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Alcoholic Hepatitis: Diagnosis and Management Procedures

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Abstract

Over alcoholic consumption for a long-time is the most common cause of alcoholic hepatitis (AH) that has significant short-term and long-term morbidity and mortality due to chronic liver disease. Alcoholic hepatitis is the most elaborate indicator of alcoholic liver disease (ALD). It is a devastating acute condition of the disease that needs early detection, diagnosis, and proper treatment. It is characterized by inflammation, fibrosis, and ultimately cirrhosis for the continual excessive drinking. It is an acute hepatic inflammation associated with an injury of the liver with the clinical syndrome of acute jaundice and coagulopathy. If it is not treated appropriately, may transform to life-threatening acute liver failure, such as hepatocellular carcinoma (HCC) and liver cirrhosis. Complete alcohol abstinence is the cornerstone therapy for AH to decrease short-term mortality and most of the patients recover for at least six months after abstinence. This review paper tries to discuss the diagnosis and treatment procedures of the AH in brief for the benefit of the patients.

Keywords: alcoholic hepatitis, abstinence, cirrhosis, diagnosis, treatment

1. Introduction

Alcohol is the oldest and the most diffuse abused liquid that is used in many cultures, and still remains the most widespread used substance worldwide, which causes advanced liver disease for successive overconsumption for a long-time (Rehm et al., 2013). Alcohol consumption is related to intestinal bacterial overgrowth with reduced alpha diversity, disruption of the intestinal tight junctions with bacterial translocation to the portal circulation, and impaired Kupffer cell clearance of lipopolysaccharide (Purohit et al., 2008).

Alcoholic hepatitis (AH) is the second stage of the alcoholic liver disease (ALD). It is characterized by the presence of a superimposed inflammatory infiltrate that causes hepatocellular injury with progressive fibrosis due to long-time excessive alcohol use (Abenavoli et al., 2016). It ranges in severity from mild to severe form and carries significant morbidity and mortality. Mortality due to AH in short-term is about 15% at 30 days, 30-50% at 90 days, and long-term mortality is greater than 50% at 1 year depending on the severity of the disease (Jinjuvadia & Liangpunsakul, 2015). At the initial stage AH is reversible and the reversibility depends on the degree of the liver injury (Dew et al., 2008). Sometimes AH advances to cirrhosis through the bridging fibrosis and nodular regeneration with the clinical manifestations of portal hypertension and liver failure which is irreversible (Teli et al., 1995). Decompensated liver disease can manifest various syndromes, such as ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, or hepatocellular carcinoma (HCC) (Keating et al., 2022).

English physician and medical researcher Thomas Addison (1795-1860) for the first time in 1836 has found that there is a relation between alcohol consumption and fatty liver. Later in 1965, Belgian-American clinical nutritionist Charles Saul Lieber (1931-2009) have identified that excess alcohol consumption can cause liver cirrhosis (Lieber et al., 1965). The AH patients are asymptomatic and remain undiagnosed for a long-time; the true prevalence of it is difficult (Jinjuvadia & Liangpunsakul, 2015). Some causes of hepatocyte injury and AH

disease development are impaired immune response, endoplasmic reticulum stress, mitochondrial dysfunction, free-radical injury induced by alcohol (Ji, 2008).

AH is reversible and prolonged abstinence from alcohol is the mainstay treatment of it. If the AH patient continues to drink alcohol may progress to cirrhosis over months to years, which is the end stage of ALD, and the patients are at the risk of hepatocellular carcinoma (HCC) development (Corrao et al., 1998). Liver transplantation is recommended for some patients with severe AH (Goel & Daugherty, 2021). Acute chronic liver failure and development of cirrhosis are the most feared complications of AH that are associated with significant morbidity and mortality. Therefore, identification of AH patients earlier during the course of the disease is critical (Chaudhry et al., 2023).

2. Literature Review

The literature review section is an important and an introductory portion of a research, where works of previous researchers are highlighted (Polit & Hungler, 2013). It helps the new researchers to understand the subject, and it serves as an indicator of the subject that has been carried out previously (Creswell, 2013). Ludovico Abenavoli and his coworkers have shown that alcohol use disorder (AUD) is a problematic pattern of alcohol use that leads to clinically significant impairment of liver. They have realized that AH is a wide spectrum of injury that may lead progressively from simple steatosis to frank cirrhosis (Abenavoli et al., 2016). Navakanth Raju Ramayanam and his coauthors have studied alcohol consumption patterns, disease severity, and laboratory parameters to determine AH prevalence and explore the association between corticosteroid resistance and clinical variables. They have emphasized on the early detection and have targeted on treatment strategies (Ramayanam et al., 2024).

