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# Prevalence of Cholelithiasis Among Multitransfused Thalassemic Patients In Basrah

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# نسبة انتشار الحصى المرارية لمرض فقر الدم البحري ذوي نقل الدم المتكرر في البصرة

**الخلاصة:**

أجريت دراسة مستقبلية على ٩٦ مريضاً (٥١ ذكراً، ٤٥ أنثى) مصابين بفقر الدم البحري متجانس الزيجات و فقر دم بحري / منحلي، فمن راجعوا مركز الثلاسيميا أو تم أدخالهم الى وحدات الأطفال في مستشفى البصرة للولادة و الطفل، أعمارهم تتراوح بين ٦ – ١٨ عاماً (معدل العمر ١٢،٣ عاماً) النسبة انتشار الحصى المرارية لمرض فقر الدم البحري ذوي نقل الدم المتكرر كانت ١٠،٥ % (٦،٥ للمرضى المصابين بفقر الدم البحري متجانس الزيجات و ١٤،٥ % للمرضى المصابين بفقر دم بحري / منجلي).

وجدت الدراسة بأن نسبة أنتشار الحصى المرارية تزداد بأزدياد العمر ليصل الى ٢٠% عند المرضى الذين تتجاوز أعمارهم ١٥ عاماً و عند الأناث أكثر مما عند الذكور. المرضى المصابين بالحصى المرارية كان معدل نسبة المادة الصفراء و الحديد لديهم اعلى و لكن قيم معامل كتلة الجسم، معدل خضاب الدم، مقيم أنزيمات الكبد لا تختلف بشكل مهم عن المرضى غير المصابين بالحصى المرارية، هذه النتائج تشير الى أن العمر، الجنس، أنحلال الدم المزمن، مرض الكبد المزمن و فرط حمل الحديد المزمن هي عوامل مهمة للأصابة بالحصى المرارية عند الأطفال المصابين بفقر الدم البحري.

**Summary:**

A prospective study was carried out on 96 patients (51 males and 45 females), with ك-thalassemia major and sickle cell / thalassemia, who were attending the Thalassemia Center or admitted to pediatric wards of Basrah Maternity and Child Hospital from the first of February till the end of July 2000. Their ages ranged from 6 - 18 years (mean age was 12.3 years). The prevalence of cholelithiasis (detected by ultrasonography) among multi-transfused thalassemic patients was 10.5% (6.5% in patients with ك-thalassemia major and 14.5% in patients with sickle 11/thalassemia).

It was found that prevalence of cholelithiasis increases with increasing age, reaching 20% in patients older than 15 years of age, and that females were affected more than males. Patients with

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cholelithiasis had higher mean serum bilirubin level and serum iron values, but their BMI, mean hemoglobin levels, alkaline phosphatase and serum aminotransferase values were not significantly different from patients without cholelithiasis.

These findings suggest that age, sex, chronic hemolysis, chronic liver disease and chronic iron overload are significant risk factors for gall stone formation among our thalassemic patients.

## Introduction:

Cholelithiasis is relatively rare in healthy children (1, 2), occurring more commonly in patients with various predisposing disorders (1). Chronic hemolysis (as in sickle cell anemia, thalassemia and hereditary spherocytosis) with consequent hyperbilirubinemia predisposes these patients to pigment gall stones (3, 4). Thalassemia genes are remarkable wide spread and these abnormalities are believed to be the most prevalent of all human genetic diseases (2), and there is a well known thalassemia belt which extends from Africa to Asia (5). The sickle cell / β-thalassemia syndromes are a heterogenous group of disorders whose clinical features depend on the severity of β-thalassemia component. These syndromes, as a group are the third most common form of sickle cell disease. They are more frequent in the Mediterranean area where the incidence of β-thalassemia is higher than that of the $B^S$ (6). Various clinical studies have demonstrated that gall stones are found increasingly in thalassemic patients older than 4 years (6), and that the prevalence of gall stones in sickle cell disorders ranges from 6 - 37% (7). However, other studies reported higher prevalence of gall stones in sickle cell patients depending on the age and diagnostic criteria (8, 9). Therefore, this study was carried out to determine the prevalence of cholelithiasis among multitransfused thalassemic patients in Basrah and to determine the correlation of cholelithiasis with selected demographic, hematological and biochemical indices.

## Patients and Methods

### Patients:

This study was carried out from the first of February till the end of July 2000, on 96 multitransfused thalassemic patients (51 males and 45 females), who were attending the Thalassemia Center or admitted to pediatric wards in Basrah Maternity and Children Hospital.

