Cerebral Venous Malformation as a Cause of Neonatal Intra-Ventricular Haemorrhage and Unexplained Infant Subdural Haemorrhage

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Rec date: Feb 01, 2016; Acc date: Feb 16, 2016; Pub date: Feb 19, 2016

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Abstract

An Intra-ventricular Haemorrhage (IVH) is a bleeding into the brain's ventricular system. Most intra-ventricular haemorrhages occur in the first 72 hours after birth. They originate in a layer of tissue (Germinal Matrix), under the lining of the ventricles (Ependymal), while it is in the process of manufacturing neurons and glia. This has normally regressed by term but may still be active in premature infants. Pathological investigations have found accumulations of peri-venous plasma and blood suggesting that excessive cerebral venous pressure has disrupted vessels, initiating the intra-ventricular bleeding observed. This has led to unsuccessful searches for evidence of A-V shunts within the developing cerebrum, or loss of auto regulation in arterioles, producing excessive cerebral venous hypertension.

An alternative mechanism, reported here, is of venous rather than arterial origin; that high venous pressure results from inadequate venous drainage. Forcing increasing cerebral flow through inadequate venous vasculature requires increasing cerebral venous pressure. This is particularly significant at birth when the brain is suddenly stimulated to widespread activity which requires increased blood flow. This would explain why this disorder occurs shortly after birth. However, if rising cerebral pressure is insufficient to cause damage at birth, the infant may survive with a chronically high cerebral venous pressure. Then, minor stresses such as short falls, vomiting in pyloric stenosis, violent coughing, etc., may provide sufficient extra pressure to initiate haemorrhaging.

In the embryo the pattern of arteries is pre-programmed, but veins climb gas gradients and their normal patterns are quite variable. Neonatal intra-ventricular haemorrhage is typically highly asymmetrical, and a typical inappropriate venous pattern is described. Recognition of inadequate venous patterns may not benefit the infant itself, but may protect any siblings from loss of home and parents.

Keywords: Cerebral venous hypertension; Germinal matrix haemorrhage; Neonatal intra-ventricular haemorrhage; Neonatal subdural haemorrhage; Shaken baby syndrome; Short falls

Introduction

The brain is, in a sense, a hollow organ, a fluid filled tube formed in the embryo. The tube has distensions known as ventricles [1]. At its front end it bifurcates to form two lateral ventricles in which much of the cerebral ventricular fluid is generated. These ventricles are lined with a layer of ependymal which is analogous to the endothelium which lines blood vessels. Blood vessels passing through, in and around the walls of the ventricles are described as sub ependymal to indicate their position. Intra-ventricular haemorrhage (IVH) is a bleeding from these vessels, through the ventricle wall, into the fluid contained in the ventricular system.

Most intra-ventricular haemorrhages occur in the first 72 hours after birth [2]. They originate in a layer of tissue (Germinal Matrix, GM), under the lining of the ventricles (Germinal Matrix Haemorrhage, GMH), while it is in the process of manufacturing neurons and glia. Neurons and glial cells do not form in the cerebrum; they are manufactured in the germinal matrix from about 8 weeks gestational age. Cerebral neuron generation is complete at about 20 gestational weeks but new glia cells (which support and position neurons) continue to be manufactured here until about 32 weeks gestational age [3]. Having served its purpose the GM then degenerates and is normally virtually absent at term (Figure 1).

Figure 1: Location of a germinal matrix between each lateral ventricle and caudate nucleus, with bleeding into the ventricle on the right.
Premature infants or those of very low birth weight are particularly vulnerable to this disorder. The haemorrhage appears to start in the germinal matrix at a level between the thalamus and the caudate nucleus [3], adjacent to the foramina of Monro. Premature infants primarily bleed in the germinal matrix, but not into the cortical mantle or white matter.

Haemorrhage is frequently asymmetrical. Volpe noted that 67% of GMH cases were unilateral; [4] if the haemorrhage is large, it ruptures through the ventricle wall into the ventricles, flooding the lateral, third and fourth ventricles (Intra-ventricular haemorrhage IVH).

