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A Dutch Cohort Study Confirms Familial Occurrence of Anogenital Lichen Sclerosus

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Abstract

Background: Lichen sclerosus is a chronic inflammatory disease mainly affecting the anogenital site chiefly in postmenopausal women with an increased risk of anogenital cancer. Its aetiology is unknown; evidence is accumulating that genetic factors increase the risk of LS in families.

Objective: To evaluate the familial occurrence of anogenital lichen sclerosus in a cohort of Dutch individuals with lichen sclerosus.

Method: To evaluate the familial occurrence of genital LS a questionnaire was given to individuals with confirmed LS attending an annual LS meeting asking for LS in family members with an option of a "certain", "likely", "not known", "definitely not" diagnosis of LS.

Results: One hundred and seventeen of 170 individuals returned questionnaires with information on 555 relatives. Ten individuals (8.6%) stated that they had at least one family member with LS diagnosed by a physician. Thirty-five (30%) attendees had family members with possible LS. Anogenital cancer was reported by one individual and in 2 of the 10 families with familial LS (20%).

Conclusions: 8.6 % of patients with LS had family members with LS. Those families may be at increased risk of developing genital carcinoma in LS lesions.

Keywords: Lichen sclerosus; Familial; Anogential cancer

Introduction

Lichen Sclerosus (LS) is a chronic inflammatory skin disease that usually involves the anogenital area where it causes persistent itching and soreness and sometimes progressive destructive scarring despite treatment; continuous follow-up is recommended [1-4]. The exact prevalence of LS is unknown; the suspected prevalence of LS varies between 0.3% and 3% in the general population. Adult men seem less frequently affected than women, with a female: male ratio varying between 1:1 and 10:1 [5-8]. The cause of LS is unknown; studies show an association with autoimmune diseases such as autoimmune thyroid disease, alopecia areata, and vitiligo and an increased incidence of circulating autoantibodies; although some studies did not confirm this [9-15]. An infective aetiology has been postulated but there are no clear data showing that LS is related to an infection [16,17]. A genetic predisposition is implicated and cases of familial LS were reported in one large study and in individual cases [18-20]. Mechanical factors are thought to play an important role in triggering and maintaining genital LS; sexual abuse being one of them, which was also reported by one patient of this study population. [10,21,22].

The aim of the study was to determine the occurrence of anogenital LS in family members of a cohort of Dutch individuals with LS. LS was confirmed by a physician in all members of the cohort; in family members the diagnosis was known to be confirmed in at least a quarter of all possible LS cases.

Materials and Methods

Questionnaire

To evaluate the familial occurrence of genital LS a questionnaire was developed asking for age of onset (first subjective signs of LS between 0-10, 11-20, 21-50, 51+ years of age), method of diagnosis (clinical/histological), family occurrence of LS (paternal, maternal, siblings, children), with options of a "certain" (diagnosis made by a physician), "likely" (clinical symptoms, diagnosis not made by a physician), "not known", "definitely not" diagnosis of LS for each family member. We also asked for partners who might have LS. Finally, patients had the option for individual comments mentioning for example the occurrence of cancer, in particular anogenital cancer or other skin diseases in themselves or family members. The study was approved by the ethics committee of the VUmc.

Questionnaires were handed out to individuals with lichen sclerosus or parents of children with lichen sclerosus attending the Dutch "Lichen sclerosus information day" in October 2010 which is the annual meeting of the Dutch LS support group which members and interested individuals may attend. The questionnaires were only handed out to members who had a diagnosis of LS.

Statistical methods

Prevalence was assessed using 95% confidence intervals computed from the Binomial Distribution. Prevalence may be influenced by underreporting (not reporting of cases) which lowers it, or over-reporting (reporting false cases) which would raise it. In these cases conclusions can be drawn using the upper and lower limit respectively.

When analyzing responses given for relatives, the denominator of

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the prevalence was taken as the number of persons for which at least one definite (positive or negative) answer is given.

For prevalences, as found above, the appropriate boundary of their confidence interval will be compared with the (suspected) prevalence derived from the literature.

