Review article

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Submicroscopic pathology of human and experimental hydrocephalic cerebral cortex

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Abstract

The ultrastructural pathology of cerebral cortex in human hydrocephalus is reviewed and compared with experimental hydrocephalus. Nerve cells show moderate and severe swelling. The neighboring neuropil exhibits notable enlargement of extracellular space, synaptic plasticity and degeneration, damage of myelinated axons, and myelination delay. The astrocytes display edematous changes and phagocytic activity. Glycogen rich- and glycogen-depleted astrocytes are observed. Some oligodendroglial cells exhibit normal morphology, and other exhibit hydropic changes. The capillary wall shows signs of blood-brain barrier dysfunction. The role of ischemia, oxidative stress, increased calcium concentration, activation of NMDA receptors, and disturbance of ion homeostasis are discussed in relationship with the fine structural alterations of hydrocephalic brain parenchyma.

Key words: human hydrocephalus, experimental hydrocephalus, nerve cell damage, synaptic plasticity, synaptic degeneration, reactive glial cells, extracellular space, electron microscopy.

Introduction

Blockage of the cerebrospinal fluid (CSF) circulation in experimental and human hydrocephalus results in a rise in intraventricular pressure with dilation of the lateral ventricles, alterations on the fine structure of choroid plexus, and disruption of the ependymal lining. Cerebrospinal fluid is infused into the white matter through the damaged ependyma, and causes severe periventricular edema, ependyma and periventricular white matter, cortical brain edema, parenchymal destruction, micro- and macrovascular changes, derangement of brain development, formation of cystic cavities, and reactive changes of glial cells. The subependymal white matter shows enlargement of extracellular space, edematous and degenerative changes in neurons, especially in axons and myelin sheath, edematous changes of glial cells, reactive astrocytosis and phagocytosis [1,6,9,10,14,30,34-36,38,40,41,43,46-49,52,56,57,63,78,79,83,85,86,89,93,101-103,114].

Since the pioneering work of Struck and Hemmer [97] very few studies have been dedicated to explore the cortical gray matter alterations in human hydrocephalus. This aspect is basically important if we consider that CSF traverses the entire cerebral parenchyma as earlier demonstrated by Milhorat and Hammock [72]. Earlier electron microscopic studies of the gray matter have demonstrated enlarged extracellular space in murine hydrocephalus and human

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normal pressure hydrocephalus [5,70]. Takeuchi and Murakami [103] described two types of congenital hydrocephalus induced in rats by X-irradiation in utero. Castejón [2] found degenerative changes of neurons and glial cells in infant patients with congenital hydrocephalus and Chiari malformation type II. Weller *et al.* [110] studied the inflammatory reaction in infected cerebrospinal fluid shunts in hydrocephalic patients. Oka *et al.* [5] described the angioarchitecture in experimental rat hydrocephalus. Richardson [91] examined congenital hydrocephalus associated to other developmental abnormalities. Glees and Voth [46], Glees *et al.* [47], Glees and Hasan [48] earlier described the pathlogical changes in infant hydrocephalus. Miyazawa and Sato [75,76] reported learning disability and impairment of synaptogenesis in HTx-rats. Jones *et al.* [5-59] confirmed that the cerebral cortex is severely distorted in congenital hydrocephalus in the HTx-rats, in a mutant mouse, and in infantile hydrocephalus. Kriebel *et al.* [62] studied the microstructure of cortical neuropil before and after decompression in experimental infantile hydrocephalus. Sada *et al.* [2] found underdevelopment or immaturity of blood-brain barrier in hydrocephalic HTx-rat brain. Harris *et al.* [51] reported dendritic damage in hydrocephalic HTx-rats. Boillat *et al.* [7,8] analyzed the damage of cortical pyramidal neurons in control, hydrocephalic and shunted HTx-rats. Shoesmith *et al.* [94] reported relative impairment of extracellular fluid movement through the cerebral cortex of young hydrocephalic rats. Aolad *et al.* [3] found extensive cell death in mice following X-irradiation. Del Bigio *et al.* [35-37,39] demostrated myelination delay and proteolitic damage in immature rats with kaolin-induced hydrocephalus. Ding *et al.* [43,44] showed neuron tolerance during hydrocephalus, extensive axon and neuropil degeneration, and that neuron death was not a mayor pathological change. Del Bigio *et al.* [36] and Del Bigio [38] found in chronic hydrocephalus destruction of white matter. Aoyama *et al.* [4] found swollen and fragmented axons in experimental hydrocephalus. Castejón [10-24] described the electron microscopic changes of nerve cell organelles, and nerve cell death in congenital hydrocephalus. Khan *et al.* [60] observed astroglial/microglial reaction in kaolin-induced hydrocephalus. Aliev *et al.* [2] reported severe edema in a murine model of congenital hydrocephalus. Aoyama *et al.* [4] reported neuronal damage in experimental hydrocephalus. Humphreys *et al.* [53] reported cerebral mantle disruption in human fetal hydrocephalus in kaolin-induced hydrocephalus. Voelz *et al.* [107] described in rat kaolin-induced hydrocephalus the dynamic of CSF circulation. Del Bigio and Enno [32] found reduced extracellular space in kaolin-induced rat hydrocephalus. Goto *et al.* [50] described defects in oligodendrocyte development, axonal damage, and subsequent hydrocephalus in Fin-deficient mouse.

The present review describes the fine structural alterations of human hydrocephalic cerebral cortex and correlates some results with those reported in experimental hydrocephalus in animal models. Experimental hydrocephalus investigations in animal models help to better understand the pathogenetic mechanisms of human hydrocephalus.

Intracellular edema of hydrocephalic nerve cells

In pyramidal and non-pyramidal neurons, moderate to severe swelling of intraneuronal compartment revealed by plasma membrane fragmentation, variable degrees of enlargement of rough endoplasmic reticulum and perinuclear cistern, and wide communications between the nucleoplasm and cytoplasmic matrix are constantly found. A degranulated rough endoplasmic reticulum also is observed [24]. The intracellular edema is prominent at the level of the smooth Golgi flattened stacked cisterns, which appear extremely dilated and fragmented [23]. The mitochondria exhibit also a wide spectrum of morphological changes ranging from light to moderate and severe swelling [13]. Lysosomes show damage of their limiting plasma membrane, and appear surrounded by areas of cytoplasmic focal necrosis (Figs. 1-3) [19].

