Interleukin IL-6 and IL-16 gene polymorphisms in Nigerian women with endometriosis

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Background

- Endometriosis is presence of ectopic endometrial glands and stroma at other sites outside the uterine cavity
- Common cause of chronic pelvic pain which is sometimes debilitating. It may predispose to infertility in 25 – 40% of women
- Genetic studies on endometriosis in Africa are lacking in literature
- Role of interleukins as proinflammatory markers, autoimmune and immune modulators have led to exploration of their role in development of endometriosis in several studies
- Paucity of information on association between genetic polymorphisms and the disease manifestations

Objectives

1. To determine serum levels of IL-6 and IL-16 in women with endometriosis (cases) and women without endometriosis (controls).
2. To determine if there is genetic polymorphism (SNP: rs1800795G/C) in Interleukin 6 gene associated with endometriosis in Nigerian women.
3. To determine if there is genetic polymorphism (SNPs: rs4072111C/T, rs11556218T/G, rs4778889T/C) in Interleukin 16 gene associated with endometriosis in Nigerian women.
4. To determine association between endometriosis-related symptoms (or disease manifestations) and single nucleotide polymorphisms (SNPs) in Interleukins 6 and 16 genes.

Methodology

- Case control study at the Department of Obstetrics and Gynaecology of Lagos University Teaching Hospital, Surulere, Lagos, Nigeria following ethical approval
- 130 consenting women (65 per group – endometriosis versus age matched controls
- Numerical rating scale was used for pain assessment in women with endometriosis
- Blood specimen was collected for genetic studies to determine polymorphism in Interleukins 6 and 16 genes and serum Interleukins 6 and 16 concentrations
- Genetic analysis at Nigerian Institute for Medical Research (NIMR)
- Statistical analysis was be done with IBM SPSS version 25.0 and GraphPad prism 5.0. Haplotypes were constructed from the patient genotypes with Haploview 4.2.

Result

- No statistically significant difference in serum IL-6 or IL-16 concentration in women with endometriosis and controls
- Serum IL-16 distribution in women with endometriosis was significantly higher (p = 0.023) in those with severe pain (23.5[17.1 – 32.0]pg.ml) compared to those who had mild pain (16.0 [16.0 – 17.8])pg/ml
- IL-6(G/C): rs1800795 was monomorphic for both the control and the case groups
- The minor allele frequency (MAF) of IL16(C/T): rs4778889 was significantly higher (p = 0.024) in the women with endometriosis (45%) compared to the control (31%) , OR 1.80 (95%CI: 1.08 – 3.02)
- Distribution of genotypes and alleles of IL16(T/G): rs11556218 and IL16(C/T): rs4072111 were similar in both groups

Table I. Demographics and characteristics of study participants

Characteristics		Control (n=65)	Case (n=65)	p-value
Age		32.8 ± 6.67	33.06 ± 6.78	0.817
BMI		25.3 ± 4.38	24.4 ± 4.19	0.842
Parity		0-4	0-3	-
Chronic pelvic pain	NO	56 (86.2)	20 (30.8)	< 0.0001
	YES	9 (13.8)	45 (69.2)	
Painful menstruation	NO	34 (52.3)	3 (4.6)	< 0.0001
	YES	31 (47.7)	62 (95.4)	
Painful intercourse	NO	60 (92.3)	32 (49.2)	< 0.0001
	YES	5 (7.7)	29 (44.6)	
	I don't know	-	4 (6.2)	
Bleeding/site of bleeding	None	-	50 (76.9)	-
	Umbilicus	-	15 (23.1)	
Blood in stool	NO	64 (98.5)	62 (95.4)	0.703
	YES	-	3 (4.6)	
	I don't know	1 (1.5)	-	
Painful defaecation	NO	65 (100)	48 (73.8)	< 0.0001
	YES	-	17 (26.2)	
Blood in urine	NO	64 (98.5)	62 (95.4)	0.400
	YES	-	1 (1.5)	
	I don't know	1 (1.5)	2 (3.1)	
Painful urination	NO	64 (98.5)	49 (75.4)	< 0.0001
	YES	1 (1.5)	15 (23.1)	
	I don't know	-	1 (1.5)	
Convulsion during menstruation	NO	65 (100)	64 (98.5)	0.317
	I don't know	-	1 (1.5)	
Coughing up blood	NO	65 (100)	63 (96.9)	0.496
	YES	-	2 (3.1)	
Ascites	NO	64 (98.5)	43 (66.2)	< 0.0001
	YES	1 (1.5)	22 (33.8)	
Pleural effusion	NO	65 (100)	54 (83.1)	0.001
	YES	-	11 (16.9)	
Type of endometriosis	Pelvic	-	35 (53.8)	-
	Extra-pelvic	-	29 (44.6)	
	Both	-	1 (1.5)	
No Symptom	NO	43 (66.2)	64 (98.5)	< 0.0001
	YES	22 (33.8)	1 (1.5)	
Family history of endometriosis	NO	65 (100)	61 (93.8)	0.056
	YES	-	3 (4.6)	
	I don't know	-	1 (1.5)	
Method of diagnosis	Laparotomy	53 (94.6)	24 (36.9)	0.120
	Laparoscopy	3 (5.4)	18 (27.7)	
	Clinical features	-	19 (29.2)	
	Histology	-	2 (3.1)	
	Thoracotomy	-	2 (3.1)	

Note: Age and BMI are presented as Mean (S.D.), Parity is presented as median (range), and others as frequency (percentage).

