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Research progress in the recognition and prevention of refeeding syndrome in patients with head and neck cancer

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Abstract: *Patients with head and neck cancer are one of the populations with high incidence of malnutrition. The nutritional support methods include oral feeding, enteral nutrition and parenteral nutrition. Refeeding syndrome, as a nutrition-related metabolic disease, often occurs in patients with head and neck cancer (HNC)when they re-feed. This article reviews the nutritional management of patients with head and neck cancer, the identification and prevention of refeeding syndrome in patients with head and neck cancer, in order to provide scientific basis for clinical staff to effectively identify and prevent refeeding syndrome.*

Keywords: *refeeding syndrome, hypophosphatemia, nutritional support, nutritional therapy*

Refeeding syndrome (RFS) is an acute metabolic disorder characterized by hypophosphatemia after refeeding in patients with severe malnutrition, which is commonly seen in critically ill patients during refeeding. Head and neck cancer refers to a series of malignant tumors originating from soft tissues including lips, oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands, and is the seventh most common malignant tumor worldwide [1]. Due to the differences in tumor characteristics and treatment methods .As a result, the incidence of malnutrition in patients with head and neck cancer is high. Therefore, nutritional support is often provided in patients with cancer at admission, but due to long-term hunger or excessive electrolyte loss, refeeding syndrome is prone to occur. Therefore, early identification of the risk of RFS in patients with head and neck cancer and the best refeeding program are crucial to prevent RFS and improve the prognosis of patients.

1. Head And Neck Cancer

HNC is one of the most common malignant tumors in the world, with more than 600,000 new cases of HNC every year [2]. The main treatment methods are surgery and radiation therapy. The complications of HNC itself and treatment affect oral feeding and thus predispose patients to malnutrition. Studies have shown that HNC has nutritional risks before, during and after treatment, and the incidence of malnutrition is second only to digestive system tumors[3,4]. Multiple studies have shown[5,6]that patients with HNC suffer from different degrees of malnutrition after surgery. Vangelov et al. [7] showed that 67% of oropharyngeal cancer patients lost more than 5% of their body weight within one month during radiotherapy. Therefore, timely nutrition management for HNC patients is an important focus of clinical nursing work. At present, enteral nutrition is mainly used to replenish energy. However, HNC patients with high tumor metabolic consumption and little food, the body is in a long-term starvation state, electrolytes and vitamins in the body are depleted in a large amount and then drop rapidly, and are prone to RFS manifestations such as hypophosphorus, hypokalemia, hypomagnesemia and even cardiogenic shock and respiratory distress when re-feeding.

2. Nutritional management of HNC patients

2.1 HNC nutritional risk screening

The guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) specify that

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nutritional risk refers to existing or potential risk of adverse clinical outcome in patients associated with nutritional factors. Rather than the risk of "malnutrition" [8]. The purpose of nutritional risk screening for patients is to determine whether there is an indication for nutritional support therapy[9]. Lu Li et al. [10]found that the postoperative nutritional risk of HNC patients could be as high as 81.25%. The latest expert consensus[11,12]and guidelines[13]show that patients with HNC radiotherapy should be screened for nutritional risk before conventional radiotherapy. Nurses of surgical patients use NSR2002 to screen nutritional risk at admission, 3 days before surgery, one day before discharge and weekly review[14].

2.2 Nutritional Assessment

Nutritional assessment is a process by which clinical nutrition professionals and technicians assess the nutritional status of patients who are found to have nutritional risks through screening by collecting clinical data of patients. Nutritional assessment should be performed within 24 hours of receipt of the application. Nutritional assessment comprehensively considers the general condition of patients, dietary survey, anthropometry, body composition determination, metabolic test, biochemical test, clinical examination and other contents[15].Tu Yi et al.[16]have positive significance for postoperative recovery of HNC patients through dynamic longitudinal and professional nutritional assessment. In addition, due to the special physiological structure of HNC patients, the oral cavity, larynx and parotid gland of patients during radiotherapy are all within the scope of the targeted area of radiotherapy, which is easy to cause symptoms such as masticatory disorders, dysphagia and hypesthesia [17].Therefore, the swallowing function of HNC patients should be evaluated.

2.3 Nutritional support methods

Jiang Chengfang[18]searched the best evidence of nutrition management for HNC inpatients undergoing surgery, formulated corresponding action strategies, and applied the evidence to clinical practice. Through the establishment of HNC multidisciplinary project cooperation team [19], after nutritional risk screening and assessment, if the patient is determined to be at high risk of malnutrition, the doctor will determine whether the patient meets the indications for surgery and carry out nutritional intervention in time. Through the evaluation, the causes of nutritional risk are attributed to dysphagia, insufficient food intake and psychological factors, and targeted nutritional management is carried out. Wang Yanli[20]were also the first to establish a multidisciplinary nutrition management team including dietitians, and those at high risk of malnutrition were intervened this morning, including daily energy intake of HNC patients[13,21], intake mode[22], and treatment of nutrition-related complications.

