GENETICS

Familial Endometriosis*

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Submitted: December 12, 1994
Accepted: December 15, 1994

Purpose: *The study aimed to identify families with endometriosis and to document disease severity within the families and the clinical characteristics of the affected women.*

Results: *Two hundred and thirty women with surgically confirmed endometriosis in 100 families were identified. The families consisted of 19 mother-daughter pairs, 1 set of cousins and 56 sister pairs. There were 5 families with 3 affected sisters, 1 family with 5 affected sisters, and 18 families with ≥3 affected members in more than one generation. The mean age at the onset of symptoms and the mean age at surgical diagnosis was 22.1 ± 8.8 SD (range 10–46) and 31.8 ± 7.9 SD (range 15–56) years respectively. Seventy-nine women (34.3%) had revised AFS Stage I-II disease, and 151 (65.7%) had revised AFS Stage III-IV disease.*

Conclusion: *The study confirms a familial tendency for endometriosis and supports the hypothesis that endometriosis has a genetic basis.*

KEY WORDS: endometriosis; genetics.

INTRODUCTION

There are two standard approaches to determine whether or not a disease has a genetic basis. These are to calculate the concordance rates in large twin studies and the prevalence of the disease in the first-degree relatives of affected individuals.

The best estimates of the prevalence of endometriosis are 0.5–2.5% in premenopausal women (1,2). An increased prevalence among relatives compared to the general population has been reported. Simpson *et al.* (3) reported an increased risk among the first-degree relatives of American patients. They found that the patients' sisters had a six times, and mothers a nine times, greater risk compared to their husbands' sisters and mothers, respectively. Coxhead and Thomas (4) showed a sixfold increased risk among the first-degree relatives of English patients compared to those of case controls without the disease. In a Norwegian population, Moen and Magnus (5) reported an eightfold increase in risk for endometriosis and/or adenomyosis among the sisters of patients compared to the sisters of case controls, and a nearly six times greater risk for the mothers. In their study, severe disease among the women with endometriosis was significantly more common in those with an affected relative.

Although data from large twin studies are unavailable, a small study showed endometriosis in 6/8 monozygotic and 0/2 dizygotic twin-pairs (6). It is therefore likely that endometriosis has a genetic basis, but the mode of inheritance is unknown.

MATERIALS AND METHODS

Recruitment of Families

We initiated recruitment of families from Endometriosis Associations in the UK, Ireland, United States, Canada, Australia, and New Zealand by placing advertisements in their newsletters. All di-

* Presented at the 50th Annual Meeting of the American Fertility Society, San Antonio, Texas, November 5–10, 1994.

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1058-0468/95/0100-0032$07.50/0

agnoses in probands and their relatives were confirmed by examining the operative records, and the histological findings if available, that were obtained from the gynecologists concerned. Families were also recruited by initially identifying probands with surgically confirmed endometriosis from the records of the John Radcliffe Hospital.

Assessment of Disease Severity

Disease severity was assessed according to the revised American Fertility Society (AFS) classification (7) and divided into Stage A (AFS Stage I-II) and B (AFS Stage III-IV).

RESULTS

One hundred families were identified each with at least two affected members. They contained 230 women from Australia (7), Canada (5), Holland (1), Ireland (4), Italy (1), New Zealand (4), Slovakia (1), UK (126), and United States (81): The families were comprised of 19 mother-daughter pairs, 1 set of cousins and 56 sister pairs, of which 8 were twins (monozygous = 7, unknown zygosity = 1). There were 5 families with 3 affected sisters, 1 family with 5 affected sisters, and 18 families with $\geq$3 affected members in more than one generation.