The hydropic changes of nuclear and cytoplasmic matrix induce an increased electron lucent aspect of nerve cells, which acquired a watery appearance. These edematous changes and the degranulated rough endoplasmic reticulum could be correlated with the impairment of protein synthesis, reduced cerebral glucose and oxygen metabolism, and changes in the levels of neurotransmitters reported in the hydrocephalic cerebral cortex [31,51,64,74,90]. Edematous changes have also been earlier observed in the experimental rabbit hydrocephalus at the level of the white matter [109]. Boillat *et al.* [7,8] earlier analyzed the damage of rat cortical pyramidal neurons, showing cluster organization, fewer mature dendrites, infrequent synapses, degenerative

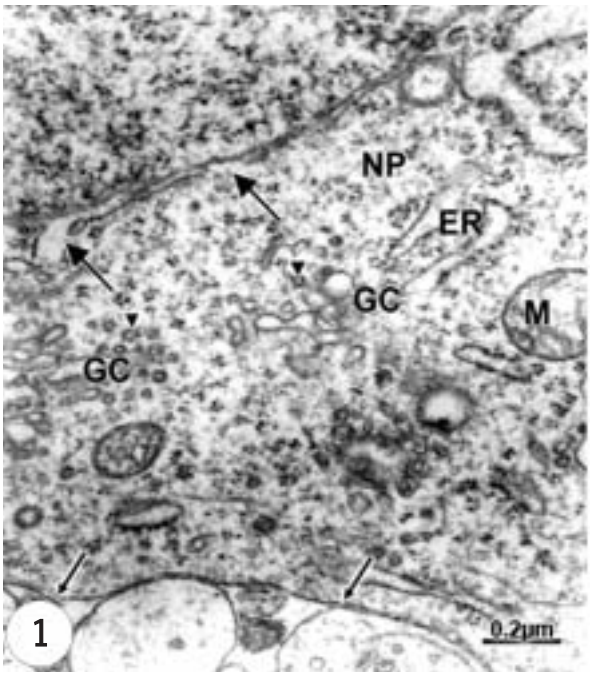

Fig. 1. Chiari malformation type II. Hydrocephalus. Right parietal cortex. 2 month-old, female infant patient. Non-pyramidal nerve cell (NP) displaying a disrupted plasma membrane (small arrows) and nuclear pore complex disassembly (long arrows). The cytoplasm shows two swollen vesicular-type Golgi complexes (GC), enlarged endoplasmic reticulum (ER), and numerous uncoated and clathrin coated vesicles (arrowheads) around the Golgi complex region.

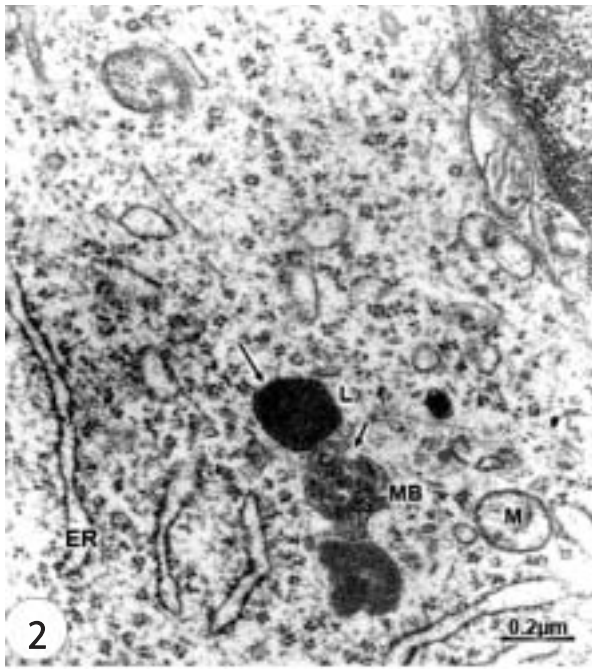

Fig. 2. Chiari malformation. Hydrocephalus. Right parietal cortex. 1 month-old, female infant patient. Edematous non-pyramidal neuron showing lysosomes (L) and a multivesicular body (MB) with disrupted limiting membranes (arrows). Note the clear edematous mitochondria (M), and the dilated rough endoplasmic reticulum (ER) embedded in an electron lucent cytosol.

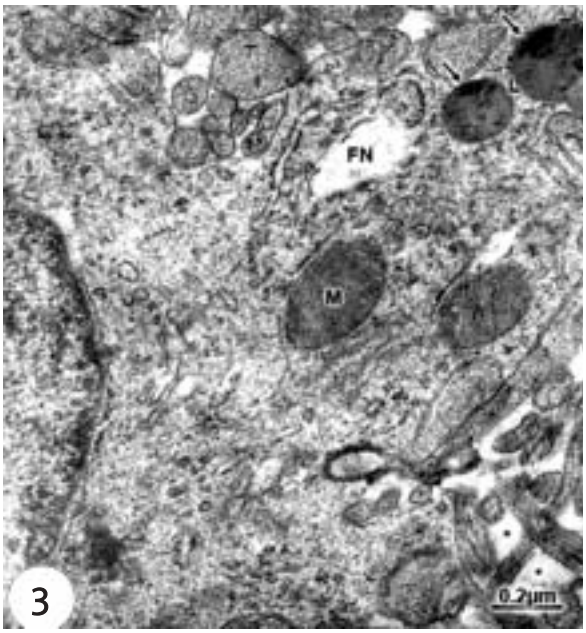

Fig. 3. Congenital hydrocephalus. Right temporal cortex. 6 months-old male infant patient. Non-pyramidal neuron showing two lysosomes (L) with an associated dense coarse granulation (arrows). Note the neighboring focal cytoplasmic necrosis (FN), and the moderate electron dense cytoplasm. The swollen mitochondria (M) also are electron dense. The asterisks label the enlarged hydrocephalic extracellular space.

changes, vacuolated cytoplasm, dilated Golgi and endoplasmic reticulum, distorted mitochondria, and single ribosomes in hydrocephalic HTx-rats. The edematous and degenerative changes of cerebral cortex in human hydrocephalus appeared to be initially of a mechanical origin due to the high cerebrospinal fluid pressure, and secondarily to the increased interstitial edema, ischemic process, and oxidative stress [22].

In addition to the neuronal edema there is also an associated ischemic process. The role of ischemia in neonatal brain injury was suggested by Del Biggio *et al.* [34]. According to Jones *et al.* and Jones and Anderson [55,59], and Harris *et al.* [51], there is a progressive reduction in energy metabolites, which leads to cell swelling with decreased osmolytes and neurotransmitters. Jones *et al.* [55] found significant increase in water, Na^+ and Cl^- content in rat infant hydrocephalus. Hydrocephalic edema also is associated with oxidative stress. According to Socci *et al.* [96], there is evidence that oxidative stress is associated with the pathophysiology of inherited hydrocephalus in the HTx-rat model.

