

# Diagnostic accuracy of spider *naevi* for liver disease detection in alcoholics

*Precisión diagnóstica de las arañas vasculares para detectar enfermedad hepática en alcohólicos*

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## Abstract

**Introduction:** Spider *naevi* are traditionally considered a sign of liver cirrhosis, particularly in patients with alcoholism. However, systematic evaluation of their diagnostic value in alcoholic patients has been scarcely performed. The aim of this study was to determine the diagnostic accuracy of the presence of spider *naevi* for liver disease detection in alcoholics using percutaneous liver biopsy as the reference standard.

**Methods:** Cross-sectional study of 229 alcoholics admitted to the hospital (67% males) undergoing percutaneous liver biopsy.

**Results:** Spiders were least prevalent in patients with fatty liver (4/104 cases, 4%). The prevalence of spiders was greater in patients with alcoholic hepatitis (15/80, 19%) than in patients with fatty liver ( $P=0.002$ ). Prevalence was even higher in patients with cirrhosis (6/21, 29%,  $P<0.001$ ), and was highest in patients with cirrhosis and superimposed alcoholic hepatitis (11/24, 46%,  $P<0.001$ ). The presence of spiders had a sensitivity of 25% (95% CI 18-34%), a specificity of 95% (95% CI 90-99%), and a positive likelihood ratio of 6.6 (95% CI 2.4-18.2) for the diagnosis of severe underlying liver disease (alcoholic hepatitis, liver cirrhosis, or both). The presence of spiders was associated with biological markers of liver dysfunction and with additional cutaneous stigmata (facial telangiectasia and palmar erythema).

**Conclusion:** The presence of spiders in an alcoholic patient strongly indicates the presence of severe underlying liver disease (liver cirrhosis and/or alcoholic hepatitis).

**Key words:** alcoholism; alcoholic hepatitis; cirrhosis; spider *naevi*.

## Resumen

**Introducción:** Las arañas vasculares son consideradas tradicionalmente como un signo de cirrosis hepática, especialmente en pacientes con alcoholismo. Sin embargo, la evaluación sistemática de su valor diagnóstico en pacientes alcohólicos apenas se ha realizado. El objetivo de este estudio fue determinar la precisión diagnóstica de la presencia de arañas vasculares para la detección de enfermedad hepática en alcohólicos usando la biopsia hepática percutánea como patrón de referencia.

**Métodos:** Estudio transversal de 229 alcohólicos ingresados en el hospital (67% varones) sometidos a realización de biopsia hepática percutánea.

**Resultados:** Las arañas vasculares fueron menos prevalentes en pacientes con hígado graso (4/104 casos, 4%). La prevalencia de las arañas fue mayor en pacientes con hepatitis alcohólica (15/80, 19%) que en pacientes con hígado graso ( $P=0.002$ ). La prevalencia fue aún mayor en los pacientes con cirrosis (6/21, 29%,  $P<0.001$ ), y la más alta fue en pacientes con cirrosis y hepatitis alcohólica sobreañadida (11/24, 46%,  $P<0.001$ ). La presencia de arañas tuvo una sensibilidad del 25% (IC 95% 18-34%), una especificidad del 95% (IC 95% 90-99%), y una razón de verosimilitudes de 6,6 (IC del 95%: 2,4 a 18,2) para el diagnóstico de enfermedad hepática de base grave (hepatitis alcohólica, cirrosis hepática, o ambas). La presencia de arañas se asoció con marcadores biológicos de disfunción hepática y con estigmas cutáneos adicionales (telangiectasias faciales y eritema palmar).

**Conclusión:** La presencia de arañas en un paciente alcohólico indica firmemente la presencia de enfermedad hepática de base grave (cirrosis hepática y/o hepatitis alcohólica).

**Palabras clave:** alcoholismo, hepatitis alcohólica, cirrosis, arañas vasculares.

## Introduction

Frequently, clinical signs are preserved in textbooks and doctor's minds despite a lack of scientific evaluation according to evidence-based medicine<sup>1,2</sup>. Spider *naevi* in alcoholics may be an example of this. Cutaneous spider *naevi*, vascular spiders, arterial spiders or spider angiomas ("spiders") are telangiectases consisting of a large arteriole with numerous radiating small vessels giving the impression of the legs of a spider<sup>3</sup>. For unknown reasons, spiders are found in the region drained by the superior vena cava, i.e. the face, neck, arms and upper torso. A small number of spiders (usually less than 3) can be found in 10 percent of the general population. They may appear in large numbers during pregnancy and usually

disappear after parturition, although some persist. They may also be seen in patients treated with estrogen and in women taking oral contraceptives<sup>3-5</sup>.

