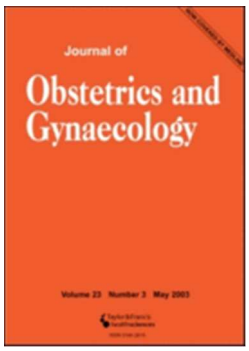

A population based case control study of aetiological factors associated with vulval lichen sclerosus

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A population based case control study of aetiological factors associated with vulval lichen sclerosus

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Running Title

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Summary

We aimed to investigate the association between possible aetiological factors and the risk of developing vulval lichen sclerosus (VLS). A population based case control questionnaire study was performed comparing women with a diagnosis of VLS (n=92) with those attending a general gynaecology clinic with no known anogenital dermatosis (n=66). After adjustment for confounders, factors associated with VLS included a family history of diabetes mellitus (OR=7.0, p=0.012) and ~~,~~ previous pelvic surgery (OR=4.75, p=0.007)~~. and current cigarette smoking (OR=5.54, p=0.044).~~ The use of barrier and progesterone only methods of contraception (OR=0.19, p=0.045), hormone replacement therapy (OR=0.209, p=0.025) or hayfever (OR=0.18, p=0.008) appeared to be associated with a reduced risk of VLS. In conclusion, we were unable to confirm many proposed aetiological theories associated with the development of VLS, in particular those associated with autoimmunity.

Introduction

Vulval lichen sclerosus (VLS) is a chronic inflammatory dermatosis affecting skin in the anogenital region of women. It is a progressive lifetime condition which runs a relapsing and remitting course of distressing symptoms including vulval itch, discomfort and pain. For women affected by VLS there can be associated functional difficulties related to architectural changes of the vulva in addition to the increase in lifetime risk of developing vulval squamous cell carcinoma (Wallace, 1971, Carli et al., 1995, Walkden et al., 1997, Van De Nieuwenhof et al., 2010). The incidence of VLS is difficult to ascertain since mild symptoms may go undiagnosed and in addition some women may not volunteer problems in the face of potential embarrassment. However previous studies have shown it accounts for at least 25% of the women seen in dedicated vulval clinics (Kirwan and Herod, 2002), and accounts for between one in 300 to one in 1000 of all patients referred to dermatology departments (Wallace, 1971).

The aetiology of VLS remains elusive, but is most probably multifactorial. A lack of aetiology affects the management of women with VLS in terms of available treatments and also counselling about the disease. Evidence for proposed aetiological stimuli is conflicting, however possibilities include an autoimmune process (Meyrick Thomas et al., 1988, Powell et al., 2000, Cooper et al., 2008), genetic susceptibility (Friedrich and MacLaren, 1984, Meyrick Thomas and Kennedy, 1986, Powell et al., 2000, Sherman et al., 2010), low endogenous sex hormone levels and age (Friedrich and MacLaren, 1984, Marren et al., 1995, Hagedorn et al., 2002, Powell and Wojnarowska, 2002, Gunthert et al., 2008), chronic genital infection (Schempp et al., 1993, Dillon et al., 1995, Farrell et al., 1999b), genital trauma and the Kobner phenomenon (Pass, 1984, Yates et al., 1985, Todd et al., 1994, Scurry, 1999, Farrell et al., 2006). In addition, aetiological studies of VLS have been hampered in the past by confusion surrounding disease definition. However, the consensus

statements from the ISSVD (Lynch et al., 2007), should increase the applicability of future VLS research.

In terms of modifiable aetiological exposure, little investigation has been undertaken, and is most often based solely upon observations of women with VLS with no comparison to rates of exposure among unaffected women. Sideri et al investigated modifiable risk factors for VLS with comparisons made with women admitted to hospital for other reasons (Sideri et al., 1989). The main differences between groups were women with VLS ~~were that they~~ had a lower dietary caritinoid intake ~~of caritinoids~~ and were parous.

Overall, previous work has been limited by the aetiological factors examined and also through the lack of comparison of exposure in appropriate control groups and incomplete exploration of general aetiological factors. Therefore, we aimed to use data from a retrospective case-control study comparing women with VLS and without an anogenital dermatosis to investigate the association between possible aetiological factors and the attached risk of being affected by VLS.

