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ORIGINAL ARTICLE

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Familial tranmission of genitovaginal prolapse

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Abstract Some females with little to no risk factors develop prolapse, while other females with multiple risk factors do not. It appears that some women may have a predisposition for prolapse in the setting of equivalent risk factors. We identified 10 patients younger than 55 years old with a family history of prolapse. Their average age was 37 years (range 27–51), the mean number of deliveries was 1.8, and their mean birth weight was 8 lbs. Genetic analysis of the inheritance pattern within these families demonstrated that pelvic organ prolapse segregated in a dominant fashion with incomplete penetrance in these families. Both maternal and paternal transmissions were observed. The relative risk to siblings of affected patients was five times that of the risk for the general population. Further investigation of these families may identify a genetic defect responsible for prolapse.

Keywords Incontinence · Cystocele · Enterocele · Hysterectomy · Genetics

Introduction

Genitovaginal prolapse, also known as pelvic organ prolapse, is a devastating and common social and medical problem. Observational studies have reported the overall incidence of vaginal prolapse to range from 10 to 40% in older females, with a majority of women having stage 1–2 disease. The incidence of stage 3 or 4 vault prolapse hovers around 2% in the adult female population [14, 16]. The lifetime risk of a female undergoing surgical repair of a female pelvic floor disorder is greater than 10% [11]. More than 200,000 inpatient surgical procedures for genitovaginal prolapse are performed each year in the United States, at an estimated cost of over 1 billion dollars [18]. Without a true understanding of the pathophysiology of pelvic floor disorders, prevention efforts cannot be effectively accomplished.

A multitude of physiological and lifestyle risk factors have been independently linked to the development of pelvic organ prolapse. In a multivariate analysis of random women undergoing routine pelvic examinations, the strongest predictors of finding pelvic prolapse were increasing age, Hispanic race, increased body mass index, and an increased weight of vaginally delivered births [17]. Other investigators have shown that multiparity, decreased hormonal status, decreased pelvic floor strength, episiotomy, smoking, constipation, and extended second stage of labor correlate with increased risk of prolapse [9–11, 14].

Ethnic and racial variations in the incidence of prolapse have been described. It was observed that women of European and Hispanic ancestry may be at greatest risk for the development of prolapse and urinary incontinence compared to women of Asian, African, and Native American ethnicity [6, 9, 17]. At a screening level, Asian women have been shown to have significantly less pelvic organ mobility, both ante- and postpartum, compared to women of Caucasian ancestry [6].

While it is generally accepted that parturition has a deleterious effect on pelvic organ support, it must be noted that the majority (>95%) of multiparous women do not develop prolapse. Conversely, in rare cases, nulliparous women may develop severe prolapse. Taken together, these observations suggest that certain women may be predisposed to develop genitovaginal prolapse. Such predisposition likely occurs at the genetic level, as the result of the millions of varied alleles that come together to provide us

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with our phenotypic individuality. We hypothesize that if a genetic predisposition exists, certain families may harbor the high-risk alleles at a much higher incidence than the general population, and that these families should have a strong family history of pelvic prolapse. Therefore, we investigated familial transmission of pelvic organ prolapse in a cohort of patients.

Methods

We identified a cohort of women treated at UCLA Medical Center for genitovaginal prolapse between June 1, 2000 and July 31, 2002. All women completed a medical questionnaire on urinary incontinence, pelvic prolapse, and family history, as well as underwent a detailed history and physical examination. The POP-Q staging system was used to stage the severity of pelvic prolapse [3]. The patient history included detailed information on patient ethnicity, age at the time of diagnosis, parity, number of vaginal deliveries, number of pregnancies, child birth weights, hormonal status, family history, and past medical and surgical history.

The study was preapproved by the UCLA Institutional Review Board. Women who met the following criteria: (1) POP-Q stage III or IV genitovaginal prolapse [3], (2) patient age less than 55 years, (3) a family history of prolapse, and (4) had relatives willing to be contacted for study purposes, were asked to participate in the study. All participants and relatives gave consent to use their data for research purposes. For families who agreed to participate, we obtained information about vaginal prolapse in all genetically linked female family members including mothers, sisters, daughters, grandparents, and second-degree relatives. When available, the medical history of female family members was obtained through direct telephone contact with the family member. Relatives who reported a surgical repair for genitovaginal prolapse or who complained of genitovaginal prolapse to the level of the introitus were recorded as disease positive. Females lacking vaginal prolapse surgery or vaginal prolapse complaints were recorded as disease negative. Females unsure of their urogynecological history were marked as unknowns and analyzed as disease negative.

Analysis of family trees was performed. Relative risk was calculated by dividing the number of affected sisters by the total number of proband sisters, represented as a percentage, then dividing by the percentage risk of stage III and IV vaginal prolapse in the general age-matched population [14, 15].

