Commentary on a Non-Human Primate Model of Aneurismal Subarachnoid Hemorrhage

Ryszard M Pluta*
Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD, 20892 USA

I and my colleagues recently presented a primate model subarachnoid hemorrhage (SAH) [1] characteristics describing medical, surgical, imagining techniques that had been used at the Surgical Neurology Branch of the National Institute of Neurological Disorders and Stroke from 1989 until 2011 when I left the NIH.

As aneurismal SAH (aSAH) leaves 50% of patients dead and almost 70% of survivors disabled, for years has been an urgent necessity to develop an animal model(s) reliably mimicking pathophysiology and clinical course of this disease. Such an animal model would allow investigation of cause or causes of a poor outcome aSAH rending a possibility for development of a cause-targeted treatment.

We, and several other research groups, quickly realized that the best mimicking clinical situation characterized by a delayed onset of intracranial arterial vasospasm has been a non-human primate model introduced by Espinosa et al. in the Bryce Weir laboratory in 1984 [2]. Over the decades of intensive, multicenter experimental effort using a non-human primate, but also other models, elucidated many mechanisms underlying deleterious effects of aSAH in some people as well as initiated a paradigm shift in goals for adequate treatment development.

For well over a half of century, a delayed intracranial vasospasm has been widely accepted as a central culprit responsible for a poor outcome after SAH due to delayed ischemic neurological deficits also known as delayed cerebral infarcts (DCI) [3]. However, this dogma has been recently challenged and new avenues of SAH-related research, like early brain injury and ultra-early vasospasm, have been pursued [4-6]. This renewed interest in mechanisms contributing to development of DCI with or without delayed intracranial vasospasm, has increased efforts to develop an adequate SAH model(s).

A non-human primate model with a direct surgical placement of blood clot around the middle cerebral artery has proven to be the most consistent and reliable model of delayed intracranial vasospasm after SAH and led to many clinical trials confirming its clinical usefulness. However, this model was inadequate to mimic clinical course of aSAH clinical consequences, as monkeys did not develop DCI. This discrepancy was explained by differences in the brain size and/or development of collateral cerebral blood flow in animals but not in humans after aSAH. However, a Clazosentan study showing a clinical efficacy confirmed that DCI and delayed cerebral vasospasm, we modified a model, in which after opening the dura matter but before opening the Sylvian fissure's bifurcation. In the latter, an intracranial bleeding could be stopped by inflation of intraarterial balloon, which should control a volume of blood accessing subarachnoid space.

To provide an insight in the SAH-related mechanisms responsible for DCI and delayed cerebral vasospasm, we modified a model, in which after opening the dura matter but before opening the Sylvian fissure's bifurcation. In the latter, an intracranial bleeding could be stopped by inflation of intraarterial balloon, which should control a volume of blood accessing subarachnoid space.

The future development and/or natural evolution of a non-human primate model of SAH should address a paradigm shift(s) in our knowledge and better our understanding of brain injury after aSAH and sources of poor outcome.

References

*Corresponding author: Ryszard M Pluta, Retired Clinical Staff Scientist at Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD, 20892 USA, Tel: 3019130278; E-mail: rysiek.pluta@excite.com

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