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Mechanisms of Injury to White Matter Adjacent to a Large Intraventricular Hemorrhage in the Preterm Brain

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Abstract

The purpose of this article is to investigate the hyperechoic lesion seen adjacent to a lateral ventricle that contains blood but is not distended. The literature on ependymal barrier dysfunction was reviewed in search of mechanisms of injury to the white matter adjacent to an intraventricular hemorrhage. The clinical literature on the clinical diagnosis of periventricular hemorrhagic infarction was also reviewed to find out how frequently this diagnosis was made. Support was found for the possibility that the ventricular wall does not always function as an efficient barrier, allowing ventricular contents to gain access to the white matter where they cause damage. Hemorrhagic infarction may not be the only or the most frequent mechanism of white matter damage adjacent to a large intraventricular hemorrhage.

Keywords

brain; preterm newborn; hemorrhage; white matter damage

Compared with neonates born at term, those born much before term are at heightened risk of a number of brain abnormalities seen on sonography (US).^{1,2} Among these is the presence of a hyperechoic lesion in the white matter adjacent to a large intraventricular hemorrhage (IVH), sometimes referred to as "grade IV IVH." The article that described the most widely used IVH classification applied the term "grade IV IVH" to a lesion that was interpreted as the result of an extension of the hemorrhage from the ventricle into the adjacent white matter.³ Although

this is possible, some authors consider it so unlikely that they have suggested eliminating the term “grade IV IVH.”^{4–6}

Among other terms proposed for the association of IVH and adjacent periventricular increased echogenicity are “intraventricular hemorrhage with periventricular echodense lesions,”⁷ “periventricular intraparenchymal echodensities,”⁸ and “hemorrhagic leucomalacia.”² Perhaps the main advantage of these descriptive terms is that they do not imply a mechanism of injury.

Another term proposed for this combination of imaging findings is “periventricular hemorrhagic infarction” (PVHI). A recent publication provided 4 references for the following definition of PVHI: “an echodense lesion in the periventricular white matter which is unilateral or, if bilateral, obviously asymmetric, and associated with a germinal matrix-intraventricular hemorrhage lesion which is usually ipsilateral or larger on the ipsilateral side.”⁹

The hyperechoic lesion adjacent to a ventricle containing a large amount of blood tends not to go around the ventricle, and therefore, is not truly periventricular. Rather it tends to be located near the lateral corner of the ventricle, suggesting that paraventricular would be a more appropriate descriptive term. The argument that the paraventricular hyperechoic lesions that accompany large IVH are due to infarction has been made elsewhere.¹⁰ A recent review of the pathogenesis of cerebral white matter injury of prematurity includes the following statement, “Although other pathologies occur in premature infants—for example, severe intraventricular hemorrhage, periventricular hemorrhagic infarction, hydrocephalus, cerebellar disease—cerebral white matter injury seems to be the predominant lesion.”¹¹ This implies that cerebral white matter injury is distinct from the lesion some call PVHI. Perhaps the pathogenesis of the hyperechoic white matter lesion adjacent to a large IVH does not differ appreciably from what is generically labeled “white matter damage.”

If the presumed mechanism leading to infarction is compression of veins by a distended ventricle, then one should expect a blood-distended ventricle. Sometimes, however, moderate-sized hyperechoic lesions are seen in the white matter adjacent to lateral ventricles that contain some blood, but not enough to result in any distention. This leads to the question of whether these white matter lesions have an etiology other than venous infarction.

MECHANICAL EXPLANATIONS FOR WHITE MATTER DAMAGE OTHER THAN INFARCTION

Compression

Some paraventricular white matter damage can be attributed to the pressure associated with ventricular enlargement. For example, 7–10 days after hydrocephalus is induced in 1-day-old rats by injection of kaolin into the cisterna magna, ventricular enlargement is accompanied by periventricular white matter edema, axon damage, and the accumulation of reactive astrocytes and macrophages.^{12,13} Two weeks later, the thickness of the corpus callosum is reduced, as is the number of mature oligodendrocytes and the amount of myelin basic protein.

The tissue compression that results from distention of the ventricle could lead to reversible diminished arterial cerebral blood flow.¹⁴ The resultant ischemia promotes excitotoxicity in the developing brain,^{15,16} which can then injure developing oligodendrocytes and lead to white matter damage.^{15–18} Such an association between a reversible diminished cerebral blood flow that accompanies elevated intracranial pressure and white matter injury has yet to be confirmed in neonates born much before term.

Trauma

By stretching the ependymal lining, the IVH can disrupt the ependymal barrier allowing intraventricular contents (whole blood, including all the proteins capable of promoting inflammation and damage) access to the surrounding parenchyma.^{19,20} The inflammation (reactive astrocytes, macrophages), which is part of this process and can contribute to the early white matter damage identified by hyperechoic lesions, is also able to clear away debris.²¹

In some models, more than 1 mechanism can lead to the perinatal white matter damage. For example, normally an intact lateral ventricle wall would serve as a barrier between the components of hemorrhagic cerebrospinal fluid and adjacent white matter. Disruption of the ependyma by mechanical factors, however, allows the influx of pro-inflammatory proteins into white matter tissue, which might have already been affected by excitotoxic, tissue-damaging mediators.

