

The Correlation between Anemia and Chronic Liver Disease in Children

Mohammed Khaleel Ibrahim*, Mohammad Fadhil Ibraheem**

ABSTRACT:

BACKGROUND:

Chronic liver disease is a major health burden on both parents and the child with a high morbidity and mortality rate, with different etiological causes: infectious, autoimmune, metabolic, vascular, drugs and some are idiopathic. Chronic liver disease is associated with many hematological abnormalities, particularly anemia, which result from combination of decreased oral intake and chronic blood loss from esophageal varices, portal hypertensive gastropathy or coagulopathy and thrombocytopenia.

AIM OF THE STUDY:

To study the prevalence and types of anemia in children with chronic liver diseases by clinical and laboratory findings.

METHODS:

A prospective study has been done in gastroenterology / Hepatology ward in Children Welfare Teaching Hospital for 73 children, aged 6 months to 14 years, with the diagnosis of chronic liver disease, over a period of 18 months, from 1st January 2019 to 31st June 2020, the patients were evaluated for their clinical manifestations of chronic liver disease and assessment for the presence of anemia, they were submitted to serial laboratory investigations:- Complete blood count, liver function test, coagulation study, serum iron, serum ferritin, and total iron binding study.

RESULTS:

The studied sample includes, 30 females (41%) and 43 males (59%), mean age of study sample were 6.6±3.7, 2_9 years high frequency age group, there were 36 (49%) children who had chronic liver disease found to have anemia, microcytic type (66.6%) from anemic patients with chronic liver disease. There were 16.4% from cases with mild anemia and 32.6% with moderate anemia.

CONCLUSION:

Microcytic, and specifically iron deficiency type of moderate severity anemia, was the most prevalent one. Children with chronic liver diseases aged > 9 years were more prone for anemia but there was no sex predominance.

KEYWORDS: Anemia, Children, Chronic liver disease.

INTRODUCTION:

Chronic liver diseases (CLD) are commonly associated with hematological abnormalities. Among these, anemia has a reported prevalence between 50%-87% and the highest prevalence being observed in patients presenting with hepatic encephalopathy and the severity of anemia can be classified according to WHO recommendation. Mild anemia corresponds to a level of adjusted Hb of 10.0–10.9 g/dl; moderate anemia corresponds to a level of 7.0–9.9 g/dl, while severe anemia corresponds to a level less than 7.0 g/dl. (1-4).

The commonest type of anemia encountered in advanced chronic liver disease is normocytic normochromic anemia, as a result of the chronic inflammatory state (5). Microcytic hypochromic anemia as a picture of iron-deficiency anemia which is attributed to acute and chronic blood loss from varices, portal hypertensive gastropathy and gastric antral vascular ectasia (6). Macrocytic anemia also may be seen due to vitamin B12 and folate deficiency, due to malnutrition and intestinal malabsorption (7). The etiology of anemia, especially in cirrhotic patients, is complex and multifactorial (8,9).

Another Several causal factors are implicated for anemia in patients with ACLD have been described:

*Children Welfare Teaching Hospital, Baghdad, Iraq

**College of Medicine – University of Baghdad, Baghdad, Iraq

ANEMIA AND CHRONIC LIVER DISEASE IN CHILDREN

- Formation of acanthocytes (spur cells) due to functional and structural defects in the lipid membrane of erythrocytes which is characterized by a short lifespan as a result of a higher susceptibility for degradation in the spleen⁽¹⁰⁾.
- Portal hypertension and splenomegaly in ACLD can induce pancytopenia by hypersplenism⁽¹¹⁾.
- The defect in hepcidin secretion by the liver; the main regulator of iron homeostasis which eventually leads to iron deficiency anemia^(9,11). Thirty two percent incidence of iron-deficiency anemia has been reported in children with end-stage liver disease^(9,10).

