

## Preface

# Hemostasis and Neuroscience—Hemostasis and Fibrinolysis Involved in Brain Pathology and Brain Disorders

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Vascular occlusive events and hemorrhage in the brain affect thousands of lives across the globe every day. Thrombosis and hemostasis impact outcome after cerebrovascular disease, and its prevention and treatment include manipulation of systemic coagulation factors. The brain also has its own unique system for regulation of hemostasis.<sup>1</sup> Local thrombin generation in the brain affects the prognosis in epileptic seizures and multiple sclerosis,<sup>2</sup> while tissue plasminogen activator (tPa) affects blood–brain barrier permeability and is involved in Alzheimer’s disease pathology.<sup>3</sup> This issue of *Seminars of Thrombosis and Hemostasis* will, in three parts, shed light on mechanisms and potential treatment targets in vascular occlusive events, in intracerebral and subarachnoid hemorrhage, and finally in the role of platelets and endogenous tPa in Alzheimer’s and Parkinson’s diseases.

## Vascular Occlusive Events

In the first section of the present issue, vascular occlusive events and thromboprophylaxis are in focus. In traumatic brain injury, prevention of hemorrhage progression is a potential therapeutic opportunity, but its use has been limited by fear of provoking vascular occlusive events. Fletcher-Sandersjö et al provides us with a cohort study in patients with moderate-to-severe traumatic brain injury, evaluating the effect of venous thrombosis on outcome.<sup>4</sup> In total, 848 patients were included and vascular occlusive events were detected in 6.4% of these patients. Outcome was assessed by Glasgow outcome scale at 12 months, and was not affected by the development of thrombosis. Hence, the study suggests that the potential benefit of preventing early hemorrhage progression may outweigh the risk of later development of thrombosis.

The incidence of cerebral venous thrombosis is low, but this severe type of thrombosis mostly affects healthy younger women. Delayed diagnosis is common, resulting in worsening of the prognosis. This matter is reviewed by Aamodt and Skattør in the second manuscript of this issue.<sup>5</sup> The review provides us with an overview of epidemiology, the vague symptoms of the disease, and pitfalls of diagnostics. The mainstay of treatment in the acute phase is low molecular weight heparin, while endovascular intervention may be a treatment option for patients with neurological deterioration despite anticoagulant treatment. Of some current relevance, cerebral venous thrombosis is a recognized risk factor for COVID-19 (coronavirus disease 2019) vaccine-induced (immune) thrombotic thrombocytopenia (VITT),<sup>6</sup> and so this review also provides some commentary around cerebral venous thrombosis in COVID-19 and VITT.

The third review in this section addresses venous thromboembolism and thromboprophylaxis in pediatric neurosurgery.<sup>7</sup> Thromboprophylaxis in pediatric populations is a matter of discussion and a rigorous evaluation of risk factors is fundamental. Panagopoulos et al gives an overview of studies including pediatric patients with traumatic brain injury or brain tumors. The risk of venous thrombosis is low in this population, but evidence is limited and the thromboembolic risk may be underestimated. Low molecular weight heparin seems to be an effective choice for prevention of thrombosis for the “at risk” pediatric population, with risk factors being age >15 years, venous catheterization, increased length of hospital stay, and traumatic brain injury.

In the last review of this section, thromboprophylaxis became a matter of discussion.<sup>8</sup> Patients with primary brain tumors have a high incidence of both thrombosis and hemorrhage. Winther-Larsen et al summarize current knowledge

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on changes in primary and secondary hemostasis as well as fibrinolysis in patients with primary brain tumor. The authors report an increased secondary hemostasis and impaired fibrinolysis, indicating a possible need for long-term thromboprophylaxis, but additional studies addressing this are warranted.

## Intracerebral and Subarachnoid Hemorrhage

The second section in this issue of Seminar of Thrombosis and Hemostasis addresses changes and challenges within coagulation in patients with intracerebral or subarachnoid hemorrhage. Spontaneous intracerebral hemorrhage is defined as non-traumatic bleeding into the brain without the presence of vascular malformation or presence of tumor. The risk of intracerebral hemorrhage can be considerably increased in congenital bleeding disorders, but to varying degrees. Aneurysmal subarachnoid hemorrhage is the most dreaded type of intracranial hemorrhage, as this type of hemorrhage is linked to a high risk of delayed cerebral ischemia, significantly increasing mortality and neurological deficits.<sup>9</sup>

First, co-editor Kwaan provides us with a review on “nonhematologic and hematologic factors in spontaneous intracerebral hemorrhage.”<sup>10</sup> Clinical factors, such as age, ethnicity, and presence of hypertension or comorbidities, are reported to be associated with outcome. Likewise, the clinical characteristics of the hematoma influence outcome. While no hemostatic therapy has proven efficient in improving outcome, lowering of blood pressure is the most promising intervention in this matter.

