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Association between vulvar lichen sclerosus and celiac disease in woman

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ABSTRACT

Objectives: Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition involving mainly the genital area with an undetermined aetiology. Recent studies show that in up to 34% of cases in adult women, VLS coexists with allergies or autoimmune diseases like celiac disease (CD), among others. However, literature data relating strictly to the co-occurrence of celiac disease and Duhring's disease (DH) in patients with VLS are very limited.

Material and methods: In our study, we sought to clarify the possible relationship between vulvar lichen sclerosus in adult women and celiac disease in its cutaneous form. The aim of the study was to demonstrate the presence of celiac disease-specific antibodies in women with VLS. The control group consisted of 41 healthy women, and the study group consisted of 50 women aged 24–83 years with diagnosed vulvar lichen sclerosus who were hospitalized in the Department of Gynaecology, Obstetrics and Gynaecologic Oncology of the Bonifraters Medical Centre in Katowice.

Results: There were no significant differences in blood serum levels of CD-specific antibodies between both groups.

Conclusions: The study conducted did not confirm the association between vulvar lichen sclerosus and celiac disease or Duhring's disease. The main limitation of the research was the small size of the study and control groups. Further studies on a larger group of patients are needed. They could clarify the possible mechanisms behind the co-occurrence of these two conditions. Earlier diagnostic will help prevent the development of severe and irreversible complications.

Keywords: vulvar lichen sclerosus; celiac disease; immunity; Duhring's disease; female sexual dysfunction

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INTRODUCTION

Vulvar lichen sclerosus is a chronic inflammatory condition involving mainly the skin and genital mucosa, which has a significant impact on patients' quality of life. The disease was first described by Hallopeau in 1881 [1]. The exact number of VLS sufferers is unknown and ranging between 1:300 and 1:1,000 women in the whole population [2].

The etiopathogenesis of VLS has not yet been clearly elucidated and is most likely multifactorial. Genetic and autoimmune factors, hormonal status, trauma to the affected area or infections are considered [3, 4]. The disease has two peaks of incidence: the first in girls aged 8–13 years and the second in adult postmenopausal women between 50–60 years [5]. These two peaks of incidence of VLS may suggest a possible influence of low oestrogen levels on the development of the condition. However, there are no studies that conclusively indicate the presence of such an association [6].

The characteristic clinical signs of VLS include the presence of well-demarcated, white skin lesions in the vulvar and anal areas. The most common complaints reported by patients include itching, burning and pain during intercourse. In the long term, adhesions and narrowing of the vaginal vestibule can occur [6–8]. According to recent guidelines, a biopsy is not required for the diagnosis of VLS and its diagnostics should be based on a thorough physical examination and a detailed medical history. Taking biopsy specimens for histopathological examination is reserved only for strictly defined cases, including lack of improvement after pharmacological treatment, presence of areas of excessive keratinization or if a neoplastic process in the lesions is suspected [9]. The current classification of the International Society for the Study of Vulvovaginal Diseases (ISSVD) classifies VLS as a

dermatosis that is not of neoplastic nature. However, in the literature, cases showing that VLS may have the potential to transform into vulvar intraepithelial neoplasia (VIN) and keratotic carcinoma of the vulva have been described [10].

Many therapeutic options are available for the treatment of VLS; unfortunately, a complete recovery from this condition is not possible. The main goal of therapy is to reduce the severity of disease symptoms and inhibit tissue remodeling to delay sclerosis of the affected area and prevent adhesions from forming [11]. The gold standard for the treatment of VLS is a

three-month topical therapy with an ointment containing 0.05% clobetasol propionate with gradual dose reduction and concomitant use of emollients [11]. Second-line therapy can include calcineurin inhibitors - tacrolimus, pimecrolimus; retinoids, phototherapy or ablative laser. The choice of therapy should be made individually, depending on the type of lesions, disease process progression and the symptoms manifested by the patient [6, 12].

A growing body of literature suggests an important role of immune mechanisms in the development of VLS. Studies show that more than 25% of VLS cases may coexist with autoimmune diseases such as vitiligo, type I diabetes, thyroiditis, celiac disease [CD] or Duhring's disease. A research by Cooper et al. [13, 14] found that 28% of women diagnosed with VLS had one or more autoimmune comorbidities, representing a more than threefold increase in risk compared to control patients.

