

Lichen sclerosus and atopy in boys: coincidence or correlation?

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Summary

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Background Lichen sclerosus (LS) is a sclerosing skin disease of presumably autoimmune origin affecting mainly the anogenital area. The aetiology is not completely understood. Comorbidity between genital LS and atopy in girls has been described but so far no controlled study has been performed.

Objectives A prospective epidemiological case-control study was designed to clarify if there is comorbidity between genital LS and atopic skin diathesis (AD) in boys. **Methods** The study included a total of 92 boys aged between 1 and 17 years. The disease group consisted of 48 boys who underwent surgery for phimosis that was histologically confirmed as LS. The control group included 44 boys who were circumcised for phimosis for other medical reasons. Both groups were examined and the parents were interviewed following the criteria of the validated Diepgen atopy score. Patients with a score > 9 were assumed to have AD.

Results Within the LS group (median age 8.7 years) 12 boys were diagnosed with AD (25%), while there were only three boys with AD (7%) in the control group (median age 5.3 years). The difference was significant using an age-adjusted logistic regression ($P < 0.05$). Prior to our study nine boys of the LS group (19%) and four boys of the control group (9%) had already been diagnosed with AD.

Conclusions We have demonstrated a significant comorbidity between LS and AD in boys. AD seems to be a priming precondition for the development of LS in boys.

Lichen sclerosus (LS) is a sclerosing dermatosis mainly affecting the anogenital area. Balanitis xerotica obliterans is the synonymous term that is predominately used by urologists to define the condition affecting the male genitalia, especially the foreskin.

LS is seen in both sexes and all ages and a predominance in girls has been reported. More recently it has been assumed that at least in prepubertal patients the rate of prevalence in both sexes could be as high as 1 : 1,¹ maybe because physicians of various specialties see patients of different ages and both sexes.

LS in boys is still an underestimated disease.²⁻⁴ Many young boys are circumcised for 'scarring' phimosis without histological verification of the diagnosis.^{5,6} Today it is thought that LS is an autoimmune disorder triggered by various factors. Especially in females a relationship between LS and other autoimmune disorders has been indicated.⁷ A few reports describe a relationship between LS and atopy in girls and women⁸ but all of these studies have been performed without

a control group and to our knowledge to date no study has investigated this correlation in boys. Thus, we designed an epidemiological prospective, single-centre, case-controlled study to clarify the comorbidity of LS and atopic skin diathesis (AD) in boys who underwent surgery for phimosis.

Patients and methods

Between September 2007 and June 2009 approximately 350 white-skinned boys were circumcised for phimosis in a single paediatric surgery clinic. The foreskin of every patient was histologically examined. Selection and randomization for the study followed the criteria of the supporting statistician. Group sizes were statistically determined after performing a pilot study with a small group of patients. The inclusion criterion for the disease group was histologically confirmed LS-related phimosis. The control group consisted of boys with a medical indication for circumcision due to chronic untractability of the foreskin without clinical or histological signs

of LS (Table 1). Circumcisions for religious reasons as well as cases with incomplete data sets were excluded from the study. As soon as surgery was scheduled topical steroid treatment was stopped to avoid influences on histological results. The time period until surgical intervention was at least 4 weeks. Follow-up in the control group was performed 4 months after circumcision and in the LS group 2 weeks and 4 months after circumcision, afterwards yearly. All of the circumcised patients with LS showed complete recovery within 4 months.

Participation in the study was done only with parental agreement. Prior to surgery parents and patients were given an information sheet according to the study approval of the ethics committee of the University of Bonn (study approval number 230/07). If patients and parents agreed to participate (disease group: 2 weeks after surgery after obtaining the histological result; control group: on day of surgery) boys were examined and parents were asked to complete a questionnaire according to the Diepgen atopy score.⁹ Atopy was assumed if the score exceeded 9 points. Familial predispositions for atopic diseases (allergies, hay fever, conjunctivitis, asthma and specific eczema) as well as for autoimmune diseases (diabetes, Hashimoto thyroiditis, vitiligo, psoriasis, alopecia areata) were queried.

