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# Developmental Neuropathology and Outcome of Perinatal Brain Damage and the Brain Microvascuar System

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**Abstract**

The cerebral cortex microvascular system of normal (unaltered) brains is described and compared with that of altered ones by perinatal brain damage. The brain' microvascular system evolves from the pial capillary plexus an important meningeal compartment poorly studied. A pial capillary anastomotic plexus already cover the cortex in 6-week-old embryos, although its vascularization will not start until the eight-week. This plexus expands covering cortex entire surface throughout life. The cortex has two basic intracerebral microvascular compartments: an extrinsic one represented by the perforating vessels and an intrinsic one represented by the anastomotic capillary plexus established among contiguous perforators. Throughout the developing and the adult cortex, the perforating vessels are separated from each other by a distance raging from 400 to 600 micrometers. The equidistant distance among perforators is considered to represent a biological constant necessary for the functional activity of gray matter neurons. All perforating vessels are within the Virchow-Robin Compartment and hence extrinsic to the nervous tissue. This compartment remains open to the meningeal interstitium and serves as the cortex sole drainage system (mammals' brain lacks a lymphatic system). The cortex' intrinsic microvascular compartment is represented by the anastomotic capillary plexus established between contiguous perforators. The neurons, glial cells, fibers terminals and synaptic profiles within the intrinsic microvascular compartment represent the functional center of each cortical region. The interexchange of information among these elements determines the blood flow through each region in response to its neurons functional demands. Each cortical region may function independently or in combination with proximal as well as distant regions functionally interconnected with it. There are more perforating vessels and intrinsic capillaries in the gray than in the white matter, which explains their different neuronal activities and different vulnerabilities to perinatal brain damage. In hemorrhagic and/or ischemic brain lesions, damaged intrinsic capillaries are replaced by post-inflammatory ones, which lack their functional efficiency. In any reappeared cortical lesion, the local neurons, intrinsic neuropil and vascularitywill are transformed. Local neuronal alterations could affect the functional activity of proximal and distant regions interconnected with them and eventually the whole brain. This ongoing mechanism could play a role in the pathogenesis of neurological sequelae secondary to perinatal brain damage.

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## INTRODUCTION

Prematurity, respiratory difficulties, obstetrics complications and trauma are mayor factors in the pathogenesis of perinatal brain damage. The ensuing lesions could either be hemorrhagic, ischemic (infarcts) and/or a combination of both. The blood capillaries are invariable involved in any type of perinatal (hypoxic, ischemic and/or traumatic) damage. Eventually, any cortical lesion will be healed and repaired and blood capillaries will also participate in these processes. The repair of any cortical lesion involves the removal of necrotic debris, revascularization, and transformation of surviving local neurons, intrinsic neuropilchange, and functional rewiring of the affected area. A variety of permanents local anatomical and functional lesions will be established on the damage cortex. The functional activity of these repaired lesions could encroach on the activity of proximal and distal regions interconnected with it and eventually affect the whole brain functional activity. This mechanism could

play a role in the pathogenesis of eventual subclinical and clinical neurological sequelae such as epilepsy. Post-injury cortical lesions have been amply documented [1-11]. The neuropathology and outcome of repaired cortical lesions and their relationships to the cortex microvascular system are explored herein.

A repaired cortical lesion functional activity and its possible infringement on the whole brain functional activity remain inadequately studied and poorly understood. Due, in part, to the difficulty in obtaining the needed fresh brain material from autopsies and in the selection of an adequate staining procedure to study them. The cortex microvascular system involvement on these ongoing processes has neither been adequately explored.

Since capillaries are invariably involved in the etiology and subsequent reparation of any type of perinatal brain damage it is essential to understand their development, composition and organization. Two fundamental questions about them are addressed herein: What are the origin, development and composition of the human cerebral cortex microvascular system? And what is its participation in perinatal brain damage and on its subsequent recovery? The term 'perinatal' used herein refers to cortical lesions that could either occur prenatally, during labor and/or early in postnatal life.

## MATERIAL AND METHOD

The material used in this study has been gathered from the author previous Golgi studies of both unaltered (normal) as well as altered (perinatal damage) neonatal brains [9-17]. Golgi studies require the use of postmortem fresh brain material not always easy and/or possible to obtain. Parental understanding and early permission as well as the close collaboration of neonatologists and pediatric nurses is not only necessary but also required for these studies [12]. These difficulties explain the few cases adequately studied and reported [9-11].

## OBSERVATIONS AND DISCUSSION

Various developmental aspects of the human brain microvascular system are explored herein, using normal (unaltered) as well as altered neonatal brains by either hemorrhagic and/or ischemic damage.

### The human brain microvascular system

From the start of development and throughout life, the human (and mammalian) brain vascular system is composed of three separate but interrelated compartments. They include: the extracerebral or meningeal compartment and both intracerebral extrinsic and intrinsic ones (Table 1). The development, composition and interrelationships of these vascular territories have been recently described [13].

The meningeal compartment has three components: an outer lamella that carries the meningeal venous sinuses, an intermediate one with arachnoidal arteries and veins and an inner one with the pial anastomotic capillary plexus (PCP) that covers the brain surface (Figure 1A, B, C). During cortical development and throughout life, the PCP provides all the vessels that enter into the brain. The PCP growth parallels that of the brain. At any time in prenatal and postnatal developmental, the PCP covers the expanding cortical surface and provides all the perforating

**Table 1:** The table illustrates the human cerebral cortexmeninges outer, intermediate and inner lamellae vascular compartments and their specific vessels. Throughout life, all vessels that enter into the developing brain originate in the pial capillary plexus.

| **Human cerebral cortex vascular components** |
|---|
| 1. Extracerebral or meningeal compartment |
| (a) Dural lamella: main venous sinuses |
| (b) Arachnoidal lamella: main arteries and veins |
| (c) Pial lamella: pial capillary anastomotic plexus |
| 2. Intracerebral extrinsic microvascular compartment * |
| (a) All perforating pial capillaries (eventually arterioles and venules) |
| (b) The establishment of the Virchow-Robin Compartment around each perforating vessel. The cerebral cortex sole drainage (prelymphatic) system |
| 3. Intracerebral intrinsic microvascular compartment * |
| (a) Anastomotic capillary plexus established between contiguous perforators. |
| (b) Blood-Brain Barrier (BBB) of human (and mammalian) neocortex |
| * Both, the brain extrinsic (directly) and the intrinsic (indirectly) microvascular compartments evolve from the pial capillary anastomotic plexus |

vessels. The PCP is first recognized in human embryos at 6-week-gestation (Figure 1A, B). At this early age, it already covers the cortex entire surface and many of its red cells are still nucleated (Figure 1A). At this age, the human cerebral cortex is at the primordial stage of development with recognizable Cajal-Retzius cells, other neuronal typesand afferent fibers all of extracortical origin and is still unvascularized (Figure 1A, B). Pial capillaries start entering into the cortex between the seventh and eighth week of gestation, coinciding with the arrival of pyramidal neurons at first lamina [12-14,18].