INFLAMMATION AS AN EXPLANATION FOR WHITE MATTER DAMAGE

Inflammation induced by hemorrhage

Intracerebral hemorrhage can be created in the rat in several ways. In 1 model, autologous blood is injected into the cerebral parenchyma.^{22,23} In another, bacterial collagenase disrupts blood vessel integrity. Inflammation is a feature common to both models of intracerebral hemorrhage, with initial neutrophil infiltration followed by monocyte/macrophage infiltration. Intracerebral hemorrhage also promotes the upregulation of tumor necrosis factor (TNF)- α ,^{24,25} adhesion molecules,²⁶ matrix metalloproteinases^{23,27,28} and glutamate.²⁹

Some constituents of blood may be more damaging than others. For instance, injecting plasminogen or thrombin into the striatum (a deep gray matter structure) of neonatal mice results in greater damage than whole blood or saline.³⁰ Adding a proteolytic inhibitor to the autologous blood reduces brain cell death and inflammation.³¹ These findings support the hypothesis that proteolytic enzymes that circulate in blood may account for an appreciable amount of the damage associated with blood in the brain. They also have special importance for the preterm newborn because the immature brain uses proteolytic systems for cell migration and growth.^{32,33} Might this be an example of “a little is good, but more is bad”?

Adding plasma to cultured rat microglial cells enhances TNF- α mRNA expression and protein production, while adding serum instead of plasma enhances interleukin-6 (IL-6) mRNA expression.³⁴ These findings document that soluble components of blood upregulate inflammatory cytokines in microglial cells, the cell type implicated in contributing substantially to white matter damage.³⁵ Plasma components, such as kal-likrein, complement C5a, GABA, and glutamate, can inhibit proliferation of perinatal rat subventricular zone cells.³⁶ Thus, extracellular blood contents might damage gray matter as well as white matter.

Excitotoxicity, which can contribute to white matter damage,^{15–18} can be produced by adding hemoglobin to cultures of cortical cells.³⁷ In adult rats, injecting blood and thrombin into the white matter parenchyma upregulates NMDA receptor subunit expression,³⁸ thereby promoting the opportunity for excitotoxic damage. Thus, hemorrhagic cerebrospinal fluid might damage the white matter via excitotoxic mechanisms.

Newborns appear to be especially sensitive to the adverse effects of blood and its components. Compared with adult mice, newborns have proportionately larger volumes of damage and more intense inflammatory reactions to autologous blood, thrombin, and plasminogen.³⁰

Newborn mice given lipopolysaccharide by intraperitoneal injection 12 hours before the intracerebral injection of blood had more brain damage than newborn mice not pretreated with

lipopolysaccharide.³⁹ This is evidence that a systemic inflammatory response can exacerbate brain damage by other stimuli.

Young adult mice showed less exacerbation of brain damage by the lipopolysaccharide than seen in newborn mice.³⁹ This adds support to the concept that newborns respond more than adults to brain-damaging stimuli.

Inflammation not induced by hemorrhage

Perhaps inflammatory proteins (not whole blood) are sufficient to damage the periventricular/para-ventricular white matter. One example is lipopolysaccharides, a very potent stimulus for inflammatory responses, including those in the brain.⁴⁰ In young rats, injecting lipopolysaccharide into 1 lateral ventricle results in white matter inflammation, documented by induction of pro-inflammatory cytokines TNF α , IL-1 β , and IL-6, and inducible nitric oxide synthase, as well as the presence of activated astrocytes and microglia/macrophages.⁴¹ Subsequently, white matter rarefaction and lateral ventricle dilation are accompanied by a reduction in the number of oligodendrocytes. Administering an antibody against IL-6 with the lipopolysaccharide diminishes some of these early and late findings, strengthening the claim that inflammation contributes to the white matter damage.⁴¹

HUMAN NEONATAL WHITE MATTER DISEASE

Diagnostic variability

In a study of 998 very low birth weight newborns, 77% of white matter lesions could be differentiated as either PHVI or PVL by US criteria.⁴² However, 11% of scans had characteristics of both these diagnoses.

In contrast, in a study of cranial US of 1607 very low birth weight infants, 47% of the scans with a white matter abnormality had features of both periventricular hemorrhagic infarction and periventricular leukomalacia.⁴³

The differences between these 2 studies are difficult to resolve. In the larger study, all US scans were read by consensus, whereas this was not the case in the smaller study. The reported observations, however, suggest that different investigators apply the existing definitions differently. This variability also leads to the inference that the name PVHI might be confusing to clinicians because it is not applied uniformly.

How intact is the ependyma?

Thickened ependyma has been identified by US in children who have a relatively small IVH without any adjacent white matter hyperechoic lesion.⁴⁴ Otherwise, ependyma is difficult to identify on US of preterm newborns.

Most of the possible mechanisms described above assume some impairment of ependymal barrier function. Although some dysfunction might not have a morphologic correlate, the integrity of the lateral wall separating ventricle contents from adjacent white matter damage is rarely described. In part, this might reflect an inability to identify the ventricle wall on US because the lesions on each side of the ventricle wall have almost identical echogenicity (Figure 1).

The inability to depict the ependyma on US is just one of the many limitations of cranial US.⁴⁵ MRI (especially with diffusion tensor mapping) is probably needed to clarify the integrity of the ependyma in the live newborn.

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FIGURE 1.

The left lateral ventricular wall cannot be identified because the echogenic clot blends imperceptibly with the adjacent hyperechoic parenchyma.