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Research

The Role of Collagen Genetic Discrepancies in Development of Pelvic Organ Prolapse in Women: A Study with Negative Results

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ABSTRACT

Introduction

Pelvic organ prolapse has a mixed aetiology – hereditary and acquired. During last decade, the role of genetics in POP becomes profoundly obvious. women with a family history of prolapse are at an increased risk of prolapse refractory to treatment. Careful literature review from the past studies reveals that several genetic mutations have been shown to correlate with increased prolapse susceptibility. These mutations can result in disordered collagen metabolism, which weaken the fascial support of the pelvic organs. This prompt us to undertake the above study, look more into genetic discrepancies and pelvic organ prolapse contemporary studies relate to this topic shows that Collagen is playing a major role in pelvic floor supportive structures. However role of single nucleotide polymorphism (SNP) of the COL1A1 or COL3A1 or COL18A1 genes remain controversial relate to pelvic organ prolapse. Some studies and meta-analysis found a strict correlation between these genetic defects and POP.

Methods

Include sample size and statistical approaches.

Results

The Results must contain sufficient data for readers to evaluate the credibility of the conclusion. All of the data does not need to be presented. The conclusion should be an inference, not a summary.

Conclusions

Readers should be able to understand the question asked in the study and why and how it was done.

Keywords: *Genetics; Single Nucleotide Polymorphism (SNP); Pelvic organ prolapse.*

INTRODUCTION

Pelvic Organ Prolapse (POP) is the herniation of viscera into the vagina,[1] generally associated with weakness of the supporting structures. Prolapse is a common condition that affect women in menopausal years. however, recent studies show that women of premenopausal years can be equally affect by this. Prolapse is likely to become more prevalent as our population ages, so a review of new evidence regarding the aetiology of this condition is timely.

Aside from the traditional risk factors such as age, parity, vaginal childbirth and increased intra-abdominal pressure (ie obesity, chronic cough

and constipation),[2] the concept of a genetic tendency towards prolapse is becoming more apparent. For example, women with a positive family history of POP are more likely to develop prolapse compared to women with no family history (OR 2.58, 95% CI 2.12–3.15).[3] Furthermore, twin studies have identified that genetic factors contribute about 43% of the variation in liability to prolapse.[4]

Most gynaecologists are aware of the link between connective tissue disorders and prolapse. For example, women who have collagen-associated disorders such as Ehlers–Danlos syndrome and Marfan syndrome have an increased prevalence of prolapse. Such women tend to have more severe prolapse symptoms and are more likely to get recurrence after vaginal repair.[5-8] Women with a history of haemorrhoids, varicose veins, hernias and abdominal striae (conditions thought to be related to collagen deficiency) are also more likely to develop symptomatic prolapse.[9-11] Conversely, women with pro-lapse are significantly more likely to develop hernias com-pared with controls (31.6% vs 5%, n= 20, *P=0.002*).[12] There is strong evidence that collagen imbalance contributes to the pathogenesis of hernias.[13]

Changes in collagen metabolism may lead to weakened fascia, which plays an essential role in the support of the pelvic viscera.[14] Over the past five years, studies have identified several genetic variants (or polymorphisms) implicated in prolapse.[15] These genetic variations affect collagen synthesis and remodelling of the extracellular matrix (ECM) .[16] This review aims to summarise recent findings regarding the role of collagen dysfunction and its relation to genetic aberrations in the pathogenesis of POP.[17]

MATERIALS AND METHODS

This case-control trial investigated the prevalence of COL1A1, COL3A1 and COL18A1 genes SNP in female patients suffering with POP in comparison with women without these symptoms. The number of the patients in the study and control groups were in 1,5:1 ratio. Inclusion criteria a study and control groups were limited to having at least one or more POP risk factors, such as: two or more births through natural paths, traumatic births, births of more than 4,000 grams, excessive physical activity, diseases accompanied by increased intraabdominal pressure (bronchial asthma, chronic bronchitis, chronic constipation), history of pelvic surgery. Exclusion criteria for both groups were hereditary diseases with a known increased risk of POP, such as Marfan or Ehlers-Danlos syndrome as well as previous surgeries for POP/SUI for control group. All women included for both treatment and control groups were Caucasian of Russian descent.

The trial was approved by Local Ethics Committee and registered in International Clinical Trials Registry Platform (N 34678).

Laboratory Tests

Participants gave a saliva sample in order to perform a genetic test. The medical history was collected and filed; pelvic floor physical exam will be done. The saliva samples will be analyzed for SNP in COL3A1 (rs1800255, rs1801184, rs111929073); in COL1A1 (rs1800012); in COL18A1 (rs2236479). Genotyping was performed by Sanger sequencing method, [8] followed by estimation of sensitivity and specificity for POP and SUI.

Primers specificity was confirmed by polymerase chain reaction (PCR) with subsequent electrophoresis in agarose gel. Sanger sequence of PCR product was performed on ABI 3730XL (Life Technologies) from one end, one reaction per template on ABI.

