Coagulopathy in Traumatic Brain Injury

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Abstract

Abnormalities in blood coagulation, although quite common after traumatic brain injury (TBI), are of unknown significance. The authors review the clinical and pathophysiological features of this phenomenon and emphasize its origin in disseminated intravascular coagulation. This connection provides a possible explanation for much of the cerebral ischemia that accompanies TBI, namely intravascular microthrombosis. The authors’ own research findings support this contention and suggest possible therapeutic avenues.

A number of compelling studies demonstrate that DIC is a common and important consequence of TBI. In particular, posttraumatic coagulopathy appears to be linked to secondary cerebral injury. Although the extent of this process has yet to be elucidated fully, coagulation abnormalities are evident soon after trauma. This allows early identification of patients likely to suffer secondary complications and provides an opportunity to evaluate promising agents that may mitigate posttraumatic DIC and related pathologies in these patients. This is an area deserving of more intensive research.

Key Words: Traumatic brain injury; coagulopathy; disseminated intravascular coagulation; cerebral ischemia; intravascular microthrombosis.

Historical Perspective

In 1960, Penick and McLendon (1) reported a number of cases of abnormal blood coagulation of diverse causes. Among them was a newborn who suffered a traumatic brain injury (TBI) during delivery and who was severely coagulopathic. The next several years were marked by a series of reports of individuals with impaired blood clotting after TBI and other brain injuries (2–6). The increasing use of routine coagulation tests on patients with severe TBI led to the discovery that some degree of coagulopathy was extremely common (7–10), although there was considerable disagreement as to its cause.

Clinical Features

The incidence of clotting abnormalities in TBI is reported to vary between 15 and 100% (11–26). This apparent lack of agreement results in large part from the diversity of injury severities among reported series, the different sensitivities of the clotting tests used, and the different times at which coagulation is tested after injury. Patients who exhibit coagulopathy after TBI tend to fall into two groups; the fact that the coagulation abnormality is not an obvious target for treatment in either group may explain the relative lack of interest in the phenomenon. One group is composed of patients with overwhelming trauma. Severe coagulopathy is merely one of a host of terminal events. The other group consists of patients in whom one or more clotting studies, abnormal on admission, is not associated with a clinically significant bleeding diathesis. Their values return to normal within hours (17,23,26).

However, this does not suggest that all is well with the latter group. Whenever the effect of coagulopathy on neurological outcome has been assessed, the results have been both significant and negative. In 1979, Pondaag reported on a small series of patients with TBI in whom early laboratory evidence of coagulopathy predicted poor outcome (27).
A comprehensive review by Kaufman and Mattson (12) in 1985 suggested the mechanisms by which early coagulation abnormalities in TBI might lead to adverse outcomes. Not long thereafter, Kaufman and his colleagues at University of Texas explored the relationship between coagulopathy and outcome in more detail. They established a direct association between the severity of coagulopathy and the likelihood of adverse outcome, a relationship that was not dependent on the severity of injury alone (15,28). Stein et al. confirmed this correlation in both adults and children, further demonstrating progressive changes on computed tomography scans as links between coagulopathy and neurological complications (17,29,30). Piek et al. (16) reviewed the Traumatic Coma Data Bank and found coagulopathy to be a significant independent predictor of an unfavorable outcome. In fact, using backward elimination, stepwise logistic regression modeling, they determined that the effect of coagulopathy was second only to that of shock. Other investigators have confirmed a link between coagulopathy and adverse outcomes in TBI (20,25,31–34).

Pathophysiology

A complete review of the blood coagulation process in normal and disease conditions is beyond the scope of this article. The interested reader is referred to Hoot’s comprehensive review of clot formation, particularly as affected by TBI (35). Briefly considered, coagulation consists of the process leading to the conversion of fibrinogen, a soluble plasma constituent, to fibrin. The latter is an insoluble polymer, the strands of which crosslink to form a dense mesh. It is this mesh, with its trapped cellular elements, that forms a blood clot. Fibrin formation completes a three-step process (see Fig. 1). The process begins with either vascular or tissue injury, which initiates a cascade of enzymatic changes. We are interested primarily in the extrinsic pathway, triggered by parenchymal injury. There is release and upregulation of tissue thromboplastin (tissue factor), which in turn sequentially activates the other procoagulant proteins of the extrinsic pathway. The brain is especially rich in tissue factor (36–38), so much so that in 1939, Quick (39) used brain homogenate to induce blood coagulation for his one-stage prothrombin time. The fibrin clot initiated by the extrinsic pathway traps platelets and stimulates further thrombosis.

The normal clotting process is accompanied by intense inflammatory activity, as a number of inflammatory mediators are released by platelets and by coagulation itself; in turn, these mediators promote further coagulation (32,40–46). Normally, mechanisms exist to hold procoagulant activity in check and thus prevent uncontrolled thrombosis.

The delicate balance outlined earlier is disrupted by the disseminated intravascular coagulation (DIC) syndrome. Various diseases, including obstetrical complications, certain snakebites, and transfusion reactions, cause massive release of thromboplastin into the circulation. The DIC syndrome consists of uncontrolled procoagulant activity, deposition of thrombi in small blood vessels, consumption of normal clotting factors, and induced fibrinolysis with hemorrhage, as well as the induction of a localized or systemic inflammatory response with vascular damage. The sequence of abnormal clotting phases of DIC involves a considerable overlap in time (see Fig. 2). The