Binay Krishna De and his coauthors have tried to compare the efficacy of pentoxifylline and prednisolone in the treatment of severe AH. They have observed that these reduced mortality, and improved risk-benefit profile and renoprotective effects of pentoxifylline compared with prednisolone suggest that pentoxifylline is superior to prednisolone for the treatment of severe AH (De et al., 2009). Ewan Forrest and his coauthors in their clinical trials on 1,200 patients with severe AH have found that corticosteroids and pentoxifylline have therapeutic benefit (Forrest et al., 2013). Francisco Idalsoaga and his coworkers have discussed on the development of new therapies based on the pathophysiology and mechanisms of liver injury that are the modulation and management of the innate immune response, gut dysbiosis, bacterial translocation, and bacteria-derived products from the intestine, and these may be used for the future AH treatment (Idalsoaga et al., 2023).

Spencer Lourens and his coworkers have examined the natural history of acute AH and have identified predictors of mortality for AH using data from a prospective multicenter observational study. They have advised that regular coffee consumption during alcohol abstinence is associated with lower risk of AH among heavy drinkers (Lourens et al., 2017). Michelle Keating and her coworkers have shown that laboratory-based prognostic scores, such as Maddrey Discriminant Function (MDF) and the Model for End-Stage Liver Disease (MELD) help to determine AH disease severity and treatment options. Supportive care, such as alcohol cessation, nutritional supply, and corticosteroids are essential for severe AH. Chest radiography and cultures of peritoneal fluid, blood, and urine are also needed to treat AH properly (Keating et al., 2022).

Astrid Marot and his coauthors have observed that after liver transplantation the percentage of alcohol relapse of AH transplanted patients is not different than that of patients with alcoholic cirrhosis who underwent elective liver transplantation (Marot et al., 2020). Lindsey C. Shipley and Ashwani K. Singal review the current status, benefits, challenges, barriers, and future prospects on early liver transplantation in patients with severe AH (Shipley & Singal, 2020).

3. Research Methodology of the Study

Research is a hard-working search, scholarly inquiry, and investigation that aims at the discovery of new facts and findings (Adams et al., 2007). It is the procedures of systematic investigation that requires collection, interpretation and refinement of data, and ultimately prepares an acceptable article, working paper, book chapter or a thesis by **the appropriate use** of human knowledge (Pandey & Pandey, 2015). Methodology is a system of explicit rules and procedures in which research is based, and against which claims of knowledge are evaluated (Ojo, 2003). It is a guideline for the accomplishment of a good research (Kothari, 2008). It relates nature and power to science, truth, and epistemology (Ramazanoglu & Holland, 2002). Research methodology provides the principles to the researchers for organizing, planning, designing and conducting a good research (Legesse, 2014). To rationalize the selection of a research methodology, a researcher must understand its philosophical origins and unique characteristics (Rieger, 2019). In this study, the research methodology is qualitative, and the procedures and techniques are of liver disease research (Reinharz, 1992). To prepare this paper we have used the secondary data sources that are related to alcoholic hepatitis (AH) (Mohajan, 2017, 2018, 2020, 2024a-e). The valuable materials for this study are included by the analysis of the published books and papers of renowned authors

(Mohajan & Mohajan, 2023a-v, 2024a-j).

4. Objective of the Study

Main objective of this article is to discuss the aspects of AH properly. Excessive alcohol consumption is a common matter worldwide that is a major risk factor for the development of AH. Other minor objectives of the study are as follows:

- to provide basic ideas and severity of AH,
- to highlight on symptoms and risk factors of AH, and
- to emphasize on diagnosis and management of AH.

5. Basic Ideas of AH

Alcoholic hepatitis (AH) is a clinical syndrome that is characterized by liver cell necrosis, impaired liver function, and progression to cirrhosis (Mohajan, 2024). The prevalence of AH varies across different populations and geographical regions due to the influence of genetic, environmental, and cultural factors on the development of the disease (EASL, 2012). After alcohol consumption, fatty acid synthesis and oxidation start in the liver and then fat gathers gradually. The major enzymes involved in alcohol metabolism are cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase, and these generate acetaldehyde and reactive oxygen species by CYP2E1-dependent Microsomal Ethanol Oxidizing System (MEOS), with resulting lipids peroxidation and DNA adduct formation that make liver injury (Beier & McClain, 2010). These enzymes influence alcohol consumption and dependency as well as alcohol-driven tissue damage (Seitz & Stickel, 2006). Every year, more than 2.8 million people worldwide die as a result of alcohol consumption. Estimated deaths per year from AH and cirrhosis in the UK are 3,500–7,000 (Anderson, 1988).

