

Review

Glial Remodeling in the Ventricular–Subventricular Zone and Corpus Callosum Following Hydrocephalus

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Abstract

Hydrocephalus is a neurological disorder caused by cerebrospinal fluid (CSF) accumulation due to impaired production, circulation, or reabsorption from trauma, neurocysticercosis, neoplasms, subarachnoid hemorrhage, or genetic mutations. This review examines glial remodeling in the ventricular–subventricular zone (V-SVZ) and corpus callosum (CC) in response to hydrocephalus, as ventricular enlargement leads to structural alterations that impact cellular composition in the V-SVZ and CC of patients with hydrocephalus. Animal models of hydrocephalus indicate V-SVZ niche remodeling, ependymal thinning, reduced neuroblast proliferation, increased microglia and astrocytes, increased cell death, and enlarged extracellular matrix structures (fractones). Alterations in the corpus callosum encompass a reduction in width, abnormalities in myelin, astrogliosis, microglial reactivity, a decreased expression of myelin-related proteins (MOG and CNPase), and a reduced number of oligodendrocytes. Additionally, this narrative review highlights important cellular and molecular findings before and after CSF diversion surgery. This primary treatment restores the ventricular size but does not completely reverse glial changes, indicating that ongoing neuroinflammatory processes may interfere with neural recovery.

Keywords: ventricular–subventricular zone; corpus callosum; hydrocephalus; microglia; astrocytes; oligodendrocytes; neuroblasts



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1. Introduction

Hydrocephalus encompasses a diverse group of pathologies characterized by abnormal enlargement of the lateral ventricles. In the absence of timely diagnosis and intervention during the early stages, the condition may evolve toward progressive neurological compromise with potentially fatal consequences. This neurological condition can manifest at any age, with a global prevalence estimated at approximately 84.7 cases per 100,000 individuals. Age-specific data indicate that the pediatric population (individuals under 18 years) exhibits a prevalence of 88 cases per 100,000. In contrast, individuals aged 19 to 64 display a considerably lower prevalence of 11 cases per 100,000. Among older adults (individuals over 65 years), the prevalence increases to 175 cases per 100,000, with reports suggesting that in those exceeding 80 years of age, it may reach as high as 400 cases per 100,000 [1]. In general, hydrocephalus is characterized by an imbalance in cerebrospinal fluid (CSF) production, circulation, or absorption, resulting in significant ventricular enlargement in patients due to congenital hydrocephalus, infection, trauma,

or obstructive mass lesions [2,3]. CSF is primarily produced by the choroid plexus within the lateral, third, and fourth ventricles, and plays a critical role in maintaining central nervous system homeostasis by facilitating the removal of metabolic waste, transporting neuromodulators and neurotransmitters, and regulating intracranial pressure. Following its production, CSF circulates through the ventricular system, passing from the lateral ventricles to the third and fourth ventricles before reaching the subarachnoid space and the external surfaces of the brain and spinal cord. Its absorption primarily occurs at the arachnoid granulations, with additional contributions from the glymphatic system and cribriform plate channels, processes that are dynamically influenced by arterial pulsation and respiratory rhythms. Pathological alterations in CSF circulation can result in intracranial hypertension, ventriculomegaly, or hydrocephalus, leading to significant disruptions in brain function and structural integrity, necessitating regulatory mechanisms such as compensatory parenchymal reabsorption in cases of obstruction [4].

Hydrocephalus typically demonstrates a gradual progression, and in its early stages, ventricular enlargement may occur without overt clinical symptoms [2,3]. Acute hydrocephalus is classified when excessive dilation of the ventricles occurs within days or weeks. In contrast, chronic hydrocephalus develops progressively over months or years, leading to ventricular enlargement with or without early symptoms, which often results in delayed diagnosis and treatment [5,6]. In most cases, hydrocephalus is a clinically treatable condition that may be reversed by surgically inserting a shunt. Ventriculo-peritoneal shunting is a complex surgery involving a ventricular catheter placed in a lateral cerebral ventricle, connected to a valve and a distal catheter inserted into the abdomen, where CSF is reabsorbed [7]. Despite surgical treatment for infantile hydrocephalus, patients retained larger lateral ventricular volumes than controls [8]. In chronic hydrocephalus, delays in diagnosis and intervention can significantly impact patient outcomes, leading to prolonged neurological impairment [6,9]. Studies indicate that ventriculo-peritoneal shunting can improve functional outcomes; however, long-term complications, such as shunt malfunction, infection, and over-drainage, remain concerns. Additionally, persistent ventricular enlargement may contribute to gait disturbances, memory decline, and executive dysfunction, particularly in patients with normal pressure hydrocephalus (NPH). Early intervention and regular postoperative monitoring are crucial to optimizing neurological recovery and minimizing long-term deficits [10].

