اپروچ به آقای ۴۴ ساله با اختلال آنزیم های کبدی در درمانگاه پزشکی خانواده

استاد راهنما: دکتر ممیز صنعت، فوق تخصص گوارش و دانشیار گروه داخلی

ارائه دهنده: مهسا معینی، کارورز پزشکی خانواده

CHIEF COMPLAINT

ضعف و خستگی

PRESENT ILLNESS

بیمار آقای ۴۴ ساله با شکایت ضعف و خستگی با تشدید در چند ماه اخیر مراجعه کرده است.

سابقه ای از تب و لرز، Abdominal pain، تهوع استفراغ، زردی، تغییر رنگ ادرار یا مدفوع یا کاهش وزن اخیر را ذکر نمی کند.

سفر اخیر نداشته است.

سابقه تزریق خون یا رفتار پرخطر جنسی اخیر ندارد.

PMH

- PMH:

DH: سابقه مصرف هیچ گونه دارویی اعم از استامینوفن یا داروی گیاهی را ذکر نمی کند

HH: سابقه مصرف روزانه ۱-۲ لیوان نوشیدنی دستساز

- AH:

- FH:

PHYSICAL EXAMINATION

بیمار آقای میانسال، هشیار و ارینته است و به خوبی برای معاینه همکاری می کند.

BP = 13/8, PR = 77, RR = 16, SpO2 = 99%, T = 36.5

BMI = 32, Weight = 98 Kg, Height = 175 cm

Ill یا Toxic نیست.

ملتحمه مختصر Pale است. ایکتریک نیست.

پتشی پورپورا ندارد.

در سمع قلب S1S2 بدون سوفل سمع شد. سمع ریه ها Clear و قرینه.

در معاینه شکم، دیستانسیون ندارد، شکم نرم و بدون گاردینگ یا تندرنس است، هپاتومگالی یا اسپلنومگالی ندارد. آسیت، Caput Medusae یا Spider Nevus ندارد.

در معاینه اندام، ادم ندارد، اریتم پالمار ندارد.

آستریکسی -

LAB DATA

WBC	4.2
RBC	4.64
Hb	13.6
Hct	42.9
MCV	92.5
MCH	29
MCHC	31
PLT	92

FBS	126
Cr	0.9
Chol	143
Tg	104
HDL	43
LDL	79
AST	121
ALT	47

TSH	1.2
Ferritin	122
25-H-vit D	13.6

ABNORMAL LIVER TESTS: OVERVIEW

- Common in asymptomatic patients
- Markers: ALT, AST, ALP, bilirubin, albumin, INR
- Enzymes reflect injury; PT/albumin reflect function
- Patterns: hepatocellular, cholestatic, bilirubin-only
- Goal: define pattern & etiology

INITIAL EVALUATION

- **History taking:** Focus on alcohol (>210 grams/week in men, >140 grams/week in women), meds (prescriptions, OTC, herbal & dietary supplements), toxins (mushrooms, vinyl chloride), viral hepatitis risk factors (parenteral exposure, travel to endemic areas, exposure to patients with jaundice)
- **Comorbidities:** Right-sided CHF (congestive hepatopathy), DM, arthritis, hypogonadism & DCOM (Hemochromatosis), obesity (MALD), IBD (PSC, gallstones), pregnancy (gallstones), emphysema (alpha1 ATD), Celiac, Thyroid disease
- **P/E:** Temporal & proximal muscle wasting (long-lasting), liver disease stigmata (spider nevi, palmar erythema, gynecomastia, caput medusae), ascites, encephalopathy, hepatomegaly, Dupuytren contractures, parotid enlargement & testicular atrophy (alcohol-associated), Virchow node & Sister Mary Joseph nodule (malignancy), right pleural effusion w/o apparent ascites (advanced cirrhosis), neurologic & psychiatric signs (Wilson)

LABORATORY TESTS

Patterns of abnormal liver tests:

- ***Hepatocellular:*** ALT/AST >> ALP ALT more specific for hepatic injury, bili may be elevated, functional tests may be abnormal
- ***Cholestatic:*** ALP >> ALT/AST, bili may be elevated, functional tests may be abnormal
- ***Isolated bilirubin:*** elevated bili with normal enzymes

R-factor helps classify mixed cases: >= 5 hepatocellular, <= 2 cholestatic, 2-5 mixed pattern

$$\text{R-value} = \frac{ALT \div upper\ limit\ of\ nl\ ALT}{ALP \div upper\ limit\ of\ nl\ ALP}$$