One hundred and sixty-two women (70.4%) had each undergone a mean number of 1.5 ± 0.9 SD (range 1–6) laparoscopies, and 86 women (37.4%) had each had a mean number of 1.3 ± 0.9 SD (range 1–9) laparotomies. Seventy-seven (33.5%) women had had a hysterectomy. The mean age at surgical diagnosis was 31.8 ± 7.9 SD (range 15–56) years. Histological confirmation of the diagnosis was obtained in 104 cases (45.2%), and adenomyosis was found in 11 of the 77 (14.3%) uterine specimens. One hundred and two women (44.3%) were infertile, and 219 women (95.2%) had pelvic pain and/or dysmenorrhoea. The mean age at which pain symptoms commenced was 22.1 ± 8.8 SD (range 10–46) years.

Seventy-nine women (34.3%) had Stage A and 151 (65.7%) had Stage B disease. In 47 of the families, all the affected members had Stage B disease. Disease severity was distributed within the families as follows and is shown in Table I: mother-daughter pairs (AA = 1, AB = 3, BB = 11, BA = 4); cousins (BB = 1); sister-pairs (AA = 9, AB = 20, BB = 27) and families with three affected sisters (AAB = 1, ABB = 1, BBB = 3). All the twins were BB, with the exception of one monozygous AA pair. There was one family with five affected sisters (AAABB = 1).

Among those families with $\geq$3 affected members in more than one generation, there were three families with a mother and two daughters (A/AA = 1, B/AB = 1, B/BB = 1), five families with a mother-daughter pair and a maternal sister (BA/A = 2, BA/B = 2, BB/B = 1), and two families with a sister-pair and a maternal cousin (AB/A = 2). The remaining families are shown in Fig. 1. They contained seven women who had been shown not to have endometriosis at laparoscopy or hysterectomy.

CONCLUSION

Previous reports have described an increased prevalence of endometriosis (3,4) and/or adeomyosis (5) in the relatives of women with endometriosis compared to the general population.

Our study confirms a familial tendency for endometriosis and documents, for the first time, the distribution of disease severity within a large number of families. The findings support the hypothesis that endometriosis has a genetic basis, although it is not possible to determine the mode of inheritance from these data. This can usually be ascertained by segregation analysis, but it is difficult to use this method within endometriosis families because the

Table I.

Disease severity	AA	AAB	AB	ABB	BB	BBB	BA
Mother–daughter pairs	1	—	3	—	11	—	4
Sister pairs	9	—	20	—	27	—	—
Three sisters	—	1	—	1	—	3	—
Cousins	—	—	—	—	1	—	—
Total	10	1	23	1	39	3	4

