Pediatric Vulvar Lichen Sclerosus

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Contributor: Agnieszka Drosdzol-Cop

Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition affecting the anogenital region, which may present in a prepubertal or adolescent patient. The most popular theories are its autoimmune and genetic conditioning, although theories concerning hormonal and infectious etiology have also been raised. The most common presenting symptoms of VLS is vulva pruritus, discomfort, dysuria and constipation. The lesions initially are white, flat-topped papules, thin plaques, or commonly atrophic patches. Purpura is a hallmark feature of VLS. The treatment includes topical anti-inflammatory agents and long-term follow-up, as there is a high risk of recurrence and an increased risk of vulvar cancer in adult women with a history of lichen sclerosus.

Keywords: vulvar lichen sclerosus ; pediatric ; adolescent

1. Introduction

VLS manifests in lesions in vulvar mucosa, which often spreads to the skin of the anus [1]. The symptoms of this condition may include whitening of the perineal area, but also itching, burning, discomfort, vaginal bleeding, and dysuria, which in sexually active girls may be mistaken for symptoms of urogenital infection [2]. In some cases, due to anorectal lesions, additional symptoms may occur, such as constipation or painful defecation, without any gastrointestinal problems in the patient's medical history [3]. The prevalence of VLS in underaged girls is understated, due to the misreading of the symptoms by GPs (general practitioners), and the delayed access to specialists in the field of pediatric gynecology or dermatology [4].

2. Epidemiology

VLS can occur at any age or in any sex, although the highest values can be observed in women aged 40–60 years old, and in pre-pubertal girls. There is a clear peak of incidence in girls aged four to six years old, which represents 7–15% of all vulvar lichen sclerosus cases [5].

It is estimated that VLS can be observed in 1:900 of premenarchal girls [4][6]. The first symptoms are usually very non-specific and misdiagnosed by non-gynecologist and non-dermatologist doctors. Some of the symptoms can spontaneously recede after the menarche, and the course of the disease can be latent. This is why the epidemiology of VLS is underestimated [6].

3. Etiopathogenesis

The etiopathogenesis of VLS remains unknown and is probably multifactorial. There are multiple theories regarding the potential etiopathogenesis of vulvar lichen sclerosus.

3.1. Immunological Theory

The available data put emphasis on the role of immunological factors. Even the first case of VLS, reported by Hallopeau, indicated the potential link with diseases such as scleroderma [7]. Recent studies show that 15–34% of cases in adult women and 14% in girls coexist with allergies or autoimmune diseases, such as the following: vitiligo, thyroiditis, type 1 diabetes mellitus, alopecia areata, or celiac disease [1].

The typical lymphocytic cell infiltration may suggest the involvement of interleukin-1 (IL-1) and the antagonist of the IL-1 receptor. It is also considered that some types of human lymphocyte antigens are connected with both a higher or lower risk of vulvar lichen sclerosus development [8].

A variety of studies also report an association with autoimmune diseases such as psoriasis, lichen planus, or morphea. Simpkin et al. found that 48% of patients with VLS present active tissue autoantibodies, whereas thyroid disorder was

found in 19% of patients. What is more, only 5% of the patients in this study had a family history of VLS. This is why patients should be screened for autoimmune diseases, although the specific antibody that can become a marker of VLS has not yet been found [9][10].

3.2. Genetic Theory

Other researchers suggest the potential role of genetic susceptibility. According to Powell et al. (2001), the family history of autoimmune disease appears to be very visible in the early onset group [4]. In the Sherman et al. work, 12% of female VLS patients had a first-degree female relative who had also been diagnosed with VLS. Numerous case reports of twin, sibling and mother–daughter relationships contribute to a genetic factor in the etiology of lichen sclerosus et atrophicus [11]. This may have implications for future treatment, and for the prediction of the disease [12]. The literature also includes other genetic factors, i.e., Turner or Down syndrome [13][14].

