

## Contact Allergy and Vulvar Lichen Sclerosus et Atrophicus

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### Abstract

Lichen sclerosus et atrophicus is a chronic inflammatory disorder that can involve skin and mucosa with a predilection for genital skin. Women with the disease have an affected vaginal mucosa that often needs prolonged treatment with topical steroids. Investigating the contact allergy rates to sensitizers and to compare these frequencies with those in a control group.

41 women, (mean age 59.5 years; range 31-86 years) with Genital Lichen Sclerosus (GLS) and 40 women in a control group (mean age 65.5 years; range 26-81 years).

The participants were tested with a patch test series based on the Swedish baseline series and a modified dental series. Before patch testing, the subjects filled in a questionnaire regarding local symptoms, exposure to metals and dental restorative materials.

The study was performed in a blinded manner.

The two study groups had almost the same number of positive patch test reactions. Participants in the GLS group had positive reactions to several more allergens, than the control group. Among 41 women in the GLS group there were positive reactions to 21 substances compared to 14 substances in the control group of 40 women.

No association was found to contact allergy to allergens known to give rise to systemic reactions or allergens that could imply a relationship to topically applied substances.

Due to the facts that the material is small, the patients usually had long ongoing disease with much subjective symptoms severe impact on quality of life and objective symptoms, we still believe that the routine of patch testing patients with newly diagnosed GLS, or a GLS that suddenly deteriorates, is important to exclude possible aggravating factors such as contact allergy.

**Keywords:** Genital lichen sclerosus; Dental materials; Systemic allergic contact dermatitis; Control; Blinded design

### Introduction

The vulvar clinic in Malmö is a special part of the Department of Dermatology where women with suspected skin diseases in the vulvar area are referred. Women with Genital Lichen Sclerosus (GLS) and with Genital Lichen Planus (GLP) are diagnosed and treated. Lichen sclerosus et atrophicus is a chronic inflammatory disorder that can involve the skin, the mucosa and nails with a predilection for the anogenital area [1,2]. It occurs in both sexes and can begin at any age; actually it has been described as an increasingly common problem in children [3-5]. There is a first peak in prepubertal girls and a second peak in postmenopausal women [1,2,6]. The two diseases, GLP and GLS, can coexist and overlap [7]. GLS was first considered to be a type of lichen planus. It has also been associated with scleroderma but today it is considered a separate entity [1].

The aetiology is still not fully understood, but hormonal mechanisms have been suggested and it is not uncommonly associated with autoimmune diseases [6-9]. Also chronic infection and genetic factors have been postulated but not proven to be causative agents [9].

GLS destroys the mucous membranes and examination may show erosions, hypopigmented, white, atrophic plaques and in many cases purpura. In women the scarring atrophy causes gradual destruction of normal vulvar architecture with resorption of the labia minora, narrowing of the introitus and burying of the clitoris [1,2]. Constrictions of the urethra and anus may lead to retention of urine, painful defaecation and constipation [1,2,5]. Pruritus, pain and dyspareunia are common symptoms and as a result there may be

a complete preclusion of sexual intercourse. Women and young girls with the disease describe restrictions in their lifestyle and a reduced quality of life [5,10-12].

Contact allergy, is usually associated with localised eczematous lesions at site of exposure. However, it is well known that also other types of reactions such as lichenoid lesions can be seen [13,14]. Such reactions may be a manifestation of a local contact with the allergen but can also be seen as a symptom of systemic allergic contact dermatitis [14,15]. Besides causing skin disease, a contact allergy can theoretically deteriorate a pre-existing skin disease through local contact with the allergen [14] or through systemic intake of the allergen, causing activation probably of both the humoral and cellular immune systems, resulting in a flare up of previous test sites [14,15], and activation of dermatitis in peripheral locations as seen in the baboon syndrome [16,17].

Thus, when patch testing searching for possible causative or deteriorating factors, it is of importance to patch test both for substances

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that might be used locally and for substances that are known to, or theoretically might, cause systemic reactions or flare up [18-22]. With regard to locally used products within the genital area, preservatives, fragrance substances, and corticosteroids are examples of sensitizers known to be present in products used in the genital area for hygiene purposes or for the treatment of GLS [2,14,20]. The major sensitizers in these groups are present in most baseline patch test series. Several of the allergens found in the dental series can cause systemic reactions [19,20] and oral lichenoid reactions may be caused by sensitizers such as mercury and gold in dental materials [19,20]. Dental materials in the mouth are constantly exposed to saliva which may extract possible sensitizers. The sensitizers may be absorbed in the gastrointestinal canal and hereby cause a systemic allergic contact dermatitis or aggravate an existing skin disease [14,20].

