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Diagnosis and treatment of hyponatremia in patients with liver cirrhosis

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Abstract
Hepatic cirrhosis complicated by hypocalcemia is a common electrolyte disorder and a sign of severe disease. This article summarized the pathophysiological research progress of cirrhosis: systemic vasodilation, water balance and effect of antidiuretic hormone, non-osmotic stimulation of the renin-angiotensin -aldosterone system, sympathetic nervous system. At the same time, we discussed the mechanism and clinical symptoms of hyponatremia complicated with hepatorenal syndrome and hepatic encephalopathy. Finally, we summarized the treatment progress of cirrhosis complicated with hypocalcemia from the aspects of water restriction, hypertonic Saline, correction of hypokalemia, albumin infusion, drug therapies. In this way, we hope to provide a reference for the diagnosis and treatment of liver cirrhosis complicated by hypocalcemia.
Keyword: Liver cirrhosis, Hyponatremia, Pathophysiology, Treatment

Background

Hyponatremia is the most common electrolyte abnormality among patients with advanced liver cirrhosis and it indicates a poor prognosis. Hyponatremia in patients with liver cirrhosis is defined as a sNa concentration ≤ 130 mmol/L, with a prevalence rate of 22%. In patients with liver cirrhosis, the prevalence rate of severe hyponatremia (sNa ≤ 125 mmol/L) is 6%, while the prevalence rate of sNa ≤ 120 mmol/L is 1.2% [1].

Hyponatremia can be divided into three clinical types, namely hypervolemic (dilutional), euvolemic, and hypovolemic types. Most of the patients with liver cirrhosis (90%) suffer from hypervolemic (dilutional) hyponatremia due to an increase in the extracellular fluid volume. Dilutional hyponatremia (HN) is a common consequence of cirrhotic portal hypertension. This is the result of severe vasodilation, resulting in increased arginine vasopressin (AVP) release and the subsequent water retention. HN is especially common in hospitalized patients and is associated with severe ascites, liver failure, hepatic encephalopathy (HE), and renal impairment [2-3]. In 10% of the cases, the hyponatremia is hypervolemic, usually caused by excessive urination.

Hyponatremia is a severity marker of liver cirrhosis and is more common in Child-Pugh C cirrhosis patients. Hyponatremia patients are less sensitive to diuretics and their hospitalization rates for spontaneous bacterial peritonitis, HE, and hepatorenal syndrome are relatively high [4]. Hyponatremia is correlated with increased mortality. sNa has been found to be an independent predictor of mortality, with a hazard ratio of 1.05, and sNa concentration decrease is between 125 mmol/L and 140 mmol/L. Due to this finding, sNa has been included in the score calculation of the Model for End-Stage Liver Disease-Na (MELD-Na). MELD-Na is a good predictor of the survival rate of liver transplantation candidates. It is estimated that compared with using the MELD score alone, MELD-Na can prevent death while waiting for liver transplantation in 7% of these patients. In patients with refractory ascites due to cirrhosis, severe hyponatremia (sNa ≤125 mmol/L) can predict mortality better than MELD-Na. Most patients with a sNa higher than 125 mmol/L are asymptomatic. The symptoms include headache, anorexia, nausea, and vomiting. Since the development of hyponatremia is a gradual process, the body, especially the central nervous system, can preliminarily adapt to the slow hyponatremic changes in the extracellular fluid by reducing the intracellular osmotic pressure. When sNa drops rapidly to below 120 mol/L, serious complications may occur, such as seizures, coma, and death [5,6]. Importantly, there is a synergistic effect between hyponatremia and increased ammonia concentration. In astrocytes, the increase in ammonia level triggers glutamine synthase, which leads to an increase in the glutamine content and thus, is favorable for water to enter astrocytes, resulting in cerebral edema and HE [7].

1. Pathophysiology of hyponatremia

Hyponatremia in cirrhosis is defined as serum sodium <130 mmol/L. As mentioned above, this complication is another consequence of advanced portal hypertension, sodium and free water retention, as well as loss of compensatory mechanisms to maintain effective arterial

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blood volume. More than half of hospitalized ascites patients have hyponatremia [8]. Hypovolemic hyponatremia refers to fluid loss from the kidneys (iatrogenic excess urination) or gastrointestinal tract (diarrhea, especially after use of lactulose). The serum sodium level is usually improved after the etiology is resolved and plasma volume replacement is performed, and it is usually related to the excretion of solute-free water that damages the kidneys. Under such circumstance, excessive secretion of arginine vasopressin (AVP) is triggered, which enhances the function of vasopressin 2 (V2) receptor in the distal renal collecting ducts and inhibits the excretion of solute-free water [9]. Under the conditions of increased AVP generation and insufficient AVP clearance caused by liver cirrhosis, V2 is excessively bound by AVP, and more water is retained by forming more water channels-2, thus triggering the further free water retention in the renal tubules [10]. Therefore, the patients cannot discharge sufficient water, which will result in a decrease in serum dilution and osmotic pressure.