3.3. Hormonal Theory

One of the most popular theories concerning the etiology of vulvar lichen sclerosus was also the hormonal background of the disease, especially the theory that suggests hypoestrogenism as a risk factor. The two peaks of incidence, one in pre-pubertal and the other in postmenopausal women, indicate the possible connection with low levels of estrogen during those periods of their life. However, there are not enough studies to prove this theory. In the past, there were also attempts to treat VLS with testosterone, as it was assumed that there was a local testosterone deficiency in the affected tissues [15]. To date, there is also not enough evidence proving this theory. The hormonal role seems to be disputable, and its significance has been falling in recent years. The increased risk of VLS in Turner syndrome, despite the use of HRT (hormone replacement therapy) and contraceptive pills, points to the disputable role of hormones [13].

3.4. Trauma Theory

At this point, it is also worth mentioning other factors that are considered to be predisposing to VLS. Some authors take into account local components. One of the well-established signs of vulvar lichen sclerosus is the Koebner response. If the skin is traumatized by a physical factor, lesions following the line of trauma appear [13]. Therefore, repeatable irritation is believed to be a possible factor contributing to the disease. Another possible causal factor may be radiation [16][17][18].

3.5. Infectious Theory

Moreover, it should be mentioned that the infectious etiology of vulvar lichen sclerosus was considered multiple times in the past. Although there was much interest in Borrelia burgdorferi and human papilloma virus (HPV), those theories were later disproved [19].

Recently, it was noted that the bacterial environment of the skin and intestines may contribute to the development of the condition. Chattopadhyay et al., in a pilot small-sample study (n = 13), showed promising results in this matter. They suggest that there may be a relation between intestinal and cutaneous dysbiosis, and the disease in children, although this needs further investigation [20].

3.6. Drug-Induced Theory

There is not much evidence about drug-induced VLS, although some authors report that carbamazepine and imatinib may contribute to the disease. Yet, interestingly, imatinib is an inhibitor of the tyrosinokinase in the cells affected by the condition, and its use is being investigated as a potential treatment method [21][22]. On the other hand, some hypertension drugs, such as ACE inhibitors (angiotensin-converting enzyme inhibitors) or beta-blockers show an inverse relationship with VLS [23].

4. Symptoms

The vulvar lichen sclerosus course is very heterogeneous; therefore, it causes diagnostic difficulties. The first symptoms are usually very non-specific and misdiagnosed by non-gynecologist and non-dermatologist doctors, thus, the time between the first examination and the definitive diagnosis may be prolonged over the course of many years [24]. Lagerstedt et al. (2013) claim that only 16% of those with VLS are diagnosed in the early stage of the disease [25]. The average age of symptom onset in girls with vulvar lichen sclerosus is 7.1 years. The average delay from symptom onset to diagnosis is 1.3 years [26].

The most common symptoms that are reported by the patients are itching, edema and a burning sensation of the vulva, accompanied by perineal pain, vaginal bleeding, dysuria, and constipation [4][27]. Further, 86% of the patients report pruritus. This particular symptom often exacerbates in the late evening hours, leading to children's exhaustion during the day. The excessive genital rubbing can lead to tearing the delicate skin, which can result in bleeding. Some of the patients present an asymptomatic course of the disease. In 30% of girls with VLS, the definitive diagnosis is delayed by ongoing vulvar infections [1][2].

In physical examination, we can detect clearly demarcated white skin lesions, which have a characteristic shape that can be compared to the "Figure 8" or the hourglass (lesions involving the labia minora, clitoral hood, and perianal region). The skin on the labia majora, clitoris, and in the anal area is atrophic, smooth and shiny [2]. **Figure 1** presents characteristic signs of VLS. We can also observe erosions, blistering lesions, scars, adhesions and bruises. It may often be incorrectly recognized as a sign of sexual harassment, but one has to remember that those two cases do not exclude each other [21][28]. In the case of bruises in the intimate areas, the factors that should raise suspicion of sexual abuse are as follows: the appearance of lesions in older girls before puberty, poor response to the treatment, and the coexistence of other infection features that may suggest the presence of sexually transmitted diseases. Occasionally, the complication of dilated veins in the perineal area may also present a similar clinical picture [29][30][31][32][33]. The above-mentioned can result in labial resorption, adherence of opposing labia, covering of the clitoris, and narrowed vestibule of the vagina. Perianal involvement is a frequent finding in young girls who may present with constipation because of painful fissuring in this area. Dysuria can also result from fissuring. One single study indicated that 10 out of 15 (66%) girls with VLS presented with perianal lesions, and the incidence of perianal lesions is much higher in female patients, including children [21]. What is important is that the extent of the anogenital lesion does not correlate with the intensity of the symptoms; thus, small lesions may result in significant complaints [22].

