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LETTER TO THE EDITOR

Experimental Aneurysmal Subarachnoid Hemorrhage: Tiding Over

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Dear Editor,

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of hemorrhagic stroke, which is associated with significant morbidity, and a case fatality of nearly 50% [6, 13, 17, 18]. Early brain injury (EBI) and delayed cerebral ischemia (DCI) are the two main determinants for functional outcome after aSAH. EBI refers to direct mechanical damage to the brain tissue and early pathophysiological changes, including increased intracranial pressure (ICP) and reduced cerebral perfusion. DCI describes a complex of reaction occurring thereafter [20]. Various mechanisms contribute to DCI, including angiographic cerebral vasospasms, microvascular spasm, microthrombosis, cortical spreading depolarization, failure of cerebral autoregulation, and inflammatory responses [20]. The individual importance of each of these pathomechanisms remains to be elucidated and it has been suggested that the etiology of EBI and DCI are linked. However, a unifying theory of these pathophysiological changes has not yet been described. Study of these pathophysiological mechanisms in humans is problematic and thus experimental animal studies have focused on investigating the mechanisms of EBI and potential therapies to either limit or reverse the extent of EBI, to reduce the incidence of DCI and improve functional outcome after aSAH.

Over a period of 15 years until 2014, more than 765 in vivo animal studies analyzed the pathophysiology of experimental aSAH and the effects of (new) therapeutic approaches on prevention of DCI [16]. Various pharmaceutics showed promising results in in vivo animal studies. However, despite the high number of animal studies, different therapeutic approaches, and numerous analyzed pharmaceutics, standard therapies of DCI have barely changed and oral nimodipine remains the only drug to improve neurological outcome in aSAH patients. All other initially promising drugs and approaches have failed to show a benefit in prospective randomized and controlled phase II or III trials. Clazosentan and the CONSCIOUS-1 trails are probably the most prominent examples for a failed translation from bench to bedside. Interestingly, clinical studies frequently showed a positive influence of a drug on vasospasms of large arteries, but did not translate into improved morbidity or mortality [3, 4].

As a consequence of the failed translation from bench to bedside, standards for planning, conducting, and reporting of aSAH animal experiments were proposed in order to align experimental and clinical research. Guidelines for a standardized reporting of animal experiments have successfully been implemented almost a decade ago [8, 9]. These standards included selecting animal models with clinical relevance, accurately calculating sample sizes, and using suitable statistics, standardizing animal treatments, and assessment of blinded outcome parameters [10–12, 14–16, 19]. Comprehensive meta-analysis and systematic reviews of existing animal data have also been proposed in order to detect effects sizes of treatment, biases, and methodological inadequacies in animal studies [15, 19]. Indeed, new developments and initiatives to improve the quality of systematic reviews of animal studies are likely to improve the translational value of animal research [5].

However, we are not convinced that a standardization and systematic analysis of existing data alone can clarify the failed translation from bench to bedside in aSAH research. Existing experimental aSAH models only partially simulate human conditions for several reasons: intracranial anatomy (e.g., the circle of Willis in rodents) and (patho-) physiology vary significantly between species. Moreover, intrinsic factors such as weight, age, genetic background, metabolism, and hemodynamics contribute to the already existing discrepancy between animal models and human physiology [1, 2]. Even in highly standardized mouse models, DCI-related responses significantly rely on the genetic background of the analyzed mice [1]. Also, pathophysiological responses and mortality rates in mice are significantly affected by the type of model which is

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used (perforation vs. injection). Mortality rates in most mouse models of DCI after experimental aSAH are significantly lower than human case fatality following aSAH [7].

Furthermore, DCI and EBI are well defined for clinical use but both lack a matching definition which is applicable for experimental aSAH. The clinical definition of DCI: DCI was clinically defined for aSAH patients by a neurological impairment lasting more than one hour which cannot be attributed to other causes [21], is useless for experimental aSAH. Determination of the Glasgow Coma Scale (GCS) to assess neurological deterioration as well as exclusion of other causes of neurological impairment by means of clinical assessment, laboratory testing, and CT or MRI scanning of the brain cannot realistically be performed in experimental aSAH. Moreover, DCI in humans only occurs from the 3rd day after the initial insult, has the highest incidence and severity after 6–8 days, and usually resolves after 12–14 days [4, 22]. In contrast, DCI in experimental animal models is frequently observed before the 3rd day after SAH, e.g., in mice six hours after SAH induction [7]. Therefore, consensus definitions of DCI and EBI, which can be applied to experimental aSAH in animal models, are required.

In summary, future efforts should systematically investigate to what extent aSAH animal models resemble the human condition and how parameters such as the experimental model, animal species, or the genetic background affect EBI- and DCI-related pathophysiological responses. Additionally, consensus definitions of DCI, EBI, and standard outcome measures suitable for experimental aSAH in different species are required.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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