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Management of elevated liver enzymes in primary care

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A 60-year old female visits her family doctor's practice for her annual check-up. Blood tests results are normal except for Aspartate and Alanine Aminotransferases (AST and ALT) (2x Upper Limit of Normal). She is 167cm tall and weighs 83kg. She has no history of Hepatitis B in her family, but she has not received a vaccination against the Hepatitis B Virus (HBV). She also reports no history of intravenous drug use and no family history of autoimmune diseases. She had received a blood transfusion in 1978 during a fracture repair surgery. She claims to consume no more than 3 glasses of wine per week.

This case vignette highlights a common clinical problem that doctors in primary care face. Current practice when managing abnormal liver tests in primary care is variable with physician strategies ranging from ignoring the results, repeating sampling, requesting additional tests or referring to specialist services. Ideally, a physician should recognize whether this elevation is clinically important and which should be the appropriate steps to clarify the etiology of this finding.

The blood tests that are used to assess liver condition include AST and ALT, Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (γGT), bilirubin (conjugated and unconjugated), Prothrombin Time (PT) and/or International Normalized Ratio (INR), serum albumin and platelet count. These tests are generally inexpensive and are commonly used in primary care for various reasons including the exclusion of chronic liver disease, monitoring for potential adverse effects of drugs and investigation of the generally unwell patient. It must be stressed that liver chemistries including ALT, AST, ALP and γGT are markers of liver injury, not liver function, and should be referred to simply as liver tests. Liver synthetic function is reflected by the levels of albumin, bilirubin and prothrombin time which can be also influenced by extrahepatic factors. Elevation of AST and ALT signify hepatocellular injury, whereas elevation of ALP and γGT usually reflect obstruction of the biliary tree.

It is not uncommon that some of these tests produce an abnormal result. Approximately 20% of the liver tests that are performed for the first time in a patient lay outside the reference range [1]. Despite the frequency that these irregularities may occur, they are not to be overlooked. A study in Germany in 1998 by Arndt et al showed that men with elevated AST (>18 IU/L) had a three times higher risk for all-cause mortality compared with men with lower values of AST [2]. Some of the most common mistakes that occur when a patient is managed in primary care include unnecessary repeat of the tests after a short period of time, disregard of the results and unnecessary referral to specialist services. Another common error is the assumption that the magnitude of derangement of a liver test necessarily correlates with prognosis. Due to the fact that, used in isolation, the aforementioned liver blood tests neither have high specificity nor can be used as exclusion tools, it is considered appropriate that these tests are followed by more accurate diagnostic tests. To offer guidance to Primary Care Units physicians on managing abnormal liver tests, both the British Society of Gastroenterology and the American College of Gastroenterology published an upgraded set of guidelines in 2018 and 2017 respectively [3, 4]. Moreover, an artificial intelligence-based algorithm was recently developed in Scotland, possibly stating a new era for the investigation of liver diseases in primary care [5]. Based on irregular values

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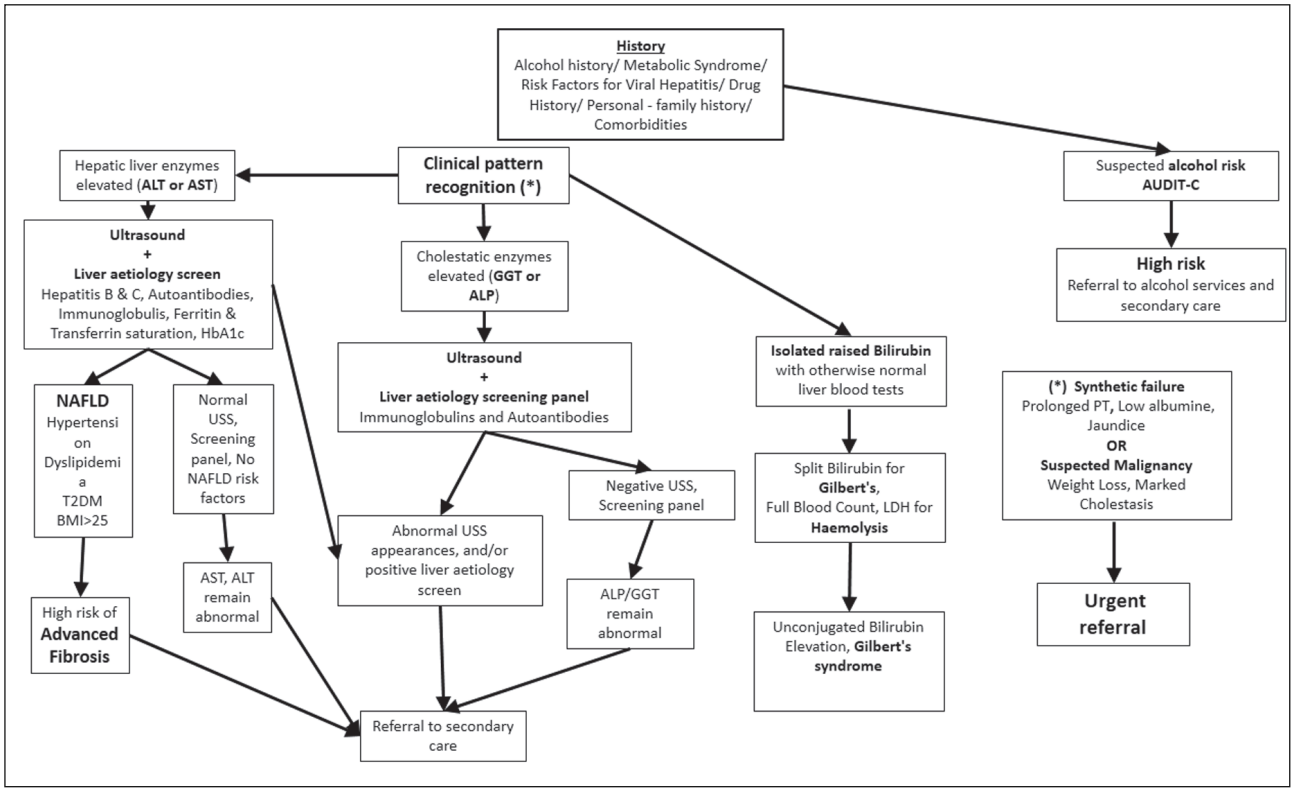

