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**Authors:** Maja J. Zieba-Domalik, Dominika Orszulak, Kacper Nizinski, Katarzyna Wilk, Marta Janik, Rafal Stojko, Agnieszka Droszol-Cop

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## **Associations vulvar lichen sclerosis with autoimmune thyroid diseases**

Maja J. Zieba-Domalik<sup>1</sup>, Dominika Orszulak<sup>1</sup>, Kacper Nizinski<sup>1</sup>, Katarzyna Wilk<sup>1</sup>, Marta Janik<sup>2</sup>, Rafal Stojko<sup>1</sup>, Agnieszka Droszol-Cop<sup>1</sup>

<sup>1</sup>*Chair and Clinical Department of Gynecology, Obstetrics and Oncological Gynecology, Medical University of Silesia, Katowice, Poland*

<sup>2</sup>*Euroimmun Polska Sp. z o.o., Wroclaw, Poland*

### **ABSTRACT**

**Objectives:** Vulvar lichen sclerosis (VLS) is defined as a chronic inflammatory skin disease that most often involves lesions on the mucous membranes of the vulva with a tendency to progress to the anal skin. The etiopathogenesis of VLS remains unknown and is likely multifactorial. Data emphasize the role of immunological factors — more than 25% of VLS cases coexist with autoimmune diseases. The purpose of the present study was to determine the correlation of the prevalence of anti-thyroid antibodies — IgG class antibodies against thyroid peroxidase and IgG class antibodies against thyroglobulin in women with vulvar lichen sclerosis, and the appropriateness of screening tests for autoimmune thyroid diseases in women with vulvar lichen sclerosis.

**Material and methods:** Fifty women with vulvar lichen sclerosis were enrolled in the study. The control group consisted of 41 healthy women. A detailed medical history was taken with all patients, followed by laboratory determinations — anti-thyroid antibodies — IgG class antibodies against thyroid peroxidase and IgG class antibodies against thyroglobulin.

**Results:** Antibodies to thyroid peroxidase were present in 12% of the study group with vulvar lichen sclerosis and 4.88% of the control group, and this difference was not statistically significant ( $p = 0.41$ ). Anti-thyroglobulin antibodies were detected in 4% of the patients with vulvar lichen sclerosis and 4.88% of the control group, and this difference was not statistically significant either ( $p = 0.76$ ).

**Conclusions:** The study did not confirm the association of VLS with autoimmune thyroid diseases. Undoubtedly, based on the data available in the literature, further studies are needed

to determine the mechanisms behind the association between vulvar lichen sclerosus and autoimmune thyroid diseases.

**Keywords:** vulvar lichen sclerosus; autoimmune thyroid disease; immunity; corticosteroids; female sexual dysfunction

### **Corresponding author**

Maja J. Zieba-Domalik

Chair and Clinical Department of Gynecology, Obstetrics and Oncological Gynecology,  
Medical University of Silesia, Katowice

e-mail: m.ziebadomalik@gmail.com

## **INTRODUCTION**

Vulvar lichen sclerosus (VLS) is defined as a chronic inflammatory skin disease of unclear aetiology that most often involves lesions on the mucous membranes of the vulva with a tendency to progress to the anal skin. Early diagnosis and prompt implementation of treatment, as well as long-term ambulatory follow-up of patients with vulvar lichen sclerosus are crucial in preventing complications of VLS [1].

Literature data show that the incidence of vulvar lichen sclerosus in the population is underestimated. Diagnostic difficulties arise from the fact that up to 30% of VLS cases are asymptomatic [1, 2]. It is estimated that the incidence of vulvar lichen sclerosus varies between 0.1% and 3% for pre-adolescent girls and older women, and 0.07% among men [3]. Additionally, lichen sclerosus affects women more often than men and the ratio varies between 3:1 and 10:1 [1].

The etiopathogenesis of VLS remains unknown and is likely multifactorial. Genetic conditions (chromosomal aberrations, Turner's syndrome, Down syndrome), as well as familial predisposition are considered in the aetiology — about 8.7% of women with VLS have a family history of the condition, but the exact pattern of inheritance of vulvar lichen sclerosus is so far unknown. Moreover, the human leukocyte antigens HLA-DQ and DR are believed to play an important role in the etiopathogenesis of VLS [4]. Urinary incontinence, hygiene neglect, and obesity are risk factors for the development of VLS in older women [5].

