the cognitive changes may precede the ICH in some cases.[76,77]

The prognosis of anticoagulation-associated ICH is usually grave, and up to 76% of patients either die or become dependent.[78] In approximately half of the patients, ICH symptoms progress slowly over 24 hours.[79,80] The unique fluid-blood interface appearance as a result of uncongealed blood can be seen within 12 hours.[81] Recently, non-vitamin K antagonist oral anticoagulant (NOAC)-related ICHs are increasingly detected due to the increasing use of NOAC. In a small observational study, patients with NOAC-associated ICH compared to those with warfarin-associated ICH had smaller ICH volumes and better clinical outcomes.[82] As specific antidotes to NOACs (andexanet alfa for factor Xa inhibitors[83,84] and idarucizumab for dabigatran[85]) have been developed, their effects on the outcome of NOAC-related ICH need to be investigated.

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https://doi.org/10.5853/jos.2016.00864