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Research article

Evaluation of Thyroid Function Tests in Children with Chronic Liver Diseases

Running title: Thyroid functions in chronic liver disease

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What is already known on this topic?
Thyroid hormone metabolism may be impaired in chronic liver diseases and subclinical hypothyroidism or euthyroid sick syndrome may occur. These data were mostly obtained from studies in adult patients, and there are very few studies in the pediatric age group investigating this issue.

What this study adds?
It should be kept in mind that children with chronic liver disease, especially glycogen storage diseases may have subclinical hypothyroidism.

Abstract
Backgrounds /Aims: Studies related to changes in thyroid hormone metabolism in the course of chronic liver diseases have been conducted mostly in adults.In this study, we aimed to investigate the thyroid dysfunction in childhood chronic liver diseases.
Methods: Between 2005 and 2018, 107 (53 female, 54 male) patients aged between 1 month and 18 year-old age who were diagnosed as chronic liver disease and had thyroid function tests in their files were included in this study. Anthropometric characteristics, laboratory data (ALT, AST, ALP GGT, total bilirubin, direct bilirubin, indirect bilirubin, albumin, total protein), and thyroid function test values were obtained from patient files.
Results: Of the 107 patients, 96 (89.7%) had normal thyroid function test and 7 (6.5%) had subclinical hypothyroidism and four (3.7%) had euthyroid sick syndrome. Of the 7 patients with subclinical hypothyroidism, one (14.2%) had glycogen storage diasease, one (14.2%) had biliary atresia, one (14.2%) had undiagnosed cholestatic liver disease, one (14.2%) had Alagille syndrome, one (14.2%) had idiopatic hepatitis, one (14.2%) had progressive familial intrahepatic cholestasis (PFIC) and one (14.2%) had congenital hepatic fibrosis.
Spearman correlation analysis showed a negative correlation between free T3 and direct bilirubin (r = -0,329, p = 0,027).
Conclusion: In conclusion, euthyroid sick syndrome or subclinical hypothyroidism can be seen in children with chronic liver diseases. Therefore, thyroid function tests should be evaluated in these cases at the diagnosis and monitoring. Moreover, this study is the first to show a negative correlation between free T3 levels and direct bilirubin, suggesting the association between the disease severity and the thyroid function test.
Key Words: Pediatric or childhood chronic liver diseases, thyroid function test, euthyroid sick syndrome, subclinical hypothyroidism.

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Introduction

Thyroid hormone synthesis occurs in the thyroid gland and is mainly controlled by thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland. The hormone that is mostly synthesized from the thyroid gland is tetraiodothyronine (T4), while the active form at the cell level is triiodothyronine (T3) (1). Iodothyronine seleno-deiodinase enzyme complex, which regulates thyroid hormone metabolism, consists of three types of enzymes: type 1, type 2 and type 3 deiodinase (2). Deiodineases are responsible for the conversion of T4 to T3 (active form), T4 to rT3 (reverse T3; inactive form) and the conversion of rT3 and T3 to diiodothyronine (T2) (2). T4, the main product of the thyroid gland, must be converted to T3 by type 1 or type 2 deiodinase enzymes in order to demonstrate thyroid activity (1,2).

Studies have shown that chronic liver diseases can lead to various conditions related to thyroid hormone metabolism (subclinical hypothyroidism, euthyroid sick syndrome (2-6).

Euthyroid sick syndrome is a condition clasically characterized by low serum T3, low or normal free T4 and normal or low TSH (7). In a prospective study of 118 patients with cirrhosis, thyroid glandular volume increased by 17% compared to controls and moreover, low total / free T3 and high rT3, which is suggesting euthyroid sick syndrome, were demonstrated in thyroid hormone profiles (8). It has been suggested that this occurs as a result of a decrease in the activity of type 1 deiodinase and an increase in the activity of type 3 deiodinase (2). In a study of adult cases with acute and chronic liver diseases, the rate of thyroid dysfunction was found to be 16% and 7% of them were reported to have euthyroid sick syndrome (9). Caregaro L et al. (10) reported that the frequency of euthyroid sick syndrome was found to be 30.6% in a recent study of cirrhotic adult patients.