Results

One hundred eighty-two females were treated in our clinic between June 1, 2000 and July 31, 2002 for stage III and IV pelvic organ prolapse. Of these women, the average age was 66±11 years (median 68, range 27–90 years). Twenty-eight patients (15%) were younger than age 55 years, 73 women (40%) underwent previous pelvic surgery including incontinence surgery and cystocele repair, and 46 patients (25%) had previous hysterectomy. The mean parity was 2.3±1.8 (median 2, range 0–9), and the mean number of vaginal births was 2.2±1.7 (median 2, range 0–9) for this population. Ten of the 182 (5.5%) women had at least one cesarian section.

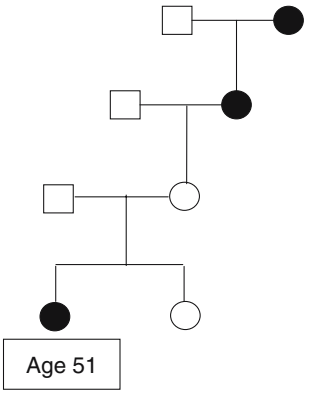

Fig. 1 Autosomal dominant transmission of genitovaginal prolapse with a high degree of penetrance. Females are *circles*, males are *squares*. Disease positive women are shaded *black*. The index patient is 51 years of age in this family

Of the 28 women younger than 55 years, 10 (36%) reported having at least one female relative with known pelvic organ prolapse. The mean age of onset of prolapse in these 10 women with familial disease was 37 years (range 27–51). The mean parity was 1.9±0.9 (range 0–3), and number of vaginal deliveries was 1.8±0.9 (range 0–3). The mean birth weight was 8 lbs in this subset. One woman was nulliparous, and one woman delivered by cesarian. Seven of the 10 women had previous pelvic surgery, including 6 women who underwent prior incontinence or pelvic prolapse surgery. Five of the 10 women (50%) had complicated labor including 3 women with episiotomy or vaginal tears, 1 with prolonged labor requiring cesarian, and 1 with forcep delivery.

Genetic analysis of the familial inheritance pattern in these 10 families showed that pelvic organ prolapse appeared to segregate in a dominant fashion with a high degree of penetrance in these families (Fig. 1). One patient had consanguinity in her family. Transmission through both maternal and paternal relatives was observed (Fig. 2). Twenty percent of sisters of probands were disease positive. The relative risk to the sisters of our index patients

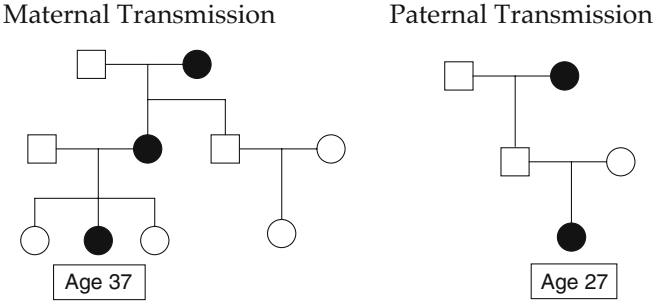

Fig. 2 Maternal and paternal transmission of genitovaginal prolapse. Females are *circles*, males are *squares*. Disease-positive women are shaded *black*. The index patient is identified by their age

was five times greater than the estimated risk for the general population.

Discussion

The purpose of this study was to determine if familial clustering of grade III–IV pelvic organ prolapse exists in select families, and if it does, to examine inheritance patterns that could help identify potential high-risk genes in the future. We found that in a fraction of females with grade III and IV pelvic organ prolapse, there was a strong familial component. The mothers, sisters, and grandmothers of our index patients had a fivefold increased risk of severe pelvic floor defects. Family tree analysis demonstrated that within these families, the transmission of pelvic prolapse followed a dominant inheritance pattern with high penetrance. Our results are consistent with the hypothesis that genetic variation and certain alleles can predispose women to develop, or not develop, pelvic prolapse. The identification of these abnormal families may allow for DNA sequencing of the families' genomes in search of redundantly transmitted genetic alleles, such as muscle and connective tissue alleles, that may predispose for pelvic prolapse. Identification of abnormal muscular and connective tissue alleles could provide us with new insight into the protective or causative mechanisms that underlay the etiology of pelvic organ prolapse.

