FREQUENCY DISTRIBUTION AND COMBINATION OF RISK FACTORS IN SONOGRAPHICALLY DECTECTED CHOLELITHASIS VERSUS CONTROLS

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ABSTRACT
Objective: *To determine the frequency of known risk factors in adult cholelithiasis patients as compared with age and gender matched controls*
Study Design: *Cross sectional analytical study.*
Setting & Duration: *Department of Radiology, Dow University of Health Sciences and Civil Hospital, Karachi from April 2005 to May 2007.*
Methodology: *A 100 adult patients without biliary calculous disease as identified by symptomatology (controls, group A) and confirmed on ultrasound were compared with a 100 symptomatic (group C) and a 100 asymptomatic patients (group B) diagnosed as having cholelithiasis on ultrasound.*
Variables compared were age gender, marital status, parity and oral contraceptives (OC) use for married females, symptoms, ultrasound findings, obesity as defined by WHO, cephalosporin use, hypercholesterolemia, bowel surgery particularly ileal resection, and hemolytic anemia. ANOVA and Pearson Chi Square testing was carried out with significance at $p < 0.05$.
Results: *The mean age was 35.4 years in group A, 43.2 years in group B and 40.5 years in group C. There were 52% females in group A, 66% in group B and 71% in group C. The most common risk factor in groups A and B was obesity (20 and 37% respectively) and cephalosporins use in group C (49%, p=0.03). Multiple risk factors were present in 42% of the controls, 71% of the asymptomatic and 84% of the symptomatic cholelithiasis groups. The most frequent combination was obesity with multiparity seen in 14% in group A, 28% in group B and 31% in group C.*
Conclusion: *Multiparous obese females had a greater frequency of cholelithiasis at a young age. Use of cephalosporins and OCC was also more common among those having cholelithiasis than in controls. Those with combination of risk factors should be followed for development of gall stones.*

KEY WORDS: *Cholelithiasis, Risk Factors, Female Gender, Obesity, Multiparity*

INTRODUCTION

Cholelithiasis is a common disease. Its prevalence in Pakistan is 15%.[1] It accounts for up to 22% of hospital admissions in a surgical unit.[2] The traditionally acclaimed risk factors for cholelithiasis are the four 'Fs'-Fat, Fertile, Forty, Female - depicting the picture of a middle aged obese lady in whom the gall bladder has been subjected to lithogenic effects of hormonal surges during multiple pregnancies.[3] But the fact in clinical practice is that gall stones have been observed in all age groups and either gender. Their revelation has increased particularly with widespread availability of ultrasound.[4] Majority remain asymptomatic, remaining clinically silent and only few become symptomatic.[5]

Apart from the risk factors described in the above clinical scenario, others include use of the antibiotic cephalosporins, rapid weight loss, bowel surgery particular ileal resection, hypercholesterolemia, oral contraceptives (OC) use, hepatic cirrhosis and presence of any type of hemolytic anemia that tends to increase the bilirubin end-products in the bile to promote its lithogenic tenden-

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cy.[6-10] It is likely that presence or combination of these risk factors promotes lithogenesis in gall bladder in different age groups and male gender i.e. other than the conventionally acclaimed risk factors which is responsible for detection of gall stones in other age groups and in males.

Although literature is abundant about sonography of gall bladder in cholelithiasis, the distribution of the known risk factors in different sub sets of the normal and diseased population is lacking. It is not determined if there is a trend of the frequency and/or combination of these risk factors. It is not known that a person having known risk factors predisposing to gall stone formation does or does not develop cholelithiasis? This aspect has not been elaborated upon in the known local literature particularly, which formed the rationale of this study.

The objective of this study was to compare the frequency of those known risk factors among sonographically determined adult controls, and symptomatic as well as symptomatic cholelithiasis patients.