Subclinical hypothyroidism (SH) is defined as a serum thyroid-stimulating hormone (TSH) level above the reference range with normal serum free thyroxin (fT4) and free triiodothyronine (fT3) levels. (11). In pediatric population, SH prevalence is reported to be slightly lower than 2%, although epidemiological studies concerning childhood and adolescence are scanty (12). In a study conducted with adult patients with acute and chronic liver diseases, subclinical hypothyroidism was found in 3.5% of patients with thyroid dysfunction (9). In the literature, there is only a few studies investigating the relationship between liver disease and thyroid dysfunction in the pediatric age group (13-15). In a study of children with glycogen storage disease (GSD), it was reported that free T4 levels were significantly lower in patients with GSD type 1a and type 1b and free T3 is reported to be significantly higher in patients with GSD type 1b than in the control group (13). In a study of children with chirrosis reported that decreased levels of thyroid hormones are correlated with the severity of disease and can be seen in more advanced cirrhosis, patients with decreased T4 levels need a liver transplant more immediately than those patients that do not have decreased T4 levels (14). In another study of children with liver chirrosis reported that FT3 was lower in patients than controls (15).

It has been suggested that there is a relationship between hypothyroidism and autoimmune liver diseases such as chronic active hepatitis and primary biliary cirrhosis (3). Thyroid dysfunction has been shown in 5% to 20% of patients with primary biliary cirrhosis and chronic active hepatitis. There is insufficient data showing the relationship between childhood chronic liver disease and thyroid dysfunction. Therefore, in this study, we aimed to identify the thyroid dysfunction that can be seen in the course of childhood chronic liver diseases and to contribute to the literature by guiding clinicians in terms of this aspect.

Subjects and Methods

Between January 2005 and June 2018, 107 (53 female, 54 male) patients aged between one month and 18 year-old age who were diagnosed as chronic liver disease by the pediatric gastroenterology and hepatology and nutrition department of our hospital were included in this study. Chronic liver disease is a disease that involves a process of progressive and irreversible damage in the liver due to some acquired or congenital diseases, and subsequent regeneration of liver parenchyma leading to fibrosis and cirrhosis. Patients with acute hepatic disease, drug use that impair thyroid function (dopamine, glucocorticoid) and known thyroid disease were not included in the study. The current study was approved by the local ethics committee in light of the Helsinki Declaration (protocol no: 2017 / 09-10).

Anthropometric data (age, gender, body weight, height, body mass index), laboratory data [alanine aminotrasferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, indirect bilirubin, albumin, protrombin time, INR, total protein], and thyroid function test values (TSH, free T4, free T3) were obtained from patient files. Body mass ındex (BMI) of each case was calculated by dividing weight (in kilograms) by the height (in squared meters). For calculation of percentiles and standard deviation scores (SDSs) of all anthropometrics according to Turkish children growth data, child metrics online calculator program (http://www.childmetrics.com) was used (16).

Subclinical hypothyroidism (SH) is defined as a serum thyroid-stimulating hormone (TSH) level above the reference range with normal serum free thyroxin (fT4) and free triiodothyronine (fT3) levels. (11). Euthyroid sick syndrome was defined as low free T3, normal / low free T4 and normal / low TSH (17). TSH, free T3, and free T4 were analyzed by chemiluminescence 'ECLIA' method and Roche Elecsys E170 (Roche Diagnostics, Indianapolis, IN, USA). TSH, fT4 and fT3 values of the patients included in the study were evaluated by reference to the age range of this kit (18). Normal range of serum TSH is between 0,72-11 µIU/mL for 6 day -3 months of

age, between 0,73-8,35 μIU/mL for 4-12 months of age, between 0,70-5,93 μIU/mL for 1-6 years of age, between 0,60-4,84 μIU/mL for 7-11 years of age, between 0,51-4,30 μIU/mL for 12-20 years of age. Normal range of free T4 is between 0,89-2,20 ng/dL for 6 day -3 months of age, between 0,92-1,99 ng/dL for 4-12 months of age, between 0,96-1,77 ng/dL for 1-6 year of age, between 0,97-1,67 ng/dL for 7-11 years of age, between 0,98-1,63 ng/dL for 12-20 years of age. Normal range of free T3 is between 1,95-6,04 pg/mL for 6 day -3 months of age, between 2,15-5,83 pg/mL for 4-12 months of age, between 2,41-5,50 pg/mL for 1-6 years of age, between 2,53-5,22 pg/mL for 7-11 years, between 2,56-5,01 pg/mL for 12-20 years of age.

