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Increased Risk of Symptomatic Gallbladder Disease in Adults With Down Syndrome

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Previous reports have documented an increased prevalence of asymptomatic cholelithiasis among children with Down syndrome. Whether this predisposes adults with Down syndrome to symptomatic gallbladder disease has not been studied. A case control study compared the rate of symptomatic gallbladder disease in 28 index cases of adults with Down syndrome and that of sex-matched controls. The rate of gallbladder disease was 25% among the Down syndrome group, compared to 4.5% among the control group ($P = 0.002$). Patients with Down syndrome were also more likely to have a family medical history of gallbladder disease. Utilizing logistic regression analysis, the adjusted relative risk for gallbladder disease among individuals with Down syndrome was 3.52.

KEY WORDS: Down syndrome; gallbladder disease; cholelithiasis

INTRODUCTION

A number of reports have documented an increased prevalence of cholelithiasis and other gallbladder abnormalities in pediatric patients with Down syndrome. Llerena et al. [1993] performed abdominal ultrasound examinations on a series of 145 patients with Down syndrome seen at a pediatric referral center; 7% had asymptomatic biliary stones. Toscano, Trivellini, and Andria [Toscano et al., 2001] performed a prospective study comparing the prevalence of cholelithiasis in children with and without Down syndrome. Of the 126 children with Down syndrome who underwent abdominal ultrasonography, 4.5% had cholelithiasis compared to 0.2% of 577 controls. All seven children with cholelithiasis were asymptomatic.

Whether this increased prevalence of asymptomatic cholelithiasis in childhood predisposes adults with Down syndrome to symptomatic gallbladder disease has not been systematically studied. In addition to whatever factors promote lithogenesis in infancy and childhood, adults with Down syndrome have significant rates of co-morbid obesity, diabetes mellitus [Anwar et al., 1998] and gluten-sensitive enteropathy [Book et al., 2001]; each of these has also been independently associated with risk for gallbladder disease [Fraquelli et al., 1999].

Using a case control design, this study examined whether adults with Down syndrome are more likely to have a history of symptomatic gallbladder disease compared to an age and sex-matched control group. We hypothesized the following: (1) symptomatic gallbladder disease would be more prevalent among the adults with Down syndrome compared to the control group; and (2) risk factors for gallbladder disease shared by adults with Down syndrome and the control group would include female sex, obesity, diabetes, and family history of gallbladder disease.

MATERIALS AND METHODS

The index cases were all adults with Down syndrome who were patients at a family practice residency clinic; the random control cases were age and sex-matched patients who also received care from the same clinic. Since pregnancy is a risk factor for biliary tract disease [Ahmed et al., 2000], and all of the females with Down syndrome were nulliparous, the female control patients were also limited to nulliparous women. The main variable of interest, a present or past history of gallbladder disease, was defined as: (1) a history of cholecystectomy; or (2) a history of choledocholithiasis as documented by endoscopic retrograde cholangiopancreatography (ERCP); or (3) a documented history of biliary colic along with an abnormal gallbladder ultrasound and/or abnormal nuclear biliary scan (HIDA scan) suggestive of acute or chronic cholecystitis, followed by recommendation for cholecystectomy by an independent surgical consultant. Data were abstracted directly from clinic charts by the study authors.

Because of the risk for ascertainment bias in the index group, all patients with Down syndrome who had undergone cholecystectomy underwent additional chart review to examine: (1) whether the surgical pathology report indicated acute and/or chronic cholecystitis; and (2) whether the symptoms attributed to gallbladder disease resolved with cholecystectomy.

A sample of 28 index cases of adults with Down syndrome was contrasted with 4 randomly selected controls for each index case. Based on sample size needs of the first hypothesis, a two group chi-square with a 0.05 two-sided significance level would have 83% power to detect the difference between a Down syndrome group proportion of gallbladder disease of 25% and a general population sample proportion of 5% when the sample sizes are 28 and 112, respectively.