The cortical spinal motor tracts run through this periventricular region [3]. The white matter is arranged with the tracts innervating the legs nearest the ventricles and those innervating the face furthest from the ventricles. When periventricular infarction damages these tracts cerebral palsy injury appears in the same leg-to-face sequence of distance from a ventricular wall.

**Current Hypotheses of Causation**

The inherent fragility of the germinal matrix vasculature, disturbance in the cerebral blood flow (CBF) and platelet and coagulation disorders have been considered as physiological vulnerability factors. Other authorities have looked for an association with hydro-mechanical forces. There has been debate about involvement of auto regulation but current thinking is that there is no association between impaired auto regulation and IVH [5]. Anstrom et al. [6] looked for pre-capillary arteriole-to-venous shunts delivering arterial blood directly to cerebral veins and so raising cerebral venous pressure. They examined 33 premature neonates at autopsy but could find none. They concluded that pre-capillary arteriole-to-venous shunts were not a significant factor leading to GMH.

Ghazi-Birry et al. examined the vessels connecting the GM to the body vasculature using alkaline phosphatase to distinguish between afferent and efferent vessels. They could find no pre-capillary arteriolar-to-venular shunts [7] and concluded that germinal matrix haemorrhage in preterm neonates is primarily venous in origin.

This raises the question, why should veins be the source of bleeding while capillaries and arterioles, which should be at higher lumen pressure, have been found to be unaffected?

**The Architecture of GMH**

Ghazi-Birry et al. [7] studied germinal matrix tissue from premature neonates of very low birth weight, with established GMH, to determine the vascular architecture of the germinal matrix in the preterm neonatal brain. They found that the overwhelming majority of haemorrhagic foci within the germinal matrix tissue were in proximity to venous vessels or confined within the peri-venous space. Also, the venous vessels within the germinal matrix of the haemorrhagic cases were invariably distorted, and the structural integrity of the veins had been lost at or near the haemorrhagic foci.

![Figure 2: Normally there is no significant space between the vein surface and the surrounding tissue (a) but in GMH cases significant perivenous spaces were observed along which haemorrhages had tunnelled (b).](image)

The normal situation is represented in Figure 2a. A vein is passing through GM tissue accepting blood from venules draining matrix tissue. Figure 2b illustrates the findings in GMH cases. The vein is surrounded by a fluid filled perivenous space, fluid that had been expressed through the vein walls by the excessive cerebral venous pressure. In life this would have distended the surrounding tissue causing it to press on the perivenous fluid. When the excess vein lumen pressure fell at death the vein would have become compressed as in Figure 2b. Near haemorrhagic foci the perivenous space would be filled with blood that had tunnelled down from the focus. They found that the venous vessels within the germinal matrix of the haemorrhagic cases were invariable distorted, and the structural integrity of the veins was lost at or near the haemorrhagic foci. This phenomenon was never seen in association with arterioles or capillaries.

Nakamura et al. [8] studied the rupture point of GMH by post-mortem injection of associated arteries, veins, and artery and vein simultaneously, to see which route had a defect that had allowed blood to escape into the hematoma. Only material injected via a vein leaked into haemorrhage, which was confirmed by stereomicroscopic and...
histologic examination. This further confirmed that germinal matrix haemorrhage is venous in origin.

The resulting mechanical factors are summarised in Figure 3. It is based on figure 11 in Ghazi-Birry's paper [7] which shows such a vein in cross-section.

Venules that had grown out of the vein into the brain interstitium have become stretched, either due to shrinkage of the vein or dilation of the perivenous space. These venules were under tension and one is shown to have torn out of the surrounding tissue. Bleeding from the damaged venule escaped out into its surrounding space forming a perivenous hematoma.