Traditionally, spiders are considered a clinical sign of chronic liver disease, particularly in patients with alcoholism. They are recognized as such in common textbooks of internal medicine<sup>6</sup>, hepatology<sup>7,8</sup>, and dermatology<sup>4</sup>, as well as in clinical practice, and even by barmaids in order to diagnose liver cirrhosis in a customer<sup>9</sup>. However, disagreements between textbooks recommendations and actual literature are not uncommon<sup>1,2</sup>. Along this line, it is noteworthy that evaluation of the value of spiders as a diagnostic test for underlying liver disease in alcoholics is scarce. Among patients with liver disease, particularly

Figure 1. Vascular spiders in an alcoholic



hepatitis C, spiders predict the presence of advanced liver fibrosis<sup>10-12</sup>. In patients with cirrhosis, spiders are associated with alcoholism<sup>13</sup>, liver dysfunction<sup>13</sup>, variceal haemorrhage<sup>14</sup>, and hepatopulmonary syndrome<sup>15</sup>. Spiders predict long-term mortality in patients with alcoholic cirrhosis<sup>16</sup>. In the only study evaluating the accuracy of clinical signs in predicting the presence of liver disease in alcohol abusers, Hamberg et al.<sup>17</sup> found that the presence of spiders was an independent predictor of cirrhosis. However, the study included only males and only a small number of patients with alcoholic hepatitis. The potential role of gender may be important because sex hormones are implicated in the pathogenesis of vascular spiders<sup>5,18,19</sup>. The inclusion of patients with alcoholic hepatitis is important because it is an inflammatory disease with significant mortality and pre-cirrhotic potential<sup>7,8</sup>. Furthermore, superimposed alcoholic hepatitis may complicate liver cirrhosis<sup>20</sup>.

The present study aimed to investigate the value of the presence of spiders for the diagnosis of underlying liver disease in alcoholic patients using percutaneous liver biopsy as the reference standard. The study included both males and females, and patients with a diagnosis of fatty liver, alcoholic hepatitis, liver cirrhosis, or liver cirrhosis with superimposed alcoholic hepatitis.

## Methods

### Setting, patients and study design

This observational study includes a consecutive series of 256 percutaneous liver biopsies performed in heavy drinkers admitted to the Internal Medicine Department of a University Hospital. A detailed description of this series has been published elsewhere<sup>21</sup>. Briefly, liver biopsy was routinely offered during the study period to heavy drinkers with either biochemical or clinical signs of liver disease and no contraindication for the procedure. Exclusion criteria for participation in the study

were: (a) current hospital admission due to complications of liver disease; (b) contraindication for percutaneous liver biopsy (including massive ascites and clotting abnormalities); and (c) evidence for additional causes of liver disease (including serological evidence of either hepatitis C virus or active hepatitis B virus infection). The present study includes the 229 patients with complete data regarding the presence of spiders. Median age was 41 years (range, 19-75 years), and 153 (67%) were males. The indications for hospital admission were as follows: alcohol withdrawal syndrome in 81 cases, infection in 34 cases, evaluation of liver biochemical alterations in 28 cases, pancreatitis in 18 cases, digestive haemorrhage in 17 cases, unspecific abdominal pain in 15 cases, and miscellaneous causes in 35 cases. All patients consented to participate in the study, which was conducted according to the Helsinki declaration. The local Ethics Committee reviewed and approved the study.

### Main determinations

**Vascular spiders.** Only typical radiating vascular lesions which blanched on pressure to the central arteriole with a pointed object and refilled again from the centre outwards were considered diagnostic of spiders (Figure 1). Vascular spiders were considered to be present when >3 of these typical lesions were present in the face, neck, arms, or upper torso. Atypical lesions were not considered and facial telangiectasia (see below) was considered separately. In a study of concordance between two independent observers using the same criterion for the presence of spiders in 30 additional alcoholic patients, the kappa index was 0.79.

**Additional physical stigmata.** Facial telangiectasia was considered to be present when vascular dilatations with the appearance of "paper money" skin were evident over the malar surfaces with persistent erythema<sup>22</sup>. Palmar erythema or "liver palms" was defined as an exaggerated mottling of the palms

or well-demarcated erythema over the hypothenar eminence spreading to other parts of the hand<sup>22</sup>. Parotid enlargement was considered when parotid glands were both visible and palpable.

