Guidelines for the diagnosis of uncomplicated cirrhosis

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Introduction

Several reasons underlie these guidelines on the diagnosis of uncomplicated cirrhosis. First, until now, only one diagnostic method – liver biopsy – has been available. However, new non-invasive methods have been introduced recently. Secondly, there is a need to improve screening for cirrhosis and prevention.

Cirrhosis is defined as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules [1]. If treatment is properly carried out and timely, uncomplicated cirrhosis can become stable and even regress.

These guidelines concern uncomplicated cirrhosis only, i.e. the stage of the disease when patients have few or no symptoms. Complicated cirrhosis, which is not covered by these guidelines, is characterised by the onset of decompensation (peripheral oedema, ascites jaundice, encephalopathy), gastro-intestinal bleeding or hepatocellular carcinoma.

The present guidelines are intended for all health professionals involved in the diagnosis of cirrhosis, in particular general practitioners, specialists in gastrointestinal diseases, infectious diseases, addiction medicine, or internal medicine, paediatricians, biologists, pathologists and radiologists. The guidelines are based on a critical appraisal of published studies that have been selected using precise methodological criteria. They were graded from A to C as shown in table I [2]. However, most of the present guidelines are based on agreement among the professionals of a 17-member multidisciplinary working group.

A 5-step diagnostic procedure

The aims of the diagnosis of uncomplicated cirrhosis are to determine the cause of the disease, identify comorbidities, and draw up a monitoring plan for the detection and/or prevention of complications [3].

The first step of the procedure is to look for circumstances that may be the cause of cirrhosis and for abnormalities that may be associated with cirrhosis (table II).

In the second step, i.e. if cirrhosis is suspected, the primary care doctor should order the tests listed in table III and, depending upon the results, decide whether to refer the patient to a specialist.

The third step is the visit to the specialist. In a small number of cases, when the clinical and biological observations (or any available imaging or endoscopic data) agree with the epidemiological arguments, the specialist can make a firm diagnosis that does not require confirmation by a liver biopsy or by a non-invasive method (professional agreement).

However, if a firm diagnosis cannot be made, as is the case for most patients, a liver biopsy or a non-invasive test has to be carried out. The procedure followed depends on the cause of the cirrhosis and is established with the patient’s agreement.

The fourth step is confirmation of the diagnosis. Two situations may arise depending upon whether the patient has chronic hepatitis C or not: (i) For chronic untreated hepatitis C patients with no comorbidities, three validated diagnostic tests for cirrhosis are available: liver biopsy, Fibrotest® and transient elastography (FibroScan®). The recommended first-line test is a non-invasive procedure (either Fibrotest® or FibroScan®). The second-line test is either the non-invasive procedure that was not used and/or liver biopsy. Monitoring of hepatic lesions by repeat non-invasive testing has not yet been validated owing to lack of data. (ii) For patients who do not have chronic untreated hepatitis C with no comorbidities, the use of the non-invasive tests has not yet been validated. In this case, liver biopsy is the only available diagnostic method. However, in view of the number of studies currently being carried out on non-invasive methods, an early reassessment is called for (within one year from the publication of these guidelines).

The fifth step is establishing whether the results obtained by the chosen diagnostic method(s) are in line with the epidemiological, clinical, biological and morphological (imaging or endoscopy) findings. If not, a second diagnostic test should be performed. If, even in this case, the results do not point to a firm diagnosis of cirrhosis, it will be necessary to consult a hepatologist working in a reference centre.

Establishing the cause and severity of the disease

Establishing the cause of the disease

The diagnostic work-up should attempt to establish the cause of the cirrhosis and identify comorbidities. Because many causes and comorbidities often co-exist, it is necessary to go back to the initial circumstances of the diagnosis. The work-up should therefore include the items given in table IV. If the results are negative, the patient should be referred to a reference centre in order to detect a less common cause, such as for instance auto-immune liver disease, Wilson’s disease, an alpha-1-antitrypsin deficiency, or the Budd-Chiari syndrome.

In this case, a liver biopsy is included in the work-up. Its result
Table I. – Grading of guidelines.
Gradation des recommandations.

