



Chronic Hepatitis

Updated: May 4, 2019.

Description. The course of illness resembles chronic viral hepatitis with serum aminotransferase elevations without jaundice and with mild if any symptoms. Serum aminotransferase levels may fluctuate over time and intermittently fall into the normal range.

Latency to Onset. The first onset of aminotransferase elevations may be within weeks or months of starting the medication, but the diagnosis of chronic hepatitis requires that elevations are present for several months or a liver biopsy showing typical features of chronic hepatitis. Sometimes the duration of the elevations is not known, but biochemical and clinical characteristics suggest chronic injury.

Symptoms. Usually minimal if present at all and include nonspecific symptoms of weakness, fatigue, intermittent nausea and abdominal discomfort.

Serum Enzyme Elevations. A hepatocellular pattern of serum enzyme elevations with ALT that persists in being above the ULN, with some values at least 2 times ULN over a period of at least 6 months. Alkaline phosphatase and serum bilirubin may be mildly elevated, but are rarely >2 times ULN. Autoantibodies are common particularly if the injury is severe.

Drugs. Medications that can cause a chronic hepatitis include isoniazid, propylthiouracil, nitrofurantoin, minocycline, fibrates, statins, hydralazine and methyldopa. These medications can also cause acute hepatitis or an autoimmune hepatitis like syndrome, so that chronic hepatitis due to medications may be a mild form of acute drug induced hepatitis in which the medication is continued so that the injury becomes chronic. Drug induced chronic hepatitis usually occurs in patients while on a medication chronically. The persistence of chronic hepatitis after stopping a medication is very uncommon and probably represents an unrelated process or autoimmune hepatitis triggered by the medication.

Differential Diagnosis. Other causes of chronic hepatitis include autoimmune hepatitis and hepatitis B, C and D and hepatitis E (due to genotype 3 HEV and usually in immunosuppressed patients). Clinical features of chronic hepatitis can also accompany celiac disease and inflammatory bowel disease. Nonalcoholic and alcoholic liver disease can cause serum aminotransferase elevations typical of chronic hepatitis, but imaging of the liver and liver biopsy demonstrate steatosis and a different pattern of liver injury (zone 3 ballooning degeneration).

Criteria for Definition. Elements important in the diagnosis are exclusion of other causes (hepatitis A, B, C and E) and features of chronic hepatitis as shown by:

1. Persistent ALT levels above the ULN on at least 3 occasions
2. Alkaline phosphatase levels of less than 2 times ULN
3. Minimal and nonspecific symptoms
4. Mild or minimal bilirubin elevations

5. Liver biopsy changes of chronic hepatitis with portal inflammation and spotty lobular inflammation and necrosis with variable degrees of interface hepatitis and portal fibrosis.

It is often difficult to distinguish between a mild, anicteric case of drug induced acute hepatitis and drug induced chronic hepatitis, but the time to onset and insidious nature of the presentation can help to distinguish the two. The mild, transient ALT elevations that occur with many medications are usually benign and nonprogressive, and can resolve even with continuation of the drug. In contrast, the ALT elevations that occur with chronic hepatitis induced by medications usually indicate significant liver injury that can lead to fibrosis and even cirrhosis. The importance of making this distinction is important both for differential diagnosis and management. The differential diagnosis of chronic hepatitis includes idiopathic autoimmune hepatitis which can present in an identical fashion. The management is to discontinue the medication, but corticosteroid therapy may be appropriate if the hepatitis is slow to resolve or severe.

Representative Cases

Case 1. Chronic hepatitis due to nitrofurantoin.

[DILIN Case: 104-0025]

A 68 year old woman was given nitrofurantoin (50 mg daily) for prophylaxis against recurrent urinary tract infections. She continued on therapy for 3 years at which time serum enzymes were found to be elevated. She had no symptoms that could be attributed to liver disease. Nitrofurantoin was stopped, but restarted one month later because of recurrence of urinary tract infections. Serum aminotransferase levels remained mildly elevated (2 to 3 times the upper limit of normal). Six months later, she had the insidious onset of nausea, fatigue and weakness. Serum aminotransferase levels were still elevated, but alkaline phosphatase and bilirubin values were normal. Anti-smooth muscle antibody was present (1:80), but other autoantibodies were not detected. Tests for hepatitis A, B and C were negative. A liver biopsy showed chronic active hepatitis with moderate to severe inflammatory infiltrates and moderate fibrosis. The symptoms persisted for several months and the medication was discontinued again. Two months after stopping nitrofurantoin, the patient had returned to her usual state of health and serum aminotransferase levels returned to normal.