**Assessment of alcohol intake.** An interviewer-administered structured questionnaire was undertaken in all patients during the first seven days of hospital admission. The questionnaire included items related to the duration of alcohol abuse (registered in years) and the average daily consumption of alcoholic beverages during the preceding six months, registered as the total number of standard drinking units (one bottle of beer, one glass of wine, or one unit of spirit, all of them approximately equivalent to 10g of alcohol).

**Liver histopathology.** Percutaneous liver biopsies performed during admission were examined by a single pathologist who was unaware of the presence or absence of spiders. Standard criteria were employed for the definition of fatty liver (with or without mild liver fibrosis –fibrosteatosis-), alcoholic hepatitis (liver cell ballooning degeneration or necrosis, Mallory bodies, neutrophil infiltration and fibrosis) or liver cirrhosis<sup>23</sup>. Furthermore, cases with liver cirrhosis were divided into two categories depending on the presence or not of superimposed alcoholic hepatitis<sup>20</sup>.

**Statistical analyses.** Sensitivity, specificity and positive likelihood ratios were calculated with their respective confidence intervals. Statistical differences between proportions were assessed by the Chi-square test with continuity correction, when needed. Mann-Whitney U-test was employed for comparison of continuous variables. For some analyses, liver steatosis (the minimal liver lesion observed, almost mandatory in heavy drinkers) was employed as the reference category. In order to assess the influence of variables which were associated with each other as well as with either alcoholic hepatitis or liver cirrhosis, two multivariate analyses (logistic regressions) were performed. The binary dependent variables were: (a) presence of cirrhosis in liver biopsy (with or without alcoholic hepatitis), and (b) presence of alcoholic hepatitis in liver biopsy (with or without cirrhosis). In these models, predictor variables (gender, duration of alcohol consumption, average daily quantity, and presence of vascular spiders) were forced to enter the equation. Age was not included in the model because of collinearity with duration of alcohol consumption. Two-tailed p-values lower than 0.05 were considered statistically significant.

## Results

Vascular spiders were present in 36 patients (17%). Table 1 compares alcoholic patients with and without spiders. The age distribution was similar in both groups, with a slightly higher proportion of females in the spider group. In comparison with patients with no spiders, patients with spiders showed

Table 1. Characteristics of patients with and without spiders

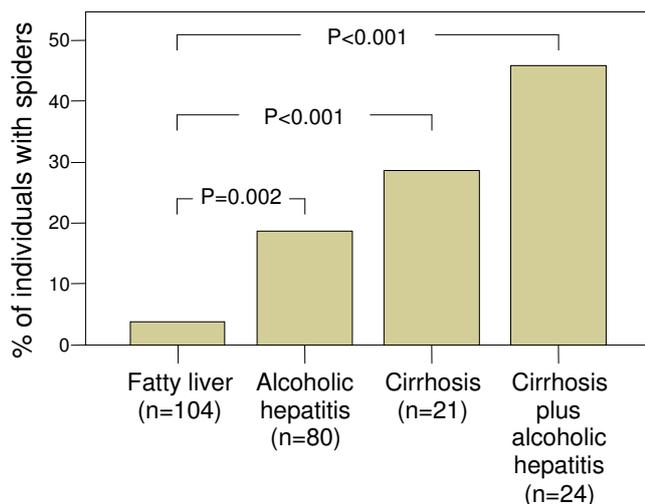
| Characteristic                                 | Patients with spiders (n= 36) | Patients without spiders (n= 193) | P-value |
|--|-------------------------------|-----------------------------------|---------|
| Age (years)                                    | 44 (25-78)                    | 41 (19-75)                        | 0.46    |
| Gender (female)                                | 16 (45)                       | 60 (31)                           | 0.11    |
| <b>Alcohol consumption</b>                     |                               |                                   |         |
| Duration (years)                               | 19 (9-40)                     | 16 (4-51)                         | 0.04    |
| Average quantity (g/day)                       | 220 (100->400)                | 175 (70->400)                     | 0.01    |
| <b>Stigmata of liver disease or alcoholism</b> |                               |                                   |         |
| Facial telangiectasia                          | 31 (86)                       | 95 (49)                           | <0.001  |
| Parotid enlargement                            | 21 (58)                       | 66 (34)                           | 0.006   |
| Palmar erythema                                | 7 (19)                        | 9 (5)                             | 0.001   |
| <b>Liver function tests</b>                    |                               |                                   |         |
| Serum AST (U/L)                                | 54 (12-135)                   | 45 (8-655)                        | 0.17    |
| Serum GGT (U/L)                                | 286 (26-1710)                 | 219 (8-2480)                      | 0.15    |
| Serum bilirubin (mg/dL)                        | 2.3 (0.5-51.0)                | 1.1 (0.2-26.3)                    | <0.001  |
| Prothrombin index (%)                          | 70 (36-100)                   | 87 (40-100)                       | <0.001  |
| <b>Liver biopsy</b>                            |                               |                                   |         |
| Fatty liver                                    | 4 (11)                        | 100 (52)                          | <0.001  |
| Alcoholic hepatitis                            | 15 (42)                       | 65 (34)                           |         |
| Cirrhosis                                      | 6 (17)                        | 15 (8)                            |         |
| Cirrhosis plus alcoholic hepatitis             | 11 (30)                       | 13 (6)                            |         |