Among patients with liver cirrhosis and ascites, up to 50% can develop hyponatremia, and the incidence of advanced hyponatremia (serum sodium ≤ 125 mol/L) can even reach as high as 10%-20%. The presence of hyponatremia is correlated with the increase in morbidity and mortality, independent of other predictors, and has recently been added to the MELD-Na score for allocation of donor liver grafts in the United States. For liver transplant patients, if the sodium per unit serum is less than 135 mol/L, the mortality rate will increase by more than 10% [10].

2. Pathogenesis of hyponatremia

2.1 Systemic vasodilation Systemic vasodilation and arterial hypoperfusion play a major role in the development of hyponatremia in patients with liver cirrhosis and portal hypertension (Figure 1). Hyperdynamic circulation characterized by increased cardiac output, significant decrease in systemic vascular resistance, and decrease in mean arterial pressure is a common cardiovascular physiological manifestation among patients with liver cirrhosis and advanced portal hypertension. The significant decrease in vascular resistance mainly involves visceral arterial circulation. The opening of the portal vein and the increase in the synthesis of circulating vasodilators, including nitric oxide (NO), glucagon, vasoactive intestinal peptide, substance P, platelet activating factor, prostaglandin, and prostacyclin play a crucial role in the pathogenesis of visceral vasodilation. Cumulative indirect evidence supports that NO plays a vital role in the pathogenesis of visceral vasodilation in patients with advanced cirrhosis and portal hypertension [11]. Nitric oxide synthase in endothelial cells is activated through multiple factors, including “shear stress”, vascular endothelial growth factor, tumor necrosis factor alpha, and more importantly, mechanical stimulation by endotoxin or bacterial DNA [12]. In liver cirrhosis, the efficiency of water removal from the gastrointestinal tract is low due to the shunt in the portal vein system and functional defects of the reticuloendothelial cells.

Some scholars believe that endotoxemia may be one of the reasons for increased systemic prostacyclin synthesis, which can be reversed to some extent by antibacterial drugs. When a vasoactive medium such as NO or prostacyclin is inhibited, other vasoactive pathways such as angiotensin II, norepinephrine, vasopressin, and enhanced sympathetic tone may be up-regulated, thus preventing the correction of visceral vasodilation. The complex relationship among these vasoactive systems indicates that none of the factors may be solely responsible for the visceral vasodilation in patients with portal hypertension. This may account for the difficulty in developing drugs to combat visceral vasodilation [13].

2.2 Water balance and effect of antidiuretic hormone (also known as arginine vasopressin) The total water volume and osmotic pressure in the body are maintained within the normal ranges by increasing the renal solute-free water excretion, after increasing water intake (usually 1.5-3 L/d; may change between 0.5-20 L/d in extreme conditions) and reducing free water excretion after reducing water intake. Serum osmotic pressure (hence serum sodium) is strictly regulated at the hypothalamus level, mainly by releasing antidiuretic hormone (ADH). The increase or decrease in serum osmotic pressure is accompanied by the corresponding increase or decrease in ADH secretion. Under normal physiological conditions, the kidneys are in an antidiuretic state and the 24-h urine osmotic pressure is higher than the plasma osmotic pressure [14].

Under normal circumstances, the water permeability of the collecting tubes is very small, but when ADH is released, the water permeability increases due to the high osmotic pressure and low blood volume. The enhanced binding of vasopressin to V2 receptors in the basal lateral membrane of the renal collecting duct wall cells leads to the production of cyclic adenosine monophosphate and the subsequent activation of protein kinase A, which in turn phosphorylates microtubule subunits. These microtubule subunits aggregate to form a specific water channel AQP-2, which is transferred from the cytoplasmic vesicles to the apical plasma membrane. This process allows a large amount of water to be reabsorbed from the collecting tubes, resulting in increased body water content and hypervolemic hyponatremia [15]. Under physiological conditions, when serum osmotic pressure increases, ADH secretion will increase, and the water channels in the renal collecting ducts will be activated, resulting in water resorption. Decreased serum osmotic pressure leads to inactivation of the renal water channels and dilute urine discharge maintains the volume state and serum osmotic

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pressure. The rapid adaptation of free water excretion depends on the presence of intact osmoreceptors in the anterior hypothalamus, the release of ADH, and the appropriate interaction between ADH and AQP.