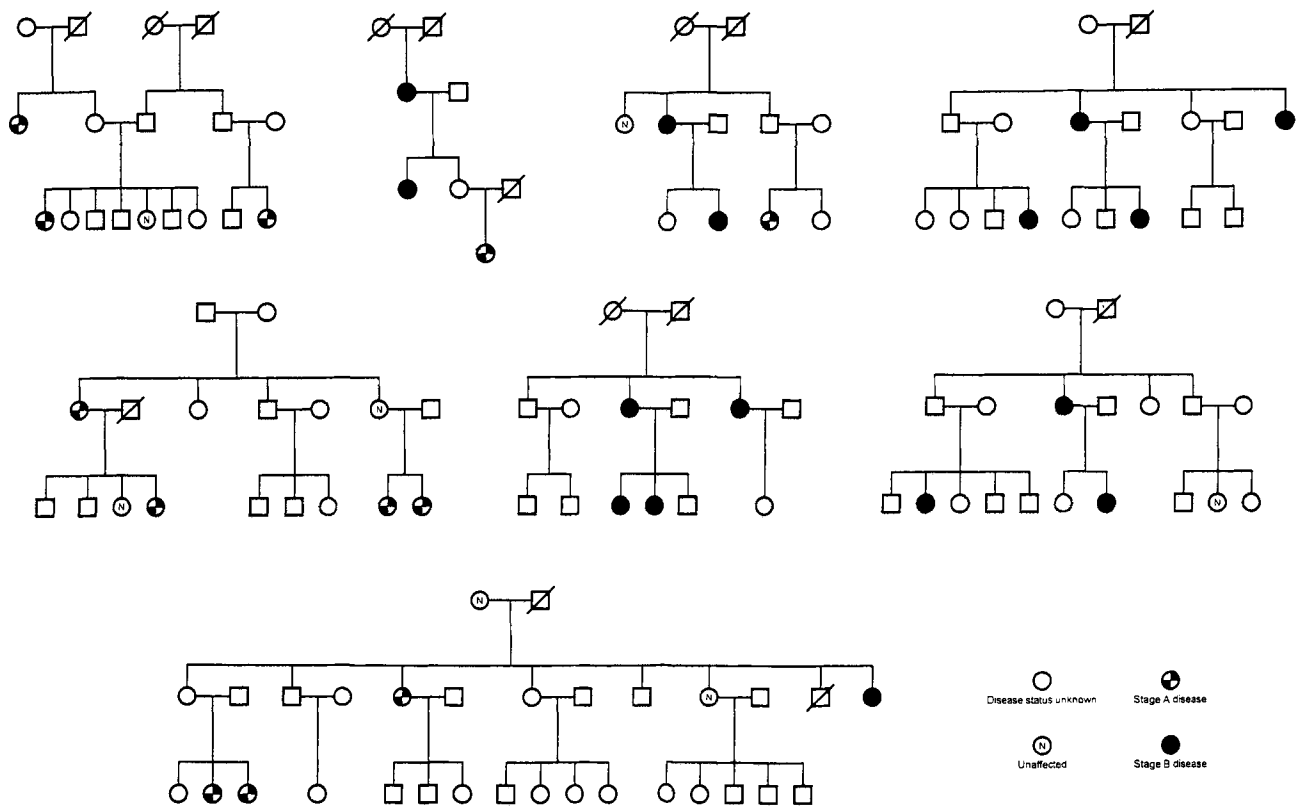

Fig. 1. Families with endometriosis.

diagnosis cannot be made or excluded without surgical intervention.

To determine if there is a genetic basis to endometriosis, we plan to investigate sister pairs with Stage B disease in an attempt to establish genetic linkage using affected sib-pair analysis (8). Families are being collected in collaboration with research centers throughout the world. The advantage of this approach is that it can be performed without knowing the mode of inheritance. The identification of a gene(s) conferring susceptibility to endometriosis would allow us to investigate the molecular and cellular processes associated with the disease.

ACKNOWLEDGMENTS

We acknowledge the help of Mary Lou Ballweg, Executive Director/President, of the Endometriosis Association; we also thank endometriosis sufferers and their gynecologists in the UK, Ireland, United States, Canada, Australia, and New Zealand for their help.

REFERENCES

1. Haupt BJ: Utilization of short-stay hospitals: annual summary for the United States, 1980. Vital Health Stat 1982;13(64):1–60
2. Houston DE, Noller KL, Meltson LJ III, *et al.*: Incidence of pelvic endometriosis in Rochester Minnesota, 1970–1979. Am J Epidemiol 1987;125:959–962
3. Simpson JL, Elias S, Malinak LR, Buttram VC: Heritable aspects of endometriosis. I: Genetic studies. Am J Obstet Gynecol 1980;137:327–331
4. Coxhead D, Thomas EJ: Familial inheritance of endometriosis in a British population. A case control study. J Obstet Gynaecol 1993;13:42–44
5. Moen MH, Magnus P: The familial risk of endometriosis. Acta Obstet Gynecol Scand 1993;72:560–564
6. Moen MH: Endometriosis in monozygotic twins. Acta Obstet Gynecol Scand 1994;73:59–62
7. American Fertility Society: Revised American Fertility Society classification of endometriosis. Fertil Steril 1985;43: 351–352
8. Suarez BK: The affected sib pair IBD distribution for HLA-linked disease susceptibility genes. Tissue Antigens 1978;12:87–93