Review paper

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Ultrastructural alterations of human cortical capillary basement membrane in human brain oedema

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Abstract

The capillary basement membranes are examined in severe traumatic brain injuries, vascular malformation, congenital hydrocephalus and brain tumours. They exhibit homogeneous and nodular thickening, vacuolization, rarefaction, reduplication, and deposition of collagen fibers. Their average thickness varied according to the aetiology and severity of brain oedema. In moderate brain oedema the thickness ranged from 71.97 to 191.90 nm in width, and in patients with severe brain oedema it varied from 206.66 to 404.22 nm. The basement membrane complex appears apparently intact in moderate oedema, and shows glio-basal dissociation in severe oedema. In areas of highly increased cerebro-vascular permeability, the basement membrane shows matrix disorganization, reduplication, and bifurcations protruding toward the endothelial cells, and acting as abluminal transcapillary channels. In regions of total brain necrosis, its structural stability is lost showing loosening, dissolution and rupture. Basement membrane swelling is due to overhydration of its protein-complex glycoprotein matrix. The thickening, rarefaction and vacuolization are induced by the increased vacuolar and vesicular transendothelial transport. The degenerated basement membrane areas exhibit a finely granular precipitate interpreted as protein, proteoglycan, glycoprotein, and agrin degraded matrix.

Key words: *basement membrane, brain oedema, electron microscopy.*

Introduction

Brain oedema is an appropriate pathological condition for studying the fine ultrastructural alteration of capillary basement membrane [16]. This structure forms the second line permeability barrier of the anatomical and physiological blood-brain barrier [70]. In the animal central nervous system, the vascular basal lamina appears as a homogeneous structure with a density similar to that observed in glomerular lamina densa [25,29]. Numerous studies based on experimental and pathological conditions performed in several vertebrates, including man, have reported the following alterations of capillary basement membrane: thickening, rarefaction, vacuolization and reduplication [4,6,12,17,23,24,28,30,32,34,47-49,54-56, 58,60,61,67,78,79,83,91]. Deposition of collagen in the basement membrane after arterial hypertension was reported by Garcia *et al*. [35], in rats after 10-minute cardiac arrest [87], in cerebral hypoperfusion considered as a risk factor for Alzheimer's disease [26], and after traumatic brain injury in the rat cerebral cortex [88]. Thickening of capillary endothelial cell basement

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membrane has been found as the most characteristic morphologic feature of diabetic microangiopathy [12,42,50], in hypertension combined with diabetes [43], and in galactosaemic rats [31]. There also is thickening of the basement membrane covering a non-vascular cell of nerve, the perineural cells [41]. Thickening of the basement membrane of cortical capillaries has also been reported in Alzheimer's disease [57,59,68,69,72,74,93], scleroderma and Raynaud's disease [11], and in glomerular diseases [71]. In addition, age-related thickening of retinal capillary basement membrane was described earlier [64]. Berzin *et al*. [3] found that agrin is associated with heparan sulphate proteoglycans in the basement membrane, and that agrin and laminin fragmentation occurs in Alzheimer's disease. Inoue [39] and Inoue and Kisilevski [40] reported abundant microfibril-like β-amyloid in the basement membrane in the cerebrovascular amyloid angiopathy of Alzheimer's disease. Sehba *et al*. [75] demonstrated an acute loss of collagen IV from the cerebral microvasculature after aneurysmal subarachnoid haemorrhage.

Plesea *et al*. [67] found focal or circumferential capillary thickening due to densification of the type IV collagen material from the basement membrane structure in hypertensive cerebral haemorrhage. Schóller *et al*. [76] demonstrated basal lamina damage correlated with blood-brain barrier dysfunction following subarachnoid haemorrhage in rats. According to Wang *et al*. [86], damage to the basal lamina causes the dismantlement of microvascular wall structures, which in turn results in the increase of microvascular permeability, haemorrhagic transformation, brain oedema and compromise of the microcirculation. In animal models, ischaemia reperfusion (IR) injury triggers membrane lipid degradation and accumulation of lipoxidative exacerbations in the neurovascular unit, leading to blood-brain barrier damage and neurologic deficits [38]. Uranova *et al*. [81] found ultrastructural abnormalities of capillaries in schizophrenia included thickening and deformation of basal lamina. String vessels or collapsed empty basement membrane tubes devoid of endothelial cells, and considered acellular capillaries, are often associated with pathologies such as Alzheimer's disease, ischaemia, and irradiation, but are also found in normal human brains from preterm babies to the aged. This causes an age-related decline in cerebral angiogenesis and results in neuronal loss. These string capillaries can re-grow by proliferation and migration of endothelial cells into empty basement membrane tubes, which provide a structural scaffold, replete with signalling molecules [7]. Castejón [21] showed thin and fragmented basement membranes with areas of focal thickening in human congenital hydrocephalus. Castejón [22] also reported that hypertrophic pericytes induce basement membrane splitting in traumatic brain oedema.