Celiac disease is an autoimmune disorder that mainly affects the small intestine and is caused by gluten consumption in genetically susceptible individuals. Over the past few decades, CD has been found to affect about 1% of the population worldwide [15]. The development of celiac enteropathy depends on a complex immune response to gluten proteins, involving both adaptive and innate mechanisms. The clinical picture of celiac disease varies widely and includes classic gastrointestinal symptoms. Extraintestinal symptoms may also be present during the course of the disease. The diagnosis of celiac disease requires a positive serologic test (IgA antibodies against transglutaminase 2 and against endomysium) and villous atrophy in the small intestinal biopsy [16].

The cutaneous form of celiac disease is Duhring's disease, which is associated with vesicular lesions in the extensor region of the head and buttocks with concurrent pruritus of these areas. The diagnosis of DH can be made on the basis of histopathological findings based on direct immunofluorescence. However, the primary laboratory test, which is used to diagnose DH is the evaluation of the antibodies against tissue transglutaminase in the blood test. The

treatment of DH is similar to that of celiac disease and involves the complete exclusion of gluten from the diet [17].

Objectives

According to the scientific literature, vulvar lichen sclerosus, more often than in the healthy population, may be accompanied by autoimmune diseases. Few papers describe the co-occurrence of VLS with celiac disease or Duhring's disease. The purpose of our study was to demonstrate the presence of celiac disease-specific antibodies against tissue transglutaminase IgG and IgA and against gliadin GAF-3X IgG in adult women with VLS. Early diagnosis of both diseases could provide patients with multidisciplinary medical care to reduce associated complications.

MATERIAL AND METHODS

The study group included 50 patients hospitalized in the Department of Gynaecology, Obstetrics and Gynaecologic Oncology at the Bonifraters Medical Centre in Katowice. The diagnosis of VLS was based — according to British Dermatological Society guidelines — on a thorough physical examination and medical history. In doubtful cases, material from the lesions was taken for histopathological examination. The control group consisted of 41 healthy women attending medical appointments in the hospital's Obstetrics and Gynaecology Ambulatory Clinic. Both groups met the study's inclusion and exclusion criteria.

Inclusion criteria for the study group:

1. diagnosis of vulvar lichen sclerosus;
2. age > 18 years;
3. absence of systemic diseases, including autoimmune diseases;
4. informed consent to participate in the study.

Exclusion criteria for both groups:

1. age < 18 years;
2. pregnancy;
3. pharmacological therapy used in the last 6 months;
4. systemic diseases;
5. lack of consent to participate in the study.

Patients qualified for the study were also presented with a form that included detailed questions about their and their immediate family's autoimmune disease comorbidities. The

questionnaire also included questions about: age, first and last menstrual period, lifestyle, treatment administered including patients' satisfaction with the effect of therapy, and the impact of the disease on their quality of life.

In the next step, in both groups 20 mL of venous blood was collected from patients into EDTA test tubes. The blood was collected on an empty stomach between 8:00 a.m. and 9:00 a.m. After centrifugation, the frozen plasma was stored at –80°C until laboratory tests were performed.

All participants were informed about the purpose of the survey and the way it would be conducted. Written consent was required from all respondents, with information about the procedures carried out included in the study protocol.

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

Determination of human IgA and IgG class antibodies against tissue transglutaminase (anti-tTG) and against gliadin: Anti-Gliadin (GAF-3X) ELISA

The assays were performed using ELISA test kits produced by Euroimmun — for IgA and IgG antibodies to tissue transglutaminase, and a new, highly specific test for anti-gliadin antibodies — Anti-Gliadin (GAF-3X) ELISAThanks to intensive scientific development, the Anti-Gliadin (GAF-3X) test employs a "newly designed" antigen whose immunologically reactive surface provides the test with a specificity of almost 100% [18]. The clinical sensitivity of the

Anti-Transglutaminase Tissue ELISA (IgA and IgG) test was determined using sera from patients with celiac and Duhring's diseases. The sensitivity of the test for antibodies in the IgA class is 95.7% with a specificity of 98%. For antibodies in the IgG class, the sensitivity is 24.5% and specificity 99.7%, respectively.