As a population with high incidence of malnutrition, improving the nutritional status of malignant tumors is the focus of clinical attention. However, studies have shown that only 60.2% of patients with malignant tumors can receive effective nutritional support[23]. When HNC patients due to dysphagia, dysphagia, cancer hypermetabolism, surgery or infection, the patient's intake is further reduced, and then increases the risk of refeeding syndrome. Studies have shown[24]that 20% of patients with head and neck malignancies developed RFS, and 72% developed hypophosphatemia in the first few days of refeeding. This may be due to inadequate supply of phosphorus from food, impaired absorption and excessive loss of phosphorus by the kidneys. In addition, the atrophy of visceral proteins and skeletal muscle induced by cancer-related cytokines can also lead to ion depletion[25].

3. Refeeding syndrome

3.1 Overview of refeeding syndrome

It is an acute metabolic disorder with electrolyte disturbance as the main clinical symptom in patients with severe malnutrition after re-ingestion of nutrients (oral, enteral, and parenteral pathways). It is mainly characterized by hypophosphatemia, hypomagnesemia, and hypokalemia, which usually occurs within 72 hours after re-ingestion[26,27].RFS was first proposed during the Second World War[28]. However, the mechanism of RFS is still unclear. In 2020, the American Society of Parenteral and Enteral Nutrition (ASPEN) published the first consensus criteria for the diagnosis of RFS[29], which classified the severity of RFS as mild (electrolyte 10~20% lower than normal) according to the percentage of electrolyte (phosphate, potassium, magnesium) deviation. Moderate (20~30% below normal) and severe (>30% below normal).

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3.2 Diagnostic criteria for RFS

The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines [30]indicate that RFS can be diagnosed if the following two criteria are met: (1) A decrease in serum concentrations of phosphate, potassium, and magnesium of varying degrees; (2) Heart failure, arrhythmia, dyspnea and other clinical manifestations occurred within 5 days after re-intake of energy.

3.3 Mechanism of RFS in HNC patients

The essence of RFS is a change in the way energy is supplied. Due to long-term malnutrition, the body of HNC is in a long-term catabolic state, with decreased blood insulin concentration, decreased exogenous energy intake, decreased insulin secretion, and increased glucagon release, increased decomposition of fat and protein. The main energy supply of the body comes from gluconeogenesis of the liver[31]. And HNC lesion area, the area of surgery and radiation therapy in patients with targeted areas are located in diet related organs, on the one hand, the patient can not through the mouth to eat, on the other hand long-term complication of radiation therapy eating less, due to the high metabolism of tumor at the same time, the body's energy storage decreases, patients of electrolyte and the depletion of vitamin in the body. At this time when patients intake nutrients after blood glucose, insulin concentration increased, the body's synthesis, increased metabolism in phosphorus, magnesium, potassium plasma into the cell[32], cause low phosphorus concentration, hypokalemia, low magnesium levels, even happen arrhythmia, acute heart failure, cardiac arrest, low blood pressure, shock, breathing difficulties and a series of clinical symptoms [33].

4. Early identification of RFS in HNC patients

4.1 Identify high-risk factors

HNC patients may experience weight loss and insufficient nutrient intake in a short period of time due to tumor characteristics. The following criteria should be used to determine the risk factors of RFS in patients: ① Main criteria: BMI < 16 kg/m2; Weight loss of more than 15% in the last 3 to 6 months; Low or no more than 10 days of nutrient intake; Low potassium, phosphate, or magnesium levels before nutritional support. ② Secondary criteria: BMI < 18.5 kg/m2; Weight loss of more than 10% in the last 3 to 6 months; Low or no more than 5 days of nutrient intake; History of alcohol abuse or medication, including insulin, chemotherapy, antacids, or diuretics. Patients who meet one major criterion or two minor criteria can be identified as high-risk patients [34].

4.2 Monitor vital signs of patients

HNC patients with high nutritional risk identified by preliminary nutritional risk screening should have their vital signs measured every 4 hours within 24 hours of re-feeding. Cardiopulmonary function was monitored according to the clinical manifestations of patients. Daily body weight and fluid volume were closely monitored. Nutritional status was assessed daily until the patient was stable, and short-term and long-term care goals were set.

5. Prevention of RFS in HNC patients

5.1 Timing of nutritional support

Electrolyte levels, especially changes in phosphate, are routinely monitored. Delay the start of nutritional support when the patient's serum phosphorus, magnesium, or potassium levels are severely low; For patients with RFS at low to moderate and high risk of electrolyte levels, consider suspending initiation or increasing energy until normal electrolyte levels are replenished before nutritional support can be initiated.