In summary they conclude that ‘All haemorrhages but one were closely associated with veins, with considerable involvement of the peri-venous space…. germinal matrix haemorrhage in preterm neonates is primarily venous in origin. A haemorrhage can tunnel along the venous perivascular space, collapsing the vein and rupturing the tethered connecting tributaries. Extraversion of blood from the arterial circulation appears to be much less common’.

A Venous Origin of Cerebral Venous Hypertension

Back pressure

To drive blood through any vessel there must be a difference of pressure between its ends. One way of treating this is to say the vessel produces a “back pressure” when attempts are made to drive blood through it. In each hemisphere the germinal matrix drains into the corresponding internal cerebral vein, red circle Figure 4. The two Internal Cerebral Veins unite into the great vein of Galen. From there blood flows through the straight Sinus to the confluence of veins (Toricular Herophili), around the transverse sinuses, and on into the jugulars. Each vein makes its own contribution to the total back pressure into which the germinal matrix drains, i.e. the GM drains into a pressure $P_{gmv}$.

$$P_{gmv} = (P_{icp} + P_{gal} + P_{st} + P_{t} + P_{ps} + P_{jug}).$$

Cerebral Venous Hypertension Due to Venous Maldevelopment

The embryological route of artery development is largely pre-programmed, but that of veins has a large component of climbing $O_2$ and $CO_2$ gradients. The veins of the cerebrum fall into two sub groups [11], the superficial medullar veins that drain the outer cortex, and the deep medullar veins draining through the subependymal veins in the walls of the lateral ventricles [11]. Initially the dural sinuses, and the straight sinus, are not present. Dural sinuses form by coalescence of multiple channels [12] between leaves of venous channels within the falx, transiently present during embryogenesis before formation of definitive sinuses, but usually regress later in fetal life. As the embryo grows, a mesh of anastomotic loops termed the “Sagittal Plexus” is seen in the primitive Falx cerebri [13]. As the choroid plexus grows (week 5 gestational age) a new system develops to drain the plexus [14]. Most of this vein later regresses, except for the most caudal portion [15]. Typical normal development is shown in Figure 4.
The major sinuses normally meet at the back of the skull, known as the "confluence of sinuses", or the “Torcular Herophili”. The superior sagittal Sinus extends from the foramen occiput to the torcula and usually drains predominantly into the right transverse sinus [16].

The Internal Cerebral Veins of each hemisphere drain the underside of their cortex and join each other at the vein of Galen which drains into the straight sinus, and on into the torcula, usually predominately into the left transverse sinus [17].

Figure 4: The principle cerebral venous vessels and sinuses.

The simplest abnormality is inadequate diameter growth of venous vessels (see left transverse sinus in Figure 4) although this can have benign origins in unusual combinations venous connections. The more serious abnormalities arise when veins do not accomplish adequate connections, or normal veins do not even form. They may be replaced by enlargement of normally small veins. Unlike arteries many variations from the "textbook" venous patterns may result that provide perfectly satisfactory gas manipulation. However some variations have serious hydrodynamic consequences. At the back of the skull there is normally a confluence of veins, the Torcular Herophili, Figures 4 and 5a. Failure of one or other of the transverse sinuses to reach communication with the torcular herophili is one such malformation that would explain the characteristic asymmetry of this disorder. The Superior Sagittal Sinus (SSS) and the straight sinus ST bring blood from the outer and inner cerebral tissue into, and the transverse sinuses on each side of the skull carry it away from, the torcular herophili to the Inner Jugular Veins.

Widjaja and Griffiths made an extensive study of the anatomy of intracranial veins and sinuses in children, using 2D time-of-flight venography [18]. They give a detailed account of “normal” and “deviant” development of venous patterns from the embryo to the neonate. Figure 5 is derived from their Figures 1A and 1B [19]. In the normal condition, Figure 5a, the right (RTS) and left (LTS) transverse sinuses are of similar calibre. The superior sagittal and the straight sinuses drain into the torcular herophili. In the case illustrated in Figure 5b the left transverse sinus failed to make contact with the torcular herophili. The right transverse sinus and right jugular vein had to convey the total sagittal sinus blood from the outer cortex in addition to the normal flow from the straight sinus blood from the right inner cortex. The blood from the germinal matrix drains through the straight cortex and so would suffer from the extra pressure required to force all this blood through the right side venous vasculature. The left hemisphere veins only had to drain local blood, through their own compensatory shunt veins. Their pressures would be insufficient to produce hemorrhage. This is the sort of vascular developmental defect that would produce the unilateral lesions described by Volpe [20] in which, where necrosis was asymmetrical, 67% of lesions were exclusively unilateral.

