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Chapter 5

Hydrocephaly: Medical Treatment

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Abstract

Hydrocephaly is a prevalent condition in all age groups. At present, the most frequent strategies used to treat hydrocephaly are surgical shunting procedures, which are still associated with multiple complications. The main goal of the medical therapy for the lowering of high ventricular pressure is to avoid shunting or to reduce and decrease intracranial pressure (ICP) until shunt surgery. Medications affect cerebrospinal fluid dynamics by decreasing secretion or increasing reabsorption. Medical treatment for manipulation of water balance or cerebrospinal fluid (CSF) production reduces mortality in both infants and adults with neurological disorders. Medical treatment has an important role in the management of hydrocephaly especially in patients not suitable for shunt and in patients whom the shunt alone is not able to control the hydrocephaly. The treatment is used to delay surgical intervention but is not effective in the long treatment of chronic hydrocephaly.

Keywords: hydrocephaly, intracranial pressure, drugs, treatment, acetazolamide

1. Introduction

Hydrocephaly is an increased volume of cerebrospinal fluid (CSF) in or around the brain that can be produced by various disorders [1]. CSF accumulation mostly occurs within ventricles, but the accumulation may occur in other sites of the brain. It can develop at any age, both in infants and in adults [2]. The cumulative 5-year complication rate was reported approximately 48% in children and 27% in adults, in a large population-based analysis in California in the 1990s [3]. According to the studies, approximately 3.4 per 100,000 per year in the adult population undergo a surgical procedure for hydrocephaly. In infants, symptoms include a large and rapidly growing head, bulging, irritability, and seizures. In adults and children,

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symptoms are headache, difficulty in walking, lossing the ability in hard activities, decrease in mental abilities, vomiting, and lethargy. A headache may even awaken the patient from sleep in case of increased intracranial pressure (ICP). Papilledema is more common in adults than children.

Hydrocephaly can be classified according to the site of CSF flow obstruction or impairment as internal hydrocephaly CSF accumulation which occurs in ventricles and external hydrocephaly in which the accumulation of CSF occurs in subarachnoid space in cerebral cortical surfaces. Hydrocephaly is classified into two groups according to its cause: communicating and noncommunicating hydrocephaly. In communicating hydrocephaly, CSF flows from lateral ventricles into cerebral and spinal subarachnoid space (SAS). In contrast, noncommunicating hydrocephaly flow of the CSF through ventricles is interrupted for any reason. The obstruction of CSF flow in noncommunicating hydrocephaly may happen either internal or external to the ventricles. On the other hand, the overproduction of CSF may cause an accumulation at any site of the brain. Hydrocephaly can be classified according to the duration of development into three groups, which are acute, subacute, and chronic hydrocephaly. Another classification of hydrocephaly is the disorder into high-pressure and normal-pressure hydrocephaly (NPH) [1–5].

2. Medical treatment options

Cerebrospinal fluid shunting is the standard treatment for hydrocephaly, but there are certain medical treatment approaches alternatively applied alone or in combination with shunting.

Treatment of hydrocephaly depends on its cause. Medical treatment is used to delay surgical procedures in hydrocephaly. Medical treatment is not effective in long-term treatment of chronic hydrocephaly but can be resumed to balance CSF dynamics (production or absorption) during this interim period. Medications include decreasing CSF secretion by the choroid plexus (acetazolamide), increasing CSF reabsorption (isosorbide, furosemide), or osmotic diuretics which increase water excretion and are used to reduce intracranial pressure (**Table 1**) [1, 2].

2.1. Reducing cerebrospinal fluid production

2.1.1. Carbonic anhydrase inhibitors

Carbonic anhydrases are a family of metalloenzymes present in the renal cortex, gastric mucosa, pancreas, liver, lungs, ciliary body, and brain, which catalyze the reversible hydration of carbon dioxide and bicarbonate. Thus, this allows to regulate intra- and extracellular concentrations of CO_2, H^+, and HCO_3^- [1, 6]. These enzymes are also found in the glia and the choroid plexus which plays secretory roles in the brain. Enzyme concentration is greater than the ciliary body in the choroid plexus [1, 6].

