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RESEARCH ARTICLE

NON ALCOHOLIC FATTY LIVER DISEASE: A SPECTRUM OF DISEASES

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ABSTRACT

Now a days Fatty liver Disease is one of the commonest cause of chronic liver disease. Non alcoholic fatty liver disease (NAFLD) is not a single disesase entity but a group of disorders characterized by fatty acid accumulation within the liver. It is usually associated with metabolic conditions like obesity, diabetes mellitus and metabolic syndrome. With increasing prevalence of these diseases prevalence of NAFLD is also increasing. Histologically it is characterized by accumulation of triglycerides within the hepatocytes. It is usually diagnosed coincidentally when ultrasosnography is done for any other purpose, as majority of patients are asymptomatic. Treatment comprise of control of metabolic conditions. If untreated it may progress to cirrhosis and hepatocellular carcinoma.

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INTRODUCTION

Non alcoholic Fatty liver disease is a relatively common but an underdiagnosed and an undertreated metabolic entity. It is an increasingly recognized cause of liver disease worldwide. It develops when there is diffuse accumulation of triglycerides in the liver cells that is hepatocytes as a result of altered lipid metabolism. When fatty infiteration is accompanied by necroinflimmatory activity then it is known as Steatohepatitis. Fatty liver disease is a broad term used to encompass an entire spectrum of liver disease ranging from simple steatosis to steatohepatitis (NASH), which can eventually lead to noncholestatic cirrhosis and probably hepatocellular carcinoma (Brunt, 2004 and Bugianesi, 2002). In near future it may become one of the common cause of endstage liver disease and hepatocellular carcinoma. It is possible that some cases of cryptogenic cirrhosis are due to longstanding NASH and fat leaves the liver as end stage liver disease develops.

Definition

A normal liver contains only 5% of weight as fat. American Association for the Study of Liver Diseases (AASLD) has now defined NAFLD as fat accumulation in the liver exceeding 5 to 10% by weight in persons who consume little or no alcohol (Neuschwander Tetri, 2003).

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Nonalcoholic Fatty Liver Disease and related definitions (Chalasani, 2012)

Nonalcoholic Fatty Liver Disease (NAFLD): Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

Nonalcoholic Fatty Liver (NAFL): Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.

Nonalcoholic steatohepatitis (NASH): Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer.

NASH Cirrhosis: Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis

Cryptogenic Cirrhosis: Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome.

NAFLD Activity Score (NAS): An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful

tool to measure changes in liver histology in patients with NAFLD in clinical trials.

Epidemiology

NAFLD is a highly prevalent condition in the United States and worldwide. Estimates in the U.S. population suggest that up to 30% of adults may have NAFLD (defined as 5% or more of liver fat). The prevalence estimates from several other countries are quite variable, but depict a highly prevalent condition with ~20% of the adult population with Ultrasound defined NAFLD (30% or more liver fat). Crosssectional and prospective data indicate that insulin resistance and obesity are two major modifiable risk factors of NAFLD (Omagari, 2002; LizardiCervera, 2006 and Omagarin 2002). NAFLD is more common in males and postmenopausal females supporting the possibility that female hormones are protective as also indicated by the use of hormone replacement therapy resulting in less likely development of NAFLD. Gender differences in fat distribution may also contribute to this finding (Clark, 2002 and Enzi, 1986). NAFLD can be found in all age groups; however the prevalence appears to increase with age. A study conducted in 1977 using liver biopsy found that the prevalence of fatty liver in the general population was 1% in people below 20 years, 18% between 20 and 40years, and 39% among 60 and older (Hilden, 1977).

Pathology

Histologically NAFLD resembles alcohol induced liver disease, by definition NAFLD develops in patients who consume little or no alcohol. At the beginning, the hepatocytes present small fat vacuoles in the vicinity of the endoplasmic reticulum (liposomes) – microvesicular fatty change. In the late stages, the size of the vacuoles increases pushing the nucleus to the periphery of the cell - macrovesicular fatty change. These vesicles are well delineated and optically empty because fat dissolves during tissue processing (paraffin embedding). Large vacuoles may coalesce, producing fatty cysts, which are irreversible lesions. Initially there is accumulation of fat only in perivenular hepatocytes but later on fat accumulates in the entire hepatic lobule.

Pathogenesis

There is increasing recognition of the role of free fatty acids (FFA) in directly promoting liver injury. There may be either increase of free fatty acids (starvation, diabetes and chronic alcoholism), reduction of free fatty acids oxidation (hypoxia, toxins, chronic alcoholism), increase of esterification of free fatty acids into triglycerides (due to increased free fatty acids or reduction of their oxidation, chronic alcoholism) and reduced export of triglycerides due to defeciency of lipid binding apoprotein (starvation / malnutrition, toxins). These FFA either undergo beta-oxidation or are esterified with glycerol to form triglycerides, leading to hepatic fat accumulation. There is now substantial evidence that FFA can directly cause toxicity by increasing oxidative stress and by activation of inflammatory pathways (Feldstein, 2004), therefore hepatic triglyceride accumulation may be a protective mechanism by preventing the toxic effects of unesterified FFA (Yamaguchi, 2007). Additionally, a further component, has been added to reflect inadequate hepatocyte proliferation (Jou, 2008). In the healthy liver, cell death stimulates replication of mature hepatocytes which replace the dead cells and reconstitute normal tissue function (Jou, 2008). However oxidative stress, a central feature of NAFLD pathogenesis, inhibits the replication of mature hepatocytes which results in expansion of the hepatic progenitor cell (oval cell) population. These cells can differentiate into hepatocyte-like cells, and both oval cell and intermediate hepatocyte-like cell numbers are strongly correlated with fibrosis stage, suggesting that cumulative hepatocyte loss promotes both accumulation of progenitor cells and their differentiation towards hepatocytes. Activation of these cells has also been implicated in hepatocellular carcinogenesis (Roskams, 2003).