Two pathologists performed histopathological examination in an unblinded fashion. LS was confirmed by epidermotropism of a lymphocytic infiltrate, sclerosing of the subepidermal corial layer and atrophy of the corium. Histological results were graded semiquantitatively as follows: (1) (early): sparse lymphocytic infiltrate with epidermotropism, small subepidermal corial sclerotic zone, no atrophy; (2) (intermediate): moderate lymphocytic infiltrate with epidermotropism, moderate subepidermal corial sclerotic zone, and low atrophy; (3) (late): dense lymphocytic infiltrate with epidermotropism, massive subepidermal corial sclerotic zone, advanced atrophy.

Clinically, LS was classified into three grades: 1, LS of the prepuce only; 2, LS of the prepuce and glans or meatus; 3, LS of prepuce and glans and meatus. Histopathological results in the control group revealed nonspecific dermal fibrosis without or with minimal/moderate inflammatory infiltrate without any correlation to the clinical findings.

All quantitative variables were collected by one observer. Statistical significance was determined with Microsoft Excel

2003 and SAS 9.1 software (SAS Institute, Cary, NC, U.S.A.) using the χ^2 or the exact Fisher test. Correlations between atopy score and LS were calculated using an age-adjusted logistic regression to avoid possible detection bias of the median age difference between disease and control group. $P < 0.05$ was considered to be statistically significant.

Results

Prior to surgery 49 of 50 histologically confirmed LS cases showed clinical signs. Two of the 50 boys with histologically confirmed LS had to be excluded for statistical bias (siblings). The boys were aged 1–17 years. Mean age of the LS group was 8.7 vs. 5.3 years for the control group. Of the 48 LS cases 35 (73%) had an acquired (secondary) phimosis (5% control) while nine boys remembered a penile trauma before onset of phimosis; 12 boys of the LS group (25%) were diagnosed with AD according to the Diepgen score (score > 9). In seven other boys AD was possible (score 8–9), and 29 boys had little or no signs of AD (score < 8).

The control group consisted of 44 boys, three of them with AD (7%), one with possible AD and 40 boys with little or no signs of AD (Table 2).

Of the 15 boys with AD (score > 9) 12 had LS (80%) and seven of the eight boys with possible AD (score 8–9) had LS, too (Table 2). Consequently, it was statistically significant that boys with LS had AD (score > 9) more often than boys without LS (score ≤ 9) ($P < 0.05$; Fig. 1).

Of all 92 patients 13 boys (14%) had a self-reported diagnosis of atopic dermatitis with nine of them (69%) also having LS. Interestingly, in two cases of formerly diagnosed atopic dermatitis the score was below 7 (no AD); one of these boys had LS. Atopic dermatitis, asthma and allergic rhinitis were significantly more frequently diagnosed in patients with LS ($P < 0.02$).

Frequencies of AD or autoimmune diseases in first-degree family members of both groups did not differ significantly. Among first-degree family members of patients with LS we found one with Hashimoto thyroiditis and insulin-dependent diabetes mellitus, and one with psoriasis; in the control group one with alopecia areata and three with psoriasis. These results were statistically not significant.

A significant correlation was observed between the histological stage of LS and the clinical classification ($P < 0.0001$; Fig. 2). A relationship between AD and histological findings or the clinical classification could not be shown.

Discussion

We show for the first time a significant comorbidity of LS and AD in boys with genital LS. In general, LS leads to a scarring phimosis with the consequent need for circumcision.⁴ The possibility of conservative treatment with clobetasol ointment has been reported¹⁰ but long-term results are still up for discussion.¹¹ According to our experience (unpublished data) there is a high risk of relapse and we prefer the definitive treatment of circumcision.

Table 1 Reasons for circumcision in patients without lichen sclerosis (control group)

Phimosis for unknown reason	23
Balanitis (acute or relapsing)	9
Familial phimosis	5
Dysuria (balloon type)	3
Secondary phimosis	2
Paraphimosis	2
Total	44

The clinical prerequisite for circumcision was unretractability of the foreskin without scarring.

