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Medical Science

A Case Oriented approach of Evaluation of Chronic Alcoholic Liver Cirrhosis associated with Chronic Pancreatitis

KEY WORDS: Alcoholic liver cirrhosis, Amylase, Chronic Pancreatitis, Lipase, Transaminases.

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ABSTRACT

Background: Chronic Alcoholic liver disease (ALD) is a serious and potentially fatal consequence of alcohol use. Chronic Alcoholic liver cirrhosis and alcoholic chronic pancreatitis are the frequent organ manifestations. Chronic Alcoholic liver cirrhosis and alcoholic chronic pancreatitis both are serious and potentially fatal. The aim of the study is to evaluate alcoholic liver cirrhosis associated with chronic pancreatitis.

Materials & methods: 100 clinically diagnosed subjects of chronic alcoholic liver cirrhosis patients were taken as cases. 100 healthy subjects were taken as controls. Serum sample was used for the estimation of fasting blood sugar (FBS), PPBS, total bilirubin, direct bilirubin, AST, ALT, ALP, GGT, total protein, albumin, amylase and lipase.

Results: In this study, serum concentrations of total bilirubin (3.25±0.71), direct bilirubin (1.92±0.67), AST (135.6±67.2), ALT (47.0±16.53), ALP (158.8±34.24), GGT (104.5±61.2), total protein (5.93±0.6), amylase (126.6±8.9) & lipase (51.42±7.8) were significantly increased in cases when compared to controls. Albumin (2.7±0.6) was significantly decreased in cases when compared to controls.

Conclusion: Chronic consumption of alcohol remains a main public health problem and is responsible for morbidity, affecting various organ systems and leads to mortality. Hence, assay serum amylase and lipase should be done in all patients with alcoholic liver cirrhosis as preliminary diagnostic tests in early detection of alcoholic chronic pancreatitis.

Introduction:

Alcoholic liver disease (ALD) is a serious and potentially fatal consequence of alcohol use. (1) The World Health Organization (WHO) estimates that 140 million people worldwide suffer from alcohol dependency, causing damage to lives and economies. Alcoholism is called a "dual disease" since it includes both mental and physical components. Alcoholic liver disease (ALD) encompasses a spectrum of clinical illness and morphological changes that ranges from injury, simple steatosis to frank cirrhosis. In cirrhosis, normal liver cells are replaced by scar tissue (i.e., fibrosis) and consequently the liver is unable to perform many of its usual functions. (2) Furthermore, sustained excessive alcohol intake favors the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma. (3)

Alcoholic liver cirrhosis and alcoholic chronic pancreatitis (ACP) are the frequent organ manifestations. Alcoholic liver cirrhosis and alcoholic chronic pancreatitis both are serious and potentially fatal. It may well represent the oldest form of liver injury known to humankind. Alcohol remains a major cause of liver disease worldwide. (4, 5) Multiple mechanisms such as oxidative stress, mitochondrial dysfunction, and alteration in gut-liver axis have been proposed for the pathogenesis of alcoholic liver disease. Alcohol related toxicity is the third most common cause of morbidity and the fifth most common cause of disease burden worldwide. Alcohol abuse is the leading cause of mortality in people aged 15–49 years, and the total expenditure amounts to billions of dollars. In developed countries, alcohol is the most common etiology of cirrhosis. (6)

The prevalence of CP was 42/100000 in the USA, 26/100000 in France, 22/100000 in Japan, and 114-200/100000 in India (the highest), respectively. 2-4 in China, an investigation on 2008 patients with CP from 22 hospitals from 1994 to 2004 showed that the incidence was 13/100000 and an increasing trend was seen. (7) Chronic Pancreatitis (CP) is a worldwide disease. This disease is common in India, particularly in South India. Kerala state in India has the highest incidence of this disease. (8)