Classification

NAFLD can be classified into primary and secondary. The primary type is commonly found among people with conditions such obesity, type 2 diabetes, and metabolic syndrome, and is thought to be caused by insulin resistance. The secondary type can be associated with the use of certain medications and a variety of miscellaneous disorders that include infectious, nutritional, and inborn errors of metabolism. Histopathologically it may be classified as Macrovescicular and Microvesicular depending on the size of fat vacuoles.

Common Causes of Secondary Hepatic Steatosis:

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation or Protein Calorie Malnutrition
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

- Acute fatty liver of pregnancy
- Jamaican vomiting sickness
- Reye's syndrome
- Jejunoileal bypass
- Medications (valproate, anti-retroviral medicines)
- HELLP syndrome
- Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Drugs implicated in fatty liver

- Antiarrhythmic Amiodarone
- Antibiotic Tetracycline
- Anticonvulsant Valproic acid
- Antiviral zidovudine, indinavir, ritonavir
- Analgesics aspirin
- Oncotherapeutic drugs asparginase, methtrexate
- Others like steroids, vitamin A and synthetic estrogens.

Risk Factors Associated with NAFLD

Conditions with established association

- Obesity

- Type 2 diabetes mellitus
- Dyslipidemia
- Metabolic syndrome

Conditions with emerging associations

- Polycystic ovary syndrome
- Hypothyroidism
- Obstructive Sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreato-duodenal resection

Clinical Features

This condition is usually diagnosed coincidentally or patient may present with right upper quadrant pain. Rarely in acute fatty liver, patient may present with nausea, vomiting, tender hepatomegaly and jaundice. Differentation between alcoholic and nonalcoholic fatty liver is history of alcoholism.

Acute Fatty liver of pregnancy

It is a rare complication of pregnacy and It usually occurs in third trimester. It is characterized by marked increase in serum bilirubin levels. There is associated increase in serum ammonia levels and incidence of hypoglycemia. Typically liver is small. It is more common when the mother is carrying a male fetus. There may be associated defeciency of long chain 3 hydroxy acyl COH dehydrogenase. It usually resolves with termination of pregnancy and recurrence is rare in subsequent pregnancies.

Diagnosis

In majority of patients diagnosis is often coincidental when sonography was done for some other purpose.Laboratory Abnormalities in NAFLD include nonpecific elevation of aspartate aminotransferase and alanine aminotransferase. There may be accompanying hypertriglyceridemia, hypercholesterolemia and hyperbilirubinemia. It is usually diagnosed by Ultrasonography. It is helpful in detecting fatty inflteration of the liver and determining liver size. Other imaging techniques like Computed tomography (CT) and magnetic resonance imaging (MRI) can also suggest increased fat in the liver. If there is diagnostic uncertainity, needle biopsy of the liver will demontrate increased fat content, presence of fibrosis and possibly the underlying primary disorder. Majority of patients are diagnosed as having fatty liver disease by using surrogate indicators of the disease, such as elevated liver enzymes or imaging studies (ultrasound [US] or computed tomography [CT]) suggesting hepatic steatosis in persons who have negative serologic tests for viral hepatitis, autoimmune liver disease, and congenital causes of chronic hepatitis. Additionally, alcohol consumption is typically restricted to ≤ 14 units/week (20 g/day), a threshold considered to be below the traditional cutoff for alcohol induced liver disease.[3] Ultrasound also has limited sensitivity when the degree of steatosis is < 30% and is considered highly operator dependent. Proton magnetic resonance spectroscopy (protonMRS) represents the best noninvasive quantitative method to measure hepatic triglyceride content and has been used in a few published studies.[15] The major drawbacks of this method are its cost and the inability to distinguish simple steatosis from fibrosis.

Treatment

The management of patients with NAFLD consists of treating liver disease as well as the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance and T2DM. Treatment focuses on the factors that may cause the disease. In case of drug induced fatty liver removal of offending drug usually results in complete recovery. Similarly dicontinuation of parenteral hyperalimentation results in disappearance of fat within 2 weeks. Other measures include proper control of diabetes, weight loss and correction of intestinal absorptive defects.

Insulin sensitizing agents

Metformin: There was only a modest improvement in hepatic steatosis and inflammation

Thiazolidinediones

Rosiglitazone improved aminotransferases and hepatic steatosis, but not necroinflammation or fibrosis. Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. Oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in subjects with NAFLD. Vitamin E is an anti-oxidant and has been investigated to treat NASH (Hasegawa, 2001 and Yakaryilamz, 2007). As the majority of patients undergoing bariatric surgery have associated fatty liver disease, there has been an interest in foregut bariatric surgery as a potential treatment option for NASH (Mummadi, 2008 and Chavez-Tapia, 2010).

Conclusion

NAFLD now represents one of the commonest causes of chronic liver disease worldwide, and the rising levels of obesity, diabetes and metabolic syndrome will ensure that it remains a major cause of morbidity and mortality. Although simple steatosis carries a relatively benign prognosis, a significant proportion of patients will progress to NASH and later cirrhosis with risk of HCC. So early diagnosis and treatment is the mainstay.

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