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Comorbidity of endocrine disorders in children with chronic liver disease visiting Children's hospital of Tabriz University of Medical Sciences

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Abstract

Introduction: Many studies over the last two decades have dealt with the comorbidity of chronic liver disease (CLD) and endocrine disorders. Nevertheless, regional differences can affect the prevalence and etiology of diseases and their complications.

Objectives: Since no similar study has been conducted in Tabriz (a populous city in Iran), this study aimed to address the comorbidity of hormonal disorders in children with CLD visiting Children's hospital of Tabriz (a center in northwest Iran).

Patients and Methods: This descriptive cross-sectional study was conducted on children (2-18 years old) with CLD who visited Children's hospital of Tabriz in 2019-2020. Of them, 60 children were randomly selected as the sample. First, the status of endocrines was examined, and then its association with CLD was determined.

Results: The mean Insulin-like growth factor (IGF 1) of participants in all age groups was lower than the standard range. There was no significant difference between participants with different endocrine disorders in the levels of calcium, phosphorus, albumin, parathyroid hormone (PTH), total protein, cholesterol, triglyceride, growth hormone, and fasting blood sugar as well as the results of thyroid function tests. However, there was a significant difference between participants with different types of endocrine disorders in terms of IGF 1 ($P=0.018$). The highest and the lowest mean values of IGF 1 were observed in patients with primary sclerosing cholangitis (PSC) (520.59±12.52 ng/dL) and patients with primary biliary cirrhosis (142.95±3.96 ng/dL), respectively.

Conclusion: Autoimmune hepatitis was the most common chronic disease among the participants of this study. CLD causes a decrease in IGF1 level and it is responsible for about one-third of all bone fractures; however, overt diabetes and thyroid diseases were not observed in these patients.

Keywords: Endocrine glands, Chronic liver disease, Child

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Introduction

Chronic liver disease (CLD) refers to a group of diseases characterized by liver inflammation and the progression of cirrhosis. These diseases not only negatively affect the patient's quality of life but cause many complications (1). Most patients require specialized treatments and care, which are complex, time-consuming, and expensive. Hepatic encephalopathy is one of the most common reasons for admission of such patients to intensive care units, most of whom die despite best efforts. Studies have shown that cirrhosis with failure of three or more organs takes the life of 90% of patients (2, 3).

For a variety of reasons such as infectious, autoimmune, metabolic, and anatomical diseases, CLD occurs in children (4). Chronic viral hepatitis, autoimmune hepatitis, fetal hepatitis of unknown cause, biliary atresia, galactosemia, progressive familial intrahepatic cholestasis or Byler disease, secondary hemosiderosis - thalassemia, Wilson's disease, glycogen storage diseases, and alpha-1-antitrypsin deficiency are all categorized under CLD (5). Endocrine disorders in CLD include malnutrition and stunted growth, pituitary insufficiency, hypothyroidism, diabetes mellitus, type-1 autoimmune syndrome, and hyperthyroidism (6). Several studies on CLD patients have reported growth hormone deficiency and insulin-like growth factor (7, 8). In the last two decades, many studies have dealt with CLD and its association with endocrine disorders (9, 10). Nevertheless, regional differences can affect the prevalence and etiology of diseases and their complications.

Objectives

Since no similar study has been conducted in Tabriz (a populous city in Iran), this study aimed to address the comorbidity of hormonal disorders in children with CLD visiting children's hospital of Tabriz (a center in the northwest of Iran).

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Implication for health policy/practice/research/ medical education

This descriptive cross-sectional study was conducted on children (2-18 years old) with chronic liver disease who visited Children's hospital of Tabriz in 2019-2020. Of them, 60 children were randomly selected as the sample. First, the status of endocrines was examined, and then its association with CLD was determined. Results show Autoimmune hepatitis was the most common chronic disease among the participants of this study. CLD causes a decrease in IGF1 level and it is responsible for about one-third of all bone fractures; however, overt diabetes and thyroid diseases were not observed in these patients

Patients and Methods

Study design

This was a descriptive single-group cross-sectional study. After getting approval from the Research Council of Tabriz University of Medical Sciences and obtaining the informed consent of children's parents, this study was conducted on children aged 2-18 years with CLD who visited children's hospital of Tabriz university of medical sciences in 2019-2020. Based on the non-random purposive sampling method, 60 children were selected as participants in the study.

The inclusion criteria were 2 to 18 years old and affliction with CLD. The exclusion criteria were poor cooperation and unwillingness to continue the study. CLD was defined based on its duration (more than 3 to 6 months) or clinical evidence (stunted growth, club nails, and spider angioma).