LABORATORY TESTS

- **Serum bilirubin** is not helpful in differentiating between the two.
- Common hepatocellular diseases associated with elevated bilirubin and jaundice: viral and toxic hepatitis (including drugs, herbal therapies, and alcohol) and end-stage cirrhosis from any cause
- If both the serum aminotransferases and alkaline phosphatase are elevated, the liver test abnormalities are characterized by the predominant abnormality.
- **ALT and AST values** less than 8 times the upper limit of normal may be seen in either hepatocellular or cholestatic liver disease; values 25 times the upper limit of normal or higher are seen primarily in hepatocellular diseases.
- Abnormal tests of synthetic function may be seen with both hepatocellular injury and cholestasis.
- A low serum **albumin** level suggests a chronic process, such as cirrhosis or cancer, while a normal albumin suggests a more acute process, such as viral hepatitis or choledocholithiasis.
- A **prolonged prothrombin time** indicates either vitamin K deficiency due to intestinal malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to correct with parenteral administration of vitamin K suggests severe hepatocellular injury.

AST TO ALT RATIO & MAGNITUDE

- AST:ALT ≥2 → alcohol-associated disease (*particularly when GGT is elevated, AST <8× ULN, ALT <5× ULN), MALD (AST & ALT <4× ULN)
- >25× ULN → *acute* viral hepatitis, toxic-related hepatitis with jaundice
- >50× ULN → ischemic hepatitis *LDH often markedly high
- *Chronic* hep C infection → Nl to <2× ULN, rarely >10× ULN
- *Chronic* hep B infection → Nl in inactive carriers, patients with chronic infection: <2× ULN, exacerbation: >10× ULN

ACUTE LIVER FAILURE

Acute liver failure is characterized by acute hepatocellular injury with liver tests typically more than 10 times the upper limit of normal, hepatic encephalopathy, and a prolonged prothrombin time (international normalized ratio greater than or equal to 1.5).

MARKED ELEVATION WITHOUT LIVER FAILURE

DDXs:

- Acetaminophen toxicity
- Idiosyncratic drug reactions
- Acute viral hepatitis (hepatitis A, B, C, D, E; HSV; VZV; Epstein-Barr virus; CMV), other viral infections
- an acute exacerbation of chronic viral hepatitis (hepatitis B)
- Alcohol-associated hepatitis
- Autoimmune hepatitis
- Wilson's disease
- Ischemic hepatitis
- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome (veno-occlusive disease)
- HELLP syndrome and occasionally acute fatty liver of pregnancy
- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Partial hepatectomy
- Toxin exposure
- Sepsis
- Heat stroke
- Muscle disorders (acquired muscle disorders [eg, polymyositis], seizures, and heavy exercise)

MARKED ELEVATION WITHOUT LIVER FAILURE

Evaluation:

Acetaminophen level, Toxicology screen, Acute viral hepatitis serologies, In some cases: anti-HSV antibodies, anti-VZV antibodies, anti-CMV antibodies, CMV antigen, and, for Epstein-Barr virus, heterophile antibody, Serum pregnancy test in women of childbearing potential who are not already known to be pregnant, Autoimmune markers (antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, IgG) Transabdominal ultrasonography with Doppler imaging to look for evidence of vascular occlusion (eg, Budd-Chiari syndrome)

Additional tests:

Ceruloplasmin level and urinary copper quantitation, Hepatitis D virus antibodies in patients with acute or chronic hepatitis B, Hepatitis E virus antibodies in patients who live in or travel to areas endemic for hepatitis E, or in patients who are pregnant, Urinalysis to look for proteinuria in women who are pregnant. Serum creatine kinase or aldolase in patients with risk factors for or symptoms of muscle disorders.

If the above testing is negative, we typically proceed with a liver biopsy if the acute elevation of the serum aminotransferases fails to resolve or decline, or if the patient appears to be developing acute liver failure. If the elevation is less than five times the upper limit of normal and the patient appears well, we may follow the patient expectantly, checking liver tests every three to six months.

MILD TO MODERATE ELEVATION WITHOUT LIVER FAILURE

Differential diagnosis of mildly and moderately elevated serum aminotransferases (<15 times upper limit of normal)

Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	**AST predominant (AST/ALT ≥1)**	
Drug-induced liver injury	Alcohol-associated hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency		Celiac disease
Congestive hepatopathy		Macro-AST
Malignant infiltration of the liver		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease.

