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A REVIEW ON FRAILTY IN PATIENT WITH LIVER CIRRHOSISAND ITS MANAGEMENT

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ABSTRACT: Frailty is an unstable phenomenon affecting multiple physiological systems, resulting in decreased reserve and vulnerable outcomes. With ageing the prevalence of frailty seems to be increasing general population as well as with cirrhosis patients. Though research are undergoing on prognostic markers, gut microbes or pharmacology in hepatology, it should be extended to a proper definition for frailty its diagnostic tool and management. Frailty score should be considered along with MELD score as a routine assessment in patients waiting for liver transplantation.Malnutrition is a common complication of cirrhosis patients which may leads to frailty, even though frailty is seen in well-nourished patients. When normal dietary supplements become ineffective the need for nutritional supplements like Branched chain amino acids (BCAA) become necessary. Combining BCAAs along with exercise therapy have shown significant improvements for lower limb muscle strength and balance ability in frail and pre-frail cirrhotic patients since muscle wasting is a major concern for them.

KEYWORDS: Frailty, Cirrhosis, Malnutrition, Sarcopenia, Branched Chain Amino Acids

I. INTRODUCTION

Frailty can be broadly defined as "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes" .Adverse outcomes include mortality[1].Higher incidence of frailty is seen with increasing age and is leading to severe adverse outcomes including short life span, poor quality of life, falls that may increasing the risk of disability ,institutionalization and hospitalization.

Frailty is multidimensional, heterogeneous and unstable phenomenon which is different from explaining with the terms disability or ageing alone [2].Sometimes frailty can be described as flip side of successful ageing [3]. It is considered widely as a state of vulnerability.

The presence of chronic illness can be a cause of frailty. Vulnerability of older adults increases with frailty as frailty leads to decreased physiological function in multiple systems [5]. Diminished strength and reduced physiological functions in frailty increases vulnerability for developing physical dependency and death. It develops earlier in persons with chronic debilitating condition such as cirrhosis and advanced heart, renal failure and respiratory disease [6].

FRAILTY IN PATIENTS WITH CIRRHOSIS

Cirrhosis is characterized by muscle wasting, malnutrition, and functional decline. 17-43% of patients with advanced liver cirrhosis have frailty [7]. The cause of liver disease in paediatric population may be either caused due to any sort of infections, or due to some drugs or toxins. Frail patients compared to nonfrail have higher prevalence of encephalopathy, low levels of sodium and albumin. Frail patients also tend to have a higher prevalence of comorbidities [8].

Frailty can be thought of as a syndrome with sarcopenia. But frailty is not synonymous with sarcopenia [4]. Frailty can be measured using a specific set of signs and symptoms. Sarcopenia and frailty are common in older persons.

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

Limited protein intake points towards both frailty and low bone mass.Sarcopenia along with frailty cause a negative impact on an individual's capability to live independently. Sarcopenia cause skeletal muscle mass loss, decline in strength function with age and cause adverse changes in individual's physical and metabolic functions leading to morbidity and mortality.Skeletal muscle loss is associated with fatigue and weight loss in frailty leads to physical function impairment. Hence we can say that there is overlap between frailty and sarcopenia. Moreover the presence of osteoporosis cans double the risk of frailty.

Inflammation induced decline in muscle mass and decrease in physical activity are the key factor for sarcopenic obesity .Sarcopenic obesity is common in aged obese persons with severe disease burden [14]. Obesity in adults leads to low physical activity contributing decreased muscle strength thus cause decline in physical functions and earlier onset of chronic disease.

Inflammation promoted erosion of muscle mass as well as decreased physical inactivity with increased adipocytes level and disease burden cause sarcopenic obesity [15].

