Are We Ready to Avert Suicide in Intracerebral Hemorrhage?

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Stoke ranks third among all causes of death behind diseases of the heart and cancer.1 Stroke accounts for about 1 in 16 deaths in the United States. Spontaneous intracerebral hemorrhage (ICH) comprises between 8% to 14% of all strokes but carries a mortality rate of up to 50% within the first 6 months after onset.1 Functional outcome of ICH survivors is poor with only 20% of them regaining independence at 6 months. Despite such dismal statistics, there has been little progress in the field of finding effective treatments that may positively impact the outcome of patients with ICH.

Several potential targets for treatment have been identified, tested or are currently undergoing testing in patients with ICH. For instance, one of the major determinants of outcome is hematoma volume.2 The possibility of early surgical evacuation of ICH to reduce mortality has been proposed. However, the Surgical Trial in Intracerebral Hemorrhage (STICH) failed to demonstrate a difference between a policy of early surgery compared with a policy of initial conservative treatment.3 Other clinical trials evaluating the benefit of surgery in ICH are currently underway for lobar intracerebral hemorrhage (STICH II), intraventricular hemorrhage (CLEAR IVH), and for deep intracerebral hemorrhage and minimal invasive surgery (MISTIE).4 It has also become known that ICH is a dynamic process with hematoma volume expansion occurring in about 38% of patients within 20 hours.5 This may contribute to mass effect and neurological deterioration. A phase II study showed that treatment with rFVIIa within 4 hours after the onset of ICH decreased the growth of the hematoma, reduced mortality, and improved functional outcomes at 90 days.6 However, a subsequent phase III trial (FAST) failed to show any beneficial effect on outcome despite a reduction in hematoma growth. Additionally, several investigators have found an independent association between elevated blood pressure on hospital admission and poor outcome after ICH.7 The Antihypertensive Treatment for Acute Intracerebral Hemorrhage (ATACH) clinical trial is currently underway to address the impact of blood pressure—lowering on outcome after ICH.8 We are eagerly waiting for the results of these ongoing studies, but in the meantime it has increasingly become evident that if we are to make a significant impact on outcome of ICH patients, we need to have a greater understanding of the pathophysiology of brain injury after hematoma onset.9

In recent years several investigators have studied the mechanisms of cell death after ICH. Cellular death occurs by cell necrosis or apoptosis after ICH. Animal models of ICH have revealed that apoptosis is a significant contributor to brain damage and apoptotic cells are found both in the hematoma and the surrounding tissue.10 Studies in humans have also shown that both types of cellular death occur, with the apoptotic phenotype being the prevailing mode particularly in the perihematomal region.11 Apoptosis mechanisms have been divided into 2 pathways triggered by either intrinsic or extrinsic signals.12 Several cytotoxic stimuli trigger the internal pathway with eventual activation of downstream caspases, whereas ligation of death receptors trigger the external pathway with direct activation of upstream caspases. Among the latter is the tumor necrosis factor receptor (TNFR) superfamily of which Fas is a member.12 Fas is expressed on the cell surface and its interaction with its ligand (FasL) triggers apoptosis. Both Fas and FasL are normally expressed in the central nervous system and are upregulated in various pathological conditions. In this issue of Stroke, Delgado et al present a very interesting report on the activation of the Fas system in perihematomal areas after ICH in humans.13 The authors studied 78 patients. In all of them they collected blood samples to determine soluble Fas (s-Fas) plasma concentrations on admission and then serially in a subgroup of 21 patients. They also analyzed brain specimens from 6 ICH patients and 2 controls to determine Fas receptor and FasL presence. The authors found that s-Fas was diminished in ICH patients but returned to normal at 24 hours. Such changes were associated with perihematomal edema growth. They also found that FasL content was highest in the perihematomal region and that no expression of Fas was found in controls. This study has some limitations including the following: lack of complete imaging data on all the study patients, relatively small sample size, and lack of tissue sampling from all study subjects. Despite these shortcomings Delgado et al suggest that in a relevant population of ICH patients, Fas-mediated apoptosis may be responsible for edema formation. This is an important finding that may lead to manipulation of Fas and FasL as potential therapies for ICH.
References


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