Association between alcohol abuse and pancreatic injury was reported as early as 1878 (Friedreich 1878). Pancreatitis is a potentially fatal inflammation of the pancreas often associated with long-term alcohol consumption. Symptoms may result from blockage of small pancreatic ducts as well as from destruction of pancreatic tissue by digestive enzymes. In addition, by-products of alcohol metabolism within the pancreas may damage cell membranes. Alcoholic pancreatitis is a potentially fatal illness that may be short term (i.e., acute) or long term (i.e., chronic). The relationship between acute and chronic pancreatitis is complex. Symptoms shared by acute and chronic pancreatitis include disabling abdominal pain and interference with normal pancreatic functions. Although the prevalence of alcoholic pancreatitis in the population is unknown, clinicians usually agree those both acute and chronic alcoholic pancreatitis is responsible for a significant amount of illness and death. (9)

Chronic pancreatitis results from a complex interaction of environmental and genetic factors. Alcohol has been regarded as one of the leading causes of Chronic Pancreatitis. Excess alcohol was the predominant factor in over 60% of cases of Chronic Pancreatitis in Western countries and about 35% in China. The other causes include hyperlipidaemia, hypercalcaemia, congenital pancreatic abnormality, pancreatic trauma or surgery, autoimmune disease, genetic mutations or defects. 20-30% patients are labeled idiopathic pancreatitis without any definite causes. Pathological changes in patients with Chronic Pancreatitis include interstitial fibrosis, dilations of pancreatic ducts, pseudocysts and acinar destruction. According to pathological changes, the disease can be divided into chronic calcified pancreatitis, chronic obstructive pancreatitis, and chronic inflammatory pancreatitis. Chronic calcified pancreatitis is the most common and characterized by sporadic interstitial fibrosis, protein thrombus or stones in pancreatic ducts. Chronic obstructive pancreatitis can lead to dilation of pancreatic ducts and acinar loss due to local obstruction or stenosis of pancreatic ducts resulting in fibrosis. Chronic inflammatory pancreatitis mainly involves the fibrosis and aplasia of pancreas and mononuclear cell infiltration. (7)

Chronic pancreatitis still remains a challenging clinical problem with many controversial issues regarding pathogenesis, outcome, and treatment. The disease comprises a spectrum of disorders that culminate as a final step in the destruction of the pancreas. Complex interaction does exist between genetic, environmental and immunologic factors leading to development of the disease. Multiple risk factors interact in a multiple-step model; the pancreatic injury may occur through different mechanisms with transition between an acute pancreatitis condition to recurrent pancreatitis and finally to Chronic Pancreatitis. (10) Chronic pancreatitis, an inflammatory disease characterized by fibrosis leading to the destruction of pancreatic exocrine and endocrine tissue, still remains a challenging clinical problem with many controversial issues regarding pathogenesis, outcome, and

treatment. Various predisposing factors have been identified over the last decades, but their impact on etiology and the natural disease course is still a matter of debate. In the Western world the disease is commonly associated with excessive consumption of alcohol. The aim of the present study is evaluate alcoholic liver cirrhosis associated with chronic Pancreatitis.

Materials & Methods:
This study is a cross sectional case-control study, conducted at Jawaharlal Nehru Medical College of Aligarh Muslim University. 100 clinically diagnosed subjects of chronic alcoholic liver disease as demonstrated abnormal aminotrasferases levels were taken as cases. 100 healthy subjects were taken as controls. The clinical history and other necessary details were obtained from the patients records. Venous blood samples were collected after taking aseptic precautions from the study subjects. 5 ml of blood was collected in plain vaccum tubes. Samples were left for 20 minutes at room temperature, and centrifuged at 3000 rpm for 4 to 5 minutes. Serum sample was used for the estimation of total bilirubin, direct bilirubin, AST, ALT, ALP, GGT, total protein, albumin, amylase and lipase by DADE BEHRING DIMENSION fully auto analyzer, and RA-50 semi autoanalyzer for GGT.

