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Incidence of Abnormal Liver Biochemical Tests in Hyperthyroidism

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Abstract

Objective—Abnormal serum liver function tests are common in patients with untreated thyrotoxicosis, even prior to the initiation of antithyroidal medications that may worsen their severity. There is a wide range of the incidence of these abnormalities in the published literature. The aim of this study was to assess the risks factors and threshold of thyrotoxicosis severity for developing an abnormal liver biochemical test upon the diagnosis of new thyrotoxicosis.

Design—Single-institution retrospective cohort study.

Patients—Patients 18 years old receiving medical care at a large, academic, urban U.S. medical center between 2002–2016.

Measurements—Inclusion criteria were a serum thyroid stimulating hormone [TSH] concentration < 0.3 mIU/L or ICD-9 code for thyrotoxicosis, with thyrotoxicosis confirmed by either a concurrent elevated serum triiodothyronine (T3) and/or thyroxine (T4) concentration [total or free] within 3 months), and an available liver biochemical test(s) within 6 months of thyrotoxicosis. The biochemical liver tests assessed were serum aspartate transaminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyltransferase (GGT), total bilirubin, and conjugated bilirubin concentrations.

Results—In this cohort of 1,514 subjects, the overall incidence of any biochemical liver test abnormality within 6 months of thyrotoxicosis was 39%. An initial serum TSH concentration

<0.02 mIU/L, male gender, and African-American race were significant predictors of an abnormal serum liver biochemical test within 6 months of the diagnosis of new-onset untreated thyrotoxicosis.

Conclusions—This study identifies risk factors for patients who develop an abnormal serum liver biochemical test result within 6 months of a diagnosis of untreated thyrotoxicosis.

Keywords

liver function; hyperthyroidism; thyrotoxicosis

Introduction

The reported prevalence of liver biochemical abnormalities in patients with untreated thyrotoxicosis varies widely, ranging from 15–79% (1–6). Processes contributing to biochemical hepatic abnormalities include excess thyroid hormone, elevated thyroid receptor antibody (TRAb) titers in Graves' disease, relative hepatic anoxia, apoptosis, and increased susceptibility to oxidative stress (2,5,7–12). Other contributing factors to hepatic abnormalities in individuals with untreated hyperthyroidism include heart failure, effects of anti-thyroid drugs, and concomitant liver disease (13).

Although the pattern of biochemical hepatic abnormalities and hepatic injury in the setting of hyperthyroidism is variable in character and severity (14), it appears to be predominantly hepatitis, (3,4,14–17) with a few case reports demonstrating a cholestatic pattern (18–20). The first report of hepatic necrosis in a patient with thyrotoxicosis occurred in 1874 (21). In 1967, liver biopsies of 23 hyperthyroid patients showed that 90% had fatty change (22). Other changes included megamitochondria with irregular volume and increased membrane volume (23). Further studies demonstrated that the degree of biochemical hyperthyroxinemia does not correlate with cellular and ultrastructural abnormalities (22,23). Liver abnormalities were mostly hepatitic with predominantly serum aspartate transaminotransferase (AST), alanine aminotransferase (ALT), and bilirubin elevations, with some increased serum alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT) concentrations (3,4,14–16). However, AP elevations may not necessarily originate from the liver and can represent elevations in the bone isoenzyme (3). Other reports of untreated thyrotoxicosis also have reported a cholestatic pattern with a predominant AP elevation and/or biopsy-proven cholestasis (18–20).

There is limited understanding regarding the patterns of biochemical liver abnormality changes that occur upon treatment of hyperthyroidism. The relationships between use of anti-thyroid drugs and biochemical liver abnormalities has been described in a few small series (24–28), while the other therapies for certain cases of hyperthyroidism (radioactive iodine and surgery) have been rarely described (13,15,29–31). This retrospective study investigates the patterns of liver biochemical abnormalities in patients at our institution with a new diagnosis of thyrotoxicosis.

Materials and Methods

We conducted a retrospective chart analysis of all patients 18 years old with thyrotoxicosis (serum thyroid stimulating hormone [TSH] <0.3 mIU/L or ICD-9 code for thyrotoxicosis; either with a concurrent elevated serum triiodothyronine (T3) and/or thyroxine (T4) concentration [total or free] within 3 months) and first available liver biochemical test(s) within 6 months of thyrotoxicosis in the UCLA electronic medical record database from 2002–2016. The biochemical liver tests studied were serum AST, ALT, AP, GGT, total bilirubin, and conjugated bilirubin concentrations. Serum concentrations were considered abnormal according to the following criteria: AST > 47 U/L, ALT > 64 U/L, AP > 113 U/L, GGT > 68 U/L, total bilirubin > 1.2 mg/dl, conjugated bilirubin > 0.3 mg/dl. Patients using medications which may affect liver biochemistries or thyroid function tests (statins, azole antifungals, isoniazid, valproic acid, amiodarone) or patients with pre-existing liver conditions (fatty liver, alcoholic/nonalcoholic hepatitis, hepatitis B and C, cirrhosis, cholangitis) were excluded.