<table>
<thead>
<tr>
<th>Level of published scientific evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
</tr>
<tr>
<td>Randomised controlled trials of high power</td>
<td>A: Established scientific evidence</td>
</tr>
<tr>
<td>Meta-analyses of randomised controlled trials</td>
<td></td>
</tr>
<tr>
<td>Decision analyses based on properly conducted studies</td>
<td></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>B: Presumption of scientific foundation</td>
</tr>
<tr>
<td>Randomised controlled trials of low power</td>
<td></td>
</tr>
<tr>
<td>Properly conducted non-randomised controlled trials</td>
<td></td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>C: Low level of evidence</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td></td>
</tr>
<tr>
<td>Comparative studies with major bias</td>
<td></td>
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<tr>
<td>Retrospective studies</td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td></td>
</tr>
</tbody>
</table>

Table II. – The causes of cirrhosis to look for and the types of abnormalities found.
Les causes de cirrhose à rechercher et les différentes anomalies observées.

Causes of chronic liver disease that should lead to suspecting cirrhosis

- Excessive alcohol consumption
- Chronic hepatitis C virus (HCV) infection
- Metabolic syndrome
- Chronic hepatitis B virus (HBV) infection
- Genetic haemochromatosis
- Autoimmune diseases (particularly primary biliary cirrhosis)

Types of abnormalities suggesting cirrhosis
(detected fortuitously or in cases of chronic liver disease)

- Clinical (hard liver, spider angioma, splenomegaly)
- Biological (thrombopenia, reduction in prothrombin time)
- Endoscopic (oesophageal varices)
- Imaging (irregular liver surface, liver atrophy or hypertrophy, signs of portal hypertension)

Table III. – Biological tests to be performed before referral to a specialist.
Tests biologiques à demander avant la consultation chez le spécialiste.

<table>
<thead>
<tr>
<th>Serum tests</th>
<th>Changes and thresholds (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemogram</td>
<td>Thrombopenia, leuco-neutropenia, macrocytosis</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>Elevated</td>
</tr>
<tr>
<td>Alanine-aminotransferase (AAT)</td>
<td></td>
</tr>
<tr>
<td>Aspartate-aminotransferase (ASAT)</td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (γGT)</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (AP)</td>
<td></td>
</tr>
<tr>
<td>Protein electrophoresis</td>
<td>β−γ bridging</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>Low albumin</td>
</tr>
<tr>
<td>Glucose</td>
<td>Decreased</td>
</tr>
<tr>
<td>Triglycerides and Cholesterol (d)</td>
<td>Elevated</td>
</tr>
<tr>
<td>Ferritin (d)</td>
<td>Abnormal values</td>
</tr>
<tr>
<td>Transferrin saturation coefficient (d)</td>
<td>&gt;300 µg/L [men]; &gt;200 µg/L [women]</td>
</tr>
<tr>
<td>HBs antigen - anti-HBs</td>
<td>Positive</td>
</tr>
<tr>
<td>- anti-HBc</td>
<td>Negative</td>
</tr>
<tr>
<td>- anti-HCV</td>
<td>Positive</td>
</tr>
</tbody>
</table>

(d) Even though threshold values are available (see laboratory thresholds), the number and type of criteria that establish a diagnosis of uncomplicated cirrhosis cannot be determined precisely because published data are incomplete and conflicting. A global approach must be used. Source: AFSSAPS 2005 guidelines: “Prise en charge thérapeutique du patient dyslipidémique”; http://agmed.sante.gouv.fr/html/5/rbp/indrbp.htm; Source: HAS 2005 guidelines: “Prise en charge de l’hémochromatose liée au gène HFE” http://www.has-sante.fr/portail/display.jsp?id=c_432802.
can determine treatment (identification and treatment of the cause of cirrhosis, tackling comorbidities).

**Establishing the severity of the disease**

To assess the severity of the disease and plan future surveillance, all patients with cirrhosis should undergo, at the very least, the panel of tests given in table V. This is in addition to the tests that have been performed before referral to a specialist (table III). The purpose of oesophageal, gastric and duodenal endoscopy is to look for signs of portal hypertension (particularly oesophageal varices) in order to institute preventive treatment against gastro-intestinal bleeding. Abdominal Doppler ultrasound is to look for liver and portal abnormalities, in particular hepatocellular carcinoma. This being a key exam in future disease surveillance, it should be performed with the utmost care by an operator trained in liver imaging and informed of the reason for the examination. The operator’s report should include the items in table VI.