Imaging studies of patients with hydrocephalus reveal persistent changes after treatment, especially around the lateral ventricles, the ventricular-subventricular zone (V-SVZ) [11], and the corpus callosum (CC) [8,9,12,13]. The V-SVZ is a neurogenic niche containing neural stem cells that generate neuroblasts, which migrate through the rostral migratory stream to the olfactory bulb, differentiating into olfactory interneurons [14,15]. The V-SVZ also plays a crucial role in generating oligodendrocyte precursor cells, which migrate to adjacent regions such as the CC, where they differentiate into oligodendrocytes and contribute to myelin formation [16,17]. As the principal commissural structure, the CC facilitates communication between the cerebral hemispheres by transmitting neural signals and integrating white matter pathways that support motor, sensory, and higher cognitive functions [14]. Disruptions in the V-SVZ and CC from chronic hydrocephalus may have lasting effects on neural plasticity, interhemispheric communication, and cognitive function. In this review, we examine the glial remodeling observed in the V-SVZ and CC in hydrocephalus, with a focus on significant cellular and molecular findings both before and after CSF diversion surgery. Understanding these persistent structural alterations is crucial for developing effective therapeutic strategies and mitigating long-term deficits that may arise after treatment. Therefore, the potential for CSF shunting to reverse V-SVZ and CC alterations induced by hydrocephalus remains uncertain.

2. Methodology

This narrative review involved searching MEDLINE/PubMed, Scopus, and Web of Science to identify studies of hydrocephalus that examined the subventricular zone or corpus callosum with a specific focus on glial remodeling. The primary search terms included “hydrocephalus,” “ventricular-subventricular zone,” “corpus callosum,” “astrocytes,” “microglia,” “neuroblast,” “ependyma,” “oligodendrocyte,” “myelin,” “CSF diversion,” and “treatment.” Boolean operators (AND, OR) were strategically employed to enhance both sensitivity and specificity. The exclusion criteria encompassed manuscripts not published in English and studies that did not provide detailed data on glial remodeling, the corpus callosum, or insights into the ventricular–subventricular zone. Articles were organized thematically based on brain regions analyzed, types of glial changes, clinical or experimental models, and therapeutic results.

3. Glial Remodeling in the Germinal Niche of the Ventricular–Subventricular Zone in Hydrocephalus

Neuropathological autopsy reports indicate that individuals with hydrocephalus exhibit ventricular enlargement, a decrease in ependymal cell density, and an increase in periventricular gliosis both before [18] and after shunting [19]. Ependymal cells are the functional units of the ventricles, forming a monolayer of ciliated epithelial cells that regulate barrier and filtration processes and facilitate cerebrospinal fluid flow along the ventricular surface [20]. The degree of hydrocephalus correlates with the severity of ependymal changes [21–23]. The cilia, the most delicate appendages of the ependymal cells, are the first structures to be lost, followed by the microvilli. In contrast, ependymal cells located on the roof of the ventricles exhibit degradation last, ultimately culminating in several areas with denuded ependyma [20,22]. Mature ependymal cells are post-mitotic epithelial cells limited in additional proliferation or repair in adults [24]. Consequently, the progressive nature of ventriculomegaly may be partly driven by the cumulative impact of replacing ependymal cells with a glial scar over time [21,25,26], which further disrupts CSF homeostasis and ventricular architecture.

The production and composition of CSF are primarily regulated by the choroid plexus, a highly vascularized and polarized epithelial structure. Its apical surface, exposed to the CSF, is covered with microvilli and contains numerous ion transporters and channels that facilitate the movement of Na⁺, Cl[−], and HCO₃[−] into the ventricular lumen, while tight and adherens junctions form the blood–CSF barrier (BCSFB). The basal membrane is enriched with transport proteins and aquaporin-1 (AQP1) channels, which modulate molecular exchange and contribute to the clearance of organic anions and cations, thereby ensuring an ionic composition distinct from that of plasma [27]. Additionally, ependymal cells lining the ventricles not only separate the brain parenchyma from the CSF but also secrete growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) and express aquaporin-4 (AQP4), which plays a critical role in osmotic pressure regulation, CSF flow, and the distribution of signaling molecules [28]. The differential expression of aquaporins such as AQP1 and AQP4 suggests that in communicating hydrocephalus, their dysregulation may reflect impaired CSF reabsorption. In contrast, in non-communicating forms, periventricular overexpression may represent a compensatory response to obstructed flow [29]. Based on these processes, various experimental manipulations targeting CSF production, circulation, or reabsorption have been employed to model hydrocephalus in rodents, facilitating the study of its underlying pathological mechanisms. Animal models of hydrocephalus are used to study brain and behavioral changes, as they closely resemble the neuropathological conditions associated with this disease. These models can be categorized into two major groups: the first consists of congenital or hereditary hydrocephalus models,

which include genetically modified mice (*hhy* or *Tg737Orpk*) and rats (H-Tx or *Ccdc85c* KO) [23,30]. The second group comprises acquired hydrocephalus models, which involve the use of aluminum silicate (kaolin), fibroblast growth factor (FGF), or transforming growth factor (TGF) to induce meningeal inflammation and fibrosis, leading to secondary obstruction at specific segments of the ventricular system [31]. Other animal models that minimize widespread inflammation utilize cyanoacrylate, acetate film, or other synthetic polymers to obstruct specific segments of the cerebrospinal fluid (CSF) system in dogs, rats, or mice. Obstructive hydrocephalus refers to disruptions in CSF circulation caused by blockage or narrowing at any point within the ventricular system or the subarachnoid space [32].

