Dermatol Ther (Heidelb) (2024) 14:759–766
https://doi.org/10.1007/s13555-024-01124-0

ORIGINAL RESEARCH

The Need of Differential Diagnosis Between Vulvar Lichen Sclerosus and Autoimmune Dermatoses in Adolescent Girls

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Received: October 28, 2023 / Accepted: February 16, 2024 / Published online: March 7, 2024

ABSTRACT

Introduction: Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition affecting the anogenital region, which can manifest in prepubertal or adolescent patients. The prevailing theories point to autoimmune and genetic factors. The primary symptoms of VLS typically include vulvar itching, discomfort, dysuria, and constipation. Physical examination often reveals a characteristic figure 8 pattern, involving the labia minora, clitoral hood, and perianal region. However, these symptoms and the age of onset are nonspecific and require differentiation from autoimmune dermatoses such as bullous diseases, pemphigus diseases, epidermolysis bullosa acquisita, and dermatitis herpetiformis. We performed this study to distinguish VLS from autoimmune dermatoses, and in doing so, uncover the underlying causes of chronic vulvar changes. This knowledge will enable healthcare providers to offer appropriate medical care to affected patients.

Methods: The study was conducted between July 2020 and February 2021, with a sample of 55 girls aged 2–18 years who did not have any systemic diseases. The study group was composed of 20 girls previously diagnosed with vulvar lichen sclerosus, while the control group included 35 girls without VLS. Questionnaires regarding the medical history of the children were completed by their legal guardians. Blood samples were collected and analyzed biochemically to assess human immunoglobulin A (IgA), IgG, and IgM antibodies against various substrates, including the desmosome of stratum spinosum, basement membrane zone, desmoglein 1 (DSG1), desmoglein 3 (DSG3), BP180-NC16A-4X, BP230gC, pemphigoid antigen, collagen type VII NC1, transitional epithelium, gliadin (GAF-3X), endomysium (EMA), and cellular nucleus (ANA).

Results: The analysis of the study group revealed that the most commonly observed signs and symptoms included: itching, soreness, burning sensations, and excoriation, as well as erythema or/and pallor of the skin and perineal mucosa. Among the assessed antibodies, only anti-GAF3x antibodies and ANA antibodies were detected. However, the results did not reach statistical significance ($p > 0.5$).

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Keywords: Adolescent; Vulvar lichen sclerosus; Autoimmune dermatoses

Key Points
Vulvar lichen sclerosus (VLS) is a persistent inflammatory skin disorder often associated with an increased risk of autoimmune diseases. It affects 1 in 900 premenarchal girls and should be differentiated from bullous diseases, pemphigus diseases, epidermolysis bullosa acquisita, and dermatitis herpetiformis.
All of the mentioned conditions are susceptible to the same type of treatment (topical corticosteroids). VLS is more concerning than autoimmune dermatoses because it is linked to a higher risk of cancer.
We performed this study to distinguish VLS from autoimmune dermatoses to uncover the underlying causes of chronic vulvar changes.
The most frequent signs and symptoms in children were itching, soreness, burning sensations, and excoriation, as well as erythema and/or pallor of the skin and perineal mucosa.
In the study group only anti-GAF3x antibodies and cellular nucleus (ANA) antibodies were detected ($p > 0.5$).
The distinction between VLS and autoimmune dermatoses is essential for providing appropriate medical care.

INTRODUCTION

Vulvar lichen sclerosus (VLS) is a persistent inflammatory skin disorder that tends to be associated with an elevated risk of autoimmune diseases. It affects approximately 1 in 900 premenarchal girls. While it is a chronic condition, its typical course is relatively benign and self-limiting [1, 2]. Many affected individuals present subtle symptoms, which can be mistakenly interpreted as mild dermatitis. The inflammation associated with VLS leads to the thickening of the skin in the vulvar and surrounding areas. Common symptoms of the disease include vulvar itching, discomfort, painful urination (dysuria), and constipation. During a physical examination, clinicians often identify a distinctive figure 8 pattern, involving the labia minora, clitoral hood, and the perianal area. These symptoms, while generally mild, can significantly impact the quality of life of patients [2].