The purpose of this review is to describe the alterations of capillary basement membrane in vascular anomaly, brain trauma, congenital hydrocephalus, and brain tumours. The following aspects are summarized: the basement membrane complex in an apparently normal basement membrane, the basement membrane thickness according to aetiology, degree of brain oedema, and age of the patients; the alterations of the basement membrane complex and the pathogenesis of glio-basal dissociation, and the transbasal membrane pathway for haematogenous oedema fluid. In addition, we have postulated a neurobiological interpretation of thickening, rarefaction and vacuolization of the basement membrane in the light of present knowledge on chemical composition of basement membrane, pathogenesis of vasogenic brain oedema, and the increased transendothelial vacuolar and vesicular transport. It is also important to make an evaluation of the structural stability of basement membrane in severe oedema and perivascular total brain necrosis, and to discuss the proliferation of collagen fibers into the basement membrane.

The normal capillary basement membrane

In human brain capillaries as observed in moderate oedematous regions of cortical biopsies of patients with vascular anomalies and congenital hydrocephalus, the basement membrane appears as a homogeneous, thin and continuous dense lamina due to its condensed filamentous pattern, embedded in a homogeneous matrix (Fig. 1).

Basal lamina splitting occurs in apparently normal areas, in which the cell body and the pericyte processes can be seen enclosed within the basal lamina compartments. This apparently normal capillary basement membrane closely resembles that observed in normal vertebrate [1,8,25,73], and invertebrate tissue [2]. In humans and in experimental animals, the basement membrane thickness varies from capillary to capillary, and even locally within a single

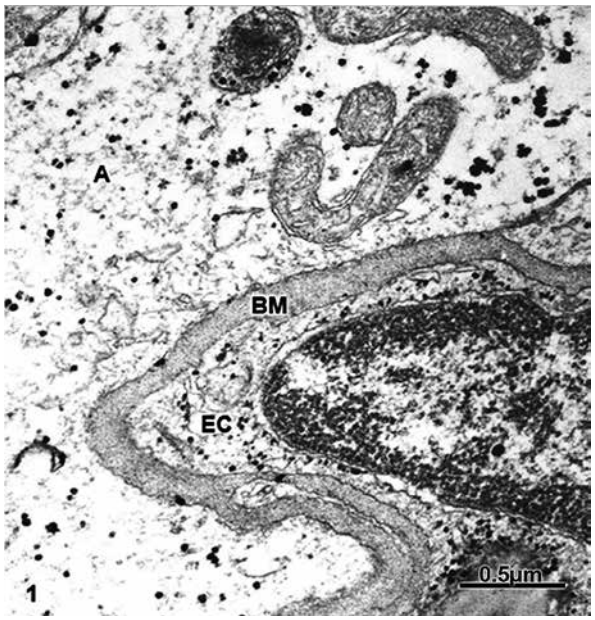

Fig. 1. Anomaly of the anterior cerebral artery. Right parietal cortex. Capillary from a moderate oedematous region showing an apparently normal basement membrane (BM) exhibiting a homogeneous dense matrix. The endothelial cell (EC) and the swollen astrocytic glial end-foot (A) plasma membranes are closely applied to the basement membrane luminal and abluminal surfaces.

capillary [73]. Furthermore, the average thickness seems to increase with the aging process [46,64]. According to Laursen and Diemer [49], the harmonic mean basement membrane thickness of normal cortical capillaries of male Wistar rats is 52.37 nm in width.

Basement membrane thickening in moderate and severe traumatic brain oedema

In patients with traumatic brain injuries, examination of moderately oedematous regions show capillaries apparently not activated by the traumatic agent. In such regions, the apparently normal capillary basement membrane width ranges from 71.97 to 191.90 nm [19] (Fig. 2).

In patients with severe traumatic brain oedema the capillary basement membrane appear thickened. The basement membrane width ranges from 206.66 to 404.22 nm [19]. In addition, the basement membrane appears vacuolated (Fig. 3).