Statistical Analysis

Statistical analyses of the data were conducted with SPSS 24.0 (IBM Corp., Armonk, New York). The distribution of data was evaluated with the Kolmogorov-Smirnov test. For numerical comparisons, the independent sample t-test or Mann-Whitney U-tests were used according to normal distribution of the measured parameters. Categorical data were expressed as frequency (%), while numerical data were expressed as median (25-75th percentile) or mean ± standard deviation. In all statistical tests, p values <0.05 were considered significant. Spearman's rho correlation was used to identify the associations between variables.

Results

A total of 107 patients with chronic liver disease were included in the study. Of all cases, 53 (49.5%) were female and 54 (50.5%) were male and the median age was 1.25 years (0.28-10.3 years). The median of BMI was 15.9 kg / m2 (14.2-17.4) and the BMI SDS was -0.80 ± 1.79 (Table 1). The distribution of cases with chronic liver disease is shown in Table 2. Twenty two patients (19.8%) had chronic liver disease due to congenital metabolic diseases, 14 (13.0%) had chronic viral hepatitis and 34 had cholestatic liver disease.

Of the 107 patients, 96 (89.7%) had normal thyroid function test and 7 (6.5%) had subclinical hypothyroidism and four (3.7%) had euthyroid sick syndrome. Of the 7 patients with subclinical hypothyroidism, one (14.2%) had glycogen storage diasease, one (14.2%) had biliary atresia, one (14.2%) had undiagnosed cholestatic liver disease, (14.2%) had Alagille syndrome, one (14.2%) had idiopatic hepatitis, one (14.2%) had progressive familial intrahepatic cholestasis (PFIC) and one (14.2%) had congenital hepatic fibrosis. The distribution of patients with euthyroid syndrome was as follows: one patient (25%) had congenital hepatic fibrosis, two patients (50%) had undiagnosed cholestatic liver disease, and one patient (25%) had cryptogenic cirrhosis (Table3). Correlation coefficients between thyroid function tests and liver function tests summarized in Table 4.There was a negative correlation between free T3 and direct bilirubin ($r = -0.329$, $p = 0.027$) according to the analysis of thyroid function tests and liver function tests. The weight, height and BMI SDS values of patients with abnormal thyroid function tests were significantly lower than those of patients with normal throid function test ($p < 0.01$, 0.043 and 0.014; respectively) (Table 5).

Discussion

In the present study, while thyroid function tests were found to be normal in 89.7%, subclinical hypothyroidism was found in 6.5% and patient euthyroid sick syndrome in 3.7% of the cases with chronic liver diseases. The distribution of patients with patient euthyroid sick syndrome is as follows: congenital hepatic fibrosis in one patient, cholestatic liver disease in two patients and liver transplantation due to cryptogenic cirrhosis in one patient. In a study of adult patients conducted by Sandeep Kharb et al. (9) was reported that 16% of patients with acute and chronic liver disease had thyroid dysfunction and, additionally, 7% of these patients with thyroid dysfunction have reported to be euthyroid sick syndrome. In a study of patients with cirrhosis, the frequence of euthyroid sick syndrome was reported to be 30.6% (10). In experimental studies have shown that the synthesis and release of T4 and T3 are adversely affected by elevated proinflammatory cytokine concentrations (17). In addition, an increase in interleukin 1 beta (IL1β) expression during acute inflammation has been shown to reduce TSH receptor expression (17). In addition, the conversion of T4 to T3 decreases and the level of rT3 increases as a result of the reduction in the function of the deiodinase type 1 enzyme involved in the transformation of serum T4 to T3 by deiodination of the outer ring and in the degradation of rT3 by deiodination of the outer ring, which is contributing to the clinical picture regarding thyroid dysfunction (17). As a result, during acute or chronic inflammation, some cytokines affect both TSH expression and deiodinase type 1 enzyme activity, supporting the role of the patient in the emergence of euthyroid sick syndrome.

Treatment is decided according to the presence of possible clinical features of hypothyroidism, the degree of TSH elevation, changes in time in TSH and free T4. In the current study, SH were detected in 7 patients. In a study conducted by Melis D et al. (13) in pediatric patients with GSD, free T4 levels were significantly lower in GSD type 1a and GSD type 1b patients and, moreover, free T3 levels were significantly higher in patients with GSD type 1b than control group. In the same study, although four of seven patients with GSD type 1b had apparent / subclinical hypothyroidism, subclinical / apparent hypothyroidism has not been reported in patient group with GSD type 1a. In the present study, there were 15 cases of GSD and one of them (6.6%), which is GSD type 1a, had subclinical hypothyroidism. The prevalence of apparent and subclinical hypothyroidism have been reported to be higher in GSD type 1b cases compared to other types (19). It is noteworthy that the rate of detecting thyroid dysfunction in cases with GSD was higher than the other patient groups, which is in accordance with the literature.