Methods

Patient selection and recruitment

We conducted a retrospective case-control study nested with in a population based cohort. We compared women with a diagnosis of VLS with women who did not have an anogenital dermatosis. All women were recruited from the Grampian region of Scotland. Cases of VLS were identified from the Grampian Gynaecology-Skin Clinic database, where secondary care of women with vulval disorders, including VLS, is centralised and staffed by Dermatology, Gynaecology and Sexual Health consultants. Approximately 35% of women attending this clinic have a diagnosis of VLS. Women were included in the VLS group if it was biopsy confirmed or found to be clinically typical by one of the consultants at the dedicated clinic. Women with VLS were recruited either during routine clinic attendance or by postal invitation. Participants in the control group were recruited during attendance at a routine general gynaecology clinic, after pre-checking referrals to ensure that they had no known anogenital disorder. Women giving informed consent were given the study questionnaire to complete. Ethical approval was obtained from the Joint Grampian Research Ethics Committee (Ref No 03/0243).

The study questionnaire was designed based on a literature review concerning possible aetiological factors responsible for the development of both systemic and anogenital lichen sclerosus in men and women. The data collected included patient demographics, personal medical history with particular inclusion of obstetric, gynaecological and autoimmune related disorders, and familial medical history. The draft questionnaire was piloted at the local vulval clinic at Aberdeen Royal Infirmary for ease of understanding.

Statistical Analysis

Women were identified by a study number only, and standard security measures were taken. Data was scanned directly into a Statistical Package for the Social Sciences Database, SPSS 15.0 (SPSS Inc., Chicago, IL) on a secure computer in preparation for analysis.

Continuous variables are expressed as median and interquartile range. Mann-Whitney U tests were used to determine differences between the two groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each potential aetiological factor using binary logistic regression analysis and statistical significance was assumed at $p<0.05$. Adjusted odds ratios are indicated in the text and were calculated for potential confounding factors including age, parity and menopausal status.

Results

A total of 158 women took part in this study; 92 women with VLS and 66 women with no vulval dermatoses acted as controls. The median age of women in the VLS group was 65.0 (IQR 58.5, 71.5) years which was significantly older than their counterparts in the control group, median age 46.0 (IQR 37.5, 53.0) years. Age was significantly associated with the presence of VLS (OR 1.13, 95% CI (1.09, 1.17), p<0.001).

Gynaecological History

Gynaecological factors were examined in two groups, firstly those associated with menarche and contraception, and secondly those associated with general gynaecology and the menopause. Data are shown in Table I.

Menarche and contraception

Using univariate analysis, age at menarche was associated with VLS, however, this was lost when adjusted for current age. In terms of contraception, barrier methods have a negative association with VLS which remained significant when corrected for current age, with a greater number of women in the non-LS groups having used barrier contraceptives. The use of progesterone only preparations was also negatively associated with VLS, but became less significant when corrected for age. The use of combined oral contraception was negatively associated with VLS, however this association was lost when corrected for current age.

General gynaecology and the menopause

In this cohort, age at menopause was not associated with VLS. Menopausal status was associated with VLS, but this association was lost when corrected for current age. When the effect of HRT

was examined and corrected for menopausal status and current age, women who have ever used HRT are less likely to be affected by VLS.

No difference in risk of VLS was found in those who had previous pelvic and vulval infections, chronic vaginal discharge, cervical treatment or had exposure of the pelvis to radiotherapy. There was an increased risk of VLS in the group who had previously had pelvic surgery (hysterectomy, pelvic floor repair, modified Fentons procedure), however the study design did not allow for analysis of reasons for surgery, and may reflect architectural changes as a result of damage by VLS rather than a stimulus for development of the condition in the first place.

Obstetric History

Associations between obstetric history and development of VLS are shown in Table II. Parity did not alter odds of being affected by VLS. However, delivery by forceps was positively associated with VLS, but this association was lost when corrected for parity and age. Interestingly, despite theories regarding a link between the genital trauma and VLS, perineal suturing and problems with perineal healing post delivery were not associated with VLS.