Also of note is the peak incidence — after menopause and in the prepubertal period, suggesting that hypoestrogenism may predispose to the development of the disease, but to date no evidence has been found to support this hypothesis [6]. Similarly, the role of infectious factors in the etiopathogenesis of VLS, such as infection with *Borrelia burgdorferi*, human papillomavirus — HPV 16, and hepatitis C virus, has not yet been proven [3, 7].

Literature data particularly emphasize the role of immune factors — studies on the etiopathogenesis of vulvar lichen sclerosus show that more than 25% of VLS cases coexist with autoimmune diseases, such as: thyroid diseases (18.9%), systemic scleroderma (5.7%), psoriasis (7.5%), alopecia areata, vitiligo, rheumatoid arthritis, celiac disease. Moreover, based on literature data, it seems that lichen sclerosus in men is not related to autoimmune factors, which supports the hypothesis of different pathogenetic pathways in the development of the disease [1, 3, 7, 8].

The diagnosis of vulvar lichen sclerosus is made based on medical reconnaissance and a thorough gynaecologic examination. Dermatoscopy is an adjunctive tool for the non-invasive diagnosis of VLS. Biopsies of the vulva are reserved, among others, for doubtful cases, especially when there is no improvement after topical treatment, and taking sections for histopathological examination should be performed from areas of skin with hyperkeratosis, erosions or suspected of cancerous process [1, 2, 6, 7].

The most commonly reported symptoms of VLS in women are itching, burning, bleeding from the genital tract and rectum, dyspareunia, and sleep disturbances [1, 2, 6, 7]. On physical examination, attention is drawn to clearly demarcated skin lesions, with features of atrophy — whitened, atrophic, smooth and shiny skin, involving the greater and lesser labia, the clitoris (85% of cases) and the perianal area (characteristic "figure-eight" shape, 30% of cases). In addition, erosions, erythema, Koebner's phenomenon, petechiae, abrasions and skin cracks are observed. Progression of the condition over time leads to scarring and adhesions, including resorption of the labia minora, narrowing of the vaginal vestibule (changes observed in up to 80% of VLS cases), significantly reducing the patient's quality of life. Extragenital lichen sclerosus represents an isolated form of the disease in only 6% of cases [1, 2, 6, 7, 9].

The main goal of pharmacotherapy for vulvar lichen sclerosus is to alleviate symptoms, as well as inhibit the progression of the condition — preventing the formation of scarring lesions and adhesions [7]. Topical glucocorticoids are the first-line therapy — the gold standard for the treatment of VLS — an ointment containing 0.05% clobetasol propionate (CP) - results in a reduction in the severity of symptoms and remission of the

disease in 75% of patients after 3 months of therapy [1, 3, 7]. Calcineurin inhibitors — 0.1% tacrolimus ointment or 1% pimecrolimus cream — are a safe and effective option for second-line therapy of vulvar lichen sclerosis (applied topically once or twice a day to the lesions for 4–8 weeks) in the absence of improvement after topical CP use or poor tolerance of first-line therapy [1, 3, 7]. Topical retinoids can be an effective treatment option for vulvar lichen sclerosis, especially for hyperkeratotic lesions on the vulva (topical application for 12–24 weeks every second day is recommended). Supportively, the use of ointments that improve skin trophicity, containing vitamin E and emollients reduces vulvar skin pruritus [1, 3, 7].

### **Objectives**

The purpose of this study was to determine the correlation of the prevalence of anti-thyroid antibodies — IgG class antibodies against thyroid peroxidase and IgG class antibodies against thyroglobulin in women with vulvar lichen sclerosis and the validity of screening for autoimmune thyroid diseases in women with vulgar lichen sclerosis.

### **MATERIAL AND METHODS**

Fifty women with vulvar lichen sclerosis diagnosed on the basis of gynaecological examination and clinical history and in doubtful cases on the basis of histopathological examination, hospitalized in the Department of Gynaecology, Obstetrics and Gynaecological Oncology of the Bonifraters Medical Center in Katowice were qualified for the study. The control group consisted of 41 healthy women reporting for a follow-up visit to the Gynaecology and Obstetrics Ambulatory Clinic of the Bonifraters Medical Center in Katowice.

