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Neuropathological Changes in Hydrocephalus—A Comprehensive Review

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Abstract

Hydrocephalus is a heterogeneous, neurological condition characterized by altered flow of cerebrospinal fluid (CSF) that can occur at any age. Neuropathological changes associated with hydrocephalus are dependent on the age of onset, rate of ventricular enlargement, and the etiology. Hydrocephalic brain damage is also influenced by contributions from both mechanical forces and metabolic changes, which increases the heterogeneity of the condition. However, as ventriculomegaly progresses, the surrounding brain tissue is compressed within the cranial vault, elevating intracranial pressure and eventually leading to severe brain damage. From this perspective, it makes sense that periventricular brain regions are the initial sites of damage as ventricular dilatation occurs. The following review of neuropathological changes in hydrocephalus will first discuss cellular and region specific damage from the ventricles and outward towards the cortex and brainstem. This will be followed by vascular and hypoxic changes associated with the condition. Both types of brain impairments are dependent on the severity of the condition, and they will be described accordingly.

Keywords

Hydrocephalus, Neuropathology, Brain, Vascular, Hypoxia

1. Introduction

Hydrocephalus is a heterogeneous, neurological condition that can occur at any age. The neuropathological consequences of hydrocephalus are dependent on the age of onset, rate of ventricular enlargement, and the etiology [1] [2] [3] [4]. Even gene expression has been shown to change in the hydrocephalic rat brain depending on the age of onset and duration of the condition [5]. Brain damage

associated with the condition is also varied with contributions from both mechanical forces and metabolic changes that are difficult to distinguish [6]; however, as ventriculomegaly progresses, the surrounding brain tissue is compressed within the cranial vault, leading to increased intracranial pressure and eventually severe brain damage. From this perspective, it makes sense that periventricular brain regions/structures are the initial sites of damage as ventricular dilatation occurs. The following description of neuropathological changes in hydrocephalus will first discuss cellular and region specific damage from the ventricles and outward towards the cortex and brainstem. This will be followed by vascular and hypoxic changes associated with the condition. Both types of brain damage/impairment are dependent on the severity of the condition, particularly before therapeutic intervention commences.

2. Structural, Regional, and Cellular Changes

2.1. Ependymal Layer

The ependyma is a layer of cells that surrounds the ventricles of the brain and central canal of the spinal cord. These cells proliferate and differentiate during prenatal and early postnatal development with minimal proliferative activity in adult mammals, and they may have critical protective barrier functions during neural tube formation and neurodevelopment; however, their function in adult brains and response to injury are not well known [7] [8] [9] [10] [11]. When hydrocephalus occurs, it is possible for the ependymal layer to remain intact [12], but it is typically affected ranging from being stretched or torn [13] [14] to being completely abolished [10], which is referred to as ependymal denudation [15] [16] [17] that leaves only small collections of cells to line the ventricular wall [8] [18]. Animal models have shown that ependymal distortion and damage can commence by around 12 hours following CSF obstruction in the ventricles [19] [20] [21]. The different columnar and cuboidal ependymal cells can stretch but remain intact [22] [23], possibly as a protective mechanism, but this is limited by the severity of ventriculomegaly and rate at which expansion occurs [24]. Ependymal damage also ranges based on the brain regions it lies deep to, where ependyma overlaying the periventricular white matter at the dorsolateral angle and roof of the lateral ventricles [21] [25] and septum pellucidum [22] are the most severely affected. Such damage is subsequently followed by an inflammatory response with macrophages emerging on the ependymal surface [3] [26]. Several studies have shown an inability for ependymal cells to regenerate after hydrocephalus develops [17] or is induced [24] [27] [28], but there is evidence that increased mitotic activity of existing ependymal cells occurs after hydrocephalus induction [22]. Thus, ependyma damage occurs early after ventricular expansion, and it is not certain whether ependymal layer regrowth is possible, particularly as ventriculomegaly worsens.

