

Review

Lichen Sclerosus et Atrophicus in Children

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Abstract

Observations: Lichen sclerosus (LS) is an inflammatory sclerotic skin disease of unknown origin. It affects all age groups and mostly involves the anogenital region. Childhood LS represents approximately 15% of total cases of the disorder and is seen in a 10:1 ratio of females to males. The etiology is unknown, lesions usually appearing spontaneously without any precipitating factor. Several mechanisms have been studied and suggest a multifactorial origin, including a genetic, autoimmune, hormonal and infectious background. Anogenital LS can be presented with a variety of symptoms. Pruritus and soreness are the most common symptoms reported by patients with LS. There is a variety of opinion for treating LS. Some guidelines still recommend a 3 month therapy with ultra potent topical steroids as the first line treatment of anogenital LS. Latest studies reveal the successful treatment of relapsing severe anogenital LS with topical tacrolimus and pimecrolimus. This review aims to give an overview of LS in children and to enlighten about some of the new approaches, made on the pathogenesis and especially on its treatment.

Introduction

Lichen sclerosus (lichen sclerosus et atrophicus: LSA) was first described by *Hallopeau* in 1887 and its typical histology defined by *Darier* in 1892 [1].

Lichen sclerosus (LS) is an inflammatory sclerotic skin disease of unknown origin. LS affect all age groups and mostly involving the anogenital region [2]. Major subjective complains are severe pruritus, dysuria, painful defecation and vaginism. LS is characterized by porcelain-white sclerotic plaques. Histological features include orthokeratotic hyperkeratosis, vacuolar degeneration of basal layer, edematous and sclerotic papillary dermis as well as lymphohistiocytic infiltrates in the mid-dermis. The

disease has a relapsing course indicating and ongoing inflammatory process. Although the exact pathogenesis of LS is still unclear, the recognized active involvement of skin immune system (e.g., activated T cells and CD1a+/HLA-DR+ dendritic cells) and the association with autoimmune disease and HLA DQ7 in women and girls with LS suggests an immunogenetic component to the disease [2, 3].

Epidemiology

LS may occur at any age and either sex. 10-15% of effected individuals have the onset before the age of 13, and 70% of childhood cases begin before age 7 [4, 5]. The youngest reported case was several weeks of age. The disease is not inherited, although famil-

ial cases have been reported [4]. There may also be a family history of autoimmune diseases including vitiligo, morphea, psoriasis and thyroid diseases [4, 6, 7].

Lichen sclerosus et atrophicus is more common among females with two distinct peaks: in the fifth to sixth decade and prior to puberty [8]. In 130 prepubertal girls reporting to a pediatric dermatology clinic with a vulvar complaint, 18% of them had LS [4, 9]. Genital LS in males occurs between the ages 15 and 50, more commonly in young men and, occasionally, in pre-adolescent males and it can be detected in significant proportion of phimosis in adulthood [4, 10].

The condition has been seen in mother and daughter, mother and son, brother and sister but not in father and son. It has occurred in monozygotic female twins and in non-identical female twins. It is uncommon in black people [11].

Etiology and Pathogenesis

The etiology is unknown, lesions usually appearing spontaneously without any precipitating factor [11]. Several mechanisms have been studied and suggest a multifactorial origin, including a genetic, autoimmune, hormonal and infectious background. Also a fibroblast dysfunction with increased collagen production probably caused by TGF- β was proven [12, 13, 14].

There is an established association between lichen sclerosus and autoimmune disease in adult patients and first-degree relatives and a higher incidence of autoantibodies in both adults and children with LS. Children with autoimmune disease show a stronger HLA associations than their adult counterparts [3]. One study demonstrated that the association with HLA-DQ7 is 66% in female children with LS [3, 14]. In another study it was found that HLA-DR and DQ antigens or their haplotypes appear to be involved in both susceptibility to and protection from LS [15].

In a recent study made by *Földes-Papp et al* [16] an extensive analysis of immune parameters associated with various autoimmune diseases in the context of LS was evaluated. A lack of any clear association between vulvar LS and any of these parameters was observed.

Besides this an autoimmune connection has been detected in connection with LS, as an auto-antibodies against extracellular matrix protein (ECM-1) [12, 17].

Several attempts have been made to identify an infectious organism as a causative factor in LS pathogenesis. Although acrodermatitis atrophicans is clearly a manifestation of *Borrelia burgdorferi*, and shares some clinical and histological resemblance to LS, to this days no clear data has shown that LS is related to an infectious organism [14].

Although Ls can express itself at any age, there is a clear predominance in prepubertal girls and postmenopausal women. This knowledge leads to the hypothesis that hormones might play a role in LS pathogenesis but we see that treatment with topical testosterone has been evaluated and abandoned shedding doubt on an etiological link between LS and androgens. There is no known association between estrogen metabolism and LS [14].

