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Anogenital Lichen Sclerosus: Literature Review and 12-patient Clinical Series in Children

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Abstract---

Background and Objectives: *Anogenital lichen sclerosus is of infrequent occurrence in children. The presented research is aimed to verify clinical features and treatment approaches to anogenital lichen sclerosus in children and adolescents.*

Methods: *We conducted a retrospective analysis of clinical presentations and treatment response of 12 patients with anogenital lichen sclerosus; all stages of the study were retrospectively registered.*

Findings: *41% of the patients had extragenital morphea. 3 children were successfully treated with tacrolimus 0.03% ointment, due to the resistance to local steroid treatment the others received systemic therapy with corticosteroids, penicillamine or methotrexate; the remission was gained in all cases.*

Conclusions: *Children with anogenital lichen sclerosus often have extragenital morphea backgrounded by immunological activity. The data suggest that step changing therapy in anogenital lichen sclerosus should start from local topic steroids and tacrolimus ointment, followed by systemic immunosuppressive medications.*

Keywords--- *Clinical Series, Literature Review, Anogenital Lichen.*

I. INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory dermatosis of the dermal papilla, characterized by the ivory-white papules and plaques, often with central atrophy. Clinical presentations of LS were first described in 1889 by the French dermatologist François Henri Hallopeau; histology pattern of the condition was defined by the French dermatologist and pathologist Ferdinand-Jean Darier in 1892.

The histology of LS is characterized by a thin flat epidermis, a sub-epidermal zone of oedematous and hyalinized collagen. It is still not established whether LS and localized scleroderma (ScL) belong to associated conditions of scleroderma spectrum diseases. Several investigators have reported (via sequential biopsies) a transition from LS to morphea or vice versa [1], while others report strong clinical and histological differences between LS and ScL [2, 3]. A. Kreuter [4], in a study with 472 patients with LS, found that the frequency of LS in patients with ScL was way above average. Another research [5] reports immunohistochemical similarities in biopsy specimens in a woman with LS accompanied by morphea.

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The etiology of LS is unknown. There is evidence of LS association with human papillomavirus infection and spirochete Borrelia burgdorferi, hormonal phenomena, and trauma [2]; genetic factors and autoimmunity are also implicated. Immunological changes on the level of T and B cells have already been described [5]. 20-30% of women with LS are reported to have autoimmune diseases, such as thyroid diseases, vitiligo, inflammatory bowel diseases, rheumatoid arthritis, morphea or psoriasis [6].

LS may affect all areas of the body, but typically it occurs in the genital area. Extragenital LS is less common: data vary between 6 to 20% of the general population [6]. Approximately 5-15% of LS cases occur in children [7]. Anogenital lichen sclerosus (AnLS) may result in severe complications, such as labial adhesion and intra-uterine stenosis, which should demand surgery in adults [8]. Squamous cell carcinoma of the vulva carries a well-recognized risk of AnLS in adults, with an estimated lifetime risk of up to 5%. There are also some reports of carcinoma in young adults, suspectedly untreated since childhood, [9].

AnLS is more prevalent in females than males, with a ratio of 10:1.4. It has bimodal age distribution in females, with a peak incidence in prepubertal girls and postmenopausal women. AnLS is quite rare in childhood, with an estimated prevalence of at least 1 in 900 children. The disease affects girls more frequently than boys. The appearance of symptoms of AnLS in children usually occurs at the ages between 2 and 5. The incidence of spontaneous remission in girls is estimated at 25%. Disease activity is likely to be reduced in puberty [7], but it rarely goes into complete remission.

AnLS in children manifests initially with slight redness, followed by depigmentation of the skin; hyperkeratosis, atrophy of skin and lacerations usually occur later in the course of the disease. AnLS in children may exist without pain and itching; complaints are associated only with patients with secondary infection of vulva, dysuria or constipation [10]. AnLS in boys is highly associated with phimosis and meatal stenosis, so it is reasonable to perform circumcision as a potential treatment approach [11].

Based on Evidence-based Guideline on AnLS (2015), biopsies should be performed if the clinical diagnosis is uncertain, malignancy is suspected or if the therapy has failed [12].

Currently, there is no single strategy for the treatment of AnLS.

The recommended initial treatment for AnLS is a three-month application of potent to ultra-potent topical corticosteroids [13]. Randomized studies had demonstrated that the application of topical corticosteroids significantly improves the condition in 75% - 90% of the patients, as compared with roughly 10% in placebo groups.