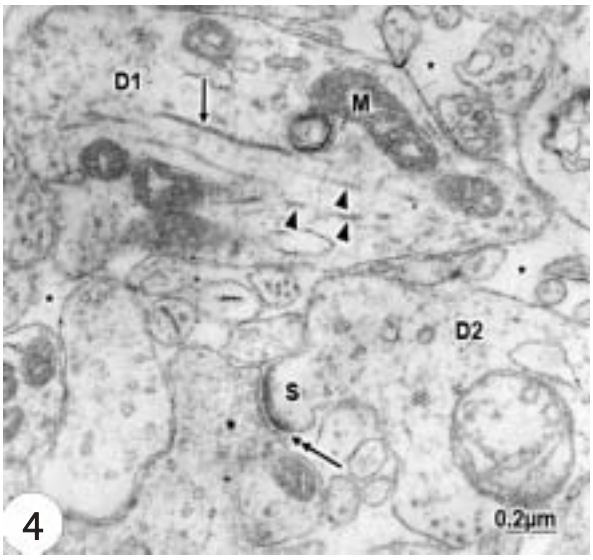

Fig. 4. Chiari malformation type II. Communicant hydrocephalus. Neuropil of a 10 days-old male neonate. Right parietal cortex. High magnification of a swollen and clear dendrite (D1) exhibiting dark swollen mitochondria (M) with clear dilated cristae, and intact (long arrow) and few fragmented microtubules (arrowheads). A neighboring clear dendrite (D2) shows an asymmetric synaptic contact (double head arrow) by means of mushroom type-dendritic spine (S). The asterisks label the enlarged extracellular space.

Pathology of myelinated axons

Earlier microscopic studies of experimental hydrocephalus show damage of axons and myelin sheath at the subependimal white matter [43,63,70,77,83,84, 111-113]. Myelinated axons are not observed in the gray matter of neonate patients with congenital hydrocephalus, especially in those patients between 10 days and 3 months of age [22]. A myelination delay in the cerebral white matter of immature rats with kaolin-induced hydrocephalus was earlier reported by Del Bigio *et al.* [35]. Del Bigio and Zhan [37] reported axonal injury in the corpus callosum one week in kaolin-induce hydrocephalus. These authors described axonal damage four weeks after severe ventriculomegaly.

Electron microscopic changes of dendrites and dendritic spines in congenital hydrocephalus

The immature hydrocephalic cerebral cortex neuropil in neonate patients with congenital hydrocephalus shows irregularly beaded shaped, and swollen and vacuolated dendritic processes with elongated and dark mitochondria. Some of them exhibit lamellipodic and filopodic processes, and endocytic vesicle formation at the limiting plasma membrane [22]. These dendrites exhibit mushroom, stubby and filiform types of dendritic spines making asymmetric synaptic junctions [14,18]. Some dendritic processes show fragmented plasma membrane and disrupted microtubules in areas of severe brain edema (Fig. 4).

Hydropic dendritic deterioration has been reported in feline-infantile hydrocephalus by Kriebel and McAllister [62]. Harris *et al.* [51] found a decreased in the total length of dendritic tree in the infant HTx-rats. McAllister *et al.* [69] reported dendritic varicosities and spine loss as the most striking dendritic alterations in experimental induced hydrocephalus in newborn rats.

In patients with congenital hydrocephalus and Chiari malformation, a variety of swollen spine shapes are found [14]: mushroom type-, filopodic and lanceolate spines. In the immature neuropil of these neonate and hydrocephalic patients, some spines appear axonless or unattached, and others making asymmetric axodendritic synaptic contacts. The immature spines exhibit mostly an elongated neck with several microtubules. Unattached or axonless elongated spines, presumably represent a compensatory mechanism to navigate in the widened extracellular space of the immature neuropil to reach axons

farther away. These spines exhibit an edematous head, a disrupted actin-like network, dilated profiles of smooth endoplasmic reticulum, swollen clear and dense mitochondria, and clusters of free ribosomes. Such alterations are due to dendrotoxicity [18].

Synaptic plasticity and synaptic degeneration features in congenital hydrocephalus

In human congenital hydrocephalus few inmmature axodendritic and axosomatic synapses are observed in infant patients ranging from 1 to 6 months of age (Fig. 5). Synaptic plasticity in mature synapses is mainly characterized by the presence of activated flat and invaginated axodendritic and axospinodendritic asymmetric synaptic contacts showing synaptic vesicles anchored to the presynaptic membrane, and short or large synaptic active zones [20]. Tsubokawa *et al.* [106] also found impaired hippocampal synaptic plasticity in the experimental chronic hydrocephalus.

The swollen and degenerated axodendritic and axosomatic synaptic contacts observed in areas of moderate and severe hydrocephalic edema exhibit enlargement of few synaptic vesicles, and lack of pre- and post synaptic densities. In addition, isolated and swollen presynaptic endings with few or numerous synaptic vesicles, disruption of limiting plasma membrane, and without postsynaptic partners are observed. Megaspines up to 2.86 µm in lenght are observed in Chiari malformation making mature axodendritic junctions with one or two synaptic active zones, and exhibiting a dilated spine apparatus (Fig. 6). Synaptic degeneration and synaptic disassembly

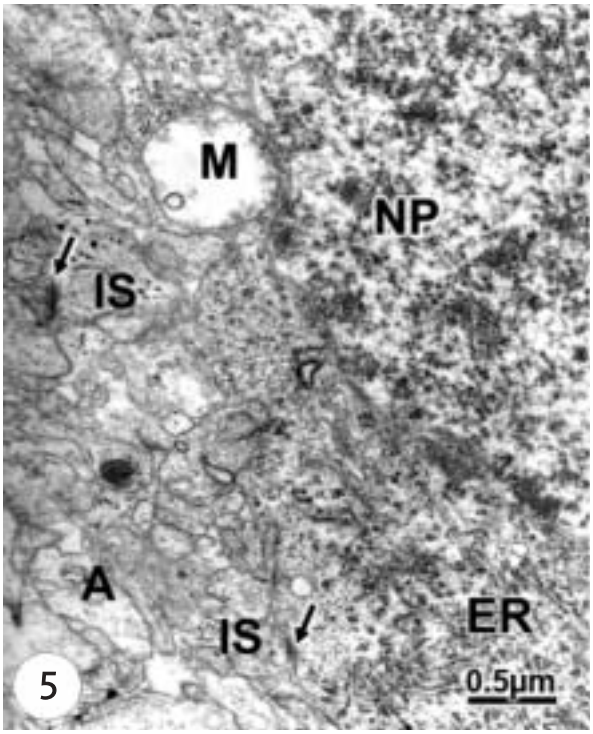

Fig. 5. Congenital hydrocephalus. Right frontal cortex. 3 months-old male infant patient. A swollen non pyramidal neuron (NP) exhibiting well developed endoplasmic reticulum (ER), and an inmmature axosomatic synapse (IS, arrow). Another inmmature axodendritic synapse (IS, arrow) is distinguished in the neighboring neuropil. The arrows label the synaptic membrane complex. Note the swollen mitocondria (M), and astrocytic process (A).

