Hyperthyroidism induced reversible hepatotoxicity a case report and brief review

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ABSTRACT

The patients presenting with high liver enzymes have multiple etiologies ranging from hepatotoxic viruses, drugs, and various toxins. While viral hepatitis continues to be the leading cause of elevated liver enzymes, other metabolic and endocrine disorders also lead to elevated liver enzymes in a given patient. There is a paucity of data regarding hyperthyroidism and the high liver enzymes. We present the clinical scenario in a young male who presented with jaundice without viral prodrome or offending drug intake. The patient had no high-risk behavior, and on evaluation, he had negative viral serologies. Autoimmune profile was negative as well. The physical examination was suggestive of irregular pulse and normal blood pressure. On further evaluation hyperthyroidism was unraveled. Following treatment with antithyroid medication, the liver enzymes in the index case settled, and he had full clinical recovery, explaining the cause and effect relationship. Report on this case and brief literature review is presented. A good clinical examination often is a lead to the cause of disease and in a Jaundiced patient, hyperthyroidism can be one of the causes of high liver enzymes which must be ruled out in a given setting.

KEY WORDS: Hyperthyroidism; Elevated Liver Enzymes; Anti-thyroid Medication; Clinical Examination Clues

INTRODUCTION

Thyroid disease occurs most frequently in females, and autoimmune thyroid disease has a peak incidence in people aged 20–40 years. The clinical symptoms of hyperthyroidism do not always correlate with the extent of the biochemical abnormality. Younger patients usually exhibit symptoms of sympathetic activation such as anxiety, hyperactivity, and tremors while as older patients have more cardiovascular symptoms such as dyspnea and atrial fibrillation. Patient with Graves disease often has more marked symptoms than patients with thyrotoxicosis from other causes. Liver cell dysfunction following hyperthyroidism is usually attributed to circulatory dysfunction followed by secondary liver cell congestion in a hyperthyroid state. There is limited data available to explain the effect of hyperthyroidism and liver cell injury, and mostly animal studies are available in the English literature regarding hyperthyroidism and liver cell dysfunction.

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CASE REPORT

A 30-year-old male presented with a history of Jaundice of 2 weeks duration without any history of viral prodrome, drug intake or fever. The patient is a non-diabetic and had no comorbid illness. There was no family history of jaundice or liver disease. On examination, the patient was conscious oriented to time place and person. The pulse at the time of presentation was 120 beats per minute regular, synchronous and there was

no radio-femoral delay. He had normal oxygen saturation on room air and the blood pressure of 120/80 mm of Hg. There was mild icterus, no scratch marks, and temperature was 37°C. Patient had no pedal edema, and his JVP was not raised. The patient was not obese and had BMI of 22 Kg/M^2. The abdominal examination revealed no hepatosplenomegaly, no free fluid. Systemic examination was unremarkable. On evaluation, he had normal hemogram as shown in Table 1. The serum bilirubin levels were 6.2 mg/dl with a direct fraction of 3.3 mg/dl. Serum glutamic-oxaloacetic transaminase and serum glutamate pyruvatetransaminase levels were 135 IU AND 157 IU. Serum Alkaline phosphatase levels were 182. An ultrasound of abdomen revealed normal echotexture of the liver, the note was made of 5 mm gallstones, but the thickness of the gallbladder wall was standard. The intrahepatic biliary radicles were not dilated. Portal vein and hepatic veins were normal. Keeping in view gallstones Magnetic resonance cholangiopancreatography (MRCP) was done which did not show any common bile duct stones and the biliary tree wasnormal. Further workup of the patient revealed that all viral markers were negative (Hepatitis B surface antigen, immunoglobulin M Hepatitis A virus, Anti-Hepatitis C virus negative, and anti Hepatitis E virus)) patient denied any high-risk behavior or drug abuse. Serum antinuclear antibodies, antimitochondrial antibody, and anti-liver-kidney microsomes were negative, and he had normal ceruloplasmin levels. There was no KF Ring on slit lamp examination. Keeping in view sinus tachycardia patient was further evaluated and found to have electrocardiogram suggestive of sinus tachycardia with no ectopics. Echocardiography was normal. The patient's thyroid profile was indicative of hyperthyroidism as shown in Table 1. He was started on anti-thyroid treatment Tablet Methimazole 5 mg daily once daily and repeat thyroid functions and liver function tests were normal after 6 weeks of treatment. Patients heart rate settled to 76 beats per minute. Patient s LFT improved as shown in Table 1.

DISCUSSION

The index case presented with features of hepatitis and no hepatobiliary obstruction was noted on evaluation. Keeping in view the presence of gallstones found on ultrasound examination it was imperative to rule out biliary obstruction in him as the ultrasound can miss common bile duct stones. MRCP was done which ruled out the biliary obstruction in the index case. He had no familial cause of hepatitis and had no evidence of fatty liver on ultrasound often leading to high liver enzymes in an era of metabolic syndrome. The only clue to the diagnosis in the index case was the presence of tachycardia which on further evaluation clinched the diagnosis of hyperthyroidism and Graves disease, highlighting the importance of a proper clinical examination in any given situation. In a series of 43 patients with hyperthyroidism liver cell dysfunction were studied by Fong *et al*.[1] Authors observed hepatomegaly and splenomegaly in instances where hyperthyroidism was associated with cardiac involvement. Serum bilirubin levels were elevated uniformly in their study, but no characteristic liver histology was noted in patients with hyperthyroidism. Authors in this study concluded that severe liver test abnormalities, including deep jaundice, and prolonged prothrombin time, can occur in patients with hyperthyroidism. They further emphasized control of hyperthyroidism in a given case before further workup for liver cell dysfunction. The index case had a

