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• *RAPID COMMUNICATION* •

Prevalence of gallstone disease in first-degree relatives of patients with cholelithiasis

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Abstract

AIM: To evaluate the influence of familiality on the prevalence of gallstone disease (GD) in Italy.

METHODS: Families of 79 subjects with gallstones (cases) and of 79 subjects without gallstones (controls) were investigated for the presence of gallstones by ultrasonography. Index cases and index controls were matched for age, sex, and operative unit. Sixty-three and sixty-two husbands and wives of index cases and index controls, respectively, were also studied.

RESULTS: Overall,the prevalence of GD was significantly higher (χ^2=14.52, P<0.001) in the 202 first-degree relatives of subjects with gallstones than that in the 201 first-degree relatives of subjects without gallstones (28.6% *vs* 12.4%, relative risk (RR) 1.80, 95% confidence interval (CI) 1.29-2.63). In particular, prevalence of GD was significantly higher in mothers, fathers, and sisters of index cases than that in the respective family members of index controls. The highest RR was observed in mothers (RR=2.35, 95%CI 1.38-4.3). Prevalence of GD was not obviously different in brothers and also in husbands and wives of index cases and index controls. Family members of index cases did not differ from family members of control cases with respect to the most important risk factors for gallstones (age, diabetes, BMI, and number of pregnancies) with an exception of a higher prevalence of diabetes in fathers of index controls than in fathers of index cases.

CONCLUSION: This study confirms that familiality plays a very important role in the pathogenesis of gallstones.

Key words: Gallstones; Familiality

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INTRODUCTION

Gallstone disease (GD) is very common among the Western civilized countries. Nonetheless the literature concerning family inheritance is scarce, although consistent. Körner[1] collected 74 family pedigrees of probands with gallbladder disease and showed that gallstones were five times more common in families of affected individuals than in families of his control group. Van der Linden and Lindelöf[2] investigated the presence of gallstones in wives and husbands of subjects with gallstones and also in siblings of the same sex of the wife or husband, demonstrating the data of a clear 2:1 ratio in favor of familial occurrence. Because familial occurrence does not necessarily reflect genetic factors, Van der Linden and Westlin[3] studied the occurrence of GD in spouses who had lived together continuously and presumably shared the same environment, especially diet, during adult life. They found that women married to subjects with gallstones do not suffer more often from the disease than do other women.

The importance of familiality has been well identified also in epidemiological studies. Jorgensen[4] in Denmark demonstrated a relative risk (RR) of 2:1 in first degree relatives of gallstone patients. The Sirmione study[5] found a RR of 3.3:1 in sons of subjects with gallstones with respect to sons of subjects without gallstones. Similarly, in Israel[6] and in India[7] too, an elevated prevalence of gallstones has been demonstrated in family members of subjects with gallstones with respect to family members of subjects without gallstones. The MICOL study[8] demonstrated that subjects with a family history of GD are at an increased risk for the presence of gallstones in their gallbladder. To our knowledge, a formal family study for gallstones is lacking in Italy. We, therefore, aimed to evaluate the influence of familiality on the prevalence of GD in Italy.

MATERIALS AND METHODS

This study was performed in 16 operative units (5 in the north, 5 in the center and 6 in the south of Italy). Each operative unit was equipped with an ultrasonographic apparatus of similar characteristics (i.e., equipped with a 3.5-MHz linear transducer) and was instructed to follow an identical protocol (all the subjects were examined in the supine and left decubitus position).

Seventy-nine families of cases and 79 families of controls were enrolled in the study. All subjects with gallstones consecutively observed by the medical staff of the operative units were included as cases (case subjects), if at least one parent and a sibling were living and gave their consent to participate in the study. For each case subject, a control subject matching the sex and age (±3 years) was selected among those who attended the outpatient echographic services of the single operative unit and did not show any presence of gallstones or were previously submitted to cholecystectomy. Cases and controls were matched not only for age and sex, but they did not differ also for the other most important risk factors for gallstones: BMI, number of pregnancies (for females) and prevalence of diabetes (Table 1). Families without a matching family within the same operative unit were excluded from the calculations.

