REDELVE INTERNATIONAL PUBLICATIONS

Archives of Neurology and Therapeutics
Volume 2019, Issue 01
Review Article: RD-NEU-10002

Intraventricular Hemorrhage, Novelties in the Pathogenesis

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Citation: *Hernández Rosales P, Valdez Sandoval, P, Chavana A, Garcia Navarro V (2019) Intraventricular Hemorrhage, Novelties in the Pathogenesis. Archives of Neurology and Therapeutics. Review | ReDelve: RD-NEU-10002.*

***Received Date:** 14 March 2019; **Acceptance Date:** 27 March 2019; **Published Date:** 01 April 2019*

Abstract

Intraventricular hemorrhage is a common pathology in preterm newborns. It originates from the germinal matrix and expands into the ventricles causing them to dilate which ends up injuring the brain parenchyma. Two factors are thought to contribute in the pathogenesis of intraventricular hemorrhage, the increased vascularity of the germinal matrix and the cerebral blood flow fluctuations. After the hemorrhage has taken place, the blood clots can produce a non-communicating hydrocephalus, but alterations in the absorption of cerebrospinal fluid end up causing a communicating hydrocephalus.

Keywords: Germinal Matrix; Intraventricular Hemorrhage; Post-Hemorrhagic Hydrocephalus

Introduction

Intraventricular Hemorrhage (IVH) is the most common neurologic complication in preterm newborns and it is associated with great morbi-mortality in this group of patients.

The hemorrhage arises from the Germinal Matrix (GM), a proliferative, transient and highly vascularized area composed by precursors of glial and neuronal cells [1,2] located in the thalamus-striate groove below the ependyma [3]. This structure has greater activity in the initial stages of embryonic development, between weeks 8 and 28 of gestation. Afterwards it begins to regress disappearing almost completely by the end of gestation, which explains its higher incidence in preterm infants (<28 weeks of gestation) [4].

The main factors involved in IVH are the fragility of the vasculature of the GM secondary to the increased angiogenesis, the alteration in the components of the blood vessels, and the alterations in the Cerebral Blood Flow (CBF). The risk of developing post-hemorrhagic hydrocephalus is based on the extension of the hemorrhage. It begins as a non-communicating hydrocephalus (obstructive process), secondary to the occlusion of the Cerebrospinal Fluid (CSF) flow and ends up being a problem in CSF absorption defined as a communicating hydrocephalus [1].

In this article we will describe the main pathophysiological mechanisms by which intraventricular hemorrhage and post-hemorrhagic hydrocephalus develop.

Pathogenesis of Germinal Matrix Hemorrhage and Intraventricular Hemorrhage

Two mayor factors are thought to contribute to IVH in the preterm infant, the inherent fragility of the GM vasculature and disturbances of the CBF [5].

IVH in preterm infants arises from de GM, a richly vascularized transient proliferative area of glial and neuronal cells precursors [1,2] located in the thalamo-striate groove beneath the ependyma that involutes at the end of gestation [3].

The high risk of hemorrhage of the GM vasculature has been attributed to a high vascularity due to increased angiogenesis, associated to fragility of the vessels caused by alterations in the components that provide structural stability to the Blood-Brain Barrier (BBB). Because of its high metabolic activity and high oxygen demand, this area is in a relative hypoxic state [5]. Hypoxia, through the transcription of hypoxia-inducible factor 1, up-regulates the production of Vascular Endothelial Growth Factor (VEGF) [6]. VEGF is the predominant angiogenic factor during development and, together with angiopoietin (ANGPT) -2, are responsible of the rapid angiogenesis in the GM [7,8]. High vascularity enhances the probability of hemorrhage. It has been demonstrated that the components of the vessels of GM differ from those in other regions of the brain [5]. The components of BBB include endothelial tight junctions, basal lamina, astrocyte end feet and capillary pericytes [9]. While there are no changes in the tight junction proteins, alterations in the other three components are thought to contribute to the fragility of GM vasculature.