6. Severe AH

Severe AH is an acute chronic hepatic inflammatory response syndrome for alcohol-induced liver injury due to the consumption of large amounts of alcohol for a long-time. It is characterized by the swelling and inflammation in the centrilobular area of hepatic acinus of the liver with a significant risk of morbidity and mortality (Mohajan, 2024). It is a potential life-threatening manifestation of alcohol-induced liver injury if it is not treated properly in due time. Despite current modern treatments, about 25% global patients die with severe AH (Dugum et al., 2015).

Every year about 20% to 40% AH diseases develop to fibrosis, about 10% to 20% progress to cirrhosis, and among these 1% to 2% are diagnosed with hepatocellular carcinoma (HCC) (Teli et al., 1995). Cirrhosis frequently develops silently and is manifested only when the patient develops hepatic decompensation with ascites or variceal haemorrhage (Moore, 2001). Liver transplantation is recommended for some patients with severe AH for the survival (Goel & Daugherty, 2021).

7. Symptoms of AH

Symptoms of AH vary significantly with the severity of the disease and the age of the patient (Kim & Kim, 2014). Some possible symptoms of it are loss of appetite, nausea and vomiting, abdominal pain, bleeding from esophageal varices, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatopulmonary syndrome, hepatic encephalopathy, and jaundice. Usually, the liver and parotid may be enlarged and tender during AH (Bouneva et al., 2003; Keating et al., 2022). Usually, an AH patient loses a considerable amount of weight, and malnutrition is common in about 90% patients (Moore, 2001). Anemia and leukocytosis are common in AH; also, thrombocytopenia may occur due to direct alcohol toxicity (Veryan & Forrest, 2019).

8. Risk Factors of AH

Many factors influence in the development and progression of AH. Some risk factors of AH are over alcohol consumption, obesity, gender, genetics, ethnicity, comorbidities, diabetes mellitus, smoking, etc. (Veryan & Forrest, 2019).

8.1 Over Alcohol Consumption

The liver is the principal organ of alcohol metabolism. Alcohol is metabolized in the liver with the enzyme alcohol dehydrogenase (ADH), cytochrome P-4502E1 (CYP2E1), and mitochondrial catalase. Over alcohol consumption and duration of it is responsible for the development of AH. According to National Institute of Alcohol Abuse and Alcoholism (NIAAA), if a man consumes 48g and a woman consumes 24g of alcohol daily are considered heavy drinkers (NIAAA, 2024). Heavy alcohol consumption, such as more than 100g daily for 10 years continuously, may result an episode of acute AH (EASL, 2012). Not all the heavy alcohol drinkers are infected by AH. Steatohepatitis and AH are developed among 35% of the patients, while cirrhosis is developed only among 10% of the patients (Friedman et al., 2018).

8.2 Obesity

Various studies collectively demonstrate that obesity potentiates the toxic effects of alcohol and hastens progression to AH development (Raynard et al., 2002). Obesity is a risk factor for developing cirrhosis, and obese alcoholic patients have a greater risk of disease evolution compared to non-obese alcoholics (Naveau et al., 1997).

8.3 Genetics

Various studies demonstrate that the susceptibility to developing AH is influenced by genetic factors. Studies on polymorphisms of gene coding for alcohol metabolism, such as alcohol dehydrogenase, acetaldehyde dehydrogenase and cytochrome P450 2E1, genes regulating the innate immune response (i.e., IL-1, TNF), and the PNPLA3 gene indicate that certain variants are associated with the risk of alcoholism (Menon et al., 2001). Also, PNPLA3 has an important role in lipid metabolism (Romeo et al., 2008).

8.4 Gender

Women are at a higher risk of developing AH with an equal daily alcohol intake compared to men. But the exact mechanisms of this situation are still not clear. However, it is believed that this state is due to decreased gastric alcohol dehydrogenase (ADH) activity, influence of sex hormones, body fat distribution, and liver volume between the two genders (Eagon, 2010). Despite the greater susceptibility of women to alcoholic liver injury, the global prevalence of AH is lower in women, compared with men due to lower levels of alcohol consumption (Manthey et al., 2019).