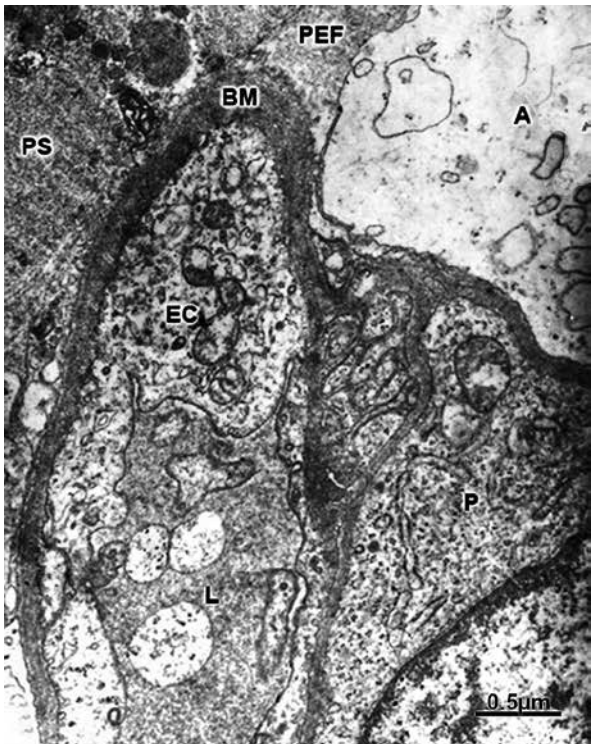

Fig. 2. Brain trauma. Right epidural haematoma. Right temporal cortex. Compact and dense capillary basement membrane (BM) showing an apparently normal structure in a moderate oedematous region. On the contrary, the clear perivascular astrocytic end-foot (A) shows a marked oedema. The pericytal cytoplasm (P) enclosed within the basement branches, the activated endothelial cell (EC), and the capillary lumen (L) are also seen. Note the presence of proteinaceous oedema fluid (PEF) in the perivascular space (PS).

Capillary basement membrane vacuolization

In patients with severe brain traumatic injuries, and loss of consciousness after alcohol ingestion, in addition to the increased vesicular and vacuolar transendothelial transport, a thickened and vacuolated basement membrane is found [14,16]. The mechanisms of increased extravasation of macromolecules across the blood-brain barrier exerted by ethanol intoxication are obscure. Theoretically, changes in vascular tones, vascular perfusion, as well as interference with blood coagulation, endothelial biogenic amine metabolism, and endothelial plasmalemma, all might contribute to this increased extravasation [66].

Endothelial vacuoles are observed discharging their content directly into the basement membrane or by means of plasmalemmal vesicles. Clathrin-coated and uncoated vesicles have also been found connected to the basement membrane surface [14,16] at the endothelial and pericytal margins. This increased vacuolar and vesicular transport induces progressive and slow alteration of the basement membrane matrix resulting in a gradual process of hydration, thickening, rarefaction, vacuolization and structural matrix disorganization. From the damaged basement, the oedema fluid penetrates into the astrocytic perivascular end-feet processes via the astrocyte cell soma [82]. The basement membrane vacuolization observed in very severe oedematous areas and in regions of brain parenchyma destruction reveals a complete loss of its diffusion-barrier function. A simultaneous vacuolization of endothelial cells, pericytes, astrocytes, and open endothelial junctions [17,23] was also encountered as the morphological substrate of enhanced transcapillary protein transport [14].

If endothelial cells, pericytes and perhaps glial cells participate in the elaboration of the normal basement membrane [25], the reverse process: the degeneration of these cells could induce basement membrane degradation and lysis. Basement membrane thickening and vacuolation also were observed by Kamyrio *et al*. [44] after gamma knife irradiation. In addition, Li *et al*. [51] have reported basement thickening in rats after simulated weightlessness.

In patients with head trauma and blood hypertension, the possibility exists that, in addition to the brain oedema, degenerative changes of capillary basement membrane should be present, as part of the degenerative changes of smaller penetrating cerebral vessels. The development of severe oedema in this case could be due in part to permeability changes to protein in penetrating vessels [27].

In several models of animal and human brain oedema, in which enhanced permeability to protein exists, loosening and swelling of the basement membrane have been earlier described [28,48,58,60,76,78].

In earlier studies [14,16,19], we have shown increased vesicular and vacuolar endothelial transport in cortical capillaries of patients with brain trauma, brain tumours, and congenital malformations. These morphological features of increased capillary permeability are closely related with the basement membrane thickening [19]. Basement membrane thickening has also been reported in different non-nervous pathological entities. Laursen and Diemer [49] reported an increase in the thickness of the brain capillary basement membrane after 30 days of portocaval anastomosis. Enlargement of the basement membrane has been described myxedema and polymyositis [84]. Basement membrane thickening in diabetes is also associated with increased capillary permeability which becomes manifest when the duration of diabetes exceeds 10 years [59]. According to these authors, the ischaemia could be a contributing factor to the basement membrane thickening. Basement membrane changes seem to be more a result than the cause of increased capillary