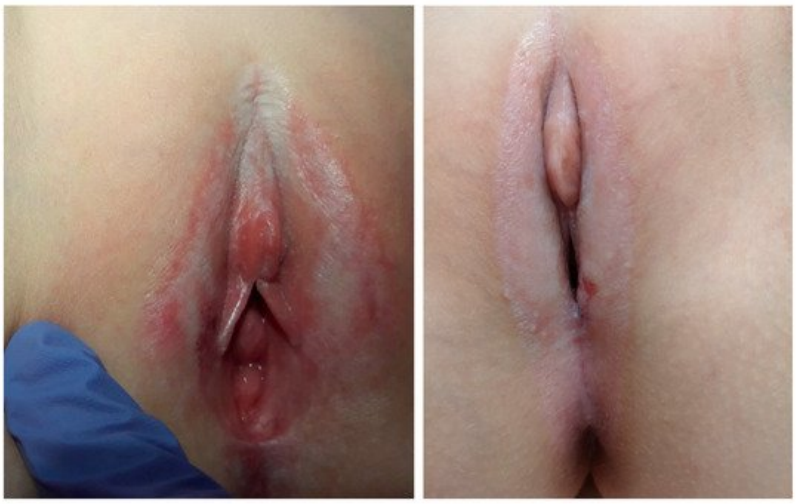

Figure 1. Classic vulvar lichen sclerosus in young girls (two cases)—own material.

In the case of eruption outside the anogenital area, these lesions can appear anywhere on the body—usually in the back, chest and breast areas, as white flat lumps that may coalesce to a form of larger foci with a shiny porcelain surface; sometimes they are surrounded by a purple halo. Less common sites include the mouth, face, scalp, hands, feet and nails [14]. As we mentioned before, the typical lesions are porcelain-white plaques, which, similarly to the genital lesions, may have follicular dells and areas of ecchymosis. It might be difficult to distinguish the lesions from those of morphoea. The clinical types of extragenital VLS include an extensive bullous form [17][19] and annular, blaschkoid and keratotic variants [20]. Koebnerization is very common at extragenital sites, arising at pressure points, old surgical and radiotherapy scars, and sites of trauma, including urostomies [16].

5. Complications in the Course of Vulvar Lichen Sclerosus

In the entire population of VLS patients, 2.6–6.7% will undergo neoplastic transformation, which is the result of chronic inflammation, altered expression of the p53 oncogene, and oxidative stress [34][35]. It should be emphasized that in pediatric patients, the incidence of vSCC is lower than in the rest of patients with VLS, and it amounts to approx. This occurs due to the pathogenesis of the neoplasm and additional risk factors—mainly age. However, the study by Halonen et al. showed that the early age of VLS diagnosis is an additional risk factor for this complication [36].

In patients with vulvar lichen sclerosus, scars and deformities of the affected areas are observed more often. It has not been determined whether the early treatment initiation improves the prognosis for the occurrence of these complications. The described changes may coexist with chronic pain and itching, significantly worsening the quality of life. In sexually active patients, penetration difficulties and dyspareunia may appear [21][36].

The narrowing of the vulval vestibule may occur as a result of the fusion of the labia. If this produces the inability to have sexual intercourse or causes problems with urination, surgery may be necessary. Topical steroids and dilators can help in the postoperative period, by preventing re-deformation. Occasionally, the clitoral adhesions result in the formation of a painful pseudocyst, which is also a condition requiring surgical intervention [37].

As a result of the inflammatory condition in the course of VLS, sensorial disturbances in the vulva may develop and lead to vulvodynia. These symptoms may persist during and after the treatment. Pain sensation is not reduced by treatment with glucocorticosteroids. In such a case, the patient should be offered a treatment aimed at neuropathic pain [37].