METHODOLOGY

A cross sectional study conducted at the Department of Radiology, Dow University of Health Sciences and Civil Hospital, Karachi from April 2005 to May 2007. It included 100 subjects in the control group (Group A), 100 patients in the asymptomatic cholelithiasis group (Group B) and 100 patients in the symptomatic group (Group C) recruited through a purposive non-randomized sampling.

The inclusion criteria for each group were as follows. Group A had adults of either gender, having neither the symptoms of gall stones (defined as biliary colic, right hypochondrial pain, jaundice and long standing dyspepsia) or a visible gall stone on an adequately visualized gall bladder on ultrasound (US). They were referred for other reasons. Group B had adults of either gender having gall stones on ultrasound but not the symptoms. Group C had adults of either gender having both the symptoms and the sonographically visible gall stone(s) as an echogenic focus in the lumen of gall bladder, causing acoustic shadowing.

Exclusion criteria were the same for every group. These were pediatric age group (due to rarity); co-existent morbidity such as cirrhosis, diabetes, pancreatitis and cholangitis; absent, non visualized or partially visualized gall bladder; and those who did not have a laboratory report of serum cholesterol done within last 6 months. The studied variables were age in years, gender, marital status, parity and OC use (for married females only), right hypochondrial pain/colic, jaundice, dyspepsia, US findings (presence/absence of gall stones, number/ mobility of stones when present), and the risk factors history (obesity, OC use, cephalosporins, hypercholesterolemia, bowel surgery particularly ileal resection, and hemolytic anemia).

All the patients fulfilling the criteria were enrolled in the study with informed consent and subjected to US of gall bladder with standard technique and preparation.[11] The variables were studied and entered on a Performa designed for this study. Body mass index as used to define obesity at values above 25 obtained measuring height and weight.[12] Hypercholesterolemia was defined as the serum cholesterol above 200 mg/dl.[13] Multiparity, for the purpose of this study, was defined as having three or more pregnancies.

Results were tabulated on frequency tables. Cross tabulation, Chi-square test, descriptive statistics and ANOVA were done as and where applicable to determine significance at p-values less than 0.05 using SPSS 13.

RESULTS

There were 100 subjects in each group. Their base-line characteristics are shown in Table I. Majority of the subjects was married females. In groups B and C i.e. the cholelithiasis groups), majority were multiparous as well. Frequency distribution of age in years is given in Table II. The mean age of controls was 35.4 years, of the asymptomatic group was 43.2 years and of the symptomatic group was 40.5 years.

The frequencies of risk factors in the three groups are presented in Table III. Cephalosporin use was the most frequent risk factor in the symptomatic cholelithiasis groups seen in 49% patients in group C. Obesity was the commonest risk factor in the control group being present in 20% and in the asymptomatic cholelithiasis group where it was present in 37%. Two or more risk factors were seen in 16% of the controls, 41% of the asymptomatic cholelithiasis and 58% of the symptomatic cholelithiasis groups (Table IV). The most frequent combination was obesity with multiparity seen in 14% in group A, 28% in group B and 31% in group C. Hemolytic anemia was not seen in any patient. Multiparity ($p=0.002$), female gender ($p=0.018$), and age under 50 years ($p=0.052$) were found to have a statistical significance. No other factor showed statistical significance.

DISCUSSION

From the above mentioned results, multiparous obese females were found to be predominantly affected by

Variable	Group A (n=100)	Group B (n=100)	Group C (n=100)
Age in Years	-35.4 ± 12.1	-43.2 ± 12.7	-40.5 ± 14.1
- mean ± SD	-40	-50	-40
Range	-55 (75-20)	-65 (85-20)	-60 (80-20)
Gender			
Male	-48	-34	-29
Female	-52	-66	-71
Marital Status			
Married	-74	-91	-95
Unmarried	-26	-9	-5
Parous			
Females	36	63	66

Table I. Base line characteristics of the three groups regarding age, gender, marital status and parity

cholelithiasis. The effect of pregnancy is particularly said to be lithogenic due to increased secretion of cholesterol into bile during the third trimester and secondly due to increased stasis. Cephalosporin and OCC use was also markedly higher in patients having gall stones.