The pathogenesis of sarcopenia in cirrhosis patients is due to multiple reasons and is often from imbalance of protein turnover. Whole body protein homoeostasis is altered in chronic liver disease due to nutritional, biochemical and metabolic abnormalities. Though the actual mechanism of sarcopenia in cirrhosis is not so clearly identified, lower level of BCAAs, testosterone, growth hormone or muscle autophagy and hyperammonia can be considered as a potential contributors. Sarcopenia though independent of liver function, it can explain survival chance before and after liver transplantation. Also connected withincreased health facility cost [16]. The chance for sarcopenia in patients with cirrhosis range from 40 -70% and the evidence shows that cirrhosis patients with sarcopenia is has low life expectancy [17].

Poly pharmacy is interconnected to chronic illness and co morbidities which increases rate of hospitalizations, reduces the ability to perform daily activities, cause cognitive impairment and mortalities. Polypharmacy increases the risk factor for sarcopenia [18]. It can cause poor nutritional status and one of the major concerns in older patients is malnutrition and drug nutrient interaction [19]. Loop diuretics are used in liver cirrhotic patients for the management of ascites induced edema and these are associated with sarcopenia [20].

Patients with chronic liver disease suffer from fatigue, loss of esteem, pruritus, depression, and other complications of cirrhosis such as hepatic encephalopathy, ascites, spontaneous bacterial peritonitis and recurrent variceal haemorrhages [21]. Mental health and emotional status of chronic ill disease patients are often not considered thereby not treated well. Due to complication like ascites, encephalopathy and varices life of these people are often miserable.

Based on a prospective cohort study conducted in University of Michigan Health System End Stage Liver Disease patients waiting for liver transplantation the Frailty and depression status was assessed using fried frailty index(FFI) and respectively. The result showed a stepwise increase in depression scores with frailty score. Consultation with psychiatric department or depression screening before transplantation ion would help the transplant care team to fully recognise and understand any comorbid burden of disease in these patients.

Depression in liver disease is associated with increased health care cost and it's further linked to mortality. A collaborative care model with psychiatric care should be provided to improve quality and value of care in ESLD patients. The Chronic Liver Disease Questionnaire (CLDQ) is a specific quality of life instrument designed for patients with liver disease, regardless of the underlining severity and aetiology of CLD. These disease-specific questionnaires such as the CLDQ and liver disease quality of life instruments are more sensitive and responsive to changes in HRQoL [22].

PATHOPHYSIOLOGY OF FRAILTY IN LIVER CIRRHOSIS

The pathophysiology of frailty is still now not clearly understood and it's very complicated. Ageing is considered to be associated with progressive dysfunction of human body thus affecting a resilient organism.

In frailty with ageing there is accelerated decline in physiological reserve and homeostatic mechanism too starts failing with many systems.

In frail patients neuronal dysfunctions occurs in areas of brain with high metabolic demands. Altered protein transport too leads to neurologic changes in frail patients. Hormones like growth hormones (GH), Insulin like growth hormones levels reduced with frailty and are reflexed in cirrhosis [23]. Gut microbes have significant relation with frailty [24]. Eubacterium dolichum and Eggerthella lenta occurs frequently with frail adults and is a leading cause of gastro-intestinal diseases. With the increase of E. dolichum significant dietary mediated lifestyle changes are associated with frailty [25].

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

While the level of Faecalibacterium prausnitzii is found to be reduced in frail compared to non-frail adults and these bacteria are thought to have anti- inflammatory effects on the gut, therefore its absence contributes to the chronic inflammatory state of frailty [26].

FRAILTY AND MELD SCORE

The scoring can predict survival in liver damaged patients [27]. MELD has reduced the mortality that often occurs due to transplantation waitlist but is not applicable to those with severe liver disease in whom MELD scoringis not used.Mortality in the post transplantation may be not only associated with liver dysfunction prior to transplantation but to other factors such as donor recipient characteristics, experience and knowledge of the transplantation crew and at the most postoperative complications whichcannot be predicted [28]. Thus it can be concluded that MELD scores obtained before liver transplantation cannot predict the survival chance for post transplantation [29]. Current research is considering MELD score with serum sodium. Cirrhosis patients with frailty (≥3 on basis of fried frail criteria) have higher MELD score compared to patients with non-frailty. Frailty patients with low MELD score (<18) had higher risk of death or transplantation than non –frail with high MELD Score. Adding frailty scores with MELD-sodium scores have shown to improved predictability of mortality/waitlist [30]. MELD scoring can predict the chance of mortality in ESLD patients. Prioritization and allocation for organ transplant can be done with score calculation .Though scoring could explain chance of mortality; quality-of-life cannot be measured for advanced liver disease patients with refractory ascites, malnutrition, and muscle atrophy [31].