The clinical sequel of anemia in ACLD includes an increased risk for hepatic encephalopathy with association of increase of serum ammonia level, deterioration of renal function and development of the hepatorenal syndrome, and fatigue⁽¹²⁻¹⁶⁾.

MATERIALS AND METHODS:

A cross-sectional descriptive study conducted on 73 pediatric patients their age ranged from 6 months to 14 years were diagnosed with chronic liver diseases (CLDs), presented to outpatient clinic or admitted to wards of gastroenterology and hepatology of Children Welfare Teaching Hospital (CWTH) during the period from 1st of January 2019 to 31st June 2020.

A thorough data was collected from the children directly or from their relatives and filled in a prepared questionnaire, which included the followings: -Sociodemographic characteristics, Causes, onset and final diagnosis of CLDs, clinical features of children with CLDs and anemia, laboratory Investigations results: Serum ALP, Serum GOT, Serum GPT, TSB, serum albumin, blood urea, serum creatinine, RBS, INR and PT, Iron study including [serum iron, TIBC, serum ferritin] of children with CLD, Complete blood count to patient with CLD.

With Specific investigation performed according to provisional diagnosis:

MS/MS for metabolic diseases, TORCH screen, CMV IgM and PCR, hepatitis screen for hepatitis B&C and viral load PCR for infectious causes of CLDs, Slit lamp examination for kayser- Fleischer ring, 24 hours collection of urine for copper with penicillamine challenge, serum ceruloplasmin and neurological symptoms and hemolytic anemia, liver biopsy and histopathological study, abdominal ultrasonography with special emphasis to size of gall bladder, OGD for diagnosis and treatment of PHG and GAVE (Gastric Antral Vascular Ectasia) .

A sample of 5 ml venous blood was drawn from patients and sent for Laboratory of CWTH that used laboratory medical devices (SIEMENS Dimension RXL Max, and Sysmex CA-600 series). The investigations done for children were Serum ALP, Serum GOT, Serum GPT, TSB, serum albumin, RBS, INR and PT in addition to IDA investigations including CBC and iron study [serum iron, TIBC and serum ferritin].

Exclusion criteria

1. Children on iron therapy over period month or more because masking the result of IDA.
2. Children with acute infections when serum ferritin increases as acute phase reactant.
3. Children with increase serum ferritin when hemochromatosis suspected.

Statistical analysis

Statistical analysis was done using SPSS version 23 used for data entry and analysis. Mean and standard deviation was used to represent numerical data, frequency and percentage for categorical data. Appropriate tests (paired sample t test, chi-square, binary logistic regression) were done for the analysis of different marker by using Odd Ratio (OR)and 95% Confidence Interval (CI). P- value of ≤ 0.05 was considered as statistically.

RESULTS:

The study included 43(59%) male patients and 30(41%) female patients, the mean age of the study sample was 6.6 ± 3.7 year with age range 1-13 years, the highest frequency of chronic liver disease occurs more with age group 2-9 in 43 patients (58.9%), as shown in table (1):

ANEMIA AND CHRONIC LIVER DISEASE IN CHILDREN

Table 1: Clinico-demographic characteristic of study sample (n=73):

Variables	No.	%	
Gender	Male	43	58.9
	Female	30	41.1
Age group/ year	< 2	10	13.7
	2-9	43	58.9
	>9-14	20	27.4

The highest frequency was documented with Wilson disease 32% followed by undiagnosed CLD 20.5%, hepatitis B 9.6%, hepatitis C 8.2%, autoimmune hepatitis 8.2% and biliary atresia were 8.2%, GSD 5.6%, giant cell hepatitis 4.1% and Alagille syndrome 2.7%, the highest frequency of Wilson disease, hepatitis B & C, undiagnosed CLD end with cirrhosis came with age group 2-9 years as shown in table (2).

Table 2: Causes of chronic liver diseases in different age group(n=73).