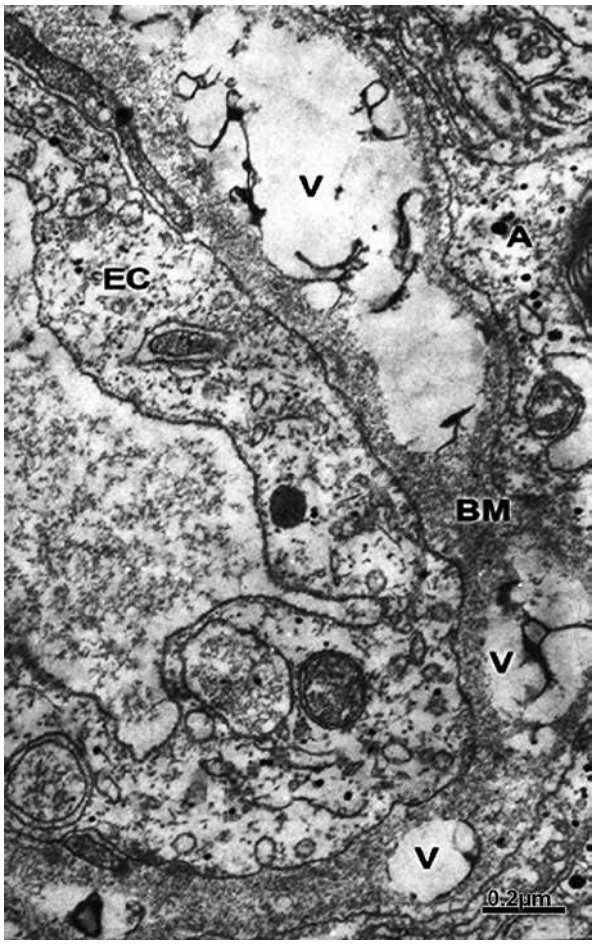

Fig. 3. Brain trauma. Right parieto-temporal subdural haematoma. Right parietal cortex. Thickened and vacuolated (V) basement membrane (BM) of a capillary localized in a severely oedematous area. The swollen and vacuolated endothelial cell (EC) and astrocytic end-foot (A) are also observed.

permeability. In addition, it has been reported that hypoxia causes oedema and disruption of endothelial basement membrane in pulmonary arteries [62]. Increased basement membrane thickness of skeletal muscle capillary in congestive heart failure has been reported by Longhurst *et al*. [54]. In congestive heart failure a high degree of local hypoxia undoubtedly occurs especially during exercise. According to these authors, an increased basement membrane thickness may be a result of local hypoxia and cell death. With the formation of new cell components, the new basement membrane material may oppose itself to the old lamina leading to significant thickening.

In an experimental model of brain oedema, such as cold injury oedema, one of the most commonly used model for traumatic vasogenic oedema [52], rarefaction and widening of the capillary basement membrane occur almost before any other vascular change. Thickening of the basement membrane has been also reported in the vasogenic brain oedema induced by intraventricular collagenase infusion [36]. The collagenase induces blood-brain barrier impairment by its action on the vascular basement membrane, not altering the structures in the brain parenchyma, and causing oedema formation and protein extravasation. Thickened capillary basement membrane is also reported in arterial hypertension [35], and diabetes [42]. Hypertension combined with diabetes also enhance basement thickening [43]. Similar findings are observed in galactosaemic rats [31], and in streptozotocin-induced diabetes [6].

Capillary basement membrane thickening in Alzheimer's disease has been widely reported by several workers [68,69,74,93]. Berzin *et al*. [3] and Salloway *et al*. [72] have implicated agrin, a synaptic organizing protein, in basement membrane damage in Alzheimer's disease.

Swollen and vacuolized capillary basement membrane in vascular anomaly and congenital hydrocephalus

In congenital malformations, such as vascular anomalies and congenital hydrocephalus, basement membrane thickening and vacuolization is also observed (Figs. 4 and 5).

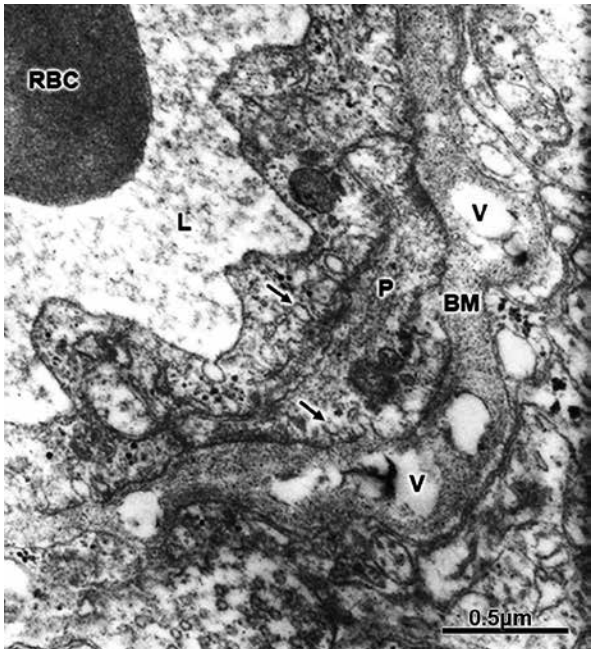

Fig. 4. Anomaly of the anterior cerebral artery. Right parietal cortex. Severe oedema. Swollen and vacuolized (V) capillary basement membrane (BM). Increased pinocytotic activity is observed in the endothelial cell and pericytal cytoplasm (P) (arrows). The capillary lumen (L) and a red blood cell (RBC) are also distinguished.

