STUDY

Does Treatment of Vulvar Lichen Sclerosus Influence Its Prognosis?

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Objective: To record the clinical features, symptomatic response to topical steroids, and resolution of clinical signs in a large cohort of female patients with vulvar lichen sclerosus.

Design: Descriptive cohort study with a mean follow-up of 66 months.

Setting: The vulvar clinics of a teaching hospital and of a district general hospital in Oxfordshire, England.

Patients: Three hundred twenty-seven patients (74 girls and 253 women) with a definite clinical diagnosis of vulvar lichen sclerosus.

Interventions: The patients received topical steroids as part of their normal care.

Main Outcome Measures: Symptomatic response to treatment (good, partial, or poor); response of the vulvar signs (total, partial, minor, or poor); and the presence or absence of moderate or severe scarring.

Results: The mean age at onset was 5.4 years in girls and 55.1 years in women and first-choice therapy was an ultrapotent topical steroid for 50% of the girls and 89% of the women. Response to treatment was recorded in 255 patients. In 244 patients (96%) symptoms improved with treatment, as 168 (66%) became symptom free and 76 (30%) showed partial response; 11 (4%) had poor response. Among the 253 patients in whom a response of the vulvar signs to topical steroid was recorded, 58 (23%) showed total response, with return to normal skin texture and color; and 173 (68%) showed partial, 18 (7%) showed minor, and 4 (2%) showed poor response. Moderate or severe scarring occurred less often in girls ($P<.001$). Squamous cell carcinoma developed in 6 women (2.4%).

Conclusion: Topical ultrapotent steroid is an effective treatment for vulvar lichen sclerosus, giving relief of symptoms in most and completely reversing the skin changes in approximately one fifth of patients.

Arch Dermatol. 2004;140:702-706

LICHEN SCLEROSUS (LS) IS A chronic inflammatory and scarring disease that preferentially affects the anogenital site,[1] although any cutaneous site may be affected, including the oral mucosa. Lichen sclerosus is 6 to 10 times more prevalent in the female than in the male population,[1] and although an infectious etiology has been proposed and an autoimmune etiology recognized, its cause is unknown. The presence of circulating IgG antibodies to extracellular matrix protein 1 has recently been demonstrated in 67% of patients with LS, but it is unknown whether these antibodies are secondary or pathogenic.[2] A recognized association with autoimmune disease[3,4] and human leukocyte antigen DQ7 in women[5] and girls[6] with LS suggests a genetic component to the disease.

There has been no large-scale clinical study of vulvar LS (VLS) since the comprehensive review that Wallace[7] presented in 1960. He studied 290 female patients, of whom 20 were children. Although some of these patients received fluorinated topical steroids, the study was reported before the widespread introduction of ultrapotent topical steroid use for first-line management of VLS.

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The use of ultrapotent topical steroids for VLS has now become accepted for first-line management of VLS in both children and adults.[8-11] Recent British Association of Dermatologists guidelines[12] advocate their use and give specific guidance on length of initial treatment and on maintenance treatment. There have been no randomized controlled trials but evidence for

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efficacy comes from several small case series.[8,13,14] In addition, it has been demonstrated that ultrapotent topical steroids can reverse some of the histologic changes caused by LS,[8,15] and that they are more effective than topical testosterone.[15] Small follow-up studies have suggested that symptomatic response to steroids is high but that resolution of clinical signs is less likely to occur.[13,14,16]

The aim of this study was to determine the clinical course of a large cohort of female patients treated in a vulvar clinic after the use of ultrapotent topical steroid became standard management of VLS.

METHODS

PATIENTS AND DATA COLLECTION

A total of 327 women and girls with the typical clinical features of VLS were included. In women, diagnosis was based on the typical clinical appearances of VLS plus confirmatory histologic studies; in girls, it was based on typical clinical appearances alone. Childhood onset of disease was defined as onset of symptoms prior to menarche and a definite diagnosis at or before the age of 16 years. We have previously reported on some of these childhood cases.[17,18] All patients attended 1 of 2 dermatology vulvar clinics at a teaching or a district general hospital in Oxfordshire, England, over a 10-year period.