Types of liver disease	Age group / year			Total
	< 2	2-9	>9	no.(%)
Wilson disease	0	14	10	24(32.9%)
Undiagnosed CLD	1	9	5	15(20.5%)
Hepatitis B	0	6	1	7(9.6%)
Hepatitis C	0	5	1	6(8.2%)
Autoimmune hepatitis	0	3	3	6(8.2%)
Biliary atresia.	4	2	0	6(8.2%)
GSD	3	1	0	4(5.6%)
Giant cell hepatitis	2	1	0	3(4.1%)
Alagille syndrome	0	2	0	2(2.7%)
Total	10	43	20	73(100%)

In study sample, the percentage of males (58.9%) while female (41.1%). In study sample, 49% were anemic and 51% were not anemic. Microcytic anemia (66.6%) is more frequent in anemic patients with chronic liver disease and about 52% IDA from anemic patients and 26% from sample study as shown in table (3):

Table 3: Association of gender, type and severity of anemia in study sample.

Variables	Cases		
	No.	%	
Gender	Male	43	58.9
	Female	30	41.1
Anemia	Anemia	36	49
	Normal	37	51
Profile of anemia	Microcytic IDA	19	52.7
	Normocytic	12	33.4
	Microcytic non- IDA	5	13.9
Severity of anemia	Mild	12	16.4
	Moderate	24	32.6
	Normal	37	51

ANEMIA AND CHRONIC LIVER DISEASE IN CHILDREN

There were significant differences in distribution of anemia regarding to age group in study sample, as 75% of 10-13 years old were anemic patients in cases group, p value ≤ 0.05 .

There were no significant differences in distribution of anemia regarding, gender as shown in table (4):

Table 4: Distribution of anemia with relation to gender and age groups instudy samples:

Variables	Cases					P value
	Anemia		Normal			
	no.	%	no.	%		
Gender	Male	22	51.2	21	48.8	0.7
	Female	14	46.7	16	53.3	
Age group/ year	<2	3	30	7	70	0.02
	2-9	18	41.9	25	58.1	
	>9-14	15	75	5	25	

Mean of liver function tests in cases group were, SGPT (285.8 \pm 310.4IU/L), SGOT (277.1 \pm 380.5IU/L), TSB (7.8 \pm 7mg/dl), Direct bilirubin (6.1 \pm 6.2mg/dl), TSP (5.9 \pm 1.6)g/dl, S Albumin (2.9 \pm 1.6g/dl), PT(16.7 \pm 5.5)seconds. Liver biopsy done in 11 cases, about 15% of

cases with CLD, whereas OGD done in 9 cases (12.3%) from children with CLD.

There was no significant difference in mean of liver function tests between anemic and not anemic patients p>0.05, as shown in table (5):

Table 5: Association of liver function tests with anemic and not anemic patients in study samples n=73):

Tests	Anemic cases	Not anemic cases	p value
	mean \pm SD	mean \pm SD	
SGPT	220.4 \pm 252IU/L	250.7 \pm 361.3IU/L	0.6
SGOT	292.1 \pm 454.7IU/L	262.5 \pm 296.8IU/L	0.7
TSB	6.8 \pm 5.5mg/dl	8.8 \pm 8.1mg/dl	0.2
Direct bilirubin	5.1 \pm 4.7mg/dl	7 \pm 7.3mg/dl	0.2
TSP	5.9 \pm 2g/dl	6 \pm 1g/dl	0.9
Serum albumin	2.8 \pm 2.1g/dl	2.9 \pm 0.7g/dl	0.9
PT	15.6 \pm 3.6g/dl	17.7 \pm 6.8g/dl	0.1

DISCUSSION:

The current study found that the most common liver disease type was Wilson disease 32% followed by undiagnosed chronic liver disease 20.5%, hepatitis B 9.6%, hepatitis C 8.2%, while Dhole S.D. *et al*⁽¹⁾ study in India revealed that metabolic liver disease was the most common liver disease (32.72%), followed by hepatitis (16.36%), autoimmune hepatitis (10.9%), the differences in etiology of chronic liver diseases may be explained by difficulties in reaching more sophisticated metabolic investigations and because of geographic and racial variations⁽⁶⁾.