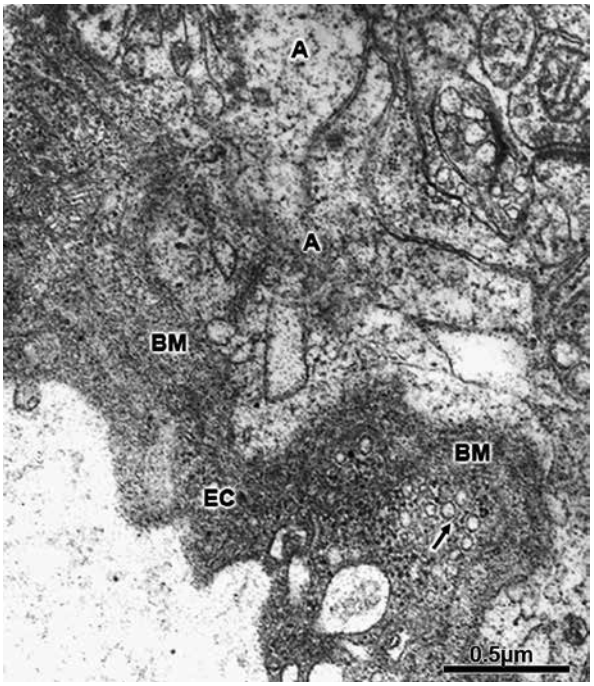

Fig. 5. Congenital hydrocephalus. Right parietal cortex. A swollen, undulated and immature capillary basement membrane (BM) is observed. Note the increased pinocytotic activity (arrow) in the dark endothelial cell (EC), and the swollen perivascular astrocytic end-feet (A).

Capillary basement membrane thickening in brain tumours

In brain tumours the capillary basement membrane also appears notably swollen, rarefacted, and exhibiting a dark and finely granular precipitate (Fig. 6).

Immunohistochemical expression of laminin 1 and 2 has been found in brain tumour vessels [80] and in breast cancer [33]. A redistribution of aquaporin-4 channels and loss of agrin has been observed by Warth *et al*. [90] in human glioblastoma.

Basement membrane bifurcations acting as abluminal channels

The basement membrane bifurcations enclosing the pericyte processes appear as irregularly dilated translucid channels, following a contoured course, approaching to the luminal endothelial plasma membrane [13,22]. These expansions originate from the basement membrane and after a short trajectory applied to the endothelial cytoplasm, converge again onto the basement membrane. These expansions lost their matrices in large segments, and appear as dilated electronlucid channels, resulting from increased capillary permeability (Fig. 7).

The swollen capillary basement membrane branches seem to function as abluminally oriented transcapillary channels for massive escape of haematogenous oedema fluid. These dilated basement membrane branches have been interpreted as basement membrane modifications in response to heightened transcapillary exchange in traumatic brain oedema [19]. Such structures, together with transendothelial, pericytal and astrocytic channels [15,17,19,23] seem to represent the basic morphological substrate for massive escape of hematogenous oedema fluid in vasogenic brain oedema.

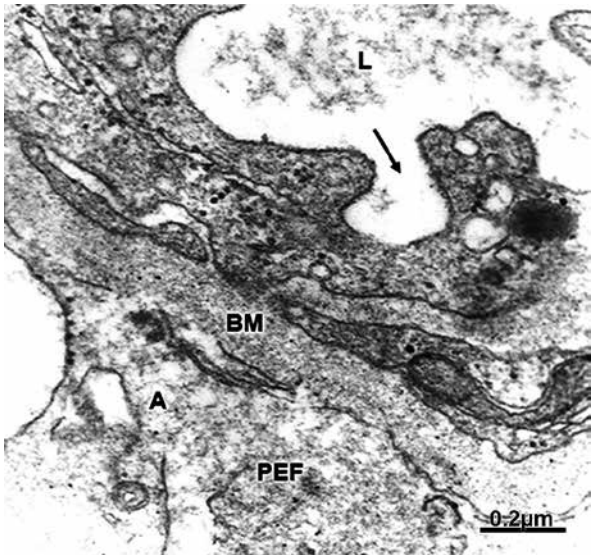

Fig. 6. Cystic craniopharyngioma. Right frontal cortex. Swollen capillary basement membrane (BM) exhibiting rarefaction and a fine and dark granular precipitate. Note the proteinaceous oedema fluid (PEF) in the perivascular astrocytic end-foot (A) similar to that observed in the capillary lumen (L). The endothelial cell shows deep invaginations (arrow) of the luminal surface to form protein containing vacuoles.