Inclusion criteria for the study group were: vulvar lichen sclerosis diagnosis, age > 18 years, no systemic diseases, including autoimmune diseases, and informed consent to participate in the study. Exclusion criteria for both groups were: age < 18 years, pregnancy, pharmacological therapy used in the last 6 months, systemic diseases, and lack of informed consent to participate in the study.

All patients were informed in detail about the course of the study and its purpose and gave written informed consent to participate in the study. The study was approved by the Bioethics Committee of the Silesian Medical University in Katowice — PCN/CBN/0052/KB1/5/II/19/21/22.

In the first stage of the study, a detailed medical reconnaissance with all women with VLS was held. It included basic demographic data such as age and place of residence. A gynaecological interview towards symptoms of vulvar lichen sclerosus and pharmacotherapy used was conducted together with VLS and autoimmune diseases family history.

In the next step, in the morning (between 8:00 and 9:00 am) while fasting, 12 hours after the last meal, 20 ml of venous blood was collected from all patients into a tube on EDTA. After centrifugation of the blood (10 min; 3000 RPM), the plasma was frozen at  $-80^{\circ}\text{C}$  until laboratory test determinations were made.

### **Determination of the blood serum presence of human IgG class antibodies against thyroid peroxidase (TPO) and against thyroglobulin (TG)**

The assays were performed using an ELISA test kit, produced by Euroimmun, catalogue no. EA 1012-9601 G for anti-TPO antibodies and an ELISA test kit catalogue no. EA 1013-9601 G for anti-TG antibodies. Both kits contained microplates with separately detachable reaction wells coated with antigen. In positive cases, IgG class antibodies bind to the antigens present on the well surface. The bound antibodies are detected during a second incubation step with antibodies directed against human IgG labelled with an enzyme, which then catalyses the colour reaction. The Euroimmun test for the determination of IgG class antibodies against thyroid peroxidase recommends interpreting the results as positive  $\geq 50$  international units (IU)/mL, while the test for the determination of IgG class antibodies against thyroglobulin for values  $\geq 100$  IU/mL. In addition, the anti-TG ELISA has a specificity of 98%, while the anti-TPO ELISA has a specificity of 100%.

### **Statistical analysis**

STATISTICA 12 PL software (Statsoft Inc., USA) and MS Excel spreadsheet were used for statistical analysis of the data. In all calculations, statistical significance was assumed at  $p < 0.05$ . The CHI 2 test was used to analyse differences between groups in qualitative variables.

## **RESULTS**

### **Patient characteristics**

The study group included 50 women diagnosed with vulvar lichen sclerosus. The average age of the study group was 53.34 years (range 24–83). The average age of onset was  $41.08 \pm$

14.3. Moreover, the diagnosis of vulvar lichen sclerosus was made after a mean duration of the disease of 16 months  $\pm$  18.12.

The control group consisted of 41 healthy women, the average age of the control group was 38.56 years (range 18–69).

### **Signs and symptoms**

All of the studied patients with vulvar lichen sclerosus reported complaints of vulvar disease. 86% (n = 43) of the women complained of itching, 66% (n = 33) of burning, and 12% (n = 6) reported bleeding from the vulvar area.

On gynaecological examination, attention was drawn to whitened skin lesions on the vulva present in 68% (n = 34) of patients, in 34% (n = 17) accompanied by erythema. Swelling of the vulva was observed in 38% (n = 19) of the study population of women, [excoriation](#) in 54% (n = 27). Hourglass-like lesions in the perianal area were present in 10% (n = 5) of women with VLS.

Significantly, 10% (n = 5) of women with vulvar lichen sclerosus associated the disease with the onset of depression, and 30% (n = 15) complained of sleep disturbances. In addition, lowered self-esteem was reported by 30% (n = 15) of the study group, a sense of isolation due to the disease — 10% of women with VLS (n = 5). Dyspareunia was declared by 68% (n = 34) of the study group, decreased libido — 30% (n = 15), and 14% (n = 7) of the patients associated vulvar lichen sclerosus with subsequent deterioration of relationships with a partner.