Personal medical history

The association between co-existing medical conditions and the development of VLS is illustrated in Table III, with multivariate analysis adjusting for differences in age at time of questionnaire. Both Type I and Type II diabetes mellitus are associated with VLS. A personal history of hayfever is negatively associated with the odds of developing VLS and remains significant even when corrected for current age. Compared with those who have never smoked, current cigarette smoking decreased the odds of developing VLS, however, this did not remain significant when corrected for age.~~Additionally, smoking history is also associated with the odds of having VLS; compared to~~

~~those who have never smoked, current smoking is positively associated with a women being affected by VLS, even when corrected for age.~~ In particular it is of interest to note that when using a control group, the presence of a co-existing autoimmune disease does not alter the odds of being affected by VLS.

Family medical history

In the VLS group, 8 (8.7%) women had a relative who was also affected by VLS, whereas no women in the healthy group had a relative with VLS. The number of relatives with diabetes is also higher in the VLS group and remains significant even when corrected for age, however the study design did not allow stratification for type of diabetes and type of relationship to relative with the condition. No other familial medical disorders were associated with developing VLS with data shown in Table IV.

Discussion

In this population based case-control study we have examined aetiological factors contributing to the development of VLS in women. We have shown a limited number of factors are associated with an increase in the odds of having VLS compared with healthy controls. These include those with a history of diabetes mellitus or~~,~~ pelvic surgery ~~and current cigarette smoking,~~ with use of barrier contraception, exposure to progesterone only methods of contraception, HRT use and a medical history of hayfever being associated with a lower risk of being affected by VLS.

Our data is in agreement with previous observational studies where the incidence of VLS among women increases with age (Marren et al., 1995, Hagedorn et al., 2002). However, although menopausal status and age are linked, when we adjusted for age, menopausal status was not associated with VLS, suggesting that older age rather than menopausal status is linked with the development of VLS.

The most commonly studied aetiological factor for VLS is autoimmune disease. Previous observational studies have found women with VLS commonly have at least one co-existing autoimmune disease, in particular thyroid disease, vitiligo and alopecia (Meyrick Thomas et al., 1988), however no healthy comparison group was studied. Histologically, VLS specimens show immunological changes at all levels of the skin, showing typically a lichenoid pattern with a predominantly lymphocytic inflammatory infiltrate in the upper dermis with accompanying epidermal basal layer damage with local cytokine changes similar to those seen in lichen planus and chronic wounds (Farrell et al., 1999a, Farrell et al., 2006, Lynch et al., 2007). Circulating IgG antibodies against extracellular matrix protein 1 (ECM1) have been found in women with VLS (Oyama et al., 2003). Moreover, vulval carcinoma in association with VLS as opposed to VIN shows transcriptional over-activation of the immune response (Santegoets et al., 2009). These

factors have lead to the suggestion that VLS is an autoimmune process and that new cases of VLS should be routinely screened for autoimmune diseases (Powell and Wojnarowska, 1999, Neill et al., 2002, ACOG, 2008, Neill et al., 2010, RCOG, 2011). Despite this, our results are in contrast to these studies with the data from our population based case-control study suggesting that the rates of co-existing autoimmune disease are similar among women with and without VLS. This finding is also supported by local data from our department which was unable to detect increased rates of autoantibodies during routine screening of new cases of VLS at clinic (Higgins et al., 2002). Additionally, co-existing skin conditions including dermatitis and psoriasis does not affect risk. Again, this is in contrast to previous studies (Simpkin and Oakley, 2007), however, this perhaps reflects differences in study design where past observational studies have not considered data from healthy comparison groups.

VLS has been linked to changes in sex steroid exposure due to its bimodal age distribution; VLS peaks in pre-menarchal girls, and post menopausal women (Marren et al., 1995, Powell and Wojnarowska, 1999, Hagedorn et al., 2002). Despite this, our data found no significant association with age at menarche or menopause. However, the data does suggest there may be a preventative benefit of systemic exogenous progesterone during the reproductive years, since women with VLS are less likely to have been exposed to progesterone only contraceptives, a risk which remains significant even when adjusted for current age. Nevertheless, this protective benefit of systemic progesterone during reproductive life seems to be lost when combined with oestrogen, since there is no change in risk of VLS in users of combined oral contraception. Furthermore, exposure to exogenous hormones in the form of HRT seems to have a protective effect against the development of VLS. These hormonal associations suggest a possible role for sex steroid receptors in the aetiology of VLS.