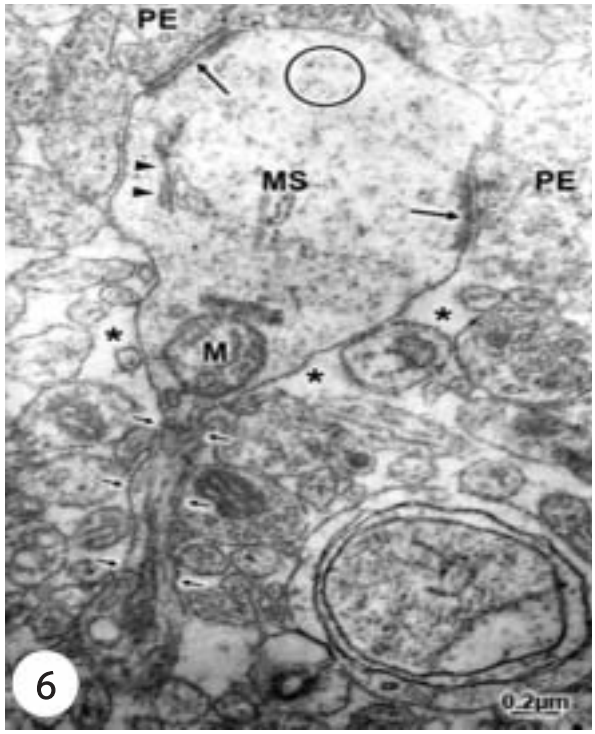

Fig. 6. Chiari malformation type II. Right parietal cortex. 2 months-old female infant patient. Neuropil showing a megaspine (MS) exhibiting a long neck (short arrows) and two asymmetric synaptic contacts (long arrows) with swollen presynaptic endings (PE). The spine head shows a disrupted actin-like network (circle), an atrophic spine apparatus (arrowheads), and a clear swollen mitochondrion (M). The asterisks label the enlarged hydrocephalic extracellular space.

occur in elevated intracranial pressure-hydrocephalus (Fig. 7). Phagocytic astrocytes appear engulfing the degenerated synapses. Hydrocephalic edema and ischemia, oxidative stress, increased calcium concentration, activation of NMDA receptors, and disturbance of ion homeostasis are apparently related with the synaptic plasticity and synaptic degenerative changes observed in human hydrocephalus [20,21].

The damage of nerve cell processes and synaptic contacts indicates nerve cell circuit alterations in the hydrocephalic cortex, which might explain some clinical and neurobiological symptoms, such as decline in intellectual functions and learning disabilities, motor deficits, and seizures observed in infant hydrocephalic patients [20,22,46,48,76].

Learning disability and impairment of synaptogenesis in HTx-rats with arrested shunt-dependent hydrocephalus have been also reported by Miyasawa and Sato [76]. Besides, changes of synaptic related proteins (SVP-38 and debrins), and of synaptogenesis have been earlier reported by Suda *et al.* in congenitally HTx-rats [98,99].

Reactive changes and phagocytic activity of neuroglial cells

Two distinct morphological types of astrocytes: Glycogen rich- and glycogen-depleted astrocytes have been found in human congenital hydrocephalus in perineuronal, interfascicular and perivascular localization (Fig. 8) [16]. These findings suggest astrocytic

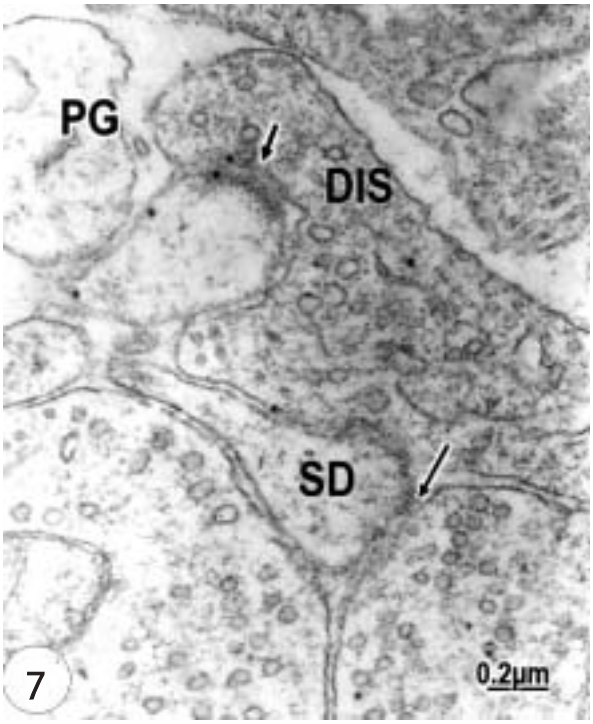

Fig. 7. Postmeningitis hydrocephalus. Right frontal cortex. 3 months-old male infant patient. Degenarated and invaginated axodendritic synapse (DIS) showing the synaptic membrane complex (short arrow), the irregularly dilated synaptic cleft, and the detachment of perisynaptic glial cell cytoplasm (PG). A neighboring synaptic disassembly process (SD) also is observed. Note the separation of pre- and postsynaptic membranes at the level of synaptic cleft (long arrow), and the absence of pre- and post synaptic densities.

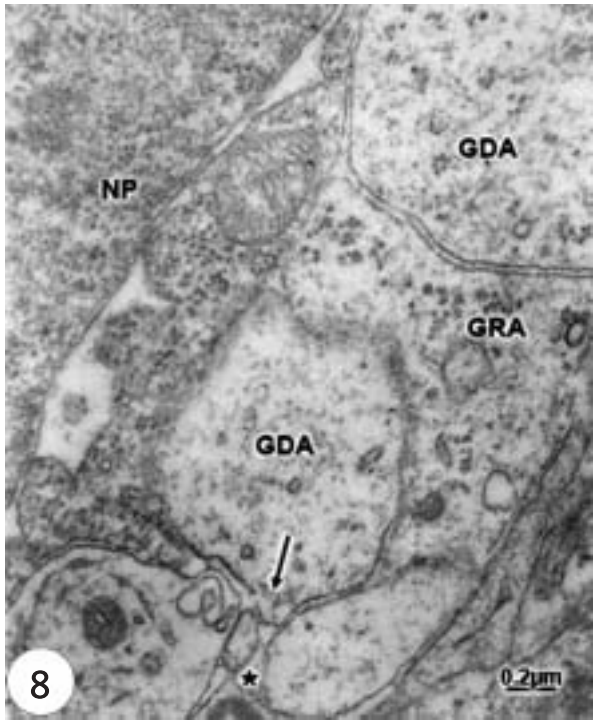

Fig. 8. Chiari malformation type II. Right parietal cortex. 2 months-old female infant patient. Glycogen-rich (GRA) and glycogen-depleted (GDA) perineuronal and swollen astrocytic processes appear enveloping an edematous non-pyramidal nerve cell (NP). Note the enlarged extracellular space characteristic of hydrocephalic edema (asterisk). The arrow labels the disrupted limiting plasma membrane.

glycogen mobilization during anoxic and ischemic conditions, revealing the important contribution of astrocytes on neuronal survival under conditions of energy substrate limitations. Astroglial cells might perform several energy-dependent functions that may aid neuronal and oligodendroglial cell survival in pathological conditions, such as congenital hydrocephalus [16].

At the level of cortical gray matter neuropil, the astrocyte cells show notable edematous changes and phagocytic activity. Gliosis and microgliosis have been reported to be a common and persistent feature in the white matter of hydrocephalic brain [67-73]. Reactive changes in astrocytes and oligodendroglial cells in kaolin-induced rat hydrocephalus have been described by Klinge *et al.* [61]. According to Mangano *et al.* [67], microglial cells constitute one important element in the gliosis that accompanies hydrocephalus.

