Inheritance of Acute Appendicitis: Familial Aggregation and Evidence of Polygenic Transmission

Milan Basta,[*,1] Newton E. Morton,[‖,2] John J. Mulvihill,[#] Zoran Radovanović,[†]
Čedomir Radojičić,[‡] and Dragoslav Marinković[§]

*Department of Pediatric Surgery, Mother and Child Health Institute; †Institute for Epidemiology, School of Medicine; ‡Military Medical Academy and §Faculty of Science, University of Belgrade; Belgrade, ‖Genetic Epidemiology Division, Memorial-Sloan Kettering Cancer Center, New York; and #Clinical Epidemiology Branch, National Cancer Institute, Bethesda, MD

Summary

We explored familiality as well as the heritability and possible mode(s) of inheritance of acute appendicitis in childhood and early adolescence. Our case-control study showed that a positive family history for reported appendectomy was significantly more frequent in families of 80 consecutive patients eventually proved to have histopathologic acute appendicitis than in families of surgical controls matched for sex, age, and number of siblings. The relative risk was 10.0 (95% confidence limits 4.7–21.4). The pattern of familial aggregation was further supported by the fact that the age-standardized morbidity ratio was four times greater among family members of cases than among controls. We then applied the unified mixed model of segregation analysis, as implemented in the computer program POINTER, to a new set of 100 multigenerational pedigrees of children with histopathologically confirmed acute appendicitis that were broken down into 674 nuclear families. Age-specific morbidity risk and lifetime incidence of acute appendicitis were estimated from relatives of controls matched for age and sex to probands. Complex segregation analysis supported a polygenic or multifactorial model with a total heritability of 56%. There was no evidence to support a major gene, although a rare gene could not be ruled out as the cause of a small proportion of cases. Specific studies to address genetic and environmental factors in this serious disease seem worthwhile; but, for now, a positive family history of appendicitis might join other evidence leading to improved clinical recognition of acute appendicitis.

Introduction

Acute appendicitis occurs in 1/7 to 1/17 people (Bierman 1968), mostly adolescents and young adults. In the century since its recognition (Fitz 1886), no progress has been made in elucidating its etiology and pathogenesis. According to the leading theory (Wangensteen and Bowers 1937), the initial event in the pathogenesis of acute appendicitis is obstruction of the lumen by fac-

tors such as fecaliths, foreign bodies, intestinal parasites, tumors, or lymphoid follicular enlargement due to a viral infection; however, obstructive elements have been identified in only 30%–40% of removed inflamed appendixes (Silen 1987). Burkitt (1971) enumerated appendicitis among the diseases related to the low-fiber Western diet but ignored the possibility that gene frequency as well as other dietary factors differ between Western and African populations. Obviously, additional determinants, perhaps interacting with these environmental factors, must contribute to the origins of appendicitis.

Little attention has been paid to the possible role of genetic predisposition. McKusick (1988, p. 72) lists the disorder as a possible autosomal dominant trait, on the basis of reports of single pedigrees with many affected individuals, some of whom shared anatomic defects of

form, size, or vascularization of the appendix (Perry and Keeler 1939). No formal genetic analysis of pedigrees with appendicitis has been reported; however, case-control studies in three different countries established the higher frequency of appendicitis among relatives of probands than among controls (Andersson et al. 1979; Arnbjornsson 1982; Brender et al. 1985). Here we report two phases of a multidisciplinary approach to understanding the etiology and pathogenesis of acute appendicitis. The first phase confirmed the familial pattern of this frequent disease. Such familial aggregation could represent common genetic determinants, shared environmental factors, or the interaction of both. In the second phase, to help distinguish from among these possibilities and to clarify the possible mode(s) of inheritance, we collected another set of pedigrees of cases and appropriate controls and subjected the data to a complex segregation analysis.