Despite the PCP importance, it is not described in most Embryology and Neuroanatomy textbook [19-21]. In Padget classic and beautifully illustrated developmental studies of the human meninges arterial and venous systems, the PCP is not mentioned [22,23]. Why such an important meningeal vascular compartment has not been previously recognized is puzzling. The smooth and avascular image of the brain surface, without meninges, is universally recognized (Figure 1B). Considering that the cortex gray matter has one of the richer microvascular systems of the body it's apparently a vascular surface becomes puzzling. Two possible explanations came to mind. Pial capillaries are microscopic (raging between 5 and 7 micrometers in diameter) and therefore invisible to the naked eye, while the other meningeal vascular components are not. A good magnifying glass (or a microscope) is needed to recognize them. Second, the meninges removal customarily and universally carried out prior to any brain examination will render its surface apparently avascular as the PCP is removed with the discarded meninges. Moreover, the absence of visible blood vessels extends to the pons, cerebellum, medulla and spinal cord surface deprived of meninges (Figure 1B). The absence of visible blood vessels applies to the brain of any mammal deprived of meninges.

The use of a good magnifying glass solves the puzzle as it demonstrates the presence of innumerable small orifices throughout the cortical surface with a severed (by the meninges removal) perforating vessel on each one. Anyone with a good magnifying glass could confirm this observation. At any prenatal and/or postnatal age, the separation between these orifices

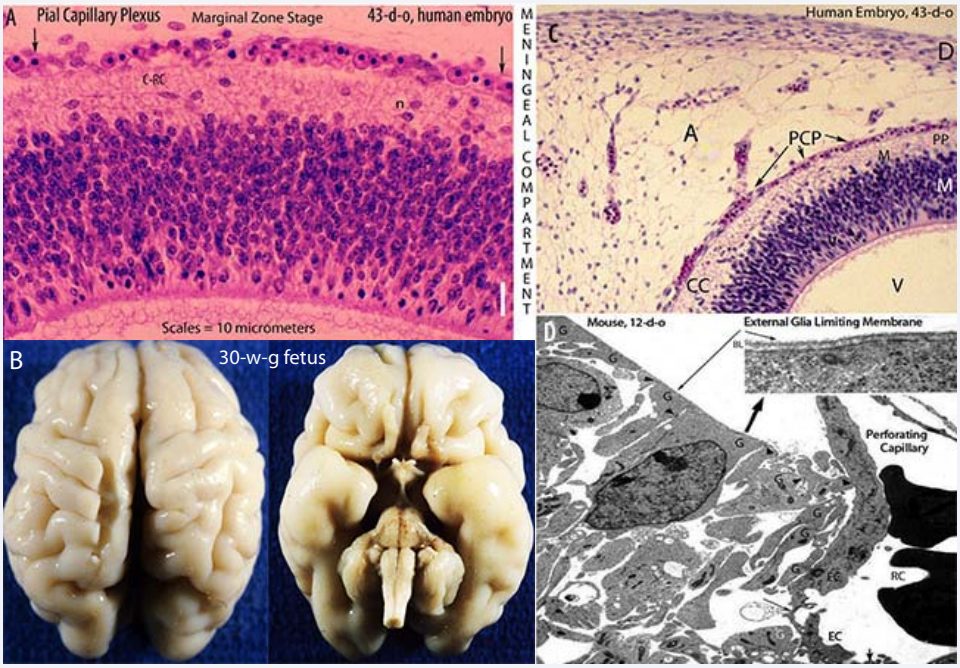


**Figure 1** Composite figure of photomicrographs illustrating various aspects of the human brain microvascular system (A, B, C) and of a mouse embryo (D). A. Detail of the cortex of a 43-d-o human embryo showing the pial capillary plexus with nucleated red cells covering its surface (arrows). At this age, the cerebral cortex is at the primordial stage with Cajal-Retzius (C-R), other neurons (n) and a hypercellular matrix zone. Scale = 10µm. B. Dorsal and ventral views of the smooth and apparently avascular surface of the brain of a 30-w-o human fetus. The lack of visible blood vessel extends to the pons, cerebellum and spinal cord. C. Detail of the meninges covering the cortex of a 43-d-o human embryo showing its three vascular compartments: the dural lamella (D) with the venous sinuses, the arachnoidal one (A) with arteries and veins and the inner one with the pial capillary plexus (PCP, arrows). The cortex (CC) at its primordial developmental stage (PP) overlies the hypercellular matrix (M). The ventricle (V) is also shown. D. Detail a pial perforating vessel entering into the cortex of a 12-d-o mouse, the insert (arrow) shows, at higher magnification, the basal lamina of the cortex external glial limiting membrane manufactured by radial glial endfeet.

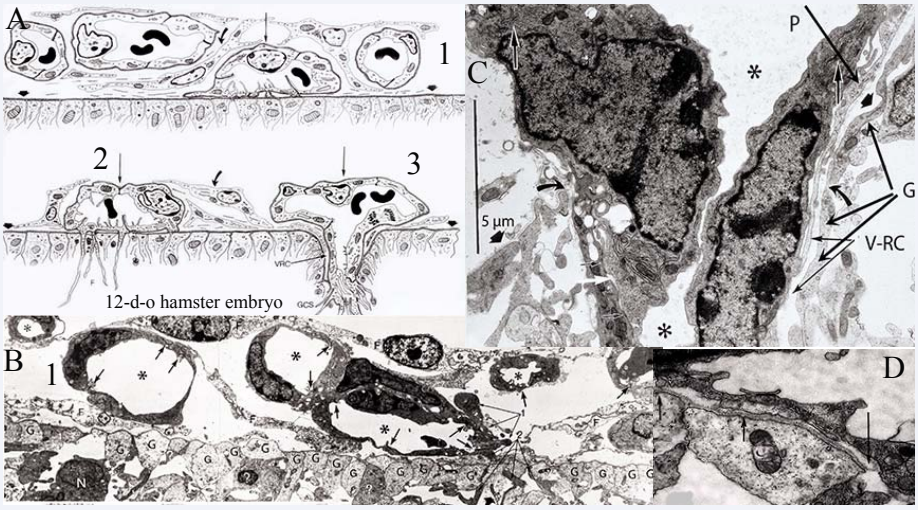


**Figure 2** Composite figure of electron microscopy photomicrographs illustrating the developmental processes (A, B, C, D, E) involve in the cortex perforation by pial capillaries. A. Schematic illustration showing the three stages of the cortex' microvascularization by pial capillaries: capillary contact (1) with the cortex EGLM with fusion of basal laminae, endothelial cell filopodia penetration (2) into the cortex through the fused basal laminae; and, pial capillary penetration into the cortex (3) with formation of the Virchow-Robin Compartment. B. Electron photomicrograph showing the cortex external glial limiting membrane composed of joined radial glial endfeet (G) covered by basal lamina and several pial capillaries (*) of different calibers. One of the capillaries has established contact with the cortical surface and some of its endothelial cell filopodia have penetrated into the nervous tissue (1 and 2 long arrows). The short arrows indicate endothelial cells junctions. C. Detail of the entrance of a pial capillary (*) into the cortex with the formation of the Virchows-Robin Compartment (V-RC), the perivascular space lined by glial endfeet (G) and the entrance of a meningeal pericytes (P) into the perivascular space. Scale 5µm. D. Detail of the fussed vascular and brain basal laminae (arrows) and the formation of a funnel (long arrow) that will accompany the pial capillary into the nervous tissue and establish the V-RC.

ranges between 400 to 600 μm throughout the cortex surface. The equidistant separation of these vascular opening and hence that of the perforating vessels could represent a biological constant necessary for gray matter neurons functional activity through the brain [12-14]. The roughly 500-μm. distances between the cortex perforators are comparable to the width of Mountcastle functional columns of the gray matter [24].