In the edematous human cortical gray matter, the oligodendroglial cells exhibit in certain regions a normal structural pattern, and in severely edematous areas moderate and remarkably hydropic changes and phagocytic activity [12].

Pathology of blood-brain barrier

The capillary wall shows evident signs of blood-brain barrier dysfunction characterized by increased endothelial vesicular and vacuolar transport (Fig. 9), closed and open interendothelial junctions, thin and fragmented basement membrane with areas of focal thickening, and discontinuous perivascular astrocytic end-feet [22,27].

In severely edematous areas with presence of disrupted neuropil, the perivascular space is notably enlarged and the capillaries appeared floating as isolated structures. They show tight or partially open endothelial junctions, increased vesicular and vacuolar transendothelial transport, and swollen and disrupted basement membrane (Fig. 10). Our findings in human hydrocephalus favor the idea of an interen-

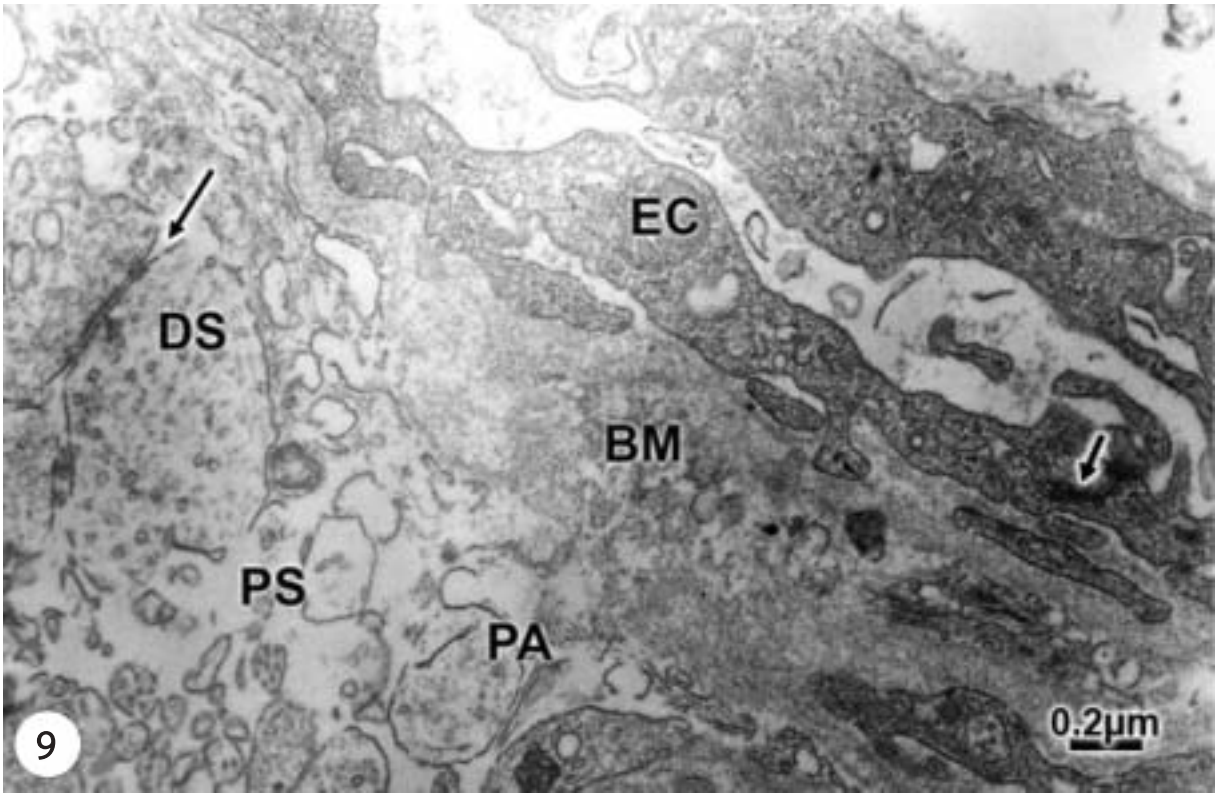

Fig. 9. Chiari malformation type II. Right parietal cortex. 12 days-old female neonate. Longitudinally sectioned capillary showing dark endothelial cells (EC) exhibiting large vacuoles and micropinocytotic vesicles, a closed endothelial junction (arrow), and a thickened basement membrane (BM). Note the enlarged perivascular space (PS), the swollen and disrupted perivascular astrocytic process (PA), and the degenerated axodendritic synapse (DS). The arrow labels the damage synaptic membrane complex.

dothelial route either for edema formation or resolution in human hydrocephalic cerebral cortex [22,27]. Nakagawa *et al.* [80] also reported widening of interendothelial clefts between the tight junctions in capillaries of the subependymal and subcortical white matter in hydrocephalic rats, and postulated the possibility of a paracellular route for hydrocephalic edema resolution. In this context, human hydrocephalus differs from the hy-3 mouse neonatal hydrocephalus [70], in which a normal operating blood-brain barrier is suggested by the presence of intact interendothelial tight junctions, no indication of increased pinocytotic activity, and perivascular astrocytes of apparently normal submicroscopic morphology.

Okuyama *et al.* [86] also have reported a disturbed microcirculation in congenitally hydrocephalic brain, especially at the level of endothelial cells of capillaries and venules in the periventricular edematous region. Glees *et al.* [48] studying the microvasculature in hydrocephalic human infants have postulated a possible role of endothelial pinocytotic vesicle as a transcellular route for hydrocephalic edema resolution, and considered that CSF or edema fluid is absorbed into the vascular system via a transendothelial pathway. Increased pinocytotic transport also occurs in traumatic human brain edema [25,26]. Since both traumatic and high pressure hydrocephalic human brain edema initially have a common mechanical origin, the reactivity and behavior of endothelial cells are apparently the same in both nosological entities. Hasan and Glees [52] have postulated a possible role of perivascular pericytes and juxtavascular phagocytes in hydrocephalic edema resolution. In an early publication [107] we have reported that pericytes also exhibit remarkable edematous changes, increased vesicular and vacuolar transport, formation of transient transpericytal channels, and tubular structures in human brain edema associated to brain trauma, tumor and congenital malformations.

