

# Mechanisms of hydrocephalus after intraventricular haemorrhage in adults

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## ABSTRACT

Intraventricular haemorrhage (IVH) is defined as the eruption of blood in the cerebroventricular system and occurs mostly secondary to intracerebral haemorrhage (ICH) in adults. Hydrocephalus is a severe complication of IVH that can serve as an independent predictor of increased mortality. In this mini-review, we focus on the mechanisms of hydrocephalus after adult IVH, including blood-clot blockage, barrier impairment, inflammation and blood components, and attempt to reconcile the current research findings into a unified framework. We expect our theoretical framework to help guide future clinical and basic research leading to improved monitoring and intervention for IVH and subsequent hydrocephalus.

## INTRODUCTION

Intraventricular haemorrhage (IVH) is an outcome of haemorrhagic stroke characterised by eruption of blood in the cerebroventricular system caused by rupture of a cerebrospinal artery spontaneously or secondarily. IVH can serve as an independent predictor of worse outcome and increasing morbidity and mortality after intracerebral haemorrhage (ICH), and can lead to severe complications, such as hydrocephalus. Hydrocephalus itself may contribute to increased mortality following IVH,<sup>1–3</sup> and can be used as an independent predictor of higher mortality<sup>4 5</sup> and worse prognosis.<sup>1</sup> Hydrocephalus may be communicating or non-communicating. Communicating hydrocephalus occurs when the flow of cerebrospinal fluid (CSF) is blocked after it exits the ventricles. Non-communicating (obstructive) hydrocephalus occurs when the flow of CSF is blocked along one or more of the narrow passages connecting the ventricles. Current data indicate that hydrocephalus, communicating or non-communicating, develops in up to 67% of patients with intraventricular extension of ICH.<sup>3 4</sup>

Both immediate and delayed hydrocephalus are possible following IVH,<sup>6</sup> yet the mechanisms by which they occur are unclear. Despite improvement in treatment of IVH

and subsequent hydrocephalus in recent years, these conditions are still life-threatening and often lead to death. Mechanistic understanding of the events that lead to IVH and subsequent hydrocephalus will guide both clinical research and basic-science experiments geared towards treating these conditions. Creating a mechanistic framework is important for clarifying the underlying pathophysiology, identifying targets for intervention and improving the monitoring of progression of IVH. With improved monitoring and means of intervention, deterioration of patients' conditions can be avoided and rate of recovery can be increased. We focus on the mechanism of hydrocephalus after non-traumatic IVH in adults. Although germinal matrix-intraventricular haemorrhage is a frequent phenomenon in premature and very-low-birth-weight (<1500 g) infants, it is beyond the scope of this mini-review, as the anatomy and physiology of IVH in infants and adults are distinct.

## BLOOD CLOT BLOCKAGE

Currently, the prevailing theory explaining acute IVH-induced hydrocephalus is blood-clot blockage in the CSF drainage pathway. Blood-clot blockage frequently takes place in cerebral aqueducts or in the outlets of the fourth ventricle, whereas tetraventricular hydrocephalus typically results from blockage at the level of the cortical subarachnoid space and, less commonly, in the fourth ventricle outlets.<sup>6</sup> After IVH, obstructive hydrocephalus can occur immediately. In these cases, multiple small blood clots form throughout the ventricular system, and obstruct the pathway through the arachnoid villi into the venous sinuses and small blood vessels leading to and from the ependymal cells.<sup>7</sup> Based on this classical theory, current therapies predominantly aim at removing the blood and blood clots, slowing down haematoma growth, and reducing haematoma size. Examples of such strategies include



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administration of recombinant tissue-type plasminogen activator (rt-PA), minimally invasive stereotactic surgery and endoscopic surgery.<sup>8</sup>

Advances in our understanding of the mechanism of hydrocephalus following IVH have been aided by observations in experimental animals. Mayfrank *et al*<sup>9,10</sup> used a swine model of IVH to demonstrate that occlusion of CSF outflow by blood clots in the ventricular system and/or distention of the ventricular walls are prominent mechanisms of hydrocephalus development, which also lead to ventricular dilation and elevation of intracranial pressure (ICP). Furthermore, the impact of the hydrocephalus on adjacent cerebral structures and local blood circulation was shown to persist in the animal model even after the acute obstructive phase.<sup>9</sup> Similar mechanisms likely control IVH-induced hydrocephalus in humans.