Although literature implicates only parentral administration of ceftriaxme for transient lithogenecity, all patients produced prescriptions for a variety of orally administered cephalosporins. This might be a chance finding since multivariate analysis could not establish a statistical significance. Yet this is a new finding requiring further validation and authentication. Combination of multiple risk factors as their co-existent occurrence was more frequent in patients with symptomatic cholelithiasis group. The long term use of cephalosporins or oral contraceptives in appropriate clinical setting can, therefore precipitate formation of gall stones as seen in the group C of this study. Female gender as was found in this study is a known risk factor for all cholelithiasis. However studies have also shown an increasing trend towards involvement of male gender[14] where definitely the role of hormones would be rendered negligible.

Hypercholesterolemia was also seen in 6-17% of these subjects while the history of ileal and bowel surgery was infrequent. Hypercholesterolemia is a known major risk factor playing important role with age and gender. Hemolytic anemia, on the other hand was not found in any of them which causes pigment calculi. It may be explained by the fact that all the subjects in this study were adults, while hemolytic anemias are often encountered in the younger age groups.[15,16]

Over all, the mean age group in was younger while the number of patients with cholelithiasis in the eldest age group i.e. 70-85 years, was only 6 out of 200 corresponding to 3%. This negates the notion that cholelithiasis

Table II. Frequency distribution of age in years

Age in Years	Group A	Group B	Group C
20 - 29	22	18	20
30 - 39	26	18	26
40 - 49	38	23	40
50 - 59	8	27	8
60 - 69	2	10	4
70 - 85	4	4	2

*** Numbers represent frequency % since calculated out of 100%**

Risk Factor	Group A	Group B	Group C
Obesity	20	37	47*
OC use	10	22*	16
Cephalosporins use	6	34	49*
Hypercholesterolemia	6	17	14
Ileal resection	-	1	3
Other bowel surgery	-	2	3
Multiparity	16	33	44*

Table III. Percentage frequency of risk factor in the three groups (*Statistical significance at p<0.05)

is more common in the elderly.[17]

More interesting was the fact that although a number of subjects in the control group had one or even more risk factors, yet none of them had calculus in gall bladder, it may be due to some hitherto unknown natural protection. Animal studies have strongly implicated genetic susceptibility due to aberrant regulation of the transport proteins responsible for solute excretion into the gall bladder lumen and lithogenecity of bile.[18] The same or analogous mechanism may well be operating in humans as well. Alternatively they may develop cholelithiasis on long term follow up. This requires longitudinal population-based follow up studies for confirmation or denial.

The main limitation of this study is a cross sectional study design with lack of follow up. It is quite possible that on follow up many of the group A control patients may come to belong to other groups. This may prove important particularly in those subjects who currently had a number of risk factors without disease. However this study has also provided some other new and valuable information particularly the high frequency of oral cephalosporins use in this series of patients. On one hand this could be due to selection of a population that was hospital based and therefore being treated with antibiotics for some. Other unrelated concurrent infection. On the other hand this may represent some new factor in development in our population that may need verification.

CONCLUSION

Under the study conditions, multiparous obese females were found as more frequently having cholelithiasis particularly at a younger age. The use of OCC and cephalosporins was also more common among those having cholelithiasis than in controls. Those with combination of more than one risk factor should undergo regular follow up for development of cholelithiasis to avoid a sudden emergent complication.

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Table IV. Multiplicity of risk factor in ach group. Figures represent absolute number of 100

Risk Factor	Group A	Group B	Group C
Nil	58	29	16
One risk factor	26	30	22
Two risk factor	14	24	32
Three risk factor	2	12	21
Four risk factor	-	5	4
Five risk factor	-	-	1

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