MILD TO MODERATE ELEVATION WITHOUT LIVER FAILURE

Evaluation:

Hepatitis B – HBsAg, anti-HBs, anti-HBc, Hepatitis C – Anti-HCV, Hemochromatosis – Serum iron and total iron binding capacity (TIBC), MALD – The initial evaluation is radiologic imaging, usually ultrasonography, or CT or MRI.

In a patient with a history of significant alcohol consumption, we do not obtain additional testing if the tests for viral hepatitis and hemochromatosis are negative.

For patients with liver test elevations less than five times the upper limit of normal, we typically recheck the liver tests in three to six months and only pursue the above workup if they remain elevated.

If risk factors for metabolic dysfunction-associated steatotic liver disease are present, their treatment should be optimized.

Additional tests:

Autoimmune hepatitis – Antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies, IgG, Wilson disease – Serum ceruloplasmin, evaluation for Kaiser-Fleisher rings, Alpha-1 antitrypsin deficiency – Serum alpha-1 antitrypsin level, Thyroid disorders – Thyroid-stimulating hormone, free T4 concentration, free T3 concentration, Celiac disease – Antibody screening with serum tissue transglutaminase antibodies

Source still unclear:

Adrenal insufficiency – 8 AM serum cortisol and plasma corticotropin (ACTH), and a high-dose ACTH stimulation test, Muscle disorders – Creatine kinase or aldolase

A liver biopsy is often considered in patients in whom all of the above testing has been unrevealing

Evaluation of isolated mild chronic elevation of serum aminotransferases*

Step 1: Initial evaluation
Review possible links to medications, herbal therapies, or recreational drugs
Screen for alcohol abuse (history, screening instruments, AST/ALT ratio >2:1)
Obtain serology for hepatitis B and C (HBsAg, anti-HBs, anti-HBc, anti-HCV)
Screen for hemochromatosis (Fe/TIBC >45%)
Evaluate for fatty liver (AST/ALT usually <1, obtain RUQ ultrasonography)
Step 2: Second-line evaluation (if initial evaluation is unrevealing)
Consider autoimmune hepatitis, particularly in women and in those with a history of other autoimmune disorders (check serum protein electrophoresis; obtain ANA and ASMA if positive)
Obtain thyroid function tests (TSH if hypothyroidism is suspected; otherwise, obtain serum TSH, free T4, and T3 concentrations)
Consider celiac disease (especially in patients with a history of diarrhea or unexplained iron deficiency: serum IgA anti-tissue transglutaminase antibodies)
Step 3: Evaluation for uncommon causes (if second-line evaluation is unrevealing)
Consider Wilson disease, especially in those <40 years of age (check serum ceruloplasmin, evaluate for Kayser-Fleischer rings)
Consider alpha-1 antitrypsin deficiency, especially in patients with a history of emphysema out of proportion to their age or smoking history (obtain alpha-1 antitrypsin level)
Consider adrenal insufficiency (8 am serum cortisol and plasma ACTH, high-dose ACTH stimulation test)
Exclude muscle disorders (obtain creatine kinase or aldolase)
Step 4: Obtain a liver biopsy or observe (if no source identified after steps 1 to 3)
Observe if ALT and AST are less than twofold elevated
Otherwise, consider a liver biopsy

ELEVATED ALKALINE PHOSPHATASE

1. **Confirm hepatic source** via GGT/5’ NT *Nl GGT → evaluation for bone disorders