The rate of symptomatic gallbladder disease was determined for both case and control groups and the difference in rates tested by chi-square statistic for independent groups. The odds ratio for gallbladder disease given Down syndrome was also computed. Next, bivariate tests of association were calculated to determine which variables constituted risk factors for gallbladder disease in this sample and also potential confounders. These variables and gallbladder disease were entered into a logistic regression analysis with Down syndrome as the classification variable. This analysis provides an adjusted odds ratio for Down syndrome and gallbladder disease, controlling for known risk factors. Utilizing methods described by

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TABLE I. Comparison of Adults With and Without Down Syndrome (DS)

Characteristic	DS group (N = 28)	Control group (N = 112)	Difference	*P*-value[a]
Female sex	54%	54%	0.0%	1.00
Mean age ± SD (years)	43.0 ± 10	43.1 ± 10	0.1	0.96
Mean BMI ± SD	29.7 ± 8.0	29.2 ± 6.3	0.5	0.73
Diabetes	0%	5%	5%	0.60
Gluten enteropathy	18%	0%	18%	0.001
GBD	25%	4.5%	20.5%	0.002
Cholelcystectomy	11%	4.0%	7%	0.12
Choledocholithiasis	11%	0.0%	11%	0.007
Biliary colic	4%	1.0%	3%	0.36
FMHx GBD	18%	1.0%	17%	0.001
HRT	0%	3.8%	3.8%	0.553

GBD, gallbladder disease; FMHx GBD, family history of gallbladder disease; HRT, hormone replacement therapy.
[a]Probabilities derived from chi-square, *t*-test, and Fisher's exact test.

Zhang and Yu [1998], an adjusted relative risk was then estimated from the odds ratio.

RESULTS

A total of 140 charts were reviewed in the study consisting of 112 individuals within the control group and 28 individuals within the Down syndrome group. Table I displays the characteristics of adults with and without Down syndrome. As intended, the groups were similar in age and gender. None of the patients with Down syndrome had diabetes or received hormone replacement therapy (HRT), whereas none of the control group had gluten sensitive enteropathy. Because four patients (two males and two females) with Down syndrome would not permit measurement of height, their heights were imputed using data derived from national norms for adults with Down syndrome and body mass index (BMI) was estimated. Analyses including and excluding the estimated BMI scores were very comparable. Neither Down syndrome nor gallbladder disease was associated with BMI. However, the rate of gallbladder disease was five times higher in the Down syndrome group compared to the control group.

Among the seven individuals with both Down syndrome group and gallbladder disease, three had undergone cholecystectomy, three had choledocholithiasis documented by ERCP, and one had episodes of biliary colic, both gallbladder ultrasound and HIDA scan suggestive of gallbladder disease, and recommendation for cholecystectomy by an independent surgeon. Among those who had undergone cholecystectomy, two of the three cases had pathology reports documenting chronic cholecystitis. In all three cases of cholecystectomy, there was no recurrence of symptoms attributed to gallbladder disease following surgery.

Table II compares all patients with gallbladder disease to those without to identify potential confounder variables. Patients with gallbladder disease were more likely to be female and have a family medical history of gallbladder disease. Family history of gallbladder disease was associated with both Down syndrome and gallbladder disease and represents a confounder variable. There was no significant difference between these groups regarding age, BMI, or co-morbid diabetes or gluten sensitive enteropathy.

Table III summarizes the two variables that remained significantly associated with Down syndrome by logistic regression analysis. Initially, four variables were included in the analysis: gallbladder disease, family history of gallbladder disease, choledocholithiasis, and gluten sensitive enteropathy. The latter two were not associated once gallbladder disease and family history of gallbladder disease were taken into account. Controlling for family history of gallbladder disease, the adjusted odds ratio for Down syndrome and gallbladder disease was 4.00. This corresponds to an adjusted relative risk of 3.52.