A full circumcision is suggested if the treatment with topical steroids in male patients with AnLS does not lead to remission; this procedure is reported to lead to permanent, lifelong remission in 90% - 100% of the cases [13].

Calcineurin inhibitors (tacrolimus and pimecrolimus) are second choice treatment options. The effects are inferior to those of topical corticosteroid [12]. Treatment with sex hormones in women – especially with testosterone – is rather less effective than corticosteroids.

Systemic treatment is indicated in refractory cases. A retrospective study of the use of pulsed steroid and methotrexate (MTX) [14] showed an improvement after an average of a 3-month treatment in AnLS cases. Patients

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received an oral dose of MTX 15 mg/wk with high-dose intravenous methylprednisolone (1000 mg), given for three consecutive days monthly; the treatment was administered for at least 6 months, the improvement was reported for all the indicators. Generalized LS involving the skin and anogenital site was successfully treated with systemic MTX 10 mg/week for 8 months; at the 6-month follow-up, the patient was still in remission. Improvement was reported in 3 weeks and an excellent response was clear after 5 months [15].

II. METHODS

We used a retrospective analysis of 12 cases of AnLS patients, who received treatment at our rheumatology department. The study was approved by the local Ethics Committee of The First Moscow State Medical (Sechenov) University.

9 out of the 12 patients (No. 1-9, Table 1) were previously unsuccessfully treated with local applications of corticosteroid ointment, skin care products, laser therapy and/or electrophoresis with lydasum. The age of the patients at the time of the disease onset varied from 3 to 13 years *(M=5.2±2.08).* There was only one male patient in our series (female\male ratio 11:1, Table 1), his LSAn onset was at pubertal age, while the manifestations of AnLS in girls occurred from the age of 3. Mean duration of the disease before AnLS was diagnosed was 2 years 3 months. Extragenital scleroderma lesions (active generalized or circumscribed morphea) were found in 5 out of 12 cases (41%) backgrounded by an elevated level of antinuclear antibodies (ANF) or positive rheumatoid factor. Extragenital scleroderma plaques were located mostly in the lower abdomen and inguinal region (Fig.1); however, one patient had a plaque on the neck (Fig.2). Clinical presentations of morphea and AnLS were recorded simultaneously. In 3 cases AnLS was diagnosed for the first time at the doctor's examination, while the parents had not previously noticed the lesions. Also, no systemic manifestations of scleroderma were detected; in all cases, lesions of the anogenital zone appeared with induration or intensive fibrosis. In 10 patients (83%) lichen lesions outbreak impacted both vulva (penile) and the anus area (Fig.3). None of our patients suffered from urinary tract infection or chronic constipation; the chief complaint was itching (50% of cases). One girl complained of pain during urination and defecation due to induration of lesions in perineum; the others have not experienced any discomfort. Among our patients were also female siblings, developed AnLS at the age of 3 and 4, with similar lesions of clitoris and labia minor. The diagnosis was uncertain by clinical presentations; however, we did not perform skin biopsies in order to minimize distress in children.

Due to several circumstances, the treatment varied: patients No 1, 2, 3 received systemic treatment with oral prednisolone (Pr) (0.5 mg/kg body weight) for 4 weeks, then withdrawn and followed by penicillamine (8 mg/kg body weight) for 2 years. These girls were admitted to our department in 1999-2000 when we had neither experience of MTX treatment of morphea, nor tacrolimus ointment available at our disposal. The previous local therapy had failed and the lesions were presented with intensive spread, induration, and fibrosis (Fig.4) of the anogenital zone. In all these cases, positive changes were noticed within a month of therapy, including the reduction of redness and edema. In 12 months the fibrotic lesions significantly reduced and in 24 months the vulva looked normal. There were no relapses within the 2-year follow-up period without treatment; the girls had experienced menarche within the appropriate timeframe (Fig.4).

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For the other 2 female patients (No 4, 5) with AnLS accompanied by morphea and immunologic disease activity, the treatment was oral Pr 0.5 mg/kg daily for 4 weeks followed by MTX 12 mg/b.sq weekly for 24 months.

The AnLS and morphea female patient No 6 had short disease duration, but she also presented with obesity, so we initiated MTX monotherapy. In 12 months we recorded the intensive reduction of AnLS lesions; she was up to full remission in 24 months.