Table 1: Liver function tests thyroid function tests and CBC

Test	Result pre-treatment (on presentation)	Result post-treatment (After 6 weeks)	Normal range
Hemoglobin	14.7	14.3	12.2–15.3 g/dl
White blood cell	5.9	6.7	6–16×109/l
Platelet	153	197	150–450×109/l
Total bilirubin	6.2	1.0	0.8–1 mg/dl
Direct bilirubin	3.3	0.8	0.0 –0.6 µmol/L
AST	135	30	5–30 U/L
ALT	157	29	5–30 U/L
ALP	182	100	50–100 U/L
GTT	497	65	7–30 IU/l
Albumin	31	39	38–54 g/l
INR	1.2	1.1	0.8–1.2
Free T4	>87	19	9–26 pmol/l
Total T3	> 8.36	2.5	1.2–2.6 nmol/l
TSH	<0.02	1.52	0.5–5.0 mU/l
TSI	471	131	<140 mg/dl
Serum glucose	100	102	65–110 mg/dl

ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALK: Alkaline phosphatase, GGT: Gamma-glutamyltransferase, INR: International normalized ratio, TSH: Thyroid-stimulating hormone, TSI: Thyroid-stimulating immunoglobulins

normal abdominal examination. He had high bilirubin levels, elevated liver enzymes but his prothrombin time was normal. We did not perform liver biopsy as the liver enzymes normalized soon after the control of hyperthyroidism.

There is limited human data regarding hyperthyroidism and liver disease, but in various animal models, investigators have observed a link between hyperthyroidism and liver dysfunction. It has been noted that there is a coexistence of hyperkinetic circulation, hypermetabolism, and hyperactivity of the sympathetic nervous system in both cirrhosis and hyperthyroidism. The authors in this rat model study suggested that control of hyperthyroidism can inhibit the development of cirrhosis reflecting a direct effect of hyperthyroid function on liver.[2] One of the reasons postulated to explain liver cell dysfunction in a given case of hyperthyroidism is high output failure and consequent congestion in the liver, but the index case had no features of cardiac failure. It is entirely possible that had the index patient not been managed in time he would develop florid signs of Graves disease and even his liver disease would have worsened over the period of time. The exact mechanism of liver toxicity caused due to the hyperthyroid state is less clearly understood. It is entirely possible that high levels of thyroxine by increasing oxygen consumption, increase free radicles in the liver; thus, induce liver cell injury as has been demonstrated in animal models by Chandra *et al*.[3] Again in another animal model, it has been observed that hyperthyroidism activates both oxidant and antioxidant system in cerebral, hepatic, and cardiac tissues.[4] In yet another animal model, it has been noted that hyperthyroidism potentiates the *in vivo* hepatotoxicity of 1,1-dichloroethylene (DCE) in rats, with a concomitant increase in [14C]-DCE covalent binding. The enhanced injury produced in hyperthyroid livers by DCE could be due to alterations in either the bioactivation or detoxification phases of DCE metabolism.[5] Whatever, the mechanism it is crucial to control hyperthyroidism to prevent damage to various organs including the liver. In the index case thyrotoxicosis induced liver damage settled after he became euthyroid and liver enzymes normalized as well. Hyperthyroidism induced liver damage can occur at any age. Even neonatal hyperthyroidism causing liver cell dysfunction, though rare, has been reported in a baby born to a mother with Graves disease. Authors in this report have demonstrated successful outcome with antithyroid medication in neonatal hyperthyroidism.[6]

Thionamides such as propylthiouracil (PTU) and methimazole (MMI) have been used for more than 50 years to treat the more common causes of thyrotoxicosis/hyperthyroidism such as Graves' disease. Unfortunately, serious adverse effects associated with thioamides in humans include idiosyncratic liver damage, agranulocytosis, aplastic anemia, and vasculitis. Both prospective and retrospective clinical studies with these drugs have failed to identify a predictive biomarker for these adverse effects.[7] We did not observe any side effect of the treatment and the patient tolerated the drug well. He had marked improvement in his symptoms, and gradual fall of liver enzymes to normal was achieved as is shown in Table 1. At times antithyroid treatment is withheld owing to serious side effects caused by the treatment. Various allergic reactions with oral MMI occur in up to 10% of patients and, when mild, can be managed with concurrent antihistamine therapy. Antihistamine therapy can thus help in continuation of MMI as has been reported has been reported.[8] Another word of caution during treatment of hyperthyroidism is that liver cell function may get further deteriorated due to MMI itself.[9] In one report the liver enzyme levels in two patients returned to normal after stopping MMI therapy. These cases highlight that patients should be informed about the earliest symptoms of serious adverse effects of antithyroid drugs, such as hepatic toxicity, and that they should be advised to stop taking the medication immediately and contact their physician if such symptoms occur.[10] Where side effects become more pronounced during control of hyperthyroidism another option would be ablation of thyroid tissue to prevent the deleterious effects of excessive thyroid hormone as reported as was reported by Vilchez FJ *et al*.[11]

CONCLUSION

To conclude the index case highlights the importance of proper clinical examination while evaluating a situation of high liver enzymes in a given situation. It also highlights the relationship of hyperthyroidism induced liver cell injury and normalization of liver cell function after hyperthyroidism is controlled. Further studies may be conducted to understand the phenomenon.

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