For all patients information was collected by direct interview, clinical examination, and review of case notes. Ethical permission to record data was obtained from the hospitals' ethics committees. Demographic information, including age and racial origin, was sought. Data were entered into a Microsoft Access database (Version 2000; Microsoft Corp, Redmond, Wash) for analysis.

ONSET OF SYMPTOMS AND DIAGNOSIS

Age at onset was taken as the age when the women first experienced LS-related symptoms in the anogenital area, or, in infants or young children, when the parents noticed the symptoms. Age at diagnosis was defined for women as the age when histologic studies confirmed the diagnosis, or, for girls, when a clinical diagnosis was established. The timing of disease onset—defined as the onset of symptoms—was grouped in relation to menstrual history, including artificial menopause, ie, hysterectomy with bilateral oophorectomy. The delay in diagnosis was recorded as the time (in years) between the patient-reported onset of symptoms and definite diagnosis. The follow-up time from diagnosis (in months) was recorded.

CLINICAL SYMPTOMS AND SIGNS

The presence or absence of anogenital pruritus, soreness, pain or burning, dryness, dyspareunia, urinary symptoms, perianal and/or bowel symptoms, and bleeding was recorded prior to treatment. Similarly, the presence or absence of vulvar clinical signs such as erythema, pallor, atrophy (revealed by wrinkled skin and textural change), purpura, erosions, hyperkeratosis, fissuring, telangiectasia, hyperpigmentation, and bullae was noted. It was determined whether LS involved the vulva alone or both the vulvar and perianal area, and whether extragenital lesions were present.

VULVAR SCARRING

Vulvar architectural change was graded as absent (no scarring), mild (minor labial fusion, adhesion, and/or reduction), moderate (loss of labia and/or partial burying of the clitoris), or severe (complete loss of the labia, burying of the clitoris, and narrowing of the introitus).

TOPICAL STEROIDS AND RESPONSE TO TREATMENT

Prior surgical and topical treatments were recorded, as well as the potency of the topical steroid applied during the initial study treatment. Symptomatic response was graded as good (symptom-free status reached during the treatment); partial (improvement and/or partial resolution of individual symptoms); or poor (no change or worsening). Response of the vulvar physical signs was graded as total (complete resolution of all signs and return to normal color and texture—architectural changes, of course, remained); partial (complete resolution of purpura, hyperkeratosis, fissures, and erosions, but persistence of pallor or textural change); minor (partial resolution of some signs); or poor (no change or worsening). Symptomatic response and changes in the physical signs were assessed after a minimum of 3 months of topical treatment or at the patients' most recent follow-up appointment.

STATISTICAL ANALYSIS

Women and girls with VLS were compared using descriptive statistics. The χ^2 test was used to examine the strength of association between individual vulvar symptoms and signs and the presence or absence of moderate or severe scarring and the timing (in childhood or adulthood) of the onset of disease. In the event of expected low cell counts, the Fisher exact test was performed.

RESULTS

ONSET OF SYMPTOMS AND SIGNS

All but 3 of the 327 study participants (74 girls and 253 women) were of Northern European descent. Their mean age at onset of symptoms, recorded from 315 participants, was 43.9 years (range, 1-86 years). Five participants (3 women and 2 girls) were asymptomatic, and their disease had been recognized by chance. Data were unavailable for the remaining 7 participants. Mean age at onset of symptoms was 5.4 years for girls and 55.1 years for women. Mean age at diagnosis for the whole cohort was 48.3 years (7.6 years for girls and 60.0 years for women). The mean delay in diagnosis overall was 4.6 years (range, 0-51 years), but it was shorter for girls than for women (2.2 years vs 5.3 years). The maximum self-reported delay in diagnosis was 11 years in a child and 51 years in a woman. Onset in relation to menarche and menopause was recorded for 323 patients. None of the 74 girls (23%) had reached menarche, and 55 (17%) of the women were in their reproductive years and 194 (60%) were postmenopausal. The average length of follow-up after diagnosis was 66 months (range, 4-350 months). The mean follow-up time for women and girls was similar (65 vs 69 months).