Key Points

Medication:	Nitrofurantoin, 50 mg daily
Pattern:	Hepatocellular (aminotransferase elevations only)
Severity:	1+ (never jaundiced, never hospitalized)
Latency:	Several years, 6 months after restarting
Recovery:	Complete within 5 months
Other medications:	Sumatriptan, alendronate, clopidogrel, estrogen, verapamil

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Nitrofurantoin started					
1 month		79	62	0.4	
3 months		115			
4 months		88			Nausea, fatigue
5 months		255			Liver biopsy

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Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
6 months	0	176	99	0.5	Smooth muscle antibody positive
Nitrofurantoin stopped					
9 months	3 months	52	101	0.7	
1 year	5 months	30	102	0.7	
Normal Values		<42	<115	<1.2	

Comment

Initially, the liver injury was believed to be caused by chronic hepatitis unrelated to medications. Because of appearance of symptoms and findings on liver biopsy, nitrofurantoin was subsequently suspected and discontinued. The resolution of liver test abnormalities and symptoms of fatigue after stopping nitrofurantoin supported the diagnosis of drug induced liver disease. While the clinical pattern resembles chronic hepatitis, the disease generally resolves when the medication is stopped. However, long term follow up to document resolution of hepatitis is warranted.

Case 2. Chronic hepatitis-like syndrome caused by long term methyldopa therapy.

[DILIN Case: 104-0034]

A 25 year old woman developed signs and symptoms of chronic liver disease after 8 months of therapy with methyldopa. Methyldopa had been started in a dose of 250 mg twice daily during a pregnancy, but was then continued after she had a Caesarian section 3 months later. After being on methyldopa for 8 months, she had the insidious onset of nausea, dark urine, itching and jaundice. She was admitted to a local hospital and laboratory testing showed an ALT of 1292 U/L and bilirubin of 7.3 mg/dL. Tests for hepatitis A, B and C were negative. Both smooth muscle and antinuclear antibody were negative. CT scans and ultrasound of the liver were normal. A liver biopsy showed changes typical of chronic active hepatitis. Methyldopa was stopped, and she was placed on prednisone. Serum aminotransferases slowly improved. Six months later prednisone was stopped and in follow up her liver tests remained normal.

Key Points

Medication:	Methyldopa
Pattern:	Hepatocellular (R=21)
Severity:	3+ (jaundice, hospitalization)
Latency:	8 months
Recovery:	Complete after 6 month course of prednisone
Other medications:	Triamterene

Laboratory Values

Months After Starting	Weeks After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Methyldopa started during pregnancy					
8	0	1292	126	10.3	Methyldopa stopped
8	1	1053	101	19.3	

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Months After Starting	Weeks After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
9	2	1140	156	24.9	Prednisone started
9	4	362	169	11.9	
10	6	88	102	3.0	
10	8	64	113	2.0	
11	12	80	61	1.0	Prednisone tapered
12	16	45	74	1.0	
14	24	29	69	0.5	Prednisone stopped
20	52	19	83	1.0	
Normal Values		<60	<126	<1.2	

Comment

This case represents a moderately severe example of chronic hepatitis induced by methyldopa. Initially, the clinical features suggested an acute drug induced liver injury, but the course and liver biopsy indicated a chronic process. The use of prednisone is controversial, but the height of the bilirubin and ALT elevation led to its use. Importantly, once methyldopa was stopped, the prednisone was withdrawn gradually, and in follow up, this patient was asymptomatic and had normal liver tests.

Case 3. Asymptomatic chronic hepatitis during long term diclofenac therapy.

[DILIN 102-0031]

A woman in her early 40s with a history of chronic knee pain was treated with diclofenac in a dose of 50 mg thrice daily. She complained of a new onset of sharp, intermittent right upper quadrant pain and itching of the lower extremities and was found to have elevated serum aminotransferase levels on routine lab work approximately 5 months after starting diclofenac. She denied fever, nausea, weight loss or jaundice. Tests for hepatitis A, B and C were negative, but antinuclear antibodies were strongly positive. A liver biopsy was consistent with chronic hepatitis of moderate to severe activity with mild periportal fibrosis. The patient was also taking atorvastatin which was discontinued on the basis of its possible role in causing the aminotransferase elevations. Despite this, ALT levels remained elevated. Subsequently, diclofenac was discontinued and both aminotransferase elevations and her abdominal pain resolved promptly.

Key Points

Medication:	Diclofenac
Pattern:	Hepatocellular (R=8)
Severity:	1+ (never jaundiced, never hospitalized)
Latency:	5 months
Recovery:	Complete recovery within 3 months
Other medications:	Atorvastatin, ibuprofen, fexofenadine, rabeprazole, propranolol, synthroid, triamterene, hydrochlorothiazide, sumatriptan, glucosamine, chondroitin

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0					Diclofenac started
5 months		332	126	0.5	Itching, RUQ pain
7.5 months		68	110	0.4	
9 months		430			Biopsy, atorvastatin stopped
16 months	0	250	119	0.5	Diclofenac stopped
19 months	3 months	29	93	0.7	
Normal Values		<42	<115	<1.2	

Comment

The association of serum aminotransferase elevations and diclofenac is supported by the resolution of the abnormalities once the medication was stopped. The nonspecific symptoms, presence of antinuclear antibody and fibrosis found on liver biopsy indicate that the injury was chronic rather than acute and argue strongly for stopping diclofenac. The presence of autoantibodies is common with drug induced liver injury and particularly with chronic injury. The resolution of disease upon stopping the medication is usually followed (more slowly) but disappearance of the autoantibodies.

Histology of Drug Induced Chronic Hepatitis

[Under Construction]