Results

Gender and age distribution in individuals with LS

There were 226 attendees of the meeting. 170 questionnaires were given to individuals with a diagnosis of LS, of which 117 were returned for evaluation (68.8 %). The respondents were 114 females and 2 males, one did not state their gender. They were between 8 and 73 years old when they or their parents attended the meeting. Onset of disease was between 1 and 10 years in age in 12 of 114 patients (10.5%), between 11 and 20 years in 15 (13.2%), between 21 and 50 years in 45 (39.5%) and over 51 years in 42 (36.3%) patient; in 3 the age of onset was unknown. LS was diagnosed clinically in 39 patients and in 69 the diagnosis was confirmed histologically; in 9 patients the mode of diagnosis was not stated.

Occurrence of LS in family members

Two sisters attended the meeting so 116 families were available for family studies. Ten individuals (8.6%) stated that they had at least one family member with LS diagnosed by a physician (Table 1). In addition, thirty-five (30%) individuals said that they had possible family members with LS as indicated by clinical symptoms like genital itch or a tight foreskin, but the diagnosis was not known to be confirmed by a physician.

Out of 2777 relatives the status of LS was known to the attendee for 555 of whom 299 were female (53.9%). Of these 555 relatives, 16 (2.9%) had confirmed LS and 55 (9.9%) were believed to have LS (together 12.8%) (Table 2). All 16 confirmed LS were female (16/299 females=5.4%). Of the suspected LS 41 were female (41/299 females=13.7%) and 14 were male (14/256 males=5.5%).

Familial cases were more common, 22%, among female relatives (mother, sisters, daughters, maternal grandmother and aunts) and were present in 5.9 % of male relatives (father, brothers, sons, paternal grandfather and uncles) and 5.4 % in male and female relatives (maternal grandfather and uncles, paternal grandmother and aunts) (Table 3).

There were 3 attendees who had a monozygotic twin; in one pair both had LS that started at the same age (40 years), in one pair only one was affected (onset between 21 and 50 years) and in the third pair this is unknown because one twin died as a baby. In addition, there was an attendee with a monozygous mother/aunt pair, both had vulval LS and both developed vulval cancer. There was one pair of heterozygous twins; only one sister was affected by LS with an age of onset after 51 years of age.

None had partners with LS.

Anogenital cancer

Anogenital cancer was reported in 2 (#14 & 25) of the 10 families with a definite diagnosis of familial LS (20%), both occurred in families with multiple LS in 3 individuals (Table 4). One female attendee (#34) reported vulval cancer herself without a family history of LS. In 3 families (#88, 61, 44) with a possible familial occurrence of LS anogenital cancer was described in three members.

Attendee	Aunt	Mother	Daughter	Sister
# 25	1 paternal vulval cancer			1 # 107
# 7	1 maternal	1		
# 14	1 maternal twin, vulval cancer	1 twin, vulval cancer		
# 91		1		1
# 92		1		
# 153	1 maternal			
# 22			1	
# 23			1	
# 24 twin				1 twin
# 103				1

* #107 and #25 are sisters, in this table only sister #25 is shown as attendee which demonstrates only 14 family cases in the table

Table 1: Ten attendees of 116 families reported of familial occurrence of LS.

		N	A	frequency	95% c.i.	
certain LS	female	299	16	5.4%	3.1%	8.5%
	male	256	0	0.0%	0.0%	1.4%
	total	555	16	2.9%	1.7%	4.6%
suspected LS	female	299	41	13.7%	10.0%	18.1%
	male	256	14	5.5%	3.0%	9.0%
	total	555	55	9.9%	7.6%	12.7%
Anogenital Ca	female	299	3	1.00%	0.21%	2.90%
	male	256	2	0.78%	0.09%	2.79%
	total	555	5	0.90%	0.29%	2.09%

N= the number of relatives of which we have information on LS
A= the number of relatives who were actually affected by LS

Table 2: Reported frequencies of LS and anogenital cancer for relatives.

