

REVIEW

Hydrocephalus after aneurysmal subarachnoid hemorrhage: Epidemiology, Pathogenesis, Diagnosis, and Management

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Abstract

Hydrocephalus is one of the most common complications of aneurysmal subarachnoid hemorrhage (aSAH), which seriously affects the quality of life and shortens the survival time of affected patients. By reviewing the recent studies on the risk factors of aSAH-associated hydrocephalus, we aimed to explicitly present the pathogenesis of acute and chronic hydrocephalus after aSAH and make a comprehensive list of the associated risk factors of aSAH-associated hydrocephalus and shunt-dependent hydrocephalus. It would help us to better explain the occurrence of hydrocephalus after aSAH, especially hydrocephalus caused by inflammation after bleeding. Many studies have recently suggested that high mobility group box 1 may be an early upstream promoter of inflammatory response after aSAH, which also provides important ideas for us to look for potential drug treatments. The surgery, such as external ventricular drain and lumbar drainage, is the most common and effective treatment. Yet, there are often complications, such as rebleeding and intracranial infection, and the optimal timing of intervention is controversial. Besides, this is also a systematic review of the recent advances in epidemiology, pathogenesis, diagnosis, and management of aSAH-associated hydrocephalus.

Keywords

Aneurysmal subarachnoid hemorrhage; Hydrocephalus; Pathogenesis; Therapeutic development; Management

1. Introduction

Subarachnoid hemorrhage (SAH) is a severe form of cerebrovascular disease, with a mortality rate of 40-60% and an incidence of 8-20/10,000 [1-3]. It is mainly consecutive to aneurysm rupture. Hydrocephalus is one of the most common complications of aneurysmal subarachnoid hemorrhage (aSAH) [4]. It can cause injury to the central nervous system including impairment of cognition abilities [5]. Most studies have shown that acute hydrocephalus is mainly caused by an obstruction in the cerebrospinal fluid (CSF) circulation pathway whereas, an abnormal secretion and reabsorption of the CSF are the most likely causes of chronic hydrocephalus [6, 7].

In recent years, the pathogenesis of aSAH has been widely studied [8, 9]. Inflammatory reaction plays an essential role in the pathogenesis of aSAH [10]. Many new targets, such as aquaporin-1, aquaporin-4 and toll-like receptor 4 (TLR-4), can be used for the non-surgical treatment of patients [10-12]. With the involvement of physics and artificial intelligence in medicine, there is a great convenience for early detection and treatment, many new diagnostic and predictive hydrocephalus

models that are developed and were used on a small scale have become more popularized [13]. In recent years, the risk factors for shunt-dependent hydrocephalus (SDHC) in patients with aSAH with subarachnoid hemorrhage have been the topic of considerable debate, with yet no consensus to date [14, 15]. Shunting is currently the most widely used surgical treatment for hydrocephalus, but there are often complications, and the optimal timing of intervention is controversial [2, 16, 17]. Surprisingly, it has been found in one survey that neurosurgeons in some areas used the opposite approach to safety (details in 5.2 Surgical treatment) [18, 19].

This paper reviews recent studies on the risk factors of aSAH-associated hydrocephalus [5, 20] with the aim to attempt to summarize and clarify the pathogenesis, diagnosis, and management of acute and chronic hydrocephalus consecutive to aSAH [21, 22]. We also aim to help health care workers in the early and active treatment and management and improve the prognosis of aSAH associated hydrocephalus patients.

TABLE 1. Ratio of SAH complicated with hydrocephalus.

Study	No. of SAH patients	No. of SAH/hydrocephalus patients	Ratio
Boswell <i>et al.</i> 2013 [23]	30	14	46.7%
Sprenker <i>et al.</i> 2015 [24]	51	18	35.3%
Konczalla <i>et al.</i> 2015 [25]	173	46	26.6%
Walcott <i>et al.</i> 2015 [26]	138	5	3.6%
Coelho <i>et al.</i> 2016 [27]	65	14	22.6%

Abbreviations: SAH = subarachnoid hemorrhage; No. of SAH patients = Number of subarachnoid hemorrhage patients; No. of SAH/hydrocephalus patients = Number of hydrocephalus after subarachnoid hemorrhage patients.

2. Epidemiology

2.1 Incidence

According to different backgrounds and clinical conditions, the incidence of hydrocephalus after aSAH ranged from 3.6% to 46.7% [23–27] (Table 1). However, this is not a strict incidence estimate, as the entire population has not been screened. Acute and chronic hydrocephalus occurs in about 20% and 10% of patients with aSAH, respectively [2, 3, 28]. Acute hydrocephalus occurs within 3 days after the bleeding, subacute within 14 days, and chronic hydrocephalus occurs after 14 days [29]. Chronic hydrocephalus, commonly defined as shunt-dependent hydrocephalus, affects 6-37% of patients with SAH [30]. The 1-year and 5-year survival rates for shunts are 57 and 37%, respectively, about 8-10% of shunts becoming infected and requiring lengthy hospitalization [31]. The prevalence of hydrocephalus is much higher in Africa and South America than in other continents, with the incidence of hydrocephalus among children in Africa (104.0/100,000) being twice as high as in North America (55.6/100,000) [28, 32].

2.2 Risk factors

Although the occurrence of hydrocephalus after aSAH has been deeply studied and some preventive measures have been well taken, its potential risk factors are still uncertain [33]. To help neurosurgeons better manage aSAH patients, and to further facilitate our understanding of the risk factors for hydrocephalus after subarachnoid hemorrhage hydrocephalus, scientists have conducted extensive studies regarding the risk factors [5, 34].