Animal models of hydrocephalus exhibit periventricular gliosis, characterized by hypertrophy and hyperplasia of astrocytes and microglia [32]. Reactive astrocyte proliferation acts as a repair mechanism after brain injury, involving neurotransmitter imbalance such as excess glutamate and decreased GABA inhibition [33]. This leads to excitotoxicity, synaptic dysfunction, and disrupted neurovascular regulation, resulting in the formation of a glial scar characterized by high expression of glial fibrillary acidic protein (GFAP), vimentin, and nestin [34]. Astrocytes can be activated into two polarization states, the neurotoxic or pro-inflammatory phenotype (A1) and the neuroprotective or anti-inflammatory phenotype (A2) [35]. In hydrocephalus, initially activated astrocytes help prevent the spread of inflammatory cells; however, in later stages, sustained A1 astrocyte activation can contribute to disease progression by forming a glial scar and releasing molecules, such as chondroitin sulfate proteoglycans, which interfere with axonal regeneration [34,36]. Microglia serve as the first line of defense in the adult brain. Under normal conditions, they exhibit a stellate morphology, characterized by small somas and long, thin processes. In pathological states, active microglia transform, acquiring an amoeboid shape and then transitioning into phagocytic cells. Ionized calcium-binding adapter molecule 1 (Iba-1) is expressed by microglia and is a reliable marker for detecting these morphological changes in hydrocephalus [37,38]. Microglia play a dynamic role in this process, influencing scar formation by secreting factors that regulate astrocytic responses and extracellular matrix remodeling. IFNs and LPS activate the pro-inflammatory microglia via the activation of NF κ B and STAT1, and then release cytokines such as IL-1 β , IL-12, IL-23, SOC3, CXCLs, CCLs, NO, TNF- α , and IL-6. The neuroprotective microglia are promoted by IL-4, IL-13, IL-10, and TGF- β via the activation of STAT3 and STAT6 [39]. Ventricular dilation, loss of ependymal cells, and astrocyte reactivity may sustain chronic neuroinflammation in hydrocephalus characterized by increased expression of cytokines such as IL-2, IL-5, IL-12, tumor necrosis factor- α (TNF- α), and macrophage inflammatory protein-1 β (MIP-1 β or CCL-4) [24,40]. Additionally, elevated levels of transforming growth factor-beta 1 (TGF- β 1), secreted by perivascular astrocytes, promote disease progression by upregulating extracellular matrix proteins such as laminin and fibronectin. These proteins interfere with vascular remodeling and CSF reabsorption, especially after post-hemorrhagic hydrocephalus [41]. Patients with idiopathic normal pressure hydrocephalus (iNPH) also exhibit significant mitochondrial damage in perivascular astrocytic endfeet, which correlates with increased astrogliosis [42] and higher levels of IL-6 and IL-8 [43], further disrupting blood–brain barrier integrity and maintaining glial activation. Therefore, reactive gliosis and microglial activation emerge as fundamental processes in tissue reorganization following focal damage to the CNS. In the initial phase, astrocytes proliferate in response to inflammation and disruption of the blood–brain barrier, contributing to the sequestration of the injured area. Concurrently, microglia undergo morphological and functional changes, shifting to an activated state characterized by increased cytokine release, phagocytosis of cellular debris, and modulation of neuroinflammatory signals [39]. Over time, periventricular gliosis intensifies

around the fibrotic core of the scar, forming a structural barrier that limits the propagation of damage and may impede regeneration. In the subsequent months, progressive remodeling of the astrocytic scar redefines the tissue architecture, with variations in astrocyte and microglial density and organization [38,44]. Despite specific resolution mechanisms, gliosis and microglial activity can persist indefinitely, sustaining functional alterations that impact neuronal plasticity and synaptic connectivity [45]. This dual role, which protects tissue integrity while potentially hindering neuronal recovery, underscores the need to understand the molecular and cellular modulators that direct their progression [39,46,47]. A focus on targeting microglial-mediated inflammation and astrocytic reactivity may present therapeutic opportunities to facilitate a more conducive environment for neural repair [48].

Over time, neuroinflammatory processes might disrupt cerebrospinal fluid dynamics, worsen ventricular enlargement, and alter neurogenesis; however, the V-SVZ has been rarely studied in humans [11,21]. The human V-SVZ retains proliferative cells and appears to retain some neurogenic capabilities throughout adulthood [49]. Its cytoarchitecture is comprised of four essential components: (I) the ependymal layer, which is comprised of multiciliated ependymal cells; (II) a hypocellular gap that contains extensions of ependymal and astrocytic cells; (III) the astrocytic ribbon, characterized by a concentration of astrocytes; and (IV) the transitional zone to the parenchyma, distinguished by an abundance of myelin and oligodendrocytes (Figure 1A) [50]. Human hydrocephalus reduces the size [11] and alters the organization of the V-SVZ [21,51]. In hydrocephalic fetuses with detachment of the ependymal layer in the lateral ventricles, disruption of the V-SVZ was exhibited, characterized by increased neuroblasts spreading throughout the astrocyte layer. Meanwhile, the denuded areas of the ependyma showed small clusters of neuroblasts on the surface, while larger aggregations often extended into the ventricular lumen through the denuded regions [21]. After two weeks of age, hydrocephalus leads to hemosiderin accumulation, nodular gliosis, ependymal cell loss, and the formation of subependymal rosettes in the subventricular region. In infants older than two months, prominent gliosis with glial nodules was observed. Cases under four months of hydrocephalus also showed glial nodules adhering to the ventricular wall [51]. Adults with chronic hydrocephalus showed a reduced V-SVZ size, possibly related to diminished neurogenic potential and structural disorganization within the subventricular niche [11] (Figure 1B). However, the effects of the treatment on the V-SVZ remain limited (Figure 1C). Notably, these alterations in the V-SVZ may not only impair neurogenic processes but also contribute to pathological conditions, as this region facilitates malignant cell proliferation through mechanistic stimuli, such as CSF-enriched growth factors or invasion-promoting conditions [52–54]. Further investigation into the human V-SVZ is essential for elucidating the glial remodeling after hydrocephalus [55].