Figures are medians and ranges (within parentheses) or absolute frequencies and percentages (within parentheses). Percentages were approximated to the nearest whole number

a longer history of excessive drinking and a higher average daily alcohol intake. The presence of spiders was strongly associated with the presence of additional stigmata on physical examination, including liver palms, facial telangiectasia, and parotid enlargement. Patients with spiders showed biochemical indicators of poorer liver function than patients without spiders, such as higher serum bilirubin levels and longer prothrombin times. However, there were no significant differences regarding markers of recent alcohol consumption or acute liver damage (serum GGT and AST, respectively) between patients with and without spiders (Table 1).

Patients with spiders showed a higher prevalence of severe liver injury (alcoholic hepatitis and/or cirrhosis) than patients without spiders (89% vs 48%,  $P<0.001$ , Table 1). The lowest prevalence of spiders was observed in patients with fatty liver. The prevalence of spiders was greater in patients with alcoholic hepatitis versus those with fatty liver. It further increased in patients with cirrhosis, and was highest in patients with cirrhosis and superimposed alcoholic hepatitis (Figure 2). After

Figure 2. Prevalence of vascular spiders in patients with the different stages of liver injury



adjusting for gender, duration of alcohol consumption, and average daily alcohol consumption, the presence of spiders was associated with liver cirrhosis (with or without alcoholic hepatitis) (OR 4.5, 95% CI 1.97-10.2,  $P<0.001$ ), and with alcoholic hepatitis (with or without liver cirrhosis) (OR 3.6, 95% CI 1.59-8.2,  $P=0.002$ ).

Overall, the presence of spiders had a low sensitivity for the diagnosis of severe underlying liver disease (alcoholic hepatitis and/or cirrhosis) in alcoholic patients (Table 2). In contrast, specificity was high. Accordingly, the positive predictive value of vascular spiders for the presence of severe underlying liver disease was high in this population with a high prevalence of alcoholic hepatitis and/or cirrhosis.

## Discussion

Clinical manifestation of disease can be thought of as a “test” for the presence of that disease<sup>1</sup>. We found that the presence of vascular spiders in an alcoholic patient strongly indicates a severe underlying liver disease (i.e. alcoholic hepatitis, liver cirrhosis, or both). Supporting this association, the presence of spiders was associated with biochemical markers of liver dysfunction (i.e., increased serum bilirubin levels and prolonged prothrombin times). In addition, spiders were associated with

additional stigmata of liver disease such as facial telangiectasia and palmar erythema, suggesting the possibility of a common pathogenetic mechanism. Importantly, cutaneous spiders are easy to detect with a good interobserver agreement<sup>24</sup>, as confirmed in the present study and therefore adding validity as a “test”.