The histology is distinctive. A skin biopsy shows thinning of the epidermis, vacuolar changes at the dermal-epidermal junction, marked edema of the papillary dermis, and a lymphohistiocytic infiltrate that is band-like and beneath the edematous zone [4]. Other characteristic findings are hyperkeratosis with follicular plugging and homogenization of collagen in the upper dermis [14]. Vulvar LS may have histologic variants; the minimal histologic criterion for LS is vacuolar interface changes in conjunction with dermal sclerosis [4].

Immunohistochemical studies have helped to characterize the inflammatory infiltrate found in vulvar LS by using monoclonal T-cell markers, macrophage markers, and HLA-DR staining. Both CD4+ and CD8+ lymphocytes were demonstrated in the band-like infiltrate with a ratio of approximately 1:1.16 The inflammatory dermal infiltration contains CD8+, CD57+ positive lymphocytes that are in general signs for chronic antigen stimulation. Some mast cells can be found also [12]. Androgen receptors are reduced. Fibrillin, collagens I and III and elastin are all abnormal. The distributions of tenascin, fibronectin and fibrinogen are abnormal also. In leukoplakia, there is some degree of hyperplasia of the epidermis with irregularity in the outline of the deeper border, together with some hy-

perkeratosis. The collagen of the superficial part of the dermis shows hyaline changes and elastic tissue is lost.

In vulvar lesions, secondary infection and superficial erosion are common, and may mask the primary changes. In lesion with sclerotic change, the epidermis shows marked thickening, irregularity and hyperkeratosis. The dermal edema tends to regress and sclerosis and dense chronic inflammation occupy the subepidermal zone [11].

Clinical Features

Lichen sclerosus most commonly affects the anogenital area (85-98% of cases), with extragenital lesions in the 15-20% of patients [18].

Childhood LS represents approximately 15% of total cases of the disorder and is seen in a 10:1 ratio of females to males [19, 20]. One study of pediatric vulvar LS reported a prevalence of 1:900, with a mean symptom onset of 5.0 years but a mean age at diagnosis of 6.7 years [6]. In another study the age on set was found to be 4.2 years, with a mean age at diagnosis of 5.2 years [19].

Anogenital LS can present with a variety of signs/symptoms (itching, soreness, purpura, dysuria, constipation, pain on defecation, soiling, perianal fissures, bleeding). Pruritus and soreness are the most common symptom reported by patients with LS [14, 19]. A study of 70 pediatric patients reported itching and soreness in 80% of them [6]. Another recent study found itching to be the most frequent complaint; it was reported in 14 (78%) of the 18 subjects. However, constipation and other gastrointestinal related complaints were also prevalent. Twelve of the 18 (67%) patients reported being constipated, and 16 of 18 (89%) had at least one other gastrointestinal complaint (bleeding with bowel movements, pain on defecation, fissuring, soiling, fecal impaction, or constipation) [19].

Observed skin changes include areas of pallor, which may be small polygonal patches or large plaques, thinned, atrophic, wrinkled, fragile skin with possible telangiectasia, purpura, erosions, tender fissures in the labial sulci and perianal area and rarely hemorrhagic blisters.

In prepubertal girls, as in adults, pruritus and soreness are the most common presenting symptoms [18]. A vaginal discharge may precede the vulvar lesions in approximately 20% [11]. There may be dysuria, and painful anal fissures that lead to constipation. The signs of LS in girls may be confused with those of sexual abuse; vulvar and perianal bruising, erosion, and fissures on a background of pallor, scarring and increased likelihood of infection and mistaken accusations have been made [18, 21]. However, sexual abuse and LS can coexist. The *Koebner* phenomenon occurs in LS, scarring or trauma may induce typical skin lesions of the disorder, and extragenital lesions commonly occur in pre-existing scars and damaged area. Sexual abuse and its associated trauma, injury, and infection may trigger the onset of LS. At menarche, symptoms and signs of the disease improve spontaneously in some cases, but there is not a precise data to show whether these girls are at long-term risk of LS, with the associated risk of vulvar cancer in later life [18].

In approximately 5% of cases the lesions are solely outside the anogenital region, and in just over 10% lesions are found both in anogenital region and elsewhere [11].

Balanitis xerotica obliterans (BXO), a genital form of LS in males may effect the foreskin, glans penis, frenulum and meatus urethra. Preputial balanitis xerotica obliterans is readily diagnosed clinically by the characteristic severe phimosis with sclerotic scarring of the preputial orifice that is sometimes accompanied by sclerogenous glandular lesions [22]. The glans and under surface of prepuce are shining and bluish white, and there can be considerable telangiectasia. There may be back pressure affecting the urinary tract, demonstrated by urography, as a result of meatal closure. This may require surgical correction [11].