Astrocyte end feet provide structural integrity to the blood vessels [5]. El-Khoury et al. observed a decreased perivascular coverage of Glial Fibrillary Acidic Protein (GFAP)-positive astrocyte end feet. GFAP is a major cytoskeletal protein that forms intermediate filaments of astrocytes and provides mechanical strength and shape to astrocyte end feet [3].

The basal lamina is composed of laminin, type IV collagen, fibronectin and perlecan [5,9]. Of these, fibronectin plays a key role in preserving structural stability of blood vessels. Xu et al. found that fibronectin expression was decreased in the GM vasculature compared with white matter and cortical vasculature and that antenatal low-dose betamethasone enhances fibronectin expression by a 1.5 to 2 folds, while high-dose regimens reduce its expression by 2 folds [9]. Pericytes are cells that wrap around the endothelial cells and provide stability and structural integrity to blood vessels [5]. Four ligands, transforming growth factor beta 1 (TGF-ß1), ANGPT, platelet-derived growth factor-B (PDGF-B) and sphingosine 1 phosphate, and their receptors are needed for pericyte recruitment. Braun et. al reported a reduced coverage and density of pericytes in the GM vessels. A reduction of TGF-ß1 was also observed. Low concentrations of TGF-ß1 stimulate endothelial proliferation through activation of activin receptor-like kinase (ALK)-1, whereas high concentrations inhibit endothelial proliferation and promotes mesenchymal differentiation into pericytes via ALK-5 [8]. Additionally, rapid angiogenesis induced by VEGF and ANGPT2 results in reduced pericyte density. In contrast, the blockade of vascular endothelial growth factor receptor 2 (VEGFR2) enhances pericyte density by upregulating ANGPT1, and decreases the risk of hemorrhage [7,8]. It is speculated that antenatal glucocorticoids help prevent IVH by increasing GFAP in astrocyte end feet and fibronectin of the basal lamina [3,9].

Disturbances of CBF are very common in preterm infants, the fluctuations of CBF due to immaturity of the cardiovascular system, together with an impaired cerebrovascular reactivity, increase the risk of Germinal Matrix Hemorrhage (GMH) [1,10].

Hypotension is the most common Blood Pressure (BP) alteration found among preterm infants, incidence ranges from 20 to 45% of Very Low Birth Weight infants (VLBW) infants [11]. Numerous studies have found a direct association between hypotension and an increased risk of IVH [10,12,13]. Hypotension, through up-regulation of neuronal nitric oxide synthases (nNOS) and increased production of nitric oxide, produces vasodilation of the brain vasculature [10], thereby increasing the risk of vessel rupture and hemorrhage. Others have found an association between GMH and a hypoperfusion-reperfusion pattern; increased blood flow in dilated vessels, combined with the immaturity of the vasculature could result in hemorrhage [14].

Fluctuations in BP and CBF velocity are thought to play an important role in the development of IVH [15]. Perlman et al., in a study of infants with Respiratory Distress Syndrome (RDS), observed a direct relationship between fluctuations of BP and a fluctuating pattern of CBF velocity, and that the latter is causally related to IVH by provoking rupture of capillaries [16]. It is thought that in infants with RDS with ventilation assistance, fluctuation in BP and CBF velocity occurs secondary to respiratory effort out of synchrony with the ventilator. An observation was made that the use of pacuronium in the first 24 hours removed infant's contribution to the ventilation, thereby reducing CBF velocity fluctuating pattern along with the incidence and severity of IVH [17]. None the less, this drug was found to have multiple cardiovascular side effects and to cause an increase in the need for higher ventilator pressures to maintain adequate oxygenation [18]. Newer ventilator modalities, such as synchronized intermittent mandatory ventilation and assist control can reduce asynchrony of patient and machine ventilation, thus reducing fluctuation [5,18]. These fluctuations are more frequent in the first 48 hours of life, which correlates with the risk period of occurrence IVH [18,19].