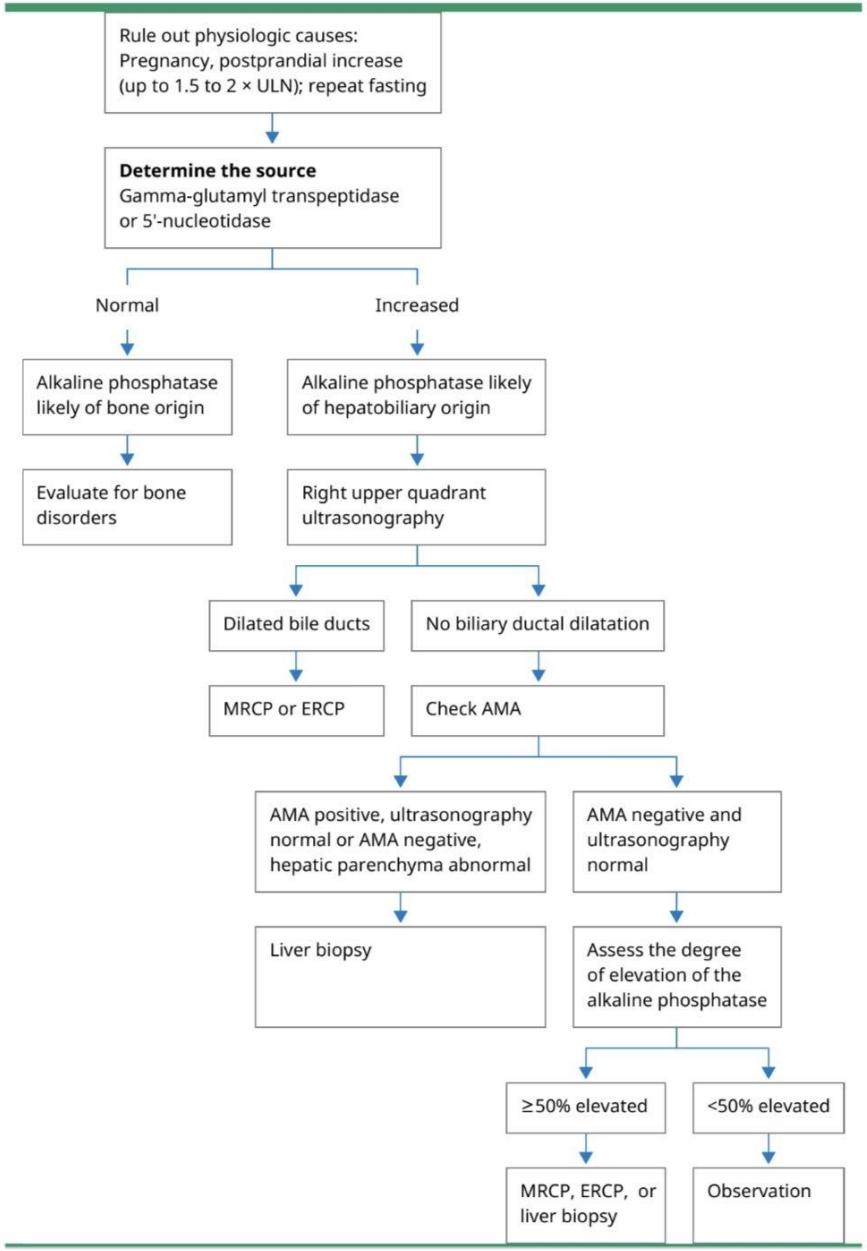
2. **RUQ U/S**: dilation (extrahepatic) vs no dilation (intrahepatic)

- Extrahepatic cholestasis → MRCP/ERCP for obstruction
- Intrahepatic cholestasis→ PBC/PSC/infiltrative causes/AMA/ANA/SMA

Causes of an elevated alkaline phosphatase

Marked elevation (≥4 times the upper limit of normal)*	**Extrahepatic biliary obstruction¶**
	Choledocholithiasis (most common) ▪ Uncomplicated ▪ Complicated (biliary pancreatitis, acute cholangitis)
	Malignant obstruction ▪ Pancreas ▪ Gallbladder ▪ Ampulla of Vater ▪ Bile duct ▪ Metastasis to perihilar lymph nodes
	Biliary strictures ▪ Primary sclerosing cholangitis with extrahepatic bile duct stricture ▪ Complications after invasive procedures ▪ Chronic pancreatitis with stricturing of distal bile duct ▪ Biliary anastomotic stricture following liver transplantation
	Infections ▪ AIDS cholangiopathy ▪ *Ascaris lumbricoides* ▪ Liver flukes
	Intrahepatic cholestasis
	Drug and toxins associated with cholestasis[Δ]
	Primary biliary cholangitis[Δ]
	Primary sclerosing cholangitis[Δ]
	Intrahepatic cholestasis of pregnancy
	Benign postoperative cholestasis
	Total parenteral nutrition
	Infiltrative diseases[Δ] ▪ Amyloidosis ▪ Lymphoma ▪ Sarcoidosis ▪ Tuberculosis ▪ Hepatic abscess
	Metastatic carcinoma to the liver[Δ]
	Liver allograft rejection
	Other cholangiopathies (eg, IgG4 cholangiopathy, ischemic cholangiopathy, COVID-19)
	Alcohol-associated hepatitis
	Sickle cell disease (hepatic crisis)
	Nonhepatic causes◊
	Transient hyperphosphatemia of infancy and childhood
Moderate elevation (<4 times upper limit normal)	**Hepatic causes**
	Nonspecific, seen with all types of liver disease including: ▪ Hepatitis: viral, chronic, alcoholic ▪ Cirrhosis ▪ Infiltrative diseases of the liver ▪ Hypoperfusion states: sepsis, heart failure
	Nonhepatic causes◊
	Physiologic (children and adolescents)
	Third trimester of pregnancy
	Influx of intestinal alkaline phosphatase after eating a fatty meal (individuals with blood type O or B)
	High bone turnover ▪ Growth ▪ Healing fractures ▪ Osteomalacia ▪ Paget disease of bone ▪ Osteogenic sarcoma, bone metastasis ▪ Hyperparathyroidism ▪ Hyperthyroidism
	Extrahepatic disease ▪ Myeloid metaplasia ▪ Peritonitis ▪ Diabetes mellitus ▪ Subacute thyroiditis ▪ Gastric ulcer (uncomplicated) ▪ Extrahepatic tumors • Osteosarcoma • Lung • Gastric • Head and neck • Renal cell • Ovarian • Uterine • Hodgkin lymphoma