CLINICAL SYMPTOMS AND SIGNS

Symptoms at presentation were ascertained in 322 patients (72 girls and 250 women), and 5 were asymptomatic. In the women, the most frequently reported symp-

Table 1. Presenting Symptoms of 322 Female Patients With Lichen Sclerosus*

Symptom	Girls (n = 72)	Women (n = 250)	Total (N = 322)	*P* Value
Pruritus	52 (72)	222 (89)	**274**	<.001
Soreness	44 (61)	172 (69)	**216**	.06
Pain/burning	5 (7)	23 (9)	**28**	.64†
Dryness	0	22 (9)	**22**	
Dyspareunia	0	75 (30)	**75**	
Urinary complaint	17 (24)	22 (9)	**39**	<.001
Constipation/bowel pain	17 (24)	5 (2)	**22**	<.001†
Bleeding	19 (26)	11 (4)	**30**	<.001
Blistering	1 (1)	0	**1**	.22†

*Values are given as number (percentage) unless otherwise indicated.
†With the Fisher exact test.

Table 2. Vulval Examination Findings in 327 Female Patients*

Finding	Girls (n = 74)	Women (n = 253)	Total (N = 327)	*P* Value
Erythema	11 (15)	83 (33)	**94**	.003
Pallor	48 (65)	243 (96)	**291**	<.001
Atrophy	26 (35)	177 (70)	**203**	<.001
Purpura	25 (34)	42 (17)	**67**	.001
Erosion	5 (7)	51 (20)	**56**	.007
Hyperkeratosis	10 (14)	94 (37)	**104**	<.001
Fissuring	14 (19)	92 (36)	**106**	<.001
Telangiectasia	6 (8)	21 (6)	**27**	.003
Hyperpigmentation	0 (0)	4 (2)	**4**	.58†
Bullae	4 (5)	5 (2)	**9**	.11†
Vaginal stenosis	0	8 (3)	**8**	.21†

*Values are given as number (percentage) unless otherwise indicated.
†With the Fisher exact test.

toms were anogenital pruritus (in 222 [89%]) and soreness (in 172 [69%]) (**Table 1**). In the 72 symptomatic children, the most frequent symptoms were pruritus (in 52 [72%]) and soreness (in 44 [61%]) (Table 1). Urinary symptoms, bowel symptoms, and local bleeding were seen significantly more frequently in girls than in women whereas pruritus was a more frequent complaint in women.

Signs at presentation were recorded for the entire cohort. Of the 327 patients 152 (59%) had vulvar and perianal involvement, but there was no significant difference in the distribution of disease between girls and women ($P=.14$). Extragenital LS lesions occurred in 35 patients (11%), with similar frequency among women and girls ($P=.69$). Pallor and atrophy (wrinkled skin and textural change) were the most frequent findings in both adults and children (in 89% and 62% of patients, respectively) (**Table 2**). Erythema, atrophy, pallor, hyperkeratosis, and ulceration were all significantly more frequent in women but purpura was more frequent in children ($P=.001$).

VULVAR SCARRING

Data on vulvar scarring was available for 324 patients; of the 221 (69%) who had some scarring, it was assessed as mild in 114 (35%); as moderate in 93 (29%); and as severe in 14 (4%). Scarring was detected in 20 girls (27%) and 201 women (79%). Moderate or severe scarring occurred significantly less frequently in girls than in women ($P<.001$). A delay in diagnosis of 2 years or less was associated with less scarring (moderate or severe) at diagnosis ($P=.008$).

TOPICAL STEROIDS AND RESPONSE TO TREATMENT

Topical steroids used as first choice were recorded in 295 patients (62 girls and 233 women). For 31 (50%) girls, first-choice therapy was an ultrapotent topical steroid, 0.05% clobetasol propionate ointment. Other topical steroids prescribed were 0.05% clobetasone butyrate in 20 girls (32%), 0.1% betamethasone in 4 (7%), 0.025% beclometasone dipropionate in 3 (5%), and 1.0% hydrocortisone in 4 (7%). One child had no topical steroid prescribed.

For 208 women (89%), first-choice therapy was an ultrapotent topical steroid, 0.05% clobetasol propionate ointment. Other topical steroids prescribed as first-line treatment were 0.05% clobetasone butyrate for 10 women (4%), 0.1% betamethasone for 7 (3%), and 0.025% beclometasone dipropionate for 7 (3%). One woman received no topical steroid therapy. Most patients were given topical steroid for intermittent maintenance self-treatment after the initial treatment period.