VLS can manifest at any age or in any gender. Nevertheless, the highest prevalence is typically found in women between the ages of 40 and 60 years, as well as in prepubertal girls. Notably, there is a distinct peak in incidence among girls aged 4–6 years, representing 7–15% of all reported cases of vulvar lichen sclerosus [3].

However, the symptoms mentioned above, as well as the age of occurrence, are very nonspecific, so they should be differentiated from bullous diseases, pemphigus diseases, epidermolysis bullosa acquisita, and dermatitis herpetiformis.

The diagnosis of autoimmune dermatoses relies on the clinical symptoms and the detection of autoantibodies against structural skin proteins and recombinant, purified antigens using indirect immunofluorescence tests (Dermatological Mosaic with a complete set of substrates), as well as monospecific ELISA or immunoblot tests. The use of these tests, or their combination, allows for a reliable diagnosis of blistering diseases, pemphigus diseases, acquired epidermolysis bullosa, and herpetic skin inflammation with an unmatched specificity of autoantibodies at nearly 100%, and sensitivity ranging from 96% to 100%. [4, 5]

Although all of the mentioned conditions are susceptible to the same type of treatment (topical corticosteroids), they require early differential diagnosis due to the long-term consequences of the disease.

According to our best knowledge, this is the largest study conducted on a pediatric group so far.

The aim of the study is to distinguish vulvar lichen sclerosus from autoimmune dermatoses, to therefore verify the origins of chronic vulvar changes and provide the patient with proper medical care.

METHODS

Patients

Our research participants were selected from the gynecological clinic Centrum Zdrowia Kobiety in Katowice, Poland, during the period from July 2020 to February 2021. We recruited a group of 20 girls who had been diagnosed with vulvar lichen sclerosus ($n = 20$). The control group consisted of 35 girls who did not have diagnosed vulvar lichen sclerosus but were under the clinical care for conditions such as genital infections and labial synechiae.

Our inclusion criteria were as follows: participants aged 2–18 years old; confirmed diagnosis of lichen sclerosus of the vulva in children, based on medical history and physical examination; absence of systemic diseases, such as cardiovascular diseases, peptic ulcer disease, or epilepsy; and consent obtained from the girl and/or her legal guardian for participation in the study.

The exclusion criteria were as follows: previous diagnosis of an autoimmune disease; use of pharmacotherapy within the last 6 months, which included hormonal medications, contraceptives, and nonsteroidal antiinflammatory drugs (NSAIDs); presence of systemic diseases, such as cardiovascular diseases, peptic ulcer disease, epilepsy, liver and kidney diseases; substance addiction; current or historical pregnancy; and absence of consent from the girl and/or her legal guardian for participation in the study.

None of the patients have undergone differential diagnosis of dermatological diseases thus far.

This project obtained ethical approval from the Ethics Committee of the Medical University of Silesia in Katowice, Poland, under the reference number KNW/0022/KB1/5/19. The project was conducted as part of the statutory research activities of the Medical University of Silesia, with the identifier KNW-1–142/N/8/K. This study was in accordance with the Declaration of Helsinki.

Anamnesis

For each individual in the study, we administered a questionnaire to collect essential demographic information, details of the neonatal period, lifestyle factors, gynecological history, and family medical history, with a specific focus on the presence of autoimmune conditions in the family. Additionally, participants in the study group provided responses regarding their specific medical condition, including the initial symptoms, diagnostic process, the treatment received, and its associated outcome.

