THERAPEUTIC SUGGESTIONS IN OCCULT CHRONIC HYPERTRANSAMINASEMIA

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Abstract. Less than 25% of asymptomatic adults have elevated levels of transaminases on a first evaluation, one third of these patients have normal values on a retest. From those who have elevated ALT on retest, some prove to suffer from an acute liver disease (with normal ALT in less than 6 months), and the others represent the category of chronic (more than 6 months) elevation of transaminases. The etiology of chronic hypertransaminasemia can be elucidated in 90% of the cases, due to liver disease with occult/atypical evolution, or extra-hepatic causes of chronic elevation of transaminases. The 10% left represent the category of unexplained (obscure cause) elevation of transaminases. The occult/atypical evolution liver diseases are represented by chronic viral hepatitis (HBV, HCV), alcohol consumption, non-alcoholic steatohepatitis (NASH), congestion liver, drugs and liver toxic substances, autoimmune hepatitis, Wilson’s disease, α1 antitrypsin deficiency, parasitic diseases. The extra-hepatic causes that can determinate chronic elevations of transaminases are haemolysis, soft muscle diseases (polymyositis), occult celiac sprue, suprarenal insufficiency, thyroid pathology. There still remains 10% of the patients in which the etiology can not be explained. Usually these patients are kept under surveillance, periodic reevaluation, and undergo a second liver biopsy; which may reveal nonspecific lesions, NASH, chronic hepatitis, cirrhosis. There are cases in which on the surveillance period it was observed a spontaneous normalization of transaminases. Chronic hypertransaminasemia is quite frequent, and has a high addressability to the physician from patients with this type of pathology, being for most of them a discovery by chance on a routine blood check. It is also important to have a clear diagnosis to start the specific treatment for those patients who can benefit out of it as soon as possible.

Keywords: liver biopsy, chronic hepatitis, NASH, autoimmune hepatitis, Wilson’s disease, cirrhosis.

Introduction

Chronic hypertransaminasemia is represented by elevated levels of transaminases at least twice their normal value (NV) on at least two determinations for a period ≥6 months. In asymptomatic adults the elevation of transaminases is significant when is >2xNV, less than 2xNV has no big clinical importance for these patients [1], although a certain degree of fibrosis may occur [2].

Less than 25% of asymptomatic adults presented elevated levels of transaminases on a first determination [3]; one third of these had normal values on a retest. From those who have elevated ALT levels on retest, some prove to suffer from an acute liver disease (with normalized ALT in less than 6 months), and the others represent the category of chronic elevated transaminasemia (more than 6 months).

In 90% of the cases the etiology due to occult/atypical evolution liver disease or extra-hepatic causes (table I) can be elucidated, but in 10% of the chronic hypertransaminasemia there is no etiology found [4, 5], so they are called chronic unexplained (of obscure cause) elevation of transaminases. There are several explorations and criteria that need to be negative in order to affirm the chronic unexplained elevation of transaminases (table I).

It is important to have a diagnostic strategy to include the chronic hypertransaminasemia in one of the three categories mentioned bellow that will further lead to a specific treatment for those diseases with clear diagnostic, or just surveillance and reevaluation in case of diagnostic unclear.

In this article we try, based on the diagnostic
strategy, to describe briefly the main hepatic and extra-hepatic diseases that lead to chronic hypertransaminasemia and their treatment. The emphasis is on the most common causes of hypertransaminasemia observed in asymptomatic adults; we do not refer to all causes of hypertransaminasemia.

**Content:** The diagnostic strategy [1, 2, 6, 7] to elucidate chronic hypertransaminasemia of obscure cause involves repeating physical examination, history and extended explorations, including in certain circumstances a second liver biopsy, all these in three steps (figure 1):

1. Finding an occult/atypical liver disease (table II)
2. In case of unclear diagnostic on step I, finding an extra-hepatic disease that may cause elevated levels of transaminases (table II)
3. If both steps I and II failed to reveal the diagnostic, the patients undergo surveillance, re-evaluation and liver biopsy.