Reported response of symptoms to topical treatment was available for 255 patients, 36 girls and 219 women. Overall, the symptoms of 244 patients (96%) improved with treatment: 168 (66%) became symptom free and 76 (30%) experienced partial response; 11 (4%) experienced poor response. Response to treatment was graded as symptom free in 26 girls (72%), partial in 9 girls (25%), and poor in 1 girl (3%). It was graded as symptom free in 142 women (65%), partial in 67 women (31%), and poor in 10 women (5%).

Response of the vulvar physical signs to treatment was determined in 253 patients, 36 girls and 217 women. Total resolution of the clinical signs, including return to normal color and texture, occurred in 8 girls (22%) and 50 women (23%). Partial resolution of clinical signs (resolution of purpura, hyperkeratosis, fissures, and erosions but no change in color and texture) occurred in 24 girls (67%) and 149 women (69%). Minor resolution was seen in 4 girls (11%) and 14 women (6%). In 4 women there was no improvement in clinical signs after treatment. Thirteen women had undergone surgical treatment (the Fenton procedure) for introital stenosis.

SQUAMOUS CELL CARCINOMA AND VULVAR INTRAEPITHELIAL NEOPLASIA

Four women developed vulvar intraepithelial neoplasia alone, 6 developed squamous cell carcinomas (SCCs) alone, and 1 developed an SCC on a grade 3 vulvar intraepithelial neoplasia. The mean age at diagnosis of the SCCs was 63.8 years (range, 39-82 years) and the mean duration of vulvar symptoms before diagnosis of an SCC was 30.8 years (range, 0-44 years). The mean age at onset of symptoms was similar in the 6 women who developed SCC and those who did not (41.7 vs 43.9 years), as was the mean age at diagnosis of VLS in patients with SCCs and those with no malignancy (58.0 vs 55.1 years). The delay in diagnosis of VLS was greater in the 6 women with SCC (15.3 vs 4.4 years). Because of the small number of tumors, the study had insufficient power to confirm a statistical difference between the 2 groups.

COMMENT

This study confirms VLS as a disease of the postmenopausal woman—with another peak of onset in childhood—and demonstrates the efficacy of treatment with potent topical steroids. It is the first study to demonstrate the reversibility of clinical signs with treatment, as in some patients it would have been impossible to make a diagnosis at follow-up. The mean age at onset of symptoms in children and adults combined was 43.9 years, which is consistent with reports from other series (45.5 years[4] and 54.2 years[7]). Because of the bimodal distribution of age at onset, it is probably more meaningful to separate childhood and adult onset of disease (mean onset age, 5.4 years in girls and 55.1 years in women). Presenting symptoms may differ in adults and children. Vulvar LS causes considerable morbidity, including disruption of sexual function, and changes in vulvar appearance and architectural change are frequent. However, ultrapotent topical steroids are effective in the treatment of VLS and may totally reverse clinical signs, including atrophy and pallor, in some patients. Early diagnosis and treatment may prevent vulvar scarring.

There was considerable delay in presentation to the vulvar clinic after onset of symptoms (2.6 years for children and 5.3 years for adults). This study relied on patients' or parents' recall of symptoms, which may introduce some bias. Even so, considering the morbidity and loss of sexual function that may result, the delay in diagnosis in adults is long. One elderly patient recalled having symptoms 51 years before diagnosis. The reasons for delay have not been addressed in this study but we have previously reported that women whose general practitioner is a woman are referred to a vulvar clinic faster than those seeing a male general practitioner.[19] Children present earlier, which may be due to increasing anxieties surrounding sexual abuse.

