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Progress in translational research on intracerebral hemorrhage: Is there an end in sight?

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ABSTRACT

Intracerebral hemorrhage (ICH) is a common and often fatal stroke subtype for which specific therapies and treatments remain elusive. To address this, many recent experimental and translational studies of ICH have been conducted, and these have led to several ongoing clinical trials. This review focuses on the progress of translational studies of ICH including those of the underlying causes and natural history of ICH, animal models of the condition, and effects of ICH on the immune and cardiac systems, among others. Current and potential clinical trials also are discussed for both ICH alone and with intraventricular extension.

Contents

Abbreviations: BBB, blood–brain barrier; ECG, electrocardiogram; ETV, endoscopic third ventriculostomy; EVD, external ventricular drain; ICH, Intracerebral hemorrhage; ICP, intracranial pressure; IL-2, interleukin-2; IVH, intraventricular hemorrhage; PPAR, peroxisome proliferator activated receptor; RBC, red blood cell; rt-PA, recombinant t-PA; SAH, subarachnoid hemorrhage; tPA, tissue plasminogen activator; u-PA, urokinase.

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1. Introduction

Intracerebral hemorrhage (ICH) is a particularly devastating form of stroke with high mortality and morbidity (Keep et al., 2012; Qureshi et al., 2009). Relative to ischemic stroke, there have been few preclinical studies and clinical trials for the development of treatments for ICH. However, increased interest in ICH over the past decade has improved our knowledge of the underlying mechanisms of ICH-induced brain injury, which have been found to differ from those of ischemic stroke (Xi et al., 2006). These findings have led to the initiation of several ongoing clinical trials investigating ICH treatment.

This review aims to describe the underlying causes and natural history of ICH, as well as the animal models employed in its study. This is followed by a discussion of the systemic effects of ICH, focusing on immune and cardiac effects, areas that have been largely neglected in research on ICH. Current and potential clinical trials in ICH alone and with intraventricular extension are also discussed, of which the latter is particularly difficult to treat and is associated with higher mortality (Hanley, 2009).

2. Causes of bleeding

Spontaneous ICH, i.e., ICH that is not related to trauma, most frequently occurs secondary to hypertension, with up to 70% of patients with ICH having a history of hypertension (Mendelow et al., 2005). However, ICH may also result from bleeding associated with amyloid angiopathy, tumors, hemorrhagic conversion of ischemic stroke, dural venous sinus thrombosis, vasculitis and vascular malformations such as cavernous angiomas, arteriovenous fistulae, arteriovenous malformations, venous angiomas, and aneurysms (Qureshi et al., 2001b; Ruiz-Sandoval et al., 1999). ICH is considered primary if there is not an identifiable underlying structural lesion that is likely to be responsible for the hemorrhage. It is most commonly associated with arteriosclerosis as a result of hypertension and amyloid angiopathy (Ritter et al., 2005; Tuhrim et al., 1999).

Hypertension is a significant contributory factor for ICH and is associated with morbidity and mortality in all age groups (Ruiz-Sandoval et al., 1999). Chronic hypertension induces degenerative changes in small arterioles, making them prone to rupture. Treatment of hypertension therefore reduces the annual risk of hemorrhage in hypertensive patients. In the elderly, amyloid angiopathy is a significant cause of bleeding. The presence of either the e2 or the e4 allele of the apolipoprotien E gene also increases the risk of ICH through β-amyloid deposition and fibrinoid necrosis in the vessel wall, rendering it more likely to rupture (O'Donnell et al., 2000).

Vascular lesions are prone to rupture, which can result in ICH, subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), or any combination thereof, with each subtype having a distinct natural history. For untreated aneurysms, the natural history varies by size, location, and shape, with large and daughter dome-containing aneurysms having higher rates of rupture. Of aneurysms in the anterior circulation, those in the anterior and posterior communicating arteries have the highest rates of rupture (Gross et al., 2013). The natural history of AVMs varies, with annual rates of rupture between 0.9 and 34%. Furthermore, depending on the study, the rate of rupture increases for hemorrhagic lesions, deeper locations, older age, larger lesions, and pregnancy (Gross and Du, 2012b; Halim et al., 2004; Hernesniemi et al., 2008; Stapf et al., 2006). Asymptomatic cavernous malformations are generally benign with annual rates of ruptures of 0–0.6%. However, if a patient is symptomatic with a prior hemorrhage, the re-bleed rate is 5–6% with the risk of re-bleeding decreasing over time. Pregnancy is not a durable risk factor for hemorrhage of cavernous malformations (Al-Holou et al., 2012; Flemming et al., 2012; Gross et al., 2013). The annual risk of hemorrhage from dural AV fistulas is dependent on the presence of leptomeningeal venous drainage, which is 0, 2, and 46% for no drainage, asymptomatic lesions with leptomeningeal venous drainage, and symptomatic lesions with leptomeningeal venous drainage, respectively (Gross and Du, 2012a).

Post-partum ICH is a rare, but increasingly recognized, cause of hemorrhage in young women and is thought to be due to angiopathy in the post-partum period (Bateman et al., 2006). The overall incidence of ICH in pregnancy and the post-partum period is 4.6–53/100,000 and is associated with significant maternal mortality (Bateman et al., 2006; Khan and Wasay, 2013).

Risk of ICH also is increased by the use of anticoagulants. In the United States, approximately 20% of patients with ICH use anticoagulants. Additional risk factors include greater age, male sex, cigarette smoking, and heavy use of alcohol (Ariesen et al., 2003), whereas high cholesterol is associated with a decreased risk of ICH (Ariesen et al., 2003).

It is still controversial whether statin therapy is a potential risk factor of intracerebral hemorrhage. Evidence suggests cholesterol lowering drugs result in hemorrhagic stroke (Goldstein et al.,