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Congestive Hepatopathy: An Unusual Complication of Graves Disease

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Abstract: Hyperthyroidism can affect multiple organ systems, commonly the cardiovascular, nervous and gastrointestinal systems. However, involvement of the hepatic system is relatively uncommon. There are several mechanisms of liver dysfunction in the setting of hyperthyroidism. Right-sided heart failure can result in passive congestion of the liver usually referred to as "congestive hepatopathy."

We describe a case of 40-year-old lady who presented with jaundice. On examination, she had icterus and features of congestive cardiac failure and thyrotoxicosis. Investigations done confirmed the diagnosis. Patient was started on treatment with Methimazole. Clinically, the patient showed improvement of liver functions following treatment.

Awareness about association between Graves' disease (GD) and hyperbilirubinaemia will help in more rapid diagnosis, prevention of misdiagnosis and in early initiation of treatment.

Keywords: Thyrotoxicosis, Graves' disease, Congestive Hepatopathy, Thionamides.

Introduction:

Graves' disease is an autoimmune thyroid disease first described by Robert Graves in 1835[(1)]. Hyperthyroidism can affect multiple organ systems, including the cardiovascular, nervous, gastrointestinal, and hepatic systems [(2)]. The prevalence of liver dysfunction in patients with thyrotoxicosis is reported to be between 15 to 76%[(3)]. There are multiple mechanisms of liver dysfunction that can occur in the setting of hyperthyroidism, including liver abnormalities due to hyperthyroidism alone, liver damage related to heart failure and hyperthyroidism, and concomitant liver disease in the setting of hyperthyroidism [(2)]. Right-sided heart failure can result in passive congestion of the liver usually referred to as "congestive hepatopathy [(2)]."

Case Report

A 40-year-old lady presented with complaints of fever for 1 week, right lower limb swelling and pain for 4 days

and yellowish discoloration of eyes since 4 days. She had history of palpitations, irregular menstrual cycles and weight loss for 1 year. She was not on and medications and had no history of any chronic disease. On initial examination she was found to have pallor, icterus, bilateral pitting pedal oedema and resting tachycardia. Diffuse thyromegaly with a bruit was present, along with proptosis. She had a raised Jugular Venous Pressure (JVP), a loud P_2 and an ejection systolic murmur in the aortic area. Abdominal examination was unremarkable.

Laboratory investigations (detailed in Table 1) showed anemia, elevated bilirubin (mainly conjugated bilirubin) and alkaline phosphatase (ALP) - suggestive of a cholestatic pattern and normal creatinine. Screening for viral markers were negative. Thyroid function tests showed a TSH of <0.005 uIU/ml, FT4 of 6.70ng/dL, T3 of 4.65 ng/ml and T4 of 12.80 mcg/dL.

Table 1: Laboratory Investigations at presentation, after 10 days, 1 month and 2 months

	At presentation	10 days	After 1 month	After 2 months
HAEMOGLOBIN (g/dL)	9.7 (12-15)	9.4	10.1	12.4
TOTAL COUNT (/cumm)	20,900 (4000-11,000)	-	10,300	9,200
PLATELET COUNT (/cumm)	3,84,000	-	3,94,000	3,89,000
INR	1.58	1.23	-	-
SERUM ALBUMIN (g/dL)	2.96 (3.5-5.2)	3.06		3.64
TOTAL BILIRUBIN (mg/dL)	12.84 (0.1-1.2)	12.62	4.02	2.05
SERUM CONJUGATED BILIRUBIN (mg/dL)	11.72 (0-0.2)	10.69	3.74	1.48
SERUM UNCONJUGATED BILIRUBIN (mg/dL)	1.12 (0.2-0.8)	1.93	0.28	0.57
SGOT(IU/L)	52 (0-35)	35	32	20
SGPT (IU/L)	18 (0-45)	12	21	9
ALKALINE PHOSPHATASE (IU/L)	193 (35-104)	139	127	158
SERUM T3 (ng/ml)	4.65 (0.8-2)	-	-	-
SERUM T4 (microgram/dL)	12.80 (5.1-14.1)	-	-	-
SERUM FT4 (ng/dL)	6.70 (0.93-1.7)	-	0.324	0.033
SERUM TSH (uIU/ml)	<0.005 (0.27-4.2)	-	<0.005	5.54

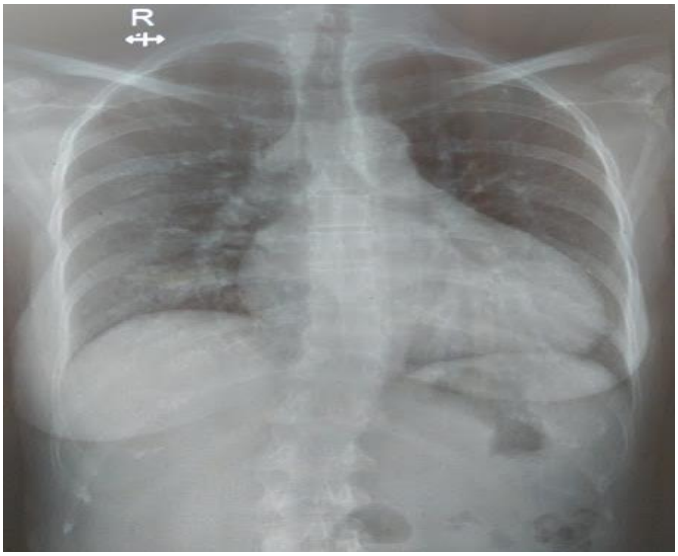

Figure 1: Chest X-Ray PA view: Cardiomegaly

A thyroid uptake scan with 99mTc showed an enlarged thyroid gland with increased uptake (Figure 2).