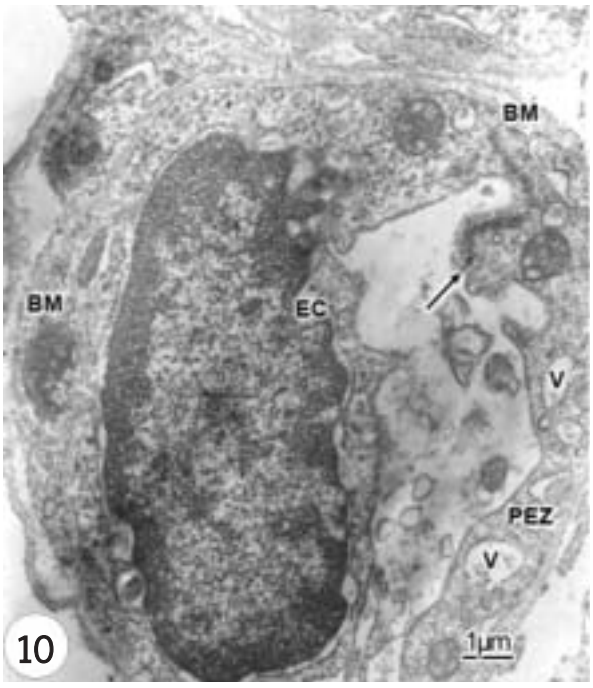

Fig. 10. Congenital communicant hydrocephalus. Right parietal cortex. 1 month-old female patient. Cross section of an isolated capillary within a disrupted neuropil showing the endothelial cell (EC) containing large vacuoles (V) at the peripheral endothelial zone (PEZ). The long arrow points out the tight endothelial junction. A thin basement membrane (BM) is observed.

Presence of myelin figures

Numerous myelin figures are observed in nerve cells and astrocytes in human congenita hydrocephalus, suggesting that the pressure exerted by the interstitial edema, and the anoxic ischemic conditions of brain parenchyma induce the concentrically arrangement of nerve cell cytomembranes [22]. Apparently these concentric lamellar formations are conformational changes induced by the high pressure exerted by the non-circulating cerebrospinal fluid present in the dilated extracellular space upon the immature plasma membranes, which have distinct macromolecular composition, characterized by changes in integral membrane proteins, cholesterol domains, and in certain carbohydrates residues and anionic sites [100]. Myelin figures could be considered markers of nerve cell degeneration, and nerve cell death.

The cerebrospinal fluid edema associated to hydrocephalus

The hydrocephalix cerebral cortex neuropil formed by an intricate complex of neuronal and neuroglial cell processes shows notable enlargement of the electron lucid extracellular space located among these processes (Figs. 3, 4, 6, 8-10), which is occupied by a non-proteinaceous and non-circulating CSF. The enlargement of extracellular space is more evident than the dilation of intracellular space. Lacunar extracellular spaces are constantly found at the meeting point of three or four

nerve cell processes. The pressure of the non-circulating CSF induces separation, indentation and rupture of nerve cell processes [22,28]. Similar observations were earlier reported by Struck and Hemmer [97] and Foncin *et al.* [45] in the gray matter of human hydrocephalus. Such observations could also be correlated with previous studies on experimental and human congenital hydrocephalus, in which enlargement of the periventricular subependymal space has been widely reported [41,70,71,78,109,110]. Kriebel *et al.* [62] also found edematous extracellular space in experimental infant hydrocephalus. The increased extracellular space of the human hydrocephalic cortical neuropil suggests the establishment of a transparenchymal route for fluid absorption through the cortical capillaries [22,70,71].

The penetration of CSF induces edematous and degenerative changes in the neighboring neurons, neuroglial cells and synaptic regions [15,17,19,20,22]. The damage of the gray matter results from both hydrostatic forces and biochemical alterations induced by the extracellular pooling of CSF, and also by the expansion forces or stretching effects produced by the ventricular enlargement.

Nerve cell death in human hydrocephalus

In human congenital hydrocephalus, nerve cells undergo a coexisting oncotic and apoptotic process, characterized by cytoplasmic and plasma membrane blebbing, remarkably swollen mitochondria and endoplasmic reticulum canaliculi and cisterns, dense nucleoplasm with a condensed chromatin, formation of apoptotic bodies, and increased number of perichromatinic granules [17]. According to Majno and Joris [66] and Trump *et al.* [105], these features have been characterized as oncosis. Both types of combined nerve cell death are considered as leading to necrosis. This later conceptualized as the changes that occur after nerve cell death [17]. Although apoptosis and necrosis are mediated through distinct pathways, in human hydrocephalus we have found a continuum oncosis, apoptosis and necrosis, depending of the severity of cerebrospinal fluid edema, the age of the patients, and the moderate or severe anoxic-ischemic conditions involved. The oligodendroglial cells appear in some cases exhibiting a normal structure (Fig. 11), and undergoing mainly apoptosis (Fig. 12) featured by nuclear chromatin condensation and formation of cytoplasmic apoptotic bodies. Oligodendrocytes also exhibit oncosis featured by enlarged and disrupted perinuclear cistern widely communicated with the vacuolated endoplasmic reticulum, and the dilated extracellular space, suggesting that the oncotic cell death is due to the high pressure exerted by the interstitial hydrocephalic edema or probably occurring in areas with milder or severe forms of ischemic damage (Fig. 13). The astrocytes also show apoptosis only (Fig. 14), or a combined oncotic and apoptotic cell death [17] featured by strong chromatin condensation, disrupted swollen cytoplasm and fragmented limiting plasma membranes. These hybrid forms of astrocyte cell death lead to necrosis (Fig. 15).

In congenital hydrocephalus, neurons suffer a clear apoptotic process characterized by chromatin condensation and formation of typical apoptotic bodies. Necrotic neurons show fragmentation and dissolution of cytoplasm, and mitochondria, Golgi complex and lysosome degeneration.

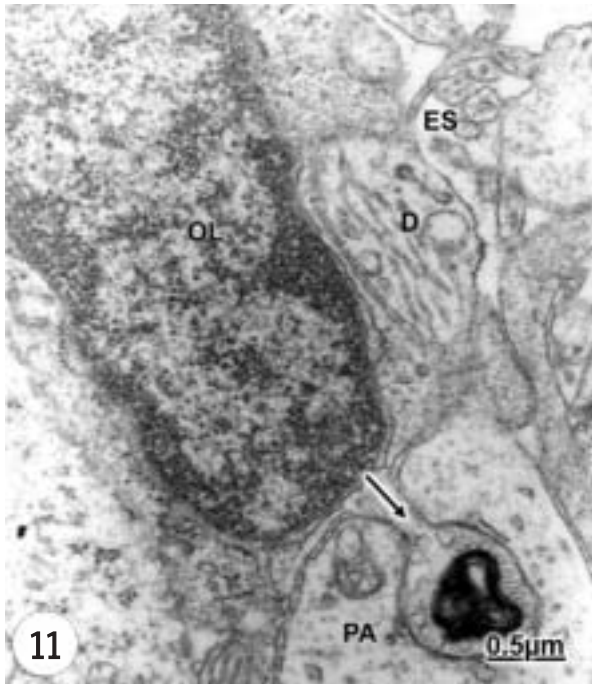

Fig. 11. Congenital hydrocephalus. Right frontal cortex. 4 months-old female patient. Oligodendrocyte (OL) showing an apparently normal morphology and a dendritic process (D) containing microtubules. The pseudopodic expansions of a phagocytic astrocytic (PA) also are seen. The arrow indicates the engulfed degenerated process. Note the dilated extracellular space (ES).

