

CLINICAL INVESTIGATION STUDY PROPOSAL

NAV1.954406.003

- I. Activity: Naval Hospital
San Diego, California 92134
- II. Title: Nonalcoholic Liver Disease in the Alcoholic
- III. Investigation:

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Internal Medicine Department
5% of time required for two years
Projected rotation date: 7/85

Associates: LCDR Peter K. Meyers, MC, USNR

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Fellow, Division of Gastroenterology
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Projected rotation date: 7/84

IV. Identification of Drugs and Devices to be used in the Study: Not applicable

V. Methods and Materials

A. Objective:

To determine the frequency of nonalcoholic liver disease in a patient population with heavy alcohol intake and evidence of hepatic dysfunction.

B. Background:

Alcohol ingestion is the major cause of chronic liver disease in the Western world.¹ In the United States, cirrhosis has overtaken diabetes as the fifth leading cause of mortality.² Unfortunately, despite intense investigation, there has been little progress in reversing or altering the progression of severe alcoholic liver injury once it has occurred.³ Because of this, it has been considered extremely important to rule out other potentially treatable causes of liver disease when dealing with an alcoholic

ENCLOSURE(94)

patient having evidence of hepatocellular dysfunction.

While some authors fail to report any non-alcoholic liver disease in large series of patients with heavy alcohol consumption,^{4,5,6} others have reported non-alcoholic liver disease with some degree of frequency.^{7,8,9} Leven et al,⁷ in a retrospective series, reported a 20% incidence of non-alcoholic liver disease in a group of 105 patients felt clinically to have alcoholic liver disease. Goldberg et al⁸ reported on 10 cases of chronic hepatitis observed in an alcoholic population over a two year period. The findings of these two reports have been emphasized in recent reviews on alcoholic liver disease.^{10,11,12} It has been suggested that liver biopsy is essential in establishing the diagnosis of alcoholic liver disease; clinical features do not allow for adequate distinction.

However, it has been our impression at Naval Hospital, San Diego, that a carefully taken history, combined with a thorough physical examination, select laboratory tests and non-invasive imaging procedures allows for a fairly accurate determination as to the presence or absence of alcoholic liver disease. While alcoholic patients are not infrequently found to have other liver diseases, a suspicion for this is generally raised prior to liver biopsy.

Historical information which may heighten a suspicion for non-alcoholic liver disease includes: 1) Hepatotoxin ingestion, 2) illicit drug abuse, 3) prior blood transfusions, 4) past history of hepatitis, 5) concurrent malignant disease, 6) family history of liver disease, etc.

Physical examination is primarily useful in establishing the magnitude of liver disease as suggested by such features as jaundice, ascites, splenomegally, caput medusa, etc. However, certain features unrelated to liver disease may give further evidence to the extent of alcohol ingestion. For example, peripheral neuropathy, evidence of cerebellar atrophy, Wernicke's encephalopathy, proximal myopathy, and Dupuytren's contracture are not felt related to liver disease, but rather alcohol consumption.

Laboratory features may aid in the diagnosis of alcoholic liver disease.^{16,17,18,19,20} Such tests include: SGOT, SGPT, GGTP, Alkaline Phosphatase, tissue autoantibodies, serum immunoglobulins and iron studies.

In short, the clinician has at his disposal a great deal of information which may allow the diagnosis of alcoholic liver disease to be

comfortably established without tissue biopsy confirmation. Therefore, in addition to determining the frequency of nonalcoholic liver disease in a heavily drinking patient population, the study is also designed to assess the accuracy of clinical impression.

C. Approach

I. Patient Population

a. Inclusions

1. Adults, males and females, judged to have consumed an average of 80 grams or more alcohol per day during the previous 12 months.
2. Evidence of diffuse hepatocellular dysfunction as determined by physical examination, consistently abnormal liver function studies and/or noninvasive imaging procedures.
3. Informal written consent to participate in study.

b. Exclusions

1. Prior liver biopsy establishing diagnosis.
2. Contraindications to percutaneous and laparoscopic liver biopsy.

II. Estimated duration of study: 24 months.

III. Number of patients to be enrolled: 100.

IV. Study Methods

All proposed liver biopsies at Naval Hospital, San Diego will be coordinated through the G.I. Department. Patients with evidence of hepatic disease, in whom liver biopsy is felt indicated, will have a detailed history taken of their alcohol consumption.^{14,15} A brief screening questionnaire will be used on all patients (see appendix). Confirmation of patients' alcohol history will be sought from relatives or close acquaintances whenever possible. Based on this compiled information, a determination as to the extent of alcohol intake will be made. Patients judged to have consumed ≥ 80 grams per day of ethanol for \geq one year will be eligible for study inclusion.

All patients will undergo a complete history and physical exam.

The following studies will be obtained on all study patients:

- (1) CBC with platelets, (2) PT/PTT, (3) Hepatic, Renal and Bone panels, (4) SGPT, (5) GGTP, (6) HB_sAg,

(7) ANA, (8) AMA, (9) Serum iron/TIBC, (10) Nuclear Medicine liver/spleen scan. In addition, special laboratory tests such as: Alpha-1-antitrypsin, ceruloplasmin, and Ferritin may be ordered when felt indicated by clinical suspicion. Pertinent information and laboratory results will be transcribed onto the patient data forms (see appendix).

On the basis of this clinical information, the involved G.I. staff member will be asked to categorize the underlying liver pathology as alcoholic or nonalcoholic. This diagnostic impression along with the patient data forms will be submitted prior to the performance of a liver biopsy.

Liver biopsy specimens will be obtained by blind percutaneous needle aspiration (Menghini technique) or by Tru-cut biopsy under laparoscopic guidance.

Biopsy specimens will be processed and reviewed by a staff Pathologist at Naval Hospital, San Diego. Subsequent review by AFIP may be requested. Tissue diagnosis will be recorded. The Pathologist will be specifically asked to state whether or not the histologic changes are due to alcohol. This will be recorded as: 1) probably alcohol related, 2) unlikely alcohol related or 3) indeterminate.

V. Data Collection

At the conclusion of the study, final histopathologic diagnoses will be reviewed. The percentage of patients having non-alcoholic liver disease will be determined.

Furthermore, the number of patients with treatable liver diseases (CAH, Hemochromatous, Wilson's disease) will be determined and calculated as a percentage of the total.

The accuracy of clinical impression in predicting underlying liver disease will also be assessed. This will be expressed as the percentage of patients correctly and incorrectly diagnosed on clinical grounds.

Results of laboratory tests will be used to assess the sensitivity and specificity of various tests in the evaluation of alcoholic liver injury.