Table 2 Atopy scores and medical history of patients with lichen sclerosis (LS) and control patients (Co)

	LS (n = 48), n (%)	Co (n = 44), n (%)	Total	P-value	Test
Atopy score					
> 9 (Atopy)	12 (25)	3 (7)	15	0.0451	log reg
8–9 (Atopy possible)	7 (15)	1 (2)	8	0.0182	χ^2
4–7 (Atopy not probable)	14 (29)	14 (32)	28	0.0047	Fisher exact
0–3 (No atopy)	15 (31)	26 (59)	41		
Medical history					
Patient					
Primary (congenital) phimosis	13 (27)	42 (95)	55	< 0.001	χ^2
Secondary (acquired) phimosis	35 (73)	2 (5)	37		
Atopic diseases	25 (52)	9 (20)	34	< 0.02	χ^2
No atopic diseases	23 (48)	35 (80)	58		
Family					
Atopic diseases	31 (65)	28 (64)	59	NS	χ^2
No atopic diseases	17 (35)	15 (34)	32		
Hashimoto thyroiditis + DM	1		1		
Psoriasis	1	3	4		
Alopecia areata		1	1		

Atopy scores were calculated with the Diepgen atopy score. DM, diabetes mellitus; log reg, logistic regression; NS, not significant.

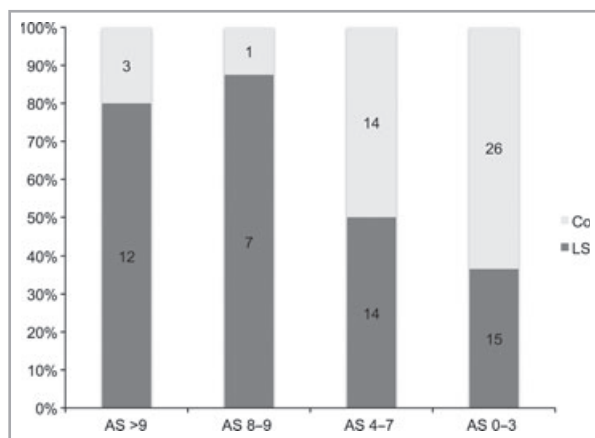


Fig 1. Cumulative percentages of lichen sclerosis (LS) cases and controls (Co) among the four different atopy score groups; absolute numbers are indicated within the bars. AS, atopy score. $P < 0.05$.

Consistent with the literature the rate of LS-related phimosis in our patients was about 15% of all patients with phimosis.^{12–14} Age and predominance of acquired phimosis were comparable with other studies.^{4,6}

Our results strengthen the assumption that school age seems to be the preferred time for incidence of LS-induced secondary phimosis. Only two boys of our control group had a secondary phimosis. We therefore suggest that any acquired phimosis at school age should be regarded to be suspicious for LS. Boys who are circumcised for phimosis of another origin (e.g. balanoposthitis) are usually younger.^{14,15}

We did not see any cases of extragenital LS. In contrast to Kiss *et al.*⁴ we found a significant correlation between the clinical occurrence of the lichenoid changes and the histological results. Contrary to Kiss *et al.*⁴ and Meuli *et al.*¹⁴ we did not

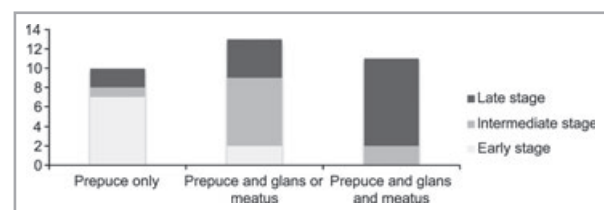


Fig 2. Correlation between histological and clinical stage. Data expressed as total number of lichen sclerosis cases with histological late, intermediate or early signs of lichen sclerosis plotted against three different clinical locations (prepuce, glans penis and/or meatus). $P < 0.001$.

use a grading classification of the phimosis to define the clinical stage of LS because based on our experience (KB, WF) most often the severity of phimosis does not correspond to the stage of lichenoid changes. Instead, we used the dimension of sclerotic changes as indicating severity of LS, related those results with the histological findings of LS and indeed obtained a highly significant correlation.