Evaluation of elevated serum alkaline phosphatase



ISOLATED HYPERBILIRUBINEMIA

- **Fractionate bilirubin:** direct vs indirect
- Indirect: hemolysis, Gilbert, meds
- Direct: Dubin-Johnson, Rotor
- Normal enzymes → benign conditions
- Further work-up only if atypical

SUMMARY

1. History & Physical — risk factors, exam clues
2. Identify Pattern — hepatocellular, cholestatic, bilirubin-only
3. First-Line Testing — viral hepatitis, metabolic labs, autoimmune work-up
4. Imaging — ultrasound → MRCP/CT if unclear
5. Advanced Diagnosis — biopsy, specialist referral

سطوح پیشگیری

Primordial prevention
Primary prevention
Secondary prevention
Tertiary prevention
Quaternary prevention

PRIMORDIAL PREVENTION

جلوگیری از ایجاد سبک زندگی ناسالم، رفتارهای پرخطر الکلی، چاقی و عادات غذایی نادرست

آموزش درباره مضرات مصرف الکل

آموزش سبک زندگی سالم و جلوگیری از بی تحرکی

آموزش رژیم غذایی متعادل

آموزش درباره مضرات داروهای گیاهی غیراستاندارد و مصرف بیش از حد استامینوفن

PRIMARY PREVENTION

قطع کامل واردات الکل

ارائه مشاوره توسط مراقبین سلامت جهت تغییر سبک زندگی:

- کاهش وزن ۷–۱۰٪
- ورزش ≤۱۵۰ دقیقه/هفته
- رژیم مدیترانه‌ای

مشاوره تغذیه جهت کنترل چربی خون و اصلاح رژیم غذایی

واکیناسیون هپاتیت ب و هپاتیت آ در مناطق اندمیک و گروه های پرخطر

SECONDARY PREVENTION

قطع کامل مصرف الکل

تشخیص زودهنگام بیماری کبدی: چک دوره ای LFT و سایر آزمایشات روتین

غربالگری دقیق هپاتیت ها

کنترل عوامل خطر: کاهش وزن، رژیم کم‌چرب، کنترل دیابت، کنترل چربی

قطع داروی هپاتوتوکسیک

درمان علت زمینه‌ای مانند دیابت، چاقی

TERTIARY PREVENTION

جلوگیری از عوارض سیروز:

- اندوسکوپی برای شناسایی واریس و شروع بتابلاکر
- اسپیرونولاکتون + فوروزماید برای کاهش آسیت
- آنتی‌بیوتیک پروفیلاکسی برای SBP
- در بیماران high-risk مدیریت آنسفالوپاتی

غربالگری منظم HCC:

- سونوگرافی + AFP هر ۶ ماه

درمان عوارض متابولیک یا عفونت‌ها: واکسن‌های HBV/HAV در افراد مستعد

لیست پیوند کبد در صورت لزوم

درمان سوءتغذیه شدید

QUATERNARY PREVENTION

جلوگیری از تست‌ها و درمان‌های غیرضروری

جلوگیری از تجویز بی رویه استامینوفن یا داروهای گیاهی بدون تایید