Chest X-Ray showed cardiomegaly (Figure 1). Echocardiogram done showed moderate TR, moderate PAH, mild MR and dilated RA and RV. RVSP was 50 + RA with an ejection fraction of 60%.

USG abdomen done showed mildly enlarged liver (15.4 cm) with mild coarse echo texture. LKM 1, Liver Kidney Microsome Antibody (Serum Immunofluorescence) was negative, hence ruling out Autoimmune Hepatitis.

Figure 2: THYROID SCAN WITH 99mTc: Thyroid gland uptake percentage of Technetium- 35.7%

She was started on Methimazole at a dose of 10 mg thrice daily and Propranolol at a dose of 40 mg thrice a day. She gradually improved clinically and

biochemically. Investigations after 7 days and 10 days are shown in Table 1.

The follow up investigations after 1 month and 2 months are shown in Table 1. There was an improvement in Hemoglobin, total counts and Bilirubin levels. However, ALP levels continued to be elevated. Two months after her discharge, lower limb edema had subsided and clinical and laboratory features of hyperthyroidism were resolving.

Discussion

Graves' disease is caused by autoantibodies that stimulate the TSH receptors in the thyroid gland and is the most common cause of hyperthyroidism [(1)].

A complex relationship exists between the thyroid and the liver [(4)]. Thyroid hormones are glucuronidase and sulphated within the liver and then excreted into the bile. They also maintain the metabolism of bilirubin by playing a role in the enzymatic activity of glucanosyltransferase and regulating the level of ligandin [(2)].

Hepatic derangement in patients with GD ranges from mild laboratory abnormalities without clinical features to overt hepatitis [(1)]. Liver injury in thyrotoxicosis can be hepatic or cholestatic [(4)].There are multiple possible mechanisms of liver injury in thyrotoxicosis. They are as follows [(1,4)]:

1. Hyperthyroidism causes an increase in the metabolic rate which then induces a relative decrease in blood flow to certain areas of the liver (centrilobular hepatocytes) resulting in hypoxic injury.
2. Direct toxic effect of thyroid hormones on the liver.
3. Congestive heart failure
4. Associated autoimmune liver disease
5. Liver injury induced by medications for thyrotoxicosis, including thionamides.

Once hyperthyroidism is controlled, cholestasis improves [(5)]. Studies show that treatment of hyperthyroidism leading to an improvement in the thyroid function is accompanied by normalization of the liver panel [(2)].

Serum alkaline phosphatase (ALP) is the most common liver enzyme to be elevated and high ALP is seen in 64% of patients with thyrotoxicosis [(5)]. This does not indicate that the liver is the source of origin, as it can originate from the bone also. ALP levels can take several months to normalise after euthyroidism is established [(1)].

Grave's disease can be associated with co-existing autoimmune liver disorders. Serum antibodies which are directed against cytochrome P450 (LKM-1) are considered as markers of autoimmune hepatitis (AIH) Type II. However, in this case report as Liver Kidney Microsome Antibody LKM 1 was negative, autoimmune hepatitis was unlikely. A confirmed diagnosis of autoimmune hepatitis can only be made after a liver biopsy.

Treatment of hyperthyroidism in patient with elevated liver enzymes poses a challenge, as Anti-Thyroid drugs (ATD) are hepatotoxic [(1)]. Methimazole usually causes cholestasis and propylthiouracil usually causes damage to the hepatocytes. Therefore prior to beginning therapy with ATD's, a co-existing liver disease should be ruled out. Other options that can be used in case of ATD-induced hepatotoxicity include substituting ATD with cholestyramine and radioiodine [(4)].

In our case report, the patient had a cholestatic pattern of liver impairment with elevated bilirubin (direct more than indirect) and ALP. After treatment with Methimazole for 3 months there was a resolution of hyperthyroidism, bilirubin levels normalised and ALP levels improved but continued to be elevated.

In our case report, as the patient responded to therapy with ATD's the cause was attributed to congestive hepatopathy.

Conclusion

Patients with GD can present with rare manifestations that have partially understood mechanisms. Hepatic dysfunction in thyrotoxicosis is not an uncommon presentation. It is therefore essential to test the thyroid functions of patient presenting with jaundice, especially if no clear explanation is found for the hyperbilirubinemia. Awareness about association between GD and hyperbilirubinemia can help prevent misdiagnosis and in early initiation of treatment.

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