Cerebral autoregulation is a physiological mechanism that maintains constant blood flow to the brain despite variations in cerebral perfusion pressure. The autoregulatory plateau is the BP range over which CBF remains constant [20]. In preterm infants cerebral autoregulation may be impaired, so their CBF becomes BP-passive [12], this means that their CBF will change in concordance with BP changes. It is speculated that cerebral pressure-passivity is a risk factor for cerebrovascular injury [10,21]. Various studies have been conducted with the use of Near-Infrared Spectroscopy (NIRS) and Spatially Resolved Spectroscopy (SRS) to determine the relationship between pressure-passivity and IVH. Some studies have found no relationship [21,22], while others have found a direct correlation with the impaired cerebrovascular autoregulation and the likelihood of occurrence of GMH [23,24].

Hypercapnia might also play a role in the impairment of cerebral autoregulation by producing vasodilation of the cerebral resistance arterioles. In the setting of an increased BP and hypercapnia, hypercapnic hyperemia will overcome the autoregulatory mechanism resulting in an increased CBF. On the contrary, when BP decreases, further vasodilation may not be possible, resulting in a decreased CBF [20]. In a study conducted by Kaiser et al. the conclusion was that increasing arterial pressure of carbon dioxide (CO_2) was associated with progressively impaired cerebral autoregulation and that hypercapnia during the first 3 days of life was a predictor for severe IVH in VLBW [25].

Pathogenesis of Post Hemorrhagic Hydrocephalus

Hydrocephalus results from an imbalance between the production and elimination of CSF. CSF is produced by the ependymal cells located in the choroid plexus, it is then mobilized in direction to the pressure gradient and reabsorbed through the arachnoid villi [26].

The mechanism by which hydrocephalus develops after GMH-IVH is still uncertain. Most common held view is that initially, blood clots obstruct the CSF flow by blocking the cerebral aqueduct or the fourth ventricle outlets, thus producing and obstructive hydrocephalus [2]. Later on, a delayed communicating hydrocephalus develops and it is speculated that it is due to an impairment of CSF resorption [1] caused by an increased production of Extracellular Matrix (ECM) proteins throughout the cerebroventricular system [27]. When analyzing the CSF of preterm infants with GMH-IVH, it was noted that TGF-ß1 was increased in those who developed Post Hemorrhagic Hydrocephalus (PHH), which led to the hypothesis that TGF-ß1 might play a role in the pathogenesis PHH by upregulating the genes encoding ECM proteins such as fibronectin and collagen [1,28,29]. TGF-ß1 is stored in platelet granules, lysis of the blood clot might be the mechanism by which it gains access to the CSF [28]. Manaenko et al. performed a study in rats using SD208, a potent inhibitor of TGF-ß1 receptor, and concluded that the inhibition of TGF-ß pathway led to significant cognitive and motor improvement and attenuated brain atrophy and hydrocephalus [29].

Others have proposed that thrombin may play a role in PHH. By binging to Protease-Activated Receptor (PAR)-1 and PAR-4, thrombin upregulates cyclooxygenase 2 (COX-2) and phosphorylated mammalian target of rapamycin (p-mTOR) signaling, thereby exacerbating inflammatory and proliferative responses that potentially contribute to increased ECM protein production and deposition [27]. Lekic et al. concluded that by inhibiting early proliferative signaling, p-mTOR pathway, GMH long-term outcome might improve [30].

Increased levels of Non-Protein Bound Iron (NPBI) are also found in the CSF of infants with GMH-IVH [31]. Iron may play a role in ventricular dilation and neuronal death by generating hydroxyl radicals and inducing oxidative damage [31,32]. Some evidence supports the role of iron in the pathogenesis of PHH. The use of iron chelators, such as deferoxamine and minocycline, were found to attenuate ventricular dilation by reducing iron overload after GMH and iron induced brain injury [32,33].