From early comprehensive descriptions<sup>3</sup> and commonly used textbooks<sup>5,7</sup>, spiders have been most frequently associated with cirrhosis, especially of alcoholic origin. However, interest in the significance of spiders in the alcoholic patient has been limited. The only (to the best of our knowledge) systematic study included 303 consecutively hospitalized, alcohol-abusing men, who underwent liver biopsy performed irrespective of clinical and biochemical findings<sup>17</sup>. This specifically investigated the accuracy of clinical diagnosis, and found spiders to independently predict liver cirrhosis (present in 49 patients) with an odds ratio of 6.1 (95% CI, 2.1-17.9). The present analysis has several similarities and indeed we observed a similar odds ratio (4.5, 95% CI 1.97-10.2) of spiders for the diagnosis of cirrhosis. However, our study, which was performed in alcoholics with biochemical evidence of liver damage, provides additional information. First, we included both males and females. This is important because sex hormone imbalance has been proposed as a mechanism for the development of spiders<sup>5,18</sup>. This hypothesis derives from the analogous presence of spiders in patients with relative estrogen excess, such as pregnancy or replacement therapy, and because estrogens have an enlarging, dilating effect on the spiral arterioles of the endometrium<sup>4,18</sup>. In addition, feminization of male cirrhotic patients is a well-known phenomenon<sup>7,8</sup>. The hypothesis is further supported by the finding of an increased serum estradiol/free testosterone ratio in male cirrhotic patients with spiders<sup>19</sup>, although controversy exists<sup>13</sup> and additional humoral factors could be involved<sup>24</sup>. In our study, there was a trend towards a higher prevalence of spiders in female than in male alcoholics, although this trend was attenuated after adjusting for underlying liver disease (data not shown). This likely reflects the increased risk of alcoholic liver disease among females, as observed in the present series<sup>21</sup>. Second

Table 2. Diagnostic performance of vascular spiders for liver histopathology in alcoholics

| Diagnostic outcome   | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Positive likelihood ratio |
|--|-----------------|-----------------|-------------------------------|-------------------------------|---------------------------|
| Alcoholic hepatitis (with or without liver cirrhosis)            | 25 (17-35)      | 92 (85-96)      | 72 (54-85)                    | 59 (52-66)                    | 3.1 (1.6-6.2)             |
| Liver cirrhosis (with or without alcoholic hepatitis)            | 38 (24-53)      | 90 (84-93)      | 47 (31-64)                    | 85 (79-90)                    | 3.6 (2.1-6.4)             |
| Severe liver injury (alcoholic hepatitis and/or liver cirrhosis) | 25 (18-34)      | 96 (90-99)      | 89 (73-96)                    | 52 (44-59)                    | 6.6 (2.4-18.2)            |

Percentages were approximated to the nearest whole number. 95% confidence intervals are represented within parenthesis.

and most important, our study included a significant number of patients with alcoholic hepatitis (35%) in contrast to the study of Hamberg et al.<sup>17</sup>, which included only 10 patients (3%) with this diagnosis. In our cohort, an additional 10% of patients had alcoholic hepatitis superimposed on cirrhosis. This probably derives from the mode of selection, which included many patients with severe dependence and alcohol withdrawal syndrome, which is linked to alcoholic hepatitis<sup>21</sup>. The large number of patients with alcoholic hepatitis allowed for the independent analysis of its relationship with spiders. According to our results, alcoholic hepatitis *per se* is associated with spiders, and alcoholic hepatitis superimposed on liver cirrhosis represents the group with the highest prevalence of spiders. Thus, the presence of spiders in an alcoholic patient not only indicates underlying liver cirrhosis, but may also indicate the presence of alcoholic hepatitis. According to evidence-based medicine<sup>26</sup>, and considering alcoholic hepatitis and liver cirrhosis altogether, these results indicate that the presence of spiders may be a good indicator of severe underlying liver disease in the alcoholic patient.

The study has some limitations. The diagnostic accuracy of a given test can only be evaluated with a specific reference to the population in question. Particularly, predictive values are very dependent on the prevalence of the outcome considered. In addition, the sensitivity of a test is often higher in studies with a higher proportion of patients with more advanced stages of the disease<sup>27</sup>. Along this line, it should be noted that the study population consisted of in-hospital patients with a long history of heavy alcohol intake and without a history or evidence of overt liver disease. Unfortunately, neither the total number nor the size of spiders was recorded in this study, precluding more in-depth analyses of their association with liver disease. Finally, it should be noted that hepatitis C virus antibodies were not systematically determined in the studied patients, although their prevalence in alcoholics from our area is very low<sup>28</sup>.

Outward and visible signs of internal disease have been fundamental to the art and science of medicine from ancient times<sup>2,3</sup>. Liver biopsy, the gold standard for the diagnosis of liver disease in alcoholism, is an invasive procedure. Updating and enhancing the literature on bedside diagnosis by systematic analysis of their accuracy may aid the physicians in clarifying the role of these signs in current practice and preventing patients from unwarranted testing<sup>2</sup>. Our data suggest that, in clinical practice, the presence of >3 spiders in heavy drinkers admitted to the hospital is indicative of severe underlying liver disease (alcoholic hepatitis and/or cirrhosis).

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