Material and Methods

Data Collection

As probands, the study enrolled 238 consecutive admissions, during a period of 19 mo beginning May 1983, to the Department of Pediatric Surgery, Mother and Child Health Institute in Belgrade. The probands, age 2–15 years, were operated on for signs and symptoms of acute appendicitis. In this 36-km^2 metropolitan area with an estimated 1984 population of 1,529,000 persons (Statistical Year Book of the City of Belgrade 1984), the acute care of children is organized so that all cases are managed on alternate days by the Mother and Child Health Institute. The control for each proband was the next child of the same age and sex who was admitted for surgery other than for suspected appendicitis, such as for orthopedic, urologic, cardiovascular, or reconstructive procedures. No diagnosis (except appendicitis) excluded controls from eligibility. For both groups, the same interviewer (M.B.) sought the same information from both accompanying parents under the same circumstances (namely, in the surgical admission room): the family pedigree as far as second-degree relatives of the patient and first cousins, ages of family members at interview or death, and histories of all surgical procedures performed on family members. Parents were never asked specifically about appendectomies, to avoid the bias of preferentially eliciting a positive family history. Confirmatory pathology reports were not sought, so the phenotype in relatives of cases and controls was, in fact, reported appendectomy. In this way we collected the sample of 238 pairs of 3-generation families before

knowing the outcome of surgery—that is, before acute appendicitis was definitively diagnosed. When the pathology reports on probands were completed, the number for analysis was reduced to 180 families of children whose surgical specimens fulfilled standard criteria for the histological diagnosis of acute appendicitis (Robbins et al. 1984, pp. 875–876). These families have been compared with an equal number of corresponding control families.

Statistical Analysis

The first 80 pairs of families, collected in 8 mo, were the subject of phase 1, the case-control study of familial aggregation. For analysis, we used McNemar's test for individually matched pairs (Fleiss 1981, p. 114) and calculated the age-standardized morbidity ratios with associated confidence limits (Lilienfield and Lilienfield 1980, p. 353). The remaining 100 pairs of families, collected in 11 mo beginning February 1984, were the subject of phase 2, the complex segregation analysis. The mixed model of segregation analysis allows simultaneous evaluation of several modes of inheritance, including the Mendelian model, the multifactorial model with polygenic control of familial aggregation, or both (Morton and McLean 1974). It assumes that affection is determined by truncation of a continuous distribution of liability, which is, in turn, determined by a major locus, polygenes, and random error. In addition to overall mean ($\mu = 0$) and variance ($V = 1$) of the liability, the parameters of the model include q (gene frequency at the major locus), t (displacement [distance between homozygote means in units of SD]), d (degrees of dominance at the major locus), H (heritability in children), and HZ (heritability in adults, where Z is the adult-to-child ratio of heritabilities). The model includes three transmission probabilities for Mendelian segregation, which are defined as τ_1, τ_2, and τ_3, and represent the respective probabilities that a parent with genotype AA, Aa, and aa transmits the normal allele A to his or her offspring. Under Mendelian transmission, these parameters are expected to be 1, 1/2, and 0, respectively. To test this hypothesis, certain parameters are held constant while the remaining parameters are estimated. The value reported is $-2\ln L + C$, where $\ln L$ is the natural logarithm of the likelihood and C is a constant, here determined by subtracting the smallest value from the others. The computer program POINTER (Lalouel and Morton 1981) was used to calculate the likelihood and the parameters under each hypothesis. The unit of analysis for POINTER is the nuclear family extended to include "pointers," individuals outside the nuclear family

who led to the selection of the family. Our 100 large multigenerational families of children with acute appendicitis consisted of 674 nuclear or component families. POINTER also requires population prevalences by specific age groups. To estimate age-specific morbidity risk of appendicitis in the Belgrade area, we used data on its frequency among relatives of controls, taking the relative morbidity risk in decennial liability class (i) as

$$P_i = \sum_{j=1}^{i} r_j / \sum_{j=1}^{6} r_j ,$$

where r_j is the number of individuals with onset in class j. The age-specific morbidity risk for age at last observation (a_i) is P_iI, where I is lifetime risk. I was calculated as A/Nb, where A is the number of affected relatives. N is the total number of control relatives, $b = \Sigma c_iP_i/\Sigma c_i$ (the mean relative risk in relatives), and c_i is the number of normal relatives observed in i.

