GENETICS

Familial Risk Among Patients with Endometriosis

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Purpose: *The objective of the present study was to determine the prevalence of endometriosis among the relatives of patients with confirmed endometriosis.*
Methods: *We analyzed the prevalence of endometriosis among first-, second-, and third-degree relatives in a group of 101 patients with varying symptoms related to endometriosis seen at two public hospitals and submitted to laparoscopy and/or laparotomy. The control group consisted of 43 women submitted to laparoscopy without a diagnosis of endometriosis.*
Results: *Among the patients with endometriosis, we detected nine families with a positive history of endometriosis, comprising one mother, six sisters, three aunts, and two cousins, as opposed to no case among the controls.*
Conclusions: *These data confirm a familial tendency for endometriosis and suggest that this disorder has a genetic basis.*

KEY WORDS: dysmenorrhea; endometriosis; hereditary disease; laparoscopy.

INTRODUCTION

Hereditary aspects of endometriosis have been observed in the literature since the 1970s (1). The first estimates of the risk for endometriosis among relatives of patients with the disease, especially first-degree ones, were made in the 1980s. Simpson *et al.* (2) reported a sevenfold increase in the risk for endometriosis among first-degree maternal relatives. Lamb *et al.* (3) calculated a 4.9% risk for endometriosis among first-degree relatives but did not include control subjects without endometriosis in their study. More recently, an epidemiological study of 515 patients with endometriosis (4) with a control of 149 women without the disease, documented by laparoscopy, demonstrated a 7.2 relative risk to develop endometriosis for mothers and sisters. These investigators also observed that the manifestations of endometriosis are more severe among patients with a positive family history.

Multicenter studies (5) carried out to locate and identify the gene that confers susceptibility to this disease and to study how this gene expresses effects on cell formation have suggested autosomal dominant inheritance of variable expressivity.

In view of the above data, the objective of the present study was to determine the prevalence of endometriosis among the relatives of patients with confirmed endometriosis, using women without endometriosis as controls, and to determine the possible presence of other concomitant diseases among patients with endometriosis.

MATERIALS AND METHODS

A total of 101 patients with endometriosis was selected for the study. The patients were seen at the Gynecologic Endocrinology Outpatient Clinics of the

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University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo (UHFMRP-USP), and of the Teaching Hospital of the Faculty of Medicine of Triângulo Mineiro, Uberaba (THFMTM). The patients had symptoms suggesting endometriosis. The diagnosis was made by laparoscopy and/or laparotomy and/or histological confirmation.

The control group consisted of 43 women who were also submitted to laparoscopy, without a diagnosis of endometriosis. All laparoscopies were performed by two of the authors (R.M.R. and J.U.R.).

The patients were submitted to specific investigation and information was obtained about family members for the elaboration of a pedigree, with special emphasis on the problems of first-degree (mothers and sisters), second-degree (grandmothers, aunts, and nieces), and third-degree (cousins) relatives related to endometriosis, infertility, pelvic pain, dysmenorrhea, gynecological surgeries, or other pathologies. All the relatives with a history suggestive of endometriosis were contacted and submitted to an interview and a diagnostic laparoscopy. Data on the presence of diseases other than endometriosis were obtained during the interview and also from the medical records of the patients.

Since we did not detect case of endometriosis among the relatives of the control population, we could not apply statistical tests to determine their differences. Data related to associated diseases were analyzed statistically by the parametric Student t test, with the level of significance set at $P < 0.05$.

All subjects gave informed consent to participate in the study, which was approved by the Ethics Committees of the two hospitals.

RESULTS

Endometriosis was staged according to the revised classification of the American Society for Reproductive Medicine (6) and was found to be minimal in 20 cases, mild in 41, and moderate in 40. Since the influence of minimal endometriosis in infertility is questioned and appears to be of no importance, we agree with Moen and Magnus (4) that it is unethical to register these patients and to interview them. For the interpretation of the data obtained in the present study we excluded the patients with minimal endometriosis, with 81 patients thus being left in the study.

The mean age of the patients with endometriosis was 31.8 years (range, 22 to 54 years) and did not differ from that of the control group (33.9 years; range, 24 to 43 years). Both groups consisted predominantly of white women (63 and 86%, respectively). All control women were married, whereas 26% of the patients with endometriosis were single.

The symptoms most commonly detected in the patients with endometriosis were dysmenorrhea (85%), pelvic pain (50.6%), and infertility (55.5%). The incidence of menstrual irregularity (22.2%) did not differ from that for the control group (21%).

Among the diseases detected in the patients studied, only uterine leiomyomatosis and repeated abortion were significantly more frequent ($P < 0.05$) among the patients with endometriosis compared to the control group (Table I). Of the 81 patients with endometriosis, 31 had endometriomas.

Of the 81 patients with endometriosis, 9 (11.1%) had a confirmed family history of endometriosis, involving one mother, six sisters, three aunts, and two cousins. A total of seven first-degree relatives (8.6%) was affected, as opposed to no cases in the control group; three (3.7%) second-degree relatives (aunts) were affected, again as opposed to no cases in the control group; and only two (2.4%) third-degree relatives (cousins) were affected, as opposed to no cases in the control group. Two of the patients has more than one relative affected: in one case the two relatives were sisters, and in the other the relatives were a sister, an aunt, and a cousin. The pedigrees of all families with a positive history of endometriosis are illustrated in Fig. 1.