One of the main limitations of this scoring is that it fails to assess the nutritional and functional status of cirrhotic patients. Modification of MELD score by including sarcopenia can improve the mortality prediction in these patients.

FRAILTY AND LIVER TRANSPLANTATION

Health outcomes of patients awaiting liver transplantation can be considered in context of prediction of survival, cognitive and psychological outcome and cost of intervention. Considering the factors age, gender, and MELD score inliver transplant patients can predict the mortality risk.Surgery is considered as the last option for cirrhosis patients [32].In liver transplant recipients bacterial infections are a major reason for morbidity [33].

Severe frail patients are at risk of adverse reactions after postoperations.Cirrhosis patients awaiting liver transplantation, frailtycan be applied as they are at increased risk for accelerated functional decline [34].

Decisions on selecting livers for transplantation is currently based on MELD score. The score includes results of three laboratory tests – International Normalized Ratio (INR), serum bilirubin and serum creatinine. It allows making prognosis on the short-term for liver disease.Higher MELD score during hospital admission leads to associated increased risk of mortality, LOS and number of comorbidities [35].

The 6 minute walk distance (6MWD) can be considered together with the MELD score to identify patients having enhanced chance of mortality before transplantation done [36].

Six minute walk test in liver transplantation

The method is a simple practical test. Cirrhosis patients suffer from muscle atrophy, malnourishment, fatigue, and weakness.

Severe deconditioning results with this physiological process in patients while waiting for transplantation of liver. In the test patients are persuade to walk as far as possible within the 6-minute test and were advised to stop if pain, dyspnoea or other symptoms developed. The patients will not be forced during the test. The walked distance (i.e., the 6MWD) was recorded in meters.

The advantage of 6MWD includes its simplicity for administration andperformance, its safety and the satisfaction in attaining final result. The 6MWD helps in analysing physical activities in LT patients. It has received littleattention for patients with ESLDand is commonly used to assess functional status and prognosis in patients with cardiac and pulmonary diseases [37]. The test will be done in patients who cannot perform standard tests. The distance walked in 6 min (6MWD) will be reduced with additional comorbidities suffering the patients. The 6MWD was significantly less for older and heavier men and women and for shorter men [38].

FRAILTY SCORING

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

Determining the depth of frailty is often not accurate. Frailty index values increase with age, are interconnected with mortality, and show higher values in women than in men.

Frailty assessment helps in early liver transplantation thereby mortality occurring while being in a waitlist for transplantation can be avoided.

Fried frailty criteria

Using the criteria frailty can be identified by the presence of five components: Patients of age > 65yrs are considered frail if three or more of the criteria below are assessed as positive[39].

1. Shrinking- weight loss of compared to previous year.

2. Weakness-grip strength less than 20%.

3. Endurance and energy-based on the Centre for Epidemiologic Studies Depression (CES-D) Scale consisting of 2 questions

- Do you feel full of energy?
- During the last 4 weeks how often you rested in bed during day.

4. Slowness-by adjusting standing height and gender, time required to walk 15 feet.

5. Low physical activity-lowest quintile of physical activity for each gender.

Those with no characteristics are considered robust whereas with increasing characters patients are grouped to Frail: ≥3 and those with 1 or 2 criteria considered intermediate or pre-frail [39].

Clinical frailty scale

The test is a seven -category frailty scale and is interconnected to theoretical model of fitness and frailty. Most elderly patient's assets over weigh the deficits and they are considered well while for others deficiency overpower the assets and hence considered frail. There is a third group that balance between the assets and ill and they are considered frail but still lives independently in the community.