1. Pial Capillary Penetration into Developing Cortex.

The cortex' vascularization is a developmental process that involves two different elements: blood capillaries of mesodermal origin and the cortex of neuroectodermal origin, each one with its own basal lamina. The cerebral cortex is covered by the external glial limiting membrane (EGLM) formed by radial glial endfeet united by junctions covered by basal lamina manufactured by them. The EGLM demarcates the cortex (and CNS) from surrounding tissues and persists throughout life. The cortex' EGLM can only be perforated by entering pial capillaries, while in other brain regions it can also be perforated by entering as well as by exiting nerves.

To enter into the cortex, pial capillaries must perforate through its EGLM (Figures 1D, 2A, B, C). Electron microscopic studies of this even demonstrated that it is characterized by three interrelated processes, namely: a) pial capillary approach and contact with the cortex with fusion of both capillary and EGLM basal laminae (Figure 2A, B, C); b) endothelial cell filopodia penetration into the nervous tissue through the fused laminae establishing a funnels that remains open to the meningeal interstitium (Figure 2A, E); and, c) pial capillary penetration into the brain with the formation of the Virchow-Robin perivascular compartment (Figures 1D, 2A, D).

Pial capillaries although capable of entering the brain are incapable of exiting it [13]. Circulatory dynamic will determine which ones will be entering arterial vessels and which will be exiting venous one. Their ratio changes during cortical maturation responding to functional demands. In the newborn brain, each exiting venous vessels is surrounded by 6 to 8 entering arterial ones. This ratio will continue to change in the course of the cortex postnatal functional maturation.

The fused basal laminae form a funnel that accompanies the perforating vessel into the brain (Figure, 2A, E). This funnel becomes the Virchow-Robin Compartment (VRC). Its outer glial wall is formed by the ongoing incorporation of glial endfeet and it elongates into the developing brain, accompany the perforating vessel, and while remaining open to the meningeal interstitium (Figure, 2A, D). The cortex EGLM seems extends around the perforating vessel by additional glial endfeet also covered by basal lamina (Figure, 2D). The V-RC outer glial wall keeps the perforation vessel extrinsic (outside) to the nervous tissue, while remaining open to the meningeal interstitium (Figure, 2A, D). Meningeal cellular elements (pericytes) enter into the V-RC accompanying the vessel (Figure, 2D). Eventually, some of them are transformed into the smooth muscles of perforating vessels. Macrophages are capable of entering and exiting VRCs.

VRCs remain open to the meningeal interstitium and serve as the cortex sole drainage system, as mammals' cortex is deprived of a lymphatic system. Eventually, the V-RC drains through the meninges interstitium into the perivascular lymphatic [13-15]. During brain normal (physiological) functional activity, the V-RC drainage capability (day and night) is adequate and effective. However, it becomes inefficient in some pathological conditions, especially in degenerative encephalopathies [15]. In degenerative encephalopathies, unremoved necrotic debris accumulates throughout the cortex causing progressive and diffuse neuronal damage, perhaps explaining their progressive clinical worsening and eventual dementia [15].

During prenatal and postnatal developments, pial capillaries continue to enter into the cortex at regular intervals, ranging between 400 and 600 μm. Therefore, their number wills increases progressively paralleling the cortex prenatal and postnatal expansions. Considering that pial capillaries enter the cortex roughly at 500 μm intervals and knowing the cortex progressive surface expansion [25], it may be possible to roughly calculate the number of perforators at different ages. Such that the number of perforators might be around 380 at 14-week-gestation, 14,000 by birth time and 23,000 in the adult brain. All the perforating vessels of the cortex represent its extrinsic microvascular compartment as they are outside the nervous tissue (Table 1). Perforating vessels, despite their large number, represent but a small component of the cortex microvascular system [11-13]. Undoubtedly, the rapid Golgi method is the best staining procedure to study the brain microvascular system [12-14].

2. Human Cerebral Cortex Microvascular System Composition and Organization

The pial vessels with their corresponding VRCs penetrate vertically into the gray and white matters and extend into the periventricular region. Capillary anastomotic plexuses will interconnects all perforating vessels throughout the brain (Figure 3B). The gray matter vascularization commences at 16-w-g, through its deeper and older pyramidal cell stratum and will ascend through its upper strata during its functional maturation [12]. By birth time, the entire gray matter is vascularized by anastomotic capillary plexuses between contiguous perforators (Figure 3A, B). While pial perforators will remain, for life, extrinsic (outside) to the nervous tissue, the anastomotic capillary plexuses between them represent the brain intrinsic microvascular system representing its essential functional system (Figure 3B). Perforating vessels are more abundant in the cortex gray matter than in the white matter. Moreover, the anastomotic plexus between perforators has more capillaries and smaller intercapillary spaces in the gray matter, where neurons reside, than in the white matter (Figure 3A, B). This fact reflects their different functional roles and explains the different vulnerability to perinatal brain damage. In perinatal hypoxic and/or ischemic brain damages, the gray matter is less vulnerable than the white matter [10,11].

Capillaries emerge from the perforating vessel, cross the VRC and must perforate through it outer glial wall to enter the nervous tissue (Figure 3B). Since the VRC outer wall is composed of joined glial endfeet covered by basal lamina, the capillary perforation through it may be a process similar to the original capillary perforation of the cortex EGLM [13]. Capillaries entering into the nervous tissue carry a single basal lamina possibly of glial