8.5 Ethnicity

Ethnicity may be considered a risk for developing AH. For example, in the USA, Hispanics and African Americans show an increased risk of developing AH with higher mortality compared to Whites (Stinson et al., 2001). The hypersensitivity to alcohol among Asian is due to the polymorphisms of genes for the enzymes ADH and CYP2E1 (Beier et al., 2003).

8.6 Comorbidities

The presence of coexisting other liver diseases, such as hepatitis B or C and hemochromatosis, may accelerate the progression of AH. Several studies have shown that presence of both pathological conditions simultaneously may increase 30 times the risk of cirrhosis (Punzalan et al., 2015).

8.7 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a risk factor for the development of liver cirrhosis owing to the pro-fibrogenic effect of glucose on hepatic stellate cells and subsequent induction of chronic inflammation (Elkrief et al., 2016). Some other studies have found that T2DM is an independent predictor for liver fibrosis and HCC development (Ioannou et al., 2019).

8.8 Smoking

Smoking increases the risk of advanced liver fibrosis and cirrhosis potentially by activation of hepatic stellate cells through nicotinic acetylcholine receptors. Also smoking results in the development of 4-aminobiphenyl-DNA adducts that increases the risk of HCC (El-Zayadi et al., 2002). Some studies have found that current smokers had an increased risk for HCC compared with those who have never smoked (Petrick et al., 2018).

9. Diagnosis of AH

Usually, an AH patient might have a bilirubin level of 540mmol/l, albumin 26g/l, alkaline phosphatase 170U/l, AST 78U/l, and ALT 35U/l (Moore, 2001). Serum level of cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and IL-8 are elevated in severe AH (Latvala et al., 2005).

There is not a single specific laboratory marker that can identify AH. Laboratory tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) are necessary to identify AH with AST higher than ALT (Nyblom et al., 2004). Level of both of these usually lies below 200U/l and rarely over 500. AST/ALT ratio greater than 2 indicates AH and cirrhosis and has a very high probability when it exceeds 3 (Giannini et al., 2002). Also mean corpuscular volume, and carbohydrate-deficient transferrin are important in evaluating potential AH (Cohen & Kaplan, 1979). Gamma-Glutamyltranspeptidase (GGT) has a high sensitivity to detect daily ethanol consumption more than 50g, and it is often useful for early detection of alcohol misuse. But it does not act properly in obesity and in advanced liver disease (Seitz, 2006).

Abdominal imaging studies, such as ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) may be useful tools for diagnosing AH. Imaging findings in patients with AH include hepatomegaly, fatty changes in the liver, evidence of underlying cirrhosis, or ascites (Borra et al., 2009). Usually,

a liver biopsy is not essential for the diagnosis and the management of AH, but in case of diagnostic uncertainty it is a helpful tool for establishing the exact diagnosis (Dugum & McCullough, 2015). Only 30-60% of AH inpatients need liver biopsy (Arab et al., 2021).

Maddrey discriminant function (MDF) system is the first scoring system developed that is used in estimating mortality among patients with acute AH. Usually, severity of AH is assessed by MDF to start corticosteroid treatment. A score of MDF>32 indicates severe AH with an increased likelihood of death about 50% (Maddrey et al., 1978). The model for end-stage liver disease (MELD) score is a measure of the severity of liver dysfunction and has been recently used in the assessment of patients with severe AH. It remains the standard for the assessment of patients with severe AH (Dunn et al., 2005). The MELD score of greater than 21 have the highest sensitivity and specificity in predicting mortality (Sheth et al., 2002). The Glasgow alcoholic hepatitis score (GAHS) have also gained interest as predictors of disease outcome in patients with severe AH (Forrest et al., 2007). On the other hand, patients with a MDF score<32 and MELD score<21 consider as moderate AH and has a mortality of up to 3-7% in the short-medium term and 13-20% at 1 year (Clemente-Sanchez et al., 2021).

10. Management of AH

Management of AH consists of a multidisciplinary approach, such as alcohol cessation, treatment of alcohol withdrawal, fluid and electrolyte development, and pharmacological therapy based on the severity of the disease (Liang et al., 2015).

10.1 Treatment of AH

The treatment of AH is controversial. At present, there is no universally accepted treatment of AH. Alcohol abstinence remains at the center of the treatment of AH. But it is often problematic. Because suddenly discontinue of alcohol use is at high risk of alcohol withdrawal syndrome. Within 24 hours of abstinence, patients can experience increased heart rate and blood pressure, along with irritability and hyperreflexia. Later, more dangerous complications, such as seizures and delirium tremens can arise. Along with a lifestyle modification, mainstay of treatment is short-term steroid therapy (Mayo-Smith et al., 2004).