In rodents, the V-SVZ is densely populated with neural stem cells and migrating neuroblasts that form chains toward the olfactory bulb. In contrast, in humans, neuroblast chains are absent, and a hypocellular gap separates astrocytes from the ependymal layer. Although both species exhibit neurogenesis, human V-SVZ neurogenic activity is more restricted, with neuroblasts dispersing individually rather than migrating in organized chains [14,50]. The adult V-SVZ of rodents contains multipotent cells, and its cytoarchitecture includes ependymal cells (type E), which form a layer that separates the ventricular cavity from the parenchyma. Type E1 cells have multiple cilia that regulate the flow of cerebrospinal fluid, while type E2 cells have elongated basal bodies and contribute to neural precursor proliferation. Beneath the ependymal layer, type B precursor cells reside in the SVZ, categorized into B1 (neural stem cells) and B2 (astrocytic-like cells). B1 cells generate rapidly dividing transit-amplifying cells (type C), which interact closely with migrating neuroblast chains and blood vessels. Type C cells give rise to migrating neuroblasts

(type A) (Figure 1D). In rodents, these neuroblasts migrate tangentially through the rostral migratory stream (RMS) to the olfactory bulb, differentiating into primarily GABAergic interneurons that contribute to olfactory discrimination [15]. Several models of hydrocephalus have shown several changes in the cytoarchitecture of the V-SVZ (Figure 1E). Models of acquired hydrocephalus exhibited a notable increase in cell death and a significant decline in oligodendrocytes and proliferative progenitors within the SVZ [56,57]. A chronic hydrocephalus model induced by partial obstruction of the cerebral aqueduct revealed thinning of the ependymal layer and a reduction in V-SVZ size, accompanied by a decrease in proliferative cells, likely neural stem cells and transient progenitors, which are essential for niche maintenance. The generation of neuroblasts in the SVZ was diminished, whereas other neuropathological changes were observed, including an increase in blood vessels, hemosiderin accumulation, astrogliosis, and increased fractones [11]. Fractones are structures within the extracellular matrix that possess a fractal configuration, with an average size ranging from 2 to 5 μm . They predominantly comprise laminin, collagen type IV, and heparan sulfate proteoglycans. The nomenclature “fractones” is derived from the term “fractal,” a concept introduced by Benoît Mandelbrot in 1975, owing to their branched morphology [58]. Within the SVZ, fractones play a crucial role in modulating the neurogenic niche, as they can capture and concentrate growth factors such as FGF2 and BMP-4, thereby facilitating cell signaling and the proliferation of neural stem cells. Studies have shown that fractones are closely associated with ependymal cells, which regulate their laminin composition [58–60]. Additionally, their central localization within rosette-like structures in the SVZ suggests they may influence adult neurogenesis [61]. In 60-day hydrocephalic mice, fractones formed extensive and highly branched networks, establishing direct contact with the ventricular wall and SVZ blood vessels. These structures were associated with prolonged cell-to-cell interactions, characterized by complex interdigitations within the ependymal layer, a phenomenon observed exclusively in this group [11]. Similarly sized fractones ($\sim 8 \mu\text{m}$) have also been reported in aged rodents, suggesting a potential link between hydrocephalus and age-related extracellular matrix remodeling [62]. Hydrocephalus and aging are closely related, particularly in the context of normal pressure hydrocephalus (NPH), a condition prevalent among older adults [63]. These findings suggest that fractones may serve as key modulators of extracellular matrix remodeling in hydrocephalus and aging, highlighting their potential role in long-term neurogenic regulation and ventricular integrity.

After treatment, several studies conducted on rodents with hydrocephalus have shown that diverting CSF leads to the restoration of the ventricular system size (Figure 1F); however, the disruption of the cellular integrity of the ventricular wall and ventricular roof persists after hydrocephalus resolution [32]. Shunting partially alleviates astrogliosis but does not entirely reverse this inflammatory reaction, even after long-term treatment [32,64]. Administering EPO in hydrocephalic rats helps prevent V-SVZ thinning, decreases astrogliosis, and sustains proliferation rates during acute periods. Thus, erythropoietin (EPO) treatment may be advantageous in mitigating astrogliosis following CSF diversion [65]. Future studies should investigate targeted strategies to enhance V-SVZ neurogenesis while reducing pathological gliosis and optimizing therapeutic outcomes [48]. The molecular mechanisms that regulate V-SVZ glial remodeling following ventriculomegaly and subsequent treatment are not well characterized and require further investigation.

