Ophthalmopathy and other influential factors for liver abnormalities in patients with Graves' disease

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Research article

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Abstract

Background

- Abnormal liver function tests (LFTs) is a common phenomenon in patients having Grave's disease that tends to affect the treatment choice. Only few data on factors and biochemical indexes that contributes to such abnormalities in Graves patients are documented till date.

Objective

- The objective of this study was to explain the potent factors including ophthalmopathy for hepatic dysfunction evoked by Grave's disease alone.

Method

- A cohort of 263 patients who were newly diagnosed and untreated for Grave's disease were studied. Clinical characteristics and all the biochemical values were collected and further analysis was done. These patients were further divided into two groups: group A with abnormal LFTs and group B with normal LFTs. Data were analyzed by using tests like the independent samples t- tests, chi-square tests and logistic regression tests.

Result

- Among them, 175(66.53%) were found to have at least one LFT abnormality. The frequencies of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ -GGT), total bilirubin (TBIL) and direct bilirubin (DBIL) were 54.9% (96/175), 29.7% (52/175), 29.7% (52/175), 38.3% (67/175), 33.1% (58/175) and 34.3% (60/175) respectively of which ALT was the commonest abnormality. In the univariate analysis, group A patients had higher FT3 and FT4 than group B while group B had higher white blood cells (WBC) count mainly granulocyte % and ophthalmopathy than group A. Results of multivariate logistic regression identified FT3 and ophthalmopathy as independent factors predicting abnormal LFTs [odds ratio (OR) = 1.062, 95% confidence interval (CI) = 1.028–1.096 and OR = 0.355, 95% CI = 0.195–0.647 respectively] .

Conclusion

- While FT3 value > 5.70 pmol/L showed consistent association with liver function abnormality in patients with Graves, in contrast, ophthalmopathy showed inverse association with liver function abnormalities.

Background

Graves disease, the commonest cause of hyperthyroidism occupies a considerably large proportion among the wide spectrum of diseases affecting the thyroid gland and typically presents in patients between 40–60 years with female predominance. The annual incidence of Graves disease has been approximated to be 5 per 10,000 people.[1] Graves ophthalmopathy though not exclusive in Graves disease, around 30–50% of Graves patients have clinically apparent ophthalmopathy with prevalence of 0.25%.[2] Many literature have been published till date in occurrence of liver dysfunction in Graves disease patients and the manifestation is quite clear. An elaborated relationship between liver and thyroid has been highlighted with hepatic injury and cholestatic injury in patients with Graves.[3, 4] In the patients of untreated thyrotoxicosis, the reported prevalence of the liver enzyme abnormalities varies widely and ranges from 15–79%.[5] The liver- thyroid interaction is very essential for the maintenance of homeostasis in both the organs. The disorders in any of these organs influence each other causing clinical and laboratory abnormalities.[6] The possible associations could be: liver damage due to excessive thyroid hormones ,autoimmune reactions, changes in thyroid hormone metabolism that is secondary to liver disease, drug- induced liver or thyroid damage due to therapy used for liver or thyroid disease.[4] There are several factors that contributes for development of liver dysfunction in such patients. However, till date only few numbers of studies have been done to predict the factors contributing to liver dysfunction in Graves disease alone with controversial results. Thus, identification of the factors that results in hepatic dysfunction is crucial.

In this small retrospective study, Graves patients with liver dysfunction are compared with those with normal liver function and the risk factors for hepatic dysfunction in those patients are investigated along with the observation of relationship between ophthalmopathy and leukocytes with such patients.

Materials And Methods

Ethics statement:

This is a retrospective study that include the brief details and analysis of clinical data of patients. Written informed consent from each of the patients was received and then approval from the ethics committee of Tianjin medical university general hospital was made. All of the clinical data were studied and analyzed anonymously.