Blood Collection

We obtained 10 ml of 12 h fasting blood samples from the ulnar vein in the morning. The blood was drawn into standard blood collection tubes containing EDTA (1.6 mg/ml EDTA-K3; S-Monovette, SARSTEDT). To prepare samples for serum analysis, we centrifuged them at 4000 rpm for 10 min at a temperature of 4 °C, after which they were stored at −80 °C. Both plasma and serum samples were subsequently frozen and preserved at −80 °C until the time of conducting the biochemical analyses.

Dermatology Mosaic—Indirect Immunofluorescence Test

An indirect immunofluorescence test (IT) with commercially available kits (Euroimmun, Poland) was performed. The substrates were incubated with diluted patients' blood samples. In positive cases, specific antibodies of the IgA, IgG, and IgM classes were bound to antigens. During the second stage of incubation, bound antibodies were detected by labeled FITC (Fluorescein isothiocyanate) anti-human antibodies. Next, the reaction was evaluated under a fluorescent microscope. In the presence of a

fluorescence reaction, the result is considered positive, while in its absence, negative.

Human IgA, IgG, and IgM antibodies against the following substrates were assessed: desmosome of stratum spinosum, basement membrane zone, desmoglein 1 (DSG1), desmoglein 3 (DGS3), BP180-NC16A-4X, BP230gC, pemphigoid antigen, collagen type VII NC1, transitional epithelium, gliadin (GAF-3X), endomysium (EMA), and cellular nucleus (ANA).

For the substrates mentioned above, fluorescence at a titer of 1:10 is considered a positive test result. Only for ANA, fluorescence at a titer of 1:100 (or more) is the basis for considering the result positive.

Statistical Analysis

We conducted statistical analysis using STATISTICA 13 PL software (StatSoft Inc., USA). Mean values with standard deviations (SD) were utilized. The chi-squared tests for 2×2 contingency tables were used to compare groups. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

Group Characteristics

The study group was composed 20 girls, with the youngest patient being 5 years old and the oldest 18 years old at the time of the study. The mean age within the group was 10 years and 9 months. Among these, six of the girls had a positive family history of thyroid autoimmune diseases.

The control group was composed of 35 individuals, with the youngest patient being 2 years old and the oldest 18 years old at the time of the study. The mean age for this group was 10 years and 9 months. Within this group, five girls had a positive family history of thyroid autoimmune diseases.

Initial Vulvar Lichen Sclerosus (VLS) Symptoms

We gathered information on the signs and symptoms, both present and preceding, the diagnosis of VLS. The most common symptoms reported in girls were itching (60%, $n = 12$), soreness or a burning sensation (50%, $n = 10$), and excoriation (55%, $n = 11$). Regarding changes in skin color and perineal mucosa, erythema (40%, $n = 8$) and/or pallor (40%, $n = 8$) were the most frequently observed. The typical figure 8 symptom was present in 20% of the patients ($n = 5$). Vulvar bleeding was reported in 40% of girls ($n = 7$), with three of them also reporting the presence of excoriation. Genital or urinary tract infections were reported in 25% of the girls ($n = 5$).

Family History

In the study group ($n = 20$), four girls had a documented personal history of asthma and/or allergies. Additionally, nine patients had first-degree relatives with autoimmune diseases. The study also assessed the occurrence of skin diseases in the first-degree relatives in the study group. The identified diseases included vulvar lichen sclerosus ($n = 1$), atopic dermatitis ($n = 1$), psoriasis ($n = 1$), and vitiligo ($n = 2$).

In contrast, none of the patients in the control group had a personal history of allergies or asthma. However, a substantial portion of the control group (22 girls) reported a family history of autoimmune diseases among their first-degree relatives. Among these, skin diseases observed in their first-degree relatives included atopic dermatitis ($n = 1$), psoriasis ($n = 6$), and vitiligo ($n = 2$).