DISCUSSION

Our findings were congruent with previous research regarding symptomatic cholelithiasis, in which female sex and family medical history of gallbladder disease have been identified as risk factors [Nakeeb et al., 2002]. This study also suggests that symptomatic gallbladder disease in adulthood is associated with Down syndrome. We encourage further confirmation of this association through analysis of Medicare or other large datasets that include adults with Down syndrome.

There were too few index cases of adults with Down syndrome to elucidate potential co-factors that might precipitate symptomatic gallbladder disease. Potential co-factors include gluten sensitive enteropathy and helicobacter pylori infection. Gluten-sensitive enteropathy, present in 5% of American children with Down syndrome, has been associated with cholelithiasis in the general population [Book et al., 2001]. Helicobacter pylori infection, more prevalent in adults with developmental disabilities than in the general population, has also been implicated in biliary tract disease [Fox et al., 1998].

TABLE II. Comparison of Adults With and Without Gallbladder Disease

Characteristic	Gallbladder Ds (N = 12)	No gallbladder Ds (N = 128)	Difference	*P*-value[a]
Female sex	83%	51%	32%	0.03
Mean age ± SD (years)	42.2 ± 13	43.1 ± 10	0.9	0.78
Mean BMI ± SD	33.2 ± 9.6	28.9 ± 6.4	4.3	0.16
Diabetes	8%	4%	4%	0.92
Gluten enteropathy	8%	3%	5%	0.94
FMHx GBD	33%	2%	31%	0.001

FMHx GBD, family medical history of gallbladder disease.
[a]Probabilities derived from chi-square, *t*-test, and Fisher's exact test.

TABLE III. Logistic Regression of Down Syndrome on Predictor Variables

Variable	B	S.E.	Wald	*P*-value	Exp (B)
FMHx of GBD	2.52	1.19	4.53	0.03	12.46
Gallbladder disease	1.39	0.72	3.73	0.05	4.00

FMHx of GBD, family medical history of gallbladder disease.

The study sample size had limited power to detect smaller effect sizes and also precluded analyses of Down syndrome adults with and without gallbladder disease in terms of testing for a greater likelihood of co-morbid conditions such as gluten-sensitive enteropathy, diabetes, and antecedent hormone replacement therapy. Whether those individuals with Down syndrome who are also obese carry a higher risk for symptomatic gallbladder disease is yet unknown.

The role of family medical history of gallbladder disease as a covariate risk factor for gallbladder disease in adults with Down syndrome also requires clarification. In this study population, the patient registration questionnaire did not include gallbladder disease under the family medical history checklist. There may have been an ascertainment bias in that specific inquiry about a family medical history of gallbladder disease likely occurred primarily when the patient was undergoing evaluation of abdominal symptoms that were suggestive of gallbladder disease. Additional sources of bias include possible sample selection bias in terms of the sample of 28 cases brought to the attention of one clinical facility.

In addition to these epidemiological issues, further study is needed regarding the clinical presentation, diagnostic test characteristics, and complications of gallstones in adults with Down syndrome. Given the episodic nature of biliary colic symptoms, there is a risk for under-recognition of symptomatic gallbladder disease, misattributing the symptoms to gastro-esophageal reflux disease, constipation, gastroenteritis, or medication side effects. On the other hand, clinicians must also avoid the pitfall of over-treating "silent" gallstones. While cholecystectomy is not generally recommended in adults with gallstones in order to prevent gallbladder cancer, one 30-year nation-wide, population study of cancer incidence in Finnish individuals with intellectual disabilities found a significantly increased risk of gallbladder cancer (standardized incidence ratio of 2.8.) [Patja et al., 2001]. Whether individuals with Down syndrome in particular carry a greater risk of gallbladder cancer is unknown. In the general population, symptomatic non-complicated gallbladder disease can be managed by a non-operative expectant approach, with a low risk for complications [Vetrhus et al., 2002]. Further study is required to determine whether such treatment strategies are equally safe in adults with Down syndrome.

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