Intracerebral hemorrhage can occur in all congenital bleeding disorders and is a dreaded complication. Dorgalaleh et al take us on a journey through congenital bleeding disorders, ranging from mild platelet function disorders to severe disorders such as hemophilia A, of which the latter can cause catastrophic hemorrhage.<sup>11</sup> Spontaneous intracerebral hemorrhage is more prevalent in adults with congenital bleeding disorders, while trauma-related intracerebral hemorrhage occurs more often in children. While being very rare in mild bleeding disorders, factor XIII deficiency carries the highest risk of intracerebral hemorrhage. Further, delivery of a child with congenital bleeding disorder needs to be well planned to prevent intracerebral hemorrhage.

The last review of this section is written by the co-editors Hvas and Hvas and is a systematic review on hemostasis and fibrinolysis following subarachnoid hemorrhage.<sup>12</sup> Rebleeding and delayed cerebral ischemia increase mortality after subarachnoid hemorrhage, and hemostatic or antifibrinolytic therapy has not been able to decrease mortality. Gathering current knowledge on changes in hemostasis and fibrinolysis, evaluated by both conventional, quantitative, and dynamic assays may reveal potential treatment targets. The authors report reduced platelet aggregation and increased secondary hemostasis following subarachnoid hemorrhage; however, changes in fibrinolysis were not convincingly demonstrated and not related to outcome. The review concludes that from a mechanistic point of

view, desmopressin may be able to prevent rebleeding while heparin may prevent delayed cerebral ischemia.

## Neuro-coagulation As a Player in Neuroinflammation and Vascular Dysfunction

This last section of the present issue aggregates around local effects of platelets, coagulation, and fibrinolysis proteins in the brain. Coagulation mechanisms are critical for maintaining homeostasis in the central nervous system. The interplay between thrombin, protein C, and the protease activator receptor-1 (PAR-1) is important for blood–brain barrier integrity.<sup>2</sup> Further, evidence shows that both coagulation proteins and platelets are involved in brain pathology attributing to diseases like multiple sclerosis, Alzheimer, and Parkinson's disease.

The first review by Stein et al focuses on neuro-coagulation from a mechanistic point of view, particularly the interplay between thrombin and PAR-1.<sup>2</sup> This interaction causes PAR-1 over-activation and blood–brain barrier disruption, which may be evident in epileptic seizures and stroke. The authors gather current knowledge on these mechanisms underlying the effects of coagulation on the physiology and pathophysiology in the central nervous system.

Numerous physiological and pathological functions have also been attributed to tPa in the central nervous system. This includes neurite outgrowth and regeneration; synaptic and spine plasticity; neurovascular coupling; neurodegeneration; microglial activation; and blood–brain barrier permeability.<sup>3</sup> Stevenson et al review a subset of these different functions and the different molecular mechanisms attributed to tPa in the context of learning and memory.<sup>3</sup> The authors demonstrate that particularly in the understanding of Alzheimer's disease it is important to understand how tPa and other proteins are involved in vascular dysfunction to develop new treatments for Alzheimer's disease and other neurodegenerative diseases.

The neurodegenerative diseases, Alzheimer's and Parkinson's disease, share a common pathology related to central inflammatory mechanisms involving neuroinflammation, neurovascular dysfunction, and hypercoagulation, possibly related to platelet activity. This triad of dysfunction is reviewed by Page and Pretorius in the last comprehensive review of this issue.<sup>13</sup> Understanding the functions of platelets in neurodegenerative conditions and how platelets collaborate in inflammatory-driven disease processes can offer an improved view of the pathological processes that drive the development of Alzheimer's and Parkinson's disease. This review examines the behavior of platelets within the inflammatory milieu of Alzheimer's and Parkinson's disease and discusses the relevance of platelet bioactivity to neuro-pathologies.

In summary, this issue of *Seminars in Thrombosis and Hemostasis* highlights several neurological clinical conditions complicated by changes in hemostasis or fibrinolysis; changes occur both locally in the central nervous system and in the systemic blood circulation. The reviews also stress on the research needed to further improve current knowledge

within the subject area of neuro-hemostasis in different clinical entities. We hope that the readers enjoy the content and that it leads to further discussion of the variety of topics presented herein.

#### Conflict of Interest

None declared.

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