### **Family history of autoimmune diseases**

16% (n = 8) of the first degree relatives (mothers) were diagnosed with vulvar lichen sclerosus. In addition, 20% (n = 10) were diagnosed with Hashimoto's disease, 12% (n = 6) with hypothyroidism, and 2% (n = 1) with hyperthyroidism. Systemic lupus erythematosus was reported in 4% (n = 2) of mothers of VLS patients, atopic dermatitis in 10% (n = 5) and psoriasis in 10% (n = 5).

### **Treatment**

64% (n = 32) of the patients received first-line treatment — an ointment containing 0.05% clobetasol propionate. Improvement after the included treatment was reported by as many as 80% of the study group. Preparations to improve vulvar skin trophicity — vaseline was used by 30% (n = 15) of women with VLS, emollients — 44% (n = 22), and ointment with vitamin

A — 44% (n = 22) of the study group. 36% (n = 18) of the patients used 0.1% tacrolimus ointment for recurrence of vulvar lichen sclerosis.

### **Co-occurrence of blood serum IgG class antibodies against thyroid peroxidase (TPO) and against thyroglobulin (TG)**

Antibodies to thyroid peroxidase were present in 12% (n = 6) of the study group with vulvar lichen sclerosis and 4.88% (n = 2) of the control group, and this difference was not statistically significant (p = 0.41). Antibodies to thyroglobulin were detected in 4% (n = 2) of the patients with vulvar lichen sclerosis and 4.88% (n = 2) of the control group, and this difference was not statistically significant either (p = 0.76).

## **DISCUSSION**

Vulvar Lichen sclerosis is a chronic inflammatory dermatosis of undetermined etiopathogenesis. It seems that the incidence of VLS in the population is underestimated — the asymptomatic course of vulvar lichen sclerosis in about 1/3 of cases causes great diagnostic difficulties, which, among other things, is associated with a delay in the final diagnosis of the disease and a higher incidence of complications of the disease [1].

The literature emphasizes the association of vulvar lichen sclerosis with autoimmune diseases, with a particular focus on autoimmune thyroid diseases, but the results of numerous studies are dissonant.

In the authorial study involving 50 women diagnosed with vulvar lichen sclerosis, IgG class antibodies against thyroid peroxidase were detected in 12% of the study group and in 4.88% of the control group of healthy women. IgG class antibodies against thyroglobulin were present in 4% of women with VLS and in 4.88% of the control group. The results obtained for both classes of antibodies are not statistically significant. These results are contradictory to those found in the literature.

The first report on the association of vulvar lichen sclerosis with autoimmune diseases, appears in the literature in 1974 — Goolamali et al. [10] on the basis of their study suggest an association of VLS with autoimmune thyroid disease (AITD) — the presence of anti-TPO antibodies was detected in 40% of the study group patients.

Cooper et al. conducted a study involving 190 women with VLS and 126 women with erosive lichen planus, assessing the prevalence of specific antibodies in women with vulvar disease compared to a randomly selected group of 112 healthy women. The results of the



study confirmed, among other things, the association between vulvar lichen planus comorbidities and autoimmune diseases (28% vs 9%,  $p < 0.001$ ), including autoimmune thyroid diseases - anti-TPO antibodies were confirmed in 16% of the study group with VLS, and this difference was statistically significant [11].

Similar observations were obtained by Kreuter — AITDs were the most common autoimmune condition diagnosed in a group of patients with vulvar lichen sclerosus. Moreover, AITD was diagnosed in 15.2% of women with VLS vs 3.8% of men with lichen sclerosus ( $p = 0.002$ ), which may suggest a different etiopathogenetic basis for the disease depending on gender [12].

Fan et al. [13] conducted a large case-control study involving 765 women with VLS and 3060 women qualified as controls. Based on the results, they found that patients with vulvar lichen sclerosus were significantly more likely to have thyroiditis (OR 2.67,  $p < 0.001$ ), autoimmune thyroiditis (OR 2.88,  $p < 0.001$ ), hypothyroidism (OR 2.34,  $p < 0.001$ ) and hyperthyroidism (OR 2.05,  $p < 0.001$ ). The etiological factors responsible for the association of VLS with thyroid disease are still unknown, and some literature data point to abnormal T-cell activity as a possible cause [13].

Bieber et al. [14] published the results of a large study, which enrolled 10004 women diagnosed with vulvar lichen sclerosus and 21672016 women in the control group from the IBM MarketScan database from 2015–2017. The published data show that AITD (6.11% vs 1.93%), vitiligo (1.95% vs 0.2%), and psoriasis (5.12% vs 1.2%) are significantly more common in women diagnosed with vulvar lichen sclerosus, suggesting the need for patients with VLS to receive interdisciplinary medical care [14].