2.2. Subventricular Zone

The brain region adjacent to the ependyma is the subependymal zone (SEZ) or

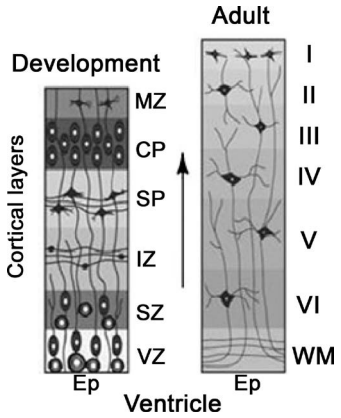

Figure 1. Cortical layering during development and adult cerebral cortex. CP—cortical plate; Ep—ependymal layer; IZ—intermediate zone; MZ—marginal zone; SP—subplate; SZ—subventricular zone; VZ—ventricular zone; WM—white matter. Image adapted from Stiles & Jernigan (2010). "The basics of brain development." Neuropsychol. Review, 20: 327-348, Figure 9b [262].

subventricular zone (SVZ) **Figure 1**. It is a thin area that persists from the embryonic germinal eminence (GE) that forms the lateral wall of the lateral ventricles, but it is virtually nonexistent over the third ventricle, cerebral aqueduct, and fourth ventricle [29] [30]. It is the site of neurogenesis where cell proliferation of newly formed brain cells continues into adulthood and is continually sent to different areas of the brain, including neurons through the rostral migratory stream to the olfactory bulbs and in the dentate gyrus of the hippocampus, as well as glial cells to the corpus callosum and cerebral cortex [31]. It has a strictly controlled cytoarchitecture containing astrocytes, small blood vessels, and three types of neural stem cells (NSCs) including self-renewing pluripotent precursors, neuroblasts or neuronal progenitor cells (NPCs), and oligodendrocyte precursors (OPCs) that are spatially located in specific positions [30] [31] [32] [33]. In humans and experimental models of hydrocephalus, periventricular reactive gliosis occurs within and surrounding the SEZ/SVZ, which may involve either or both hyperplasia or hypertrophy of glial cells [8] [17] [19] [34]-[39]. Various studies have also shown changes in cell numbers and mitotic activity within this region associated with hydrocephalus, where some studies have shown increased cell quantity [28] and cell proliferation [22] [40]. More recent work tends to show appreciable thinning and disorganization of the SVZ, along with a substantial decrease in cell proliferation overall [35] [37] [41] [42] [43] [44], as well as impaired mitotic cell cycling and migration of germinal cells away from the SVZ [45] [46], which may be associated with aberrant expression of neurotrophic factors in the ventricular zone (VZ) [43] [47] [48]. These impairments could disrupt neuronal organization [49], but human fetuses with hydrocephalus often exhibit no abnormalities in the germinal matrix and cortical organization [6]. There is also an increase in oligodendrocyte [40] and activated cell death in the SVZ and periventricular regions [44], as well as a decrease in Olig2-positive cells that could be indicative of glial precursor or mature oligodendrocyte li-

neage [35]. Overall, the SEZ/SVZ is an important proliferative brain region that seems to be affected greatly by ventricular expansion.

2.3. Periventricular Axons and White Matter

With hydrocephalus, primary destruction of periventricular axons and white matter occurs early after onset with ventricular expansion causing physical stretching and compression to eventual axonal destruction as brain damage progresses [4] [50]. In humans and animal models, severe hydrocephalus is associated with appreciable corpus callosum thinning and compression of periventricular and subcortical white matter [4] [6] [14] [17] [35] [40] [41] [51]-[56]. Callosal injury is caused primarily by stretching, but dorsal grooving of the corpus callosum can occur from impingement on the falx cerebri [57], and such damages can lead to hemispheric disconnection [58] [59]. Destruction of the corpus callosum and fimbria/fornix in rat and human brains produces myelin degradation products and correlates with motor and cognitive deficits [60], whereas callosal size in hydrocephalic patients showed no correlation to cognition [61]. Compared to adults with hydrocephalus, early-onset hydrocephalus tends to show more compression of periventricular regions surrounding the occipital horn of the lateral ventricles because their expansion is more pronounced early in life [62] [63]. Axonal injury and focal petechial hemorrhage can occur in acute hydrocephalus, particularly at the angles of the ventricles [6]. Axonal degeneration and damage are commonly reported in hydrocephalic brains [28] [35] [55] [56] [64] [65] [66], where axonal cytoskeletal damage occurs through a calcium-mediated activation of proteolytic enzymes [67], and varicose enlargements of damaged but intact axons that are immunoreactive for amyloid precursor protein can be observed shortly after the onset of hydrocephalus [6] [68]. Chronic hydrocephalus is also associated with a loss or disconnection of axons [68] [69] [70], and degenerative changes can occur in human corticospinal tracts and animal spinal cords [4] [6] [60] [65] [71] [72]. Myelin loss occurs secondarily to axonal damage and loss [3] [39] [73] [74] [75], which may be caused by periventricular white matter edema [56] [76] [77] or related to elevated CSF levels of pro-apoptotic factor soluble FasL [78], but these remain uncertain. Myelin deposition in the young rat, cat, and infant brain is delayed by hydrocephalus [40] [51] [79] [80] [81], and myelin turnover is increased in chronic hydrocephalus [60]. There is also increased oligodendrocyte and apoptotic cell death, as well as reactive astroglial and microglial changes and phagocytosis that occur in the white matter [3] [35] [40] [51] [52] [73] [82].