The total blood volume and duration of blood and blood-clot presence in the ventricular system are the main factors contributing to the intensity of communicating hydrocephalus, which occurs mostly in a delayed phase when an inflammatory reaction is generated as a result of the debris accumulating as the blood products are broken down.<sup>11</sup>

## BARRIER IMPAIRMENT

Hydrocephalus occurs because of increased production, inappropriate flow or decreased reabsorption of CSF. Barrier-impairment mechanisms leading to hydrocephalus, including dysfunctional ependymal cells, blood-brain barrier (BBB) and the relevant molecular structures are summarised below.

The ependyma is the thin epithelium-like lining of the ventricular system. Ependymal cell integrity is important for CSF production and flow. Postnatal ependymal cells are non-renewable, multiciliated, cuboidal epithelial cells lining the entire ventricular system. Their function includes CSF production, which is regulated by the CSF components and by neurotransmitters such as serotonin.<sup>6,12,13</sup> The ependymal cells vary in morphology and metabolism during development, and become relatively uniform in adults. They are vulnerable to injury,<sup>12</sup> which may occur as a result of increased ICP<sup>14</sup> and/or inflammation.<sup>15</sup> The structural characteristics and enzymatic function in mature mammalian cerebral ependymal cells ensure integrity of the barrier at the brain-CSF interface, which is responsible for scavenging and detoxifying various substances in the CSF, such as oxidants and pathogens.<sup>16</sup> The cilia of ependymal cells have a dual function—as sensory compartments, and as mediators of fluid and cell movement.<sup>17</sup>

Inevitably, the ependymal surface is damaged after IVH.<sup>6</sup> Mayfrank *et al*<sup>10</sup> observed marked loss of the ependymal cells covering the ventricular walls in their swine IVH model. Two complementary mechanisms underlying ependymal cell damage and leading to hydrocephalus following IVH have been proposed: (1) disruption

of the ependymal surface (cells and their cilia) results in collapse of the cerebral aqueduct walls or in aqueductal stenosis and CSF flow occlusion<sup>6</sup> and (2) IVH leads to failure regulating the transfer of fluid, ions and small molecules between the cerebral parenchyma and the ventricular fluid, due to injury-caused dysfunction of the ependymal cells.<sup>12</sup> The relative contribution of each mechanism awaits further study.

IVH causes not only ependymal cell damage, but also disruption of the BBB. The BBB is composed of cerebral endothelial cells and their linking tight junctions.<sup>6</sup> In addition to protecting the brain from pathogens and unwanted molecules, the BBB also is important for maintaining the CSF protein content and the osmotic pressure in the brain.<sup>6</sup> Krishnamurthy *et al*<sup>18</sup> injected hyperosmolar dextran and fibroblast growth factor (FGF) 2 into the ventricles to mimic the condition of increased protein content and osmotic overload resulting from breakdown of BBB after IVH. These solutions that increased the osmotic load in the ventricles and water influx (through the choroid plexus CSF secretion and/or through the brain) into the ventricles to normalise this osmotic gradient successfully induced secondary hydrocephalus in a model of adult rats. However, whether increasing osmolarity or protein content in the ventricles would be able to maintain hydrocephalus is unclear.

Aquaporins (AQPs) are water channels facilitating water movement across cell membranes. In the human brain, the main water channels are AQP1 and AQP4. AQP1 is a predominant component of the apical membrane of the choroid plexus, whereas AQP4 is the main channel in the basolateral surface of ventricular ependymal cells.<sup>19</sup> Choroidal AQP1 appears shortly after the choroid plexus in embryonic development and decreases with ageing. Its substantial contribution to CSF production has been demonstrated by experiments in adult mice and rats.<sup>19</sup> In severe chronic hydrocephalic rats,<sup>20</sup> upregulation of brain AQP4<sup>21</sup> and its relocation from astrocyte end-feet to the entire plasma membrane of hypertrophic astrocytes might be protective response mechanisms developed to maintain water homeostasis, possibly by allowing absorption of transependymal CSF into the brain capillaries.<sup>19</sup>