MTX monotherapy parentally for 2 years was used in 2 girls with AnLS without morphea with good results as well; 1-year follow-up showed no exacerbations.

We used local therapy with tacrolimus 0.03% ointment on patients No 10, 11, 12 (among them was the only male patient) with significant success. The 13-year-old teenager with LS on the glans penis received tacrolimus 0.03% (8 weeks) with a good response; however, this patient dropped out at a later stage. Penile kraurosis and lesions after treatment can be seen in Figure 3. The girls received the treatment twice a day for 12 weeks, then once a week for 2 months. The effect of tacrolimus application was noticed in 2 weeks; the reverse of signs of AnLS was recorded after 8-10 weeks (see Figure 5).

III. Results

The described clinical series of 12 children with AnLS were heterogeneous for treatment approaches. In resistant cases we used Pr with MTX or penicillamine with positive effect, in the other cases, the local tacrolimus was proven to be successful.

IV. Discussion

AnLS is a rare condition in children, which occurs in girls more often than in boys; the same goes for lichen striatus and planus [16, 17]. It has interdisciplinary character and the awareness of pediatricians and general practitioners on AnLS in children serves to help in making a timely diagnosis and avoid possible complications. Medical practitioners should not pass over the routine examination of the whole skin surface including the anogenital zone since AnLS and morphea usually coexist.

Our somewhat modest treatment experience of AnLS nevertheless testified that all the patients in our series were resistant to local therapy with topical steroids; 41% of participants had AnLS accompanied by morphea of the trunk. On one hand, the use of a systemic treatment may be considered to be aggressive, which is probably influenced by rheumatology profile of our department; on the other hand, it was quite well tolerated and resulted in remission in all the cases observed.

The local therapy should be clearly the first choice medication in the treatment of children with AnLS without concomitant morphea. Still, cooperative interdisciplinary investigations are needed for developing a treatment strategy for children with AnLS, including indications for systemic immunosuppressive therapy.

A thorough examination of the skin and mucosa helps to make a timely diagnosis. Modern therapy of AnLS is stepwise, starting with local topic steroids and tacrolimus ointment, followed by systemic steroids and MTX in case of treatment resistance.

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V. CONCLUSIONS

AnLS in children could cause severe complications, so timely diagnosis and stepwise therapy, first and foremost with local topic steroids and tacrolimus ointment, or, with the usage of systemic steroids and MTX in case of poor response, significantly improves the disease prognosis.

Table 1: Characteristics of Patients with AnLS.

No. / Gender	***Physiological age***	***Age at the onset of the disease***	***Extragenital skin manifestations***	***Serum Antibodies***	***Treatment***	***Efficacy***	***Follow –up period***
1. F	7	3	Circumscribed deep morphea	1:160	Prednisone 0.5mg/kg + Penicillamine 8 mg\kg	good	6 years
2. F*	11	3	_	_	Prednisone 0.5mg/kg + Penicillamine 8 mg\kg	good	4 years
3. F*	12	4	_	_	Prednisone 0.5mg/kg + Penicillamine 8 mg/kg	good	4 years
4. F	6	5	Circumscribed deep morphea	ANF 1:320, RF +	Prednisone 0.5mg/kg + MTX 12mg/b.sq.weekly	good	5 years
5. F	9	8	Generalized morphea	ANF 1:640 RF +	Prednisone 0.5mg/kg + MTX 12mg/b.sq.weekly	good	1 year
6. F	8	7	Generalized morphea	ANF 1:640	MTX 12mg/b.sq.weekly	good	2 years
7. F	8	6	Generalized morphea	-	MTX 12mg/b.sq.weekly	good	1 year
8. F	9	6	-	-	MTX 12mg/b.sq.weekly	good	1 year
9. F	4	4	-	-	MTX 12mg/b.sq.weekly	good	3years
10. F	3	3	_	_	Tacrolimus ointment 0.03%	good	6 mo.
11. F	4	4	_	_	Tacrolimus ointment 0.03%	good	6 mo.
12. M	14	13	_	_	Tacrolimus ointment 0.03%	moderate	3 mo.

* Patients are siblings

VI. LIST OF ABBREVIATIONS

LS - lichen sclerosus

ScL - localized scleroderma

AnLS -anogenital lichen sclerosus

MTX - methotrexate

Pr - prednisolone

ANF - antinuclear antibodies

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