2.4. Extracellular Spaces and Water Content

In the periventricular region, human and animal studies have shown that the hydrocephalic brain is edematous in association with increased intracranial pressure [83] [84] [85]. Brain tissue water content is elevated as far as 3 mm from the ventricle surface in hydrocephalic animals [86] [87] [88] [89] [90].

Extracellular spaces in the brain and periventricular white matter have been histologically shown to be enlarged in humans [91] [92] and animals [56] [73] [93], but these have only been verified ultrastructurally to 200 μm from the ventricular surface [13] [22] [55] [94]. Numerous researchers believe that increased extracellular spaces may serve as diffusional pathways for "displaced CSF" based on using tracer agents from the ventricles into periventricular parenchyma [95] [96] [97] [98], but this is not certain because the brain produces extracellular fluid that flows into CSF spaces [99]. Alternately, research with hydrocephalic mice [100] [101] and rats [102] found compression of extracellular spaces in the gray matter of the cortex, while humans showed increases [103] that are not present in the caudate nucleus [22] [23]. However, it should be noted that some changes might be artifactual in some of these studies based on tissue fixation methods. Meanwhile, studies with hydrocephalic humans [104] and animals [105] [106] [107] have also shown decreased water content in the whole brain, cortex, and/or gray matter. CSF outflow and clearance of metabolic waste products and neurotransmitters are decreased in the hydrocephalic brain, and these extracellular changes further disrupt the microenvironment, which could impede neuronal function [4] [8] [108] [109].

2.5. Cerebral Cortex and Subcortical Regions

The cerebral cortex and subcortical structures are also affected by hydrocephalus, particularly as ventriculomegaly becomes more severe, where cortical thinning and distention are prevalent, along with stretching of the septum pellucidum [17] [19] [110]. In young infants with ventricular enlargement, cortical thinning is most apparent in the occipital regions [3] [8], and some infants may develop polygyria due to intrasulcal cortical unfolding [6] [111]. The cortical subplate can be disrupted, which could lead to subtle developmental abnormalities [42] [112]. Ventricular expansion can lead to cortical compression, which could eventually cause destruction of deep layers of the cortex, focal cortical dysgenesis, and neuronal loss, particularly if the white matter is completely destroyed [3] [6] [8] [39] [51] [73] [113]-[118]. The infundibular recess of the hypothalamus is typically enlarged in hydrocephalic children [119] [120] [121]. It has also been documented that hydrocephalus could impair the functional organization of the brain in children, along with disrupted structural brain development [122]. In this regard, microgyria has been found in hydrocephalic humans [121], as well as impaired NPC proliferation and migration in some infants [49]. Severe hydrocephalus can eventually cause swollen dendrites and axons, a decrease in dendritic spines and branching or even elimination of neuronal dendrites in the cortex and hippocampus [123]-[128] corresponding to an accumulation or loss of synaptic vesicle proteins (such as synaptophysin) and a loss of synapses [40] [127] [129] [130] [131] [132] and atrophy of the cerebral cortex and basal ganglia [8] [51] [64] [92].