However, due to the low number of GSD cases in our study, further studies including large case series are needed to clarify the relationship between GSD and thyroid dysfunction.

Congenital liver disease and hypothyroidism may be manifestations of an underlying genetic defect. For example, *JAG*1 gene defect causes Alagille syndrome type 1 and hypothyroidism. In a study that was conducted in 21 Alagille patients by de Filippis et al (20), some variants in the *JAG1* gene have suggested to cause to congenital thyroid defects and unexplained mild hypothyroidism (20). In our study, one cases with Alagille syndrome had SH. However, this study was designed as a cross-sectional study and long-term thyroid function test monitoring was not performed. This may be the reason why thyroid disorder is not detected in these patients. In this respect, thyroid function test monitoring of Alagille patients is very important.

One (14.2%) of seven patients with SH was biliary atresia. The relationship between biliary atresia and thyroid abnormalities is not yet clear. In a study investigating the genetic etiology of 35 cases with biliary atresia by using single nucleotide polymorphism (SNP) genotyping arrays, heterozygous 2q37.3 deletions was detected in two of these patients (one of whom had congenital hypothyroidism) (21). Further studies have shown that 2q37 region contains 18 genes and two of these genes (*ATG4B, ING5*) are highly expressed in thyroid gland except T / B cells. These genetic findings may explain the development of thyroid hormone abnormalities in patients with biliary atresia.

In addition, it was reported that there is a relationship between primary sclerosing cholangitis and autoimmune thyroiditis. However, there were no cases of primary sclerosing cholangitis among the patients with cholestasis with subclinical hypothyroidism in our study. Additionally, in the present study, the correlation analysis between thyroid function tests and liver function tests revealed a negative correlation between free T3 and direct bilirubin ($r = -0{,}329$, $p = 0{,}027$). It is reported that free T3 serum concentrations are associated with the severity of liver function test; however, there is no data on the relationship between direct bilirubin and free T3 (22). Further studies are needed to better define thyroid dysfunction in cholestatic liver diseases. Furthermore, in the present study, weight SDS, height SDS and BMI SDS values of patients with impaired thyroid function tests were found to be significantly lower than those with normal thyroid function test. This result suggests that insufficient weight gain due to nutritional deterioration may be higher in children with thyroid hormone dysfunction, which is may be related to the disease severity. There are lack of studies regarding this issue in the literature and additional studies are needed.

Study Limitation

There are some limitations of our study to be acknowledged. These are: i) low number of cases, ii) lack of long-term follow-up of thyroid function tests, and iii) ignoring the impact of other drugs on thyroid functions. Moreover, in this retrospective study, since no further investigation (thyroid antibodies, imaging) was performed in patients with thyroid function test abnormalities, no evaluation could be made in this respect.

Conclusion

In conclusion, euthyroid sick syndrome or subclinical hypothyroidism can be seen in children with chronic liver diseases. Therefore, thyroid function tests should be evaluated in these cases at the diagnosis and during follow-up. In addition, different types of thyroid dysfunction, according to the type or stage of liver disease, may be seen. Further studies with large case series are needed to better understand the effect of chronic liver disease on thyroid function.

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Table 1: Age, sex distribution and anthropometric characteristics of patients

Parameters	**Values**
Age at diagnosis (year)	1.25 (0.28-10.3)
Gender [female (%) / male (%)]	53 (49.5%) / 54 (50.5%)
Weight (kg)	10.1 (4.9-32.0)
Weight SDS	-0.94±1.44
Height (cm)	76.5 (55.8-140.0)
Height SDS	-0.76±1.41
BMI (kg/m^2)	15.9 (14.2-17.4)
BMI SDS	-0.80±1.79

SDS; standard deviation score, BMI; body mass index, data are given as mean ± SD or median (25th-75th percentile)

Table 2: Classification of patients according to their diagnosis

Diagnosis	**Number (n)**	**Percent (%)**

Chronic viral hepatitis*	14	13.0
Autoimmune hepatitis	5	4.7
Wilson Disease	11	10.2
Chronic liver disease due to congenital metabolic diseases**	22	19.8
Idiopathic chronic hepatitis	8	7.5
Cirrhosis ***	5	4.5
Cholestatic liver disease	34	31.5
Cystic Fibrosis	3	2.8
Idiopathic Portal Hypertension	3	2.8
Hydatid Cyst	2	1.9
Total	107	100