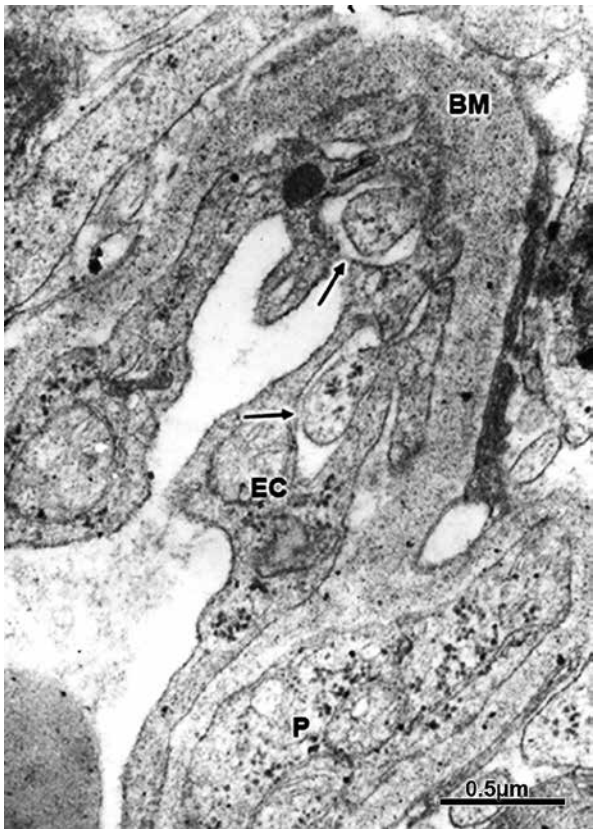

Fig. 7. Brain trauma. Contusion and fracture of the frontal region. Left frontal cortex. Dilated and contorted basement membrane branches (arrows) approaching to the endothelial cell (EC), and acting as abluminal transcapillary channels. Note the continuity with the swollen basement membrane (BM). P labels the enclosed pericytal cytoplasm (P) within the basement membrane.

The glio-basal dissociation process

In some severe brain oedema areas, the astrocytic end-feet limiting membrane appears slightly detached from the basement membrane outer surface and follow an undulated trajectory. In these areas, the astrocytic glial end-feet are extremely swollen and glial filaments are frequently absent. The lack of attached glial filaments probably induced the glio-basal dissociation process [19] (Fig. 8).

Astrocytic invaginations precede the formation of astrocytic vacuoles, by means of which the oedema fluid seems to be transported to the neighbouring neuropil [16,82]. Apparently in the severe oedema, the swollen and fragmented astrocytic processes release the already up-taken haematogenous oedema fluid in the neighbouring enlarged extracellular space which, in turn, dissects the astrocytic membrane from the basement membrane complex [19]. In areas of total brain tissue necrosis due to traumatic alteration of the blood-brain barrier, evinced by presence of extravasated erythrocytes, a severe alteration of basement membrane is observed consisting of loosening up and dissolution of its matrix.

As illustrated in Fig. 9, the denuded basement membrane tends to loosen up and shows evidence of the actual rupture not preventing the spreading of perivascular haemorrhages.

After a long evolution time of a brain trauma, the basement membrane and the perivascular glia still persist, demonstrating that these structures are the most resistant barrier elements of the vessel walls. This fact indicates the high structural stability of basement membrane in relationship to endothelial cells, pericytes and astrocytic end-feet, as it has been previously pointed out by Blinzinger *et al*. [5] in areas of cold-induced total cortical necrosis.

Proliferation of collagen fibers in the basement membrane

In some cases, the thickened basement membrane exhibits proliferation of collagen fibers (Fig. 10).

Proliferation of collagen fibers has also been reported by Long *et al*. [53] in malignant brain tumours, and by Calhoun and Mottaz [10] in experimental cerebral infarction. Nevertheless, these authors reported the presence of fibroblast in the pericapillary space. Although chemical evidence of a collagenous protein exists in the basement membrane [77], electron microscopy has not demonstrated collagen fibrils in the normal brain capillary basal lami-

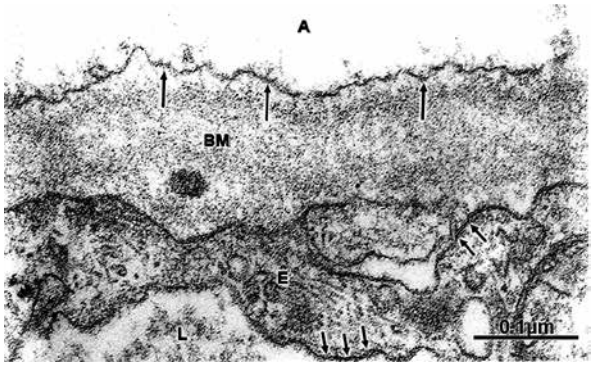

Fig. 8. Brain trauma. Left parieto-occipital subdural hygroma. Capillary of left parietal cortex. The thickened basement membrane (BM) exhibits matrix rarefaction and a finely granular appearance, corresponding to uranyl and lead staining of the swollen and degenerated basement membrane matrix. The luminal and abluminal endothelial (E) membranes are structurally intact (short arrows). The astrocytic end-foot (A) membrane follows an undulated course (long arrows) and the glio-basal dissociation process is initiated. The capillary lumen is labelled with an L.

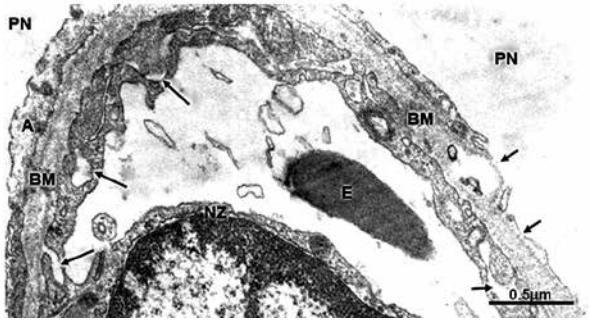

Fig. 9. Brain trauma. Subdural hygroma. Left parietal cortex. Capillary located in area of brain tissue necrosis showing a denuded and vacuolated (short arrows) basement membrane (BM). A thin layer of perivascular astrocytic end-foot (A) is still appreciated. The long arrows indicate swollen basement branches invaginating the endothelial cytoplasm, and acting as abluminal channels. Note the absence of perivascular neuropil (PN), the prominent endothelial nuclear zone (NZ), and a partial view of an intraluminal erythrocyte (E).