Statistical Analysis:
Data were expressed as mean ±SD. P value <0.05 is considered as statistically significant. Statistical analysis was performed using SPSS 20.0

Results:
Total number of patients were 100 out of this 12 (12%) were with chronic pancreatitis. The serum concentrations of total bilirubin (3.25±0.71), direct bilitubin (1.92±0.67), AST (135.6±67.2), ALT (47.0±16.53), ALP (158.8±34.24), GGT (104.5±61.2), total protein (5.93±0.6), amylase (126.6±8.9) & lipase (51.42±7.8) were significantly increased in cases when compared to controls. Albumin (2.7±0.6) was significantly decreased in cases when compared to controls.

Table 1: Comparison of liver function tests, amylase & lipase between cases & healthy controls

Parameters	Cases (n=100) Mean ± SD	Controls (n=100) Mean ± SD	P -value
Total Bilirubin	3.25±0.71	0.64±0.15	<0.0001*
Direct Bilirubin	1.92±0.67	0.28±0.11	<0.0001*
Indirect Bilirubin	1.37±0.32	0.38±0.20	<0.0001*
Aspartate transaminase (AST)	135.6±67.2	25.8±7.35	<0.0001*
Alanine Transaminase (ALT)	47.0±16.53	25.8±7.3	<0.0005*
Alkaline phosphatase (ALP)	158.8±34.24	48.5±19.0	<0.0001*
- Glutamyl transferase (GGT)	104.5±61.2	28.36±11.6	<0.0003*
Total Proteins	5.93±0.6	6.7±0.4	<0.0001*
Albumin	2.7±0.6	4.1±0.3	<0.0001*
Globulin	5.2±0.9	2.6±0.6	<0.0001*
Amylase	126.6±8.9	57.7±28.5	<0.0001*
Lipase	51.42±7.8	31.27±11.8	<0.0001*

*statistically significant

Discussion:
Chronic pancreatitis (CP) is a progressive inflammatory process of the pancreas leading eventually over several years to pancreatic "cirrhosis". Clinically, CP is usually characterized by an initial stage of recurrent acute pancreatitis (early stage CP) and progressive pancreatic dysfunction and/or calcification (late-stage CP). Alcohol abuse is the prominent risk factor of CP (70%), while CP remains a etiologically undetermined in about 25% or is related to rare causes such as genetic mutations, hyperparathyroidism, trauma or "autoimmunity" (11) The role of alcohol is the cornerstone of the pathogenesis of chronic pancreatitis, at least in Western countries. Durbec and Sarles clearly demonstrated that alcohol is a risk factor for chronic pancreatitis; in fact, they showed that the relative risk would be multiplied approximately by a factor of 1.4 when passing from one 20-gram intake to the next. Furthermore, the increase appears to be more rapid when passing from the class of nondrinkers to that of 20-gram of alcohol intake per day. The mechanism which determines the main manifestation of chronic pancreatitis, i.e., fibrosis of the pancreatic gland, has been well-summarized by Taludkar et al. In brief, the oxidation of ethanol to acetaldehyde determines the activation of the pancreatic stellate cells in the quiescent state without any pre-activation; this process generates a state of oxidant stress within the pancreatic stellate cells which subsequently activates the downstream pathways of the fibrogenesis. This finding implies that, in the human pancreas, pancreatic stellate cells may be stimulated early during chronic alcohol intake even in the absence of necroinflammation. The importance of the oxidative stress in chronic pancreatitis patients has also been reported using breath analysis. Regarding tropical pancreatitis, several hypotheses have been made, in particular, the malnutrition theory, the cassava hypothesis and the oxidant stress hypothesis Thus, also in this particular form of the disease, it is possible that there is activation by certain substances of the pancreatic stellate cells. However, according to this postulated pathogenesis, alcohol seems to induce pancreatic fibrosis as has frequently been found in autopsy-series of alcoholics without clinical history of chronic pancreatitis.(12)