There are some explorations that can be done to find usual causes that have an occult or atypical evolution:

- HBV-DNA and HCV-RNA by PCR in blood, hepatocytes, circulating peripheral mononuclear cells
- Auto-antibodies (anti SLA, anti ASPGR, pANCA)
- Carbohydrate deficient transferrin test
- Metabolic syndrome diagnosis, finding insulin-resistance, insulinemia
- Alpha 1 antitrypsin (α1ATT) phenotyping, immunohistochemistry
- Liver biopsy
- Repeated testing for levels of copper in urine and seric ceruloplasmin.
- Also, there can be done explorations to find extr-hepatic causes of hypertransaminasemia:
  - Haemolysis evaluation tests
  - Creatinkinase, aldolase for muscular diseases
  - TSH, T3, T4 for thyroid diseases
  - ACTH test for suprarenal insufficiency
  - Anti-endomisium antibodies, jejune biopsy for celiac sprue

**Occult/atypical evolution liver diseases**

**Occult chronic viral hepatitis**

**Occult HBV infection:** evolves with a low viral load (<10000c/ml) on patients AgHBs negative, but with present HBV-DNA (in blood, liver and peripheral mononuclear cells by PCR). HBV-DNA was detected by PCR in <5% of those with no serological marker of viral infection (seronegative occult HBV infection), in 10% of those declared cured of hepatitis B (Anti HBs positive), and in 25% of those with Anti HBc positive [8] (seropositive occult HBV infection). “Seropositive” subjects are positive for antibodies to hepatitis B core antigen (anti-HBc) and can be further divided into 2 subgroups: with and without anti-HBs. “Seronegative” subjects are negative for both anti-HBc and anti-HBs. The HBV-DNA detection rate is highest in subjects who are anti-HBc positive/anti-HBs negative (probably some of these individuals have low-level HBV infection with subdetectable HBsAg), intermediate in subjects who are positive for both anti-HBc and anti-HBs (individuals may have recovered from previous infection but may have persistent low levels of HBV), and lowest in seronegative subjects (individuals have recovered from previous infection but lost all serologic markers of HBV infection; rarely, they may be infected with HBV mutants that do not express HBV serologic markers) [9]. Occult HBV infection has the risk of transmission, reactivation and developing hepatocellular carcinoma risk. The goals of treatment are to eliminate HBV-DNA and obtain seroconversion from HBeAg to anti-HBe and for this interferon (usually IFN α2b) or lamivudine are used.

**Occult HCV infection:** evolves with negative anti-HCV and RNA-HCV undetectable in blood, but RNA-HCV detectable in liver and peripheral mononuclear cells by PCR [7]. Occult HCV infection must be differentiated from inactive carriers of HCV in which anti-HCV are positive, RNA-HCV is undetectable in blood, but is detectable in hepatocytes and peripheral mononuclear cells, ALT level is normal. Permanently elimination of HCV-RNA with normalization of transaminases and cessation of histologic progression are the aims of treatment obtained by combination therapy with pegylated interferon α plus ribavirin.

**Alcohol consumption**

Although is denied by patients, it is possible that a moderate alcohol consumption (<50g/24h) could generate alcoholic liver disease. ALT usually

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**Table I.** Explorations and criteria that affirm the chronic unexplained elevation of transaminases

<table>
<thead>
<tr>
<th>No alcohol consumption</th>
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<tbody>
<tr>
<td>No drugs or liver-toxic substances</td>
</tr>
<tr>
<td>AgHBs negative, Anti VHC negative</td>
</tr>
<tr>
<td>BMI, glycemia, HDL cholesterol in normal limits</td>
</tr>
<tr>
<td>Auto antibodies (ANA, ASMA, LKM1) negative</td>
</tr>
<tr>
<td>Alpha 1 antitrypsin, copper levels in urine/blood, seric ceruloplasmin in normal limits</td>
</tr>
<tr>
<td>Normal levels of seric iron, ferritin, total binding iron capacity, transferrin saturation coefficient</td>
</tr>
<tr>
<td>Normal electrophoresis</td>
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<td>Normal hepato-biliary ultrasound</td>
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</tbody>
</table>

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Chronic hypertransaminasemia
is >5xNV, and AST >8xNV. Arguments for alcoholic liver disease are AST/ALT >2, γGT >2xNV (especially associated with AST/ALT >2). There can still be some diagnostic issues; AST/ALT >1 can be found in haemolysis and muscular diseases. ALT elevation should disappear within weeks of abstinence (mainstay of treatment), if it was due to alcohol.