The risk factors for vaginal prolapse are multifactorial. Vaginal parity, increased infant birth weight, vacuum or forceps delivery, episiotomy, prolonged second stage of labor, obesity, and prior surgery have all been associated with vaginal prolapse [10, 21]. Regarding parity alone, the currently available data are conflicting. While some studies show a strong influence of parity on the risk for female pelvic floor disorders [5], other studies do not [2]. Importantly, risk factors alone fail to fully explain the genesis and progression of pelvic prolapse. Severe pelvic prolapse has been observed on occasion in nulliparous women with minimal risk factors, and a majority of multiparous women do not develop severe pelvic prolapse. The disease onset typically occurs decades after any inciting pelvic trauma, suggesting that molecular alterations from the trauma rather than the trauma itself are important in the pathophysiology. Therefore, a genetic or molecular predisposition is seemingly likely.

For instance, several studies have demonstrated that the heritability of bladder neck mobility is associated with abnormal connective tissue syndromes. In the largest study, an analysis of 178 nulliparous white female twins aged 18–24 demonstrated that bladder neck mobility was genetically heritable, and that additive genes accounted for up to 59% of the variance observed [7]. Several investigators have attempted to identify the molecular markers and genetic alleles at the root of this variability, hypothesizing that individuals who also harbor the gene (both sporadic or familial) would be at increased risk.

Our results support the hypothesis that a genetic or familial component may underlie a women's risk to develop vaginal prolapse. In our cohort of young women with grade III–IV prolapse, 10 of the 28 patients (35%) reported having family members with pelvic organ prolapse. We chose to limit our investigation to patients under the age of 55, as we felt these were the women most likely to come from families harboring the high-risk alleles. In support of this hypothesis, Rinne and Kirkinen [13] found that the familial incidence of genital prolapse was 30% in women aged 45 years or younger who underwent pelvic prolapse repair.

All of our female study patients were referred to our specialty clinic specifically for the treatment or retreatment of their pelvic organ prolapse; thus, we did not attempt to perform an epidemiologic study. Existing epidemiologic data have shown that in women with stage II and III prolapse, 27% of women with prolapse reported a mother with prolapse, and 30% reported a sister with prolapse [5]. The calculated odds ratios (OR) for prolapse in the mothers and sisters in this study were 3.2 and 2.4 compared to those in the age-matched controls. These numbers are similar to the fivefold OR we found in the siblings of our probands.

The purposes of our study were to identify high-risk families and to analyze their family trees. For the majority of our female relatives, we used telephoned medical interviews to obtain their medical histories, as we did not have access to their outside medical records. While this is a potential limitation to of our study design, all of the relatives we contacted were able to provide sufficient information regarding their genitourinary history, including the severity and duration of their prolapse symptoms, as well as their surgical treatment procedures. In the case of one family, several of the sisters and the mother were patients in our clinic, and their histories and exams were verified. Due to the immense geographic distribution of several of the other families and the fact that the majority of relatives reported their prolapse was already surgically repaired, we did not attempt to examine the female relatives in our clinic.

We believe it is important to analyze the familial clustering and genetic transmission of pelvic prolapse since several investigators are exploring the molecular and genetic alterations found in the skeletal muscles of women predisposed for pelvic prolapse. For instance, the skeletal protein calpain is decreased in women with prolapse, while actin and myosin show differential gene expression in women with and without prolapse [4]. Other studies have found that myosin binding proteins and skeletal muscle myosin heavy chain 3 are drastically underexpressed in women with severe pelvic prolapse [20].

In addition to skeletal muscle, changes in connective tissue are implicated in the pathogenesis of prolapse. Support of the vagina and anterior bladder wall is provided by complex interactions between the levator avi and connective tissues. The connective tissue, composed predominantly of collagen, elastin, glycoproteins, and proteoglycans, largely determines the stability and strength of the pelvic floor. The deterioration of connective tissue is hypothesized to lead to the development of pelvic organ prolapse [21]. Several reports in the literature have shown

that a decreased collagen content is present in the pelvic fascia of women with pelvic floor disorders compared to controls [8, 12]. Hydroxyprolene, a component of collagen synthesis, is 40% lower in women with pelvic floor disorders compared to controls [19]. Several authors have reported an association between pelvic floor disorders and joint hypermobility, such that 84% of women with joint hypermobility had severe genitoprolapse [1]. In addition to collagen, changes in elastin have been implicated, and investigators have demonstrated that elastin proteins and mRNA synthesis are significantly down-regulated in the fibroblasts of prolapse patients [22].

Numerous additional genes up-regulate and down-regulate in various pelvic prolapse gene arrays; however, the breadth of these markers is too numerous to discuss in this paper. These uncertainties underlie the importance of pursuing more powerful genetic techniques such as familial genotyping and linkage analysis. In our study, we identified familial clustering of pelvic organ prolapse in 10 families, including one with consanguinity. There is potential that linkage analysis of common genes within these high-risk families may one day shed light onto the genetic and musculoskeletal risk factors that predispose certain women to develop pelvic organ prolapse.