Figure 1. Diagnostic algorithm of liver tests elevation.

in liver blood tests, the algorithm automatically triggers a series of diagnostic blood tests, in order to find the cause of this irregularity. In the end, it proposes a diagnosis, which the physician has the right to accept or dismiss facilitating the whole investigation process.

During the discussion with a patient with abnormal liver blood tests, it is essential that a physician assesses the possibility that these irregularities are related to alcohol consumption. This can be aided with the use of specific questionnaires like AUDIT-C, which consists of 3 simple questions; a) how often does one drink, b) how many units of alcohol does one consume and c) how often does one "binge drink" [6]. Provided that the patient is in high risk for alcohol related liver disease and the liver synthetic function is compromised, the physician should refer him to alcohol services and to a specialist center. Apart from ethanol consumption, it is important to know whether the patient has been exposed to risk factors of contracting a viral hepatitis, such as intravenous drug use or blood transfusion before 1992. Moreover, the patient's history should include a personal and family history of liver and autoimmune diseases. Naturally, it is of paramount importance to reveal any relevant symptoms, comorbidities and concomitant medication including those purchased without medical prescription.

As shown in Figure 1, there are three distinct patterns of liver enzyme elevations. The primary care physician should be in place to correctly categorize the patient and subsequently follow the corresponding follow-up process. At any point, should the physician suspect either liver synthetic failure because of otherwise unexplained jaundice, low albumin and prolonged INR or malignancy because of weight loss or other related symptoms he should refer the patient to a specialist center urgently.

In the event that AST and/or ALT levels are elevated, as in the patient of the case vignette, a liver etiology screening panel and an upper abdomen ultrasonography should be performed. The "screening panel" should include ferritin and transferrin saturation levels, serum immunoglobulin levels, autoantibodies for autoimmune hepatitis and primary biliary cholangitis as well as a screening panel for Hepatitis B and C (HbsAg and anti- HCV with follow-on PCR if positive) and Hemoglobin A1c to test for type 2 diabetes mellitus. In addition, the patient should be evaluated for any component of the metabolic syndrome (arterial hypertension, central obesity and dyslipidemia) as Non-Alcoholic Fatty Liver Disease (NAFLD) is considered

its hepatic component. If any test of the liver etiology screening panel or the ultrasound is "positive" then the patient should be managed accordingly either locally or in a specialist center. In case the liver etiology panel is negative but the ultrasound suggests hepatic steatosis, the patient is in high risk of suffering from NAFLD. In this case, it is recommended that a first-line, non-invasive assessment of liver fibrosis, such as Fibrosis-4 (FIB-4) or NAFLD Fibrosis Score (NFS), is undertaken to identify patients with advanced fibrosis [7,8]. Patients with low FIB-4 (<1.3) or low NFS (<-1.455) can be managed in primary care and should be encouraged to make lifestyle changes in order to lose weight. Patients with intermediate FIB-4 (1.3-3.25) or NFS (-1.455-0.675) should undergo further testing with transient elastography (Fibroscan®) or ARFI elastography. Referral should be considered for patients with Fibroscan values >7.8 kPa along with patients with elevated FIB-4 (>3.25) and NFS (>0.675). Lastly, if all the results come back negative, then the physician should follow the patient and refer him/her to a specialist center for further diagnostic investigation in case of persistently abnormal results.

In case that the cholestatic enzymes (ALP and GGT) are elevated, an upper abdomen ultrasonography and a liver etiology screening panel should be ordered. The "screening panel" should definitely include serum immunoglobulin levels and autoantibodies for autoimmune liver diseases, namely autoimmune Hepatitis (Antinuclear Antibodies [ANA], Antibodies against Smooth Muscle [ASMA] and Liver/Kidney Microsome Antibodies [anti-LKM]) and primary biliary cholangitis (Anti-mitochondrial Antibodies [AMA]). Once there is an abnormal result, a referral should be made to a specialist center for management of the liver disease. If, on the other hand, the results come back negative, the cholestatic liver blood tests should be repeated. If still elevated, a referral should be again made so that further investigation may take place.

Finally, in the scenario that the liver blood tests are normal except for an isolated elevation of bilirubin, the physician should order some additional blood tests. Split bilirubin (unconjugated and conjugated) as well as a full blood count and lactate dehydrogenase (LDH) levels to test for hemolysis should be performed. If the tests for hemolysis are negative, the most probable diagnosis is Gilbert's syndrome which raises the unconjugated branch of bilirubin and is completely benign.

Liver disease's incidence is increasing in contrast to many other conditions, predominantly driven by the increasing prevalence of NAFLD. Elevation of liver tests is a common laboratory finding that is largely associated with liver diseases. Primary care physicians should be able to investigate the etiology of this finding and manage their patients accordingly. In this way, they will contribute substantially to the early diagnosis of liver diseases, thus halting their progression.

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