This study shows chronic liver disease occurs more (58.9%) in children with age 2-9 year, this

result is nearly similar to Dhole S.D. *et al*⁽¹⁾ study demonstrated that the incidence of chronic liver disease was maximum in the age group of 6-12 years. This variation because of different classification of age groups was used in the studies.

The present study found anemia in 49% of children with chronic liver disease and IDA reported in 26%, in contrast to Zareifar S *et al*⁽¹⁷⁾ study in Iran which showed that 54.5% have anemia and IDA reported in 9% of the children with cirrhosis. This may be explained by that we recruit in our study all chronic liver diseases with wide variety of severity, not only children with liver cirrhosis.

ANEMIA AND CHRONIC LIVER DISEASE IN CHILDREN

Current study revealed that mean Hb level 10.3 ± 2.2 , which was lower than what was found by Zareifar S *et al*⁽¹⁷⁾ study 11.45 ± 3.07 g/dL in our study conducted to chronic liver disease while other study to patient cirrhosis.

Current study found that mean corpuscular volume was 74.4 ± 10 fl, TIBC 355.8 ± 107 μ g/dl, these values were lower than a result of Zareifar S *et al*⁽¹⁷⁾ study found that the MCV was 83 ± 5.5 fl, and mean TIBC were 365 ± 60 μ g/dl because in later study did not involve metabolic liver disease and patient with blood loss or PHG which lead to decrease Hb and MCV.

Current study found that mean S Iron was 61 ± 28 , which was higher than mean SI (55 ± 25.4) that revealed by Zareifar S *et al*⁽¹⁷⁾ study because wide normal range of S. iron and many patients have normal serum iron which affect mean S. iron.

Present study reveals SGPT elevated in 50.8% (220.4 ± 252) and SGOT was elevated in 50.7% (292.1 ± 454.7), Patel N *et al*⁽¹³⁾ study found serum AST is elevated (mean 70.59 IU/ML) and Serum ALT (mean 31.64 IU/ML).

Most of children (32.6%) with chronic liver disease in the current study were of moderate type anemia, similar result was found by Patel N *et al*⁽¹⁸⁾ and Kumar E.H. *et al*⁽¹⁹⁾ studies.

Present study noticed that, among patients who had chronic liver disease, there was no significant sex predominance regarding anemia, which was same to what was found by Zareifar S *et al*⁽¹⁷⁾ study, while significant predominance among males was reported by Dhole S.D. *et al*⁽¹⁾ study.

In the present study, among children who had chronic liver disease, anemia occurs more (75%) in children aged > 9 years in contrast to Zareifar S *et al*⁽¹⁷⁾ study that found no relationship between age and IDA in patients.

Current study reported no significant difference in mean liver function tests between anemic and not anemic patients; this result was supported by Zareifar S *et al*⁽¹⁷⁾ study.

Similar to the current study Lin CC *et al*⁽²⁰⁾ study in China found that serum Fe were significantly lower in the patients with chronic liver disease.

In contrast to current study, Raouf A.A *et al*⁽²¹⁾ study found that serum Fe, ferritin, was significantly higher in the CLD group.

Liver enzymes (AST, ALT, ALP, GGT) and total and direct bilirubin were significantly higher in the CLD patients, while total iron-binding capacity were significantly lower in the CLD patients which is in agree with Raouf A.A *et al*⁽²¹⁾ study in Egypt.

CONCLUSION:

Anemia, as a complication of chronic liver diseases, was higher than studies conducted in previous time in different places.

Anemia was moderate severity, iron deficiency type characterized by low mean Hb, SI, S. ferritin, MCV and high TIBC.

Children with chronic liver diseases aged > 9 years were more prone for anemia but there was no sex predominance and no mean difference of liver function tests between anemic and not anemic patients.