Complete choroid plexus carbonic anhydrase inhibition reduces cerebrospinal fluid (CSF) production by 50%. Many studies have shown that inhibition of carbonic anhydrase reduces

Intervention	Indication	Outcome	Complications
Medication (furosemide, acetazolamide)	Decrease production of CSF due to increased fluid excretion	Temporary relief of increased CSF until surgical intervention is possible	No direct evidence of effectiveness versus waiting until surgical intervention is possible; potential increased risk of complications
Lumbar puncture	Remove excess CSF through the spine to reduce pressure	Temporary relief of increased CSF until surgical intervention is possible	Possible increased risk of infection from multiple perforations
Shunt placement	All classifications of hydrocephaly in which patient can undergo surgery	Relief through drainage of excess CSF	Shunt collapse, infection, shunt failure, possible need for surgical adjustment or replacement
ETV	Obstructive hydrocephaly, shunt failure	Relief through drainage of excess fluid	Occlusion of puncture site, difficulty performing procedure, infection, hemorrhage, nerve damage

CSF, cerebrospinal fluid; ETV, endoscopic third ventriculostomy [2].

Table 1. Treatment options for hydrocephaly.

cerebrospinal fluid production. In clinical practice, the most frequently used drug which inhibits carbonic anhydrase and treats hydrocephaly patients is acetazolamide (ACZ) [6–11].

2.1.1.1. Acetazolamide

Acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) is a sulphonamide derivative with a potent inhibitory effect on carbonic anhydrase, which was first synthesized by Roblin and Clapp in 1950 [12]. Acetazolamide has been used in the treatment of cardiac edema, glaucoma, urinary alkalinization, metabolic alkalosis, and acute mountain sickness [1, 10, 13].

Numerous experimental and clinical studies have shown reduction in CSF production after ACZ administration. Effective doses of acetazolamide, which penetrate the blood-brain barrier to reach the choroid plexus and depress CSF flow, are on the order of 20 mg/kg [2, 6, 11, 14–18]. However, there is no standard dose of acetazolamide; the starting dose is 500 mg two times daily and a maximum dose of 4 g twice daily [19]. Recommended starting dose in children is 25 mg/kg per day with a maximum dose of 100 mg/kg or 2 g per day [20]. Complete inhibition of choroid plexus reduces CSF production by 50%, which was obtained after administration of 5–20 mg/kg of ACZ [6, 11].

In some cases, despite the reduction in CSF production, ACZ treatment could not reduce intracranial pressure, on the contrary of increasing it. This unexpected effect may be due to an indirect effect of ACZ on cerebral vessels and blood flow of the cerebrum [1].

Hypersensitivity especially sulfur allergy and hepatic failure are contraindications for ACZ and also relatively contraindicated in patients with a history of renal stones [19]. An important side effect of acetazolamide is the development of hyperchloraemic metabolic acidosis with hypokalemia. Other adverse effects include dysgeusia, paresthesia, fatigue, nausea, diarrhea, and polyuria [17]. These side effects are usually dose related. For this reason monitoring of

electrolytes is suggested during acetazolamide treatment, and potassium and bicarbonate replacement therapies are required for reducing the adverse effect of ACZ [1].

In expert opinion, acetazolamide is the most suitable drug alone or in combination with furosemide for treatment of hydrocephaly [1].

2.1.2. Furosemide

Furosemide selectively inhibits sodium reabsorption in the nephron at the loop of Henle, which is a potent loop diuretic used to treat high blood pressure, congestive heart failure, and swelling due to excess body water and also used in hyperkalemia and acute renal failure [1, 10]. Studies have shown that furosemide reduces the production of cerebrospinal fluid by inhibiting the transport of Cl^- to the cerebrospinal fluid [21–24]. In the medical treatment of hydrocephaly, the usual dose of furosemide is 1 mg/kg/day divided into two doses/day [25, 26]. Adverse effects of furosemide therapy are serum electrolyte disturbances, hypotension, and ototoxicity; for this reason, electrolyte levels have to be followed closely [10].

2.1.3. Combined therapy of furosemide and acetazolamide

Studies have shown that combination therapy of furosemide and acetazolamide was not effective in decreasing the frequency of shunting or death. Therefore, this therapy is not recommended [2, 26–29].

2.2. Osmotic diuretics

The proximal tubule and descending limb of Henle's loop are freely permeable to water. Osmotic diuretic agents are freely filtered at the glomerulus, undergo minimal reabsorption by the renal tubules causes water to be retained in these segments and promotes water diuresis. Four osmotic diuretics are available: glycerin, isosorbide, mannitol, and urea; mannitol is the most commonly used in clinical practice and the most extensively studied. Osmotic diuretics are used to increase water excretion and to promote prompt removal of renal toxins and also are used to reduce intracranial pressure [10, 30].