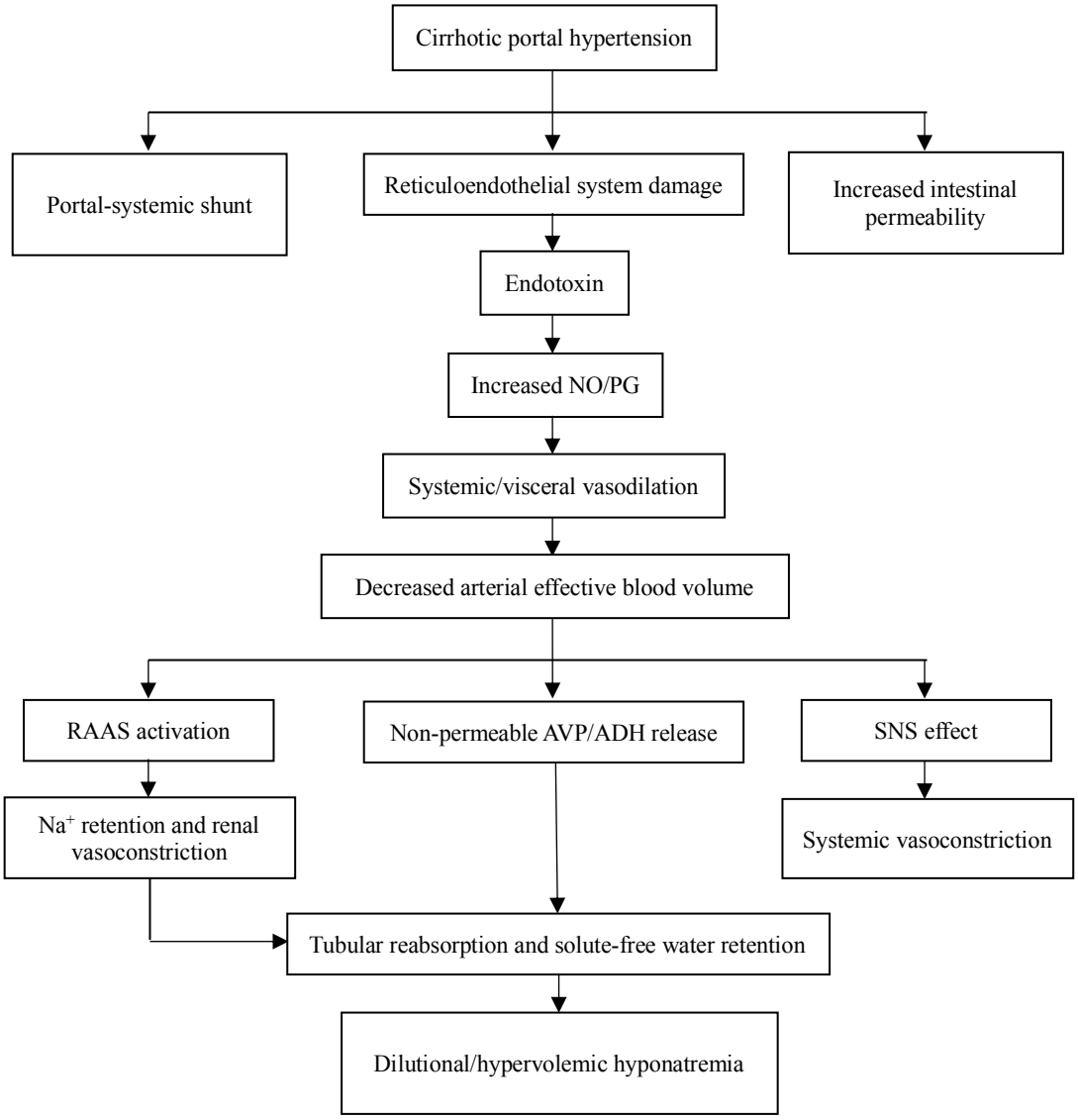

Figure 1 Pathogenesis of hyponatremia

No: Nitric oxide; PG: Prostaglandin; RAAS: Renin-angiotensin-aldosterone system; AVP: Arginine vasopressin; ADH: Antidiuretic hormone; SNS: Sympathetic nervous system

ADH is a polypeptide hormone synthesized in the supraoptic nucleus and paraventricular nucleus of the hypothalamus and stored in the posterior pituitary. Increased plasma osmotic pressure and low blood volume are the main physiological stimulation factors of vasopressin secretion. Therefore, both osmotic and impermeable stimuli can regulate ADH release. Osmotic pathways are mediated by osmoreceptors located in the anterior hypothalamus near the supraoptic nucleus. These receptors sense the water content in cells through the expansion and contraction of the neurons and respond linearly to the changes in plasma osmotic pressure. The main non-osmotic pathway of ADH release involves the autonomic nervous system, which is mediated by baroreceptors located in the atria, ventricles, aortic arch, and carotid sinus. These baroreceptors communicate with the hypothalamus through the parasympathetic pathway and cause ADH release when the blood volume is low [13].

2.3 Non-osmotic stimulation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and ADH Systemic/visceral vasodilation and arterial hypoperfusion in patients with liver cirrhosis and portal hypertension lead to a reduction in the effective circulation volume as well as a reduction in the carotid and renal baroreceptor extension. In order to restore the effective circulation capacity, sodium retention neurohumoral mechanisms such as the renin-

angiotensin-aldosterone system, sympathetic nervous system, and ADH are activated, resulting in maximum retention of sodium and water.

In decompensated liver cirrhosis patients with ascites and edema, water and sodium retention caused by the impaired renal function of removing solute-free water has been clearly shown. Such damage may be subclinical and can only be found through the water load test of compensated cirrhosis. Bichet et al. [16] measured plasma ADH concentration before and after the water load test in patients with and without ascites and studied the role of ADH in regulating this abnormal water excretion. Although the serum osmotic pressure in patients with decompensated cirrhosis is lower, the ability to inhibit ADH in patients with decompensated cirrhotic ascites after the water load test is significantly different from that in patients with compensated cirrhosis.