Excessive ethanol consumption is a common risk factor for acute and chronic pancreatitis. Ethanol could lead to the onset of pancreatitis in a number of ways; the most recently discovered is its effect on intrapancreatic digestive enzyme activation, by either sensitizing acinar cells to pathologic stimuli or stimulating the release of a secretagogue (cholecystokinin) from duodenal I cells. (13) The mechanism which determines the main manifestation of chronic pancreatitis, i.e., fibrosis of the pancreatic gland, has been well summarized by Taludkar et al. brief, the oxidation of ethanol to acetaldehyde determines the activation of the pancreatic stellate cells in the quiescent state without any pre-activation; this process generates a state of oxidant stress within the pancreatic stellate cells which subsequently activates the downstream pathways of the fibrogenesis. This finding implies that, in the human pancreas, pancreatic stellate cells may be stimulated early during chronic alcohol intake even in the absence of necro-inflammation. The importance of the oxidative stress in chronic pancreatitis patients has also been reported using breath analysis. In this study, H2S, NO and a substance having a molecular mass of 66 u (M66) were those which had significantly higher breath concentrations in chronic pancreatitis patients than in healthy subjects after adjustment for the ambient air; no significant differences in H2S, M66, and NO were found between patients with and without alcoholic pancreatitis.

Alcoholic pancreatitis usually occurs in men in their forties. Initial symptoms include vomiting as well as acute abdominal pain, which may be localized to the back and upper abdomen and is relieved by leaning forward. In mild cases, the pain may last 2 to 3 days; the short-term prognosis in such cases is very good. In severe cases, however, the pain may persist for several weeks and the risk of death rises to about 30 percent. Less commonly, pancreatitis can be completely painless and is only diagnosed from symptoms of insufficient pancreatic function, such as diabetes and steatorrhea (excess fat in feces). Approximately 5 to 6 years after the onset of the disease (especially in patients who continue to drink), evidence of chronic pancreatic disease develops as a result of progressive destruction of pancreatic tissue (i.e., parenchyma). A clinical diagnosis of pancreatitis is usually made on the basis of an attack of severe abdominal pain and tenderness, accompanied by a rise in the blood level of a pancreatic enzyme that digests starch (i.e., amylase) to more than three times the normal limit. (9) Alcohol when taken orally is known to increase mucosal perfusion and also to stimulate production of secretin. Both can affect pancreas microcirculation indirectly. Ethanol is also known to affect pancreatic blood flow when given intravenously and via intragastric route (14). McKim et al (15) investigated the effect of

chronic intragastric ethanol administration which induced pancreatic hypoxia and oxidative stress in vivo. Pancreatic hypoxia induced by chronic alcohol appears to be secondary to increase in oxygen consumption by pancreas or to decrease in local blood supply without alteration of hemodynamic patterns. Chronic ethanol ingestion was associated with dose related inhibition of basal pancreatic protein secretion which was reversed upon alcohol withdrawal (16). Increased susceptibility to chronic alcoholic pancreatitis may be through a hyperstimulation mechanism due to combination of neurohormonal factors. In exocrine pancreas, alcohol induces secretory alteration which varies by manner and duration of alcohol exposure. Ethanol effects on pancreatic secretion appear to be primarily caused by systemic cholinergic mechanisms of the vagus nerve (17).

Conclusion:

Unhealthy alcohol consumption remains a main problem for the public health and is responsible for a high rate of morbidity, affecting various organ and systems, and mortality. The pathophysiology of ALD is quite complex, encompassing factors related to genetics, gender, ethnicity, consumption patterns and co-morbid conditions. Alcohol abuse/alcoholism are a major cause of pancreatitis. Combining alcohol abuse with smoking aggravates the condition further. Despite numerous reported studies the pathogenesis of alcoholic pancreatitis remains obscure. Although the mechanisms responsible for the development of pancreatitis in alcoholics needs to be fully clarified, significant progress in this direction has been made in the past decade, particularly with respect to understanding the direct toxic effects of alcohol on the pancreas. These effects may create a "primed" setting within the pancreas, which, in the presence of an additional (as yet unidentified) trigger factor, could lead to acute, clinically evident pancreatic injury. Repeated episodes of acute pancreatic injury may lead to chronic disease. Progression of alcoholic pancreatitis may also be aided by alcohol-induced deposition of protein plugs within small pancreatic ducts.

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