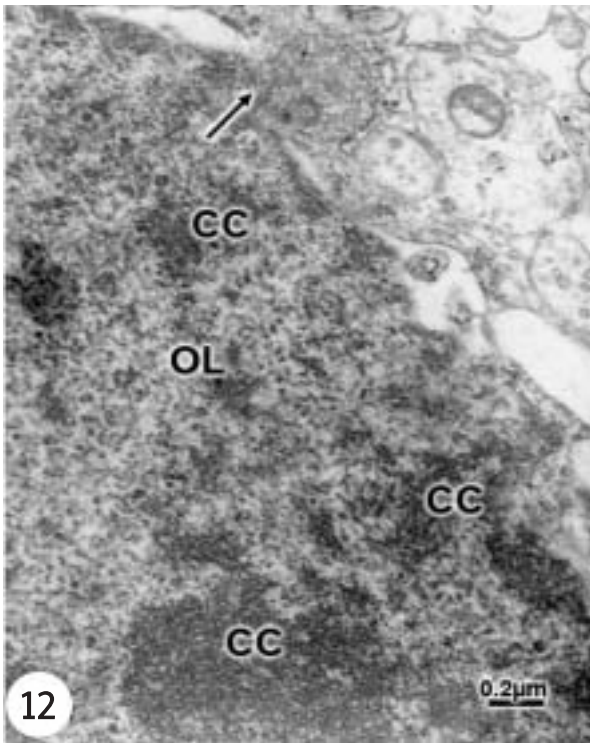

Fig. 12. Communicant hydrocephalus. Right frontal cortex. 7 months-old male infant patient. Apoptotic oligodendrocyte (OL) showing chromatin condensation (CC), and protrusion of nucleoplasm toward the cytoplasm (arrow).

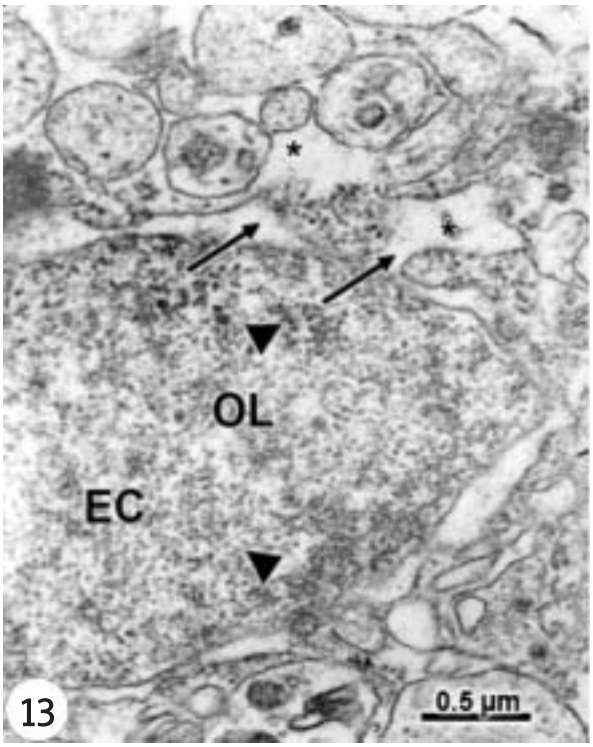

Fig. 13. Chiari malformation. Communicant hydrocephalus. Right frontal cortex. 10 days-old neonate. Severely edematous oligodendrocyte (OL) leading to oncotic cell death featured by wide communications between the perinuclear cistern and rough endoplasmic reticulum (arrows) and the extracellular space (asterisks). Note the decondensed state of nuclear euchromatin (EC) featured by granular and fibrillar organization (arrowheads).

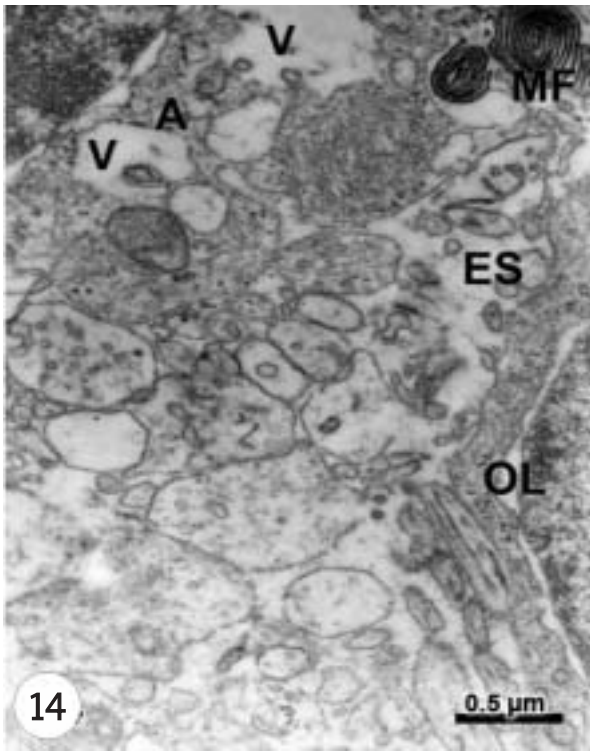

Fig. 14. Postmeningitis hydrocephalus. Right frontal cortex. 3 months-old male infant patient. Swollen astrocyte (A) showing oncotic cell death type and vacuolar degeneration (V) of cytoplasm. Myelin figures (MF), a swollen oligodendrocyte (OL), and the enlarged extracellular space (ES) also are distinguished.

In congenital hydrocephalus and Chiari malformations we are dealing with immature brains, where oncosis, apoptosis and necrosis also occur as a continuum, as previously described by Martin [68] in inmmature brain parenchyma. In these cases the nerve cell populations exhibit high vulnerability, and support the hypothesis of Portera-Cailliau *et al.* [88] that excitotoxic neuronal death in the immature brain is not an uniform event but rather overlapped morphological processes, with a distinct phenotype of neurodegeneration. Autophagic cell death has not been reported until now in human hydrocephalus.

The nerve cell death in congenital hydrocephalus is related with the severity of brain edema, anoxic-ischemic conditions of brain parenchyma, oxidative stress, glutamate excitotoxicity, calcium overload, and caspase dependent and independent mechanisms [11,17,105].

In relationship with nerve cell death in experimental hydrocephalus, Naruse and Keino [81] earlier described abnormal apoptosis inducing hydrocephalus. Del Bigio and Zhang [37] found nerve cell death in kaolin-induced rat hydrocephalus. Mori *et al.* [77] reported neuronal and oligodendrocyte cell death in the thalamus of hydrocephalic HTx-rats. More recently, Nonaka *et al.* [82] postulated a molecular mechanism related with accumulation of tau protein that induces neuronal death in the cerebral cortex of compensated HTx-rat hydrocephalus.