The relative roles of osmotic and non-osmotic pathways in ADH hypersecretion in patients with liver cirrhosis have been controversial. Most patients with liver cirrhosis have low serum osmotic pressure and sodium levels. If the stimulation mainly comes from the osmotic pressure receptors, one would expect to see ADH release being inhibited. After the water load test, ADH, norepinephrine, aldosterone levels, and renin activity were significantly increased in patients with ascites due to cirrhosis, suggesting the activation of the sodium-maintained neurohumoral mechanisms. The decrease in systemic vascular resistance seems to lead to effective arterial hypoperfusion, which leads to pressure receptor-mediated impermeable stimulation of ADH and other vasoconstriction systems, thus activating sodium-preserving neurohumoral mechanisms to restore perfusion pressure. These findings may indicate that the low-permeability stimulation inhibiting ADH release is covered by the non-permeability stimulation secondary to the arterial hypoperfusion [17]. Therefore, in order to prevent the impending vascular collapse from consuming the effective circulation volume, the body sacrifices osmotic homeostasis and releases ADH in response to the impermeable stimulation of endogenous vasoconstrictors. The final result is increased retention of sodium and water to correct the consumption of circulating volume despite increased systemic extracellular sodium, plasma volume, and cardiac output. Due to the need to inhibit the release of ADH in order to discharge the water load, the kidneys cannot excrete water in the presence of ADH release triggered by impermeability, resulting in the occurrence of dilutional or hypervolemic hyponatremia. Therefore, hyponatremia is purely dilutional in this group of patients and does not reflect the sodium deficiency.

Many other factors, including increased atrial natriuretic factor, decreased PGE-2 production in the kidneys; and decreased ADH metabolism are all related to the development of hyponatremia in liver cirrhosis.

3. Hyponatremia and hepatorenal syndrome

Vasodilation in the visceral and systemic circulations is one of the main factors leading to hyponatremia in cirrhosis, hyponatremia, and the hepatorenal syndrome (HRS) (Figure 2). Vascular ectasias occurs when high portal vein pressure leads to the formation of portal hypertension. An unclear factor (one of the vascular endothelial growth factors) triggers the production of nitric oxide and other vasodilators [18,19]. Such vasodilation leads to a reduction in the effective arterial volume, as well as activation of various vasoconstrictors and anti-atrial neurohumoral systems (the renin-angiotensin-aldosterone system and sympathetic nervous system), resulting in the retention of renal sodium and water and an increase in the vascular internal volume, thus leading to a hyperdynamic state of the circulatory system.

At the advanced stage of liver cirrhosis, progressive vasodilation will not only lead to sodium retention (ascites formation, diuretics cannot be used now), but will also trigger the impermeable release of antidiuretic hormone or arginine vasopressin (AVP). The biological effect of AVP on promoting water resorption is mediated by G protein coupled receptors, especially vasopressin 2 (V2) receptor located on the basolateral membrane of the collecting duct main cells. When activated by AVP, V2 receptor transfers selective water channels (called aquaporins) from the cytosol to the lumen of the plasma membrane of the collection tube, increasing water permeability. This increase in water resorption exceeds the increase in sodium retention, resulting in dilutional hyponatremia. Therefore, V2 receptor is a potential target for drugs (antagonists) treating such dilutional hyponatremia.

Progressive vasodilation also leads to further activation of the vasoconstriction systems (mainly renin and angiotensin), resulting in renal vasoconstriction and a reduction in the renal blood flow. In addition, the relative reduction in cardiac output in this high-output heart failure state (or cirrhotic cardiomyopathy) may further lead to the reduction in renal blood flow. Decreased renal blood flow leads to decreased glomerular filtration rate and prerenal kidney injury (i.e. HRS) [20-21].

The above hepatic and renal physiology may exist in many patients with advanced liver cirrhosis, who may develop HRS without clear inducing events. However, in more cases, the heart rate is caused by factors that may lead to a reduction in the effective arterial blood volume, such as rapid fluid loss (e.g., excessive diuresis and gastrointestinal bleeding) or caused by drugs (e.g., nitrates, carvedilol, and angiotensin-converting enzyme inhibitors) or through systemic inflammatory reactions (e.g. infections).