Table 1 Levels of the most important risk factors for gallstones in cases with or without gallstones

	Cases $n=79$	Controls $n=79$	*P*
Male/female (*n*)	30/49	30/49	NS
Age (yr); mean (CI)	48.6 (45.8–51.4)	48.5 (45.7–51.4)	NS
BMI; mean (CI)	25.5 (24,9–26.4)	25.7 (24.7–26.7)	NS
Number of pregnancies (females); mean (CI)	1.71 (1.29–2.13)	1.47 (1.04–1.89)	NS

All the available first degree relatives of cases were invited to participate in the study. Husbands and spouses were also studied, when available. Participations among living first degree relatives of cases and controls were 82% and 80%, respectively; among living spouses and husbands of cases and controls were 88% and 89%, respectively. A precoded questionnaire regarding personal, physiological and pathological history, dietary habits and number of pregnancies (females) was administered by a member of the medical staff to all the family members. Each family subject was also submitted to anthropometric measurements (weight and height) and ultrasonographic examination of the biliary tract. BMI was calculated by dividing the weight (kg) by the square of height (m).

Subjects were considered as having GD, if they showed presence of gallstones in their gallbladder or had already been submitted to cholecystectomy.

Statistical analysis

All statistical analyses were carried out with the NCSS statistical software program, 329 North 1000 East Kaysville, UT 84037, USA. The Student's *t*-test and the χ^2 test were used when appropriate. A *P* value less than 0.05 was considered statistically significant. We computed Mantel-Haenszel estimates of RR with 95% confidence intervals (CI).

RESULTS

Overall, prevalence of GD was significantly higher (χ^2=14.52, *P*<0.001) in the 202 first-degree relatives of subjects with gallstones than that in the 201 first-degree relatives of subjects without gallstones (28.6% *vs* 12.4%, RR 1.80, 95%CI 1.29-2.63)(Table 1).

In particular, 13 of the 31 (41.9%) fathers of the index cases and 6 of the 34 fathers of the index controls had GD. The difference was significant according the χ^2 test although the lower limit of the 95%CI of the RR was below 1 (Table 2). Fathers of cases and controls did not differ for age and BMI, but fathers of controls had a significantly higher prevalence of diabetes (Table 2).

Prevalence of GD was significantly higher among the 51 mothers of index cases as compared to the 51 mothers of index controls (56.9% *vs* 21.6%, RR 2.35 95%CI 1.38-4.3, Table 2). Mothers of cases did not differ from mothers of controls as far as the most important risk factors for gallstones were concerned, i.e. age, BMI, prevalence of diabetes, and number of pregnancies.

Brothers of cases and brothers of controls (Table 3) showed similar prevalences of GD and similar levels of risk factors for gallstones, i.e. age, BMI, and prevalence of diabetes. Among the sisters, prevalence of GD

Table 2 Prevalence of GD and levels of the most important risk factors for gallstones in fathers and mothers of subjects with or without gallstones

	Fathers of		Mothers of	
	Cases $n=31$	Controls $n=34$	Cases $n=51$	Controls $n=51$
Age (yr); mean (CI)	70.0 (66.7-73.4)	70.9 (67.6-74.2)	72.4 (69.2-75.5)	71.8 (71.8-74.8)
BMI; mean (CI)	25.7 (24.4-27.0)	27.5 (26.3-28.6)	26.3 (25.1-27.6)	26.3 (25.4-27.3)
Diabetes (%)	3.4[a]	20.6	20.0	21.2
Number. of pregnancies; mean (CI)	-	-	2.9 (2.4-3.4)	2.9 (2.5-3.4)
GD (%)	41.9[c]	17.6	56.9[b]	21.6

[a]*P*<0.05 *vs* controls (χ^2=4.15); [c]*P*<0.05 *vs* controls (χ^2=4.66; RR=1.75 (0.98-2.6 95% CI); [b]*P*<0.001 *vs* controls (χ^2=13.32; RR=2.35 (1.38-4.3 95% CI).