		N	A	frequency	95% c.i.	
certain LS	female	241	14	5.8%	3.2%	9.6%
	male	203	0	0.0%	0.0%	1.8%
	mixed	111	2	1.8%	0.2%	6.4%
	total	555	16	2.9%	1.7%	4.6%
suspected LS	female	241	39	16.2%	11.8%	21.5%
	male	203	12	5.9%	3.1%	10.1%
	mixed	111	4	3.6%	1.0%	9.0%
	total	555	55	9.9%	7.6%	12.7%
Anogenital Ca	female	241	2	0.83%	0.10%	2.97%
	male	203	1	0.49%	0.01%	2.71%
	mixed	111	2	1.80%	0.22%	6.36%
	total	555	5	0.90%	0.29%	2.09%

Table 3: Reported frequencies by gender.

	Families (n=116)	Families with anogenitalca
Familial LS in one relative	6	-
Familial LS in two relatives	4	2 (#14,25 in 3 members)
Possible familial LS	35	3 (#34,44,61)
Probably no familial LS	71	1 (#34)

Table 4: Anogenital carcinoma occurring in familial Lichen sclerosus.

For familial LS and anogenital cancer we considered 5 reported relatives out of 555 (0.9%). Of these, 3 were female (1.0%) and 2 were male (0.8%). Furthermore, one attendee reported a family history of monozygotic twins with vulval LS who both developed vulval cancer.

Discussion

A positive family history of LS was observed in 12% and 8.7% of patients with vulval LS in two British studies [9,18]. Our results of a

Dutch cohort with genital LS show that at least 8.6% of patients have family members with genital LS; another 30% stated that there are family members with clinical symptoms pointing towards a diagnosis of LS. Our results suggest a minimum of 3% of males and 12% of females with LS have relatives with probable LS, similar to the recent UK study [18]. This also supports the observation of Aslanian et al. that undiagnosed family members of LS patients are not uncommon suggesting an unexpected strong familial / genetic background in LS [19,20]. Furthermore, our results show that there are more female relatives who have LS than males. At least 3.2% of all LS patients had relatives with LS; whereas between 8.6% and possibly 38.6% of female patients in our study had relatives with LS. This is in contrast to the finding of Kyriakis et al. who observed equal gender distribution in a cohort of LS patients in a Greek general hospital,[7] but concurs with many other reports [15]. Leibovitz et al. report that 1 in 30 (3.3%) unrelated old women in a nursing home had LS [6].

Our questionnaire did not explicitly ask for anogenital cancer and only one individual reported having vulval cancer herself. However, the report of anogenital cancer in 2 of the 4 families with multiple familial LS (vulval carcinoma occurred in one monozygotic twin pair with LS and an in an aunt of a monozygotic twin with LS) and in 3 members of families with a possible family history of LS versus only one individual with no family history of LS is all the more remarkable. This may point towards a genetic background of cancer development in familial LS. Our observation is supported by the finding by Sherman et al. who report that vulval cancer was significantly increased (4.1% vs 1.2%, $p<0.05$) in their patients with a family history of LS [18].

The accumulation of reports of an increased risk of anogenital cancer in familial LS may justify family screening for LS and may help to select patients who need long term follow-up in order to detect anogenital carcinoma early.

Conclusion

In conclusion, at least 10% of patients with LS have family members with LS and it may be as high as 38.6%. Those families may be at increased risk of developing genital carcinoma in LS lesions. In the clinic investigation of LS patients' families to detect and treat LS early and identify familial cases of LS who may have an increased risk of cancer development is recommended. Further genetic studies are needed to unravel the genetic background of LS which may enable us to develop new therapeutic strategies and help to identify the patho-mechanisms of cancer development in LS.

What's already known about this topic?

- About 12% of a cohort with anogenital LS in the UK have a positive family history for LS (cohort of 1052 female patients of 95 families); the occurrence of vulval cancer was increased in patients with a family history of LS.

What does this study add?

- A Dutch cohort shows that at least 8.6% (10 of 117 families) of patients with LS will have family members with anogenital lichen sclerosus. However, the risk of having a further family member with LS may be as high as 38.6 % in our study. This high figure has to be confirmed by studies that only include cases with a confirmed diagnosis of LS.
- We also confirmed that the risk of anogenital cancer is increased in families with familial occurrence of LS.
- If future studies confirm this suspected high prevalence of LS in families who may be at risk of anogenital cancer appropriate screening methods need to be developed.

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