5.2 Maintain serum electrolyte balance

Electrolyte supplementation is an effective measure to prevent the occurrence of RFS in high-risk patients. In patients with high risk factors, electrolyte levels were measured every 12 hours for the first

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3 days of energy intake; According to the standard of care and the patient's condition, electrolytes should be replenished in time, including potassium (2~4mmol/kg/d), phosphate (0.3~0.6mmol/kg/d) and magnesium (0.2mmol/kg/d intravenously, 0.4mmol/kg/d orally) by oral or intravenous administration [35]. If electrolyte disturbances are difficult to correct or decline dramatically during the start of nutritional support, reduce energy by 50% every 1 to 2 days, depending on the patient's clinical presentation; When electrolyte levels are severely decreased or the patient's life condition is at risk, it is recommended to consider discontinuing nutritional support based on the physician's judgment and clinical presentation.

5.3 Thiamine and vitamin supplementation

Thiamine, also known as vitamin B1, is a water-soluble vitamin and a cofactor of key enzymes in glucose metabolism, which plays an important role in maintaining the balance of oxidative metabolism in the brain. Patients with HNC suffer from chronic malnutrition, and thiamine deficiency in the body will lead to cardiovascular and cerebrovascular metabolic disorders. Thiamine supplementation is therefore an essential means of nutritional support. The oral dose of thiamine varies from 100 mg/d (100 mg/d, once/day) to 300 mg/d (100 mg/d, 3 times/day), depending on the patient's overall condition. Intravenous administration should be performed 30 min before meals at a dose of 50-250 mg/d (once a day) [36]. For high-risk patients or patients lacking thiamine, thiamine 100mg/d should be supplemented for more than 5~7 days [35]. For patients receiving oral or enteral nutrition, oral or enteral multivitamins were administered once daily for more than 10 days, depending on the clinical situation and treatment regimen.

5.4 Progressive energy Replenishment

HNC patients are at high nutritional risk due to surgery and radiotherapy. Nutritional support for such patients should be gradual to avoid high caloric energy intake at the beginning. On the one hand, gastrointestinal intolerance may occur, and on the other hand, RFS may be induced. It is recommended that patients with high nutritional risk should start with energy supplementation of up to 10 kcal/kg/d, and slowly increase energy within 4~7 days of refeeding, and reach the target energy after one week. For patients at very high risk (BMI < 14 kg/m2), the dosage of nutritional support should start from 5kcal/kg/ day [34]. In patients at moderate to severe risk for RFS, the energy produced by intravenous glucose solution should also be considered. If the patient has received a large amount of intravenous glucose, has stable electrolyte levels, and has no other clinical symptoms, the recommended amount of nutrition may be slightly higher. The NICE guideline also mentions that low protein and low calorie can prevent the occurrence of RFS [34]. Therefore, the selection of appropriate nutrients is one of the key measures to prevent RFS in clinical work.

5.5 Select the appropriate nutritional support method, nutrient solution temperature and feeding speed

HNC patients have different severity of disease and different strength of gastrointestinal function. Choosing appropriate nutritional support methods according to the overall situation of patients is also one of the important measures during disease treatment. Some studies have shown[37]that patients who use nasogastric tube for nutritional support have a lower risk of RFS than those who use nasointestinal tube. Maintaining appropriate temperature and feeding speed of enteral nutrition solution is also a key measure to prevent the occurrence of RFS. When the temperature of nutrition solution is too high or the feeding speed is too fast, it will promote the rapid absorption of nutrients in the gastrointestinal tract and deplete electrolytes, especially phosphate and thiamine, which may increase the risk of RFS. Studies have shown that [38] keeping the temperature of enteral nutrition solution between 36~37℃ can reduce gastrointestinal intolerance in patients. At the beginning of feeding, the feeding rate was controlled within 20 ml/h and gradually increased by 10-50 ml/h every 4-24 h[33]. The performance of HNC patients after refeeding was observed, electrolyte levels were closely monitored, and malnutrition risk screening was performed.

6. Conclusions

In conclusion, as a nutrition-related syndrome, RFS is more common in patients with malnutrition. HNC patients have a high incidence of RFS. It is necessary to pay more attention to the changes of

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electrolyte levels when patients re-take energy, develop professional nutrition management programs, timely identify high-risk factors, and prevent the occurrence of RFS. At present, the incidence of malignant tumors has been increasing year by year, and the prognosis of most of them is very poor. The impact of its location, pathological type, stage and treatment on RFS is not completely clear, and needs to be further explored.

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