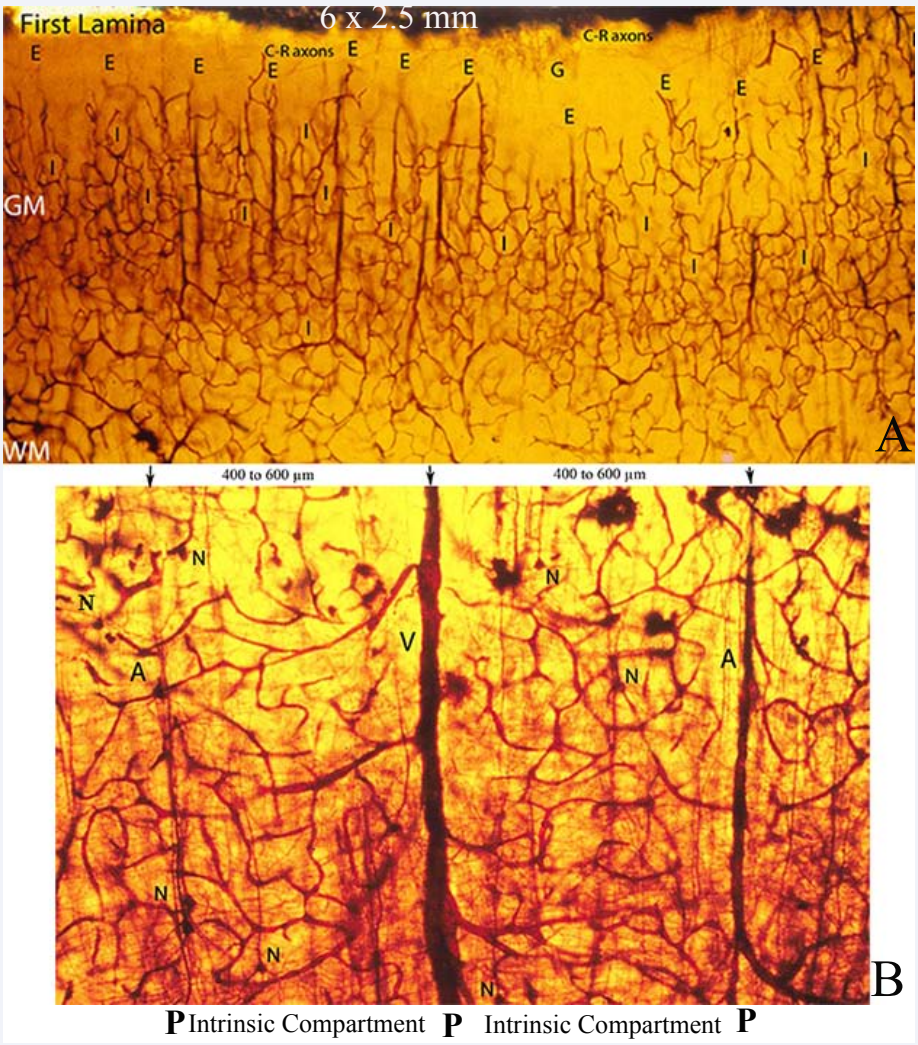


**Figure 3** Composite figure of color photomicrographs illustrating low (A) and high (B) power views of the cortex microvascular system from rapid Golgi preparations of a newborn infant motor cortex. A. Low power view of a rectangular area (6 by 2.5 mm) of the motor cortex showing the numerous equidistant perforating extrinsic (E) vessel through the gray (GM) and white matter (WM) and the anastomotic plexus of intrinsic capillaries (I) establishes among them. There are more perforating extrinsic vessels and more intrinsic capillaries throughout the gray matter, where neurons resided, than throughout the white matter essentially composed of axonic fibers and a few and scattered neurons. These vascular differences explain their different vulnerability to perinatal brain damage. B. Detail of the anastomotic plexus of intrinsic capillaries established between an exiting venous vessel (V) and two contiguous arterial ones (A) showing the large number of intrinsic capillaries and intercapillary spaces where neuron (N) reside. Intrinsic capillaries exit from both arterial and venous perforating vessels, as they are incapable of reentering them. Circulatory dynamics will determine which ones become arterial and which ones venous. The intrinsic capillaries together with local neurons, glial cells and axonic terminals represent the functional operating center of any region throughout the cerebral cortex.

origin. Emerging capillaries from perforating vessels although capable of entering into the nervous tissue they are incapable of re-entering the perforating vessels. Circulatory dynamic determines which capillaries will be arterial ones and which ones venous. Their ratio will change continuously reflecting the local neurons functional needs. In the anastomotic plexus all vessels are capillaries ranging from 5 to 7 µm in diameter. Their length ranges between 10 to 15 µm. Some are longer than others; the shorter ones are those involve in the formation of capillary loops between cortical strata [13,14]. The intrinsic capillaries are renewed throughout life.

The intrinsic microvascular compartment represents the brain functional center of each region (Figure 4). Within the short-linked capillary anastomotic plexus, neurons, protoplasmic astrocytes and axonic terminals reside maintaining close anatomical and functional interrelationships (Figure 4). Local neurons, protoplasmic astrocytes and capillaries interchange information that will determine the blood flow through the region in response to its neurons functional activity (Figure 4). There are, probably, more functional capillaries in the gray matter intrinsic microvascular compartment that anywhere else in the body. During cortical maturation, the arterial and/or venous nature of the intrinsic capillaries constantly changes adapting to the each region functional need. The intrinsic microvascular compartment together with the neurons, axonic terminals and protoplasmic astrocytes could very well be one of the most active

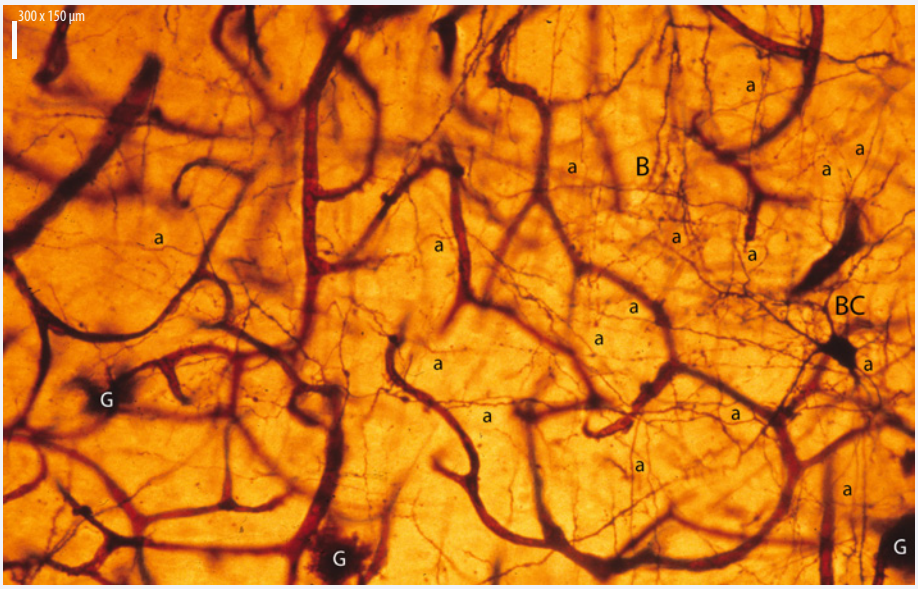


**Figure 4** High power microscopic view of the intrinsic capillary plexus of a newborn motor cortex showing its composition and the interrelationships among blood capillaries, neurons (BC), protoplasmic astrocytes (G) and axonic (a) terminals, from rapid Golgi preparations. The area represents a rectangular zone of the gray matter measuring 300 x 150 micrometers. Neurons, glial cells, capillaries and axonic terminals (synapses) interchange information that will determined the blood flow throuth the region in response to its neurons functional demands. It should be pointed out that if all neurons, glial cells and axonic terminals of this region were stained it will be completely black and useless. Such cortical regions represent local functional centers that could operate independently or in combination with others, proximal as well as distant ones.

functional systems of the body. The functional capabilities as well as the vulnerability of this complex microvascular compartment are significant and must also have, mostly unknown, physiological safeguards. Its dysfunction might underlay many subclinical and clinical neurological disorders primary and/or secondary to perinatal brain damage. Additional studies are needed to elucidate these questions.

The cortex microvascular system has two different venous drainage routes: a superficial and rapid one for the gray matter (where neurons reside) and a deep and slow one for the white matter deep penetrating vessels. Through the gray matter, blood circulates rapidly, entering through local arterial perforators and exiting through contiguous venous ones. These vessels are tributary of meninges arachnoidal arterial and venous system, respectively. In the newborn cortex, each exiting venous vessels is surrounded by 6 to 8 entering arterial ones. Blood circulate independently supplying the functional needs any cortical region. Moreover, local neuronal-glial assemblages are capable of controlling independently the blood flow of their vascular territories in response to the functional activity of local neurons. Magnetic resonance image brain studies employ this property to localized functionally active cortical areas.

