Management of Intracerebral Hemorrhage: Looking to the Future

Written by Maria Vinall

The majority of the cell death after hemorrhage occurs around hematomas. It has been theorized that this is partially related to oxidative stress. Jaroslaw Aronowski, PhD, Texas Medical Center, Houston, TX, discussed insights from animal models of oxidative stress that may provide potential treatment targets for intracerebral hemorrhage (ICH).

The transcription factor Nrf2 has the potential to upregulate a massive number of genes that are responsible for antioxidative activities. Prof. Aronowski's laboratory has had success activating Nrf2 and thus reducing oxidative damage, inflammation, and neurological deficit with a compound called sulforaphane (a naturally occurring substance in cruciferous plants) in animal models.

An alternative is to prevent oxidative stress from occurring by increasing phagocytosis of red blood cells as a target for amplifying clearance of blood from the brain. PPARγ in macrophages has been shown to act as an important factor in promoting hematoma absorption and protecting other brain cells from ICH-induced damage by inhibiting proinflammatory gene products in the microglia [Zhao Z et al. *Ann Neurol* 2007].

Gary K. Steinberg, MD, PhD, Stanford University School of Medicine, Stanford, CA, discussed hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation has been highly successful in improving the outcome for a variety of diseases, but, like stroke therapy, it is a nascent field.

A variety of stem cells have been used for transplantation, but one particularly interesting cell line is hNT, which differentiates into pure, postmitotic cells after treatment with retinoic acid and functions as CNS progenitor cells [Kleppner et al. *J Comp Neurol* 1995].

Results from a phase I trial of cerebral transplantation of LBS (hNT) neurons in 12 patients with substantial fixed motor deficit after cerebral infarction showed no adverse cell-related serological or imaging-defined effects. European Stroke Scale (ESS) score improved 3 to 10 points in 6 patients; mean improvement was 2.9 points in all patients. Improved motor outcome correlated with increased metabolic activity in the stroke (p=0.02) and surrounding regions (p=0.006) [Kondziolka D et al. *Neurology* 2000].

Another recent phase II study evaluated the safety and efficacy of implantation of LBS (hNT) neurons compared with no implantation in patients with fixed motor deficits following stroke (9 ischemic; 9 hemorrhagic) in the basal ganglia. Subjects were randomly assigned to receive 5 million cells (n=7), 10 million cells (n=7), or no implantation (n=4). All subjects received cyclosporine for 6 months plus 8 weeks of constraint-induced rehabilitation. Four of the 7 patients who received 5 million cells and 2 of the 7 patients who received 10 million cells had an improved ESS score after 6 months, although the difference was not significant compared with control or baseline. Action Research Arm Test scores improved significantly compared with both control (p=0.017) and baseline (p=0.001). The Stroke Impact Scale score improved compared with baseline (p=0.045) but not with controls (p=0.056). There were no cell-related adverse serological or imaging-defined effects [Kondziolka D et al. *J Neurosurg* 2005; Stilley CS et al. *Neurology* 2005].

Although these studies demonstrate the safety and feasibility of neuronal transplantation for patients with motor stroke, said Dr. Steinberg, many unresolved issues remain. Further phase I and II clinical studies should be pursued, initially in ischemic stroke and then in hemorrhagic stroke.

J. Claude Hemphill III, MD, University of California, San Francisco, CA, discussed currently available neuromonitoring measures and what new measures need to be developed for ICH.

Tissue PO_2 monitoring increasingly is being used, but it is unclear whether it is a surrogate for cerebral blood flow or a direct measure of oxygen metabolism. Dr. Hemphill and his group have done work in a swine model, showing that cerebral hemorrhage that is induced by direct blood injection clearly produces metabolic effects on ICP and on contralateral and ipsilateral $P_{bt}O_2$ that occur early on but return to near normal rates within about 1 hour [Hemphill JC et al. *Neurocrit Care* 2006].

Cerebral microdialysis is a well-established laboratory tool that is used to provide online analysis of brain tissue biochemistry during neurointensive care. Although more commonly used in patients with traumatic brain injury (TBI), there have been some reports of its use in ICH. Nilsson and colleagues recently showed that the area that is close to an evacuated ICH exhibits a biochemical pattern that is similar to that of the biochemical penumbra zone that surrounds focal traumatic brain contusions [Nilsson OG et al. *Neurosurgery* 2006].

Autoregulation status also may be an important monitoring measure in ICH. Studies in TBI have suggested that impaired PRx (a measure of whether the brain's autoregulation status is intact) is associated with a worsened outcome. Results from a recent study also found evidence for impaired cerebral vasomotor activity in 19 patients with spontaneous ICH, using PRx as a measure. In this study, impaired autoregulation (PRx >0.2) was common (12/19 patients), and in those patients with impaired autoregulation, CPP showed a linear relationship to outcome [Diedler J et al. *Stroke* 2009].