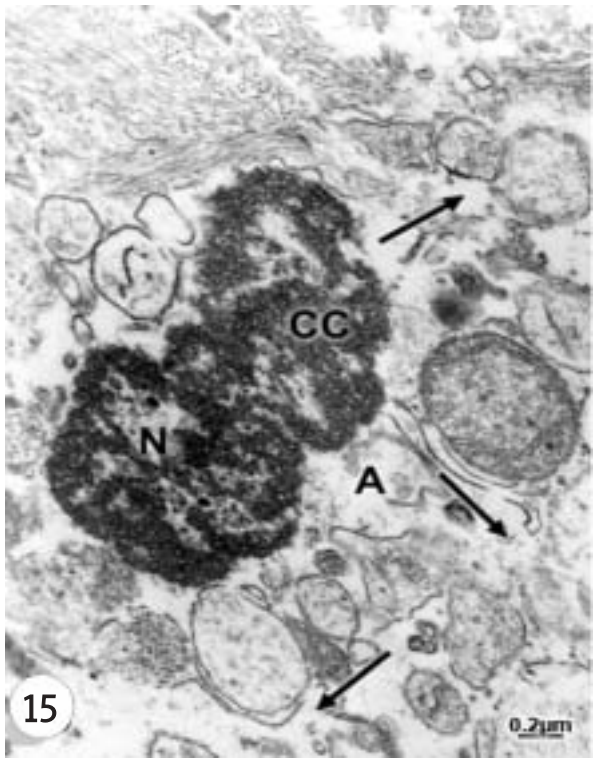

Fig. 15. Chiari malformation type II. Hydrocephalus. Right parietal cortex. 2 months-old female infant patient. Swollen astrocyte (A) showing a combined oncotic and apoptotic cell death process leading to necrosis characterized by a disrupted and swollen cytoplasm, and a fragmented plasma membrane communicated with the enlarged extracellular space (long arrows). Note the shrunken lobulated nucleus (N), and the strong chromatin condensation (CC).

Concluding remarks

Hydrocephalic nerve cells exhibit intracellular edema characterized by dilation of endoplasmic reticulum canaliculi and perinuclear cistern. Some degranulated areas of rough endoplasmic reticulum, edema and degenerative changes of Golgi apparatus, variable degrees of mitochondrial swelling, lysosomal damage, and fragmented limiting plasma membrane are observed. These edematous changes and the degranulated rough endoplasmic reticulum could be correlated with the impairment of protein synthesis, reduced cerebral glucose and oxygen metabolism, and changes in the levels of neurotransmitters reported in the hydrocephalic cerebral cortex. Myelination delay and axonal and oligodendroglial cell damage are reported in both human and experimental hydrocephalus. Damage of myelinated axons is found in the white matter. Myelinated axons are not observed in some neonate patients. The dendrites show edematous changes, irregularly beaded shaped, vacuolization and elongated dark mitochondria. A variety of swollen spine shapes are found such as mushroom type, filopodic and lanceolate spines. Some spines appear axonless or unattached, and others are making asymmetric axodendritic synaptic contacts. Signs of synaptic plasticity and synaptic degeneration are observed. Megaspines also are distinguished. The damage of nerve cell processes and synaptic contacts indicates nerve cell circuit alterations in the hydrocephalic cortex, which might explain some clinical and neurological symptoms, such as decline in intellectual functions and learning disabilities, motor deficits, and seizures observed in infant hydrocephalic patients. Hydrocephalic edema and ischemia, oxidative stress, increased calcium concentration, activation of NMDA receptors, and disturbance of ion homeostasis are

Table I. Comparison of major findings in human and experimental hydrocephalus.

Nerve cell alterations	Human hydrocephalus	Experimental hydrocephalus
Neurons	Intraneuronal edema, degenerative changes of nerve cell body, dendrites, and axons, demyelination (Castejón [18-24], Glees and Voth [48])	Neuronal degenerative changes in HT-x rats (Boillat *et al*. [7,8]); myelination delay (Del Bigio *et al*. [35]); dendritic alterations (Kriebel *et al*. [62], Mc Allister *et al*. [69], Harris *et al*., [51]); extensive cell death (Aolad *et al*. [3]); swollen and fragmented axons (Aoyama *et al*. [4]); axonal injury (Del Bigio and Zhan [37])
Glial cells	Proliferation of olidendrocytes vacuolation of microglia (Glees and Hassan [47]); defect in oligodendrocyte development (Goto *et al*. [50]); phagocytic astrocytes (Castejón [15,16,22]); glycogen rich- and glycogen depleted-astrocytes (Castejón [16])	Astroglial and microglial reaction (Khan *et al*. [60], Aoyama *et al*. [4], Klinge *et al*. [61])
Synaptic changes	Synaptic plasticity and degeneration (Castejón [20,22])	Synaptic plasticity (Tsubokawa *et al*. [106])
Nerve cell death	Apoptosis, oncosis, necrosis as a continuum (Castejón and Arismendi [17])	Apoptosis (Naruse and Keino [81]); nerve cell death (Del Biggio and Zhan [37], Mori *et al*. [77], Nonaka *et al*. [82])
Blood-brain barrier	Increased vesicular and vacuolar endothelial transport (Castejón [25]); closed and open endothelial junction, fragmented capillary basement membrane; enlarged perivascular space (Castejón [22,25,27]); transendothelial and pericyte route for hydrocephalic edema resolution (Glees *et al*. [46,52], Hassan and Glee [52])	Normal operating BBB, intact endothelial junctions in hy-3 mouse neonate hydrocephalus [70], open endothelial junctions (Nakayawa *et al*. [80])
Extracellular space	Marked extracellular space (Struck and Hemmer [97], Castejón [28], Foncin *et al*. [45])	Reduced extracellular space in kaolin induced hydrocephalus (Del Bigio and Enno [32]); enlarged extracellular space (Weller *et al*. [111,112], Mc Lone *et al*. [71], Mori and Raimondi [78], Kriebel *et al*. [62], Alliev *et al*. [2])

apparently related with the synaptic plasticity and synaptic degenerative changes observed in human hydrocephalus. Astrocyte cells show notable edematous changes and phagocytic activity. Glycogen rich- and glycogen depleted astrocytes are found in congenital hydrocephalus. These latter findings suggest astrocytic glycogen mobilization during anoxic and ischemic conditions, revealing the important contribution of astrocytes on neuronal survival under conditions of energy substrate limitations. The capillary wall shows evident signs of blood-brain barrier dysfunction characterized by increased endothelial vesicular and vacuolar transport, closed and open interendothelial junctions, thin and fragmented basement membrane with areas of focal thickening, and discontinuous perivascular astrocytic end-feet. The perivascular space is notably dilated and widely communicated with the enlarged extracellular space in the neuropil. The increased extracellular space of the human cortical neuropil suggests the establishment of a transparenchymal route for fluid absorption through the cortical capillaries. In human congenital hydrocephalus, non-pyramidal neurons and astrocytes undergo a coexisting oncotic cell death and apoptotic process leading to necrosis. Oligodendrocyte cells exhibit mainly oncotic cell death. The nerve cell death in congenital hydricephalus is related with the severity of brain edema, anoxic-ischemic conditions of brain parenchyma, oxidative stress, glutamate excitotoxicity, calcium overload, and caspase dependent and independent mechanisms.

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