The Prevalence of Antibodies in Study and Control Groups (Table 1)

Human IgA, IgG, and IgM antibodies against the following substrates were assessed: desmosome of stratum spinosum, basement membrane zone, desmoglein 1 (DSG1), desmoglein 3 (DGS3), BP180-NC16A-4X, BP230gC, pemphigoid antigens, collagen type VII NC1,

Table 1 Frequency of the presence of characteristic antibodies in the study population

	ANA 1:100	anty-GAF-3x
Study group (n = 20)	6 (30%)	5 (25%)
Control group (n = 35)	22 (51%)	7 (20%)
p (Chi-squared test)	0.193 (NS)	0.634 (NS)

transitional epithelium, gliadin (GAF-3X), endomysium (EMA), and cellular nucleus (ANA). In assessed material only anti-GAF3x and ANA antibodies were found.

We obtained positive IIFT (indirect immunofluorescence technique) results only for anti-GAF3x antibodies that were present in five patients (25%) from the study group and seven patients from the control group (20%) (p = 0.643).

ANA antibodies in a titer of 1:100 were found in 6 patients (30%) from the study group and 22 patients from the control group (51%) (p = 0.193).

DISCUSSION

The occurrence of vulvar lichen sclerosus (VLS) and various autoimmune diseases is a rising topic within the medical community [6, 7] This study was conducted to investigate the correlation between VLS and various vulvar pemphigoid diseases in young female patients.

The significant role of autoimmunity in the development of VLS is emerging more and more often. A higher proportion of patients with VLS, in contrast to the general population, presents autoimmune-related conditions, autoimmune antibodies, or has family history of autoimmune diseases. Thyroiditis, alopecia areata, vitiligo, and pernicious anemia are the most frequently observed autoimmune conditions among patients with VLS. Less commonly associated conditions are autoimmune bowel disease, localized scleroderma/morphea, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [8].

Patients with VLS commonly experience symptoms such as itching, swelling, and a burning sensation in the vulva, along with pain, bleeding, and constipation. A significant portion (86%) reports itching, which often worsens at night, causing daytime fatigue in children. This itching can lead to skin tearing and bleeding. Some patients show no symptoms, and in 30% of girls with VLS the diagnosis is delayed due to the recurring infections [1, 2, 9, 10].

Upon physical examination, distinct white skin lesions resembling a figure 8 or hourglass shape can be seen, especially around the labia and perianal region. The skin is atrophic and shiny. Other observations include erosions, scars, and bruises. Notably, the severity of symptoms does not always match the lesion's size, meaning even small lesions can cause significant discomfort [1, 2, 11].

In our study, the initial symptoms of VLS, such as itching, soreness, and excoriation, were consistent with the ones previously described in the literature. The presence of the figure 8 symptom in only 20% of the patients suggests that it may not be as common an indicator as previously thought or it occurs in the late stage disease.

The course of the vulvar lichen sclerosus varies widely, making it challenging to diagnose. Initial symptoms are often vague and can be overlooked by doctors who are not gynecologists or dermatologists [12].

The symptoms mentioned above are nonspecific. Veronesi et al. (2021) describe the significance of the differential diagnosis of VLS and vulvar vitiligo (VV). The study presents VVVLS, a superficial variant of LS in which the clinical presentation typically includes hypopigmented or depigmented patches accompanied by minimal inflammation and sclerosis, resembling features commonly seen in vitiligo. The vitiligo-like symptoms are probably LS post-inflammatory hypopigmentation. However, VV and VLS may coexist [17].

Recurrent vulvar erosions may also be observed in the presentation of bullous diseases, pemphigus diseases (bullous pemphigoid and cicatrical pemphigoid), epidermolysis bullosa acquisita, and dermatitis herpetiformis [18].

While these autoimmune dermatoses are extremely rare in the pediatric population, many authors have presented case reports on this topic. This indicates the need for a thorough differential diagnosis [13–16]. The study of Borghi et al. is in line with our concerns, suggesting that early treatment offers therapeutic advantages for patients with VLS. The "window of opportunity" hypothesis suggests that there is a critical period during which interventions or exposures can have a significant impact on development or outcomes. Achieving complete clearance of symptoms and signs is challenging, but initiating treatment within 12 months of onset significantly improves the likelihood of symptom relief, sign resolution, and improved quality of life, particularly concerning dyspareunia. These results underscore the importance of early diagnosis and prompt intervention in managing VLS effectively [19].