In recent years, the risk factors for subarachnoid hemorrhage SDHC in aneurysms have become a hot topic [35]. Although in some studies women had a higher dependency to shunt [35–38], most have shown no significant gender differences [20, 35, 36, 39]. Bae *et al.* have shown a higher incidence of chronic hydrocephalus in people over 60 years old [36], and more studies show that the older you get, the worse the clinical outcome with more complications [14, 34, 40–43]. But Virta *et al.* recently reported that getting older did not make the outcome worse. However, we still believe that more care should be given to patients over 60 years old [44].

The Hunt-Hess [20, 36, 37, 41, 45] and Glasgow coma scales (GCS) [5] were used to assess the risk factors in many studies. The Hunt-Hess scale is widely used to assess patients with

ruptured aneurysms [41]. Also, the High Fisher grade [35, 36], increasing failure risk index [37], higher World Federation of Neurological Surgeons grade [14, 15] are independent risk factors. García *et al.* proposed, for the first time, the use of a modified Graeb score, which maintains the simplicity of the qualitative score while increasing the assessment of acute hydrocephalus, which may improve the overall predictive power of SDHC [46].

Many studies have found that acute hydrocephalus [34, 35, 41, 42, 45, 47] predicts shunt-dependent hydrocephalus, while others have found no significant correlation between acute hydrocephalus and the need for shunt [39]. The presence of intraventricular hemorrhage (IVH) [34, 36, 45, 48–51] is significantly associated with the need for a shunt in patients with aSAH, in both univariate and multivariate analyses. IVH after aSAH is a common cause of acute hydrocephalus and often requires an external ventricular drain (EVD) treatment [52]. And many studies considered EVD placement [34, 47, 50, 53, 54] as the strongest predictor of acceptance after aSAH. How this acute hydrocephalus changes to chronic communicating hydrocephalus after aSAH remains to be elucidated. However, Savarra *et al.* suggested that there is no significant difference between EVD and SDHC [39]. Besides, many studies have analyzed a large number of clinical data and concluded that vasospasm [3, 14, 38], cerebral infarction [15], and meningitis [47] are closely associated with SDHC after aSAH.

Currently, the treatment of aneurysms (e.g., microsurgical clipping and intravascular coiling) remains controversial because of the risk factor for SDHC [55]. Park *et al.* reported that microsurgery clipping leads to a higher incidence of chronic hydrocephalus [56]. They hypothesized that intraoperative manipulation of small blood vessels would interfere with CSF homeostasis and induce vasospasm. However, other studies have found that there is no significant difference in the incidence of SDHC between the two [45, 53].

It is essential for medical personnel to identify the factors that increase shunt dependency and eliminate or mitigate reversible factors that put patients with aSAH at risk of SDHC. Also, identifying predictive variables and patients at risk for SDHC can prevent increased neurological morbidity, improving functional outcomes and quality of life, and prevent a prolonged hospital stay associated with chronic hydrocephalus [52] (Table 2).

TABLE 2. Risk factors for shunt-dependent hydrocephalus after aneurysms subarachnoid hemorrhage.

Type	The risk factors
Patient-related	(1) increasing age (2) female gender, (3) preexisting hypertension
Disease-related	(4) Hunt-Hess grading ≥ 3 , (5) poor post subarachnoid shunt score, (6) GCS score < 8 , (7) poor modified Graeb scale, (8) high Fisher grade, (9) vasospasm, (10) cerebral infarction, (11) meningitis, (12) fever, (13) infection
Treatment-related	(14) endovascular aneurysm treatment, (15) microsurgical clipping, (16) ventriculostomy, (17) EVD placement, (18) rapid weaning, (19) lack of CSF shunt

Abbreviations: GCS = Glasgow coma scales; EVD = external ventricular drain; CSF = cerebrospinal fluid.

3. Pathogenesis

After aSAH, the blood mixes with the CSF and diffuses in the subarachnoid space (SAS) [9]. Blood and hemoglobin degradation products can be directly introduced into SAS to damage the neurons [57]. Many inflammatory mediators (IL-1, IL-6, and tumor necrosis factor- β (TNF- β)) are released into the CSF along with neutrophil and exacerbate the neuronal damage [15, 58]. Therefore, various blood products entering the CSF after subarachnoid hemorrhage may cause damage to SAS and the brain parenchyma [8].

Although the exact molecular mechanism behind the pathophysiology in aSAH remains elusive, most studies show that acute hydrocephalus is mainly caused by an obstruction in the CSF flow, whereas an abnormal secretion and/or resorption of CSF are more likely the causes that lead to chronic hydrocephalus [9]. A better understanding of hydrocephalus' pathogenesis after aSAH is important to the development of clinical treatment (Fig. 1).

3.1 Acute hydrocephalus

Acute hydrocephalus causes early brain injury, which is usually considered a non-communicating (or obstructive) type, mainly due to the narrowing in the ventricles and the cerebral aqueduct or the blockage by blood clots that prevent CSF from flowing out of the cranium [57, 59].

It has been demonstrated in animal models that the flow of CSF after SAH is obstructed [60]. The obstruction mechanism seems to be widely recognized in acute hydrocephalus but the pathophysiology mechanisms are still unclear. Many have been conducted to unveil the mechanism behind the pathophysiology of hydrocephalus. The deposition of fibrin in the perivascular space after SAH may play an important role [61]. Golanov *et al.*'s results suggest that CSF obstruction may not be caused by thrombosis, and tissue factor III may participate in the regulation of CSF flow under normal conditions [62].

