ORIGINAL RESEARCH PAPER

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CEREBRAL EDEMA DUE TO TRAUMATIC BRAIN INJURY: PATHOPHYSIOLOGY AND ROLE OF NOVEL TARGETED THERAPIES

KEY WORDS: edema, TBI, traumatic brain injury, targeted therapies

Dr Ridham Khanderia* Mch Neurosurgery- Senior resident*Corresponding Author

Dr Rajkumar Pannem Mch Neurosurgery- Senior resident

Dr Vineet Singh Mch Neurosurgery- Senior resident

ABSTRACT

Cerebral edema is the accumulation of water in intracellular and interstitial brain tissue due to some neurological pathology. There are three principle mechanisms for cerebral edema: Cytotoxic edema, Vasogenic edema, Hydrostatic edema. There are multiple options available for treating cerebral edema including: medical management and surgical management. But none of the current treatment modalities address the underlying pathogenetic mechanism. So, targeted therapies are need of the hour. It may include NKCC1 antagonists, aquaporin inhibitors, Sur1-Trpm4 channel inhibitors, NHE inhibitors and VEGF inhibitors; which are in different stages of development. But, there are very few human trials that are conducted to assess the role of these pharmacologic agents in cerebral edema due to traumatic brain injury

Introduction

Cerebral edema is the accumulation of water in intracellular and interstitial brain tissue due to some neurological pathology [1]. The symptomatology due to primary neurological pathology is usually worsened by the cerebral edema that caused it. This is one typical example of positive feedback loop that leads to swelling of brain cells which typically exacerbates the process. The clinical manifestations range from neurological deficits to coma to brain death. This review is done with the purpose of understanding the pathophysiological mechanisms leading to cerebral edema and discusses the current and future treatment strategies.

Pathophysiology of Cerebral Edema

There are three principle mechanisms for cerebral edema [2]

1. Cytotoxic edema
2. Vasogenic edema
3. Hydrostatic edema

Cytotoxic Edema

Cytotoxic edema occurs because of influx of Na+ and Cl- ions into the cells from interstitial space carrying water with it; leading to cellular swelling. Among all cell types in central nervous system including neurons, astrocytes, microglia and ependymal cells; astrocytes seem to be most sensitive. [3]

Because of this rearrangement of ions, there are many maladaptive changes which are required for maintaining osmotic and electrical neutrality. All this leads to swelling in cells and depletion of ATP. [4]

If we see the particular transporter on the glial cells, then "NKCC1" is one such transporter located on astrocytes, that gets activated in acute settings of ischemia, trauma and acute liver failure [5]. So molecular regulation of this transporter may help in regulation of cytotoxic edema. Another such example is , aquaporin-4 (AQP-4).These aquaporin facilitate the transport of water across blood brain barrier leading to worsening of cerebral edema in pathological states[6]. Similarly, another such membrane transporter is sodium-hydrogen anti-porter which contributes to cyto-toxic edema[7]. Transporters- Trpm4 and Sur1 physically associate to form Sur1Trpm4, which has been implicated in astrocyte and brain edema [8].

Cytotoxic edema additionally results from exposure to endogenous toxins. One such endogenous toxin is glutamate. After ischemic insult or traumatic injury; there is accumulation of glutamate which leads to lysis of neuronal cells and astrocyte swelling. One possible mechanism implicated is mGluR5 receptor activation. (metabotropic glutamate receptor 5)[9].

Vasogenic Edema

Vasogenic edema occurs due to accumulation of fluid in the interstitial compartment owing to absence of intact blood brain barrier (BBB).In vasogenic edema ;hydrostatic forces are the primary driver. Due to cerebral insult/injury there is disruption of BBB or increased permeability. One of the mechanisms could be increased expression of vascular endothelial growth factor (VEGF)[10]. This factor leads to disruption of tight junctions at cellular interface leading to increased permeability. One another such factor is matrix metalloproteinase (MMP) which also contributes to edema formation. Also this of disruption of BBB may lead to leakage of blood products in interstitial space. These are toxic to brain cells [11].