Chronic genital infection has been proposed as a potential causative agent in the development of VLS (Schempp et al., 1993, Dillon et al., 1995, Farrell et al., 1999b). This may be supported in part by our data where women unaffected by VLS are more likely to use barrier contraceptives, which can prevent exposure to infective agents. However, this link is difficult to justify since within our study, other data did not support a role for chronic infection in VLS.

We did show that women with VLS were more likely to have a first degree relative has affected by VLS, supporting proposals of a genetic predisposition (Friedrich and MacLaren, 1984, Meyrick Thomas and Kennedy, 1986, Powell et al., 2000). However, it may simply be related to the nature of the study and issues connected with gynaecological conditions. Firstly, individuals affected by any type of disease entity are more likely to have explored possible reasons for its developments, and therefore know if any other family members are affected. Secondly, it is also likely to reflect the nature of vulval diseases and the associated embarrassment and lack of discussion of gynaecological problems within the general population.

In relation to genital trauma and the development of VLS, our data did not demonstrate any association indicated by number and type of vaginal deliveries, perineal suturing and pelvic radiotherapy. Pelvic surgery rates among women with LS are higher. However, this is most likely to reflect firstly the higher number of hysterectomies and pelvic floor operations performed in the older age group of women, and secondly, it may be reflection of the need for surgery to correct architectural changes caused by VLS, rather than being an aetiological factor per se. Unfortunately our study design did not allow further stratification.

Although our data is interesting and provide a useful basis for focussed aetiological research and patient counselling, the recognised drawbacks of retrospective, questionnaire based case control

studies must be acknowledged. These include our selection of controls, all of whom were identified from secondary care, and therefore may not truly reflect the overall population. There will inevitably be an element of recall bias within our data since we have relied on patient self reporting, which is not as consistent as review of medical notes or ideally prospective studies. Additionally, our response rates in each group may be considered as low, and with a relatively uncommon condition it may have ultimately been underpowered to address some of the factors, in particular autoimmunity. However, this data set is the first of its kind and should be considered as providing pilot data on which to base future larger and sufficiently powered aetiological studies.

In conclusion, despite an international consensus as to disease definition of VLS (Lynch et al., 2007), aetiology remains uncertain with multiple factors proposed. Using our data set, we have been unable to confirm many of the currently proposed factors. We have however, shown that exposure to controlled doses of exogenous hormones in the form of contraceptive preparations and HRT, may have some protective effect. In addition, the lack of association between co-existing auto-immune disease and VLS in our study does not support the current guideline suggesting autoantibody screening in women with VLS.

Declaration of Interest

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Table I: Association between gynaecological history and probability of being affected by VLS. Multivariate association performed to include current age* or current age and menopausal status**