Sometimes first-line treatment of severe AH patients is given a trial of steroids, usually corticosteroid, such as prednisolone 40 mg/day for one month (Poynard et al., 1991). Prednisolone has been used widely for the treatment of severe acute AH patients. But it is not free from the adverse effects (De et al., 2009). Also, pentoxifylline, a phosphodiesterase inhibitor that blocks transcription of TNF-α to decrease serum levels of the gene product has been found to be useful in patients with severe AH (MDF score ≥32) to reduce mortality (Akriviadis et al., 2000).

Metadoxine (pyridoxol and L-2-pyrrolidone-5-carboxilate) is one specific drug useful for the treatment of severe AH that is involved in the amino acid metabolism through the glutathione pathway, and it facilitates de novo ATP synthesis and prevents ATP decrease in the liver of rats acutely intoxicated with ethanol, increasing the metabolic degradation rate of ethanol. S-adenosyl L-methionine (SAMe) is a precursor of glutathione that is involved in regulation of gene expression and the process facilitating the generation of the antioxidant glutathione from homocysteine. It can reduce mortality in patients with alcoholic cirrhosis (Leggio et al., 2011).

Recently, some medications, such as antioxidants, colchicines, calcium channel inhibitors, propylthiouracil, and d-penicillamine are trying to use for the treatment of AH. But these drugs have less success in the AH treatment. On the other hand, TNF-α produces in macrophages and Kupffer cells that plays an important role in the pathogenesis of severe AH. Many new therapies are also undergoing for clinical trials (De et al., 2009).

10.2 Nutritional Support

AH has a strong association with malnutrition (Mendenhall et al., 1995). Malnutrition is defined as a disorder of inadequate nutritional intake that leads to a decrease in body cell mass. It is a common complication among AH patients due to systemic inflammation that may have a high impact on disease progression and increases the risk of infections and death (McClain et al., 2021). Enteral nutrition is necessary immediately to manage the complications of liver failure. Proper nutritional status maintains by a dietitian and nutritional including nasogastric or intravenous feeding are necessary for AH patients. Nutritional support improves the liver function and increases the survival rates (Singal & Charlton, 2012).

Protein-calorie malnutrition is a common comorbidity to AH due to decreased nutritional intake, decreased gut absorption, and catabolic metabolism (Keating et al., 2022). A patient needs to be given energy about 35 to 40 kcal/kg/day, and 1.5 g/kg/day as protein (Plauth et al., 1997). To maintain proper electrolyte and fluid levels sufficient sodium, potassium, phosphate, and magnesium are required. The AH patients also require multivitamin (including riboflavin, B_{12}, and vitamin A), zinc, folic acid, and thiamine supplementations (McClain et al., 2021).

10.3 Liver Transplantation

Liver transplantation (LT) for AH has been a matter of great medical and social controversy. Actually, the AH patients are responsible for their own illness led to caution when contemplating LT. On the other hand, many countries of the world require six months of abstinence from alcohol before placing a patient on the liver transplant list due to donor shortage and risk of recidivism (Singal & Duchini, 2011).

11. Conclusions

From this study we have observed that alcoholic hepatitis (AH) is a devastating complication of liver due to excessive alcohol use for a long-time. High rates of concomitant infections, systemic inflammation, and multi-organ failure lead to significant morbidity and mortality among AH patients. As the local and global burden of AH is increasing; in the parallel the social, health, and economic burdens are also increasing gradually due to heavy alcohol drinking. Therefore, the coordination of multidisciplinary sections of health sector should be established at local, national, and international levels for the successful management of the disease; and to prevent and reduce burden, morbidity, and mortality. Early detection and accurate prognostic and prompt intervention of AH may alleviate misery and healthcare cost of the patients. Patients with AH often suffer from serious malnutrition and require nutritional support, such as adequate calorie, protein supply, vitamin B, and mineral. Although some therapeutic treatments are available for survival those who are in severe AH, yet overall prognoses remain gloomy. Novel therapies and medications are urgently needed for severe AH patients to decrease mortality and misery of this devastating disease. But yet there is a major gap in the development of new therapies due to the lack of attention to AH. Liver transplantation is a last option for survival of severe AH patients; but it remains controversial.

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