No differences in clinical characteristics were detected in the patients suffering from endometriosis with versus without a family history of the disease, such as infertility (33 vs 51.4%), pelvic pain (33 vs 37.5%), dysmen-

Table I. Frequency of Associated Diseases Among the Patients with Endometriosis and the Controls

	Group			
	Endometriosis (n = 81)		Control (n = 43)	
Associated disease	n	(%)	n	(%)
Myoma	13*	(31.7)	1	(2.3)
Bicornis uterus	1	(1.2)	0	
Polycystic ovarian syndrome	3	(3.7)	1	(2.3)
Hyperthyroidism	1	(1.2)	0	
Hyperprolactinemia	3	(3.7)	0	
Repeated abortion	4	(4.9)	0	
Fetal losses	1	(1.2)	0	
Diabetes mellitus	1	(1.2)	0	
Arterial hypertension	2	(2.4)	2	(4.6)

* Statistically significant at the $P < 0.05$ level.

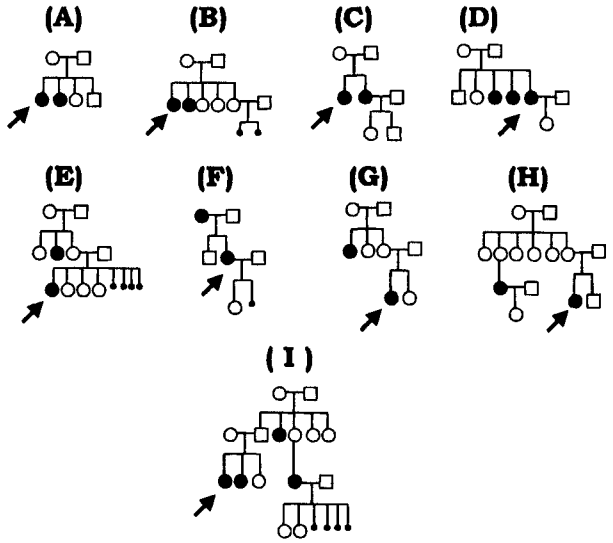

Fig. 1. Partial pedigree of the nine families with a positive history of endometriosis (the arrows indicate the purpose patients).

orrhea (77.7 vs 58.3%), and a pelvic mass (33 vs 29.2%).

DISCUSSION

There is substantial uncertainty about the nature of the inheritance of endometriosis since many researchers are looking for a specific gene or a group of genes that could be accountable for the high prevalence of endometriosis among relatives of patients with endometriosis. The literature has also reported familial cases of adenomyosis (7). Arnold *et al.* (8) reported a case involving three generations in which the grandmother, the mother, and two sisters had adenomyosis, indicating a genetic basis for these cases consistent with autosomal dominant or X-linked inheritance of variable expressivity. Pandis *et al.* (9) reported three cases of adenomyosis whose chromosome analysis from tissue culture revealed a clonal finding of deletion of the long arm of chromosome 7 in all of them, a deletion also frequently observed in uterine leiomyomas (10).

The high prevalence of patients with more severe endometriosis in the group with a positive family history for the disease not only may have genetic implications but also may suggest that this familial trait requires a more aggressive diagnosis directed at affected relatives.

The low incidence of endometriosis among second-degree relatives, and especially the absence of this finding among grandmothers, may also be related to the precarious diagnostic method available for the detection of endometriosis in that generation. Taken together with our small population sample and the hypothesis of incomplete penetrance, these conditions impair a true determination of this occurrence. However, another hypothesis, such as paternal inheritance, may also be raised, as illustrated by the pedigree of case I (Fig. 1).

The genetic basis for endometriosis has been proposed to be mutation of a dominant gene of low penetrance and variable expressivity or multifactorial polygenic inheritance (2). The observation of endometriosis in monozygotic twins is compatible with these two hypotheses (4,11). The pedigrees of the nine families studied here confirm a familial tendency for endometriosis, but it is difficult to establish a correlation between our findings and a Mendelian pattern of inheritance. Pedigrees A, B, C, and D involve only one generation, with more than one affected person, but no consanguinity was found. In pedigree H, only one generation is involved, with cousins rather than sisters being affected. In pedigrees E, F, and G more than one generation is involved and at least one affected subject is present in each generation. Pedigree I (and, likewise, pedigrees E, F, and G) could be explained by an autosomal dominant mutation (with incomplete penetrance and variable expression) or an X-linked dominant inheritance, both limited by the sex (males do not have a uterus).

This study supports the hypothesis that this disorder has a genetic basis, although there is considerable uncertainty about the pattern of inheritance associated with this disease. The linkage analysis of the familial cases could help find genes involved in the development of endometriosis. These data confirm a familial tendency for endometriosis and suggest that this disorder has a genetic basis.

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