Patients and methods:

Patient population-

A total of 263 patients who were diagnosed as Graves disease and hospitalized and not under any sort of anti- thyroid drugs were included in this study. The study was done among the patients who presented to Tianjin medical university general hospital from January 2013 to December 2015. They all were either newly diagnosed Graves disease patients or patients who had medicine withdrawal time for more than

one month and there was absence of other autoimmune diseases. The diagnostic criteria used for Graves disease included: -

1. Establishment of diagnosis of hyperthyroidism [elevated T4/T3 and low thyroid stimulating hormones (TSH)]
2. Positive thyrotropin receptor antibody (TRAb)
3. Goiter/ diffuse thyroid enlargement
4. Ophthalmopathy/ infiltrating exophthalmos
5. Pretibial myxedema

Where, a and b are pre-requisite for diagnosis and c/d/e aid further in drawing the diagnosis. All the patients having subclinical hyperthyroidism, having medicine withdrawal time less than 1 month, diagnosis of autoimmune liver diseases, positive for hepatitis B surface antigen and positive for hepatitis C antibodies were all excluded from the study. Similarly, patients with drug- induced liver dysfunction, alcoholic and non-alcoholic fatty liver diseases were also excluded from this study. In order to exclude all the other apparent causes of liver damage, various tests like abdominal ultrasound, echocardiography, auto-antibodies testing etc. were performed along with physical examinations and proper history.

Collection of data and grouping

Collection of data regarding age, gender, course of disease of hyperthyroidism, thyroid volume, duration of treatment received, serum FT3, serum FT4, TSH, TRAb, antithyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), body mass index (BMI), presence of goiter, WBC count, granulocyte %, were done for all the patients. Similarly, data on LFTs including AST, ALT, ALP, γ -GGT, TBIL, DBIL were also collected. Diagnosis of hepatic dysfunction was made on criteria of having at least one abnormality in LFTs. Patients were divided into two groups namely A and B where group A constituted cases of Graves disease with abnormal LFTs (at least one) and group B involved patients with Graves disease with normal LFTs. The normal laboratory reference ranges were: ALT (5-40 U/L), AST (8-40 U/L), ALP (40-150 U/L), TBIL (3.4-20 μ mol/L), DBIL (0.1-6.8 μ mol/L) and γ -GGT (7-49 U/L). Likewise, the normal laboratory reference ranges used for thyroid hormones and autoantibodies were: FT3 (2.63-5.70 pmol/L), FT4 (9.01-19.05 pmol/L), TSH (0.350-4.940 uIU/mL), TRAb (0-1.75 IU/L), TPOAb (0-35 IU/L) and TgAb (0-35 IU/L).

Laboratory methods

All of the patients admitted to hospital underwent the fasting venous blood assay for assessment of thyroid and liver functions. Normal cases were assumed according to the normal reference range provided by the laboratory as stated above. Serum levels of FT4, FT3 and TSH were directly measured by chemiluminescence immunoassay (ADVIA CENTUR XP SIEMENS). TgAb and TPOAb were measured

using enzymatic amplification chemiluminescence immunoassay (COBAS 6000, ROCHE DIAGNOSTIC GmbH, GERMANY). Likewise, TRAb was detected using MEDIPAN Germany by ELISA method (enzyme-linked immunosorbent assay). All the liver function indexes were measured using a routine automated biochemical analyzer (Modular DPP, ROCHE DIAGNOSTICS GmbH, Germany, Mannheim). Thyroid volume was estimated by ultrasonography. At the same time, liver ultrasonography was also done and the results were interpreted by an experienced radiologist. Thyroid volume was obtained by ultrasonographic calculation of length(mm) x width(mm)x height(mm) of both the lobes and any nodules/ cysts present in the thyroid gland were included in the calculation. The body mass index (BMI) was calculated using the formula [weight(kg)/ height(m²)].