The required data, including demographics and laboratory and clinical results, were collected using an author-made questionnaire. The validity of the questionnaire was confirmed by 5 professors of the pediatric's department. The questionnaire consisted of items about age, gender, type of liver disease, duration of disease, family history of liver disease, history of bone fracture, hair loss, height, weight, spleen size, liver size, and presence of ascites (based on clinical examinations and ultrasound showing fluid in the peritoneal cavity). Other items of the questionnaire were about taking corticosteroids, immunosuppressive drugs, calcium supplements, vitamins, propranolol, and diuretics, results of liver functioning tests (aminotransferases, bilirubin, alkaline phosphatase, prothrombin time) and thyroid functioning tests, fasting blood sugar, fasting blood cholesterol, fasting blood triglyceride, albumin, total plasma protein, total blood calcium, blood phosphorus, blood parathyroid hormone (PTH), growth hormone, and insulin-like growth hormone. The medical history and the results of physical examinations were recorded in the relevant questionnaire. After briefing the parents about the research objective and procedure, 5 ccs of blood were taken from veins for laboratory tests. Blood samples were sent to the hematology, hormonal, and biochemistry departments of the laboratory of the studied hospital.

Statistical analysis

Data were analyzed in SPSS version 21 using descriptive statistics (frequency tables, mean, and standard deviation) and inferential statistics (paired *t* test, independent *t* test, chi-square test, and Fisher's exact test).

Results

During the study period, 60 children with CLD visited Children's hospital of Tabriz. The mean age of participants was 9.42 ± 3.92 years. In terms of gender, 35 children were female and the rest of them were male. The study results indicated that autoimmune hepatitis was the most common CLD among the participants (one-third of the participants were afflicted with this disease) (Table 1).

The results of biochemical tests indicated that not all biochemical and hormonal factors were within the normal range (Table 2).

The statistical analysis demonstrated that the mean Insulin-like growth factor 1 (IGF 1) of participants in all age groups was lower than the standard range. There was no significant difference between participants with different endocrine disorders in the levels of calcium, phosphorus, albumin, PTH, total protein, cholesterol, triglyceride, growth hormone, and fasting blood sugar as well as the results of thyroid function tests. However, there was a significant difference between participants with different types of endocrine disorders in terms of IGF 1 ($P = 0.018$). The highest and the lowest mean values of IGF 1 were observed in patients with primary sclerosing cholangitis (PSC) (520.59 ± 12.52 ng/dL) and patients with primary biliary cirrhosis (142.95 ± 3.96 ng/

Table 1. Demographic and clinical information of participants

Variable	No. (%) or Mean ±SD
Age (years)	9.42 ± 3.92
Height (cm)	125.41 ± 10.56
Weight (kg)	28.14 ± 3.96
Hepatomegaly	12 (20)
Ascites	33 (55)
Splenomegaly	25 (41.66)
Taking corticosteroids	31 (51.66)
Taking immunosuppressive drugs	31 (51.66)
Taking diuretics	30 (50)
Autoimmune hepatitis	18 (30)
Biliary atresia	2 (3.33)
Cryptogenic cirrhosis	10 (16.66)
Congenital hepatic fibrosis	10 (19.66)
Metabolic disorders	9 (10)
Idiopathic neonatal hepatitis	7 (11.66)
Primary biliary cirrhosis	2 (3.33)
Primary sclerosing cholangitis	3 (5)
Wilson's disease	6 (10)

Table 2. Results of biochemical and hormonal tests

Variable	Mean±SD
AST (IU/L)	201.42 ± 25.65
ALT (IU/L)	151.95 ± 15.92
ALP (IU/L)	540.59 ± 45.19
Total bilirubin (mg/dL)	3.42 ± 0.19
Direct bilirubin (mg/dL)	1.2 ± 0.14
Prothrombin time (s)	14.59 ± 1.85
Albumin (g/dL)	4.41 ± 1.12
Total protein (g/dL)	7.19 ± 2.14
Cholesterol (mg/dL)	151.52 ± 10.41
Triglyceride (mg/dL)	110.85 ± 14.26
T3 (MIU/L)	128.85 ± 5.59
T4 (MIU/L)	10.59 ± 1.85
TSH (MIU/L)	3.90 ± 1.10
Paratormone (ng/L)	48.19 ± 2.96
Calcium (mg/dL)	92.85 ± 9.32
Phosphorus (mg/dL)	4.42 ± 0.12
GH (ng/dL)	15.01 ± 1.14
IGF-1 (ng/dL)	90.20 ± 8.37
FBS (mg/dL)	95.52 ± 8.85
T3 (MIU/L)	128.85 ± 5.59

AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, TSH; thyroid stimulating hormone, GH; growth hormone, IGF-1; Insulin-like growth factor 1, FBS, fsting blood sugar.

dL), respectively. The results indicated that one-third of patients had a history of bone fractures in the past, but there was no statistically significant difference between patients with different types of chronic liver diseases in terms of fractures ($P = 0.524$).

