Perihematoma Edema: A Potential Translational Target in Intracerebral Hemorrhage?

Magdy Selim • Kevin N. Sheth

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Secondary injury in intracerebral hemorrhage (ICH) is becoming increasingly well characterized and is the subject of intense investigations. After the initial injury caused by tissue disruption and mass effect of the hematoma, products of coagulation, clot retraction, and hemoglobin breakdown initiate a secondary cascade of deleterious events including apoptosis, necrosis, iron-mediated oxidative stress, inflammation, autophagy, and edema formation [1–3]. Tissue swelling, in particular, may contribute to neurological deterioration and disability.

Vasogenic (extracellular) edema is most commonly described after ICH. However, there is evidence that cytotoxic (intracellular) edema also contributes, at least in part, to perihematomal edema (PHE) [4]. A number of clinical studies examined several drugs targeting these secondary processes and PHE formation over the past years [5]. These included the glycine antagonist, gavestinel [6]; the free radical trapping agent, NXY-059 [7]; citicoline [8]; mannitol and glycerol [9, 10]; the sphingosine-1-phosphate receptor agonist, fingolimod [11]; and the PPAR- γ receptor agonist, pioglitazone [12]. Currently, the iron chelator deferoxamine mesylate is being investigated in a phase II trial [13], and several other agents are in the pipeline for future clinical investigations.

Unlike interventions targeting hematoma expansion where the targeted effects of therapy on ICH growth can be easily assessed in proof-of-concept pre-phase III studies, there are

currently no reliable intermediate endpoints that can assist in identifying highly promising or clearly futile therapies targeting secondary injury. Randomized controlled phase III clinical trials are expensive and difficult to take. Pragmatic, efficient, smaller, phase I-II studies including evaluation of biological or radiological endpoints attributed to the experimental intervention are often required before moving forward to phase III testing.

Evaluating the effect of therapies targeting secondary injury on the development and progression of PHE is often viewed as a surrogate measure of the efficacy of these interventions. Should PHE be used as a radiological marker to assess the potential efficacy of an intervention in improving outcome? Is PHE a translational target for therapies targeting secondary injury? If yes, what is the best imaging modality, quantitative measure, and time to evaluate PHE? To answer these questions, one must first address the following questions: What is PHE and how to define it? What are the pathophysiological changes underlying PHE? What is the time course and natural history of PHE? What is the relationship between PHE, recovery, and functional outcome?

The perihematomal hypodensity seen on CT scan (or its MRI counterpart; hyperintensity on fluid attenuation inversion recovery (FLAIR) sequence) is commonly interpreted to represent edema of the surrounding brain tissue, i.e., PHE. However, the accuracy of this interpretation has been questioned, and the terms “perihematomal CT lucency or perihematomal MR hyperintensity” were proposed to reflect the controversial nature of this radiological phenomenon [14]. There is a poor correspondence between the increase in “PHE” and the change in ipsilateral hemispheric volume [14], suggesting that while a small increase in brain water may contribute to PHE, other processes that increase PHE without a matching increase in brain volume such as clot retraction and diffusion of serum from the initial clot along the white matter tracts result in redistribution of existing water from the initial hemorrhage.

M. Selim (✉)
Division of Stroke and Cerebrovascular Disease, Department of
Neurology, Beth Israel Deaconess Medical Center, 330 Brookline
Avenue, Palmer 127, Boston, MA 02215, USA
e-mail: mselim@bidmc.harvard.edu

K. N. Sheth
Division of Neurocritical Care and Emergency Neurology,
Department of Neurology, Yale New Haven Hospital,
New Haven, CT, USA

Using changes in the PHE region as an indicator of mass effect or brain edema, therefore, may not be very accurate.

The radiological signal in the PHE region continuously progresses for weeks after ICH, where trans-endothelial flux of electrolytes and water from the intravascular to the interstitial compartment results in ionic edema within the first few hours. In contrast, inflammation, hemolysis of red blood cells, and subsequent hemoglobin- and iron-mediated neurotoxicity contribute to delayed PHE from days 2 to 3 onwards [15]. Human studies suggest that PHE progression is fastest during the first few days and that it starts to increase significantly within 1 day after ICH [16, 17]. Evaluating the effects of a specific intervention on PHE is a delicate task because these chronological changes in PHE, their underlying pathophysiological mechanisms, and the presumed actions of the intervention should be carefully considered when interpreting the results.

There is a knowledge gap in our understanding of the relationship between PHE and outcome after ICH. Clinical data on the influence of PHE on long-term outcome after ICH are inconsistent [16–22]. However, there is evidence that early edema progression correlates with early neurological deterioration [18–21], suggesting that PHE could potentially be a translational therapeutic target in ICH. Since PHE growth during the early time period seems to be more clinically relevant, it seems intuitive to limit assessment of PHE as a therapeutic target to the first few days after ICH. On the other hand, inconsistent impact of PHE on ICH outcome and negative results of previous randomized trials of mannitol and glycerol in ICH [9, 10] might suggest that PHE is not an optimal therapeutic target. However, PHE might still be a reasonable marker of ongoing biological process or approaches to attenuate those processes even if it has an incremental or negligible impact on outcome.

The assessment of imaging signal characteristics in the perihematoma region to accurately quantify PHE also poses technical challenges. Delineation of PHE on CT scan, the most widely used imaging modality in ICH patients, can be difficult particularly when the borders of both the high- and low-attenuation regions become indistinct over time. Although, this limitation can be somewhat improved by using a semiautomatic Hounsfield-unit, threshold-based, algorithm for PHE measurement. The use of MRI might facilitate more accurate quantitative assessment of PHE. MRI might also help to differentiate between vasogenic vs cytotoxic components of the PHE. Whereas vasogenic edema is best seen of fluid-attenuated recovery (FLAIR) images, cytotoxic edema is visualized as restricted diffusion on diffusion-weighted imaging attributed to cellular swelling caused by failure of ATP-dependent ion transport [4]. The feasibility and related costs of MRI, however, can be prohibitive. It is also unclear what the best parameters to assess PHE should be. Some suggest using relative PHE volume (i.e., the absolute PHE volume

divided by the hematoma volume) to detect serial changes in edema volume while adjusting for subsequent hematoma expansion or retraction [23]. Others argue that relative PHE may not be a suitable parameter when analyzing the impact of PHE on clinical status and mortality because unlike absolute PHE, which strongly correlate with ICH volume, relative PHE has an inverse correlation with ICH size [17]. We argue that the rate of PHE (i.e., rapidity of growth over time, especially early on), and not absolute or relative PHE volumes, together with the combined total hematoma and PHE volumes may be most important [24].

Overall, available clinical data on the development and severity of PHE and its association with long-term outcome are inconsistent likely reflecting different definitions, methodologies, and time periods studied. If present and future investigations of PHE are to be successful, investigators must take the preceding concerns into account when planning studies aiming to target PHE. Until the issues of timing, measures, and quantification of PHE are standardized and its impact on clinical outcome is better defined, PHE might be better suited to serve as an imprecise surrogate marker of drug's biological activity on the brain tissue. Clearly, more work in this important area is needed.

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Conflict of Interest Dr. Selim and Dr. Sheth declare that they have no conflict of interest.

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