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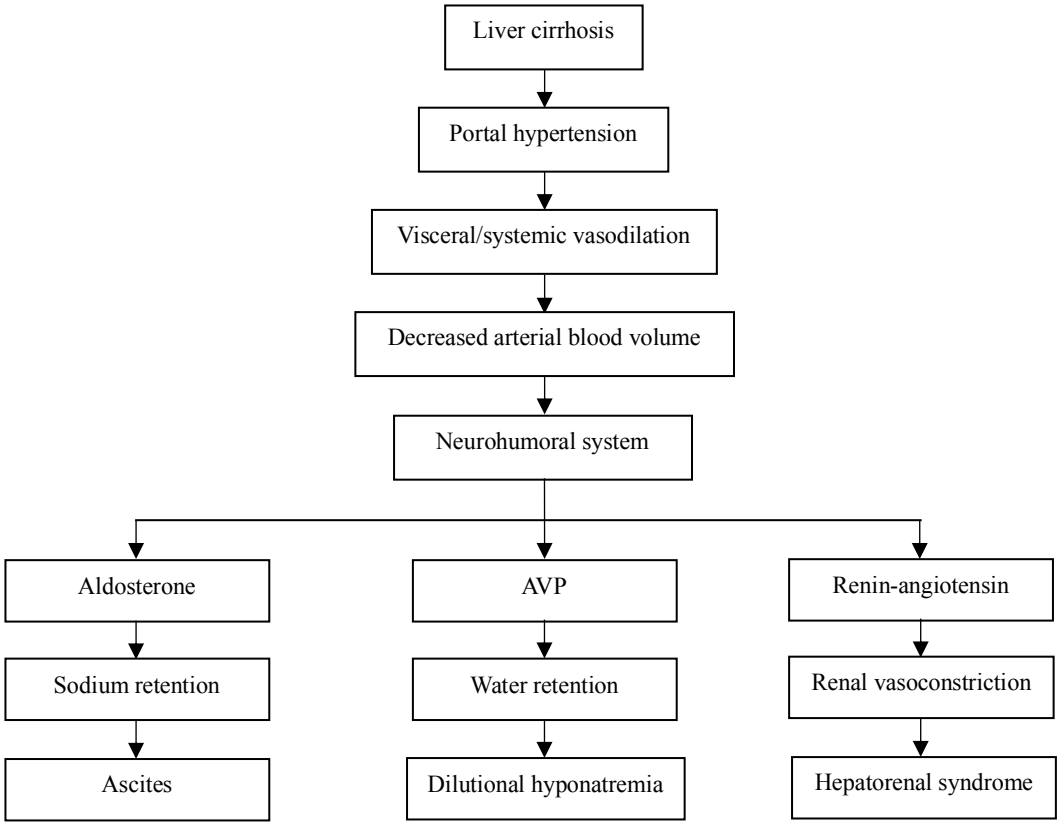

Fig. 2 Pathophysiology of hyponatremia in cirrhosis and hepatorenal syndrome

Cirrhosis and portal hypertension lead to visceral and systemic vasodilation, resulting in a reduction in the effective circulation volume, which in turn causes the impermeable release of various ADHs of vasoconstriction and anti-atrial neurohumoral systems (renin-angiotensin-aldosterone system, sympathetic nervous system). This initially causes water and salt retention to increase the volume of blood vessels and allows the continuous formation of ascites. However, as liver cirrhosis deteriorates (or there are abrupt changes), visceral/systemic vasodilation deteriorates, resulting in a significant increase in the ADH release and water retention (exceeding sodium retention), leading to dilutional hyponatremia. Activation of the largest vasodilation and vasoconstriction system (renin-angiotensin) leads to renal vasoconstriction and HRS development. AVP: Arginine vasopressin.

4. Hyponatremia and hepatic encephalopathy

Hyponatremia is related to various nervous system manifestations. Its intensity is not only related to the degree of serum sodium reduction, but it is also mainly related to the rate of decline. In fact, patients with acute hyponatremia have a higher incidence of neurological symptoms than those with chronic hyponatremia [22]. Recent evidence shows that chronic hyponatremia may be related to attention deficit, gait disorder, fall risk, and cognitive impairment. These neurological defects are related to the decline in the quality of life and may be an important cause of death. Studies have found that continuous reduction in serum sodium ion concentration can lead to gait disturbance, promote the disappearance of peripheral fear memory, cause cognitive disorder in a new-object recognition test, and impair the long-term potentiation at CA3-CA1 hippocampal synapses. Micro dialysis *in vivo* showed an increase in extracellular glutamate concentration in the hippocampi of chronic hyponatremia rats. The persistently low extracellular sodium concentration also reduces the absorption of glutamic acid by primary astrocytes, which indicates the potential mechanism of long-term enhancement of damage [23].

In patients without liver diseases, the clinical effect of hyponatremia is related to cerebral edema, such as headache, disorientation, confusion of consciousness, focal neurological deficits, epileptic seizures, and in some cases, death caused by cerebral hernia. In addition, hyponatremia causes substantial changes in the brain

cell environment to limit intracellular hydration. These defense mechanisms include rapid release of intracellular electrolytes, especially potassium, within 24 hours. Subsequently, low molecular weight organic compounds, especially inositol, are also released. These changes require time to restore. Therefore, the rapid increase in serum sodium concentration will overcome the adaptability of cells and may lead to brain atrophy. This will trigger demyelination of pontine and extrapontine neurons, leading to neurological dysfunctions, including quadriplegia, pseudobulbar palsy, epileptic seizures, coma, and even death. Interestingly, in addition to malnutrition, potassium deficiency, alcoholism and cortical hypofunction, liver cirrhosis also increases the risk of these complications [24].

In liver cirrhosis, hyponatremia usually develops slowly and gradually. Therefore, the hypotonia and hypotonic extracellular fluid in the brain is adjustable, so that the incidence rate of the nervous system manifestations directly attributed to hyponatremia is relatively low. However, as hyponatremia occurs against the background of end-stage liver diseases, it is usually difficult to determine to what extent the clinical manifestations are caused by the reduction in serum sodium concentration or HE. In fact, hyponatremia is favorable for astrocyte swelling and thus becomes the main risk factor for the occurrence of this complication, especially in diuretic therapy, bacterial infections, and trans jugular intrahepatic portosystemic shunt.