Statistical analysis

Mann-Whitney U- test, Chi-square test, independent T-test and logistic regression were performed to compare the differences among the groups of patients. Pearson's chi-square test was used to compare categorical variables like gender and ophthalmopathy. Continuity correction was followed for goiter variable. Parametric test like independent T-test was used for continuous variables with normal distribution. For all the other continuous variables without normal distribution, non- parametric Mann-Whitney U-test was used. Continuous variables with normal distribution were expressed as mean± standard deviation and those without normal distribution as median. Missing values were assigned to the mean level. To identify risk factors for hepatic dysfunction in Graves patients' Binary logistic regression analysis was used for all the variables meeting the criteria of P-value of 0.05 or low. Statistical analysis was carried out with help of SPSS software version 16.0 system for windows (SPSS, Chicago IL). All P-values presented were two-tailed and value of 0.05 or less were considered as statistically significant.

Results

Distribution of liver biochemical abnormalities in patients with hepatic dysfunction (group A):-

The patients with Graves disease after all the exclusion criteria were divided into two groups: group A as patients of Graves disease with hepatic dysfunction and group B as patients without hepatic dysfunction. Liver dysfunction was defined on the basis of any one of the liver function abnormalities among ALT, AST, ALP, TBIL, DBIL and γ-GGT. Patients with all the normal LFTs were grouped into group B. Out of total 263 patients of Graves disease, 175 cases (66.5%) had at least one hepatic function test abnormality and 88 cases (33.5%) had no hepatic abnormalities. With respect to hepatic dysfunction, the frequency of each liver biochemical abnormalities in group A patients was summarized. Frequencies of

ALT, AST, ALP, TBIL, DBIL and γ -GGT were 54.9% (96/175), 29.7% (52/175), 29.7% (52/175), 33.1% (58/175), 34.3% (60/175) and 38.3% (67/175) respectively (**Figure 1**). ALT abnormality was found to be the most common among all.

Comparison between two groups on basis of biochemical, demographic and clinical characteristics

Characteristics of patients including age, gender, BMI, thyroid volume, course of disease, FT3, FT4, TSH, TRAb, TPOAb, TgAb, ophthalmopathy, total WBC count, granulocyte % and goiter were all compared between two groups A and B. The results showed that the gender composition was similar ($P=0.605$). There were no significant differences found in age ($p = 0.311$), course of disease ($p = 0.070$), BMI ($p = 0.362$), thyroid volume ($p= 0.676$) and goiter ($p =0.074$) in between two groups. Regarding the laboratory tests for thyroid function and autoantibodies, there were no significant differences between TPOAb, TRAb, TgAb and TSH ($P = 0.340$, $P = 0.455$, $P = 0.123$ and $P = 0.376$ respectively). But there were significant differences between ophthalmopathy, FT3, FT4 level, WBC count and granulocyte % in between the two groups showing higher concentration of FT3, FT4, WBC count and granulocyte % in group A along with absence of ophthalmopathy when compared with those with group B ($P = 0.000$, $P = 0.000$, $P = 0.012$, $P= 0.002$ and $P = 0.000$ respectively).

Logistic regression analysis

Binary logistic regression was conducted to analyze the correlation between elevated liver enzymes variables among Graves patients and results showing significant differences (**table 1**). Similarly, the variables goiter and course of disease being near to the level of significance ($P = 0.074$ and $P = 0.070$ respectively) were also included in univariate analysis. Variables that were significant in the univariate analysis were entered into the stepwise multivariate logistic regression analysis. The results showed that patients with higher serum FT3 level and without ophthalmopathy were more likely to have abnormal LFTs with OR 1.062, 0.355, CI values 1.028 - 1.096, 0.195 - 0.647 and P value 0.000, 0.001 respectively (**table 2**). Thus, this indicates that higher level of FT3 was the independent risk

factor for liver function abnormalities in patients with Graves disease while ophthalmopathy was inversely related to those patients (**figure 2**).