BBB, Blood-Brain Barrier; CBF, Cerebral Blood Flow; GFAP, Glial Fibrillary Acidic Protein; GM, Germinal Matrix; HIF-1, Hypoxia-Inducible Factor 1; IVH, Intraventricular Hemorrhage; nNOS, Neuronal Nitric Oxide Synthase; VEGF, Vascular Endothelial Growth Factor.

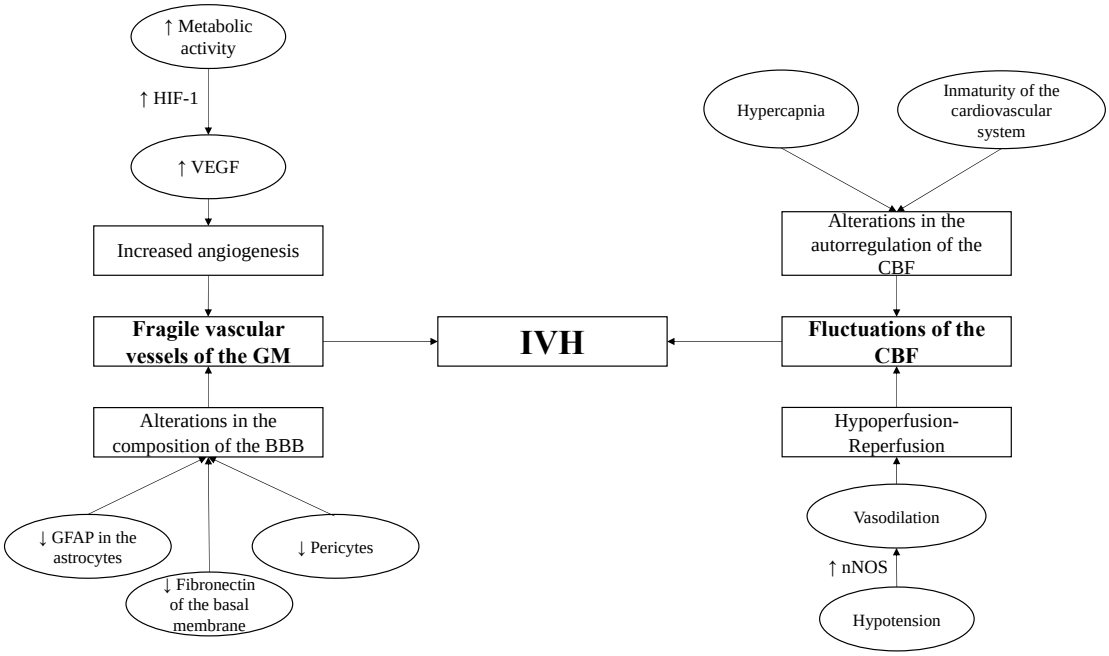

Figure 1: Two main factors contribute to the pathogenesis of IVH: the intrinsic fragility of the vascular vessels of the GM and the fluctuations of the CBF. The former is caused by an increase in the angiogenesis that results from the high metabolic activity of this region and the state of relative hypoxia that lead to an enhanced signaling of VEGF. Additionally, the BBB composition in this area of the brain differs to the rest, with a decreased GFAP, fibronectin and pericytes, which decreases the structural stability of the vessels. The latter is conditioned by a decreased capacity of autoregulation of the CBF, which has been attributed to the immaturity of the cardiovascular system and hypercapnia, and a hypoperfusion-reperfusion pattern secondary to hypotension and subsequent vasodilation.

Conclusion

IVH is a pathology commonly associated with a poor prognosis resulting in severe language, cognitive and motor impairment. There is no established intervention that guarantees a good outcome in all patients and management is still focused in the control of ventricular dilation instead of preventive measures that could help lower the incidence.

It is possible that with a wider comprehension of the pathophysiology, new lines of research and preventive measures can be established for the improvement in the prognosis of patients with IVH and secondary hydrocephalus.

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