Conclusions

There are multitudes of articles and editorials arguing the benefits and controversies of elective cesarean section to avoid pelvic floor disorders. The ability to discern women at high and low risk of developing pelvic prolapse following vaginal delivery would provide tremendous insight into this hotly debated argument. Our results demonstrate that familial clustering and transmission of pelvic prolapse occurs in a subset of patients, and within these families, there is a dominant pattern of inheritance with high degree of penetrance and an increased relative risk to siblings. Further investigation of these families with linkage analysis may identify genetic defects contributing to the etiology of pelvic organ prolapse. Such genetic defects may play a role in the genesis or progression of prolapse and other connective tissue disorders.

References

1. Al-Rawi ZS, Al-Rawi ZT (1982) Joint hypermobility in women with genital prolapse. Lancet 1:1439–1441
2. Buchsbaum GM, Chin M, Glantz C, Guzick D (2002) Prevalence of urinary incontinence and associated risk factors in a cohort of nuns. Obstet Gynecol 100:226–229
3. Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO, Klarskov P, Shull BL, Smith AR (1996) The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 175:10–17
4. Chen GD, Chen YC, Lin LY (2004) Different expression of calpains in the anterior vaginal wall of women with and without uterovaginal prolapse. J Soc Gynecol Investig 11:113–117
5. Chiaffarino F, Chatenoud L, Dindelli M, Meschia M, Buonaguidi A, Amicarelli F, Surace M, Bertola E, Di Cintio E, Parazzini F (1999) Reproductive factors, family history, occupation and risk of urogenital prolapse. Eur J Obstet Gynecol Reprod Biol 82:63
6. Dietz HP (2003) Do Asian women have less pelvic organ mobility than Caucasians? Int Urogynecol J Pelvic Floor Dysfunct 14:250
7. Dietz HP, Hansell NK, Grace ME, Eldridge AM, Clarke B, Martin NG (2005) Bladder neck mobility is a heritable trait. BJOG 112:334–339
8. Jackson SR, Avery NC, Tarlton JF, Eckford SD, Abrams P, Bailey AJ (1996) Changes in metabolism of collagen in genitourinary prolapse. Lancet 347:1658–1661
9. Kim S, Harvey MA, Johnston S (2005) A review of the epidemiology and pathophysiology of pelvic floor dysfunction: do racial differences matter? J Obstet Gynaecol Can 27:251–259
10. Mant J, Painter R, Vessey M (1997) Epidemiology of genital prolapse: observations from the oxford family planning association study. Br J Obstet Gynaecol 104:579–585
11. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL (1997) Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 89:501–506
12. Rechberger TDH, Baranowski W, Jakowicki J (1993) Female urinary stress incontinence in terms of connective tissue biochemistry. Eur J Obstet Gynecol Reprod Biol 49:187–191
13. Rinne KM, Kirkinen PP (1999) What predisposes young women to genital prolapse? Eur J Obstet Gynecol Reprod Biol 84:23
14. Samuelsson EC, Arne Victor FT, Tibblin G, Svardsudd KF (1999) Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am J Obstet Gynecol 180:299
15. Smith AR, Hosker GL, Warrell DW (1989) The role of partial denervation of the pelvic floor in the aetiology of genitourinary prolapse and stress incontinence of urine. A neurophysiological study. Br J Obstet Gynaecol 96:24–28
16. Swift SE (2000) The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 183:277
17. Swift S, Woodman P, O'Boyle A, Kahn M, Valley M, Bland D, Wang W, Schaffer J (2005) Pelvic organ support study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 192:795
18. Subak LL, Waetjen LE, van den Eeden S, Thom DH, Vittinghoff E, Brown JS (2001) Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol 98:646–651
19. Ulmsten UEG, Giertz G, Malmstrom A (1987) Different biochemical composition of connective tissue in continent and stress incontinent women. Acta Obstet Gynecol Scand 66:455–457
20. Visco AG, Yuan L (2003) Differential gene expression in pubococcygeus muscle from patients with pelvic organ prolapse. Am J Obstet Gynecol 189:102
21. Weber AM, Buchsbaum GM, Chen B, Clark AL, Damaser MS, Daneshgari F, Davis G, DeLancey J, Kenton K, Weidner AC, Word RA (2004) Basic science and translational research in female pelvic floor disorders: proceedings of an NIH-sponsored meeting. Neurourol Urodyn 23:288–301
22. Yamamoto K, Yamamoto M, Akazawa K, Tajima S, Wakimoto H, Aoyagi M (1997) Decrease in elastin gene expression and protein synthesis in fibroblasts derived from cardinal ligaments of patients with prolapsus uteri. Cell Biol Int 21:605