Histological changes in the cerebral cortex are subtle and have often been

overlooked [3] [8], but neuronal pyknosis and degeneration have been found in children and adults with hydrocephalus [133] [134], as well as cytoplasmic vacuolization in the hippocampus [135]. Hydrocephalic animal models have identified similar findings, as well as shrunken and dark cell changes, swelling, cell loss, and membrane disruption of neurons in the cerebral cortex, hippocampus, septal area, caudate nucleus, thalamus, and hypothalamus [8] [56] [64] [119] [121] [136]-[143]. Chronic severe hydrocephalus is also associated with reactive astrogliosis in the cortex, as well as neurofibrillary tangles in cortical, hippocampal, and brainstem neurons [8] [114] [144]-[149]. Reactive changes can occur in neurons as well, which may be protective, including upregulation of bcl-2, growth-associated protein-43 (GAP-43), nerve growth factor, and other protective proteins [5] [150] [151] [152] [153]. Meanwhile, neurochemical changes in the septohippocampal system of hydrocephalic patients [154]-[159] and animals [160] [161] [162] [163] are associated with memory and learning impairments. However, one study found that memory dysfunction in hydrocephalic adults was associated with septohippocampal changes when it was due to aqueductal stenosis, whereas memory deficits in normal pressure hydrocephalus appeared related to prefrontal structural damage [164]. Hydrocephalus may also impair neuronal function by changing neural conduction along functional pathways [165]-[170], impeding long-term potentiation [127] [171], and decreasing the responsiveness or size of neurons in the visual cortex [138] [172]. Other damage has been documented along the visual pathway due the ventricular enlargement including damage to the geniculo-cortical pathway/optic radiations, distention of the pineal recess of the third ventricle leading to upward gaze palsy, or even ischemic damage due to compression of the posterior cerebral artery [169] [173] [174] [175] [176] [177]. Hydrocephalus is also associated with changes in the concentrations or function of different neurotransmitters, neuropeptides, and receptors [8] [157] [178]-[188], disrupting the clearance of various metabolites from the brain [108] [118] [189] [190], and inducing neuroendocrine disturbances by altering hormone production or secretion that may be due to distortions of the pituitary or hypothalamus [191]-[196].

2.6. Cerebellum and Brainstem

There are also neuropathological changes in the cerebellum and brainstem. The shape of the cerebellum is distorted in people with spina bifida and hydrocephalus [197]. Although the Chiari II malformation is associated with cerebellar, brainstem, and fourth ventricle deformities [17] [198] [199] where subsequent hydrocephalus often develops, this malformation likely occurs secondary to myelomeningocele instead of ventriculomegaly [200] [201]. There may be abnormal degeneration and stunted growth of the central lobes of the cerebellum, which seems to develop normally at first [202], which could be associated with ischemic changes [203] [204] [205]. There are also changes in neurotransmitter levels in the cerebellum of hydrocephalic animals [190] [206], as well as increas-

es in reactive oxygen species after ventricular dilatation commences in the hydrocephalus Texas (H-Tx) rat [207], which may account for impaired cerebellar functioning observed in those with spina bifida [208]. Historically, a severely misshapen medulla oblongata was often reported in the literature [17], but such brainstem changes are not observed that often today, which are possibly due to early surgical intervention on affected individuals or increased abortions rates [4]. As mentioned previously, descending axons and white matter corticospinal tracts in the brainstem and spinal cord can be damaged as hydrocephalus progresses [4] [6] [60] [71], and neurofibrillary tangles can be observed in brainstem neurons with chronic severe hydrocephalus [8]. Thus, cerebellar and brainstem changes can occur with hydrocephalus, but more detailed investigations are necessary to determine more clearly how these brain structures are affected by this condition.

3. Vascular and Oxidative Pathogenesis

3.1. Cerebral Blood Flow and Vascular Changes

As the cerebral ventricles enlarge, tissue compression and axonal stretching and tearing occur, but hydrocephalus also adversely affects cerebral metabolism, cerebral blood vessels, and cerebral blood flow especially in the white matter [4] [8] [209] [210] [211] [212] [213]. In particular, white matter ischemia or hypoperfusion happens simultaneously to the tissue damage [50] [68] [214], and there is reduced cerebral blood flow, which is correlated with the size of the ventricles in infants [215] [216] [217] [218]. Adults with hydrocephalus also experience reduced cerebral blood flow, particularly in the frontal lobes [8] [219], and extended periods of elevated intracranial pressure above normal cerebral perfusion thresholds often lead to worse outcomes for young and older patients with the condition [220]. Animal studies also show reduced cerebral blood flow and ischemic changes with hydrocephalus, as well as changes in oxidative metabolism in the cortex and subcortical regions, including the hippocampus [79] [87] [207] [213] [221] [222] [223] [224], which are more prominent during early stages while ventricular enlargement is actively taking place [2] [88].