The perforating vessels that have penetrated deeply into the white matter will use a different and slower venous drainage route. Deep perforators drain through the dual veins of Rosenthal and their tributaries. The Rosenthal veins are united by anterior and posterior communicants and receive anterior, medial and posterior tributary veins establishing the brain ventral venous circle. The meningeal ventral venous system drains into the dural venous sinuses through the Ampulla of Galeni [26].

The cortex microvascular system composition, organization and functional activity remain essentially unchanged during its entire prenatal and postnatal maturations. It is remarkable, that the extrinsic and intrinsic microvascular compartments remain essentially identical in newborn and adult brains [12,13]. Despite the fact that adult are three times larger than newborn brains. Additional studies of the nature and functional relevance of the human cortex intrinsic microvascular compartment are needed in both the normal brain as well as in the altered one by disease.

## Perinatal Brain Hemorrhagic Damage

The cortex microvascular system is invariable involve in any type of perinatal brain damage. A variety of factors (hypoxia, ischemia and/or trauma) would interfere with cortical development and result in local hemorrhagic lesions. In brain damage, as in any other region, cells (neurons of glia), blood vessels and fibers may be lethally and/or partially affected. Death neurons will be reabsorbed and eliminated and will cause no symptoms. However, partially damaged ones survive and undergo morphological and functional transformations that could contribute in later-life neurological sequelae. Damaged axonic terminals will also regenerate but will encounter a transformed region as well as modified functional targets. Damaged local capillaries also regenerate but as post-inflammatory one that will lack the functional efficiency of the intrinsic ones. Damaged local protoplasmic astrocytes will also regenerate but as fibrillar astrocytes that participate in the affected region glial scarring (Figure 6D). Fibrillary astrocytes do not have the functional efficiency of protoplasmic ones and will lack the needed interrelationship with capillaries for controlling the flow of blood through the region. These alterations may become permanent features of any damaged area. A repaired lesion could also affect

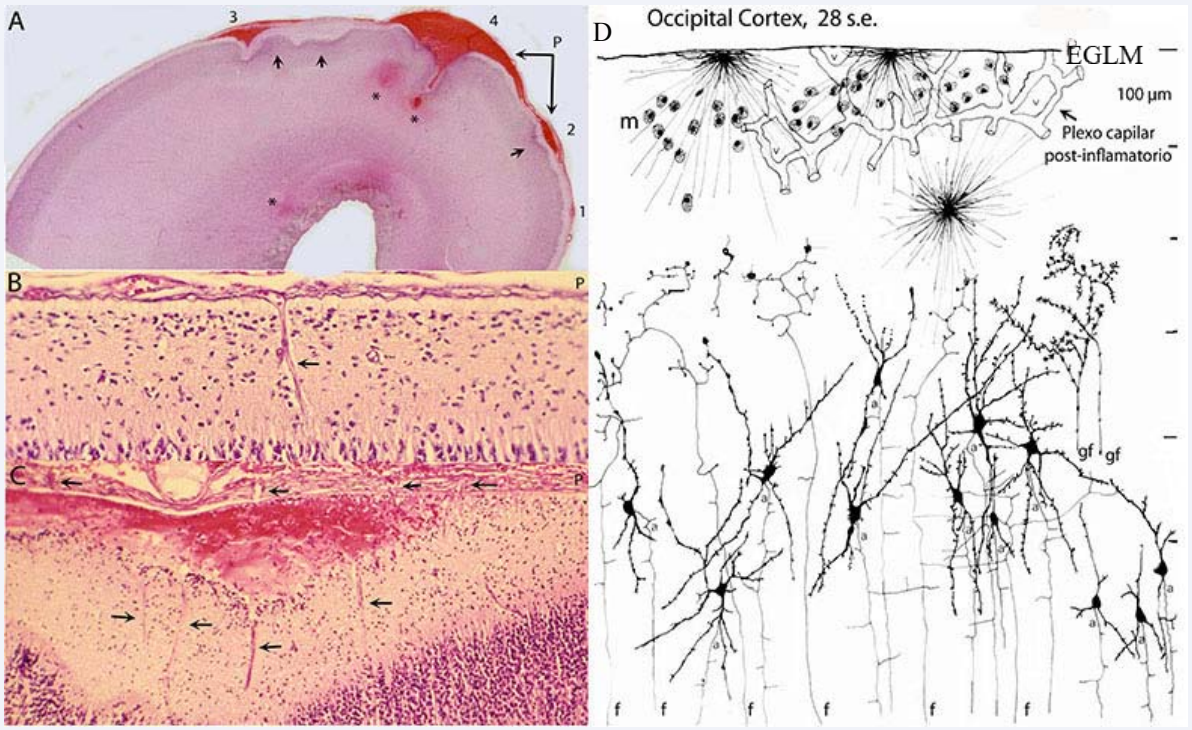


**Figure 5** Composite figure of color photomicrographs (A, B, C) of H&E preparations of the cerebral cortex of infants with subpial hemorrhages secondary to perinatal brain damage and a composite drawing (D) of a repaired lesion. A. The size of subpial hemorrhages ranges from microscopic (1) to visible ones (2, 3, 4). The underlying gray matter is invariable affected and deformed. The cortex EGLM is often ruptured and the bleed extent into the leptomeningeal space (4). They are often accompanied by local gray matter (*) and periventricular (*) hemorrhages. B. Early stages of pial damage are characterized by radial glial endfeet edema with elongation of the perforating vessels. C. Subpial hemorrhages are caused by the rupture of local perforating vessels (arrows) and involve the first lamina and the underlying gray matter components. D. Composite figure of camera lucida drawings from repaired subpial hemorrhages showing fibrous astrocytes that have replaced damaged protoplasmic ones, a post-inflammatory capillary plexus and numerous hemosiderin laden' macrophages. The pyramidal neurons terminal dendrites, within the first lamina, are destroyed (amputated) by the hemorrhage. Some dendrotomized pyramidal neurons survive and are transformed into irregular stellate neurons. Axonic (f) and radial glial fibers (gf) terminals, destroyed by the bleed, also regenerate but will encounter their targets transformed. Eventually a permanent cortical lesion, anatomically and functionally abnormal, develops at the hemorrhage site.

proximal and distal regions interconnected with it [9-11]. This ongoing process could play a role in the pathogenesis of clinical sequelae secondary to perinatal brain damage.

Hemorrhagic brain damage often involves regions that have vulnerable capillaries such as the pial and periventricular regions. The temporal vulnerability of these regions blood vessels explains the frequent occurrence and multiple locations of hemorrhages at those sites [9].