Recently, Close *et al.* reported a particular case that provided evidence of the rapid development of hydrocephalus with periventricular inflammation, without aqueduct stenosis [63]. In the case of aquaporin-4 dysfunction, such as in neuromyelitis optica, changes in the CSF absorption can lead to acute hydrocephalus through a non-blocking mechanism [64]. However, obstruction is not specific to acute hydrocephalus.

Blood from the SAS and subsequent hemoglobin degradation can trigger a cascade of inflammation, which is thought to be the critical biomolecular mechanism that causes acute hy-

drocephalus by breaking down the blood-brain barrier (BBB) [65, 66]. Inflammation may lead to scarring, which blocks the flow of CSF through the cerebral aqueduct, fourth ventricular outlet, basal cisterns, and arachnoid granulations [66]. Degradation products of red blood cells in SAS may lead to the accumulation of hemoglobin and its products (methemoglobin, heme), which activate the toll-like receptor 4 (TLR-4) and trigger an inflammatory cascade reaction [65]. Hemin is associated with the release of redox-active iron, altering the balance between oxidants and antioxidants [67]. Redox-active iron depletes antioxidants such as nicotinamide adenine dinucleotide phosphate and glutathione, producing both superoxide and hydroxyl radicals as well as lipid peroxidation [67]. Iron-induced oxidative stress leads to decreased ciliary function, which may trigger hydrocephalus [68]. Previous experimental studies have shown that iron-induced inflammation is involved in hydrocephalus formation after acute hemorrhage [69]. Mahaney *et al.* found no elevated levels of several iron scavenger proteins in the CSF of newborns with post hemorrhagic hydrocephalus, suggesting that hydrocephalus is a disease condition that occurs when the endogenous iron scavenger mechanism fails [70]. Recently, Zhang *et al.* confirmed that a lower serum iron content (13.1 mmol/L) after aSAH is a predictor of acute hydrocephalus and adverse outcomes [71].

In 2015, Sokó *et al.* reported for the first time that elevated high mobility group protein B1 (HMGB1) protein levels in consecutive samples of CSF from SAH patients were associated with adverse neurological outcomes [72]. HMGB1 is a well-characterized prototypical protein of damage-associated molecular pattern molecules (DAMPs) [73]. When the blood enters SAS through a ruptured aneurysm, it causes an increase in intracranial pressure. Damaged or compressed central nervous system cells will release DAMPs [74]. The oozing blood and its degradation products also damage various cells in the surrounding area, releasing DAMPs [75]. The over-expression of the mediators (IL-1, IL-6, and TNF- β) and receptors (TLR-2/4, receptors for advanced glycation end-products) activates the destruction and repair process [76]. Sun *et al.* reported data showing that HMGB1 translocations precede other cytokine increase, HMGB1 may be an early upstream promoter of inflammatory response after SAH. So we can speculate that HMGB1 plays a vital role in the development of acute hydrocephalus [73].

The choroid plexus epithelium (CPE) secretes more CSF than other epithelial cells and acts as a blood-CSF barrier, introducing immune cells into the central nervous system [77]. Karimy *et al.*'s mouse model of post hemorrhagic hydro-