HE is a neuropsychiatric syndrome, which can occur in patients with advanced liver cirrhosis, portal hypertension and portosystemic shunt. The pathophysiology of this complication is complex and is related to the effects of several toxins. These substances include β-mercaptan, γ-aminobutyric acid, endogenous benzodiazepine, etc., but increasing ammonia production in the intestinal tract also plays a major role [25]. Once ammonia crosses the blood-brain barrier, the activity of glutamine synthetase in astrocytes increases, which converts glutamate to glutamine. This mechanism is aimed at detoxifying ammonia and causing accumulation of glutamine in cells. The infiltration effect of this substance is the cause of excessive hydration and swelling of cells. As a result, intracellular concentrations of osmotically active substances (including inositol, which is the main osmotically active molecule in the human brain), choline, creatine, taurine, and N-acetyl-aspartate, which are called osmotically active molecules, are significantly reduced [25-27].

Hypotonia of the extracellular fluid caused by hyponatremia is favorable for the infiltration of glutamine. Therefore, cell swelling and cerebral edema caused by hyperammonemia are enhanced. In addition, hyperammonemia and hyponatremia can change inositol metabolism in brain cells. Therefore, it can be easily understood that hyponatremia enhances the neurological effect of ammonia metabolism changes [27]; therefore, low blood sodium concentration and high blood ammonia are the main factors that determine an abnormal EEG in liver cirrhosis. In other words, the negative correlation between the plasma ammonia concentration and the average dominant frequency moves to the abscissa as the serum sodium concentration decreases [28].

5. Treatment

The treatment of hyponatremia in patients with moderate-to-severe ascites is challenging for both doctors and patients. Hypovolemic hyponatremia should be restored by fluid resuscitation and the precipitating factors should be stopped (usually diuretic therapy). On the other hand, the ideal treatment for patients with liver cirrhosis with hypervolemic /dilutional hyponatremia is to restrict the fluid flow and take measures to promote the excretion of solute-free water from the kidneys. Most patients find it difficult to adhere to fluid restriction. Discontinuation of diuretics may further worsen the ascites and pleural effusion, requiring repeated puncture or thoracentesis.

The serum sodium level for treatment has not been determined in clinical trials. The benefits of treatment must be weighed against the potential risk of excessive rapid correction of serum sodium and the risk of rare but severe osmotic demyelination complications. In general, patients with serum sodium < 130 mmol/L should be considered for treatment.

Severe hyponatremia with serum sodium level < 120 mmol /L is not common in patients with liver cirrhosis, and the incidence rate is less than 1.2%. In the case of severe hyponatremia with epilepsy and other symptoms, correction to a safe level must be considered to prevent recurrence and nerve injury. This is a case where hypertonic saline is recommended and care should be taken to avoid excessively rapid correction. It is suggested that the serum sodium concentration should be increased by < 10 mmol/L within 24 hours and by < 18 mmol/L within 48 hours. The use of hypertonic saline in patients with liver cirrhosis can lead to aggravation of the ascites and edema secondary to nephron's natremia and it is only used in acute cases [29].

Limiting free water to below 1.0-1.5 L/d has become a standard practice for the treatment of patients with liver cirrhosis and hypervolemic hyponatremia, and may have some benefits in preventing the further decrease in serum sodium [5]. Studies including liquid restriction control groups (< 1.5L/d) showed no significant benefit in free water clearance or serum sodium [31-32]. This method has not been confirmed in clinical trials and is often difficult to monitor. Many patients cannot actually comply with this restriction.

The introduction of a new drug called "vaptans" is

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predicted by its potential benefits in liver cirrhosis-related hyponatremia. These drugs, as direct antagonists of the V2 receptor in nephrons and collecting ducts, significantly increase the clearance rate of free water. Tolvaptan (Samsca) is currently the only oral V2R antagonist approved for use in the United States. Lixibatan and shasitatan have also been studied in liver cirrhosis and hyponatremia.

Rapid correction (> 9 mmol/L within 24 h) of serum sodium can lead to severe neurological complications, such as central pontine myelinolysis or epileptic seizures. If liver transplantation is to be performed, hyponatremia may pose a major risk to the patient, because the fluctuation of serum sodium level cannot be kept below 10 mmol /L for 24 hours. However, hyponatremia may be the cause when serum sodium is lower than 120 mmol /L or neurological symptoms occur in patients.

5.1 Water restriction Limiting free water below 1.0-1.5 L/d has become a standard practice for the treatment of patients with liver cirrhosis and hyponatremia of high blood volume and may have some benefits in preventing the further decrease in serum sodium. A study including a liquid restriction control group (< 1.5 L/d) showed no significant benefit in free water clearance or serum sodium [30]. This method has not been confirmed in clinical trials and is often difficult to monitor. Many patients cannot actually comply with this restriction.