**Subpial Hemorrhages:** Growing pial capillaries involve in the cortex vascularization are particularly vulnerable. Subpial hemorrhages are frequent and often multiples in premature infants with respiratory difficulties (Figure 5A). They range from microscopic to visible ones (Figure 5A). An early sign of EGLM damage is glial endfeet edema that causes elongation of local perforating vessels (Figure 5B). If the edema persists rupture of local perforating vessels occurs resulting in subpial hemorrhages (Figure 5C, arrows). Invariably, the underlying gray matter will be affected and deformed (Figure 5A). Subpial hemorrhages damage the terminal dendrites of local pyramidal neurons, the afferent fibers terminals, the radial glia and first lamina components. Local dendrotomized pyramidal cells, afferent fibers and radial glial fibers survive throughout the region (Figure 5D). Surviving dendrotomized pyramidal neurons are transformed into irregular stellate neurons (Figure 5D). Regenerating afferent fibers terminals will encounter locally transformed functional target (Figure 5D). Regenerating radial glial fibers endfeet participate in the reparation and reconstruction of the damaged EGLM. Eventually, the first lamina will be transformed into a permanently altered local lesion both anatomically and functionally [9-11].

In pial hemorrhages, the cortex EGLM is invariably damage resulting in local disruptions as well as ruptures. Small EGLM ruptures are rapidly repaired by the incorporation of additional radial glial endfeet. However, larger EGLM ruptures will take longer and may allow gray matter element (neurons, axons and radial glial) to scape into the leptomeninges resulting in permanent local heterotopias (LMHs) within the meningeal space. Their size ranges from small to large ones depending on the extent of the original injury. The larger ones are visible to the naked eye and are often associated with epilepsy [9,10].

The gray matter underlying LMHs is invariably deformed. The first lamina is often obliterated by the displacement of gray matter elements into it, some of which could penetrate into the meninges [9,11]. Ascending afferent fibers, radial glia, gray

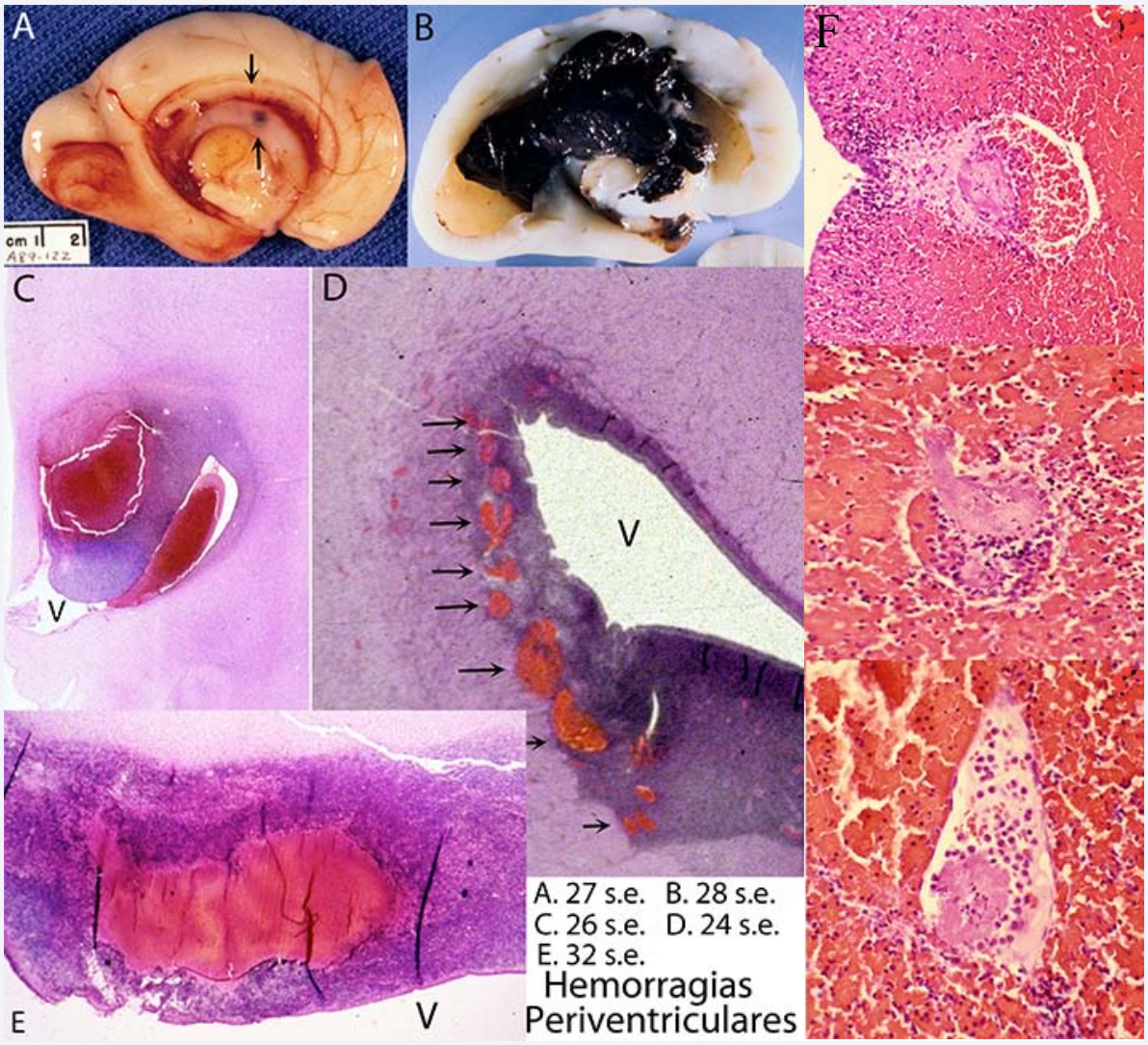


**Figure 6** Composite figure of color photomicrographs illustrating the variable neuropathology of periventricular hemorrhages (A-E) of children born prematurely. Examples of small (A), large (B, C) and confluent (E) periventricular hemorrhages are shown. D. This case illustrates the multifocal nature (arrows) of early periventricular hemorrhages. Early multifocal hemorrhages have a tendency to coalesce into larger and devastating ones (B, C, E). F. Three microscopic views of early periventricular hemorrhages showing the damaged vessels with focal endothelial cell necrosis fibrin thrombus formation rupture of the wall and local perivascular bleeds. One of the damaged vessels (middle one) shows an ejection of the fibrin thrombus through the rupture vessel wall. The three damaged vessels are thin walled and relatively large (venous?). Are these damaged matrix vessels regressing? Key: s.e. = week of gestation

matter neurons, blood vessels and astrocytes may be displaced into the heterotopia establishing permanent leptomeningeal heterotopias. Damaged capillaries through the affected region are transformed into post-inflammatory ones that will lack the functional efficiency of the intrinsic ones. The transformed cortical region may have an abnormal functional activity often detectable by fMIRs and electroencephalography. It could also affect the functional activity of neighboring as well as distant regions functionally interconnected with it. Their altered functional could eventually underlie the pathogenesis of ensuing subclinical as well as clinical neurological disorders, including epilepsy [9,16,17].

**Periventricular Matrix Hemorrhages:** The developing brain periventricular matrix zone is a hypercellular and well-vascularized region. Perforating vessels establish an anastomotic plexus of thin-walled vessels throughout the matrix zone. These vessels have incomplete basal lamina and are either sprouting and/or regressing. Vessel regression (reabsorption) occurs as matrix cells are leaving the zone. The matrix zone reaches its greater width and number of cells around the 26$^{th}$, 28$^{th}$ of gestation. After this gestational age, the number of cells and the zone thickness start to diminish as many of its cells migrate toward upper cortical regions. Regressing (reabsorbing) matrix vessels are particularly vulnerable to perinatal brain damage resulting in periventricular hemorrhages which are often multiple (Figure 6D. arrows).