Using the Diepgen atopy score we found evidence for AD in 25% of boys with LS. The Diepgen score is a validated scheme to summarize distinct symptoms of atopy with the aim to conceive a more objective diagnosis of atopic skin diathesis with a sensitivity of 88% and a specificity of 84% if the diagnostic 'gold standard' eczema of the antecubital and popliteal fossae is absent or if there is eczema without AD.⁹ In our study it is unclear whether the group of boys with possible AD (score 8–9) could have been integrated to have AD. According to Diepgen *et al.*⁹ the probability for AD in these patients is at least 80%. We found a high comorbidity with LS in this subgroup. Thus, inclusion of the patients with possible AD would have increased the correlation between LS and AD

from 25% to 40% being more consistent with other studies. Marren *et al.*¹⁶ reported 41% of their 142 patients with LS to be atopic. Powell and Wojnarowska⁸ found 59% of their cohort of 70 girls with LS to have a personal history of atopy. In contrast, Ditkowski *et al.*,¹⁷ the first group investigating a comorbidity between LS and atopy in childhood, noted six types of allergic manifestation in eight girls but questioned a relationship. To our knowledge, to date only Lipscombe *et al.*¹² have investigated an association between atopy and LS in male patients and found a history of atopy in 34% of patients with LS. However, all of their patients were adults and the study was performed without a respective control group. Our study supports the observations of a relationship between LS and atopy in boys but the correlation between LS and atopy seems to be lower in boys than in girls.

The reported association between LS and autoimmune diseases in patients or first-degree relatives⁷ could not be proven in our LS group. One reason could be the lower co-occurrence of autoimmune diseases and LS in male patients than in females.^{12,13,18} Furthermore, the diagnostic rate of familial autoimmune diseases increases with age. The mean age in our LS group was 8.7 years. Including a broader age range and a larger cohort of patients might have resulted in different results.

The aetiology of LS is not completely understood. There is evidence for isomorphic phenomena (Köbner),⁵ genetic predisposition,¹⁶ hormonal influences¹⁹ as well as autoimmune processes,^{20–23} e.g. against extracellular matrix proteins.²⁴ While atopic diseases are usually dominated by a Th2 response, many autoimmune diseases are linked to Th1 assuming that an augmented Th1 response should protect against allergies.^{25,26} Recently, LS and lichen planus have been linked to Th1²⁷ but other studies showed no or even a stronger association between autoimmune diseases and AD.^{28,29} However, it still needs to be illuminated whether LS and AD share aspects of a common immunological defect or if LS develops on top of atopic disturbed skin. Our data are consistent with the postulation of a permissive but no protective effect of atopy²⁹ facilitating the development of LS. Genetic defects causing a lack of filaggrin have been reported in 50% of all AD cases,³⁰ underlining the pathogenetic hypothesis that a disturbed atopic skin barrier is more susceptible to infectious and allergic³¹ and possibly LS-triggering agents.

Consequently, additive to a genetic background, under an age-dependent hormonal influence – perhaps triggered by an injury – AD might be a further permissive condition for starting the LS-specific inflammatory process.

One limitation of this study is the lack of age-adjusted disease and control groups but we tried to exclude any detection bias by using an age-adjusted logistic regression to analyse our data. Another limitation is the lack of blinded pathologists for examination of the histological results that would have meant an extraordinary excess of workload in the daily routine for the two involved pathologists.

We now have an idea of the prevalence of atopy in boys and girls with LS. Atopy should be regarded as a relevant risk

factor for development of LS in childhood and it would be useful to look for the prevalence of LS in atopic patients in general.

Further studies are needed to illuminate the underlying immunological mechanisms in both entities to clarify the linkage between AD and LS.

What's already known about this topic?

- Comorbidity between lichen sclerosis (LS) and atopy has been described in girls but so far it has never been studied in a controlled fashion.
- In an attempt to investigate this phenomenon in boys we performed an epidemiological prospective case-control study.

What does this study add?

- We found a significant comorbidity between LS and atopic skin diathesis in boys.
- Atopy seems to be a priming precondition for the development of LS.

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