Differences in the frequencies of biochemical liver abnormalities were assessed by Chi-square tests. Cox regression models were used to determine significant predictors of a biochemical liver abnormality. P-values < 0.05 were considered significant. The study was approved by the UCLA Institutional Review Board (IRB).

Results

There were 1,514 patients (mean±SD age 60.0±19.1 years; 77% women; 60% White) with a new diagnosis of thyrotoxicosis and available biochemical liver test(s) within 6 months of the onset of thyrotoxicosis during the study period (Table 1). Age, gender, race, and ethnicity were self-reported, as recorded in the medical record.

The overall incidence of any biochemical liver test abnormality within 6 months of thyrotoxicosis was 39%. Of the 811 patients whose serum TSH level was below the detection limit (≤ 0.02 mIU/L), 45% had an abnormal liver biochemical test (13% AST, 13% ALT, 35% AP, 2% GGT, 9% total bilirubin, 6% conjugated bilirubin). In comparison, of the 697 patients whose serum TSH level was above the detection limit (> 0.02 mIU/mL), 33% had an abnormal liver biochemical test (18% AST, 14% ALT, 22% AP, 2% GGT, 15% total bilirubin, 12% conjugated bilirubin (Figure 1).

Serum TSH concentration ≤ 0.02 mIU/L, male gender, and African-American race were significant positive predictors for a biochemical liver abnormality (Table 2). Serum TSH concentration ≤ 0.02 mIU/L, male gender, and African-American race were significant positive predictors for abnormal alkaline phosphatase; non-Hispanic or Latino and other ethnicities were significant negative predictors for abnormal alkaline phosphatase (Table 3). There were no significant positive predictors for abnormal serum GGT concentrations.

Serum TSH concentration ≤ 0.02 mIU/L and non-Hispanic or Latino and other ethnicities were significant negative predictors for abnormal total bilirubin and abnormal conjugated bilirubin (Table 4, Table 5); male gender was a significant positive predictor for abnormal total conjugated bilirubin (Table 4); male gender and African American race were significant

positive predictors for abnormal conjugated bilirubin (Table 5). Male gender and African-American race were significant positive predictors for abnormal serum ALT and AST concentrations (Table 6, Table 7); not Hispanic or Latino ethnicity was a significant negative predictor for abnormal serum AST concentration (Table 7).

Discussion

In this retrospective cohort study of patients at a large, urban academic medical center, there was a 39% incidence of liver biochemical abnormalities within 6 months of a new diagnosis of thyrotoxicosis. Increased risks were observed in those with an initial serum TSH concentration of ≤ 0.02 mIU/L, in men, and in African-Americans.

Although there are many previous studies that have linked thyrotoxicosis with liver biochemical abnormalities(1–6), few have investigated whether the severity of thyrotoxicosis affects the presence of abnormal LFTs. The present findings indicate that amongst patients with the diagnosis of thyrotoxicosis, serum TSH concentration ≤ 0.02 mIU/L, as compared to those with a serum TSH > 0.02 mIU/L, is a significant distinction as a predictor of any LFT abnormality, as well as for specific LFT abnormalities, including alkaline phosphatase, total bilirubin, and conjugated bilirubin. However, this distinction does not seem to be significant in analyses of abnormal serum ALT, AST, or GGT concentrations.

Unlike previous studies in which the prevalence of liver biochemical abnormalities were not significantly affected by gender(7), this study consistently indicates that male gender is a significant positive predictor for LFT abnormalities, including serum alkaline phosphatase, total bilirubin, conjugated bilirubin, ALT, and AST concentrations. Additionally, few studies in the past have investigated race and/or ethnicity as predictors of abnormal biochemical tests in hyperthyroidism. The African-American race is not known to be a predictor for LFT abnormalities independent of hyperthyroidism. In this cohort, African-American race is found to be a significant positive predictor for abnormal serum alkaline phosphatase, conjugated bilirubin, ALT, and AST concentrations. This may be explained by increased severity of thyrotoxicosis compared to other racial groups, or the presence of comorbidities with a higher prevalence in African-Americans that affect thyroid and/or liver function.

Limitations to the study include the low frequency of positive serum thyroid autoantibodies in our cohort, which may be an important covariate for the development of liver function test abnormalities. Rather than investigating the effect of thyroid medications on liver biochemical patterns (24–28), we have excluded patients who were using propylthiouracil or methimazole, as well as any other drugs that may affect liver metabolism, from this patient cohort. The study focused on predictors of incident abnormal LFTs, rather than changes in abnormal LFTs after treatment for thyrotoxicosis. Although we excluded patients who used medications which may affect liver biochemistries or thyroid function tests, as well as patients with pre-existing liver conditions, other possible conditions that may affect liver and thyroid function, such as cardiac disease, remain as potential confounding variables in this study. Finally, the study did not assess for the time course of resolution of the abnormal liver biochemical tests.