6. Diagnosis

The differentiation of symptoms in the course of vulvar lichen sclerosus causes great diagnostic difficulties. In only 16% of cases, girls are diagnosed with vulvar lichen sclerosus in the initial stage of the disease. Changes in the course of VLS may imitate the clinical symptoms of many dermatoses. The differential diagnosis of vulvar lichen sclerosus includes lichen simplex chronicus, lichen planus, eczema, psoriasis, atopic dermatitis, seborrheic skin lesions, vitiligo, sexual harassment, vulvar injuries, and linear IgA disease of the childhood (chronic bullous dermatosis) in cases when VLS presents with bullae [38].

In most cases, the diagnosis is made on the basis of a thorough medical history interview with the patient/guardian, and as the result of a physical examination. This is particularly true in children and men. However, the histological examination is recommended if there are atypical features or diagnostic uncertainty, and it is essential if there is any suspicion of a neoplastic lesion. It is important to remember that vulva biopsies are reserved for doubtful cases, especially when there is no improvement after treatment [21][37][38].

According to the guidelines of the British Dermatological Society, skin biopsy should be performed in the following cases (taking material for histopathological examination, with particular emphasis on hyperkeratotic lesions):The disease fails to respond to an adequate treatment, or an alternative/additional therapy with a potent topical steroid is to be implemented;There is an extragenital lichen sclerosus that has features mimicking the morphoea;There are pigmented areas to exclude abnormal melanocytic proliferation;There is a suspicion of neoplastic lesion. These are usually lesions with a persistent area of hyperkeratosis, erosion or erythema, or new warty or papular lesions. Several mapping biopsies may be required if there is an extensive abnormality. If there are any lesions that are highly suspicious of an SCC, the patient should be referred urgently to a gynecologist for the excision of the whole lesion for an adequate staging [37].

As we mentioned before, in children, a vulval biopsy is usually not performed, because it may be very traumatic for the child. It should be reserved only for cases with an uncertain diagnosis, and for those who fail to respond to treatments [39]. The typical histological features of VLS are orthohyperkeratosis, epidermal atrophy, basal cell degeneration, dermal hyalinization, and a band-like lymphocytic infiltrate [21].

7. Pharmacotherapy

In the natural course of vulvar lichen sclerosus, periods of remission and relapse are observed. In the absence of VLS remission symptoms in children until puberty, the prognosis is uncertain and may be associated with the lack of full recovery. The main goal of pharmacotherapy for vulvar lichen sclerosus is to alleviate the bothersome clinical symptoms, and prevent complications such as scars and adhesions [38]. **Table 1** summarizes VLS treatment options with their effectiveness and side effects.

Table 1. Management for pediatric vulvar lichen sclerosus.

Treatment	Effects	Side Effects
High-potency corticosteroids	• 0.05% ointment containing clobetasol propionate—“golden standard”; • 65–100% improved; • complete reversal of signs in 20–70% (55% are without continuous treatment); • treatment well tolerated.	**Prolonged use of topical steroids can be associated with:** • thinning of the dermis; • secondary superimposed infections; • erythema; • rarely hypothalamic–pituitary–adrenal axis suppression.
Calcineurin inhibitors—tacrolimus, pimecrolimus	**Tacrolimus 0.03% ointment:** • complete response in 79% after 10 months; • individual approach to each adolescent patient; • maintenance treatment necessary. **Pimecrolimus:** • effective in majority (relief of itch); • no effect on sclerosis.	• side effects of TCIs included stinging and burning; • concern for the use of TCIs stems from the intrinsic malignant potential that TCIs may increase the risk of SCC development in patients with LS especially with long-term use (not recommended for use in children under two years of age).
Retinoids	• not recommended for monotherapy treatment; • the resolution of symptoms and disappearance of skin lesions; • 76% of patients no longer suffered from itching.	**No report.**
Topical sex hormons	**No report in children.**	**No report.**
Cyclosporine	**In patients with refractory VLS with symptomatic improvement and decrease in erythema and erosions after one month of therapy.**	• no side effects observed; • limited data.
Phototherapy	**No report in children.**	**No report.**
Vitamins D, A and E	**Additional data are needed to assess the usefulness of vitamin supplementation in the treatment.**	**No report.**

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