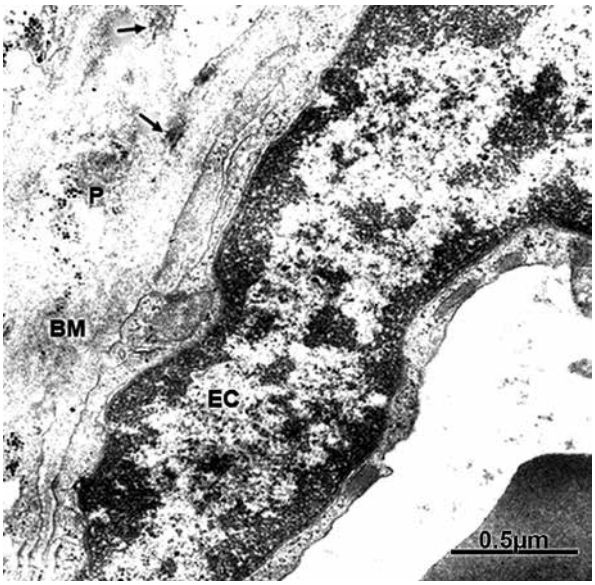

Fig. 10. Meningioma of the frontal cortex. Capillary of the right frontal cortex. Proliferations of collagen fibers (arrows) are observed within the basement membrane (BM) surrounding the pericytal cytoplasm (P). The endothelial cell (EC) is also seen.

na [25]. Proliferation of collagen fibers at the level of the basement membrane coexists with the presence of dark neuroglial cells, apparently pericytal microglia [63] attached to its outer surface, replacing the astrocytic pericapillary layer. We infer that pericytal microglia acquire fibroblastic properties and elaborate collagen properties, as an adventitial reaction. If, as considered by Bar and Wolff [1], the basement membrane plays a role in regulating the differentiation of adjacent neuroglial cells, it seems plausible that the capillary basement membrane could regulate the differentiation of this neighbouring pericytal microglia. It is also possible that this cell participates in the formation and maintenance of the reduplicated basement membrane. Collagen fibrils have been found beneath the basement membrane by García *et al*. [35] after arterial hypertension, by Walski *et al*. [87], and Walski and Gajkovska [88] after traumatic brain injury in rat cerebral cortex, and within the basement membrane in aged rats [26]. β-amyloid fibrils have been described in the capillary basement membrane in Alzheimer's disease [39,40]. Plesea *et al*. [67] encountered densification of the type IV collagen material in the basement membrane of cerebral vasculature in hypertensive intracerebral haemorrhage.

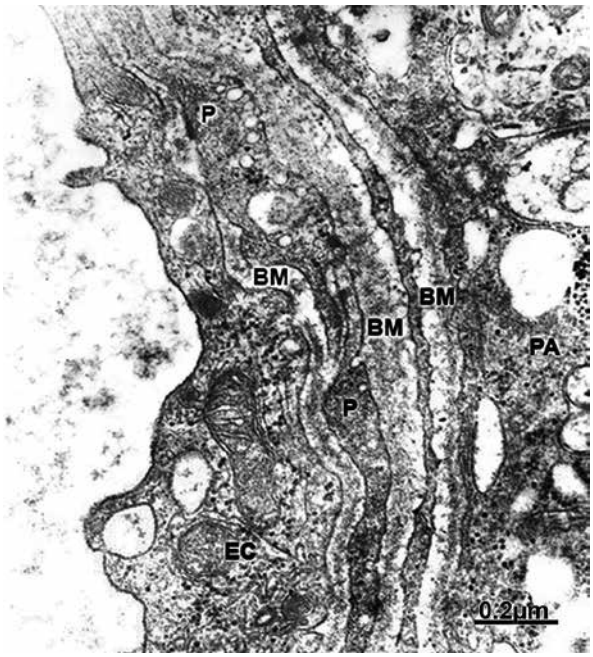

Fig. 11. Brain trauma. Right parieto-temporal subdural hematoma. Left parietal cortex. Cortical capillary showing reduplicated basement membranes (BM) which appear separated by thin bands of pericytal cytoplasm (P). The vacuolated endothelial cell (EC), and dark perivascular astrocytic end-foot (PA) are also seen.

Reduplication of capillary basement membrane

Reduplicated capillary basement membranes have been also found in our patients with brain oedema associated to brain trauma and tumours (Fig. 11).