Chronic viral hepatitis*: 13 cases with hepatitis B ve one with hepatitis C
Chronic liver disease due to congenital metabolic diseases **: Tyrosinemia, glycogen storage diseases, zelweger's disease, galactosemia, hemochromatosis
Chirrosis***: 3 cases with cryptogenic cirrhosis, 1 case with congenital hepatic fibrosis and 1 case with liver fibrosis secondary to chemoteropy

Table 3: Age, Free T3, free T4 and TSH levels of patients with thyroid dysfunction

Patient no	Age	Diagnosis	Thyroid disorders	TSH	Free T4	Free T3
9	2 months	Biliary atresia	SH	22.80	1.13	1.67
19	17.0 years	PFIC	SH	4.55	1.10	1.99
35	1 year	Cholestatic liver disease	SH	7.70	1.04	3,95
48	13 years	Congenital hepatic fibrosis	SH	5.03	1.11	3.12
82	1 year	Idiopatic hepatitis	SH	6.40	1.10	3,65
89	1.5 years	Glycogen storage disease	SH	11.87	0.93	3,56
96	2 months	Alagille syndrome	SH	18.80	0.96	3,21
17	10 years	Hepatic fibrosis secondary to chemoteropy	ESS	0.19	0.79	1.78
20	1.5 months	Cholestatic liver disease	ESS	0.17	0.94	1.17
50	8 years	Cryptogenic cirrhosis	ESS	0.23	0.85	1.20
69	1.5 months	Cholestatic liver disease	ESS	0.09	1.13	0.90

SH: Subclinical hypothyroidism, ESS: Euthyroid sick syndrome

Normal TSH levels between 0,72-11 µIU/mL for 6 day -3 months, between 0,73-8,35 µIU/mL for 4-12 months, between 0,70-5,93 µIU/mL for 1-6 years, between 0,60-4,84 µIU/mL for 7-11 years, between 0,51-4,30 µIU/mL for 12-20 years.
Normal free T4 levels between 0,89-2,20 ng/dL for 6 day -3 months, between 0,92-1,99 ng/dL for 4-12 months, between 0,96-1,77 ng/dL for 1-6 year, between 0,97-1,67 ng/dL for 7-11 years, between 0,98-1,63 ng/dL for 12-20 years.
Normal free T3 levels between 1,95-6,04 pg/mL for 6 day -3 months, between 2,15-5,83 pg/mL for 4-12 months, between 2,41-5,50 pg/mL for 1-6 years, between 2,53-5,22 pg/mL for 7-11 years, between 2,56-5,01 pg/mL for 12-20 years.

Tablo 4: Correlation coefficients between thyroid function tests and liver function tests				
		TSH	free T3	free T4
AST	r*	-0.093	0.012	-0.053
	p	0.340	0.936	0.586
ALT	r*	-0.081	0.083	-0.078
	p	0.406	0.590	0.423
GGT	r*	0.115	0.088	0.016
	p	0.239	0.565	0.869
ALP	r*	-0.023	-0.46	0.105
	p	0.811	0.765	0.280
Total Bilirubin	r*	-0.017	-0.159	0.040
	p	0.858	0.297	0.684
Direct Bilirubin	r*	-0.102	-0.329	0.051
	p	0.298	0.027	0.601
Indirect Bilirubin	r*	0.070	0.043	0.012
	p	0.476	0.779	0.902
Total protein	r*	-0.098	0.188	-0.273
	p	0.319	0.221	0.005
*Spearman's correlation analysis; Serum free T3, free T4, and TSH as dependent variable ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, TSH: thyroid stimulating hormone				

Table 5: Comparison of body weight and height SDSs of patients with normal and impaired thyroid function tests			
	Normal Thyroid function test (n=96)	Impaired thyroid function test (n=11)	P
Age (years)	1.50 (0.3-11)	1.2 (0.1-10)	0.640[a]
Weight SDS	-0.77±1.36	-2.36±1.44	<0.001[b]
Height SDS	-0.67±1.40	-1.56±1.38	0.043[b]
BMI SDS	-0.44 (-1.72 – 0.23)	-2.70 (-4.90 – -0.60)	0.014[a]
[a]Mann-Whitney U test, [b]Student's T test, data are given as mean ± SD or median (25th-75th percentile), SDS; standard deviation score, BMI; body mass index			