	VLS	No VLS	Univariate Association		Multivariate Association	
Factor	Median (IQR) [Range]	Median (IQR) [Range]	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p value
Age at menarche (years)	13 (12, 14) [10, 16]	13 (12, 14) [9, 16]	1.30 (1.03,1.63)	0.025	1.19 (0.90,1.59)	0.222*
Age at menopause (years)	49 (44,50) [35,55]	47 (40,51) [31,55]	1.06 (0.97,1.15)	0.193	0.95 (0.85,1.06)	0.349*
	N (%) with condition	N (%) with condition				
Barrier contraception	6(6.5%)	20 (30.3%)	0.16 (0.06,0.43)	<0.001	0.20 (0.06,0.61)	0.005*
Female sterilisation	16(17.4%)	13 (19.7%)	0.86 (0.38,1.93)	0.712	0.64 (0.24,1.71)	0.370*
Copper IUD	6(6.5%)	9 (13.6%)	0.44 (0.15,1.31)	0.140	0.50 (0.14,1.83)	0.293*
COCP	33(35.9%)	45 (68.2%)	0.26 (0.13,0.51)	<0.001	0.70 (0.30,1.62)	0.403*
Progesterone contraception	3(3.3%)	10 (15.2%)	0.19 (0.05,0.72)	0.014	0.19 (0.03,0.96)	0.045*
Vaginal skin infections	32 (34.8%)	21 (31.8%)	1.14 (0.58, 2.24)	0.697	1.33 (0.57, 12.49)	0.507*
Pelvic infections	5 (5.4%)	3 (4.5%)	1.21 (0.28, 5.24)	0.802	2.08 (0.35, 12.49)	0.424*
Vaginal discharge	45 (48.9%)	44 (66.7%)	0.48 (0.25, 0.92)	0.028	0.75 (0.32, 1.75)	0.504*
Treatment to cervix	12 (13.0%)	20 (30.3%)	0.35 (0.16, 0.77)	0.009	0.43 (0.16, 1.19)	0.103*
Pelvic surgery	30 (32.6%)	8 (12.1%)	3.51 (1.49, 8.28)	0.004	4.75 (1.53, 14.74)	0.007*
Pelvic radiotherapy	2 (2.2%)	0 (0%)	/	/	/	/
Childhood vulval problems	3 (3.3%)	1 (1.5%)	2.19 (0.22, 21.54)	0.501	2.52 (0.19, 33.89)	0.486*
Post-Menopausal	72 (78.3%)	27 (40.9%)	5.20 (2.59,10.44)	<0.001	1.22 (0.46,3.25)	0.692*
HRT ever used	33 (35.9%)	24 (36.4%)	0.98 (0.51, 1.89)	0.949	0.209 (0.053, 0.818)	0.025**

Table II: Association between obstetric history and probability of being affected by VLS. Multivariate association performed to include current age* or current age and parity**.

	VLS	No VLS	Univariate Association		Multivariate Association	
Factor	N (%) with condition	N (%) with condition	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Parity≥1	78 (84.8%)	49 (74.2%)	1.93 (0.88,4.27)	0.103	1.43 (0.51, 4.03)	0.500*
SVD	67 (72.8%)	42 (63.6%)	1.53 (0.78,3.02)	0.219	0.43 (0.11,1.61)	0.208**
Caesarean section	6 (6.5%)	6 (9.1%)	0.70 (0.22,2.27)	0.549	4.77 (1.04,21.80)	0.044**
Forceps	22 (23.9%)	6 (9.1%)	3.14 (1.20,8.26)	0.020	2.46 (0.71,8.56)	0.157**
Ventouse	1 (1.1%)	3 (4.5%)	0.23 (0.02,2.27)	0.231	0.17 (0.10,2.76)	0.211**
Tear requiring sutures	52 (56.5%)	28 (42.4%)	1.76 (0.93,3.34)	0.082	0.86 (0.33,2.24)	0.759**
Problems with perineal healing	10 (10.9%)	10 (15.2%)	0.68 (0.27,1.75)	0.427	0.41 (0.12,1.34)	0.140**

Table I: Association between gynaecological history and probability of being affected by VLS. Multivariate association performed to include current age* or current age and menopausal status**