To determine the correlation of pelvic floor dysfunction with a combination of polymorphisms rs1800012, rs1800255, rs2236479, rs1801184 the method of logistic regression with the inclusion of all independent factors was used.

RESULTS

The study group included 150 Caucasian women with POP (mean age 64.4years, from 40 to 70 years old). One hundred women matched with age and risk factors but without POP were included as a control group.

The COL1A1 gene encodes the alpha-1 protein of the type I collagen chain. A section of DNA in the regulatory region of the COL1A1 gene at position 1245, in which guanine (G) is replaced by thymine (T), was investigated. As a result of substitution, the nature of gene transcription changes and the normal ratio of collagen chains is violated, which leads to a violation of the fiber structure.

The gene COL1A1 at the locus +1245G>T (rs1800012) has 2 alleles: G-major allele (main) and T-minor allele (replacement, mutation). The T allele is associated with increased transcription of the type 1 collagen gene and is associated with many connective tissue disorders. The incidence of the T allele in the European population is 20 %. Possible marker genotypes: G/G; G/T; T / T. The results of the comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic variant +1245G>T (rs1800012) of the COL1A1 gene in the study and control groups showed that carriers of the minor allele" T " polymorphism rs1800012 gene COL1A1 were 28% of patients with POP (26% heterozygous and 2% homozygous genotypes) and 33% of patients in the control group (32% heterozygous and 1% homozygous genotypes).

To determine the significance of the polymorphic variant 2209G>A (R. Ala698Thr, rs1800255) in the α-chain gene COL3A1 in the development of DTE, we conducted a comparative analysis of allele frequencies and genotypes in the study and control groups. Gene COL3A1 locus 2209G>A (R. Ala698Thr, rs1800255) has 2 alleles: major (main) allele G and minor (replacement) allele A. Possible marker genotypes: G/G; G/A; A / A. Results of comparative analysis of frequency distribution and genotypes of polymorphic variant 2209G>A (R. Ala698Thr, rs1800255) of gene COL3A1 revealed that carriers of the minor allele A polymorphism rs1800255 gene COL3A1 were 36% of patients with POP (29.3% heterozygous and 6.7% homozygous genotypes) and 36% of patients in the control group (28% heterozygous and 8% homozygous genotypes).

With the same manner, we found no difference in the polymorphic variant rs1801184 and rs111929073 in the type 3 collagen α-chain gene (COL3A1) in patients with POP and control group.

A polymorphic variant of rs2236479 (G>A) of the COL18A1 gene was also considered. The COL18A1 gene at the rs2236479 locus has 2 alleles-major allele-G and minor allele-A. Possible genotypes of this marker are G\G; G\A; GA. There was no statistically significant difference between groups in it as well.

A logistic regression with forced inclusion of all independent factors was conducted. As a dependent variable, the patient's belonging to the study or control group was used. The binary variables of genetic polymorphisms presence were used as independent variables:

rs800012, rs1800255, rs2236479, rs1801184. There were no association of the combination of the studied polymorphisms and POP

STATISTICAL METHODS

Statistical data processing was performed using the PASW Statistics 22 program.

Descriptive statistics were presented in the form of mean and standard deviation, median and 25th and 75th percentiles, minimum and maximum values in the sample for quantitative variables, and frequency of occurrence and proportion in the sample for qualitative variables.

Prior to the construction of the predictive model, independent parameters were compared in two studied Groups in order to determine the set of parameters that are most suitable for inclusion in the multi-factor model. The Mann-Whitney U-test was used to compare quantitative UES In two unrelated samples. The exact Fischer test was used to compare nominal variables in two unrelated populations. The significance level (p) was assumed to be 0.05 in all the above comparisons.

After conducting a preliminary analysis, variables whose occurrence in the total sample was less than 10% were excluded from the list of independent factors participating in the model, taking into account the absence of statistically significant differences in the Overall indicators in the two studied populations.

Taking into account the presence of significant differences between the two studied Groups in the quantitative variable "Age", the ESN variable was reduced to a categorical form for its inclusion in the multi-factor predictive model. In order to find the condition for dividing the variable "Age" into 2 categories, we used the method of constructing classification trees using the CART algorithm.

Taking into account the available literature, as well as the above conditions for the frequency of occurrence of variables in the General sample, 8 categorical variables were included in the initial model.

To build a multi-factor predictive model, we used the method of logistic regression with step-by-step elimination of variables using the Values algorithm. The step selection criteria were assumed to be between 0.01 and 0.45. Model compliance statistics were evaluated using the Omnibus test for model coefficients, as well as the Hosmer-Lemeshev test at each step of the model. The subject's membership in the Study or control group was used as a dependent variable. Categorical variables that meet the selection conditions described above were used as independent variables. The regression equation has the form: $y=\exp(b0+b1*x1+\ldots+bn*xn)/[1+\exp(b0+b1*x1+\ldots+bn*xn)]$,

xi – independent variable,

y – dependent binary variable

bi – regression coefficient

A classification table was constructed for initial (zero) and at the last step of the regression algorithm with a fixed threshold classification = 0.50. To find the optimal threshold classification sensitivity and specificity was found to be of prognostic models were constructed ROC curve, where the check variable was used, the probability of the predicted values as a state variable – Study group. Descriptive statistics. [Table 1,2].