The stages of frailty were categorized as the following:

- Very fit-people active, robust, energetic and are able to do physical activity regularly.
- Well - occasionally active with disease symptoms absent and perform exercise seasonally.
- Managing well-can perform routine walking with medical problems under controlled
- Vulnerable-disease symptoms limited regular activities, but still not frankly dependent on others.
- Mild frail-These group show more evident slowing, and requires assistance in handling finances, taking their own medications or even doing heavy housework. This stage progressively impairs shopping and walking outside, transportation alone.
- Moderately Frail- Requires assistance in both outside as well as handling household activities. They need assistance for doing personal activities.
- Severely Frail – liability of mortality is less but completely dependent for personal care.
- Very Severely Frail – at risk of last stage of life. Completely dependent and they could not recover even from minor illness.
- Terminally Ill - life expectancy less than half of a year [40].

Short physical performance battery

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The Short Physical Performance Battery (SPPB) has arised as one of the most promising tools to evaluate functional capability.

Balance, gait speed and chair stand test evaluated by examining ability to stand with the feet together in the side-by-side, semi-tandem, and tandem positions, first and second gait speed test by analysing time to walk 8 feet.If the patient use a cane or other walking aid and if they feel they need it to walk a short distance, then may use it. Single and repeated chair stand test by calculating time to rise from a chair and return to the seated position 5 times unassisted and without use of arms [41].

This test can be considered as an indicator of health status and vulnerability. Older frail patients with poor lower extremity performance are at increased risk for adverse events. Test strongly predicts subsequent chance for hospitalization or mortality. Poor lower extremity is a predictive of hospitalization for geriatric population [42].

An SPPB score less than 10 point towards mortality. The SPPB scorecalculation in clinical practice provides information on the risk that may leads to mortality. SPBB can be used to initiate rehabilitation programs or treatments that improve health .Frailty can be assessed by the tool and it is simple to perform, response obtained is accurate with good validity and reliability. Without excessive time consumption that is within five to ten minutes SPBB can be performed hence it can be considered as better in patient management [43].

Edmonton frail scale

The "Edmonton Frail Scale" (EFS) can be used as a valid measure of frailty. EFS have good validity, reliability and consistency is often acceptable .The interview covers 9 areas due to multidimensional presentations of frailty. The EFS assesses nine domains of frailty. Test results points that higher score has a higher degree of frailty [44].

MANAGEMENT OF FRAILTY IN LIVER CIRRHOSIS PATIENTS

Preserving the muscle function is important in maintaining an independent lifestyle. Essential amino acids are crucial for muscle protein synthesis [9].Inadequate intake of protein, reduced ability to utilize available protein, increased demand for protein leads to age related protein shortage. Lower protein intake may be due to genetic predisposition, physiological changes, medical condition, physical demand, and mental disorder and socio economic conditions [10]. Determining the appropriate protein intake by geriatric population is important because proteins deficiency can cause enhanced disability. Older adults compared to younger adults eats less protein diet, hence they require large amount of proteins and it should be distributed uniformly at each meal time. A protein intake of more than 30g per meal stimulate maximum amount of protein synthesis and hence it can be considered as a beneficial strategy for increasing protein and protecting muscle mass in older adults. Protein intake and its distribution are correlated with frailty and sarcopenia [11]. Muscle atrophy is considered as a consequence of ageing and sarcopenia because of increased disability. Muscle degradation in the lower limb leads to high chance of fall and therefore causing impairment in performing daily activities [12].

With ageing decline in muscle tissue cause a disturbance in regulating protein turnover in skeletal muscle leading to imbalance between muscle protein synthesis and degradation. Skeletal muscle contractile proteins are the functioning storage system for the amino acids as there is no inactive storage site for amino acids like for glucose and triglycerides and muscle losses will be prominent during fasting or severe illness. Patients with trauma, sepsis and burns exhibit a proportional increase in proteolysis and protein synthesis [13].Evidence shows that muscle protein synthesis is responsive to exercise.