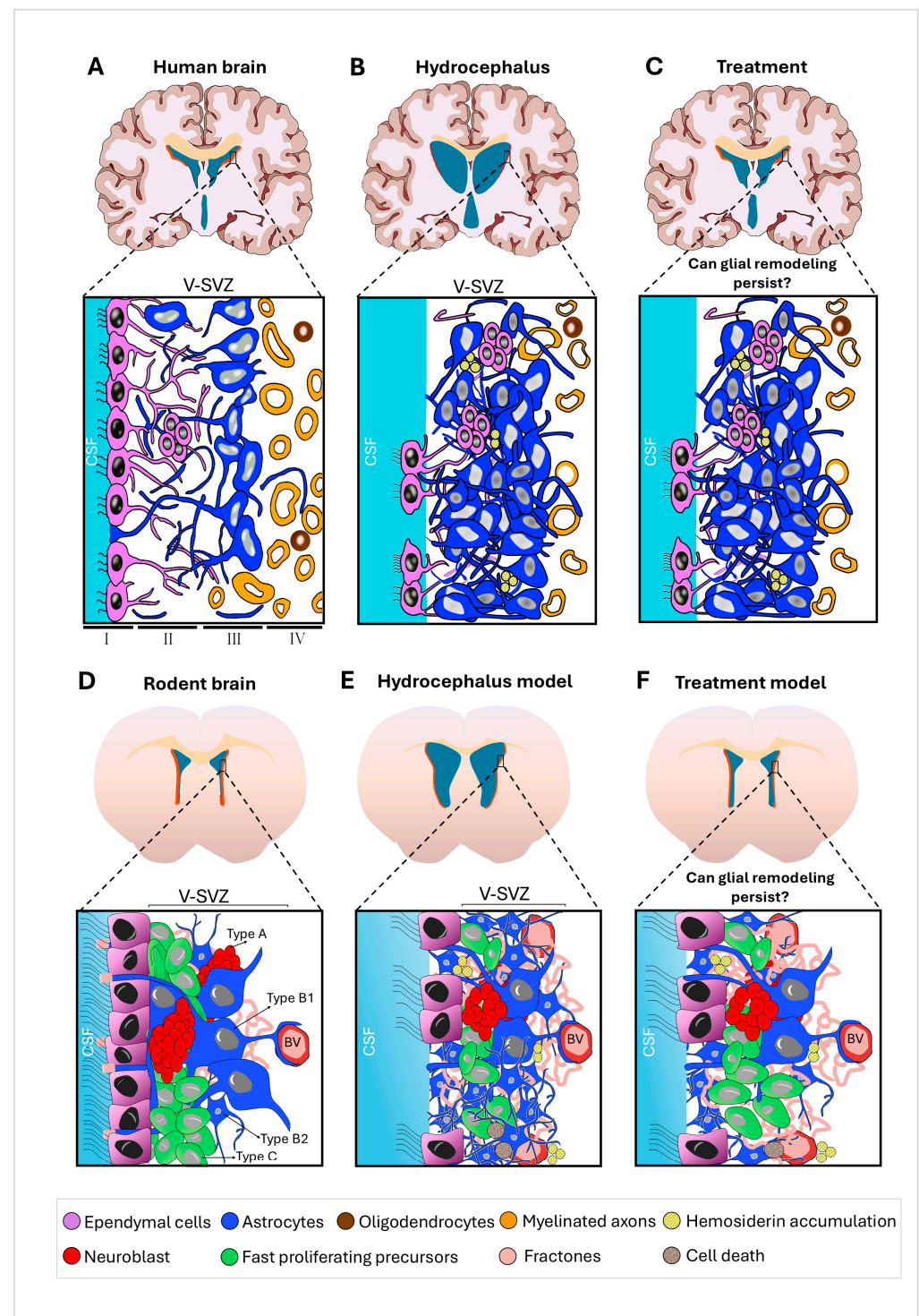


Figure 1. Illustration of the cytoarchitecture of the ventricular-subventricular zone (V-SVZ) of a healthy human and rodent brain (A,D) compared to a brain with glial remodeling after hydrocephalus (B,E) and a brain after undergoing CSF diversion treatment (C,F). In the human brain, the V-SVZ has four layers: I (ependymal layer), II (hypocellular gap), III (the astrocytic ribbon), and IV (transitional zone). In the rodent brain, the V-SVZ cytoarchitecture includes an ependymal layer; type A cells (migrating neuroblasts); type B1 (neural stem cells), type B2 (astrocytic-like cells), and type C (fast proliferating precursors). Hydrocephalus alters the cellular composition of the V-SVZ, exhibiting neuropathological features. After CSF diversion treatment, there is no consensus about whether glial remodeling persists or reverts to normal conditions. BV: blood vessel; CSF: cerebrospinal fluid.