Additional rodent experiments have shown that AQP4 is important in maintaining the ependymal layer integrity in mice, whereas its role in maintaining the integrity of the BBB and CSF dynamics has been a subject of debate.<sup>19</sup> Li *et al*<sup>13</sup> demonstrated that the majority of AQP4-null mice presented smaller ventricle size, decreased CSF production, higher brain water content and decreased expression of the gap-junction protein connexin 43 in the ependymal cells compared to wild-type mice. In addition, another AQP4-null mouse model was reported to develop hyperpermeability of the BBB, emphasising the role of AQP4 in maintaining BBB integrity.<sup>22</sup> Feng *et al*<sup>23</sup> found hydrocephalus develops in 10% of AQP4-null mice, which display an incomplete

ependymal structure and consequent obstruction of small CSF apertures, such as the cerebral aqueduct and fourth ventricular outlets, leading to deficient water transport. Qing *et al*<sup>24</sup> reported iron overload and increased levels of AQP4 located in the perihematoma area in an adult rat model of ICH and suggested that both contributed to the development of brain oedema after ICH. They hypothesised that AQP4 was upregulated in response to iron accumulation in the periventricular area to mediate hydrocephalus after IVH because AQP4 expression was shown to correlate with iron concentration in that model, and AQP4 upregulation was inhibited by the iron chelator, deferoxamine.<sup>25</sup> However, to the best of our knowledge, there have currently been no reports on studies directly examining the role of AQP1 or AQP4 in the mechanism of hydrocephalus after IVH, and there is a dearth of human data regarding aquaporin function in hydrocephalus.<sup>19</sup>

### INFLAMMATION AND FIBROSIS

The inflammation-related theory of hydrocephalus is well established in neonatal hydrocephalus after IVH, for example, dysfunction of arachnoid granulations due to obliterative arachnoiditis<sup>26</sup> or CSF flow obstruction due to fibrotic blockage.<sup>27</sup> In contrast, the theory and evidence to support or disprove it are limited in adults. After acute obstructive hydrocephalus, inflammation and subsequent scarring of the arachnoid granulations are major contributors to the secondary reaction, in which the flow of CSF through the cerebral aqueduct, fourth ventricular outlets, basal cisterns and/or arachnoid granulations, is prevented, resulting in communicating hydrocephalus,<sup>6, 28</sup> a frequent sequel of IVH, in which dilation of all the ventricles occurs, in contrast to obstructive hydrocephalus.<sup>15</sup>

Inflammatory reaction in response to blood-breaking products reaching the arachnoid granulations with subsequent development of communicating hydrocephalus have been shown in animal experiments, including a swine, rat and mouse.<sup>29</sup> However, blockage is a relative phenomenon. For example, subarachnoid space occlusion may be present in communicating hydrocephalus.<sup>6</sup> Complement activation may also play a role in hydrocephalus. However, only when the BBB is disrupted or blood extension into the ventricular system occurs, are components of the complement system (beneficial or detrimental) allowed to pass into the ventricular system and possibly induce immune reaction in the brain parenchyma, including cell lysis and inflammation, leading to hydrocephalus.<sup>30, 31</sup>

Inflammation following IVH is mediated also by the transforming growth factor (TGF) family members, TGF $\beta$ 1 and TGF $\beta$ 2, which are among the most abundant and functionally versatile cytokines in the mammalian central nervous system (CNS).<sup>32</sup> Normally, TGF $\beta$ 1 is restricted to the choroid plexus and meningeal cells, two sites that are key to the development of

hydrocephalus.<sup>33</sup> TGF $\beta$ 2 is located mainly in neurons and astroglial cells.<sup>32</sup>

TGF $\beta$ 1 is a highly ubiquitous cytokine that can be synthesised by virtually all cells, and almost all cells have been shown to have receptors for TGF $\beta$ 1.<sup>33</sup> Thus, the presence of TGF $\beta$ 1 in the CSF could originate from the haemorrhage itself or from the choroid plexus.<sup>34</sup> TGF $\beta$ 1 is stored in platelet granules and, therefore, substantial amounts of TGF $\beta$ 1 gain access to the CSF after IVH as platelets accumulate within intraventricular blood clots.<sup>33</sup> TGF $\beta$ 1 induces upregulation of the cognate genes encoding extracellular matrix proteins, such as fibronectin and laminin, which are important mediators of wound healing and scar formation.<sup>34</sup> The major roles of TGF $\beta$ 2 are scarring and fibrosis.<sup>35, 36</sup> When these events occur in the ventricular system and TGF $\beta$ 2 acts in the CSF, the result can be hydrocephalus.