Table 1: Demographic characteristics and thyroid parameters of patients between two groups.

characteristics	Group A (n = 175)	Group B (n = 88)	p- value
Age (years)	45 (31-55)	42 (27-53)	0.311
Gender ^c			0.605
Male	49(28%)	22(25%)	
Female	126(72%)	66(75%)	
Course of disease ^a	5 (2-36)	6 (3-24)	0.070
BMI (kg/m ²) ^a	21.55 (19.10-24.5)	22.3 (19.43-24.82)	0.362
Goiter ^c	172(98.28 %)	82(93.18 %)	0.074
FT3 (pmol/L) ^a	25.12 (15.39-30.8)	16.4 (9.34-25.93)	0.000
FT4 (pmol/L) ^a	62.97(41.84-93.35)	47.25(28.77-69.27)	0.000
TSH (mIU/L) ^a	0.006(0.004-0.01)	0.006(0.004-0.01)	0.376
TRAb (IU/mL) ^a	13.5(6.20-26.34)	16.01(7.60-27.28)	0.455
TgAb (IU/mL) ^a	39.75	20	0.123
TPOAb (IU/mL) ^a	2.065	1.96	0.340
Thyroid volume (g) ^a	2.53 (1.67-3.52)	2.56 (1.55-3.55)	0.676
Ophthalmopathy ^c	37 (21.14 %)	37 (42.04 %)	0.000
WBC count ^a	5.18(4.36-7.27)	6.21(5.03-7.81)	0.012
Granulocyte % ^b	50.98±12.69	56.27±12.98	0.002

^aResults are expressed as medians (Interquartile range). ^bResults are expressed as mean $\pm$ standard deviation (SD). ^cResults are expressed as n (%). FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid stimulating hormone, TRAb = thyrotropin receptor antibodies, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, WBC = white blood cell, BMI = body mass index.

Table 2: Influential factors of liver function abnormalities induced by Grave's disease

characteristics	OR	95% CI	P-value
FT3 concentration	1.062	1.028 - 1.096	0.000
Ophthalmopathy	0.355	0.195 - 0.647	0.001

CI= confidence interval, FT3= free triiodothyronine, OR= odds ratio

Receiver Operating Characteristic (ROC) curve

In order to evaluate the accuracy of FT3 and ophthalmopathy for prediction of hepatic dysfunction caused by Graves disease, ROC curve was drawn (**figure 3**). The value that affords highest sum of sensitivity and specificity was the optimal cut-off value in the ROC curve.[7, 8] The results depicted that optimal cut-off value for FT3 was 20.93pmol/L with sensitivity and specificity of 57.1% and 67.0% respectively. (AUC= 0.653; P < 0.001; 95% CI =0.592- 0.710). Similarly, sensitivity and specificity for ophthalmopathy were 50% and 73.01% respectively.

Discussion

Since the first description regarding hepatic dysfunction in patients with hyperthyroidism given by Habershon, the liver function abnormalities or damage seen in patients with hyperthyroidism is widely reported.[5, 9–12]. It is well known fact that various tissues are affected by elevated thyroid hormones through different mechanisms involving cardiovascular, nervous and gastrointestinal systems. [13] This study somehow confirmed that liver biochemical abnormalities are frequently observed in patients with newly diagnosed and untreated Graves disease. In this small retrospective study, 66.5% of Graves patients have at least one of the liver biochemical abnormalities. Although hepatic dysfunction is common in patients with Graves disease, most of them are not severe enough requiring different treatments and rather improves following anti- thyroid treatment. Comparing with previous study[14], the

prevalence rate in this study is higher for liver function abnormalities with an incidence of 66.5%. Likewise, some other studies show higher prevalence rate for liver function abnormalities [10, 12] which suggests this study being consistent with them. Among many mechanisms for liver damage, some of them as reported by many researchers includes: - inadequate perfusion to hepatocytes leading to hypoxia and free radical damage thus attributing biochemical disturbances in the liver, direct elevated thyroid hormones toxic effect in liver, mitochondrial dysfunction and production of reactive oxygen species through oxidative stress causing hepatic damage, autoimmunity leading to hepatocyte injury, anti- thyroid drug related liver damage etc.[9, 15–17] [18] In a recent study, it was depicted that elevated TRAb level also led to liver dysfunction in Graves patients[12]. Upadhyay et.al in 2004 used rat models both in-vivo and in-vitro showing that excessive T3 induces apoptosis of hepatocytes and causes hepatic dysfunction through activating mitochondrial- dependent pathway.[19] Although various mechanisms had been described so far, the exact pathogenesis involved in liver damage is yet to be straightened out.