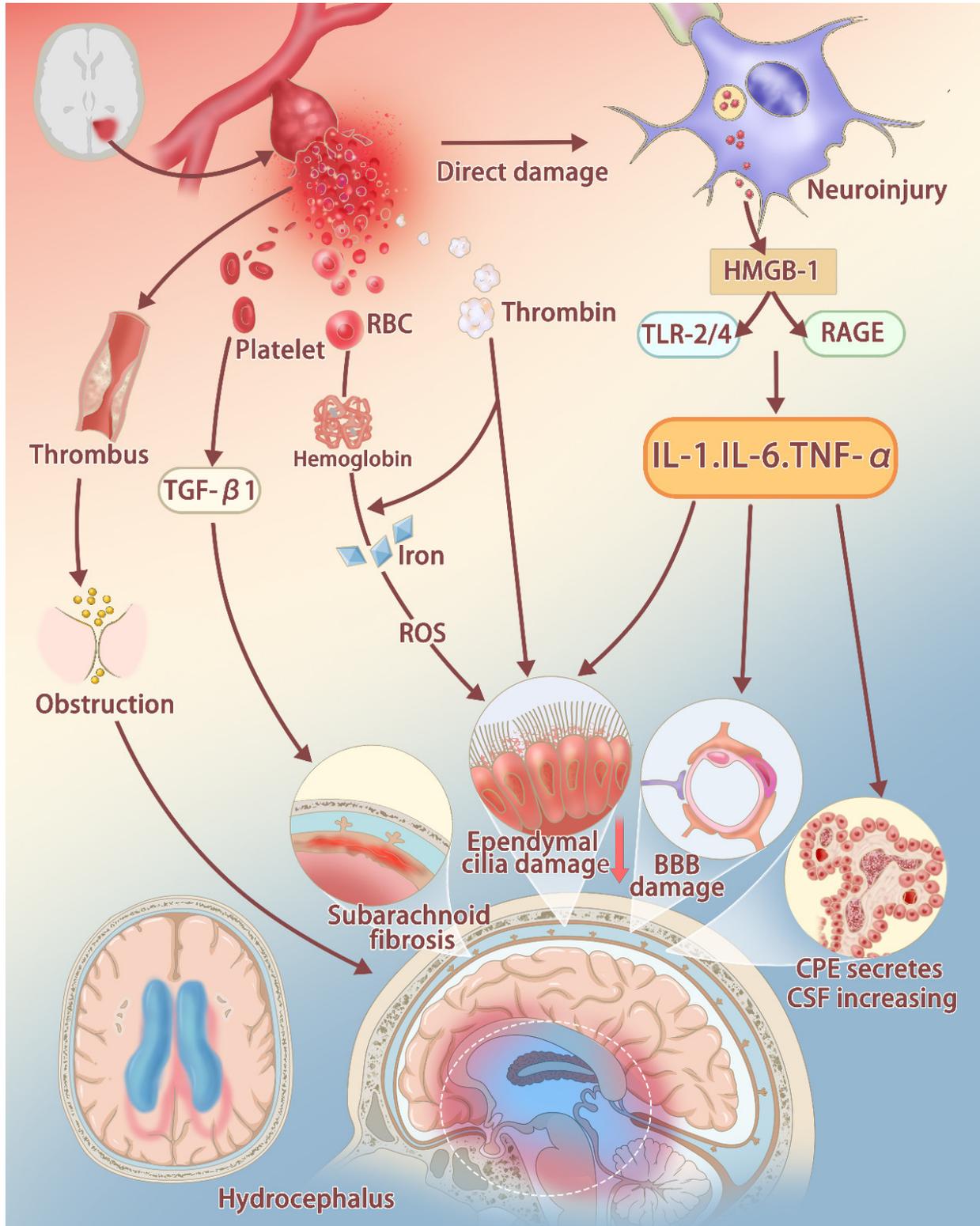


FIGURE 1. The formation mechanism of hydrocephalus after aSAH. Numerous studies have reported direct damage and compression of central nervous system cells when blood enters the subarachnoid space through a ruptured aneurysm, extravasated blood and its degradation products can also damage various cells in adjacent regions and trigger inflammatory cascades that block circulation through a complex series of processes, with the CPE secreting more brain crest fluid, the fibrosis of CSF affects the absorption of CSF and promotes the development of hydrocephalus. Many studies have recently suggested that HMGB1 may be an early upstream promoter of inflammatory response after SAH. **Abbreviations:** HMGB1 = high mobility group protein B1; RAGE = receptors for advanced glycation end products; IL-1 = Interleukin 1; IL-6 = Interleukin 6; TNF- α = tumor necrosis factor α ; CPE = choroid plexus epithelium; CSF = cerebrospinal fluid; CPE = choroid plexus epithelium; TGF- β 1 = transforming growth factor- β 1; TLR 4 = Toll-like receptor 4; ROS = reactive oxygen species; RBC = red blood cell.

cephalus (PHH) showed that IVH caused a threefold increase in TLR-4 and NF- κ B-dependent inflammatory responses in the associated CPE in bumetanide-sensitive CSF secretion [78]. The data revealed the role of previously unrecognized CSF overproduction in the pathogenesis of PHH and demonstrate the new role of TLRs in regulating the brain environment. Moreover, high levels of circulating cytokines, such as IL-1, IL-6, and IL-18, transforming growth factor - β 1/2 (TGF- β 1/2), and TNF- α were detected in acute hydrocephalus after aSAH [33, 79–81].

3.2 Chronic hydrocephalus

In the end, some acute hydrocephalus after aSAH will evolve into chronic communicating hydrocephalus [22]. There is considerable evidence in the fibrotic pathway that chronic hydrocephalus is of “communication” type because of the fibrotic and adhesion of pia mater and arachnoid granules [38].

As discussed above, inflammation is strongly associated with acute hydrocephalus after aSAH, but its role in chronic hydrocephalus is equally significant [39]. Inflammation is related to the pathogenesis of some types of hydrocephalus, especially with fibrotic arachnoiditis, meningeal fibrosis, and subependymal gliosis [78]. Wessell *et al.* showed that persistent systemic inflammation following aneurysmal subarachnoid hemorrhage was associated with SDHC and predicted its occurrence [82]. Chaudhry *et al.* first reported a significant increase in serum IL-10 levels in SAH patients with chronic hydrocephalus on Day 7 [83]. IL-10 is an essential anti-inflammatory cytokine secreted by almost all immune cells [84]. Elevated levels of IL-10 are usually associated with elevated pro-inflammatory cytokines [85]. Therefore, the significant increase of IL-10 after SAH may reflect the up-regulation of inflammatory response and immunosuppression induced by SAH. A high serum level of IL-10 predicts infection and poor prognosis after SAH [85].

TGF β 1, Vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) play a vital role in the pathogenesis of chronic hydrocephalus after aSAH [86, 87]. TGF β 1 is a fibrogenic molecule. There is evidence that subarachnoid fibrosis may be the cause of subarachnoid edema [88, 89]. High levels of TGF β 1 in CSF of patients with subarachnoid hemorrhage increases the risk of chronic hydrocephalus [90, 91]. Studies have shown that the core proteoglycan can attenuate chronic hydrocephalus by inhibiting the TGF β 1/Smad/CTGF (connective tissue growth factor) pathway in a rat subarachnoid hemorrhage model [90, 92]. Tan *et al.* also demonstrated that cannabinoid receptor two agonists inhibit the fibrosis of the ventricles and reduce hydrocephalus after IVH by inhibiting the action of TGF β 1 [93]. After subarachnoid hemorrhage, Chen *et al.* stated that transplantation of human umbilical cord-derived MSCs (hUC-MSCs) into the brain’s ventricles significantly reduces chronic hydrocephalus, inflammation, and behavioral disorders [92]. The transplantation of hUC-MSCs after SAH may play a beneficial role, possibly by inhibiting the TGF- β 1/Smad2/3 signaling pathway [92].