**Non-alcoholic steatohepatitis (NASH)**
Elevated levels of transaminases ≤3xNV are usually the only abnormality of NASH. ALT>AST without cirrhosis pleads for NASH, while AST/ALT >2 pleads for alcoholic cause. The diagnostic is suggested by elevated transaminases in the presence of a hepatomegaly that can be painful, with fatty liver ultrasound or CT on a subject with obesity associated with diabetes and/or metabolic syndrome. These elements should summarize on a patient with negative viral and autoimmune markers, with no history of alcohol consumption or drug-induced hepatitis [10, 11, 12, 13]. Liver biopsy can not always

**Table 2. Etiology of chronic hypertransaminasemia**

<table>
<thead>
<tr>
<th>Occult/atypical evolution liver diseases</th>
<th>Extra-hepatic causes</th>
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<tbody>
<tr>
<td>Chronic viral hepatitis (VHB, VHC) with negative viral marker</td>
<td>Haemolysis</td>
</tr>
<tr>
<td>Alcoholic liver disease and NASH</td>
<td>Soft muscle diseases (polymyositis)</td>
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<tr>
<td>Autoimmune hepatitis ANA, ASMA, LKM1 negative</td>
<td>Occult celiac sprue</td>
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<tr>
<td>Vascular congestion of the liver</td>
<td>Suprarenal insufficiency</td>
</tr>
<tr>
<td>Drugs and liver-toxic substances</td>
<td>Thyroid pathology</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Anorexia/Bulimia</td>
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<tr>
<td>Alpha 1 antitrypsin deficiency</td>
<td>Elevated transaminasemia in healthy people</td>
</tr>
<tr>
<td>Parasitic diseases</td>
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</table>

**Figure 1. Diagnostic strategy for chronic hypertransaminasemia**
differentiate pure steatosis from steatohepatitis, and sometimes it can not evaluate the stage of fibrosis [11, 13]. Liver biopsy should be indicated if one or more of the predictive factors for fibrosis are present: age >50 years, BMI >28Kg/m², diabetes mellitus type 2, ALT >2xNV, AST/ALT >1 [6, 12, 14]. Therapy consists in elimination of potential risk factors and causes such as dyslipidemia, heavy weight, hyperglycemia, drugs or toxins.

Vascular congestion of the liver

It consists in elevated transaminases 2-4xNV with a higher elevation of AST (myocardial source) and a decrease in approximate 7 days from the onset of congestive heart failure treatment. Usually clinical findings of cardiac disease, echocardiography and clinical signs of congestion liver lead to diagnostic. Treating the underlying disease leads to improvement of liver function.

Drug-induced hepatitis

Most of liver diseases due to drugs are acute, only 5% are chronic [15]. The amount of hepatic injury can be drug- and dose- dependent or can be idiosyncratic. Examples of drugs that commonly cause hepatitis include acetaminophen, rifampin, isoniazid, oral contraceptives, aspirin and methyldopa. If drug-induced hepatitis is suspected, the therapy consists in drug withdrawal, with further evaluation if liver function abnormalities persist despite drug withdrawal. Diagnosis can be difficult, even with liver biopsy, because drug-induced liver injury is usually not associated with a specific histopathology. Nevertheless, liver biopsy may provide information that may rule out a drug as a cause of liver injury.

Autoimmune hepatitis

Can evolve without classical auto antibodies (ANA, ASMA, LKM1), or with insignificant titers of them. Arguments for this diagnostic are: young woman, association with other autoimmune diseases (on the patient or her relatives), therapeutic test with prednisone, liver biopsy with dominant plasmocites, absence of viral markers (by PCR), presence of other antibodies (SLA, pANCA), and histocompatibility antigens (DR3, DR4). In case of negative results on all this tests, the disease will be included in the category of cryptogenic hepatitis/ cirrhosis. Survival is prolonged by corticosteroids with or without azathioprine.

Wilson’s disease

It can generate moderate elevation of transaminases in absence of any other manifestation. The decrease of circulating ceruloplasmine is present in 90% of the cases, but can be absent in 10%, the Kayser-Fleisher rings are absent in 50-70% of the cases, the urine level of copper can be normal on a single evaluation, and the neurological manifestations can be absent. There are patients in whom all this criteria are negative (9%) [16], in these patients, ceruloplasmine levels and urine copper levels will be periodic evaluated. Liver biopsy can appreciate liver copper, values >250μg/g dry hepatic tissue are diagnostic. Chelating drugs, especially penicillamine are lifelong treatment and zinc acetate is used in patients who can not tolerate penicillamine.

Alpha 1 antitrypsin deficiency

It can be certified by direct serological evaluations, and by the absence of a peak in the alpha-globulin bands. Sometimes seric α1ATT can be false normal or elevated in the presence of inflammation, or PiMZ heterozygote phenotype, or SZ, or FZ, which evolve with liver disease and α1ATT at a lower normal limit. For diagnostic are necessary immunohistochemistry techniques, isoelectric focalization of circulating α1ATT [17]. There is no curative treatment for this deficiency, just supportive therapy in liver disease.