The severity of cirrhosis is usually rated using the Child-Pugh score (table VII) [4] which, however, does not account for complications such as gastro-intestinal bleeding and hepatocellular carcinoma. The higher the score, the more severe the disease (class A: 5-6 points; class B: 7-9 points; class C: 10-15 points). Most patients with compensated cirrhosis are in class A. Decompensated cirrhosis corresponds to classes B or C.

The visit to the specialist should also be a time to complete the diagnostic work-up and its interpretation, to discuss specific (e.g. antiviral) treatment, to manage any comorbidities (in particular alcohol abuse), and to initiate surveillance [3]. This is also the appropriate time to set up measures to...
Advantages and drawbacks of available diagnostic methods

The diagnostic methods provide likelihood ratios for cirrhosis. It is therefore necessary to explain to the patient how the results have been interpreted.

Liver biopsy

Liver biopsy is currently considered to be the gold standard diagnostic method since the definition of cirrhosis is based on histological criteria. However, the findings are not always easy to interpret; they depend mostly on the length of the biopsy specimen. Together with blood tests (viral, immunologic and biochemical), liver biopsy helps establish the cause of the cirrhosis and to look for comorbidities.

The strong points of liver biopsy are: (i) a low false positive rate (overestimated fibrosis due to biopsy of subcapsular liver tissue), (ii) few cases when the test cannot be performed by either the percutaneous or transjugular route. Its major drawbacks are: (i) false negative results due to sampling errors (a biopsy specimen that is fragmented or too small), (ii) substantial inter-observer and intra-observer variations, (iii) constraints such as the need for a stay in hospital, precautions to be taken before carrying out the biopsy, and cost, (iv) complications (in particular bleeding) that can put off patients and non-specialist practitioners.

Fibrotest®

The Fibrotest® combines the variables age and gender with 5 biomarkers (alpha2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma-glutamy transferase), three of which (alpha2-macroglobulin, haptoglobin, apolipoprotein A1) are not routine markers in the management of liver disease. All the studies conducted so far have shown similar diagnostic performance. Reproducibility is satisfactory provided that the manufacturer’s recommendations are followed. A likelihood ratio of 0.75 or above is strongly indicative of cirrhosis but this threshold needs to be confirmed. Currently, the test has been validated for untreated chronic hepatitis C only. Two points are important (grade B): (i) the laboratory performing the test must use the appropriate assay technique and ensure proper quality control (e.g. with regard to sample storage), (ii) the person who prescribed the test must consider confounding factors when interpreting test results. Patients should have no intercurrent illness, in particular acute inflammation, haemolysis, or Gilbert’s syndrome and should be taking no medications causing elevated bilirubin levels.

Transient elastography (FibroScan®)

Transient elastography (FibroScan®) is an ultrasound technique that measures the speed of propagation of a shear wave in the liver and enables the estimation of an elasticity coefficient (“liver stiffness”). It has yielded consistent results for the diagnosis of cirrhosis in patients with chronic hepatitis C in the studies carried out so far. The technique is reproducible but the equipment is not always accessible. The technique has been validated in patients with chronic untreated hepatitis C but the conditions of use have to be complied and results have to be correctly interpreted (grade B). The threshold value in adults that is strongly indicative of cirrhosis is > 13-15 kPa according to published studies, but this needs to be confirmed. The main drawbacks are: (i) the equipment has been installed in only a few centres in France, (ii) it does not provide a reliable result in obese patients or in patients, such as children, with a narrow intercostal space.

Unselected — or not yet validated — tests and scores to confirm a diagnosis of cirrhosis

Routine blood tests in the management of liver disease

The following blood tests — aspartate and alanine transaminases, prothrombin time, and platelet count — are routine tests in the management of liver disease and are included in the recommended initial work-up (table III). However, they are not reliable enough to be used on their own to diagnose cirrhosis. Diagnostic performance is poor and precise threshold values have not been established. They cannot be recommended even when combined amongst themselves or with other simple clinical tests.