Forty seven patients were diagnosed to have β-thalassemia major and 49 patients with sickle cell / thalassemia, their ages ranged from 6 - 18 years. A thorough medical history and physical examination were done for each patient. A detailed past medical history was obtained with particular attention given to the patient age and age at diagnosis, frequency of blood transfusion, frequency of admission and cause of admission, and cause of admission (blood transfusion, vaso-occlusive crises, abdominal pain, infection or jaundice) and desferral therapy.

The anthropometric measurements including weight and height were recorded. Body Mass Index (BMI) was calculated as weight in (kg.) divided by the square of height (in meters).

**Methods:**

A blood sample was aspirated from each patient for hemoglobin level (Hb), liver function tests including total serum bilirubin (TSB), direct and indirect, alanine aminotransferase (ALT), asparate aminotransferase (AST) and alkaline phosphetase (ALP), serum iron and total iron binding capacity.

Ultrasonography was performed at the hospital by experienced radiologists. Sonographic tests of the gall bladder and common bile duct were offered to each case which were performed at morning following an overnight fast. No examination was considered complete without thorough examination of the gall bladder using a real time device with the patient in both supine and lateral position. Sonographic findings were considered positive when gall stones were defined as discrete echogenic objects within the gall bladder lumen that maintain their shape and move with rotation of the gall bladder.

Statistical analysis was performed using $X^2$ - test, t-test and Fisher's exact test. P value of less than 0.05 was considered to be statistically significant and less than 0.01 as highly significant.

**Results:**

Ninety six thalassemic patients were included in the study. Cholelithiasis was detected in 10 patients (10.5%). Table (1) demonstrates the distribution of cholelithiasis according to patients age, sex and type of anemia. It shows that the prevalence of cholelithiasis increases significantly with increasing age of thalassemic patients and it is significantly higher in females compared to male patients. Although the percentage of cholelithiasis is more among patients with sickle cell / thalassemia, the difference is statistically not significant.

BMI, selected hematological variables and results of liver function tests in thalassemic patients with and without cholelithiasis are illustrated in Table (2). There is no significant difference among patients with and without gall stones regarding BMI, mean Hb level, serum aminotransferase and alkaline phosphetase levels. However, mean serum iron and mean total serum bilirubin levels were significantly higher in thalassemic patients with gall stones.

Five patients (out of ten) with cholelithiasis were symptomatic and the rest were asymptomatic and they were discovered during the period of the study. Abdominal pain which is localized to the right upper quadrant was the main presenting feature in the symptomatic group. Two of them presented with acute abdominal pain and vomiting and emergency cholecystectomy was done for them, the other three patients presented with recurrent abdominal pain, Table (3).

**Discussion:**

Various clinical studies were done to study the prevalence of gall stones in sickle cell disorders worldwide. However, few studies were done to demonstrate the prevalnce of gall stones in thalassemic patients with contradictory results, although in view of population migration, the distribution of thalassemia genes appear to be world wide and to affect every ethnic group (5). The prevalence of cholelithiasis in this group of multitransfused thalassemic patients was 10.5%. The frequency of cholelithiasis was higher among patients with sickle cell / thalassemia (14.5%) than patients with β-thalassemia major (6.5%). Other studies had demonstrated different results especially in patients with β-thalassemia major. Although it have been mentioned that gall stones are found increasingly in patients with β-thalassemia, and two thirds of patients older than 15 years have gall stones (6), a study done in North India in 1997 found that multitransfused thalassemic patients were not prone to develop gall stones (10). However, the prevalence of cholelithiasis in patients with sickle cell / thalassemia was comparable to that reported in other studies in Basrah (7), and United Kingdom (11) where they reported a prevalence rate of 10% and 17% respectively.

The current study has identified that there is a significant increase in the frequency of cholelithiasis with increasing age reaching 20% in patients older than 15 years. This is in agreement with other studies (6, 8, 12). The study has demonstrated also that the prevalence of cholelithiasis is influenced by sex of the patients; females being affected significantly more than males, with a female to male ratio 4:1. Other studies had revealed conflicting results, some of them had demonstrated increased prevalence in females (6, 8), while other didn't show a significant influence of sex on the prevalence of gall stones (7, 12).