It is essential to determine the risk factors for hepatic dysfunction in patient who presents with higher frequency of liver damage with untreated Graves disease. In this study, analysis of some of the related factors was done such as age, course of disease, gender, goiter, ophthalmopathy, thyroid hormones, thyroid autoantibodies, thyroid volume, WBC count with granulocyte % etc. using univariate analysis. No differences in between age, gender, course of disease, presence and absence of goiter were seen. The values for BMI, thyroid volume, TPO-Ab, TgAb, TRAb were all similar in between two groups which indicates that there is no correlation between these factors with the incidence of having abnormal liver functions. Compared to previous study where FT4, TRAb, TPO-Ab, weight of thyroid and heart rate were risk factors[20], in this study FT4, FT3 were the associated risk factors and WBC count, granulocyte %, ophthalmopathy was inversely related to Graves patients having liver dysfunction. Likewise, a retrospective cohort study shows higher FT3, FT4 and TRAb in Graves patients with liver dysfunction suggesting that excess of thyroid hormone leads to liver tissue hypoxia because of enhanced hepatic and splanchnic oxygen demand[21]. In contrast, there are studies which advices that elevated thyroid hormones and liver biochemical abnormalities are not inter- related [9, 22]. In a study done by Till Ittermann et. al, FT4 levels and hepatic steatosis were reciprocally inter-related. There was not any consistent relationship of TSH and serum FT3 with hepatic steatosis and serum FT4 (thyroxine) concentration was much lower in patients having hepatic steatosis.[23] When there are several studies done for association between treatment used for Graves ophthalmopathy (e.g. steroids) and liver dysfunction [24, 25], no studies have been done suggesting Graves ophthalmopathy alone being associated with hepatic dysfunction. In this study, patients in group B were more likely to have ophthalmopathy than patients with group A which suggests that involvement of eye have inverse association between Graves patients having liver dysfunction ($p = 0.001$, OR = 0.355). Graves ophthalmopathy is commonest among many extrathyroidal manifestations of Graves disease of which the main risk factors includes the prophylaxis of steroids. Steroid therapy has been linked up with liver damage in such cases.[26] When drug- induced hepatic damage is common in Graves ophthalmopathy, it is yet unclear why hepatic damage occurs in untreated patients of Graves ophthalmopathy.

Liver has an essential function in thyroid hormone metabolism. Liver function abnormalities are very common in patients with Graves disease as excess of thyroid hormones increases liver burden and can have direct toxic events over liver tissues.[13, 15]. In a large cohort study done, there was no significant differences between hepatic dysfunction and normal hepatic function in Graves patients in the levels of FT3 and FT4 [12]. Similar results have been reported in few more studies done previously [23, 27]. However, in this study, there was significant differences between the thyroid hormone levels in-between the two groups which corroborates with existing studies [19, 21]. Regarding the total white blood cells count (WBC) and agranulocytosis, there are varieties of studies done previously. Graves disease is often associated with leukopenia, mainly agranulocytosis and the specific mechanisms thought to be involved includes marrow depression, anti- neutrophil antibodies etc.[28] It has been suggested that a cross antigenicity between TSH receptors and polynuclear neutrophils, a decreased circulating time of granulocytes and reduced marrow granulocyte reserve are the causes of neutropenia in thyrotoxicosis. [29, 30] However, these still remain controversial .When slight leucopenia, neutropenia and thrombocytopenia are common manifestations of Graves disease even in untreated cases and believed to be an autoimmune process, use of anti- thyroid medications mainly Thiamazole could cause serious life- threatening agranulocytosis. This critical condition however occurs only in 1% of patients within the 1st few weeks or months of the treatment.[31] Irvine et.al in 1977 found significant difference in the blood count mainly reduction in total leukocyte count which has attributed to a fall in absolute neutrophil count. [32] Relative lymphocytosis with a normal range or slightly lower WBC count are the characteristics laboratory findings in Graves disease, called as Kocher's blood picture.[33] Viral infections in liver (hepatitis), alike other infections causes ineffective leukocyte production in bone marrow as well as shifts of cells from the circulation towards marginal blood pool. Also, they may bring about peripheral destruction of WBC due to both immune as well as non- immune processes.[34] However, this study excluded all the observed cases of hepatitis initially. The results of this study demonstrated significant difference between the two groups in context of WBC count and granulocyte %. Patients of group A were slightly lower in WBC count and granulocyte % ($P = 0.007$, OR = 0.858 and $P = 0.003$, OR = 0.968 respectively) showing inverse association between Graves patients with liver dysfunction and WBC count along with granulocyte %. This concludes that patients in group A were found to have leukopenia (mostly neutropenia) in their circulating blood.