Recommendations:

- All patients with chronic liver diseases need to be evaluated and followed for the investigation regarding anemia and types of anemia and liver function test.
- For further research, large population-based studies are recommended in order to determine the scope of this problem nationwide.

REFERENCES:

1. Dhole SD, Kher AS, Radha G, et al. Chronic Liver Diseases in Children: Clinical Profile and Histology, *J Clin Diagn Res.* 2015; 9:SC04–SC07.
2. Gkamprela E, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. *Ann Gastroenterol.* 2017;30: 405–13.
3. Qamar AA, Grace ND, Groszmann RJ, et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin Gastroenterol Hepatol.* 2009;7:689-95.
4. Kalaitzakis E, Josefsson A, Castedal M, et al. Hepatic encephalopathy is related to anemia and fat-free mass depletion in liver transplant candidates with cirrhosis. *Scand J Gastroenterol.* 2013;48:577-84.
5. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011-1023.
6. Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015;373:485-86.
7. Lee YG, Chang Y, Kang J, Koo DH, Lee SS, et al. Risk factors for incident anemia of chronic diseases: A cohort study *PLOS ONE* 2019;14: e0216062.
8. McHutchison JG, Manns MP, Longo DL. Definition and management of anemia in patients infected with hepatitis C virus. *Liver Int WILEY.* 2006;26:389-98.
9. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. *Dig Dis Sci* 2010; 55: 548-59.

10. Alexopoulou A, Vasilieva L, Kanellopoulou T, Pouriki S, Soultati A, Dourakis SP. Presence of spur cells as a highly predictive factor of mortality in patients with cirrhosis. *J Gastroenterol Hepatol*. 2014;29:830-34.
11. Lv Y, Yee Lau W, Wu H, et al. Causes of peripheral cytopenia in hepatic cirrhosis and portal hypertensive splenomegaly. *Exp Biol Med (Maywood)*. 2017;242:744-49.
12. Maruyama S, Hirayama C, Yamamoto S, et al. Red blood cell status in alcoholic and non-alcoholic liver disease. *J Lab Clin Med*. 2001;138:332-37.
13. Mathurin SA, Agüero AP, Dascani NA, et al. Anemia in hospitalized patients with cirrhosis: prevalence, clinical relevance and predictive factors. *Acta Gastroenterol Latinoam*. 2009;39:103-11.
14. Kalaitzakis E, Josefsson A, Castedal M, et al. Factors related to fatigue in patients with cirrhosis before and after liver transplantation. *Clin Gastroenterol Hepatol*. 2012;10:174-81, 81.e1.
15. Les I, Doval E, Flavià M, et al. Quality of life in cirrhosis is related to potentially treatable factors. *Eur J Gastro Hepatol*. 2010;22:221-27.
16. Gungor G, Akyildiz M, Keskin M, et al. Is there any potential or additive effect of anemia on hepatorenal syndrome? *Turkish J Gastroenterol*. 2016;27:273-78.
17. Zareifar S, Dehghani SM, Rahanjam N, et al. Prevalence of Iron deficiency anemia in children with liver cirrhosis: A cross-sectional study, IJHOSCR. 2015; 9:3.
18. Patel N, Shah N. A Prospective Study of Anemia Profile of Chronic Liver Diseases Patients JMSCR 2017; 5:18144-48.
19. Kumar EH, Krishnan AR. Prevalence of Anemia in Decompensated Chronic Liver Disease. *World Journal of Medical Sciences* 2014;10:56-60.
20. Lin CC, Huang JF, Tsai LY, et al. Selenium, iron, copper, and zinc levels and copper-to-zinc ratios in serum of patients at different stages of viral hepatic diseases. *Biol Trace Elem Res* 2006; 109:15-24.
21. Raouf A.A, Radwan G.S, Konsowa H.A, et al. Serum zinc, copper, and iron in children with chronic liver disease, *Egyptian Liver Journal* 2013;3:63-72.