Many studies were done to study the clinical and biochemical predictors of cholelithiasis in patients with chronic hemolytic anemias. Our study has identified that Body Mass Index (BMI) and mean hemoglobin levels were not significantly different among thalassemic patients with and without cholelithiasis. This is in contrast to other studies which have shown that BMI had a significant positive association with increased likelihood of gall stone formation (13), and that the prevalence of cholelithiasis was related to a low hemoglobin level (7, 12). Other biochemical indices which had a significant positive association with increased likelihood of gall stone formation in our study were high serum iron and total serum bilirubin, other studies had identified similar results concerning the importance of serum bilirubin as a predictor for gall stone formation (4, 7, 8, 12). However, none of these studies had taken the serum iron level as a risk factor or predictor for gall stones formation. Chronic iron overload is an inevitable complication of frequent blood transfusions for thalassemic patients, which may lead to liver cirrhosis (14), and liver damage in such patients may result from cholestasis, hemosiderosis and chronic congestion due to heart failure.

Five out of ten patients with cholelithiasis presented with abdominal pain, in two of them the presentation was acute and ultrasonography has revealed common bile duct obstruction and emergency cholecystectomy was done for them, while in other two patients elective cholecystectomy was done because of recurrent abdominal pain. Controversy surrounds the recommendation of cholecystectomy for asymptotic stone or stones, associated with non specific symptoms.

It has been urged that the high prevalence of complications and the desire to simplify management of future attacks of abdominal pain justify prophylactic cholecystectomy in patients with asymptotic stones (15, 16). As nearly 50% of thalassemic patients included in the study were asymptotic and some of the underwent emergency cholecystectomy and with the improvement in preoperative management, adequate hydration, oxygenation, in addition to blood transfusion, we recommend cholecystectomy for all patients with gall stones whether symptomatic or asymptotic.

**Table (1)**

**Distribution of cholelithiasis according to patients' age, sex and type of anemia**

| Variable | Gall stones present | | Gall stones absent | | Total | P value |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **Age (Years)** | | | | | | |
| 6 – 10 | 2 | 6.25 | 30 | 93.75 | 32 | |
| 11 – 15 | 3 | 8 | 36 | 92 | 39 | < 0.05 |
| ≥ 16 | 5 | 20 | 20 | 80 | 25 | |
| Total | 10 | 10.5 | 86 | 89.5 | 96 | |
| **Sex** | | | | | | |
| Male | 2 | 4 | 49 | 96 | 51 | < 0.05 |
| Female | 8 | 17.8 | 37 | 82.2 | 45 | |
| Total | 10 | 10.5 | 86 | 89.5 | 96 | |
| **Type of Anemia** | | | | | | |
| $\beta$ -thalassemia major | 3 | 6.5 | 44 | 93.5 | 47 | > 0.05 |
| SC/thalassemia | 7 | 14.5 | 42 | 85.5 | 49 | |
| Total | 10 | 10.5 | 86 | 89.5 | 96 | |

**Table (2)**

**BMI, selected hematological variables and liver function tests in thalassemic patients with and without cholelithiasis**

| Variables | Gall stones present No. (10) | Gall stones absent No. (86) | P value |
|---|---|---|---|
| BMI | 17.2 ± 3.16 | 16.32 ± 2.16 | NS |
| Hb | 5.34 ± 1.05 | 5.58 ± 1.57 | NS |
| S. iron | 150 ± 35.3 | 122 ± 34.6 | < 0.05 |

| Variables | Gall stones present No. (10) | Gall stones absent No. (86) | P value |
|---|---|---|---|
| TSB | 4.4 ± 2.2 | 2.67 ± 1.96 | < 0.05 |
| ALT | 28 ± 11.3 | 22.3 ± 15.5 | NS |
| AST | 20 ± 5.3 | 20.3 ± 4.8 | NS |
| ALP | 19.5 ± 8.7 | 18.8 ± 11.6 | NS |

The values are expressed as mean ± SD

Table (3)

**Clinical feautures of patients treated by cholecystectomy ***

| Pts No. | Age (Year) | Sex | Symptoms | Finding |
|---|---|---|---|---|
| 1 | 14 | F. | Acute R.U.Q. pain, vomiting and fever, Murphy's sign positive | Multiple gall stones Emergency cholecystectomy |
| 2 | 18 | F. | Acute R.U.Q. pain, vomiting, increasing jaundice | Multiple gall stones Emergency cholecystectomy |
| 3 | 18 | F. | Recurrent R.U.Q. pain, fever (4 attacks) | Elective cholecystectomy |
| 4 | 10 | M. | R.U.Q. pain, increasing jaudice | Elective cholecystectomy |

R.U.Q.: Right Upper Quadrant

* Five of the remaining 6 patients were asymptomatic and they were discovered during the period of the study and one patient had recurrent attacks of mild upper abdominal pain and he is waiting for elective cholecystectomy.

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