This study used a multivariate logistic analysis divulging that Graves disease patients with high levels of FT3 and/or those without ophthalmopathy had greater risk of developing LFT abnormalities. The sensitivity and specificity of serum FT3 using 20.93 pmol/L as cut –off for predictor of LFT abnormalities were 57.1% and 67.0% and sensitivity and specificity of ophthalmopathy were 50% and 73.01% respectively. It is believed that except the principle role in thyroid hormone regulation, TSH also acts on TSHR in hepatocytes leading to abnormal LFTs. The exact mechanisms are poorly understood and thus is an area for further research. Since this study is retrospective, possibility of its effect in epidemiological significance cannot be overlooked. Another limitation lies in patient evaluation as some of the tests were not carried out in all the patients. For instance- ultrasound for thyroid volume was not done in some patients, some of the autoantibodies linked with autoimmune hepatitis were not measured.

Also, FT3 and FT4 were selected as thyroid function indexes ignoring total T3 and T4 while total T3 has been shown to affect hepatic function.[19] Likewise, due to the limited sample size, liver damage could not be further divided into hepatocellular, cholestatic and mixed types. Therefore, in order to confirm these prefatory results, further larger prospective studies are demanded.

Conclusion

Hepatic dysfunction is common in patients with Grave's disease. The evidence presented in this paper demonstrates that liver biochemical abnormalities relate to the elevation of FT3 and such elevation of FT3 may contribute to liver dysfunction independently in patients suffering from Grave's disease. Additionally, Graves ophthalmopathy however tends to have inverse relationship with the patients of Grave's disease having liver dysfunction. It calls for advanced research in larger study groups as the findings will open new doors for early intervention and specific therapy.

Abbreviations

LFTs- Liver function tests

ALT- Alanine aminotransferase

AST- Aspartate aminotransferase

ALP- Alkaline phosphatase

γ-GGT- Gamma glutamyl transpeptidase

TBIL- Total bilirubin

DBIL- Direct bilirubin

WBC- White blood cells

FT3- Free triiodothyronine

FT4- Free thyroxine

OR- Odds ratio

CI- Confidence interval

TSH- Thyroid stimulating hormone

TRAb- Thyrotropin receptor antibody

BMI- Body mass index

TPOAb- Thyroid peroxidase antibody

TgAb- Thyroglobulin antibody

TSHR- Thyroid stimulating hormone receptor

Declarations

Ethics approval and consent- This is a retrospective study that include the brief details and analysis of clinical data of patients. Written informed consent from each of the patients was received and then approval from the ethics committee of Tianjin medical university general hospital was made.

Consent for publication- Not applicable to this study.

Competing interests- The authors declare that they have no competing interests.

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Availability of data and materials- The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Inquiries for data may be sent to following address zhongshuma@sina.com.

Author's contribution- Kalpana Pudasaini and Shaoqin Yang equally contributed to this article.

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Figures

Figure 1

Figure 2

The relative distribution of different LFT abnormalities in Grave's disease patients with abnormal LFTs.

Figure 3