The aim of this study was to investigate the GLS patients in our vulvar clinic with regard both to contact allergy as a causal or deteriorating factor [21], to patch test with regard to allergens giving possible local and possible systemic reactions and to compare the results with a control group.

## Materials and Methods

### Subjects

In this study 84 women with known GLS who had consulted the vulvar clinic during 2005-2008, and had been diagnosed with GLS were invited to participate by phone call. If the patient accepted, a letter was sent with information on the study. 41 women (mean age 59.5 years; range 31-86 years) agreed to participate in the study. The women in the control group (age-correlated) had been referred to the Department of Dermatology and diagnosed with either actinic keratosis or basal cell carcinoma. They were contacted by telephone call and then given an information letter where they were asked to participate as a control group. Of the 104 women who were invited to participate, 40 accepted (mean age 65.5 years; range 26-81 years). Most women who declined to participate referred to the lack of time due to full-time work or the fact that they lived far from the hospital. This applied to both groups.

The study was blinded; the dermatologist who was reading the patch test was not informed whether the subject belonged to the GLS group or the control group. Both the dermatologist and the study subject were instructed not to talk to each other until both readings were finished.

### Questionnaire

Before patch testing all the participants filled in a questionnaire with thirteen questions regarding exposure to metals, dental restorative materials and their snuff and smoking habits. We also asked if they had had any signs or symptoms from the skin or mucous membranes.

### Patch testing

All the women were patch - tested with a patch test series based on the Swedish baseline series and a modified dental series. All test preparations were purchased from Chemotechnique Diagnostics, Vellinge, Sweden. The test preparations were applied in Finn Chambers® (Epitest Ltd. Oy, Tuusula Finland) diameter 8 mm attached to Scanpor® tape (Norgeplaster, Vennessla, Norway) on the upper back. On each patch test unit 20 mg was applied for substances in petrolatum [23], and 15 µl for liquids using a micropipette [24]. After 48 hours the patch tests were removed from the back. Readings were performed

by experienced dermatologists according to the International Contact Dermatitis Research Group guidelines on day 3 and day 7.

Before the dermatologist met the participant the nurse put a cloth over the participant's head and shoulders so the reading of tests could be performed in a blinded manner.

The dermatologist had no knowledge of the answers to the questionnaire and was unaware of whether the study participant was a control or a patient with GLS.

No one was informed about the test results until both readings were finished.

### Statistical methodology

Fisher's exact test, two - sided, was used to compare differences in questionnaire responses and numbers of patch test reactors between the two groups, GLS and controls.

A p-value of <0.05 was considered statistically significant.

### Ethics

The patients gave written informed consent to the study which was approved by the Ethics Committee of the Faculty of Medicine, Lund University. The study was conducted in accordance with the ethical standards specified in the Declaration of Helsinki and ICH guidelines on Good Clinical Practice.

### Results

Answers to the questions in the questionnaire are shown in [Table 1](#). There was a difference in the answers regarding symptoms from the mucosa. Twice as many women in the GLS group reported symptoms from the oral mucosa, 13 compared to 6 (13/38 vs. 6/37;  $p=0.07$ ). With regard to symptoms from the genital mucosa 39 females in the GLS group compared to 4 in the control group reported this,  $p<0.001$ .

The women in the GLS group had more itch, flush or swelling in the skin after contact to gold 10/41, compared to the controls 4/40 ( $p=0.04$ ).

Patch test results are shown in [Table 2](#).

The results showed that 24/41 (59%) of the women with GLS and 23/40 (58%) from the control group had at least one positive patch test reaction but the GLS group had positive reactions to more allergens (21/69) than the control group (14/69).

### Discussion

A high contact allergy rate with a frequency of almost 60% of the females in both the GLS group and in the controls was found.