Table 3 Prevalence of GD and levels of the most important risk factors for gallstones in brothers and sisters of subjects with or without gallstones

	Brothers of		Sisters of	
	Cases $n=50$	Controls $n=47$	Cases $n=39$	Controls $n=44$
Age (yr); mean (CI)	48.5 (45.4-51.6)	44.9 (41.4-48.3)	43.9 (39.0-48.8)	48.9 (44.9-52.8)
BMI ; mean (CI)	25.6 (24.6-26.5)	25.5 (24.4-26.6)	24.8 (23.4-26.1)	25.8 (24.5-27.1)
Diabetes (%)	5.9	0	2.7	11.4
No. of pregnancies; mean (CI)	-	-	1.3 (0.9-1.7)	1.5 (1.0-1.9)
GD (%)	10.0	8.5	25.6[a]	9.1

[a]$P<0.05$ *vs* controls ($\chi^2=4.04$; RR = 2.03 [0.94-6.22 95%CI])

was significantly higher among the sisters of index cases as compared to the sisters of controls (25.6% *vs* 9.1%; $\chi^2=4.04$, $P<0.05$), but the lower limit of the RR confidence interval was below 1 [RR = 2.03 (0.94-6.22 95%CI)]. The sisters of cases and sisters of controls did not differ in age, BMI, prevalence of diabetes, and number of pregnancies.

None of the sons of the cases and controls had GD.

No significant difference was observed in prevalence of GD among husbands and spouses of the index cases and controls (Table 4). Husbands and wives of index cases or controls also did not differ for the most important risk factors for gallstones (Table 4).

Table 4 Prevalence of GD and levels of the most important risk factors for gallstones in husbands and wives of subjects with or without gallstones

	Husbands and wives of		*P*
	Cases $n=63$	Controls $n=62$	
Males/females	40/23	39/23	NS
Age (yr); mean (CI)	50.2 (48.8-51.4)	50.6 (48.9-51.7)	NS
BMI ; mean (CI)	25.9 (24.9-26.6)	26.0 (24.9-27.0)	NS
No. of pregnancies (female); mean (CI)	1.5 (1.0-2.2)	1.6 (0.8-2.1)	NS
Diabetes (%)	4.8	3.2	NS
GD (%)	9.5	11.2	NS

DISCUSSION

This study confirms that genetic factors play a very important role in the pathogenesis of GD. Overall, the prevalence of GD was significantly higher in the first-degree relatives of subjects with gallstones than in those of subjects without gallstones. The highest relative risks were found in female family members (mothers and sisters). This finding might be explained by the fact that GD is inherited as a sex-linked dominant trait. One might argue that an increased familial prevalence of gallstones might not necessarily involve a genetic defect, but rather reflects a common environmental risk factor. However, our results regarding the prevalence of GD in husbands and wives of index cases and index controls were in agreement with previous data by Van Der Linden and Westlin[3] and Leoci *et al*[9]. On the other hand, family members of index cases and control cases had similar levels of the most important risk factors for GD. These results support the hypothesis that the differences in GD prevalences were due to genetic rather than to environmental factors.

The results of our study further confirmed that a positive family history of GD might be included among the variables that can be used in order to select populations with a higher prevalence of gallstones than that predicted simply on the basis of age and sex. Using a similar approach[10], we were able to demonstrate that selection of subjects with multiple factors associated with gallstones increases the a priori probability of gallstone diagnosis by a factor 2 in females and 3 in males.

Some studies have identified genes (Lith1 on Chr 2, Lith 2 on Chr 19, Lith 3 on Chr 17) that are resporsible for increased gallstone formation in mice[11-18]. Although there is no evidence yet, that any of the Lith genes in the mouse is important in human gallstone susceptibility, some are likely to be and an era of "pre-gallstone disease" identification and possibly prevention seems open.

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