Parasitic diseases

Malaria, schistosomiasis will be sought in the absence of the previous occult hepatic diseases. Treatment involves antiparasitic drugs.

Extra-hepatic causes of chronic hypertransaminasemia

Occult celiac sprue (gluten enteropathy)

The diagnostic is sustained by the presence of anti-endomisium antibodies (A-EmA), which are IgA with a 100% specificity and 85-90% sensibility for celiac disease, and jejune biopsy. Almost 10% of the chronic hypertransaminasemia in asymptomatic adults are caused by this disease [18]. Strict adherence to a gluten-free diet is the mainstay of therapy in celiac disease.

Haemolysis

Is a source of elevated transaminases, that evolves with an AST/ALT >1. It is evaluated by Coombs test, haptoglobin levels. Patients with severe haemolysis should receive a daily supplement of folic acid.

Soft muscle diseases

Polymyositis, hard effort can generate elevated transaminases with an AST/ALT >1, but it is observed also an elevation of creatinkinase and aldolase levels, same as or higher than the transaminases levels. Treatment consists in anti-inflammatory and immunosuppressive drugs.
Suprarenal insufficiency

May be accompanied by elevated transaminases, the diagnostic involves the ACTH test, and treatment is hydrocortisone.

Other causes

Most frequent are thyroid pathology, anorexia bulimia. Moderate elevations can appear in 2.5% of healthy people (without hepatic lesions or other disease) [6], and they were correlated with lunch, effort, BMI, alcohol, drugs.

If the source of elevated transaminases remains obscure

After steps I and II, liver biopsy will be considered for those whose elevated transaminases have no source and do not decrease in time. Liver biopsy was recommended especially on elevated transaminases >2xNV, and for asymptomatic adults with elevated transaminases <2xNV surveillance and periodic reevaluation is recommended [1]. However, there are studies that show that the degree of fibrosis is equal for both patients with elevated transaminases >2xNV or <2xNV [2].

The actual tendency is to delay liver biopsy and to regroup its indications only for those cases in which it will prove to be indispensable.

A study [4] of biotical fragments in cases of chronic hypertransaminasemia on asymptomatic patients found non-specific lesions (38%), NASH (19%), chronic hepatitis (36%), cirrhosis (7%). In this study as exclusion criteria were respected all the situation mentioned in paragraphs I and II, with DNA-HBV and RNA-HCV detection by PCR, and also the presence of metabolic syndrome was an exclusion criteria.

Conclusions

This article does not refer to all causes of hypertransaminasemia, the focus is on the most frequent diseases indicated by the diagnostic strategy observed in asymptomatic adults.

Chronic hypertransaminasemia has a high addressability to the physician, is quite frequent, being for most patients a discovery by chance on a routine blood check. This makes important the fact of having a diagnostic strategy to establish the underlying causes of chronic hypertransaminasemia that will lead to specific treatment.

The etiology of chronic hypertransaminasemia can be elucidated in 90% of the cases, due to liver disease with occult/atypical evolution or extra-hepatic causes. These patients benefit from appropriate treatment once their diagnostic is clear.

There still remains 10% of the cases in which the etiology cannot be explained. Usually these patients receive no treatment; they are kept under surveillance, periodic reevaluation, and in some cases undergo a second liver biopsy. There are cases in which, during the surveillance period it was observed a spontaneous normalization of transaminases.

There are studies [19, 20] that have shown the efficacy of using Ursodesoxycholic acid (Urso-falk) to improve levels of aminotransferases. One of these studies [19] proposes to use high-dose Ursodesoxycholic acid (28-35mg/Kg/per day) for one year in NASH patients, obtaining improved aminotransferase levels, serum fibrosis markers, with a better control of blood glucose and insulin resistance.

In another study [20], Ursodesoxycholic acid was administrated in dose of 20mg/Kg/per day for three weeks to morbidly obese patients with with suggested fatty liver disease awaiting bariatric surgery. At follow-up 6 months after surgery patients had decreased their BMI by approximately 10 kg/m², which resulted in significant improvements of liver function tests, insulin sensitivity and glucose tolerance.

Complementary to Ursodesoxycholic acid therapy, there are recommended exercise, weight loss, and alcohol consumption prohibition until the appearance of new diagnoses elements that might elucidate the etiology of occult chronic hypertransaminasemia, or until disappearance of hypertransaminasemia.

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