The frequency of contact allergy in women with GLS has not been extensively studied. In a retrospective study regarding patients with pruritus vulvae [21] it was found that of the patients with lichen sclerosus 44% (7/16) had positive reactions when tested with the European Standard Series, selected preservatives, perfumes, local anaesthetics and medicaments. In this latter study it was implied that the patient's local products could contain allergens that was a deteriorating factor for the disease. These individuals were more likely to improve when they avoided the allergens. As a general rule it is often argued that skin with a chronic condition where topical medicaments are applied over a longer period of time should be more prone to contact allergy [18,22]. It is also known that patients with anogenital

Questions	GLS n= 41			Control group n=40			P-value
	Yes	No	Don't know/ No answer	Yes	No	Don't know/ No answer	
Have you had itch, flush or swelling after skin contact to golden jewellery such as earrings or finger rings.	10	25	6	4	35	1	0.045 ↑
Have you had itch, flush or swelling after skin contact to jewellery or other objects in metal (not gold)?	16	18	7	16	22	2	
Have you ever pierced your ears?	31	9	1	33	7	0	
Have you ever pierced skin /mucosa?	0	40	1	0	40	0	
Do you have or have had dental gold material?	21	15	5	25	13	2	
Do you have any symptoms from the oral mucosa?	13	25	3	6	31	3	0.073 ↑
Do you have any genital symptoms?	39	1	1	4	33	3	0.0001↑
Do you smoke?	4	36	1	5	35	0	
Are you a snuff user?	0	38	3	2	38	0	
Do you regularly use chewing gum?	4	36	1	6	33	1	
Do you work or have been working with material which contains gold, for example as a jeweller?	2	38	1	0	40	0	
Do you work or have been working with nickel or material containing nickel?	2	35	4	0	39	1	0.234↑
Do you take or have taken drugs containing gold?	1	33	7	0	34	6	

When no values are given, P -value > 0.3

**Table 1:** Questionnaire answers regarding exposure to metals and dental materials in patients with Genital Lichen Sclerosus (GLS) and controls

dermatoses are hyperreactive to local irritants [25,26]. This and the fact that the area often is occluded, and with a high temperature, should predispose to contact sensitization [18,25,26]. Our hypothesis was therefore that the patients with GLS should present with more contact allergies to allergens frequently used in this area.

The results from this study however, do not indicate an increased contact allergy rate for allergens that could be correlated to topical used medicaments/products or to allergens known to give rise to local reactions. Our baseline series includes many substances present in locally applied ointments/medicaments and other products. Since the aim was to perform a blinded larger study, it would have been virtually impossible to patch test with own products. Therefore, as a screening tool we considered our baseline series sufficient.

A possible explanation to the high frequency of contact allergy also in the control group is of course selection bias due to the fact that when given information on the study the subjects having skin /mucosa problems might be more inclined to participate.

As a major aim of the study was to explore the possibility that contact allergy to dental materials might be significant for GLS as a manifestation of systemic allergic contact dermatitis, it was necessary to include a control group. The design with exactly the same patch testing, mixing the GLS patients and the controls when reading as well as not allowing any communication between the reading dermatologist and the tested subject, is fairly unique for studies within the area of contact dermatitis including contact allergy and genital diseases. The study design eliminated bias with regard to patch test reading. With regard to systemic contact allergy this has not been studied in GLS patients as far as we know.

In terms of contact allergy to substances known to cause systemic reactions, patients with GLS were not overrepresented. In our findings, there was not a significant overrepresentation of metal allergy in the GLS group indicating the significance of metal allergy as such as the etiological factor for GLS. This does not exclude the importance of a metal allergy and systemic effects as a deteriorating factor. When looking at dental materials only, apart from gold, there is a trend for an overrepresentation of dental allergens in the GLS group; this patient

group also reported more symptoms from the oral mucosa.

The women in the GLS group had significant more itch, flush or swelling after skin contact to gold (10/40) compared to the control group (4/41). With regard to symptoms from skin when in contact with metals apart from gold, the two groups did not differ. The number of positive patch test reactions was almost the same between the two groups but the women in the GLS group had positive patch test reactions to several more substances compared to the controls.

The duration and the severity of the GLS disease was very varied among the participants, some of them had suffered from the disease for several years, others had recently been diagnosed.