Frailty can be reversed by appropriate intervention, especially by proper protein intake or by regular exercise and cognitive interventions. These all have shown to improve frailty scores.

Exercise

For cirrhotic patient's guidelines recommends minimum one hour mild exercise a week, but should avoid contact exercise and strenuous activity. Exercise induced protein synthesis are due to nutrient stimulated vasodilation and nutrient delivery to muscle, moreover study results showed resistance exercise in older adults are effective enough to reverse muscle loss and low muscle protein synthesis.

Nutrition

Cirrhotic patient unintentionally follow low diet either due to loss of appetite or alcohol induced anorexia or even due to satiety from impaired gastric functioning. These all often leads to malnutrition. Malnutrition in liver disease

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

is often undiagnosed.Malnutrition influence protein turnover, decrease serum albumin level, increase susception to infections and also make the patients immunocompromised. The reason for malnutrition is often due to altered sense of taste secondary to vitamin A or zinc deficiency, restricted sodium diet, decreased absorption or impaired bowel motility etc. Thus malnutrition can affect the quality and quantity of life in liver cirrhosis patients.

Patients who are at risk for malnutrition can be identified by several possible scoring tools. The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) score can be used to correlate with clinical deterioration, severity of disease (CP score, MELD score)and clinical complications such as ascites, hepatorenal syndrome, and HE. The tool is based on patient-directed questions. Improvement in RFH-NPT score can be considered as better chance for survival. Adhering to a Mediterranean-style diet can lower risk of frailty, due to improved physical activity and walking speed

Long-term nutritional support for cirrhotic patients can be attained by diet therapy. When normal diet therapy is not enough to maintain adequate nutrition demanded by cirrhotic patients long term oral nutritional supplements is prescribed.Disease related malnutrition can lead to frailty and sarcopenia thereby resulting in increased dependence, fall and death. Even though high protein diets are recommended for older adults there is concern that kidney function may worsen due to same. Hence for patients with mild dysfunctions standard protein is recommended.

Evidence supports that Branched Chain Amino Acid supplementation along with high dietary protein and late night snacks can improve sarcopenia in liver cirrhosis patients.

BRANCHED CHAIN AMINO ACIDS

If cirrhosis patients are unable to have necessary oral intake of nutrients,providing oral nutritional supplements becomes necessary. The branched chain amino acids (BCAAs), valine (Val), leucineLeu) and isoleucine (Ile)are essential amino acids for human beings [45]. BCAAs can reduce the protein loss, moreover helps in synthesising proteins, as well as they can improve the nutritional status of patients. Recent study reported that elder individuals require greater amount of BCAAs for muscle metabolism than young individuals[46].They are the source of nitrogen for glutamate synthesis, that detoxify ammonia in the skeletal muscle as well as they are an essential substrate forthe synthesis of body proteins[47].

Many patients experience gastrointestinal (GI) related difficulties such as nausea, vomiting, early satiety, diarrhoea, constipation, indigestion, abdominal pain/distension, ascites and reflux all of which lead to decreased oral intake[48]and these associated factors contribute to deprived body fat and protein stores .Hospitalized patients with HE due to the change in their mental status have poor nutrient intake. Protein is an important compound for cirrhotic patients and it is absolutely critical to avoid Protein Calorie Malnutrition (PCM)[49].

Low level of plasma BCAA is seen in patients with cirrhosis. Depleted levels of BCAAs such as leucine, isoleucine, and valine protein synthesis and protein turnover will be inhibited [50].BCAAs supplementation is beneficial in improving muscle strength, ascites and edema in adults with liver cirrhosis. Protein deficiencies in liver cirrhosis could lead to decreased albumin level. Reduced quality of life (QOL) due to following deficiencies can be improved by the supplementation of BCAA [51].Subjects with liver cirrhosis have characteristic alterations in the blood due to depletion of branched chain amino acids and a rise in phenylalanine, tyrosine and tryptophan ,aromatic amino acids. These play important role in pathogenesis muscledeterioration and encephalopathy[52].