Reduplicated capillary basement membrane has been earlier reported by Luse and McDougal [55] in allergic encephalomyelitis; by Kiser and Kending [47] in the capsule of cerebral abscesses, by Ward *et al*. [89], Ferrer and Lopez-Pousa [30], and McLone [61] in brain tumours. According to Vracko and Benditt [84], the accumulation and lamellation of basement membrane would be a result of repeated episodes of cell death and regeneration. Therefore, Vracko [85] considers that layering, splitting or lamination of basement membrane is due to cell death and cell replenishment. The individual layer has been deposited there by new cell generation and gives an indication of the number of cell generations which have occurred at that particular site. The reduplication of the basement membrane could also be

a phenomenon induced by pericyte cell hypertrophy [15]. A multilayered basement membrane has been described by Yoshida *et al*. [92] in the repair process of cerebral infarction in rats, in subarachnoid haemorrhage [56], and in capillary vessels of neurohypophysis after focal ischaemia of cerebral cortex [32].

Basement membrane thickening and the aging process

We have studied a group of patients with congenital hydrocephalus whose age ranges from several months up to ten years, which exhibit focal swelling of basement membrane [18,21], and in patients with traumatic head injuries up to 80 years of age [20]. We have tried to establish a correlation between the age of the patient and the basement membrane width, in order to elucidate if, besides the pathological basement membrane thickening associated to brain oedema, there is also an increase in basement membrane thickness due to the aging process, as earlier suggested by Kilo *et al*. [46], and Nagata [64]. An increased basement membrane thickness is found up until 60 years of age. However further changes were not detected between 60 and 80 years [19]. Bruns *et al*. [9] have earlier reported an increased basement membrane thickness of cortical capillaries with increasing age in the cerebral cortex of the aging primate, *Macaca nemestrina*. The authors reported an increased basement membrane thickness between 4 and 10 years, but no further changes between 10 and 20 years. According to these authors, a regression analysis revealed no significant increase in thickness of the basement membrane with increasing age. In our study we have considered that only 45% of the variability of basement membrane width is due to the aging process, and the remaining 55% of the variability is related to the associated brain oedema [19]. A further study should be done in normal old subjects to really evaluate the possible changes of basement membrane thickness during aging. This study is obviously limited for ethical reasons in the normal human central nervous system.

A neurobiological interpretation of capillary basement thickening

We have considered the basement membrane enlargement in brain oedema as an unspecific reaction due to overhydration of its protein polysaccharide matrix. According to Hall [37] and Spiro [77], the basement membrane can be conceived as a network of collagen molecules having positive charges, surrounded by negatively charged mucopolysaccharides. According to Pease [65] in the presence of water, polysaccharides occupy large areas or domains compared to the weight of the molecule and not only water may penetrate these polysaccharide domains, but ions and small molecules. Berzin *et al*. [3] demonstrated that agrin is associated with heparan sulphate proteoglycans in the basement membrane. These biochemical data could explain the basement membrane thickening in human brain oedema. As we have previously postulated [16,19], the increased transcapillary passage of ions and water in brain oedema would produce a high state of hydration of the basement membrane matrix. Since the fundamental alteration in vasogenic brain oedema is an increased transcapillary transfer of fluids, ions, proteins and small molecules, we infer that the enlargement of the basement membrane can be initially considered as a state of overhydration of its protein – polysaccharide matrix or anionic sites. Consequently a notable loss of the role of the basement membrane as a semipermeable filter [45] or permeability-barrier function occurs in brain oedema. A discontinuity in the distribution of anionic sites can be associated with an increased capillary permeability, as observed in scrapie-infected mice [83].

Through the effect of cerebral oedema, collagen or proteins similar to collagen, proteoglycans and glycoproteins of the basement membrane are degraded, presumably producing a selective precipitation of uranyl and lead salts in these areas, as observed in the transmission electron microscopic images stained by these electron staining techniques [19]. Fragmentation of agrin, a synaptic organizing protein, found in the basement membrane [3,72] could also be implicated as the molecular substrate for basement membrane granularity.

Concluding remarks

The capillary basement membranes are examined in severe traumatic brain injuries, vascular malformation, congenital hydrocephalus and brain tumours. The capillary basement membrane exhibits homogeneous and nodular thickening, vacuolization, rarefaction, reduplication, and deposition of collagen fibers. Their average thickness varied according to the aetiology and severity of brain oedema. In

moderate brain oedema the thickness ranged from 71.97 to 191.90 nm in width, and in patients with severe brain oedema it varied from 206.66 to 404.22 nm. The basement membrane complex appears apparently intact in moderate oedema and shows glio-basal dissociation in severe oedema. In areas of highly increased cerebro-vascular permeability, the basement membrane shows matrix disorganization, reduplication, and bifurcations protruding toward the endothelial cells, and acting as abluminal transcapillary channels. In regions of total brain necrosis, its structural stability is lost showing loosening, dissolution and rupture. Basement membrane swelling is due to an overhydration of its protein-complex glycoprotein matrix. The thickening, rarefaction and vacuolization are induced by the increased vacuolar and vesicular transendothelial transport. The degenerated basement membrane areas exhibit a finely granular precipitate interpreted as protein, proteoglycan, glycoprotein, and agrin degraded matrix.

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