Should patients with GLS be patch - tested? An impaired skin barrier is well known to be an important factor favouring sensitization. Thus, patients with vulvar dermatoses as well as patients with leg ulcers are known to frequently develop contact allergy to locally used medicaments [18,27]. GLS has an inflammatory phase as well as a sclerotic one, and we do not know whether - as the mucosa becomes sclerotic - the penetration of possible allergens changes; perhaps the patients with a more sclerotic mucosa do not get sensitized so easily. There is also evidence supporting the theory that patients with an autoimmune disease do not get sensitized as easily as patients with normal skin [28]. Autoimmune mechanisms are one of the etiological factors used to explain LSA and patients with the disease often have another autoimmune disease as well [9].

These women are severely affected; studies indicates that the disease has a large effect on quality of life and many suffer from sexual dysfunction as well [5,10-12]. Even a small improvement will make a difference for the women and therefore we do think that patch testing these patients is important.

A suggestion is that the GLS patients should be routinely patch tested with a modified baseline series and possible allergens that might cause systemic symptoms and their local products when they are diagnosed. After treatment, especially if the symptoms do not improve or if an improved patient suddenly deteriorates despite treatment, they should have a repeat test and then also with their own material for local treatment and personal care.

Patch test preparations	Conc (%)	GLS n=41	Controls n=40	P-value
<b>Metals</b>				
Mercury	0.5	2	0	
Copper sulfate	2			
Palladium chloride	2	2	1	
Aluminium chloride hexahydrate	2	1	0	
Tin	50			
Titanium	50			
Calcium titanate	10			
Silver sulfate	10			
Ammonium hexachloroplatinate	0.1 *			
Titanium nitride	5			
Gold sodium thiosulfate	2	6	9	
Mercury	1.6 *	2	0	
Zinc chloride	1			
Manganese chloride	2			
Potassium dichromate	0.5			
Cobalt chloride (hexahydrate)	1			
Nickel sulfate (hexahydrate)	5	6	11	0.181 ↓
<b>Corticosteroids</b>				
Tixocortol pivalate	0.1			
Budesonide	0.01			
<b>Fragrances</b>				
Myroxylon pereirae	25	4	8	0.225 ↓
Fragrance mix II	14	0	1	
Fragrance mix I	8	2	4	
Lichen acid mix	0.3	0	3	0.115 ↓
Lylal	5	3	0	0.240 ↑
Eugenol	2			
<b>Antibiotic</b>				
Neomycin sulfate	20			
<b>Fungistat, antiinfective</b>				
Quinoline mix	6			
<b>Flavor</b>				
Carvone L_form	5	4	1	
<b>Topical anaesthetics</b>				
Caine mix II	10	1	2	
<b>Rubber chemicals</b>				
Black rubber mix	0.6			
Mercapto mix	2			
Thiuram mix	1	1	0	
<b>Resins</b>				
Colophonium	20	1	1	
Epoxy resin	1			
p-tert-Butyl phenol formaldehyde resin	1			

<b>Preservatives</b>				
Formaldehyde	2*	2	1	
Formaldehyde	1*			
Quaternium-15	1			
Paraben mix	16			
Diazolidinyl urea	2*			
CL + ME – isothiazolinone, Kathon CG	0.02*	1	0	
Methyldibromo glutaronitrile	0.5			
Sodium metabisulfite	2	1	1	
<b>Desinfections</b>				
Glutaraldehyde	0.2			
<b>Plastic - related substances</b>				
N, N- Dimethyl – p – toluidine	5			
2-Hydroxy – 4 – Methoxybenzophenone	10			
Benzoylperoxide	1	1	1	
Ethyl p-toluenesulfonamide	0.1			
p-Tolyldiethanolamine	2			
Methylhydroquinone	1			
Camphoroquinone	1			
Tinuvin P	1			
<b>Plant</b>				
Sesquiterpene lactone mix	0.1			
<b>Emulsifier</b>				
Amerchol L 101	100	1	0	
<b>Stabilizer</b>				
Ethylendiamine dihydrochloride	1	1	0	
<b>Miscellaneous</b>				
para -phenyldiamine	1	1	1	
Canada balsam	25	1	0	

Conc w/w % in petrolatum

\*w/v % in water, When no values are given, P-value >0.3

**Table 2:** Reactions in Patch test series based on the Swedish baseline series and a modified dental series

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