The study utilizes a large cohort of patients seen at a large, academic, urban U.S. medical center to provide further understanding of the patients who were evaluated for liver biochemical abnormalities upon the onset of a new diagnosis of thyrotoxicosis. In the patient populations in which increased risks for abnormal liver biochemical tests were found (initial serum TSH concentration 0.02 mIU/L, men, African-Americans), clinicians may consider monitoring liver function at an earlier time (1–3 months immediately after initial diagnosis of thyrotoxicosis), to prevent progression to liver disease. Further research is needed to explore the reasons for increased risk of liver biochemical abnormalities in certain populations, the time course to resolution, and guidance for use of antithyroidal therapy in such patients.

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Figure 1.
Liver Biochemical Abnormalities Grouped by TSH

Table 1

Demographics of patients (n=1,514)

Age (years)	
Mean $\pm$ SD	60.0 $\pm$ 19.1
Median (IQR)	51.0 (35.6 – 65.5)
Gender, n (%)	
Female	1,167 (77.1%)
Race, n (%)	
White or Caucasian	907 (59.9%)
Asian	211 (13.9%)
Black or African-American	131 (8.6%)
Other	265 (17.5%)
Ethnicity, n (%)	
Hispanic	214 (14.13%)
Not Hispanic or Latino	1164 (76.88%)
Other	136 (8.98%)

Table 2

Cox regression model predicting initial liver biochemical test abnormality

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	1.42	(1.19, 1.68)	<.0001
Age (in 10 year increments)	0.96	(0.91, 1.00)	0.0555
Gender (women vs. men)	0.48	(0.40, 0.57)	<.0001
Race			
White or Caucasian	Reference	-	-
Asian	0.89	(0.69, 1.15)	0.3602
Black or African American	1.63	(1.25, 2.12)	0.0003
Other	0.83	(0.63, 1.09)	0.1798
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.59	(0.47, 0.73)	<.0001
Other	0.62	(0.43, 0.91)	0.0136

Table 3

Cox regression predicting abnormal serum alkaline phosphatase concentration

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	1.58	(1.29, 1.94)	<.0001
Age (in 10 year increments)	0.96	(0.91, 1.02)	0.1621
Gender (women vs. men)	0.49	(0.40, 0.60)	<.0001
Race			
White or Caucasian	Reference	-	-
Asian	1.10	(0.83, 1.46)	0.5264
Black or African American	1.73	(1.28, 2.35)	0.0004
Other	0.88	(0.64, 1.20)	0.4153
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.57	(0.44, 0.74)	<.0001
Other	0.63	(0.40, 0.97)	0.0362

Table 4

Cox regression predicting abnormal total bilirubin concentration

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	0.59	(0.43, 0.80)	0.0008
Age (in 10 year increments)	1.01	(0.93, 1.09)	0.8527
Gender (women vs. men)	0.38	(0.28, 0.52)	<.0001
Race			
White or Caucasian	Reference-	-	-
Asian	0.61	(0.35, 1.07)	0.0828
Black or African American	1.55	(0.96, 2.51)	0.0733
Other	0.71	(0.42, 1.19)	0.1910
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.46	(0.32, 0.66)	<.0001
Other	0.37	(0.16, 0.84)	0.0174

Table 5

Cox regression predicting abnormal serum conjugated bilirubin concentration

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	0.53	(0.37, 0.77)	0.0008
Age (in 10 year increments)	1.00	(0.91, 1.09)	0.9713
Gender (women vs. men)	0.27	(0.19, 0.38)	<.0001
Race			
White or Caucasian	Reference-	-	-
Asian	0.77	(0.42, 1.43)	0.4098
Black or African American	2.09	(1.25, 3.50)	0.0052
Other	0.58	(0.3, 1.14)	0.1127
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.40	(0.26, 0.60)	<.0001
Other	0.28	(0.09, 0.86)	0.0263

Table 6

Cox regression predicting abnormal serum ALT concentration

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	0.94	(0.7, 1.24)	0.6411
Age (in 10 year increments)	0.94	(0.87, 1.01)	0.0843
Gender (women vs. men)	0.46	(0.34, 0.61)	<.0001
Race			
White or Caucasian	Reference-	-	-
Asian	0.94	(0.61, 1.45)	0.7773
Black or African American	1.59	(1.02, 2.48)	0.0418
Other	0.82	(0.51, 1.31)	0.4006
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.73	(0.5, 1.07)	0.1065
Other	0.86	(0.45, 1.65)	0.6508

Table 7

Cox regression predicting abnormal serum AST concentration

	Hazards Ratio	95% CI	p-value
TSH (0.02 vs. >0.02 mIU/L)	0.70	(0.53, 0.91)	0.0087
Age (in 10 year increments)	1.00	(0.94, 1.08)	0.9082
Gender (women vs. men)	0.47	(0.36, 0.62)	<.0001
Race			
White or Caucasian	Reference-	-	-
Asian	0.95	(0.63, 1.45)	0.8181
Black or African American	1.86	(1.24, 2.79)	0.0029
Other	0.66	(0.41, 1.06)	0.0842
Ethnicity			
Hispanic	Reference	-	-
Not Hispanic or Latino	0.51	(0.36, 0.71)	<.0001
Other	0.63	(0.33, 1.21)	0.1655