VEGF levels rise significantly in hydrocephalus patients and rabbit models, which is thought to be a result of inflamma-

tion in the brain. VEGF inhibits the BBB by reducing the expression of occluding and tight junction proteins claudin-5 and promoting vascular permeability [94]. Inhibition of VEGF signaling lowers vascular permeability and causes deposition of fibrin in the choroid plexus [95, 96].

Not only VEGF, but HGF is also worthy of attention in the development of hydrocephalus. Naureen *et al.* reported significantly higher VEGF and HGF in delayed hydrocephalus than neonatal hemorrhage without hydrocephalus [97]. In adult rats with chronic hydrocephalus after SAH, the expression of VEGF and HGF increases significantly [98]. Recently, Feng *et al.* reported that urokinase-type plasminogen activator (uPA), by promoting the release and activation of HGF, effectively inhibits subarachnoid fibrosis in rats and inhibits the development of communicating hydrocephalus, which may further regulate TGF- β 1 expression in CSF [99].

4. Diagnosis

4.1 Clinical presentation

The etiology and dynamics of hydrocephalus are still unclear [100]. Acute, rapidly developing hydrocephalus is a life-threatening disease that requires immediate neurosurgical treatment [59]. An acute increase in intracranial pressure can lead to a temporal lobe herniation through the transtentorial notch and/or cerebellar protrusion into the foramen magnum [60]. However, acute hydrocephalus after aSAH has no specific clinical symptoms and signs, and the incidence of acute hydrocephalus is parallel to the clinical grade of SAH (according to Hunt-Hess standards) [101]. So imaging data are often needed for the diagnosis.

In contrast, chronic hydrocephalus usually has no symptoms or fewer such as headaches, dizziness, impaired vision, and attention [102]. Other typical symptoms are morning vomiting and papillary edema of the optic nerve seen in the ophthalmologic examination, which is due to a gradual increase in intracranial pressure [103].

4.2 Imaging examination

Different methods have been used to diagnose hydrocephalus, including physical, neurological, and imaging tests [104, 105]. Imaging studies in particular have shown high accuracy for hydrocephalus [101]. Three main types of imaging are performed for hydrocephalus, including ultrasound, computed tomography (CT), and MRI.

For patients with acute hydrocephalus and clinical manifestations of acute loss of consciousness, CT is the leading examination method because of the short examination time and thus presenting quick results; otherwise, the alternative examination is MRI [106]. If acute hydrocephalus is clinically suspected, a fluid-attenuated inversion recovery scan is sufficient to exclude the impairment of CSF circulation, and both detection and exclusion of CSF extravasation are indirect signs of increased intracranial pressure [104]. For obstructive hydrocephalus, any intracranial tumor of a particular size may block the CSF pathway, theoretically [104]. So different sites of MRI diagnosis need to be distinct. For example, about 60% of colloid cysts show high signal on T1-weighted (T1*w)

MRI scans [107]. In traffic hydrocephalus formed by aSAH, in the case of the slow development of hydrocephalus after hemorrhage, cerebral CT usually cannot detect blood residue. However, changes after hemorrhage can be detected on T2*w MRI scans for a much longer time [108].

Current guidelines recommend the use of the Evans Index (EI) as a radio diagnostic marker for hydrocephalus, which is based on electroencephalographic findings of hydrocephalus in children reported in the early 1940s [105]. The calculation is to divide the maximum width of the frontal horns by the maximum width of the frontal inner table [109]. $EI > 0.30$ is considered to be an indicator of hydrocephalus, independent of age [110]. Subsequent CT studies confirmed the reliability of the diagnosis with EI [111]. Besides, the ventricular shunt-related complications (SRC) index is also used [112]. The ventricular SRC index is estimated by the distance (measured from the medial side of the skull) between the Frontal Horn and the dual frontal diameter at the same level, which average measurement is thought to be 30 percent [40, 112].

Ionizing radiation increases the risk of tumors, especially in children with shunt hydrocephalus [113]. Ultrafast brain MRI (UFB-MRI) and transfrontal cranial ultrasound are recommended for children under six months [114]. Marchese *et al.* developed a new clinical pathway to not only reduce the overall radiation dose in children but also reduce the CT X-ray dose in hydrocephalus patients [115]. This pathway discourages unnecessary shunt series and reduces effective radiation dose by 51% [115].

So far, the MRI technique that can show CSF movement is the phase-contrast MR imaging [116]. The degree of aqueduct signal loss is thought to reflect the rate of pulsating CSF motion, which in turn depends on relative ventricular compliance and surface area [117]. Successful treatment can be achieved by understanding CSF flow patterns and restoring these flow patterns when under abnormal conditions [118]. The permeability of the endoscopic third ventriculostomy (ETV) was evaluated using a series of image parameters, including changes in ventricular size, flow gap signal intensity, and MR patency, using cine phase-contrast MR imaging [116].

4.3 Artificial intelligence

Artificial intelligence (AI) is gaining popularity in medicine, especially in medical image recognition, auxiliary diagnosis, medical robots, drug research and development, health management, and so on [119].

Machine learning algorithms help discover the contribution of nonlinear variables in complex environments, such as predicting tumor growth or identifying surgical candidates [120]. Based on transfer learning, Duan *et al.* established the AI diagnostic model of hydrocephalus by using CT images and diagnosed hydrocephalus by reading the CT images of the brain through analyzing the factors such as ventricular shape, volume, Evan Index, age, etc. [121].

During a hydrocephalus treatment, radiologists spend a lot of time manually segmenting CT images to assess [122]. The assessment of these segments is often highly subjected to intra-observer variability [123]. To improve this, Klimont *et al.* proposed the use of a U-Net convolutional neural network for

automatic segmentation of brain CT scans [124].