Decreased concentration of BCAAs and increased concentration of AAA leads to lower Fischer's ratio (BCAA/AAA).Factors responsible for the cause of decreased level of plasma BCAA level include hyperinsulinemia, hyperglucagonemia, catecholamines, and starvation[53]. Increase in AAA level is due to inability of diseased liver to metabolize these amino acids. In cirrhosis patients during fasting the plasma concentrations of BCAA decreased by 20 to 35% compared to normal subjects.

Long term oral BCAA supplementation over other isocaloric and isonitrogenous supplementation have the advantage in preventing progressive liver failure, death, hospital admission and other outcomes such as anorexia, worsened Child Pugh score, serum bilirubin level and health-related quality-of-life[54].

Changes in systemic insulin and glucose levels provoke changes in growth hormone, epinephrine, glucagon, and adrenal corticoids, all of which may alter nitrogen metabolism. Systemicinsulinization, either by glucose or insulin infusion, lowers plasma levels of some amino acids while others remain unaffected. Since the uptake of BCAA is

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insulin dependent, the hyperinsulinemia of cirrhosis may be responsible for loweringplasma levels of BCAA [55].Insulin resistance and increased blood glucose levels in male cirrhotic patients can be reduced with oral BCAA [56].

Administrating BCAAs stimulates the synthesis of hepatic protein in CLD patients thereby chance of malnutrition is reduced and life standard is improved. Cirrhosis patients often suffer nutrition deficits with low serum levels of BCAA.

Hyperammonia lowers the levels ofBCAA in plasma and muscle [57]. Patients with chronic liver diseases have functional dyspepsia due to defect in motility of gut [58]. Due to complications of cirrhosis deficiency of proteins and minerals occurs due to their uncontrollable loss. The primary goal for ESLD patients should be to maintain their weight with diet rich in macro- and micronutrients.

One of the well accepted clinical condition for BCAA is in patients with HE who are intolerant to enteral proteins. In cirrhosis patients with HE brain uptake of tryptophan increased due to decreased ratio of BCAA/tryptophan. Long-term BCAA in liver cirrhosis leads to an increase of serum protein of approximately 10% [59].

. Treatment with BCAA reduces average hospital admission rates; improve nutritional parameters, liver function tests, quality of life and anorexia. The Child–Pugh score in several patients was found to be decreased with BCAA supplementation.[60].

BCAAs help in protein synthesis and energy metabolism also helps in production of ammonia and glutamine in muscle [61].

In healthy individuals as well as in liver cirrhosis patients skeletal muscle has an important role in glucose metabolism. According to the studies conducted in rats found that leucine and isoleucine in BCAA improved glucose metabolism as they had pharmacological effects on skeletal muscle [62]. Therefore, dietary supplementation with BCAAs will reduce the chance of sarcopenia and improve the medical conditions[63].BCAA thrice a day can improve muscle glucose uptake, muscle mass, elevation in serum albumin level and thereby survival rate of cirrhotic patient also improved. Studies proved that combining BCAA intake along with exercise therapy can improve lower limb muscle strength and balancing strength with greater efficiency even in frail elderly patients [64].

CONCLUSION

Research on frailty and its management has a growing interest in hepatology. With the growing evidence of frailty supportingprognosticmarkers it can be incorporated into routine assessment of cirrhotic patients undergoing LT.Identifying patients who are at risk of approaching the state of malnutrition and correcting the nutrient deficit at earliest can improve the outcome.

Sufficient dose of BCAA supplementation for a long term use is showing beneficial effects .Since BCAA is involved in hepatic protein synthesis in liver cirrhosis patients it can contribute to improving nutritional status and resulting in better quality of life. Long term BCAA supplementation was found to show improvement on prognostic markers.

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ISSN- 2394-5125VOL 7, ISSUE 15, 2020

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