Table 1. A classification table was constructed for initial (zero) and at the last step of the regression algorithm with a fixed threshold classification = 0.50.

			Group	
			Controls	**Study**
Age	Valid N		100	150
	Mean		54.7	57.3
	Standard Deviation		9.2	8.6
	Maximum		70	70
	Minimum		40	40
	Median		55	58.5
	Percentile 25		46	51
	Percentile 75		62	64
Pelvic organ prolapse (POP)	No	Count	100	58
		Column N %	100.00%	38.70%
	Yes	Count	0	92
		Column N %	0.00%	61.30%
POP + OAB	No	Count	100	36
		Column N %	100.00%	24.00%
	Yes	Count	0	114
		Column N %	0.00%	76.00%
POP + SUI	No	Count	100	93
		Column N %	100.00%	62.00%
	Yes	Count	0	57
		Column N %	0.00%	38.00%
Obesity	No	Count	86	116
		Column N %	86.00%	77.30%
	Yes	Count	14	34
		Column N %	14.00%	22.70%
Pelvic floor surgery	No	Count	74	110
		Column N %	74.00%	73.30%
	Yes	Count	26	40
		Column N %	26.00%	26.70%
Constipation	No	Count	44	82
		Column N %	44.00%	54.70%
	Yes	Count	56	68
		Column N %	56.00%	45.30%
Menopause	No	Count	29	35
		Column N %	29.00%	23.30%
	Yes	Count	71	115
		Column N %	71.00%	76.70%
Chronic pulmonary disorders	No	Count	58	94
		Column N %	58.00%	62.70%
	Yes	Count	42	56
		Column N %	42.00%	37.30%
More than 2 deliveries	No	Count	36	56
		Column N %	36.00%	37.30%
	Yes	Count	64	94
		Column N %	64.00%	62.70%
Traumatic delivery	No	Count	59	72
		Column N %	59.00%	48.00%
	Yes	Count	41	78
		Column N %	41.00%	52.00%
Rs 18,00,012 GT	No	Count	68	111
		Column N %	68.00%	74.00%
	Yes	Count	32	39
		Column N %	32.00%	26.00%

Rs 18,00,255 AG	No	Count	72	106
		Column N %	72.00%	70.70%
	Yes	Count	28	44
		Column N %	28.00%	29.30%
Rs 2,23,6479 AG	No	Count	76	127
		Column N %	76.00%	84.70%
	Yes	Count	24	23
		Column N %	24.00%	15.30%
Rs 18,01,184 TC	No	Count	61	92
		Column N %	61.00%	61.30%
	Yes	Count	39	58
		Column N %	39.00%	38.70%
Rs 18,00,012 TT	No	Count	99	145
		Column N %	99.00%	96.70%
	Yes	Count	1	5
		Column N %	1.00%	3.30%
Rs 18,00,255 AA	No	Count	92	140
		Column N %	92.00%	93.30%
	Yes	Count	8	10
		Column N %	8.00%	6.70%
Rs 22,36,479 AA	No	Count	94	139
		Column N %	94.00%	92.70%
	Yes	Count	6	11
		Column N %	6.00%	7.30%
Rs 18,01,184 CC	No	Count	96	141
		Column N %	96.00%	94.00%
	Yes	Count	4	9
		Column N %	4.00%	6.00%
Rs 11,19,29,073 TT	No	Count	100	150
		Column N %	100.00%	100.00%
	Yes	Count	0	0
		Column N %	0.00%	0.00%
Rs 11,19,29,073 TG	No	Count	100	150
		Column N %	100.00%	100.00%
	Yes	Count	0	0
		Column N %	0.00%	0.00%

* Variables marked with a yellow marker are excluded from further analysis due to the low frequency of occurrence in the General sample.

Table 2. Comparison of parameters in two independent sets Quality parameters. The exact Fisher criterion

Crosstab					
			Group		Total
			Control	Study	
POP	No	Count	100	58	158
		% within Group	100.00%	38.70%	63.20%
	Yes	Count	0	92	92
		% within Group	0.00%	61.30%	36.80%
Total		Count	100	150	250
		% within Group	100.00%	100.00%	100.00%

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	97.046	1	0		
Continuity Correction	94.427	1	0		
Likelihood Ratio	128.771	1	0		
Fisher's Exact Test				0	0
Linear-by-Linear Association	96.658	1	0		

CONCLUSION

Our study shows that single nucleotide polymorphisms polymorphisms in COL3A1 (rs1800255, rs1801184, rs111929073), in COL1A1 (rs1800012), and in COL18A1 (rs2236479) as well as their combinations were not associated with female POP. We draw some conclusions from our study, that further research into POP is deem necessary to ascertain if there is link between genetics and environmental factors POP.

CONFLICTS OF INTEREST

None.

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