Presenting symptoms differed in girls and women. Girls were more likely to have urinary or bowel symptoms at first presentation than women, although perianal disease was present in the same proportion. This has been noted previously,[17,20] and may be due to a child's inability to describe complex symptoms such as itching and burning. Potent topical steroids were very effective at relieving symptoms, as 72% of girls and 65% of women were completely symptom free after treatment. This finding is similar to that reported by Lorenz and colleagues[13] in their study of 81 women treated with 0.05% clobetasol proprionate cream, 77% of whom experienced complete response. Also, Dalziel and colleagues[8] and Bracco and colleagues[15] noted remission of symptoms in 13 of 15 and 17 of 20 patients, respectively. Information on the course of VLS around puberty was not specifically sought in this study but we know from previous work that 75% of girls will have persistent signs of VLS after puberty despite improvement in symptoms.[18]

There were differences in vulvar signs at diagnosis between women and girls. Purpura was significantly more frequent in girls for reasons that are not understood. We found a prevalence rate of extragenital disease of 11%, which was slightly lower than the 18% reported in a previous study,[7] and similar rates in women and girls. There has been recent debate regarding the ability of ultrapotent topical steroids to do more than alleviate symptoms. This study demonstrates that ultrapotent topical steroids may return the vulvar skin to normal appearance. Response of the vulvar signs to topical steroids was good overall. We took total resolution to include resolution of all signs (apart from scarring), including pallor and atrophy. In 23% of women the resolution of vulvar signs was total, ie, it would have been impossible to make a clinical diagnosis after treatment. Changes in clinical appearance have not been specifically addressed except in the study by Bracco et al[15] of 55 patients, 31% of whom had total resolution of the clinical signs of VLS. We found significantly more scarring in patients who presented with a symptom duration of 2 years or less than in those for whom the delay was greater ($P=.008$); therefore, this study provides the first indirect evidence that topical steroids may prevent scarring if used early in the course of the disease. Most of the patients in this study (89% of the women and 50% of the girls) were treated

initially with an ultrapotent topical steroid. It is now our policy to treat all newly diagnosed patients with an ultrapotent topical steroid but, increasingly, referred patients have already received a less potent topical steroid from their general practitioner. The numbers of patients treated with topical steroids other than 0.05% clobetasol propionate ointment were too small to allow analysis of comparative efficacy.

Six women with VLS in our cohort developed SCCs, giving a prevalence of less than 3% in the adult study population over a mean follow-up period of 69 months for women. Three previous studies have shown a small but definite risk of developing an SCC.[7,21,22] The lifetime risk has been estimated at 5% in women with known VLS,[7] although this is an underestimate as not all cases are detected. The number of SCC cases in our study was so small that it was not possible to statistically evaluate it; and although there seemed to be a trend between SCC development and a longer delay in diagnosis of VLS (mean, 15.3 vs 4.4 years), we cannot exclude the possibility that the trend had arisen by chance. The low number of SCC cases might be attributed to the relatively short follow-up period in our cohort; it may also be that early extensive treatment may prevent malignant changes. Six additional cases of SCCs arising on a background of VLS were identified by searching histology databases in our region over 10 years (G. Tasker, MRCOG, e-mail communication, August 4, 2003). A much larger multicenter, longitudinal study will be necessary to evaluate accurately the characteristics of those who develop SCCs. It is unknown whether early treatment of VLS lessens the risk of malignancy. It is also possible, although unlikely, that topical steroids, acting as local immunosuppressants, may increase the risk of malignant transformation.

Ultrapotent topical steroids have the potential to cause atrophy, and skin thinning may last for up to 14 days after application in normal skin.[23] The extent to which topical steroids applied intermittently, as in our study for maintenance, may contribute to skin thinning is uncertain as atrophy is part of the LS process. It is possible that topical calcineurin inhibitors such as tacrolimus ointment, which produce less skin atrophy, may play a role in the treatment of LS in the future.[24-26] The theoretical disadvantage of topical calcineurin inhibitors is an increased risk of malignant transformation due to local immunosuppression.

We speculate that, with early intervention, all clinical signs of VLS may resolve, with prevention of scarring. Although guidelines suggest an initial treatment of 3 months with an ultrapotent topical steroid, should the intial treatment be continued if there is inadequate response? The disadvantage might be an increase in the adverse effects of local steroids such as erythema and telangiectasia; however, in our experience, these adverse effects always reverse with reduction of topical steroid use. If the aim of treatment is to be the disappearance of abnormal signs as well as the resolution of symptoms, undertreatment rather than overtreatment may be currently the main problem in therapy.

Accepted for publication March 2, 2004.

We thank the Henry Smith Charity Fund for funding this work and Noel McCarthy for performing the statistical analysis.

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