In our study we did not find the antibodies against the following substrates: desmosome of stratum spinosum, basement membrane zone, desmoglein 1 (DSG1), desmoglein 3 (DGS3), BP180-NC16A-4X, BP230gC, pemphigoid antigens, collagen type VII NC1, transitional epithelium, and endomysium (EMA) in the study group nor in the control group. We obtained positive IIFT results only for anti-GAF3x antibodies that were present in five patients (25%) from the study group and seven patients from the control group (20%). The results are not statistically significant ($p = 0.634$), however, such patients should be subject to increased monitoring in the future, i.e., increased frequency of visits to the gynecologist and possible re-diagnosis in the perimenopausal period.

In contrast to our research, the study of Baldo et al. found antibodies against BP 180 in three girls with VLS, which could be interpreted as an auto-immunological background of the disease- [20] However, the study was conducted on nine children. Both groups are therefore relatively small and it is difficult to compare them to obtain statistical significance.

ANA antibodies in a titer of 1:100 were found in 6 patients (30%) from the study group and 22 patients from the control group (51%).

ANA antibodies are very nonspecific, often associated with multiple autoimmune diseases.

However, all patients with positive ANA from the control group reported a family history of autoimmune diseases, particularly Hashimoto's thyroiditis and rheumatoid arthritis. All of the above-mentioned are associated with positivity for ANA antibodies, particularly in women. [21]

Intermediate immunofluorescence testing is necessary because, even though regression of symptoms can occur during the reproductive age, in the case of symptom recurrence after menopause, VLS is an acknowledged premalignant disorder (unlike pemphigoid). [22]

We are aware of the limitations of our study. The number of patients participating in the study is relatively small, although it still represents the largest study conducted on a pediatric population to date. The coronavirus disease (COVID) pandemic significantly hindered the recruitment of a larger number of patients, as some declined to participate in the study due to health concerns.

CONCLUSIONS

The distinction between VLS and other autoimmune dermatoses is essential for providing appropriate medical care. Vulvar lichen sclerosus is more concerning than autoimmune dermatoses because it is linked to a higher risk of cancer. This research improves our understanding of these conditions and supports more precise diagnosis to provide a holistic approach to the disease.

Author Contributions. Conceptualization: Agnieszka Dulska. and Agnieszka Drosdzol-Cop.; methodology: Agnieszka Dulska., Marta Janik., and Agnieszka Drosdzol-Cop.; software: Jakub Bodziony.; formal analysis: Jakub Bodziony.; investigation: Agnieszka Dulska., Jakub Bodziony., and Marta Janik; data curation: Agnieszka Dulska and Jakub Bodziony; writing—original draft: Agnieszka Dulska and Jakub Bodziony; visualization: Agnieszka Drosdzol-Cop; supervision: Agnieszka Drosdzol-Cop. All

authors have read and agreed to the published version of the manuscript.

Medical Writing and Editorial Assistance.

The authors didn't receive any medical writing or editorial assistance for this article.

Funding. No funding or sponsorship was received for this study. Part sponsorship for the Rapid Service Fee was funded by Medical University of Silesia.

Data Availability. The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical reasons.

Declarations

Conflict of Interest. Author Marta Janik was employed by Euroimmun Polska Sp. z o.o. The other authors declare that they have no conflicts of interest.

Ethical Approval. This project received a positive opinion from the Ethics Committee of the Medical University of Silesia in Katowice, Poland, obtaining the experiment approval no. KNW/0022/KB1/5/19 on 29 January 2019. Informed consent was obtained from all subjects involved in this study.

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