Periventricular hemorrhages have a tendency to coalesce into larger and devastating ones (Figure 6C, E). Larger hemorrhages

may damage the ependymal epithelium resulting in lethal intraventricular bleed (Figure 6B, C). Some may be visible to the naked eye (Figure 6A). Neuropathologic studies of larger hemorrhages are fruitless as everything in them is destroyed and their original etiology obliterated.

To explore the etiology of periventricular hemorrhages is necessary to locate and study early microscopic bleeds with minimal tissue destruction and, hopefully, with the originally damage vessel still recognizable (Figure 6F). Originally damaged matrix vessels are relatively large, thin walled and venous in nature [9]. Early damaged vessels show focal endothelial cell necrosis, rupture of the vessel wall, fibrin thrombus formation and perivascular bleeds (Figure 6F). Ejection of the fibrin thrombi through the rupture vessels wall has been occasionally observed in these early bleeds (Figure 6F). Primary endothelial cell damage with local rupture of the vessels wall is considered to be the underlying cause of most periventricular hemorrhages. Both hypoxia and the vessel temporary vulnerability are contributory factors [9].

Everything within the hemorrhagic site is destroyed, including local matrix cells, radial glial fibers as well as already migrating cells. Consequently any subsequent ascending migration of matrix cells will cease. During the lesion repair, a post-injury capillary plexus is formed throughout the affected region surrounded by debris-removing macrophages and other irregular glial elements [9]. After the removal of the necrotic debris by macrophages, the ependymal epithelium will be repaired by surviving local ependymal cells and fibrillary astrocytes will fill the affected zone and contribute to its scarring. The retraction balls of damage radial fibers of are recognized throughout the damage region. Some matrix cells may survive and could be the source of, later-life, periventricular heterotopias.

The most important sequelae of matrix zone hemorrhages in the formation of local heterotopias by the surviving residual matrix zone cells (Figure 7B). Periventricular heterotopias are composed of groups of irregular neurons, axonic terminals and glial cells [10,16,17]. They establish their own microvascular system, receive afferent fibers from the adjacent white matter and send axonic terminals into it [17]. They become permanent lesions that could interfere with brain. They have been frequently described in later-life epilepsy [10,11,17].

## Perinatal Brain White Matter Ischemic Damage

The perinatal ischemic damage involves primarily the white matter resulting in a massive destruction of afferent and efferent fibers throughout the region with significant repercussions on the overlying, often unharmed, gray matter, where neurons reside. White matter infarct is common in older premature and newborn infants who suffered perinatal asphyxia, vascular disturbances and/or trauma. The neuropathology of white matter infarcts of the developing brain has been amply documented [1,2,4,6-8,10,27]. The neuropathology of the surviving gray matter overlying white matter infarcts has also been recently documented [10,11]. Extensive white matter infarcts are often associated, later-life, with neurological sequelae, such as epilepsy and cerebral palsy.

Different types, sizes, locations, degrees of damage and different nomenclatures have been used to describe white matter infarcts in the neonatal brain (Figure 7A-E). The clinical relevance of these differences is relative and could be the source of misconceptions. What is important to know about any white matter infarct are three essential features shared all of them regardless of size, location and variable nomenclature. First, axonic fibers (afferent as well as efferent) through the affected region are destroyed, degraded and removed by macrophages resulting in empty cavities of variable sizes, often crossed by trabeculae containing blood vessels and residual axonic fibers. Second, the overlying gray matter often survives due to its unique and independent microvascular system (Figure 7F, G). Third, the surviving gray matter (where neurons reside) becomes functionally disconnected from the rest of the brain incapable of receiving and/or sending inputs, at least temporarily. From neuropathological and clinical perspectives, the third feature is the most important as it my relevant to the clinical outcome of white matter infarcts.

## Perinatal Brain Gray Matter Damage

Because of its unique microvascular system, the gray matter frequently survives white matter infarcts (Figure 7A-E). An anastomotic venous plexus is established bordering the damage white matter that interconnects all the perforating vessels permitting the blood to circulation throughout the region (Figure 7F, G). The circulating blood will supply all the functional needs of the surviving gray matter neurons. Local neuronal and glial assemblages within the surviving gray matter may still be capable of controlling the local blood flow in response to its neuronal functional demands.

The amount of surviving gray matter overlying white matter infarcts varies depending on the damage extent. In many cases, the entire gray matter survives and these are optimal cases to be studied the evolution (pathologic as well as clinical) of the surviving gray matter. In other cases, the gray matter is partially damaged and only its upper strata (layers) survive. In some cases a significant portion of the overlying gray matter may be destroyed. In cases in which only the first lamina survives, Cajal-Retzius cells and their long axonic fibers can be recognized. These neurons long axonic processes could interconnect the damaged region with neighboring undamaged and carry clinical implications [11].

In recent (days-weeks) white matter infarcts the structural organization and the essential neuronal morphology of the overlying surviving gray matter is still unaltered. The morphology of pyramidal neurons including the deep axotomized ones by the infarct remains essentially unaltered. Cajal-Retzius, pyramidal, by tufted and baskets cells are also recognized as well as the gray matter essential lamination. The proximal axonic collaterals of deep axotomized pyramidal neurons survived and project either toward upper gray matter regions and/or bordering the necrotic zone for considerable distances. In old infarcts (months-years) the structural organization of the overlying gray matter in significantly altered, the laminations are obliterated and the morphology of many of its neurons has been altered. Scattered large (hypertrophic) neurons identified as basket cells by the formation of pericellular nests around pyramidal cells somas are a prominent features of the surviving gray matter. Unusually