Results

Familial Aggregation

Family history for at least one relative with reported appendectomy was positive in 82% of families of appendicitis patients and in 26% of families of controls (table 1). The difference was highly significant ($\chi^2 = 35.2$, $P < .001$) by McNemar's test. The pattern of familial aggregation in 26 "false" probands (those whose surgical specimen failed to show appendicitis) resembled that of the controls more than it resembled that of the true probands, since their rate of positive family history was 32%. The relative risk of a positive family history for appendectomy was 10.0 (95% confidence limits 4.7–21.4): in other words, the chance of appendicitis was 10 times greater in a child with at least one relative with reported appendectomy, compared with that in a child with no affected relatives. No other risk factors were explored. To adjust for the different number of persons with history for appendectomy and unequal number of person-years of exposure, we computed the age-standardized morbidity ratio, i.e., the ratio of observed over expected number of persons with history for appendectomy, adjusting for the age differences. The 95% confidence limits of these ratios do not overlap, so the fourfold excess among relatives of cases is a statistically significant difference (table 2).

Familial Incidence

In 100 3-generation families of children with acute appendicitis, there were 2,054 relatives in first-, second-, and third-degree relationships. Each of 282 family members (140 males and 142 females) with a history for appendicitis was taken as a proband, and the frequency of appendicitis was determined among his or her first- to third-degree relatives (table 3). The proportion of relatives with appendicitis varied directly with the degree of relationship: 21% in first-degree relatives (sibs, parents, and children), 12% in second-degree relatives (grandparents, grandchildren, uncles, aunts, nieces, and nephews), and 7% in third-degree relatives (first cousins).

Segregation Analysis

As a next step in our analysis, the age-specific morbidity risks (table 4) were incorporated into the collected information. All sibships were analyzed under incomplete selection. Since the data depend critically on completeness and accuracy of surgical histories reported by relatives, we first considered sibships of the probands (table 5, Index sibships) as possibly the most validly reported. The polygenic model is preferred by Akaike's (1974) information criterion (AIC), which penalizes less parsimonious models by adding to -2 ln$L$ twice the number of estimated parameters. Familial predisposition is highly significant ($\chi_1^2 = 13.05 - 5.17 = 7.88$). Analysis of all sibships gives much greater evidence for familial predisposition than do just index

Table 1

History for Appendectomy among Families of Cases and Individually Matched Controls

	CONTROLS		
CASES	Positive Family History	Negative Family History	TOTAL
Positive Family History	16	50	66
Negative Family History	5	9	14
Total...................	21	59	80

Table 2

Frequency of Appendectomy in Family Members of Cases and Controls

Family Members of	No. of Persons with History of Appendectomy	No. of Person-Years	Age-standardized Morbidity Ratio[a] (per 10,000)	95% Confidence Limits
Cases..........	113	39,034	156.9	127.4–186.4
Controls	26	38,041	38.8	23.6–54.0

[a] The population of family members of both cases and controls was used as a standard.

Table 3

Frequency of Reported Appendectomy among First- to Third-Degree Relatives of Affected Persons

PROBANDS	FREQUENCY (%) OF REPORTED APPENDECTOMY				
	Sibs	Parents and Children	Grandparents and Grandchildren	Uncles, Aunts, Nieces, and Nephews	First Cousins
142 Females	65/236 (27.5)	82/374 (21.9)	45/312 (14.4)	83/546 (15.2)	33/492 (6.7)
140 Males........	42/187 (22.4)	61/380 (16.1)	35/342 (10.2)	51/504 (10.1)	35/470 (7.4)
282 Total	107/423 (25.3)	143/754 (19.0)	80/654 (12.2)	134/1,050 (12.8)	68/962 (7.1)

Table 4

Age-specific Morbidity Risks for Reported Appendectomy

Age (years)	i	c_i	No. of Relatives with Onset in i	Relative Morbidity Risk p_i	a_i
0–9	1	286	79	.191	.011
10–19	2	329	174	.612	.037
20–29	3	311	94	.840	.050
30–39	4	677	34	.922	.055
40–49	5	468	24	.974	.058
50+	6	517	11	1.000	.060