Statistical analysis

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

RESULTS

Patient characteristics

The study group consisted of 50 adult women diagnosed with vulvar lichen sclerosus. The mean age of the study group was 53.34 years (range 24 –83). The mean age of onset of disease symptoms was 41.08 +/– SD 14.3 while the mean age of VLS diagnosis was 43.04 +/– SD 14.5. The diagnosis of vulvar lichen sclerosus was made after a mean duration of disease of 16 months +/– SD 18.12. Whereas 41 healthy adult women were included in the control group. The mean age of the control group was 38.56 years (range 18–69).

Signs and symptoms

The most common symptom reported by patients with vulvar lichen sclerosus was pruritus, which was present in 86% of patients (n = 43). This was followed by patients complaining of burning in the intimate area 66% (n = 33) and recurrent reproductive tract infections in the past 38% (n = 19), while 12% (n = 6) of them experienced bleeding from the vulvar and perineal area. In addition, dyspareunia was declared by 68% (n = 34) of the women in the study group.

On physical examination, the most common finding was the presence of well-demarcated, whitened lesions around the vulva, which were present in up to 86% of patients (n = 43). Interestingly, the "figure eight symptom" characteristic for VLS involving the presence of the above-mentioned lesions also around the anus was observed in only 10% of patients (n = 5). In 54% of the patients (n = 27), excoriations in the labial area together with dry and scaly skin were noticed. Swelling of the vulva was observed in 38% (n = 19) of women, while another 34% (n = 17) also had erythema.

In terms of the psychosocial health consequences of this condition, 30% of women (n = 15) in the control group complained of sleep disturbances, and 10% of them (n = 5) associated the disease with the onset of depression. In addition, 7 patients with vulvar lichen sclerosus (14%) linked the appearance of the disease in their lives with the deterioration of the relationship with their partner.

Family history of autoimmune diseases

The most common autoimmune conditions in first-degree relatives (mothers) of VLS patients are thyroid conditions. 20% of them (n = 10) were diagnosed with Hashimoto's disease, while 12% (n = 6) had hypothyroidism. Hyperthyroidism was present in only 2% (n = 1). Atopic dermatitis was reported in 10% (n = 5) of mothers of VLS patients, systemic lupus erythematosus in 4% (n = 2), psoriasis in 10% (n = 5). Vulvar lichen sclerosus was present in 16% (n = 8) of first-degree relatives — mothers, and in 4% (n = 2) — sisters. In addition,

celiac disease was present in only 4% (n = 2) of sisters of patients in the control group. No first-degree relative was found to have Duhring's disease.

Treatment

64% (n = 32) of patients received first-line treatment: three-month treatment regimen with an ointment containing 0.05% clobetasol propionate with gradual dose reduction. Improvement after the applied treatment was reported by 80% of patients. During treatment, preparations improving skin trophism such as Vaseline — 30% (n = 15), emollients — 44% (n = 22) and ointment with vitamin A — 44% (n = 22) were used. Due to recurrence of the symptoms, 0.1% tacrolimus ointment was used as second-line therapy in 36% (n = 18) of patients and photodynamic therapy in 48% (n = 24) of patients.

Co-occurrence of IgG and IgA class anti-tissue transglutaminase (anti-tTG) antibodies in blood serum and anti-gliadin (GAF-3X) IgG antibodies

IgA class anti-tissue transglutaminase antibodies were present in 2% (n = 1) of the study group with vulvar lichen sclerosus and in 2.44% (n = 1) of the control group. This difference was not statistically significant (p = 0.56).

In contrast, no patient in the study and control groups had IgG class antibodies to tissue transglutaminase.

GAF-3X anti-gliadin antibodies were detected in 2% (n = 1) of patients with vulvar lichen sclerosus and 2.44% (n =1) of the control group, and this difference was not statistically significant either (p = 0.56).

DISCUSSION

The aetiology of VLS is not fully ascertained, while more and more data suggest an important role of autoimmune mechanisms in the development of the condition. The conclusions drawn from the analysis of the scientific literature indicate that VLS co-occurs with autoimmune diseases such as allergies, vitiligo, type I diabetes, thyroiditis, celiac disease or Duhring's disease in 34% of cases [19].

It is assumed that genetic predisposition may be important for the development of the immune response leading to VLS. A large cohort study conducted by Sherman et al. [20] on a group of 1,052 women with vulvar lichen sclerosus showed that 12% of them had a positive medical history of VLS. Moreover, vulvar cancer was more common in the group with a positive history of VLS [20]. In patients with vulvar lichen sclerosus, antibodies against the

basement membrane zone were also detected, and a large proportion of them had specific antibodies directed against extracellular matrix proteins [21].