The main treatment for hyponatremia in patients with liver cirrhosis is to limit the liquid (1-1.5 L/d) to a level sufficient to cause negative water balance. If the patient has neurological symptoms, which may be due to hyponatremia or serum sodium below 120 mmol/L (about 1% of cirrhosis patients have this symptom), fluid flow restriction should be considered [3]. For patients with mild asymptomatic hyponatremia, conventional free water restriction has no effect. In order to be effective, the intake of liquid should be less than the discharge of urine to explain the water produced in the body. According to research, even in a hospital environment, these patients' compliance with fluid restriction is poor and fluid restriction is often difficult to achieve. Patients who strictly restrict fluid can quench their thirst with borneol or lollipop. A good indicator of adequate water restriction is the changes in plasma sodium concentration in the first 24-48 h. If the plasma sodium level does not increase within the first 48-72 h, the patient either failed to comply with the water restriction measures or needs stricter water restriction measures. Sodium restriction (2 g/d) should continue except for fluid restriction, as these patients also have ascites.

5.2 Hypertonic saline Hypertonic saline is only applicable to symptomatic patients who are intolerant or unresponsive to free water restriction, patients with severe hyponatremia (< 110 mmol/L), or within hours after liver transplantation to prevent a slight increase in the serum sodium level (between 120 and 130 mmol/L). Special attention should be paid not to excessively correct the serum sodium level exceeding 9 mmol/L every 24 hours to avoid the risk of central pontine myelinolysis, quadriplegia, coma, or death. Due to the increase in ascites and edema caused by hypertonic sodium chloride infusion, it is usually not recommended for the treatment of hypervolemic hyponatremia, except for patients with severe hyponatremia.

5.3 Correction of hypokalemia In patients with liver cirrhosis and hyponatremia, correction of hypokalemia also seems to be very important for two reasons: Hypokalemia promotes the progression of HE; correcting hypokalemia tends to increase serum sodium concentration. Hypokalemia can lead to HE by at least two mechanisms: Hypokalemia can increase renal ammonia synthesis; the accompanying alkalemia can increase the content of free ammonia in plasma. Since potassium and sodium have the same osmotic activity, supplementing potassium can improve serum sodium and osmotic pressure in hyponatremia patients [13].

5.4 Albumin infusion Albumin infusion can be used as a method to treat hyponatremia in cirrhosis. The available data are limited, including a few patients with short-term follow-up, but it is suggested that its benefits need to be explored in larger randomized trials [31]. A randomized pilot study in 24 patients with serum sodium < 130 mmol/L found that albumin significantly increased the serum sodium level by 9 mmol/L on average compared with the control group. Albumin also significantly increased compared with the control group, and it can regulate the free-water clearance rate and serum vasopressin level of patients [31]. It is suggested that albumin may be conducive for improving circulatory dysfunction and reducing the impermeable release of AVP.

Intravenous albumin infusion may be useful in the short-term, although its long-term use has not been studied, and this method is expensive and impractical.

5.5 Drug therapies The purpose of drug therapies is to increase the excretion of solute-free water. In order to achieve this goal, there are many attempts, but the success rates are different. This is an evolutionary field. The goal of drug therapies is to release or act on ADH (AVP). Possible options include blocking the release of ADH by the central nervous system with κ-opioid receptor agonists, blocking V2 receptor of ADH with specific antagonists, and finally changing the role of ADH at the level of the renal collecting ducts. Democycline (minocycline) can block the function of ADH in the collecting duct, but it can cause renal failure, so it is not recommended. Therefore, only κ-opioid agonists and V2 receptor antagonists have been studied in animals and humans.

5.5.1 κ-opioid agonists κ-opioid agonists inhibit the release of neurohypophysial ADH and have been proven to have water-retaining effects in animal models

and liver cirrhosis patients. In the only human study, niravoline (0.5-2.0 mg, intravenous injection) was used in 18 patients with liver cirrhosis. It had significant water retention effects within 1-2 h after administration and returned to the basic value after 24 h [32]. The effect of aquaporin was not sustained, and it was related to major neurological side effects, including personality disorders and mild confusion. Due to the many side effects, there is no large-scale research or application of opioid agonists at present.

5.5.2 Vasopressin receptor antagonist (AVP) The biological effects of AVP (ADH) are mediated by specific receptors called V1a, V1b, and V2 receptors. ADH's antidiuretic property is mainly mediated by V2 receptors, which only exists in the renal collecting duct. Activation of V2 receptor is responsible for reabsorption of water. Therefore, the development of V2 receptor antagonist is a reasonable step to treat fluid overload and hyponatremia because effective V2 receptor antagonist can theoretically produce pure hydrolase.

The preliminary study of vaptans in cirrhotic patients was carried out on cirrhotic patients without hyponatremia. These studies have proven that oral vaptans can increase urine output and solute-free water excretion, resulting in a negative liquid balance. Subsequent research on vaptans has proven its effectiveness in improving serum sodium level in a short period of time [33-34], but the mortality rate of liver cirrhosis patients has increased.

Tolvaptan, stavatatan, and lixiwasitan are all oral drugs that selectively block V2 receptor. Intravenous drug conivaptan blocking V2 and V1 receptors can further reduce blood pressure and increase the risk of variceal hemorrhage through V1a receptor blocking [35]. Tolvaptan is a selective non-peptide V2 receptor antagonist. When the drug was added to standard diuretic therapy for 25-60 days in patients with heart failure, compared with patients receiving placebo, the weight of the patients receiving the therapy was significantly reduced and edema and serum sodium level were also significantly improved [36-37]. The drug was initially approved by the U.S. Food and Drug Administration (FDA) for treating hyponatremia in a randomized controlled trial involving major patient groups including patients with congestive heart failure. However, based on the results of a multicenter trial evaluating the effect of tolvaptan on the progression of polycystic kidney disease, FDA determined that tolvaptan should not be used for patients with liver disease or cirrhosis due to the risk of liver failure and death.