2.2.1. Isosorbide

Isosorbide (1,4:3,6-dianhydro-d-glucitol) is an osmotic agent developed for the treatment of glaucoma. It has also been shown to reduce the intracranial pressure [31, 32]. The single oral dose of isosorbide significantly reduces intraventricular pressure. Multiple studies showed the usual dose of isosorbide, which is 2–3 g/kg/day given at intervals of 6–12 h [33, 34].

Lorber et al. have studied the use of isosorbide in patients with various types of hydrocephaly; they reported that patient did not require shunt insertions after prolonged medication with isosorbide. But isosorbide did not replace than surgery and was less efficient than surgery [34–36].

Lorber concluded that isosorbide was safe in a large number of patients; adverse effects were less, and less frequent biochemical monitoring was required [34].

Only recommend isosorbide for short-term treatment of hydrocephaly with constant surveillance to prevent hypernatremic dehydration. However, osmotic agents are not preferred in the treatment of hydrocephaly at present [1, 31, 33, 37].

2.2.2. Mannitol

Mannitol is a six-carbon alcohol with a molecular weight of 182. This osmotic agent is not metabolized and is excreted by glomerular filtration, without any important tubular reabsorption or secretion. Also, mannitol induces an increase in serum osmolality and an osmotic gradient between the serum and intracranial compartment. Thus, removal of brain water causes to reduce ICP. Mannitol has been widely used to reduce intracranial and intraocular pressures because of its osmotic diuretic action and presumed antioxidant properties for many years. Mannitol is poorly absorbed from the gastrointestinal tract if administered orally; it would cause osmotic diarrhea, so it must be given parenterally [10, 38–40].

A dose of 0.25–1 g/kg (20% solution) mannitol is administered intravenously and infused over 5 min. Intracranial pressure should fall in 60–90 min [1, 10]. In most cases, after the administration of a bolus of mannitol, intracranial pressure rapidly decreases, but in some patients, it can worsen intracranial hypertension [10].

The effect of mannitol in the treatment of hydrocephaly has been reported in only a few studies. Hayden et al. showed that the administration of mannitol induces rapidly decreased ICP, but this effect lasted only 3–4 h and was followed by a rebound of ICP above baseline [41]. Ma et al. showed that mannitol and corticosteroids represent an effective treatment approach for patients with autoimmune diseases associated with hydrocephaly [42].

Mannitol produces a diuresis more than a natriuresis, and if free water losses are excessive, hypernatremia and hyperkalemia may ensue [10].

2.2.3. Glycerol

Glycerol is an oral osmotic agent, reduces intracranial pressure in adults with brain tumors, and was suggested as a possible agent for managing hydrocephaly [43]. On the contrary, uncontrolled trials did not support its use. Glycerol had no effect in premature infants with hydrocephaly and did not treat hydrocephaly in adults with metastatic brain cancer [44, 45].

2.3. Increasing CSF absorption

2.3.1. Glucocorticoids

Glucocorticoids have been used for decades in a range of neurological disorders associated with raised intracranial pressure [2]. Experimental studies have shown that glucocorticoids reduced CSF production and CSF flow [46, 47]. Glucocorticoids have also been used to reduce the fibrosis in the subarachnoid compartment [2].

In intraventricular hemorrhage (IVH) cases, the blood clot in the ventricular system can interrupt normal CSF flow. After the acute period of the subarachnoid hemorrhage and

bacterial or carcinomatous meningitis, cerebrospinal fluid absorption can be reduced. Glucocorticoids can slow this inflammatory response after these conditions. However, steroids do not inhibit fibroblast growth or collagen synthesis. Intrathecal or intravenous steroids have been used to prevent or alleviate arachnoiditis with poor results [1].

Some studies have shown that in autoimmune diseases associated with hydrocephaly glucocorticoids have been beneficial and corticosteroids should be considered as first-line treatment choice [42, 48–50].