Non-routine blood tests and scores

Other routinely measured serum markers (alpha2-macroglobulin, apolipoprotein A1, haptoglobin, and hyaluronic acid) are not included in the work-up for the management of liver disease. The diagnostic performance of hyaluronic acid alone or of a composite score based on these markers is not good enough to diagnose cirrhosis. The inclusion of other hepatic markers has not solved the problems of inter-laboratory variations and interpretation errors due, for the most part, to disorders unrelated to liver disease. Even so, it is recommended that the measurement of all these markers be standardised (in particular, of the transaminases, gamma-glutamy transferase, proteins [albumin, alpha2-macroglobulin, apolipoprotein A1, haptoglobin] and hyaluronic acid) in order to improve inter-laboratory consistency and to allow implementation of common thresholds.

The composite score that has been validated is the Fibrotest®. Other scores are being developed (e.g. FibroMetre® and Hepascore®). Their diagnostic performance is highly satisfactory but too few studies (one for FibroMetre®, two for Hepascore®) have been performed on the diagnosis of cirrhosis to recommend routine use in this indication. Further studies are needed on the interpretation of findings, conditions of use, and choice of threshold.

Table VII. – Child-Pugh score [4].

<table>
<thead>
<tr>
<th>score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Grade I-II</td>
<td>Grade III-IV</td>
</tr>
<tr>
<td>Ascite</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (total) [µmol/L]</td>
<td>&lt;35</td>
<td>35-50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>&gt;50</td>
<td>40-50</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

The higher the score, the more severe the disease (class A: 5-6 points; class B: 7-9 points; class C: 10-15 points).
Other blood tests and liver function tests

The assay of extracellular matrix proteins and the use of composite scores based on these assays (e.g. European Liver Fibrosis (ELF) score, Fibrospect II®), as well as the use of liver function tests, have not been fully validated in the diagnosis of cirrhosis. Further studies are needed.

Imaging techniques

Although the diagnostic performance of imaging techniques (mainly Doppler ultrasound) is good, these techniques contribute relatively little to the diagnostic strategy because they require a trained operator. Nevertheless, they are part of the diagnostic work-up and of surveillance (table V).

Diagnosis of cirrhosis in children

Cirrhosis is rare in children and presents specific features with regard to cause and disease progression. Most non-invasive methods have not been studied or validated in children. The patient should be referred to a paediatric hepatologist who will adapt the diagnostic strategy and work-ups as appropriate.

Cost comparisons

A health economics assessment covering both costs and outcomes was not feasible owing to lack of data. Instead, the cost of the methods for measuring hepatic fibrosis and the economic impact of their use were analysed, using published data and the tariffs currently used for the procedures in France. The cost of liver biopsy depends on the method used to calculate costs and on whose point of view is taken. According to the French National Health Insurance tariffs, the cost of the procedure (sampling and analysis) ranges from 11 to 182 euros. The total cost of the test (preoperative work-up and hospital stay) is 439 to 579 euros. The cost of the Fibrotest® is 97 euros of which 50-58 euros account for use of equipment funding and use. Because of the high purchase and maintenance costs, the cost of the procedure probably depends heavily on patient throughput. Procedure costs cannot be compared directly because the contribution of the procedures to the diagnostic strategy differs, particularly in relation to the cause of the liver disease. The economic impact of non-invasive methods of measuring hepatic fibrosis cannot be evaluated on the basis of available data, as both the costs generated by the techniques and the costs saved have to be taken into account.

The working group recommended that (i) the real cost of methods for diagnosing cirrhosis, and especially of the FibroScan® technique, be assessed, (ii) a study comparing the costs and outcomes of the non-invasive methods for measuring liver fibrosis be performed. This should take into account the contribution of each method to the diagnostic strategy. However, such a comparison requires that further studies be conducted.

Updating of the guidelines

These guidelines should be updated in one year time on account of the work currently being carried out on: (i) the development of new composite scores, (ii) the performance of non-invasive tests in cases of cirrhosis that are due to causes other than chronic hepatitis C (i.e. chronic hepatitis B, co-infection with HIV, alcohol abuse, metabolic syndrome). This performance concerns both the diagnosis of cirrhosis and patient surveillance. Clinical and economic data in these areas will be provided by ongoing studies supported by the French Hospitals Directorate (STIC protocol using FibroScan®) and by the French National Agency for Research on Aids and Hepatitis (ANRS) (the Fibrostar study and the viral cirrhosis (CirVir) cohort study).

REFERENCES