Discussion

Since children with CLD face several complications, correct and timely diagnosis of these complications is critical in lowering mortality and preventing further complications of this disease. This study found that [higher] fasting blood sugar levels are normal in these patients and are not indicative of diabetes (11). Several studies (12-14), however, found that patients with CLD are more likely to develop diabetes, which is referred to as a change in carbohydrate metabolism. The prevalence of diabetes and glucose intolerance in chronic liver patients ranges between 10% and 50% and up to 70%, respectively; but a normal fasting blood sugar will never reject a predisposition to diabetes. To demonstrate this, a GTT glucose tolerance test, which was not performed on the subjects of this study, is recommended. On the other hand, studies have shown that the incidence of diabetes in CLD patients increases after liver fibrosis, which is associated with the disease's late stages. Although the results of this study did not show overt diabetes in CLD patients, future studies are recommended to assess this predisposition through glucose tolerance testing (15, 16).

This study indicated that the reduction in IGF1 levels was one of the complications of CLD among the participants of all age groups. When patients with different types of liver disease were compared, it was shown that the highest and the lowest mean values of IGF 1 were related to patients with PSC and those with primary biliary cirrhosis, respectively (17). The difference between the groups in this regard was statistically significant. Age seems to be an important factor in serum IGF1 levels, as patients with PSC are usually in their late childhood and adolescence, whereas biliary atresia is a disease that typically occurs in infancy, and children with this disease usually do not live to adulthood without a liver transplant (18). Another major factor in this factor is the severity of liver dysfunction; in other words, liver problems are more common among infants with biliary atresia than those with PSC. The mean duration of the disease in this study was 60 months in patients with biliary atresia and 36 months in those with PSC. Acquired resistance to growth hormone and the GH-IGF1 axis disorder have been reported to occur in the early stages of CLD. Several other studies have reported decreased serum IGF1 levels, increased GH, and other components of this axis in patients with CLD. The results of this study indicated that thyroid hormones were within the normal range in most participants, which is not consistent with the results of previous studies (19, 20).

Studies on thyroid hormone levels in CLD patients suggest that although most patients are euthyroid, the measurement of their thyroid hormone levels indicates a decrease in the serum-free T3 levels and an increase in T4 levels, which could be due to a defect in the environmental conversion of T4 into T3. As a result, it is recommended that similar studies be conducted on larger samples using more robust methods. According to this study, autoimmune hepatitis was the most common CLD among the participants. The disease's underlying causes are unknown, though genetic predisposition, viral infections, or drug exposure may have played a role. The results of a similar study (21, 22) showed that after CLD following thalassemia, the most common CLD is biliary atresia. The prevalence of autoimmune hepatitis and its causes reported in this study need to be supported in future studies.

This study showed that about one-third of participants had a history of bone fractures. This rate in patients with CLD reaches 62%. Although a history of bone fractures was not associated with serum calcium and phosphorus levels as well as taking corticosteroids, calcium supplements, and diuretics, it suggests a possible decrease in the bone mass density of these patients; however, bone scans were not performed in this study. Some studies have argued that dietary changes, hormonal disorders, and cholestasis caused by liver diseases are responsible for osteoporosis and osteomalacia in these patients (23). Various studies show a decrease in bone mineral content and bone mineral density in the majority of children

with CLD. A study found that bone fractures are more common in the later stages of liver failure in patients with a higher body mass index (14). As a result, the severity of the disease and the stage of failure both play a role in causing this complication. The majority of fractures occur at the end of the spine. It is noteworthy that the study findings showed that high PTH and normal calcium levels in different types of CLD increase the risk of secondary hyperparathyroidism, which is consistent with the results of similar studies. Some studies have reported a decrease in IGF1 level, as well as bone changes and multiple fractures in CLD patients; but this study revealed no statistically significant difference in the mean IGF1 level between participants with and without fractures (24,25).

Conclusion

The study findings suggested that autoimmune hepatitis was the most common chronic disease among the participants, and CLD decreases IGF1 levels and causes bone fractures in about one-third of cases. However, overt diabetes and thyroid hormone disorders were observed in none of the participants.

Limitations of the study

One of the limitations of this study was the poor methodology (single-group cross-sectional) and the impossibility of performing some relevant experiments. Although diabetes is the most common endocrine disease in children, it was not possible to investigate it because its diagnosis requires measuring fasting blood sugar and [non-fasting] blood sugar separately two hours after a meal. Additionally, the participant all visited the hospital early in the morning while fasting, and many of them did not agree to visit the hospital twice a day. Another research limitation was the impossibility of performing an insulin stimulation test for measuring the growth hormone level.

Authors' contribution

LS is the single author of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Tabriz University of Medical Sciences approved this study. The institutional ethical committee at Tabriz University of Medical Sciences approved all study protocols(IR.TBZMED.REC.1400.1228). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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