It has been shown that childhood BXO is a relatively common cause of phimosis, with the incidence of 10% to 19% [22]. A lot of authors have suggested that BXO might be more frequent than was indicated in previous studies; however, its true incidence is not known, because this condition has been insufficiently recognized and tissue removed at circumcision is rarely examined histologically [18, 22]. In a large study made

recently by Kiss et al [22], in 471 patients with histologically confirmed BXO out of 1178 consecutive patients (40%). The mean age of patients with BXO was 8.7 years, with the highest incidence in those aged 9 to 11 years. The youngest boy with BXO was 2 years old. Of the BXO patients, 438 (93%) had secondary phimosis (acquired phimosis after a period of well retractability of a normal foreskin), while in the boys without BXO, secondary phimosis appeared in 236 instances (32%) and those showed nonspecific chronic inflammation [22].

The apparent absence of perianal lesions in boys (and adults males) contrasting with their frequent presence in females of all ages is interesting [1, 11, 18].

Prognosis

The prognosis of childhood vulvar LS remains unknown [19]. Powell and Wojnarowska [23] followed 21 girls through puberty; 16 patients had an improvement of symptoms, but 11 of them still required topical corticosteroids to treat pruritus. Sixteen of the 21 still had physical signs of LS including pallor, atrophy, labial resorption, and purpura [19, 23]. In another report by Powell and Wojnarowska [6] 18 children were followed through puberty and only 2 had complete remission. These studies concluded that LS may improve symptomatically but may not resolve entirely at puberty [6, 19, 23].

Extragenital lesions usually clear before menarche. In approximately two-thirds, anogenital LS involutes before or around the menarche [11]. In children in whom the disease does not involute, atrophy of the clitoris and labia minora may occur, sometimes with fusion of the latter and stricture of the introitus. The disease may be reactivated years later in patients who have improved, especially during pregnancy or after the use of oral contraceptives. Males with LS of the glans may require urethral dilation, meatomy, and circumcision in childhood, adolescence, or adulthood [2]. Premalignant changes and squamous cell carcinoma may develop [11].

Treatment

There is a variety of opinion for treating LS. The British guidelines still recommend a 3 month therapy with ultra potent topical

steroids for the treatment of anogenital LS.

However, a randomized evidence-based study has not yet confirmed this [12].

Clobetasol propionate 0,05% is recommended treatment in UK. Alternative effective topical steroids include beclomethasone dipropionate and diflucortolone valerate. The treatment rapidly improves the intense pruritus and gradually resolves the hyperkeratosis, ecchymoses and white plaques that give a crinkled appearance to the skin. Scarring process are not recovered but phimosis can be reversed.

Some cases of LS do not respond to a potent steroid particularly if there is marked hyperkeratosis clinically, or acanthosis histologically. In these patients an oral or topical retinoid may be used in combination with topical steroid [24]. There are some reports to treatment with laser therapy [24, 25]. Some other treatment tried are cryotherapy and more recently photodynamic therapy. Childhood LS failing to respond treatment should raise suspicions of other factors including the possibility of sexual abuse [24].

In a recent study of Cooper et al [26] Response to topical steroids treatment was recorded in 255 patients. In 244 patients (96%) symptoms improved with treatment, as 168 (66%) became symptom free and 76 (30%) showed partial response; 11 (4%) had poor response. Topical ultra potent steroid is an effective treatment, giving relief of symptoms in most and completely reversing the skin changes in approximately one fifth of patients. Ultra potential topical steroids have the potential to cause atrophy, and skin thinning may last for up to 14 days after application in normal skin. The extent to which topical steroids applied intermittently may contribute to skin thinning is uncertain as atrophy is a part of LS process [26].

Latest studies reveal the successful treatment of relapsing severe anogenital LS with topical tacrolimus [2, 12, 13]. A successful treatment with low-concentration topical tacrolimus ointment has been reported also [27]. Another important multicentre study was made by Hengge et al in 84 patients; 49 women, 32 men, 3 girls. The patients were treated with topical tacrolimus ointment 0,1% twice daily for 16 weeks. The primary endpoint (clearance of active lichen

sclerosus) was reached by 43% of patients at 24 weeks of treatment. Partial resolution was reached in 34% of patients. As a result topical tacrolimus ointment 0,1% was found safe and effective for the treatment of long-standing active lichen sclerosus [28].

Another new treatment choice is topical pimecrolimus. Böhm et al [29] reported the efficacy of twice-daily application of 1% pimecrolimus cream in four prepubertal girls. Goldstein et al [30] reported a case of LS in a premenarchal girl, who was treated with clobetasol initially but she had a recurrence after three months of her remission. She was then treated with pimecrolimus and remission was achieved and she had no recurrence.

In boys topical corticosteroids, sometimes for short periods under a condom, or intralesional injections of triamcinolone may soften the sclerotic lesions of BXO and reduce phimosis. Circumcision may be helpful or even curative if only the foreskin is involved.

Radical surgery may also be required if carcinoma develops. Surgery may also be required for severe narrowing of the introitus [11].

There is no confirmed effective treatment for extragenital lesions. Calcipotriol may be helpful and low-dose UVA-1 has been reported to be of benefit. Mycophenolate mofetil was dramatically effective in one severe case seen by the authors [11].

However, even by a consequent treatment not all of the complications associated with LS could be avoided [12].

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