Table 5

Segregation Analysis of Appendicitis under Incomplete Section

Hypothesis	d	t	q	Polygenic Heritability H	Z	τ_2	$-2\ln L + C$	AIC
Index sibships:								
Sporadic	. . .	. . .	(0)	(0)	. . .	. . .	13.05	13.05
Single locus	.20	2.71	.411	(0)	. . .	(.5)	3.93	9.93
Polygenic.....................	. . .	. . .	(0)	.426	(1)	. . .	5.17	7.17
Multifactorial	. . .	. . .	(0)	.459	.307	. . .	4.86	8.86
Nonmendelian transmission	.25	3.40	.265	(0)	. . .	.943	0	8.00
All sibships:								
Sporadic ....·.............	. . .	. . .	(0)	(0)	. . .	. . .	123.19	123.19
Single locus	.59	2.69	.311	(0)	. . .	(.5)	6.70	12.70
Polygenic.....................	. . .	. . .	(0)	.560	(1)	. . .	4.17	6.17
Multifactorial	. . .	. . .	(0)	.544	.295	. . .	0	4.00
Nonmendelian transmission	.29	3.02	.333	(0)	. . .	.394	1.62	9.62

NOTE.—Numbers in parentheses are parameters specified by hypothesis.

sibships (table 5, All sibships). Estimates agree closely, but the most acceptable model is multifactorial, in which different heritabilities, H and HZ, respectively, were allowed for children and their parents. The value of Z in the multifactorial model is .295 and is significantly less than unity ($\chi_1^2 = 4.17$). No major locus model with Mendelian transmission has a higher likelihood than the polygenic model. The fact that the polygenic model has fewer parameters to test may account for this observation to a certain extent. Non-Mendelian transmission has a lower likelihood than the multifactorial model and is less acceptable by the AIC.

Discussion

The results of our study demonstrated significant familial aggregation of reported appendectomy among young cases of acute appendicitis in largest city of Yugoslavia. Detailed mathematical modeling indicated that this familial pattern was best explained not by a single major dominant or recessive gene but by significant polygenic inheritance with substantial environmental determinants as well. Our study represents the first formal genetic analysis of this frequent disease.

The three previous studies of familial appendicitis differ from ours in design and have limitations, especially in respect to data collection. Andersson et al. (1979) and Arnbjornsson (1982) used controls of the same mean age as patients. In the study of Brender et al. (1985), as in ours, cases and controls have been individually matched for age and sex. All three prior studies paid no attention to the possible differences in family sizes of cases and controls. If the families of cases are bigger than those of the controls, then the cases would, by chance, have more affected relatives. However, by taking family size into consideration by computing the morbidity ratio for cases and controls, we have shown that this bias, if present, does not explain the greater aggregation of appendectomy in the families of probands. Brender et al. (1985) looked for the history of appendicitis only in first-degree relatives (i.e., within the nuclear families of cases), whereas in our study and those studies conducted in England (Andersson et al. 1979) and Sweden (Arnbjornsson 1982) the unit of observation was a 3-generation family. This variation in the definition of "exposure" may account for the fact that the familial appendicitis tendency in Brender's study was not so great as suggested by the three other reports.

As have previous investigators, we relied on parents' reports about the familial history of appendectomies.

Although our probands had histologically confirmed appendicitis, no pathology reports were sought for the relatives of cases and controls. Since there was no reason to believe that rates of false appendicitis were unequally distributed in families of cases and controls, serious bias was probably not introduced by such an approach. Still, to reduce further any possible recall bias, our method of questioning parents differed significantly from that employed by previous studies, in which parents were asked directly, either by phone or by questionnaire, about appendectomies among relatives. Such direct questioning may elicit better recall by parents of children with suspected acute appendicitis than by parents of controls. Instead, we asked parents of both groups about all operations in their families and not just about appendectomies.

Still, in a study of this magnitude, there are issues in the methods of data collection and analysis that deserve comment before recommendations may be made for clinical implications and further research. The primary data have the strength of being collected by one investigator over a brief period of time and as a consecutive series at a single primary-care institution that had essentially complete ascertainment from a large metropolitan area. Ideally, one might want to confirm, with operative and histological reports, the surgical histories reported by parents of our probands, especially since some 20%–30% of appendectomies typically result in a surgical specimen that fails to meet histopathological criteria for acute appendicitis. This rate of "unnecessary" appendectomies is an acceptable frequency worldwide (Jacob et al. 1975). Indeed, in our series 32 (24%) of the initial 132 probands were excluded from analysis once the final histopathological diagnosis was made. No serious bias in collecting family histories arose by our procedure, since we applied it equally to cases and controls; further, there is no reason to believe that the rate of falsely positive diagnosis of acute appendicitis differed between relatives of cases and controls. Conducting independent interviews of other relatives was beyond the means of the data collector and, in the end, would not be a vigorous means of validating our information. Positive (but not negative) confirmation would require requesting pathology records, but such efforts would be futile because of large migration into Belgrade since 1945, the destruction of hospital records by war, and the low frequency of histopathologic examination of "routine" appendectomies.