3. Other treatment options

3.1. Prevention of inflammatory and fibrotic process

Intraventricular hemorrhage, subarachnoid hemorrhage, and infection (e.g., meningitis), which can lead to restriction of CSF, are all associated with secondary inflammation and fibrosis in the subarachnoid compartment. Although many mechanisms have been proposed to explain the pathophysiology of hydrocephaly, it has not yet been fully elucidated. Common theories: hemorrhage debris or clot obstruction of the CSF circulation of the arachnoid, subarachnoid, and arachnoid fibrosis, inflammation, apoptosis, autophagia, and oxidative stress [51–54].

3.2. Cerebrospinal fluid pathway modulation

Gliocytes play a destructive and curative role in the abundance of cytokines released when the brain is exposed to various lesions [55]. It also contributes to the inflammatory side by causing the structurally and functionally cleavage of the vegetative nervous system and glia cell which join the blood-brain barrier [53]. Inflammation of CSF and fibrosis is one of the general features of hydrocephaly and leads to a restriction in CSF flux. Conditions that may cause restriction include intraventricular hemorrhage, subarachnoid hemorrhage, or infection (e.g., meningitis), are all associated with secondary inflammation and fibrosis in the CSF tract, especially in the subarachnoid compartment. In children, intraventricular hemorrhage and bacterial meningitis are associated with meningeal fibrosis, which completely abolishes the subarachnoid space. In subarachnoid hemorrhagic adults, inflammation occurs in the arachnoid villi during the first week, and it is followed by collagen production [56]. Enzymatic resolution of intraventricular or subarachnoid blood collections, intervention in the inflammatory process, and the production of extracellular matrix molecules are the ways to reduce hydrocephaly development, and investigation is still going on.

3.3. Thrombolytic therapy

Some researchers have conducted experimental studies to investigate the efficacy of thrombolytic therapy in preventing posthemorrhagic hydrocephaly. In 1986, Pang et al. tested the efficacy of fibrinolytic (urokinase; uPA) in the treatment of hydrocephaly for the first time

and found that intraventricular administration of uPA effectively attenuated ventriculomegaly [52]. Similarly, several empirical studies have shown that intraventricular tPA administration is effective in preventing hydrocephaly after subarachnoid hemorrhage and regressing ventricular dilatation [57]. However, the development of perihematomal edema after tPA administration has increased question mark on this treatment method. Meta-analyses for the comparison of the uPA and tPA regarding the dissolution of the clot after intraventricular hemorrhage were made [58, 59]. Studies have shown that both uPA and tPA cause a decrease in ventricular volumes, but only uPA improves functional recovery significantly.

3.4. Anti-inflammatory therapy

There is a clear relationship between inflammation in the CSF tract and subsequent hydrocephaly development. Anti-inflammatory agents have been experimentally tested to prevent hydrocephaly after meningitis and posthemorrhage. There are numerous studies showing that corticosteroid therapy after acute bacterial meningitis significantly reduces hearing loss and neuroleptic sequelae, but the effects on hydrocephaly development are not fully known. Some studies have shown that the use of steroids does not change the likelihood of developing hydrocephaly or that this risk can be elevated in children [60–62].

3.5. Vasoactive drugs

Nimodipine is widely used as a calcium channel blocker for the control of hypertension. Experimental studies have shown that nimodipine reduces motor and cognitive function impairment after hydrocephaly [63]. Clinical trials showed that nimodipine is safe, but there is no definitive evidence for the effectiveness in the treatment of hydrocephaly. Magnesium, a calcium antagonist, also has a weaker protective effect [64].

3.6. Antioxidative therapy

Mechanical factors and reduced white matter blood flow into axonal and oligodendroglial damage can lead to neuropathophysiological damage [65]. Hypoxic changes in proteins of white matter glial and endothelial cells have been found in hydrocephaly by immunohistochemical detection of pimonidazole [66]. Antioxidant therapy is a potential pharmacological treatment for oxidative stress that is associated with brain damage in hydrocephaly. Dietary supplementation of antioxidants like oral coenzyme Q10 (CoQ10), ascorbic acid, glutathione, and lipoic acid in humans and animals reduces oxidative stress by decreasing lipid peroxidation [67].