4. Structural and Glial Remodeling in the Corpus Callosum in Hydrocephalus

The corpus callosum (CC), the largest commissural pathway of the brain, comprises over 200 million topographically arranged axons with extensive myelination. Variations in myelin thickness and the length of Ranvier nodes facilitate the efficient integration of motor, sensory, and cognitive information between hemispheres [66]. The process of myelin generation begins at birth and continues into adulthood. In mammals, myelination begins in the brainstem and progresses toward the forebrain and spinal cord. In the earliest stage, myelination occurs in the sensorimotor roots and brainstem, which are essential for developing reflex behaviors and survival [17]. In humans, oligodendrocyte precursor cells are observed in the prosencephalon at 10 weeks of gestation. Immature oligodendrocytes appear between 18 and 28 weeks of gestation. From this point, mature oligodendrocytes expressing myelin basic protein (MBP) and other essential proteins for myelin formation and assembly develop throughout life. However, it is important to highlight that childhood and adolescence represent key periods of myelination processes. This development begins in the prenatal stage, progresses rapidly during the first 2 to 3 years of life, and continues into early adulthood. Following dendritic branching and synaptogenesis, neuronal connections are strengthened through axonal myelination. This process is fundamental for brain maturation and the consolidation of neuronal connections, influencing motor, cognitive, and emotional abilities throughout life [17]. In congenital or pediatric hydrocephalus, the abnormal accumulation of cerebrospinal fluid can disrupt the timely development of oligodendrocytes and subsequent myelination [67], potentially leading to agenesis of the corpus callosum [68]. This process typically begins in utero and accelerates during early childhood, playing a crucial role in the maturation of neuronal circuits [67].

Furthermore, the dynamics of oligodendrocyte formation and maintenance vary across brain regions. For instance, in the corpus callosum, 90% of myelinating oligodendrocytes present at two months of age survive until 20 months of age. In contrast, in the motor cortex, although 100% of oligodendrocytes are established by eight months of age, only 70% remain over the following 20 months in rodents [69]. These findings indicate regional differences in myelin vulnerability. This inherent variability in oligodendrocyte survival and myelin maintenance makes the corpus callosum particularly susceptible to pathological conditions such as hydrocephalus, regardless of the age at which the disease manifests. The progressive ventricular enlargement characteristic of hydrocephalus exerts mechanical stress on white matter tracts, disrupting interhemispheric connectivity and exacerbating myelin degradation over time [8,70]. This vulnerability underscores the importance of early intervention to mitigate structural damage and preserve functional integrity in hydrocephalus patients.

Oligodendrocyte lineage progression involves transitioning from motile, bipolar oligodendrocyte progenitor cells (OPCs) to stationary, extensively branched mature oligodendrocytes, reflecting a dynamic process of differentiation and functional specialization. OPCs can be classified based on their expression of specific markers such as chondroitin sulfate proteoglycan type 4 (NG2/CSPG4), oligodendrocyte transcription factor 2 (Olig2), and platelet-derived growth factor receptor alpha (PDGFR α). Differences in the expression of these markers may be associated with specific functions such as migration, proliferation, differentiation, or survival [71]. Immature oligodendrocytes represent an intermediary stage within the differentiation pathway originating from OPCs, although they have yet to achieve complete functional maturity. During this developmental phase, these cells begin to extend cellular processes toward axons and initiate myelin production, although this occurs alongside a significantly reduced proliferative capacity compared to OPCs. As

differentiation progresses, the expression of markers specific to OPCs gradually decreases, while low-level expression of key proteins associated with myelination initiation begins to appear. The protein 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase) is expressed at early phases of oligodendrocyte maturation at a low level, particularly during the initial organization of myelin sheaths around axons, thus indicating the onset of the myelination process [71]. This process forms a myelin membrane that is 30% protein and 70% lipid. The main proteins of myelin include myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), MBP, and proteolipid protein (PLP). Furthermore, receptor-interacting protein (RIP) is primarily localized to the membrane of mature oligodendrocytes and the myelin sheaths that form around axons, making it a useful marker for studying both myelin sheath integrity and the overall oligodendrocyte state [72] (Figure 2A). Oligodendrocyte formation and maintenance dynamics vary across brain regions [69,73]. Research on human and animal models indicates that hydrocephalus contributes to corpus callosum thinning, primarily due to the compression of periventricular and subcortical WM caused by lateral ventricle enlargement [8].

In patients with hydrocephalus, structural abnormalities in the CC and white matter (WM) have been observed, including scalloping, lifting, stretching, and thinning [11,74–78]. After treatment for acute hydrocephalus, the morphology of the corpus callosum is restored [74]. In contrast, several patients with chronic hydrocephalus exhibit only partial re-expansion of the corpus callosum after CSF shunting [12,13]. This increase in corpus callosum size may result from decompression, re-expansion, interstitial fluid accumulation, or structural changes due to cerebral reorganization. After surgery, the re-expansion of the genu and rostral body of the corpus callosum has been associated with improvements in neuropsychological and clinical outcomes in these patients [12]. Fractional anisotropy analysis showed that the splenium and isthmus are also vulnerable CC regions in shunted infants with hydrocephalus, despite asymptomatic status and clinical stability during the first two years of life [8]. Furthermore, in adult patients who do not respond to shunting (shunt non-responders), the functional activity of the corpus callosum remains reduced [75]. The structural and functional recovery of the corpus callosum in hydrocephalus varies with chronicity and treatment response, with persistent alterations potentially associated with myelin integrity, axonal connectivity, or edema, reflecting regional differences in oligodendrocyte maintenance and myelin vulnerability [13]. Distinct glial protein profiles, including GFAP, MBP, and vimentin, are observed in the CSF of neonates diagnosed with hydrocephalus. For instance, the increased presence of GFAP in cases of post-hemorrhagic hydrocephalus suggests reactive astrogliosis. Conversely, elevated levels of MBP in instances associated with spina bifida may indicate demyelination. This underscores the diagnostic and prognostic potential of cerebrospinal fluid biomarkers across various subtypes of hydrocephalus [79]. Emerging evidence suggests that elevated ventricular MBP levels, but not lumbar concentrations, may reflect cerebral tissue damage and serve as a prognostic marker for clinical outcomes following shunt surgery in iNPH [80]. These findings suggest that ventricular MBP elevations may serve as molecular indicators of myelin disruption within structurally vulnerable regions, such as the corpus callosum, reinforcing the utility of CSF biomarkers in detecting ongoing white matter pathology and predicting therapeutic response in diverse forms of hydrocephalus.