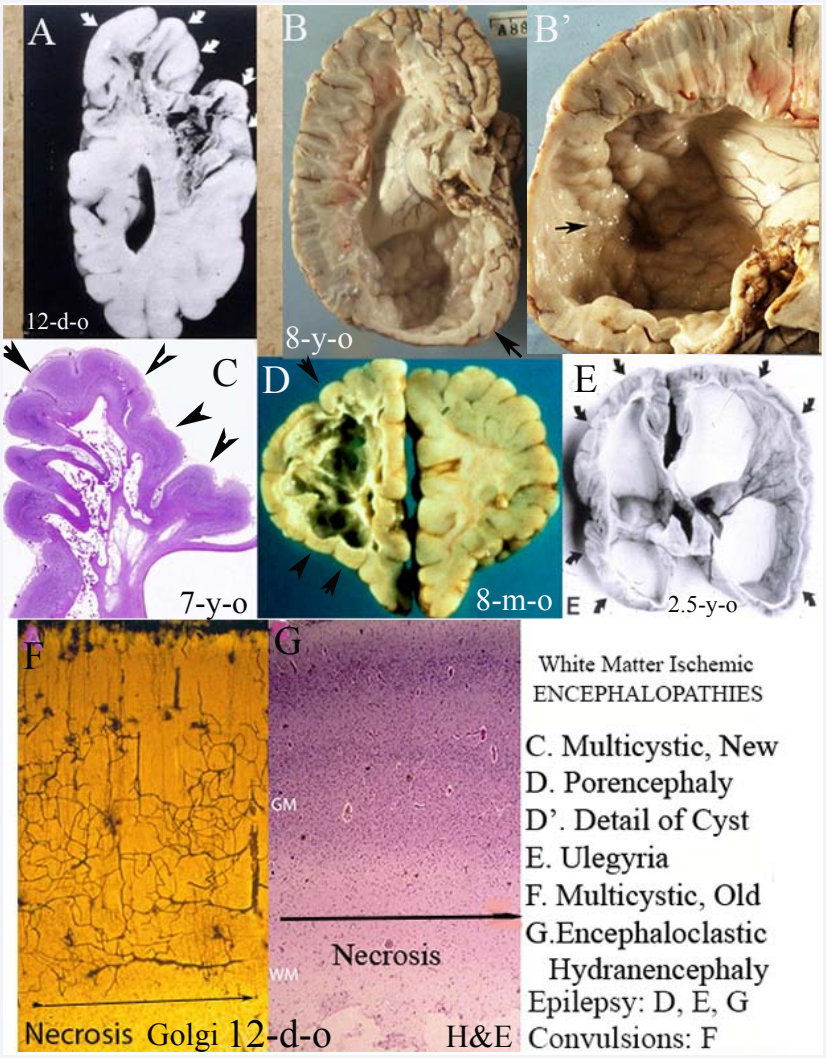


**Figure 7** Composite figures of photomicrographs illustrating the variable neuropathologic features of white matter ischemic damage, including: a recent multicystic (A), an occipital porencephaly (B), an ulegyria (C), an old multicystic (D), and an encephaloclastic hydranencephaly (E) encephalopathies. Despite the different degrees of white matter damage and the different nomenclatures used, they are all characterized by the massive destruction of afferent and efferent axonic, the formation of residual cystic cavities and the survival of the overlying gray matter, where neurons reside, regardless of the extent of the original damage. The gray matter unique microvascular system protects its neurons despite of been anatomically and functionally disconnected and incapable of receiving or sending information. A venous anastomotic plexus is established (F) between the damaged white and the undamaged gray matters that interconnects all the perforating vessels and will permit the circulation of blood throughout the gray matter. In the surviving gray matter, blood circulates between local entering arterial perforators and exit through contiguous venous ones. This venous plexus can only be recognized using rapid Golgi preparations (F) since routine H&E ones (G) fail in demonstrating it. B'. View of the inside of the porencephalic cyst (B) showing several mounts that represent local gray matter sulcus deprived of white matter and smaller nodules (arrow) representing periventricular heterotopias.

large (hypertrophic) neurons have been often described in the cerebral cortex of children with epilepsy [11,28-31] including large inhibitory ones [32]. The surviving gray matter neuropil is also rich and complex due to an increase number of intrinsic interconnections among the surviving neurons deprived of afferent inputs by the white matter damaged. These morphological alterations imply functional ones as well [11].

Another interesting observation it the fact that the amputated axons of deep pyramidal neurons develops long horizontal axonic collaterals that extend bordering the damaged white matter and/or the residual cystic cavities [11]. This axonic collateral could eventually reach adjacent undamaged cortical regions and reestablish some new connections [11]. These long axonic collaterals could represent another possible connection between damaged and undamaged cortical regions. The possibility that some neurons from damaged gray matter could eventually establish functional contacts with adjacent undamaged regions is intriguing and clinically relevant and should be further investigated. It has been proposed such connections might be capable of altering the functional activity of adjacent unaffected cortical regions and, eventually, play a role in the pathogenesis of ensuing neurological sequelae [11]. Some of these gray matter alterations (acquired cortical dysplasia) have been associated with later-life epilepsy.

To study the clinical outcome of the surviving gray matter secondary to white matter infarcts, fresh postmortem brain tissue must be studied with an appropriate method such as the rapid Golgi procedure. Because few children die, the gathering of fresh brain material will take years to collect and hence only a few cases have been adequately studied [9-11,16,17]. Postmortem neuropathologic studies of the brains of children that survive any type of perinatal brain damage and later in life died should be encouraged because our understanding of their clinical outcome remains inadequate.

## CONCLUSION

The human cerebral cortex has two interconnected microvascular compartments: the extrinsic one represented by the perforating vessels and the intrinsic one represented by the anastomotic capillary plexus established between contiguous perforators. All perforating vessels remain within the Virchow-Robin Compartment (V-RC) and hence extrinsic (outside) to the nervous tissue. The V-RC remains open to the meningeal interstitium and serves as the brain sole drainage system as it lacks of a lymphatic system. While the V-RC pre lymphatic drainage capability is adequate for the brain normal functional activity it becomes inadequate in many degenerative encephalopathies. Unremoved necrotic debris became the source of progressive neuronal damage, perhaps explaining their clinical progression to an eventual dementia.

In the developing and the mature cerebral cortex, an equidistant distance that ranges from 400 to 600 μm separates perforating vessels from each other. The equidistant separation among the perforating vessels is considered to represent a biological constant needed for the functional activity of gray matter neurons. Neurons, axonic terminals, protoplasmic astrocytes and blood capillaries reside within the cortex intrinsic microvascular compartment. Together they represent the cortex functional control center of each region. Neuronal-glial assemblages are capable of controlling the local flow of blood responding to the activity of its local neurons. Each cortical region could function independently by controlling its own blood supply as well as in combination with others interconnected regions. Brain magnetic resonance image studies (fMRIs) employ this property.

Frequently, perinatal brain hypoxic and/or ischemic damage involves areas that, in the course of development, have vulnerable blood capillaries, such as the pial and periventricular regions. Pial capillaries involve in the process of entering into the cerebral cortex are particularly vulnerable at this stage. Reabsorbing (regressing) periventricular matrix vessels are also vulnerable to perinatal brain damage. For these reasons, pial and periventricular hemorrhagic lesions are often multiple. Contrarily, ischemic (infarcts) damage frequently occurs in the white matter because it has fewer perforating vessels, fewer intrinsic capillaries and larger intercapillary spaces than the gray matter. In perinatal brain damage, the gray matter (where neurons reside) is often protected because of its unique microvascular system. In the gray matter blood circulates rapidly entering through local arterial perforators and exiting through contiguous venous ones. Deep perforators that penetrate into de white matter have a different venous drainage route through the veins of Rosenthal and the ventral meningeal venous circle.

Any type of perinatal brain injury will be eventually repaired and result in permanent cortical lesions. Surviving neurons, axonic terminals, intrinsic neuropil and intrinsic capillaries are progressively transformed. A post-inflammatory vascular plexus will replace the damaged capillaries of the affected region. This plexus vessels lack the functional capabilities of the intrinsic capillaries. Damaged gray matter protoplasmic astrocytes will be also replaced by fibrous ones that participate in the affected region' glial scarring. Fibrous astrocytes lack the functional efficiency of protoplasmic ones and may be unable of controlling the blood flow (in conjunction with neurons) throughout the affected region. Any repaired cortical lesion become permanently altered both anatomically and functionally implicating some clinical unbalances.

Any repaired cortical lesion (secondary to perinatal brain damage) could eventually disturb proximal as well as distant cortical regions functionally interconnected with it and encroaching on their functional activity. Eventually, the whole brain functional activity might be more or less disturbed. This ongoing mechanism could play a role in the pathogenesis of neurological disorders secondary to perinatal brain damage. These processes remains insufficiently studied and poorly understood and must be further investigated.

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