Our analysis depended much on the accuracy of the estimate of age-specific morbidity risks. This estimation was subject to several possible errors. By establish-

ing 10-year classes in the face of small numbers, we neglected the fact that individuals were distributed over their liability class, not concentrated at the end of it. This assumption could lower the magnitude of observed familial aggregation. The patient's parents may not have recalled appendectomy in a relative, especially if surgery had occurred many years earlier, and so the frequency of early operations in relatives may have been underestimated. We could include only patients under 16 years of age, because of the admission policy of the Mother and Child Health Institute, so the frequency of early-onset appendicitis was overestimated in index sibships. These errors were, to a degree, compensated for in segregation analysis.

The results of our preliminary analysis (Basta et al. 1986), which favored the role of a major recessive gene, are not necessarily contradicted by the present analysis. The finding of higher heritability in sibs than in parents by Falconer's (1965) method is expressed in complex segregation analysis as a significant reduction of generation ratio (Z) from unity. Even though the segregation analysis did not support major gene inheritance, this could not be ruled out as the cause in some families. A total heritability of 56% means that almost half of the variability in risk for acute appendicitis is due to random environmental factors. Further research could be aimed at investigating these postulated genetic and environmental determinants. For now, clinicians attempting to refine their diagnostic accuracy when patients present with acute abdominal pain might inquire about family history of appendicitis.

Acknowledgments

References

Akaike H (1974) A new look at the statistical model identification. IEEE Trans Automatic Control 19:716–723

Andersson N, Griffiths H, Murphy J, Roll J, Sernyi A, Swann I, Cockcroft A, et al (1979) Is appendicitis familial? Br Med J 2:697–698

Arnbjornsson E (1982) Acute appendicitis: a familial disease? Curr Surg 39:18–20

Basta M, Marinković D, Radovanović Z, Radojičić Č (1986) Inheritance of acute appendicitis (AA). Am J Hum Genet 39:A50

Bierman HR (1968) Human appendix and neoplasia. Cancer 21:109–112

Brender JD, Marcuse EK, Weiss NS, Koepsell TD (1985) Is childhood appendicitis familial? Am J Dis Child 139:338–340

Burkitt DP (1971) Pathogenesis of acute appendicitis. Br J Surg 58:695–699

Falconer DS (1965) The inheritance of liability to certain diseases estimated from the incidence among relatives. Ann Hum Genet 29:51–77

Fitz RH (1886) Perforating inflammation of the vermiform appendix. Trans Assoc Am Phys 1:107–115

Fleiss JL (1984) Statistical methods for rates and proportion, 2d ed. Wiley Interscience, New York

Jacob ET, Nathan MB, Iuchtman M (1975) Error rate factor in the management of acute appendicitis. Lancet 2:1032–1034

Lalouel JM, Morton NE (1981) Complex segregation analysis with pointers. Hum Hered 31:312–321

Lilienfeld AM, Lilienfeld DE (1980) Foundation of epidemiology, 2d ed. Oxford University Press, New York and Oxford

McKusick VA (1988) Mendelian inheritance in man, 8th ed. Johns Hopkins University Press, Baltimore

Morton NE, MacLean CJ (1974) Analysis of family resemblance. III. Complex segregation analysis of quantitative traits. Am J Hum Genet 26:489–503

Perry T, Keeler CE (1939) Thirty-nine cases of appendicitis in a single family pedigree. Am J Surg 46:259–261

Robbins SL, Cotran RS, Kumar V (1984) Pathological basis of disease, 3d ed. WB Saunders, Philadelphia

Silen W (1987) Acute appendicitis In: Harrison's principles of internal medicine, 11th ed. McGraw-Hill, New York, pp 1304–1306

Statistical Year Book of the City of Belgrade (1984) Statistical Institute, Belgrade

Wangensteen OH, Bowers WF (1937) Significance of the obstructive factors in the genesis of acute appendicitis. Arch Surg 34:496–502