According to the latest report by Li et al. [38], the effect of vaptans on the clinical outcomes of patients with liver cirrhosis was systematically evaluated. The results showed that 18 randomized controlled trials included 3,059 patients with cirrhosis ascites and/or hyponatremia. Meta-analysis showed that vaptans had no significant effect on the risk of all-cause mortality (RR: 1.02, 95% CI: 0.87-1.08, P = 0.83; I^2 = 2%), consistent with short-term (< 26 weeks) and long-term (> 26 weeks) follow-up studies. In addition, vaptans had no effect on the incidence of variceal hemorrhage (RR:0.96, P = 0.86), while the incidence of HE showed a downward trend (RR:0.86, P = 0.09), significantly reducing the incidence of spontaneous bacterial peritonitis (RR:0.75, P = 0.03), but had no significant effect on the risk of HRS or renal failure (RR:1.09, P = 0.36). Vaptans had no effect on the incidence of adverse events in patients with liver cirrhosis.

Although vaptans therapy can reduce the risk of HE and spontaneous bacterial peritonitis in patients with liver cirrhosis, it is not related to the improvement of survival rate in patients with liver cirrhosis. Limitations of the current study include the limited number of available studies, the small sample size included in the study, changes in baseline patient characteristics, and differences in dose and duration of vaptans.

The study found that vaptans can reduce the risks of HE and SBP in patients with liver cirrhosis, which was not observed in previous meta-analyses. Since the pathogeneses of HE and SBP are both related to the severity of ascites, vaptans can be estimated to reduce the risk of HE and SBP by reducing ascites. In addition, recent studies showed that the use of tolvaptan to correct hyponatremia in patients with liver cirrhosis is related to the improvement of cognition, quality of life, nuclear magnetic resonance brain edema and concomitant burden [39, 40], which indicates that the correction of hyponatremia may also be the mechanism of potential vaptans favorable for HE risks. This has been further confirmed by a recent study, which showed that the improvement of hyponatremia in patients with liver cirrhosis led to an increase in the speed of complex information processing [41]. Whether vaptans' effect on HE and SBP is related to other mechanisms warrants further investigation in future studies.

Meta-analysis results show that the use of vaptans in cirrhotic patients does not seem to increase the risk of adverse events. However, the U.S. FDA has also raised some issues worthy of attention, which should be paid attention to by clinicians. For example, in order to start and restart vaptans treatment, hospitalization is required to monitor serum sodium and blood volume. In addition, rapid correction of hyponatremia should be avoided, as hyponatremia may lead to osmotic demyelination, dysarthria, silence, dysphagia, lethargy, emotional changes, spastic tetraplegia, seizures, coma, and even death. However, moderate and severe liver dysfunction in patients with liver cirrhosis does not affect the exposure of tolvaptan to a clinically relevant extent, so the dose of tolvaptan does not need to be adjusted.

In summary, meta-analysis results show that vaptans treatment in cirrhotic patients was not associated with

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improved survival rate, although it might reduce the risk of HE and SBP in these patients. In addition, vaptans is safe for patients with liver cirrhosis and cirrhosis patients with ascites or hyponatremia should be considered before treatment.

DeMeCox, another ADH antagonist, cannot be used for liver cirrhosis due to its potential nephrotoxicity; therefore, it should not be used for the hyponatremia of liver cirrhosis. Since most hyponatremia patients have advanced liver cirrhosis, the side effects of a single-dose discovery study must be carefully explained, just like the preliminary study of vaptans, because adverse events are more likely to occur after long-term administration in unselected population with greater comorbidities.

Terlipressin has therapeutic potential in portal hypertensive hemorrhage and HRS due to its strong effect on vasopressin V1 receptor. It is also a partial agonist of the renal vasopressin V2 receptor. Acute reduction in serum sodium levels has been recorded for patients taking terlipressin [42]. The resulting hyponatremia, although severe in some patients, is usually reversible after discontinuation of the terlipressin therapy. Therefore, when patients are treated with terlipressin, the serum sodium level should be monitored.

Conclusion

Hyponatremia is very common in patients with liver cirrhosis. Routine correction of asymptomatic hyponatremia is not recommended. The main indication for correcting hyponatremia is the presence of neurological symptoms that may be caused by hyponatremia and serum sodium below 120 mmol/L. The only exception is patients who may receive liver transplantation within hours when the serum sodium concentration is lower than 130 mmol/L, so as to avoid the operating room, because it may be related to serious neurological complications. Treatments are mainly correction of hyponatremia and fluid restriction. Under monitoring, hypertonic saline can be given to correct severe hyponatremia (serum sodium < 110 mmol/L) and hypertonic saline can be given immediately before liver transplantation to prevent the risk of osmotic demyelination syndrome. At present, it is believed that the prevention and treatment of hyponatremia should focus on liver cirrhosis as its primary disease.

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