Kazandi et al. [15] also confirmed the association of VLS with thyroid disease, which was diagnosed in 18.2% of a study group of 82 women with vulvar lichen sclerosus. Similar results were obtained by Birenbaum — the prevalence of thyroid disease in a group of women with VLS reached almost 30% and was 5–30 times more frequent than in the general population [16].

In a study by Azevedo et al. [17] 25.4% of patients with VLS were diagnosed with Hashimoto's disease, and these results are consistent with the literature data.

The hypothesis of molecular mimicry (structural similarity between microbial antigens and HLA) suggests a potential etiopathogenetic factor to transform the defensive immune response into an autoimmune response in genetically predisposed individuals. AITDs are thought to be associated with HLA-DR3, -DR4, -DR5, -DR8 and -DR9 [18].

Based on the results obtained, it is important to note the impact of vulvar lichen sclerosis on women's psychosexual functions. Significantly, 10% of women with vulvar lichen sclerosis associated the disease with the onset of depression, and 30% complained of sleep disturbances. In addition, lowered self-esteem was reported by 30% of the study group, and dyspareunia was declared by 68% of the study group of patients. These results are consistent with those available in the literature.

Sivalingam et al. [19] suggest that delayed diagnosis, ignoring patients' reported complaints at follow-up gynaecological visits, are the cause of inadequate health care for patients with vulvar lichen sclerosis.

Arnold et al. [20] evaluated the experiences of patients with VLS and the impact of the disease on quality of life, taking into account the quality of medical care, including the time of VLS diagnosis from the first symptoms, learning to function daily with a chronic disease, or assessing the degree of isolation and loneliness in interpersonal interactions due to vulvar dermatosis. Based on their research, they suggest establishing support groups, educational programs to combat the stigma associated with vulvar diseases [20].

A retrospective case-control study by Jabłowska et al. [21] involving 51 patients with VLS and 45 healthy women also showed that women with vulvar lichen sclerosis have a reduced quality of sexual life, are more likely to be screened for depression and the course of the disease affects work quality and productivity.

Another study by Yildiz et al. [22] involving 59 women with VLS and 21 patients with vulvar lichen planus showed that these patients were more critical of their own genital appearance, and more likely to report sexual dysfunction and anxiety.

## **CONCLUSIONS**

The study conducted did not confirm the association of VLS with autoimmune thyroid diseases. Undoubtedly, based on the data available in the literature, further studies are needed to determine the mechanisms behind the association between vulvar lichen sclerosis and autoimmune thyroid diseases. Anti-TPO antibodies are present in almost 95% of patients with Hashimoto's disease, which is considered one of the leading causes of hypothyroidism. In the long-term care of a patient with vulvar lichen sclerosis, it is necessary to take into account the possibility of co-occurrence of VLS with autoimmune thyroid diseases, among others. Therefore, many authors suggest considering testing for AITD in women with vulvar lichen sclerosis, with the aim of including the patient in multispecialty care. The main limitation of the conducted study was the small size of the study and control groups, as well as the lack of

TSH, fT4, fT3 determinations performed. However, it should be remembered that a positive result of anti-TPO antibodies and anti-TG antibodies is a sensitive marker in the diagnosis of autoimmune thyroid diseases. Further research in this direction, with an increase in the size of the study group of female patients is needed.

Most of the available data in the literature emphasize the therapeutic approach to the condition, with significantly less focus on the impact of VLS on patients' quality of life. Future prospective studies should focus, among other things, on the impact of vulvar lichen sclerosus on the psychosexual function of patients, with the goal of providing comprehensive multispecialty care, including support groups, assistance of a psychologist, psychiatrist and sexologist in dealing with the impact of vulvar lichen sclerosus on patients' quality of life.

### **Article information and declarations**

#### ***Acknowledgments***

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#### ***Author contributions***

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#### ***Ethics statement***

The study was approved by the Bioethics Committee of the Silesian Medical University in Katowice — PCN/CBN/0052/KB1/5/II/19/21/22.

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#### ***Conflict of interest***

The authors declare no conflict of interest.

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