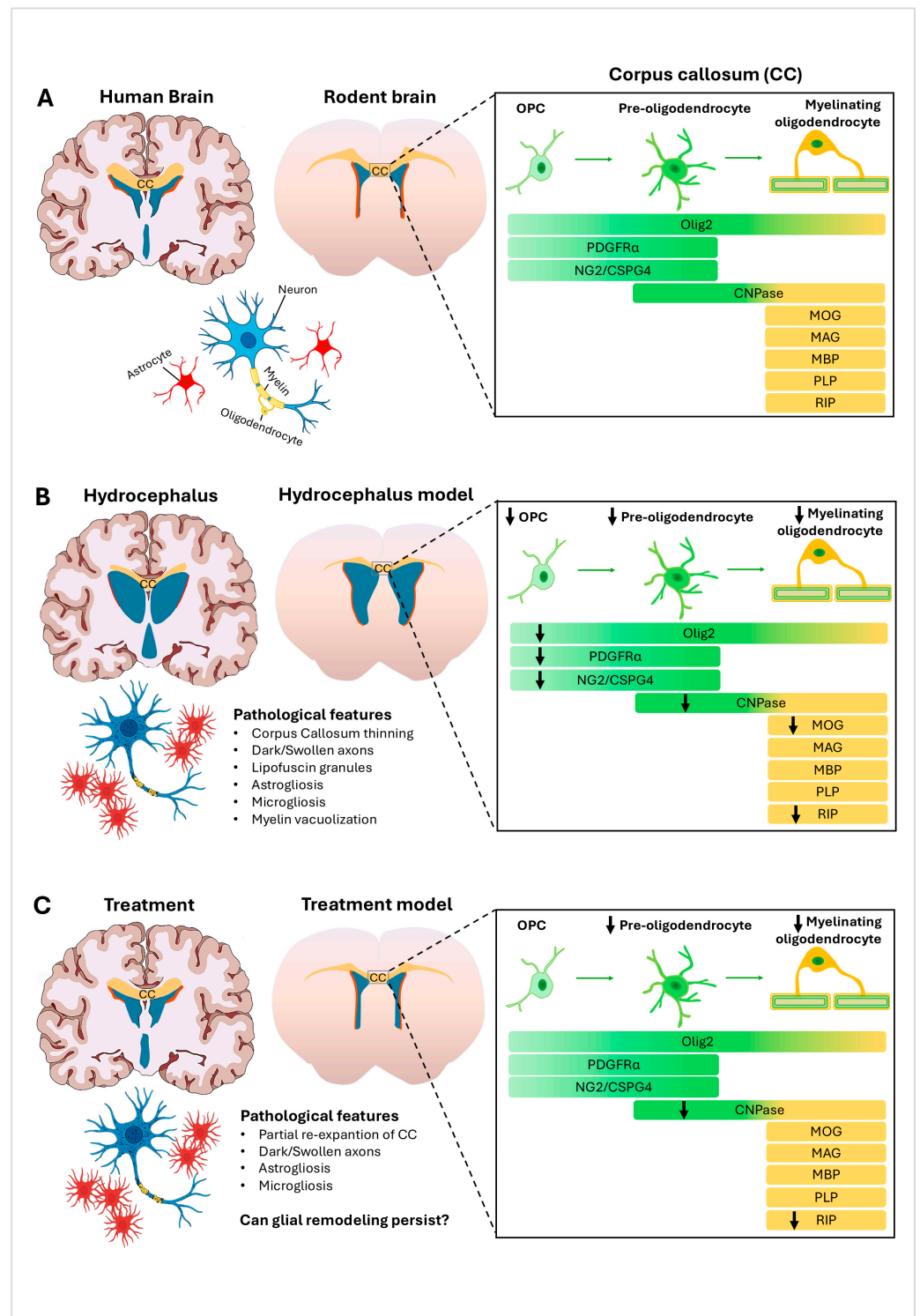


Figure 2. Comparison of myelin integrity in the corpus callosum (CC) of a healthy human and rodent brain (A), a brain exhibiting cytostructural modifications and protein dysregulation following hydrocephalus (B), and a brain after CSF diversion treatment with persistent altered features (C). Olig2 (Oligodendrocyte lineage transcription factor 2), PDGFR α (Platelet-derived growth factor receptor alpha), NG2/CSPG4 (Neuron-glia antigen 2/Chondroitin sulfate proteoglycan 4), CNPase (2',3'-Cyclic-nucleotide 3'-phosphodiesterase), MOG (Myelin oligodendrocyte glycoprotein), MAG (Myelin-associated glycoprotein), MBP (Myelin basic protein), PLP (Proteolipid protein), RIP (Receptor-interacting protein).