5. Treatment

Researchers have been trying to develop non-surgical treatments for hydrocephalus. However, most non-surgical treatments remain in animal trials and have not yet entered clinical trials. Their goals are to prevent hydrocephalus or to find supplemental treatment to shunt [10]. There is no definitive treatment for hydrocephalus, and most patients use a silicone tube and valve system, in which the CSF is transferred from the ventricles to another part of the body [2]. However, shunt therapy is often associated with complications, especially obstruction and infection in infants, increasing morbidity and mortality, and the optimal timing of intervention is unknown [18].

5.1 Non-surgical treatment

As the mechanisms of hydrocephalus have been gradually unveiled in recent years, some experimental drugs, such as isosorbide, have been found to have potential effects in improving the prognosis of patients by controlling the production of CSF, diuresis, fibrinolysis of blood clots, or the control of subarachnoid fibrosis, and more importantly, results have been achieved in various animal trials [125]. Still, there is no specific drug treatment because of the lack of reliable clinical trials to demonstrate a sustained and convincing remediable effect and the current treatments are simply to relieve symptoms. Here are a few current advances in nonoperative treatment [126] (Table 3).

In the 1950s and early 1960s, when shunts were introduced, hydrocephalus was treated with drugs that reduced the production of CSF or dewatered the brain through diuresis, such as isosorbide. But isosorbide is an unpleasant substance that can lead minor vomiting, diarrhea and even failure to gain weight at the normal rate during isosorbide therapy, and this has further proven that thrombin is an essential factor in hydrocephalus after intracerebral hemorrhage as discussed previously [126, 127].

Aquaporin-1 and aquaporin-4 (AQP1 and AQP4) are involved in the pathogenesis of hydrocephalus [125]. Lon *et al.* investigated the dynamic changes of AQP1 and AQP4 after SAH by injecting autologous blood into the cisterna magna of the rat to cause secondary hemorrhage [11]. AQP1 was involved in the production of CSF and the increase of AQP4 might be the compensatory regulation of re-absorption of ependymal CSF [128, 129]. Acetazolamide is a carbonic anhydrase inhibitor that has been reported to reduce cerebrospinal fluid production [130, 131]. Its role in regulating AQP expression may be involved in the mechanism of reducing CSF production [132–134]. Early clinical trials have shown that acetazolamide combined with furosemide may have a therapeutic effect on hydrocephalus [135]. But in this study, the combination of acetazolamide and furosemide also showed a higher risk of hypercalciuria and even nephrocalcinosis. In other studies, the combination of acetazolamide and furosemide has been found to be ineffective in reducing shunt placement and is associated with increased neurological morbidity [136, 137].

TABLE 3. Drug treatment of hydrocephalus in clinical practice.

Drug	Method and dosag	Treatment object	Result	Country
Cilostazol [42]	50 or 100 mg/2 or 3 times per day orally or enterally	87 SAH patients with SDHC	decreased tenascin-C level and probability of SDHC after SAH	Japan
Isosorbide [127]	2 gm/kg body weight at 6-hour intervals, 2 or 2.5 gm/kg every 4 hours orally	60 hydrocephalic infants	67% of patient with less severe symptoms	England
Acetazolamide and furosemide [135]	Furosemide 1 mg/kg daily and acetazolamide 20 mg/kg daily increasing daily by 10 mg/kg up to 100 mg/kg daily intravenously or by mouth	10 post-hemorrhagic hydrocephalus infants	9 infants avoided shunting	America
Acetazolamide and furosemide [136]	Acetazolamide (100 mg/kg/d) and furosemide (1 mg/kg/d) orally	177 infants who had ventricular expansion following IVH	85% (72/85) infants assigned drug therapy died or disabled or impaired at 1 year compared	Worldwide
Acetazolamide and furosemide [137]	Acetazolamide (100 mg/kg daily) and furosemide (1 mg/kg daily) orally	129 infants who had ventricular expansion following IVH	84% (52/62) of infants assigned drug therapy died or disabled or impaired at 1 year	Worldwide
Dexamethasone [141]	0.4 mg/kg per day to 0.1 mg/kg per day intravenously for 4 weeks	43 patients with tuberculous meningitis	no significant difference	Vietnam
Prednisolone [142]	2 mg/kg/day or 4 mg/kg/day for 4 weeks	63 children with tuberculous meningitis	higher risk of hydrocephalus in the high-dose group	India

Abbreviations: SAH = subarachnoid hemorrhage; CSF = cerebrospinal fluid; SDHC = shunt-dependent hydrocephalus; IVH = intraventricular hemorrhage.

Now acetazolamide is also not recommended for management of hydrocephalus [138]. Other drugs that target AQPs, such as erythropoietin, have shown good results in animal models of hydrocephalus [12, 139]. More clinical trials need to be done to make sure the efficacy and possible side effects of erythropoietin.

Inflammation in the SAS has been considered a starting factor for secondary brain injuries such as hydrocephalus, cerebral edema, and vasospasm [85]. It was also found that bacterial meningitis may cause marked changes in the size of the ventricle and increased brain ventricle size was associated with increased mortality [140]. As a classic anti-inflammatory, cortisol does not show a significant therapeutic effect in hydrocephalus [141]. And even in another study, the use of high doses of prednisolone has shown potential of increasing the risk of hydrocephalus [142]. After aneurysmal subarachnoid hemorrhage, chronic hydrocephalus is associated with the induction of tenascin-C, a matricellular protein that may be induced by inflammation [143, 144]. Nakatsuka *et al.* reviewed 87 cases of Fisher grade 3 SAH patients with chronic SDHC and found that a higher dose of cilostazol could effectively inhibit the level of tenascin-C between day one and day twelve after SAH, to prevent the development of chronic hydrocephalus [42]. However, due to the anti-inflammatory effect of cilostazole itself, it cannot be ruled out that cilostazole may have therapeutic effect through other mechanisms independent of tenascin-C [145, 146]. The prevention of the

development of chronic hydrocephalus is possible through eliminating unnecessary shunt surgery [42].