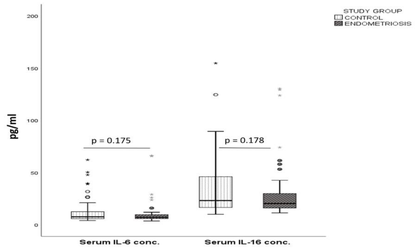

Figure 1. Serum levels of IL-6 and IL-16 concentration in the control and case groups

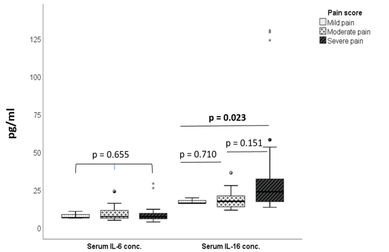

Figure 2. Serum levels of IL-6 and IL-16 according to pain score

Table II. Genotype and allele frequencies of Interleukin (IL)-6 and IL-16 SNPs in control and endometriosis patients

	Control	Case	p-value; OR (95% CI)
IL-6 (G>C): rs1800795			
GG	62 (100)	64 (100)	-
IL16 (C/T): rs4778889			
TT	29 (46.8)	19 (29.7)	p = 0.08
TC	27 (43.5)	32 (50)	
CC	6 (9.7)	13 (20.3)	
HWE	0.938	0.943	
T	85 (0.69)	70 (0.55)	**p = 0.024**
C	39 (0.31)	58 (0.45)	1.80 (1.08 – 3.02)
IL16 (T/G): rs11556218			
TT	39 (65.0)	36 (58.1)	p = 0.640
TG	17 (28.3)	23 (37.1)	
GG	4 (6.7)	3 (4.8)	
HWE	0.275	0.782	
T	95 (0.79)	95 (0.77)	p = 0.480
G	25 (0.21)	29 (0.23)	1.16 (0.63 – 2.13)
IL16 (C/T): rs4072111			
CC	58 (96.7)	55 (88.7)	p = 0.094
CT	2 (3.3)	7 (11.3)	
HWE	0.896	0.638	
C	118 (0.98)	117 (0.94)	p = 0.121
T	2 (0.02)	7 (0.06)	3.53 (0.72 – 17.35)

HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; CI: confidence interval

Table III. Distribution of IL-16 SNPs and serum IL-16 levels in both the control and case groups

	Control	Case
	Serum IL-16 (pg/ml)	**Serum IL-16 (pg/ml)**
IL16 (C/T): rs4778889		
TT	23.2 [16.6 – 40.4]	20.3 [15.8 – 26.7]
TC	20.3 [16.2 – 47.6]	18.1 [16.0 – 27.9]
CC	25.2 [20.2 – 33.2]	26.8 [17.2 – 34.5]
p-value	0.986	0.475
IL16 (T/G): rs11556218		
TT	29.1 [16.7 – 46.3]	20.6 [16.0 – 28.2]
TG	24.6 [16.6 – 48.4]	17.9 [15.9 -30.0]
GG	19.6 [13.8 – 28.0]	29.9 [28.3 – 51.9]
p-value	0.488	0.224
IL16 (C/T): rs4072111		
CC	25.2 [16.6 – 46.5]	20.9 [16.2 – 31.4]
CT	15.6 [14.9 – 16.2]	15.9 [14.7 – 25.2]
TT	-	-
p-value	0.149	0.221

Discussion

- Endometriosis affects the immune system and involves inflammatory responses like the cytokines
- IL-16 plays a key role in inflammation, and pain is a hallmark of inflammation, and this may be a reason for the association observed between serum IL-16 and severity of pain in women with endometriosis
- rs4778889 (T/C at position -295) in the promoter region of the *IL16* gene may be associated with altered levels of gene expression and account for the increased levels of IL-16
- This study found 80% significantly greater odds of Nigerian women with endometriosis having polymorphisms in IL-16 (rs4778889) gene. Similar finding in Chinese women
- Studies evaluating associations between pain perception and gene polymorphisms in endometriosis are lacking in the literature and there is a need for further multicentric research to explore this association and assess variations among various ethnic groups

Conclusion

Gene polymorphism occurs significantly in IL-16 (rs4778889) gene of Nigerian women with endometriosis and the elevated serum concentration of IL-16 was associated with severity of chronic pelvic pain

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