3.2. Microvascular Changes

Microvascular changes in hydrocephalus were first identified long ago by Penfield [134] who was apt to recognize that ventricular enlargement likely impeded the vascular supply to the brain. Later studies were able to show decreased density of capillaries in the corpus callosum of humans with hydrocephalus [52], as well as decreased number, caliber, and patency of capillaries in periventricular white and gray matter of experimental and mutant animal models of hydrocephalus [64] [117] [211] [225] [226] [227] [228]. Some of these studies suggested that capillary loss may be due to the combinatorial effect of increased CSF pressure and distortion of brain tissue, and reduced cerebral blood flow could result if this loss was extensive enough. When examining the endothelial cells of capil-

laries in hydrocephalic human brains, they were found to have numerous pinocytotic vesicles [6] [229] [230] and enlarged extracellular spaces [231]. In experimental animal studies, some report a normal ultrastructure [56] [94], while others have observed edema of endothelial cell cytoplasm [137] and separations of endothelial tight junctions in periventricular white matter [226] [227], which might be associated with an alternate route for CSF absorption. Related to this, the blood-brain barrier (BBB) appears to remain intact with hydrocephalus, so the role of BBB alterations in hydrocephalus is unclear [50]. Indirectly, it is known that the composition of CSF [108] and extracellular fluid is altered in hydrocephalus [3]. In addition, the movement of water and extracellular tracers are restricted [106] [214] [232] [233], whereas water normally exchanges across the BBB relatively freely [234] [235] [236]. Other suggestive evidence of altered permeability of the BBB has been observed in hydrocephalic adult patients who display changes in the relative levels of CSF albumin and plasma-derived immunoglobulin G [237]. In addition, one study found that aquaporin 4, but not aquaporin 1 or 9, expression was elevated in hydrocephalic rat brains, and it was postulated that this change might facilitate the efflux of water from the brain through astrocytes into the capillaries [238]. Meanwhile, another study showed that hydrocephalic rats exhibited only focal and perhaps transient increased opening of BBB permeability, which was speculated to relate mainly to mechanical disruption of small periventricular blood vessels rather than a generalized capillary phenomenon [239].

3.3. Choroid Plexus

The choroid plexus is a tight epithelium surrounding a vascularized stroma that is located within the roof of all four ventricles and produces most of the CSF in circulation. Because of its unique location, the choroid plexus is a circumventricular organ that forms one of the interfaces between the blood and the CSF, and it is important for contributing to brain homeostasis, where it is involved in various biochemical exchanges supplying or removing nutrients, peptides, hormones, metabolites, and waste [240]. In regards to its main function, CSF overproduction by the choroid plexus is a rare a cause of hydrocephalus [3] [8] [241]. Some studies of experimental hydrocephalus have reported a normal choroid plexus [24] [64] [242], whereas many others have described various alterations including distortion of microvilli, compression and vacuolization of choroidal cells, increased intracellular spaces and inclusions, and epithelial atrophy [26] [70] [243] [244] [245] [246]. In humans with chronic hydrocephalus, atrophy of the choroid plexus epithelium and stromal sclerosis have been observed [8] [17] [50] [92] [121]. Such changes have been suggested to be associated with reduced secretory functioning of the choroid plexus [34] [50] [247] [248] [249] [250]. In addition to the choroid plexus, other circumventricular organs have shown changes in hydrocephalic animals, such as increases in angiotensin II receptor content in circumventricular organs [251], the subcommissural organ that is de-

creased in size [252] and exhibits decreased glycoprotein immunoreactivity [253], and the subfornical organ can become damaged as the condition progresses [254].