5.2 Surgical treatment

Non-surgical measures to improve the flow of CSF after aSAH have little effect on the recovery of intracranial pressure, and most patients ultimately require surgical treatment, such as EVD, lumbar drainage, CSF shunts, and ETV [18]. According to clinical guidelines, CSF drainage, such as EVD and lumbar drainage, is recommended to treat acute symptomatic hydrocephalus; EVD (Loe III; Gor B) is recommended for acute hydrocephalus with IVH in the third or fourth ventricle; lumbar drainage is recommended in cases without IVH and supratentorial Hernia (Loe IV; Gor C) [2, 16, 17].

Permanent CSF shunt can take many forms. According to the part of the shunt, can be divided into subdural - peritoneal shunt: remove the CSF from epidural inferior vena to peritoneal cavity [147]; ventriculoperitoneal shunt (VPS) to transfer CSF from the brain to the peritoneal cavity (the potential gap between the abdominal wall and the abdominal organs) [148]. There are a few special shunt valves that deserve to be mentioned. The anti-siphon, which closes when the pressure inside the valve is inversely related to the ambient pressure to prevent excessive drainage. This would occur when the patient is sitting, standing, or rapidly changing position [149]; Antibiotic-impregnated can significantly reduce a patient's risk of infection [150].

It has been reported that the neurological function of patients with acute hydrocephalus can be improved by EVD [34]. Whether EVD surgery increases the risk of rebleeding and intracranial infection remains controversial [54, 151]. Hasan *et al.* prospectively studied 473 patients and reported that the rate of rebleeding within 12 days after onset of aSAH was significantly higher in patients with EVD (43%) than in patients without EVD (15%, $P = 0.025$) [55]. Besides, Zhu *et al.* argued in a systematic review that the use of antiplatelet and/or anticoagulant drugs in endovascular aneurysm treatment of ruptured aneurysms in patients with aSAH might increase the risk of EVD related bleeding [152].

The timing and strategy for stopping ventricular drainage remain controversial. Caption *et al.* surveyed 14 neurosurgical departments in Scandinavia concerning the management of EVD treatment in aSAH patients and found that 85% of respondents said they were unaware of international guidelines for EVD discontinuation in patients with hydrocephalus after aSAH [18]. In 74% of patients, the EVD discontinuation strategy was mainly based on the patient's clinical condition and drainage volume [18]. Besides, Chung *et al.* distributed information about EVD management practices to 72 critical care units in the United States and found that most organizations use a single primary management method of EVD, and the consensus is to continuously open EVD to allow CSF drainage in secure aneurysm patients, at the same time, adopt a gradual weaning strategy [19]. Surprisingly, the best available evidence suggests that the opposite approach is safe and reduces the period of ICU hospitalization [19].

Lumbar drainage is also an option [153–155]. However, large hematomas and obstructive hydrocephalus are contraindications [156]. A Study has reported high rates of non-functional lumbar cistern drainage and a variety of complications, but fortunately, there are usually no significant long-term sequelae [157]. Repeated lumbar puncture has also been shown to reduce the incidence of CSF infection in aSAH after vascular coiling [153].

ETV has been performed in pediatric patients over the past few decades with successful effects [158–160]. Besides, ventriculostomy is beneficial for patients with acute subarachnoid hemorrhage [161]. Routine ventriculostomy does not reduce the incidence of SDHC and should not be performed routinely [2]. However, ventriculostomy may increase the risk of rebleeding and meningitis/ventriculitis, which was reported to be associated with age and etiology [162, 163].

There is no established standard for an ideal EVD clamp test in non-traumatic subarachnoid hemorrhage patients before inserting a ventricular-peritoneal shunt [164]. Ascanio *et al.* found that VPS's surgical placement was associated with complications [165]. A large percentage of patients in this study were found to have passed the second and third EVD clamp tests without subsequent shunt insertion. These data support multi-clamp testing before shunt placement [165]. Besides, Akinduro *et al.*'s retrospective study of 489 patients with aSAH found that patients who had failed the first or subsequent EVD clamp tests had a lower risk of developing delayed hydrocephalus but ultimately required VPS [166]. Ilic *et al.* have shown that VPS placement using the ventriculostomy site does not significantly increase the risk of VPS-related

infections or VPS-related bleeding [148].

Kamenova *et al.* [167] report that the incidence of bleeding events after VPS appears to be comparable in patients receiving low-dose acetylsalicylic acid (ASA) treatment and in patients not receiving ASA treatment. Al-Holou *et al.* found in a multicenter retrospective study that gastrostomy tube placement significantly increased the risk of VPS infection [168]. Zhang *et al.* reported that using a modified VPS to place a distal shunt catheter lateral to the hydrocephalus could reduce the possibility of reoperation due to the complications of catheter obstruction and infection [169] (Table 4).

6. Prognosis

The readmission rate is increasingly accepted as a quality indicator [170, 171]. Dasenbrock *et al.* reported that 3,387 patients had a 30-day readmission rate of 10.2% ($n = 346$) and that hydrocephalus was one of the most common causes of readmission for SAH [172].