Several small studies using serologic typing have shown an increased prevalence of HLA-DR11, DR12, DQ7, DQ8, and DQ9 haplotypes in case of lichen sclerosus [LS] [11, 22]. The association between the development of celiac disease with the class II genes HLA-DQ2 and HLA-DQ8 is well known [23]. Given the fact that genes from the HLA system have a considerable influence on the pathogenesis of celiac disease, Duhring's disease as well as lichen sclerosus, we can expect a genetic predisposition to develop these diseases simultaneously in the same person.

Celiac disease is an immune-mediated disorder that is clinically characterized by a variety of symptoms and complications. Duhring's disease is considered to be the cutaneous manifestation of celiac disease. CD occurs in 1% of the population. It is estimated that about 13% of patients with this disease will develop DH. Both of these diseases, which are conditions with complex aetiologies, share certain genetic features and pathogenetic mechanisms that are responsible for their characteristic skin and intestinal symptoms [24]. The current literature does not clearly define a theory to explain the coexistence of celiac disease with other autoimmune disorders. However, there is growing evidence that the loss of intestinal barrier function typical for celiac disease may be responsible for the development of other autoimmune diseases [25].

However, scientific information relating strictly to the co-occurrence of celiac disease in patients with VLS is very limited. Some studies suggest that individual vulvar diseases may be a symptom of generalized pelvic floor disorders, as well as other nearby structures such as the bladder or intestines. Patients with lichen sclerosus have been found to have a significantly higher incidence of overactive bladder (OAB) syndrome, urinary stress and urge incontinence, and irritable bowel syndrome [26].

Soderlund et al. [27] in a retrospective study on a group of 455 women (mean age 64) diagnosed with lichen sclerosus showed that the risk of developing CD is significantly increased in patients with VLS. Interestingly, this study did not show an increased risk of developing Crohn's disease and colitis ulcerosa.

Halonen et al. [28] came to similar conclusions. Using information from nationwide Finnish registries, they analysed data from 43,000 women from 1998–2016 who were diagnosed with vulvar lichen sclerosus. The study found that both the diagnosis of celiac disease and Crohn's disease increased the likelihood of developing VLS [28].

In 2014, Jacobs et al. [29] described the cases of three girls with celiac disease, aged 3–5 years, who were diagnosed with vulvar lichen sclerosus. In the same year, a case of VLS was also described in a 53-year-old woman who reported chronic abdominal pain and diarrhoea during treatment. After performing laboratory tests, the presence of anti-endomysial and anti-gliadin antibodies were found. In addition, the diagnosis of CD was confirmed by a duodenal biopsy image [30].

In our authorial study on a group of 50 adult women with VLS, there was no increased prevalence of anti-tissue transglutaminase IgG, IgA and anti-gliadin GAF-3X IgG antibodies characteristic for celiac disease. Although the association between VLS and other autoimmune diseases has been previously documented in a number of studies, the co-occurrence of celiac disease in patients with VLS has not been widely reported. We found only one published study describing the coexistence of celiac disease in 3 girls with VLS, and another one being a case report of celiac disease in a woman with lichen sclerosus. The other 2 studies, are retrospective studies. Nevertheless, in the light of the available scientific literature, celiac disease should be considered when monitoring patients with VLS.

CONCLUSIONS

The study did not confirm the association between vulvar lichen sclerosus and celiac disease or Duhring's disease. The main limitation of the study was the small size of the study and control groups. The etiopathogenesis of VLS has not yet been clearly elucidated and is most likely multifactorial. Genetic and immunological factors are increasingly being taken into account. The relationship between vulvar lichen sclerosus and other autoimmune diseases has been documented in numerous studies. However, literature data on the co-occurrence of VLS and celiac disease or Duhring's disease are very scarce. There is growing evidence that the loss of the intestinal barrier typical for celiac disease may be responsible for the development of other autoimmune diseases. Further studies on a larger group of patients are undoubtedly necessary to clarify possible pathogenetic mechanisms behind the co-occurrence of these two conditions. Earlier diagnosis, prompt implementation of effective treatment and providing patients with multi-specialist care will help prevent the development of severe and irreversible complications, significantly improving the quality of patients' life.

Article information and declarations

Ethics statement

This project obtained ethical approval from the Ethics Committee of the Medical University of Silesia in Katowice, Poland, under the reference number 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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