4. Hypoxic, Oxidative, and Nitrosylative Changes

Since hydrocephalus is associated with tissue compression, reduced cerebral blood flow, and periventricular white matter ischemia, studies have also shown that periventricular white matter undergoes hypoxic, oxidative, and nitrosylative changes [255]. In particular, pimonidazole hydrochloride, which forms adduct with thiol groups in proteins of hypoxic tissue [256], is detectable in periventricular capillaries and white matter glial cells [255]. Numerous studies have found that hydrocephalic rodent brains exhibit oxidation and lipid peroxidation, which proceeds oxygen free radical damage to cell membranes and is indicative of hypoxic and oxidative changes [36] [207] [255] [257] [258] [259] [260]. In the CSF of hydrocephalic children, various metabolites suggestive of hypoxic metabolism have also been detected [108] along with lipid peroxidation [261]. Some studies with H-Tx rats found decreased intensity of histochemical staining of neurons for NADPH-diaphorase [139] and detected protein nitrosylation associated with oxidative stress [207]. Meanwhile, other studies found increased nitric oxide synthase (NOS) immunostaining [222] and elevated mRNA levels of a neuronal NOS inhibitor in hydrocephalic rats [5]. Lastly, nitrotyrosine has also been detected in periventricular white matter vessels along with increased nitric oxide production in the brains of hydrocephalic rats, which are suggestive of nitrosylative, hypoxic changes associated with the condition [255].

5. Summary and Future Research Prospects

Hydrocephalus is a neurological condition characterized by altered CSF flow leading to an accumulation of CSF inside the cranial vault. The neuropathological changes associated with hydrocephalus arise from both mechanical forces and metabolic changes, and they are heterogeneous due a variety of factors including the age of onset, rate of ventricular enlargement, and the etiology. Ventriculomegaly causes compression of brain tissue within the cranial vault, which increases intracranial pressure and leads to severe brain damage. In this review, hydrocephalic neuropathological changes have been described based on research with humans and animal models of the condition, which includes cellular and region specific damage, along with vascular and hypoxic changes. Overall, hydrocephalus can occur at any age from multiple causes and displays varied levels of severity, which is why neuropathological changes associated with the condition are highly heterogeneous. Despite the wealth of knowledge about the neuropathological changes associated with hydrocephalus, these changes are derived from multiple factors and are not completely understood. Moreover, there is currently no definitive cure for hydrocephalus, which is strongly associated with the multifactorial etiology and heterogeneity of the condition. Current strategies

to treat hydrocephalus are primarily through surgical intervention by way of ventricular shunting and/or endoscopic third ventriculostomy, but these procedures are associated with both similar and unique complications. Nonsurgical pharmacological approaches for treatment are being extensively investigated through preclinical animal models of hydrocephalus. Though various therapeutic agents have potentially shown beneficial outcomes, they have mainly been tested in rodent models and are not necessarily curative on their own. Thus, future research should be focused on using gyrencephalic animal models to confirm the neuropathological changes observed in rodent models and establish credibility of therapeutic effects obtained in those studies to advance towards clinical trials with these pharmacological agents. There is also very little to no animal or clinical data on the synergistic effects of combined surgical and nonsurgical approaches in treating hydrocephalus. Thus, it is integral that future research is aimed towards examining drug agents that have shown promise for various aspects of brain protection in response to ventriculomegaly, and then administer them in conjunction with surgical interventions. Such attempts would ensure that a surgical procedure is performed to reduce mechanical pressure and ventricular enlargement associated with CSF buildup, while therapeutic agents would be aimed at reducing tissue or cellular damage. If more imaging, behavioral, tissue, and cellular data are collected using this dual approach and beneficial and lasting effects are observed, it is likely that this could progress towards more clinical trials and establish further understanding of the neuropathological changes associated with hydrocephalus.

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Abbrevations

BBB	blood-brain-barrier
CSF	cerebrospinal fluid
GAP-43	growth-associated protein-43
GE	germinal eminence
H-Tx	hydrocephalus Texas
NOS	nitric oxide synthase
NPCs	neuronal progenitors cells
NSCs	neural stem cells
OPCs	oligodendrocyte precursors cells
SEZ	subependymal zone
SVZ	subventricular zone
VZ	ventricular zone