In rodent models, chronic hydrocephalus lasting over nine months leads to significant motor deficits, CC thinning, and myelin damage, similar to human cases [81]. In adult hydrocephalic mice, there was reduced corpus callosum thickness, decreased proliferation and differentiation of OPCs [38,82], a lower total number of oligodendrocytes, and diminished expression of MOG and CNPase in the CC. The corpus callosum also showed neuropathological features, including disorganized myelinated axons with hyperdense and darker cytoplasmic areas, lipofuscin granules, swollen axons, astrogliosis, microgliosis, and myelin vacuolization (Figure 2B) [38]. WM alterations depend on the duration of hydrocephalus, severity of ventriculomegaly, and treatment response [83,84]. In juvenile cats, the corpus callosum is restored following shunting 14 days after kaolin injection [64]. Additionally, rats with seven days of hydrocephalus exhibited recovery of corpus callosum morphology after CSF shunting [85,86]. In contrast, kaolin-induced hydrocephalus in rats exhibits swollen axons and reactive astrocytes in the CC after four weeks of hydrocephalus. However, after shunting, severe reactive gliosis and scattered swollen axons persisted [87]. Furthermore, adult hydrocephalic mice exhibit reduced corpus callosum thickness, which persists for at least 120 days after the onset of hydrocephalus. Even after 60 days of CSF diversion treatment, hydrocephalic mice continued to show thinning of the corpus callosum, a reduced oligodendrocyte population, lower CNPase expression, astrogliosis, and microgliosis (Figure 2C) [38].

These findings highlight the impact of hydrocephalus on white matter integrity and the cytoarchitecture of the subventricular zone, with the potential for recovery influenced by age, the duration of ventricular enlargement, and the effectiveness of treatment. However, in chronic cases, ongoing deficits in neurogenesis, myelin integrity, oligodendrocyte populations, and inflammatory responses underscore the difficulties in achieving complete structural and functional restoration. In addition to CSF diversion, depending on the type of hydrocephalus, clinical trials are also exploring other pharmacological treatments (such as dexmedetomidine, prophylactic antibiotics, acetazolamide, and urokinase) and surgical approaches to improve the management of hydrocephalus; see details in Anwar et al. [48] and Del Bigio et al. [88]. Several studies have reported that an effective treatment for hydrocephalus, administered promptly, can partially restore damage to the CC and V-SVZ (Table 1).

Table 1. Treatments for hydrocephalus and their effects on glial cells in V-SVZ or CC in preclinical models.

Treatment	Animal Model	Result after Treatment	Potential Functional Role	Reference
Erythropoietin administration	Rat	Decreased GFAP and Iba1 expression in V-SVZ	Attenuation of glial scar/inflammatory response	[65]
CSF diversion	Mouse	Decreased GFAP expression in V-SVZ	Attenuation of glial scar/inflammatory response	[32]
Tethered liquid perfluorocarbon (TLP) + CSF diversion	Pig	No differences in GFAP expression in VZ	-	[89]
CSF diversion	Rat	Decreased GFAP expression in CC	Attenuation of glial scar/inflammatory response	[85]

Table 1. Cont.

Treatment	Animal Model	Result after Treatment	Potential Functional Role	Reference
CSF diversion	Mouse	Reestablishment of Olig2, PDGFr α , NG2, and MOG expression in CC	Partial OPCs and myelin repair	[38]
CSF diversion	Mouse	No differences in GFAP or Iba1 expression in CC	-	[38]
Memantine administration + CSF diversion	Rat	Decreased GFAP expression in CC	Attenuation of glial scar/inflammatory response	[86]
Celecoxib administration + CSF diversion	Rat	No differences in GFAP expression in CC	-	[90]
Quercetin administration	Rat	No differences in GFAP expression in CC	-	[91]
CSF diversion	Rat	No differences in GFAP expression in CC	-	[92]
Camellia sinensis administration	Rat	Decreased GFAP expression in CC	Attenuation of glial scar/inflammatory response	[93]
Mesenchymal Stem Cells transplantation	Rat	Decreased GFAP expression in CC	Attenuation of glial scar/inflammatory response	[94]

5. Limitations of the Study

Considering the limited research available on glial remodeling within the corpus callosum and subventricular zone related to hydrocephalus subtypes and their respective treatments, this review employs an integrative analytical approach. As scientific knowledge continues to advance, future reviews may benefit from a more detailed classification of hydrocephalus, thereby improving the specificity and applicability of clinical and experimental treatments.

6. Conclusions

Hydrocephalus induces persistent glial remodeling in the V-SVZ and corpus callosum, resulting in chronic impairments in neuroblast migration, oligodendrocyte maintenance, and myelin integrity. Moreover, persistent gliosis and neuropathological changes indicate ongoing neuroinflammatory responses that could hinder recovery. Although pharmacological treatments and CSF diversion normalize ventricular size, they do not fully repair white matter or ventricular wall damage, highlighting the need for more effective therapies. Future research should focus on strategies that enhance neurogenic capacity, mitigate pathological gliosis, and promote functional recovery after severe or chronic hydrocephalus.

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