3.7. Neuron vs axon protection

Neuronal damage in the cortex has been attributed to the disturbed activity of the noradrenergic and dopaminergic neuronal systems and synaptogenesis caused by hydrocephaly [68, 69]. Morphological changes in the hydrocephalic brain with ventricular dilation occur most characteristically in the white matter [70]. Periventricular axons in hydrocephalic brains may sustain the damage in some neurons. Studies on hydrocephaly demonstrated that hippocampal neurons show various secondary abnormalities due to deafferentation [71]. In the immature brain,

hydrocephaly affects developmental processes of cell genesis and myelination [68]. Potential early therapeutics are antioxidative, anti-inflammatory, antiapoptotic, and anti-excitotoxic drugs that can be used in neonatal hypoxic-ischemic brain injury. Memantine, a noncompetitive NMDA receptor antagonist, protects neurons and axons [72]. The neuronal cytoskeleton has been shown to play an important role in the maintenance of cytoplasmic morphology and axonal transport [15]. The functional effects of early shunt placement have been reported to prevent impairment of synaptogenesis and learning disability [73].

3.8. Cerebral stimulants

Bifemelane is a monoamine oxidase inhibitor used as an antidepressant and cerebral metabolic activator to normalize norepinephrine in the striatum and cerebral cortex [74]. Methylphenidate acts by blocking the dopamine and norepinephrine transporters and was administered to NPH patient at the dose of 20 mg after shunting improved cognitive performance and reduced apathy [75]. In another case reports, patients with hydrocephaly and akinetic mutism responded well to bromocriptine and ephedrine [76, 77]. An unshunted severe hydrocephaly patient with self-injurious behavior responded well to trazodone (200 mg/day) [78].

4. Conclusions

Hydrocephaly can be defined briefly as the excess formation of cerebrospinal fluid (CSF) leading to an increase in the fluid volume of ventricles and subarachnoid spaces of the brain [1, 2]. Water is distributed in four compartments within the brain: (i) the intracellular space, (ii) the interstitial space, (iii) the cerebral ventricles and subarachnoid spaces, and (iv) the cerebral blood vessels. CSF flow obstruction in hydrocephaly leads to transependymal flow of water and electrolytes from the enlarged ventricles into the interstitial space of the brain adjacent to the ventricular wall which is called hydrocephalic edema [79]. The osmotic agents in these patients increase serum osmolality by drawing fluid from the interstitial space into the capillaries and then out of the cranium to the general circulation. Currently used osmotic diuretics for the treatment of hydrocephaly include isosorbide and mannitol. Fibrin can also deposit in arachnoid villi that can block its openings which is resulted in reduced CSF absorption. This can be ameliorated by the administration of fibrinolytic agents injected directly into the CSF or ventricular system. Hydrocephaly secondary to an IVH has been managed with intraventricular fibrinolytic therapy, alone or in combination with carbonic anhydrase inhibitors. Another situation is the reduction of CSF absorption that can be present in the acute period after subarachnoid hemorrhage and bacterial or carcinomatous meningitis. Steroids can regulate the inflammatory response after inflammation, but fibroblast growth or collagen synthesis cannot be inhibited by steroids [2].

Hydrocephaly treatment can be classified as nonsurgical and surgical, which in turn can be divided into nonshunting and shunting procedures. Nonsurgical treatment includes reducing CSF formation, and the most common drugs used for this purpose are acetazolamide and furosemide. Hydrocephaly secondary to intraventricular hemorrhage (IVH) has been treated

by serial lumbar punctures [67] to maintain normal-pressure hydrocephaly. The aims of this process are to reduce protein and blood in the CSF and thereby to prevent the formation of fibrin. Nonshunting surgical options include endoscopic third ventriculostomy in CSF obstructions at, or distal to, the aqueduct and fenestration of the lamina terminals [80].

The major three mechanisms of medical treatment of patients with hydrocephaly are based on (i) reducing CSF production, (ii) decreasing brain water content, and (iii) increasing CSF. About two-thirds of CSF is formed at the choroid plexus, and the other third is formed in the brain and spinal cord [80]. After the filtration of water across the choroidal epithelium, the increased pressure of CSF then involves active transport of water and ions across the choroidal sacs which are controlled mainly by Na+/K+ ATPase. Active secretion of water and ions by the choroidal epithelium into the ventricles are controlled by the activity of carbonic anhydrase [76]. Digoxin and ouabain are effective drugs that are used as Na+/K+ ATPase inhibitors [78]. Carbonic anhydrase inhibitors are effective drugs still used to decrease the rate of CSF production in the choroid plexus. Loop diuretic agents, such as furosemide, have also been used to reduce CSF formation.

Conflict of interest

No conflict of interest was declared by the authors. The authors declared that this study had received no financial support.

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