coagulation. Although the brain is rich in phosphatidylserine and tissue factor, nothing was known on the impact of brain-derived microparticles on coagulation. The authors thus surmised that microparticles produced in the brain could convey phosphatidylserine and tissue factor into the systemic circulation and thereby impact coagulation.

To verify this hypothesis, the authors modeled trauma brain injury in mice and verified the appearance of brain-derived microparticles in systemic circulation. They observed that concomitant with the arrival of brain-derived microparticles in blood, mice subjected to brain trauma injury developed a hypercoagulable state. The accelerated clotting time was due to microparticles, as their elimination by centrifugation abrogated the effect (see figure).

To ensure that the microparticles they detected were indeed of brain origin and not produced in the periphery, the authors confirmed the expression of multiple neuronal and glial markers (neuron specific enolase, glial fibrillary acidic protein, Na+/K+ ATPase α3, and glutamate transporter-1). For comparison, they verified that microparticles shed from platelets, which represent the majority of the microparticles in blood at steady state and might also express a subset of neuronal proteins, were absent in this set of markers.

As the brain-derived microparticles found in blood circulation expressed phosphatidylserine and tissue factor, one major finding from this study is that microparticles generated from brain injury can pass into the circulation.

Next, the authors went on to confirm the causal role of brain-derived microparticles in the modulation of coagulation. Isolated brain-derived microparticles generated in vitro were highly procoagulant due to surface phosphatidylserine and tissue factor expression. Another mechanism by which brain-derived microparticles may impact blood coagulation is through direct interaction with platelets. Platelets efficiently bound brain-derived microparticles, which triggered platelet activation. Notably, intravenous injection of brain-derived microparticles into uninjured mice led to fibrin deposition in the microvasculature and to fibrinogen consumption. Thus, consistent with the prolonged clotting time seen in trauma patients, the infusion of brain-derived microparticles in mice led to consumptive coagulopathy. Intriguingly, although the mice subjected to traumatic brain injury had a hypercoagulable state, those injected with brain-derived microparticles displayed coagulopathy. The rate at which the brain-derived microparticles were released into the circulation (over time in trauma vs bolus injection), possible qualitative differences between microparticles derived from the traumatic brain in vivo and those produced experimentally in vitro, and a potential contribution of microparticles produced by blood cells during trauma brain injury might explain these opposing observations.

One major question that arises is, How do microparticles egress the confined brain environment to reach the systemic circulation? The authors demonstrate that the blood-brain barrier is much more permeable after trauma, potentially facilitating the passage of small components, such as brain-derived microparticles, into the blood. To verify this, they modeled microparticle transmigration through an artificial endothelial barrier and observed that brain-derived microparticles could ramble through disrupted endothelial cell junctions. Activated platelets facilitated this process, possibly through histamine and serotonin, mediators already recognized as highly efficient at creating gaps between endothelial cells with dimensions compatible with those of microparticles. That the blood-brain barrier might permit the passage of extracellular vesicles is not new. In fact, other studies suggested that vesicles, biological or synthetic, in blood might invade the brain. What is novel and counterintuitive in this present study is that this process might not be unidirectional.

Thus, assuming that the mechanism of action of brain-derived microparticles, unveiled in this study, also occurs in humans with trauma brain injury, the authors suggest that the neutralization of the key actor phosphatidylserine, by annexin V or lactadherin, for instance, may have therapeutic value. Furthermore, these observations, which are important for the understanding of coagulopathy in traumatic brain injury, might also be relevant to other disorders in which the blood-brain barrier is more permeable and during which hemostasis is defective.

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REFERENCES
transplantation of children with mucopolysaccharidosis type I–Hurler syndrome (MPS-IH), along with an analysis defining a path to better these outcomes.\(^1\)

In an essay entitled \textit{The Star Thrower}, philosopher Loren Eiseley paints a picture of a perilous seashore on which thousands of sea creatures are washed up and left to die. In the midst of what one could conceive as carnage, a lone figure picks up starfish, one by one, and throws them back into the ocean so they can survive.\(^2\) Is this futile? In the face of ongoing destruction, does this action make a difference? Caring for children with mucopolysaccharidoses, one can often feel like the Star Thrower, trying to nurture not only life but quality of life in children with a relentless disease that affects the brain, joints, heart, lung, liver, and skeletal and other tissues and is only partially treated with hematopoietic cell transplantation (HCT). Which of the many tissues in these children’s bodies are we preserving with HCT, and how can we do better?\(^2\)

Earlier work by this group of investigators and others has documented a steady increase in survival\(^3,4\) and highlighted the importance of donors who are asymptomatic carriers of the gene defect also seems to result in lower iduronidase levels,\(^5\) and transplant centers are now often passing on matching sibling donors in favor of a noncarrier unrelated donor. But is it worth forgoing the use of a carrier sibling in favor of unrelated donors, especially cords, often associated with high risks for transplant-related mortality?\(^6\)

The data put forward by Aldenhoven et al strongly suggest that such a previously unorthodox choice of using an unrelated cord over a matched sibling may be justified. The figure shows adverse long-term outcomes noted by the authors in children transplanted for MPS-IH and outlines modifiable predictors with potential actions that transplant physicians could take that may make a difference in outcome.\(^1\) For many key organ/tissue outcomes (growth impairment and orthopedic, cardiac, ophthalmological, and audiological complications), the key risk factor was a post-HCT iduronidase level below local reference range. Chances of better outcomes in so many areas are so heavily dependent on this level that it seems to be of highest importance to avoid carrier donors and use approaches that maximize chances of full-donor chimerism. Some of the other modifiable predictors are very easy to address (avoid total body irradiation), but some take effort and organization on the part of physicians caring for the patient (rapid referral and receiving HCT as soon as possible). The most challenging, and perhaps the most important, of the factors, however, is arriving at a diagnosis very early in life, before significant neurological and other organ damage. Too many of these patients are diagnosed at 1 to 2 years of age, by which point significant damage to the brain and tissues has occurred in most patients. In addition, patients can worsen after HCT, before stabilization. Patients transplanted with high intelligence quotient/developmental quotient and minimal organ/skeletal defects clearly do better both short- and long-term. This is a strong argument for the development and implementation of newborn screening techniques for MPS-IH that are cost-effective and feasible.

The better knowledge of modifiable factors noted in this article that can have an effect and improve the lives of children with this disease allows transplant Star Throwers to be hopeful in the face of a disease that challenges the best of us.

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**REFERENCES**


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Long-term outcomes in MPS-IH: throwing stars

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