In recent years, the long-term prognosis of patients with aneurysmal subarachnoid hemorrhage has received increasing attention. In a retrospective study, Wang *et al.* found that more than 50% of patients with aSAH had a good functional prognosis after rehabilitation and hyperbaric oxygen therapy [173]. The degree of neurological impairment can predict a poor prognosis. Clinical follow-up after discharge has improved the understanding and treatment of late-onset hydrocephalus, according to a new study [22].

Early rehabilitation is useful in a range of acute neurological disorders, but it has not been established as part of the subarachnoid hemorrhage guidelines for the treatment of aneurysms [174]. This may be due in part to a fear of aggravation of the development of aSAH complications. In a prospective interventional study, Karic *et al.* found that early mobilization and rehabilitation after aSAH was safe and feasible [175]. The rapid improvement allows patients to be early and highly active without increasing neurosurgical complications [176]. Early recovery from each mobilization step within the first four days after repair can relieve cerebral vasospasm, reducing the risk of severe and clinical vasospasm by 30% [175].

Patients with aneurysmal subarachnoid hemorrhage hydrocephalus have significant cognitive deficits in attention function, short-term and long-term memory, concentration, and motor coordination, and are severely impaired in quality of life and emotion; it might have something to do with white matter being damaged in the subacute phase [177]. The presence of cognitive impairment in survivors requires the establishment of a multidisciplinary clinic for the long-term management of aSAH patients [21, 22].

7. Conclusions

This paper helps us to better understand the occurrence of hydrocephalus after aSAH, especially hydrocephalus caused by inflammation after bleeding, which deserves our attention. It also provides important grounds for potential drug treatments. We provided a more comprehensive risk factor analysis of SDHC and discussed in detail the potential mechanisms

TABLE 4. Surgical treatments and their results.

Treatments	Years	Patients	Number	Results	References
ETV	2005	hydrocephalus in children less than 2 years of age	97	66.6% in post-hemorrhagic hydrocephalus	[162]
ETV	2006	tumor-induced obstructive hydrocephalus	42	success rate 68%	[161]
EVD catheters impregnated with silver nanoparticles	2008	acute obstructive hydrocephalus	19	no catheter-associated ventriculitis (compared to 5/20 in control)	[151]
LD	2009	ICP with TBI or SAH	45 + 55	45% died	[155]
ETV	2010	hydrocephalus patients	41	primary success rates 75.8%; secondary success rates 55.6%	[159]
LD	2011	increased intracranial pressure secondary to aneurysm rupture	6	ICP was reduced from 30.2 mmHg \pm 6.7 to 9.7 mmHg \pm 7.4	[154]
ETV or VPS	2013	patients with INPH and a positive response to the tap test	42	VPS group better improvement (ETV = 50%, VPS = 76.9%)	[160]
EVD or LD	2014	grade III aSAH	76 + 72	LD is better than EVD	[163]
VPS with open distal shunt catheter placement	2015	hydrocephalus	5	reduce the necessity of repeat surgery	[169]
VPS	2018	in infants with obstructive hydrocephalus	27	success rates 88.5%	[164]
ETV/choroid plexus cauterization	2018	in infants with obstructive hydrocephalus	22	success rates 68.2%	[164]
VPS	2019	patients with ICP	28	a revision rate of 11%	[149]
EVD	2020	aSAH	138	31.9% died or had withdrawal of care during admission	[166]

Abbreviations: ETV = endoscopic third ventriculostomy; EVD = external ventricular drain; LD = lumbar drainage; ICP = intracranial hypertension; TBI = traumatic brain injuries; SAH = subarachnoid hemorrhage; CSF = cerebrospinal fluid; VPS = ventriculoperitoneal shunt; INPH = idiopathic normal pressure hydrocephalus; aSAH = aneurysms subarachnoid hemorrhage.

of hydrocephalus after aSAH. There is still a debate about the risk of serious complications from EVD surgery, such as the increased risk of aneurysm rebleeding and intracranial infection. Therefore, more evidence is needed. Hydrocephalus consecutive to aSAH is a pathology that cannot be ignored. We hope that our review will help healthcare professionals to understand the causes and mechanisms of hydrocephalus development and improve the patient's prognosis through early and active treatment and management.

ABBREVIATIONS

AI, artificial intelligence; AQP1 and AQP4, aquaporin-1 and aquaporin-4; aSAH, aneurysmal subarachnoid hemorrhage; BBB, blood-brain barrier; BMSCs, bone marrow mesenchymal stem cells; CPE, choroid plexus epithelium; CSF, cerebrospinal fluid; CT, computed tomography; CTGF, connective tissue growth factor; DAMPs, damage-associated molecular pattern molecules; EI, Evans Index; ETV, endoscopic third ventriculostomy; EVD, external ventricular drain; GCS, Glasgow coma scales; HGF, hepatocyte growth factor; HMGB1, high mobility group protein B1; IVH, intraventricular hemorrhage; PHH, post hemorrhagic

hydrocephalus; SAH, subarachnoid hemorrhage; SAS, subarachnoid space; SDHC, shunt-dependent hydrocephalus; SRC, shunt-related complications; TGF- β 1/2, transforming growth factor - β 1/2; TLR-4, toll-like receptor 4; TNF- β , tumor necrosis factor- β ; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; VPS, ventriculoperitoneal shunt's.

AUTHOR CONTRIBUTIONS

YCW and XQW collected the related paper. CWT, CSW, ZT and ZPZ drafted and revised the manuscript. JPL and GLX participated in the design of the review and helped to draft and revise the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

There are no ethical/legal conflicts involved in the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT FOR PUBLICATIOIR

All authors have read and approved the content and agree to submit this manuscript for publication consideration to your journal.

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