	VLS	No VLS	Univariate Association		Multivariate Association	
Factor	Median (IQR) [Range]	Median (IQR) [Range]	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p value
Age at menarche (years)	13 (12, 14) [10, 16]	13 (12, 14) [9, 16]	1.30 (1.03,1.63)	0.025	1.19 (0.90,1.59)	0.222*
Age at menopause (years)	49 (44,50) [35,55]	47 (40,51) [31,55]	1.06 (0.97,1.15)	0.193	0.95 (0.85,1.06)	0.349*
	N (%) with condition	N (%) with condition				
Barrier contraception	6(6.5%)	20 (30.3%)	0.16 (0.06,0.43)	<0.001	0.20 (0.06,0.61)	0.005*
Female sterilisation	16(17.4%)	13 (19.7%)	0.86 (0.38,1.93)	0.712	0.64 (0.24,1.71)	0.370*
Copper IUD	6(6.5%)	9 (13.6%)	0.44 (0.15,1.31)	0.140	0.50 (0.14,1.83)	0.293*
COCP	33(35.9%)	45 (68.2%)	0.26 (0.13,0.51)	<0.001	0.70 (0.30,1.62)	0.403*
Progesterone contraception	3(3.3%)	10 (15.2%)	0.19 (0.05,0.72)	0.014	0.19 (0.03,0.96)	0.045*
Vaginal skin infections	32 (34.8%)	21 (31.8%)	1.14 (0.58, 2.24)	0.697	1.33 (0.57, 12.49)	0.507*
Pelvic infections	5 (5.4%)	3 (4.5%)	1.21 (0.28, 5.24)	0.802	2.08 (0.35, 12.49)	0.424*
Vaginal discharge	45 (48.9%)	44 (66.7%)	0.48 (0.25, 0.92)	0.028	0.75 (0.32, 1.75)	0.504*
Treatment to cervix	12 (13.0%)	20 (30.3%)	0.35 (0.16, 0.77)	0.009	0.43 (0.16, 1.19)	0.103*
Pelvic surgery	30 (32.6%)	8 (12.1%)	3.51 (1.49, 8.28)	0.004	4.75 (1.53, 14.74)	0.007*
Pelvic radiotherapy	2 (2.2%)	0 (0%)	/	/	/	/
Childhood vulval problems	3 (3.3%)	1 (1.5%)	2.19 (0.22, 21.54)	0.501	2.52 (0.19, 33.89)	0.486*
Post-Menopausal	~~64~~72 (~~69.6~~78.3%)	2~~2~~47 (~~36.4~~40.9%)	5.20 (2.59,10.44)	<0.001	1.22 (0.46,3.25)	0.692*
HRT ever used	33 (35.9%)	24 (36.4%)	0.98 (0.51, 1.89)	0.949	0.209 (0.053, 0.818)	0.025**

Table IV: Association between familial medical history and probability of being affected by VLS. Multivariate association performed to include current age

	Vulval LS	No vulval disease	Univariate Analysis		Multivariate Analysis	
Family History Medical Condition	N (%) with condition	N (%) with condition	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
LS	8 (8.7%)	0 (0.0%)	/	/	/	/
DM	22 (23.9%)	3 (4.5%)	6.60 (1.89, 23.11)	0.001	7.00 (1.54, 31.84)	0.012
Thyroid Disease	25 (27.2%)	9 (13.6%)	2.36 (1.02, 5.47)	0.050	2.50 (0.87, 7.15)	0.088
SLE	1 (1.1%)	1 (1.5%)	0.71 (0.04, 11.63)	1.000	0.19 (0.01, 5.07)	0.320
Pernicious Anaemia	3 (3.3%)	1 (1.5%)	2.19 (0.22, 21.54)	0.641	1.54 (0.11, 20.76)	0.746
Vitiligo	6 (6.5%)	2 (3.0%)	2.23 (0.43, 11.43)	0.470	0.81 (0.14, 4.82)	0.816
Alopecia	1 (1.1%)	1 (1.5%)	0.71 (0.04, 11.63)	1.000	0.19 (0.01, 5.07)	0.320
Hayfever	22 (23.9%)	18 (27.3%)	0.84 (0.41, 1.73)	0.711	0.89 (0.36, 2.22)	0.803
Eczema/Dermatitis	15 (16.3%)	12 (18.2%)	0.88 (0.38, 2.02)	0.831	1.53 (0.53, 4.48)	0.433
Psoriasis	8 (8.7%)	3 (4.5%)	2.00 (0.51, 7.84)	0.362	1.37 (0.23, 8.15)	0.731
Skin Cancer	6 (6.5%)	1 (1.5%)	4.54 (0.53, 38.60)	0.240	6.05 (0.56, 65.36)	0.138
Coeliac Disease	3 (3.3%)	3 (4.5%)	0.71 (0.14, 3.62)	0.695	0.51 (0.07, 3.91)	0.514
Rheumatoid Arthritis	14 (15.2%)	10 (15.2%)	1.01 (0.42, 2.43)	1.000	1.01 (0.36, 2.89)	0.980
Allergies	13 (14.1%)	14 (21.2%)	0.61 (0.27, 1.41)	0.286	0.68 (0.25, 1.86)	0.453