However, when Kaestner and Dimitriou tried to detect the distinct behaviour of TGF $\beta$ 1 and TGF $\beta$ 2 following subarachnoid haemorrhage (SAH) and IVH in adults,<sup>32</sup> they found that TGF $\beta$ 2 concentration in the plasma did not change over time, and displayed a parabolic concentration change in the CSF with a peak at day 6 post ictus. In contrast, plasma levels of TGF $\beta$ 1 increased markedly over time in the early phase after the haemorrhage, whereas the CSF levels constantly decreased. These findings suggest that the mechanisms of development of posthaemorrhagic hydrocephalus in adults is unlikely to be mediated by TGF $\beta$ 2, while whether it involves the crucial role of TGF $\beta$ 1 is lacking convincing proof, as well.<sup>32, 33, 37</sup>

### BLOOD COMPONENTS

#### Iron

Heme is degraded in the brain by hemoxygenase (HO) into iron, carbon monoxide and biliverdin, the latter of which is subsequently converted to bilirubin by biliverdin reductase.<sup>31</sup> In response to haemorrhage, HO plays a dual role. It stimulates protective activity by virtue of the anti-inflammatory, antiapoptotic and antiproliferative actions of one or more of the three heme breakdown products,<sup>38</sup> but at the same time promotes harmful effects by causing brain iron overload.<sup>39</sup>

Normal ependymal cells take up iron from the CSF and prevent iron diffusion to the rest of the brain.<sup>6</sup> Thus, destruction of ependymal cells following IVH may be one of the causes for increased non-protein-bound iron—which is cytotoxic—in the CSF, and in turn may increase ependymal cell damage and exacerbate patients' conditions.<sup>6</sup>

Gao *et al*<sup>40</sup> found that intraventricular injection of lysed red blood cells (RBCs), but not packed RBCs, resulted in ventricular enlargement in rats 24 h postinjection. Similarly, intraventricular injection of iron also resulted in ventricular enlargement and ventricular wall damage, whereas co-injection of deferoxamine with lysed RBCs was protective against ventricular enlargement.

These results suggest that iron, a degradation product of haemoglobin, has an important role in development of hydrocephalus after IVH. Systemic deferoxamine treatment has been found to partially reverse brain iron accumulation, hydrocephalus, bilateral enlargement of the lateral ventricles and hippocampal tissue loss, in an adult rat model of IVH.<sup>41</sup> In that model, iron accumulation was found associated with upregulation of HO-1 and ferritin (a key iron storage protein) in the hippocampus and periventricular areas.<sup>41</sup>

The role of free iron in IVH-induced hydrocephalus may be tightly linked to the inflammatory response. Complement-mediated erythrocyte lysis may expose the CSF and brain to the damaging effects of free iron ions.<sup>6 42 43</sup> Intraventricular macrophages express transferrin receptors and may be involved in iron regulation,<sup>44</sup> which is also of possible importance after IVH as haemosiderin, an iron-storage complex containing ferritin, is found within macrophages after haemorrhage.<sup>6</sup> In animal models of hydrocephalus, the level of complement receptor type 3 in intraventricular macrophages is elevated, suggesting a possible role of complement activation in hydrocephalus development.<sup>45</sup> The precise relationships among complement activation, macrophage action and hydrocephalus after IVH need to be delineated further.

### Thrombin

Thrombin is serine protease that acts as part of the fibrinolytic system to induce blood coagulation after injury when bleeding is involved. Highly regulated procoagulant and anticoagulant zymogens and cofactors control the blood coagulation cascade, which comprises a series of proteolytic reactions.

Liu *et al*<sup>46</sup> reported that intraventricular injection of thrombin (20 U from bovine plasma) in adult rats caused BBB breakdown with reduction of brain microvascular endothelial cell and perivascular astrocyte immunoreactivity. Our group established an IVH model in adult rats to investigate what role thrombin plays in the mechanism of IVH-induced hydrocephalus.<sup>47</sup> We found that injection of heparinised blood, in contrast to non-heparinised blood, resulted in decreased hydrocephalus when the rats were examined by MRI between 1 and 28 days postinjury.<sup>47</sup> Intraventricular injection of thrombin alone caused significant hydrocephalus, ventricular wall damage and periventricular BBB disruption. Thrombin-induced hydrocephalus was reduced by co-injection of the protease-activated receptor 1 (PAR-1) antagonist SCH79797. Based on these results, we concluded that mediation of thrombin's effect through the PAR-1 pathway is an important contributor to hydrocephalus development after IVH.

### CONCLUSION

Hydrocephalus, a severe complication after IVH, can independently increase the risk of mortality. The

mechanisms of hydrocephalus following IVH in adults are distinct from those in infants. Our mini-review focused on research findings in adults and animal models, including blood-clot blockage, barrier impairment, inflammation and blood components, including iron and thrombin.

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