Hydrostatic Edema

This occurs because of increased CSF accumulation in ventricles leading to trans-ependymal movement of CSF into brain parenchyma. CSF diversion is the main stay of treatment.[12]

Non-targeted Therapies

Among non-targeted therapies; there are multiple options. Hyperosmolar therapies include mannitol and hypertonic saline. It usually works on principle of generating osmotic gradient across the intact BBB. Other options include use of diuretics, sedation, hypothermia and glucocorticoids.[13]

Targeted Therapies

There are multiple potential options available as targeted therapies. These include NKCC1 antagonist, aquaporin inhibitors, Sur1-Trpm4 channel inhibitors,NHE inhibitors and VEGF inhibitors.[14]

1) NKCC1 antagonist:Bumetanide

Bumetanide is a loop diuretic used for the management of fluid retention in chronic heart failure. It is found that it also inhibits NKCC1 transporter.Thus,it can be used in patients with cerebral edema. It usually transports sodium from intravascular space to endothelial cells which then transports it to interstitium. In cerebral stress, there is increased expression of this transporter. Animal studies have been done which has shown its effect on cerebral edema in diabetic

ketoacidosis, ischemic stroke and traumatic head injury cases. But, still there are no reports of its use on humans.[15]

***2)* AER 271 & curcumin: Aquaporin inhibitors**

AER 270 is an inhibitor of aquaporin-4. AER 271 is a phosphorylated pro drug of AER 270.Both of them may have a potential role in cerebral edema management. In animal models, there is some success in reducing cerebral edema. Thus, it has been tried in humans and currently it is in phase 1 clinical trial for use in acute ischemic stroke.[16]

One another aquaporin inhibitor is curcurmin- a curry spice – curcuma longa. It is inhibitor of NF-KB and IL-1Beta. Through, these effects; it potentially inhibits aquaporin 4 channel. This mechanism has shown some evidence in rodent models of traumatic brain injury, ischemic stroke and cerebral neoplasms.[17]

3) Glibenclamide: Sur1-Trpm4 inhibitor

Sur 1(Sulfonylurea receptor 1) is a cation channel which gets activated in case neuronal injury and gets combined with Trpm4 leading to formation of a non selective cation channel which permits water and ions leading to cerebral edema. Animal models have shown good results in TBI.Two human clinical trials have shown that glibenclamide decreases the contusion expansion rates and improvement in short term functional outcome. There is an RCT ; GAMES-RP which has shown that IV administration of glibenclamide leads to improvement in midline shift,alertness,NIH stroke scales cores and mortality.[18]

4)NHE (Sodium hydrogen exchange) inhibitors:SM-20220 & HOE-642 & Amiloride:

There are two isoforms of NHE- NHE1 and NHE2. Both of them have an important role in BBB permeability. A murine model study has demonstrated that SM-20220& HOE-642 can reduce cerebral edema due to ischemic cause. Amiloride,which is a diuretic also has been shown to decrease cerebral edema. But there have been no studies done in humans to prove their efficacy.[19]

5)VEGF- inhibitor :Bevacizumab

VEGF inhibitors have generally be shown to have role in neoplasms. But, it has also shown to reduce cerebral edema and rat models have shown its role in traumatic brain injury. But there have been no clinical trials done in humans for investigating its effect on cerebral edema in humans.[20]

Surgical treatment:

When these medical therapies fail; then surgical management remains the only available choice. Decompressive craniectomy is one such option. But, it doesn't address the underlying problem and only allows an alternate method of reducing intracranial pressure.[21]

Conclusion

There are multiple options available for treating cerebral edema that occurs in traumatic head injury. But, majority of the options are non-targeted and does not address the underlying pathogenetic mechanism. It is the need of the hour to find ways that specifically targets the underlying abnormality. Since, different pharmacological agents discussed here, are in different stages of development, we require a large number of clinical trials in humans , so that we can assess its potential role for treating this life threatening condition.

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