In cases like Figure 5b no true vein of Galen or straight sinus has formed [14]. Early in embryonic life before the dural sinuses have developed, drainage paths in the falx cerebri exist. They usually regress, but if such a developmental shunt persists a true Galen vein and straight sinus may not develop.

In a study of cerebral venous flow in 50 children being investigated for developmental delay, using the Magnetic Resonance "time-of-flight" flow imaging (fMRI) [18] Widjaja and Griffiths [19] found 54% had a dominant right transverse sinus and 36% had left dominance, but in only 8% of these children with developmental delay were the transverse sinuses co-dominant.

**Discussion**

The fragility of the Germinal Matrices and their high metabolic requirements are well known and there is evidence of hypertensive injury in their venous vasculature. In the disorder known as “Malformation of the Vein of Galen” arterio-venous shunts are found which not only raise cerebral venous pressure, but may carry bypass flow to embarrass cardiac output [21]. No such shunt paths have been found in GMH [6]. The study presented here suggests that the cause is of venous, not arterial, origin. It arises not from excessive flow into the GM, but from various forms of obstructed outflow.
Simple inadequate diameter of venous vessels could raise cerebral venous pressure excessively, but that would not explain the extreme asymmetry characteristic of this disorder. The explanation offered here is failure during embryonic/fetal life to establish mature patterns, such as where one of the transverse sinuses does reach the torcular herophili. The other sinus then has to carry the additional flow from the superior sagittal sinus etc., requiring raised venous pressure to drive it. Such adaption may be adequate in utero, but with the sudden cerebral stimulation at birth, and consequent surge in cerebral blood flow, the resultant rise in cerebral venous pressure may cause venous rupture. This would explain the occurrence of GMH in the first 72 hours of the neonatal period.

Some infants may survive the initial stress at birth although they have malformed venous drainage. But they will have chronic cerebral venous hypertension in one or possibly both hemispheres. If this chronic cerebral venous pressure is subsequently supplemented by the stresses of everyday life, (low falls, paroxysms of coughing, or during vomiting in pyloric stenosis or pylorospasm) [21] intracranial hemorrhages may appear, apparently spontaneously [10].

Diagnostic features

It is known that there is a natural asymmetry of jugular vein flows but it may be possible to determine a level of asymmetry (e.g. Using MRI time of flight techniques) to give warning of risk of IVH under stress. Post-mortem study of venous vasculature may reveal asymmetry evidence of congenital malformation, especially if associated asymmetrical intra cerebral hematomas.

Conclusions

The initial damage that leads to IVH occurs in the veins of the GM. Currently this is attributed to the well-established delicate nature of the GM and hypoxia due to possible malfunction of its perfusion supply. This present study raises the possibility of hydro-mechanical damage, caused by excessive cerebral venous pressure due to inadequate cerebral venous development. Marked asymmetry of IVF suggests failure of a transverse sinus to reach the torcular herophili at the embryological stage of development. This condition is manifested at birth when the malformed cerebral venous vasculature is unable to cope with the increased flow demanded by the stimulated brain. It would appear that survivors may remain, vulnerable at any time to external causes of additional cerebral venous pressure, such as paroxysms of coughing or during vomiting in pyloric stenosis or pylorospasm.

Unfortunately, diagnosis of this condition will not benefit the infant itself because it would involve inserting a double ended shunt in an inaccessible position under the cortex. It would however protect siblings and parents from misguided “protection measures” causing family destruction.

References